Appendix A Preferred Reporting Items for Overviews of Reviews (PRIOR) checklist

Section topic	Item No	Item	Location where item is reported
Title			
Title	1	Identify the report as an overview of reviews.	"Evidence review" is preferred term for HRB titles
Abstract			
Abstract	2	Provide a comprehensive and accurate summary of the purpose, methods, and results of the overview of reviews.	Executive summary
Introduction			
Rationale	3	Describe the rationale for conducting the overview of reviews in the context of existing knowledge.	Section 1.3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) addressed by the overview of reviews.	Section 1.4
Methods			
Eligibility criteria	5a	Specify the inclusion and exclusion criteria for the overview of reviews. If supplemental primary studies were included, this should be stated, with a rationale.	Section 2.1
	5b	Specify the definition of "systematic review" as used in the inclusion criteria for the overview of reviews.	Section 2.3
Information sources	6	Specify all databases, registers, websites, organisations, reference lists, and other sources searched or consulted to identify systematic reviews and supplemental primary studies (if included). Specify the date when each source was last searched or consulted.	Appendix B
Search strategy	7	Present the full search strategies for all databases, registers and websites, such that they could be reproduced. Describe any search filters and limits applied.	Appendix B
Selection process	8a	Describe the methods used to decide whether a systematic review or supplemental primary study (if included) met the inclusion criteria of the overview of reviews.	Section 2.5
	8b	Describe how overlap in the populations, interventions, comparators, and/or outcomes of systematic reviews was identified and managed during study selection.	Section 2.8
Data collection process	9a	Describe the methods used to collect data from reports.	Section 2.6
	9b	If applicable, describe the methods used to identify and manage primary study overlap at the level of the comparison and outcome during data collection. For each outcome, specify the method used to illustrate and/or quantify the degree of primary study overlap across systematic reviews.	Section 2.8.3
	9c	If applicable, specify the methods used to manage discrepant data across systematic reviews during data collection.	Not applicable

Data items	10	List and define all variables and outcomes for which data were sought. Describe any assumptions made and/or measures taken to identify and clarify missing or unclear information.	Appendix F
Risk of bias assessment	11a	Describe the methods used to assess risk of bias or methodological quality of the included systematic reviews.	Section 2.7, Appendix E
	11b	Describe the methods used to collect data on (from the systematic reviews) and/or assess the risk of bias of the primary studies included in the systematic reviews. Provide a justification for instances where flawed, incomplete, or missing assessments are identified but not reassessed.	Sections 2.6, 2.7, Appendix E
	11c	Describe the methods used to assess the risk of bias of supplemental primary studies (if included).	Not applicable
Synthesis methods	12a	Describe the methods used to summarise or synthesise results and provide a rationale for the choice(s).	Section 2.8
	12b	Describe any methods used to explore possible causes of heterogeneity among results.	Not applicable
	12c	Describe any sensitivity analyses conducted to assess the robustness of the synthesised results.	Not applicable
Reporting bias assessment	13	Describe the methods used to collect data on (from the systematic reviews) and/or assess the risk of bias due to missing results in a summary or synthesis (arising from reporting biases at the levels of the systematic reviews, primary studies, and supplemental primary studies, if included).	Not applicable
Certainty assessment	14	Describe the methods used to collect data on (from the systematic reviews) and/or assess certainty (or confidence) in the body of evidence for an outcome.	Section 2.8.4
Results			
Systematic review and supplemental primary study selection	15a	Describe the results of the search and selection process, including the number of records screened, assessed for eligibility, and included in the overview of reviews, ideally with a flow diagram.	Section 2.5.4
	15b	Provide a list of studies that might appear to meet the inclusion criteria, but were excluded, with the main reason for exclusion.	Appendix C
Characteristics of systematic reviews and supplemental primary studies	16	Cite each included systematic review and supplemental primary study (if included) and present its characteristics.	Appendix I
Primary study overlap	17	Describe the extent of primary study overlap across the included systematic reviews.	Section 3.7
Risk of bias in systematic reviews, primary studies, and supplemental primary studies	18a	Present assessments of risk of bias or methodological quality for each included systematic review.	Appendix J
	18b	Present assessments (collected from systematic reviews or assessed anew) of the risk of bias of the primary studies included in the systematic reviews.	Appendix F
	18c	Present assessments of the risk of bias of supplemental primary studies (if included).	Not applicable
Summary or synthesis of results	19a	For all outcomes, summarise the evidence from the systematic reviews and supplemental primary studies (if included). If meta-analyses were done, present for each the summary estimate and its precision and measures of	Section 3.7

		statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	19b	If meta-analyses were done, present results of all investigations of possible causes of heterogeneity.	Not applicable
	19c	If meta-analyses were done, present results of all sensitivity analyses conducted to assess the robustness of synthesised results.	Not applicable
Reporting biases	20	Present assessments (collected from systematic reviews and/or assessed anew) of the risk of bias due to missing primary studies, analyses, or results in a summary or synthesis (arising from reporting biases at the levels of the systematic reviews, primary studies, and supplemental primary studies, if included) for each summary or synthesis assessed.	Not applicable
Certainty of evidence	21	Present assessments (collected or assessed anew) of certainty (or confidence) in the body of evidence for each outcome.	Section 3.7, Appendix K
Discussion			
Discussion	22a	Summarise the main findings, including any discrepancies in findings across the included systematic reviews and supplemental primary studies (if included).	Section 4.1
	22b	Provide a general interpretation of the results in the context of other evidence.	Section 4.2
	22c	Discuss any limitations of the evidence from systematic reviews, their primary studies, and supplemental primary studies (if included) included in the overview of reviews. Discuss any limitations of the overview of reviews methods used.	Section 4.3
	22d	Discuss implications for practice, policy, and future research (both systematic reviews and primary research). Consider the relevance of the findings to the end users of the overview of reviews, eg, healthcare providers, policymakers, patients, among others.	Section 4.4
Other information			
Registration and protocol	23a	Provide registration information for the overview of reviews, including register name and registration number, or state that the overview of reviews was not registered.	Section 2.2
	23b	Indicate where the overview of reviews protocol can be accessed, or state that a protocol was not prepared.	Section 2.2
	23c	Describe and explain any amendments to information provided at registration or in the protocol. Indicate the stage of the overview of reviews at which amendments were made.	Section 2.9
Support	24	Describe sources of financial or non-financial support for the overview of reviews, and the role of the funders or sponsors in the overview of reviews.	Not applicable
Competing interests	25	Declare any competing interests of the overview of reviews' authors.	Not applicable
Author information	26a	Provide contact information for the corresponding author.	Page 2
	26b	Describe the contributions of individual authors and identify the guarantor of the overview of reviews.	Not applicable
Availability of data	27	Report which of the following are available, where they can be found, and under which conditions they may be accessed: template data collection forms; data collected	Data collection form

and other materials	from included systematic reviews and supplemental primary studies; analytic code; any other materials used in the overview of reviews.	Appendix D, data collected from included reviews Appendix F

Source: Gates *et al.* (2022)

Appendix B Search strategies

Search results numbers

Appendix Table 1 Results of primary database searches

Bibliographic databases (clinical/ psychological/ sociological/ international)		Search date	Results
Ovid MEDLINE		09 Jun 2022	6075
Ovid Embase		09 Jun 2022	10214
OVID PsycINFO		09 Jun 2022	1691
EBSCO CINAHL Complete		09 Jun 2022	979
EBSCO SOCIndex with Full Text		09 Jun 2022	263
LILACS		10 Jun 2022	511
SCielo		10 Jun 2022	212

Appendix Table 2 Results of primary review-related resource searches

Review-related search resources	Search date	Results
Cochrane Library	09 Jun 2022	42
Campbell Library	09 Jun 2022	6
Epistemonikos	09 Jun 2022	1331
Agency for Healthcare Quality and Research Systematic Review Data Repository	09 Jun 2022	2
Database of Abstracts of Reviews of Effects (DARE)	10 Jun 2022	26
Database of promoting health effectiveness reviews (DoPHER)	10 Jun 2022	57
Joanna Briggs Institute (JBI) Evidence Synthesis	10 Jun 2022	5
International Health Technology Assessment (HTA) database	10 Jun 2022	37
PROSPERO	11 Jun 2022	1167
Health Evidence	11 Jun 2022	46

Appendix Table 3 Other search resources

Preprint resource: MedRXiv/BioRXiv	11 Jun 2022	46
Preprint resource: Osf.io	11 Jun 2022	56
Preprint resource: ResearchSquare	11 Jun 2022	4
Search engine: Bielefeld Academic Search Engine (BASE)	10 Jun 2022	2510
Search engine: DuckDuckGo	11 Jun 2022	300
Search engine: Google Scholar	12 Jun 2022	282
Open access research aggregator: Core	10 Jun 2022	290
Topic-specific resource: International Alliance for Cannabinoid Medicines	12 Jun 2022	15

Appendix Table 4 Final results numbers

Final results	Search date	Results
Total results from database searches		25888
Total deduplicated results		14636

Screened on title and abstract		14636
Screened on full text	Oct 2022	**392**
Final included citations from database searches		40
Total results from supplemental searches	Jan 2023	8477
Total deduplicated supplemental results		5571
Screened on full-text		57
Final included citations from supplemental searches	Jan 2023	7
Final included citations from all searches and supplemental methods	Feb 2023	47

Search strategies for each database/resource

Ovid MEDLINE

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions 1946 to June 08, 2022

Platform: Ovid

Search date: 09 Jun 2022

Search line	Search term	Results
1	Medical Marijuana/	1971
2	Cannabis/	12030
3	exp "Marijuana Use"/	6817
4	exp Cannabinoids/	16831
5	exp Cannabinoid Receptor Modulators/	13376
6	(Mari#uan* and (clinical$ or therap$ or medic$ or trial$ or patient$ or placebo$ or randomi$ or adminis$ or ameliorat$ or treat$ or manage$ or tolerat$ or intervention$ or prescrib$)).mp.	15348
7	(Cannabis and (clinical$ or therap$ or medic$ or trial$ or patient$ or placebo$ or randomi$ or adminis$ or ameliorat$ or treat$ or manage$ or tolerat$ or intervention$ or prescrib$)).mp.	18091
8	((Cannabid* or cannabin*) and (clinical$ or therap$ or medic$ or trial$ or patient$ or placebo$ or randomi$ or adminis$ or ameliorat$ or treat$ or manage$ or tolerat$ or intervention$ or prescrib$)).mp.	19844
9	Exocannabi*.mp.	30
10	(Tetrahydrocannabi$ and (clinical$ or therap$ or medic$ or trial$ or patient$ or placebo$ or randomi$ or adminis$ or ameliorat$ or treat$ or manage$ or tolerat$ or intervention$ or prescrib$)).mp.	5851
11	phytocannabi*.mp.	946
12	((CBD not (cortical bone density or common bile duct$)) and (clinical$ or therap$ or medic$ or trial$ or patient$ or placebo$ or randomi$ or adminis$ or ameliorat$ or treat$ or manage$ or tolerat$ or intervention$ or prescrib$)).mp.	4469
13	((THC not (total hydrocarbons or telephonic health coaching or total hospital charge$)) and (clinical$ or therap$ or medic$ or trial$ or study or studies or patient$ or placebo$ or random$ or adminis$ or ameliorat$ or treat$ or manage$ or tolerat$ or intervention$ or prescrib$)).mp.	7295

14	THCVS.mp.	1
15	(("C.indica" or "C. sativa" or "C. ruderalis") not Camelina sativa).tw.	347
16	((((Hash or hashish) not (hash1 or "hash function" or hashtag$ or hash value or hashing or "hash code")) or Ganja or bhang or canabis) and (clinical$ or therap$ or medic$ or trial$ or patient$ or placebo$ or randomi$ or adminis$ or ameliorat$ or treat$ or manage$ or tolerat$ or intervention$ or prescrib$)).mp.	583
17	((hemp or Cannabac$) and (clinical$ or therap$ or medic$ or trial$ or patient$ or placebo$ or randomi$ or adminis$ or ameliorat$ or treat$ or manage$ or tolerat$ or intervention$ or prescrib$)).tw,hw,kf.	791
18	((weed* or joint*) and (cannab* or marij*)).mp.	729
19	(Dronabinol* or Marinol or Syndros).mp.	8121
20	(Nabiximols or Sativex or "GW 1000-02" or "GW-1000-02" or "GW 1000" or Tetranabinex or Nabidiolex or "SAB 378").mp.	392
21	(Nabilone or Cesamet or Canemes).mp.	385
22	(Epidiolex or Epidyolex).mp.	133
23	(Tilray or Bedrobinol or Transvamix or "VER-01" or Bedrocan or Bediol or Bedica or Bedrolite or Aurora Sedamen Softgels or Namisol or CannEpil).mp.	40
24	(maconha or dagga or marihuaanat or marihuwana or marigwana or mariuana or tshuaj maj or "marihuána" or "marijúana").mp.	64
25	("11-OH-THC" or "11-Hydroxy-THC" or "11-Hydroxy-delta9-tetrahydrocannabinol" or 11-Hydroxyhexahydrocannabinol or "11-OH-delta9-THC" or "11-Hydroxycannabinol (11-OH-CBN)").mp.	280
26	("delta-1-Tetrahydrocannabinol" or "delta(1)-Tetrahydrocannabinol" or "delta1-tetrahydrocannabinol" or "1-tetrahydrocannabinol" or "delta(1)-THC" or "delta1-THC" or "1-THC").mp.	225
27	("delta-8-tetrahydrocannabinol" or "delta(8)-tetrahydrocannabinol" or "delta8-tetrahydrocannabinol" or "8-tetrahydrocannabinol" or "delta(8)-THC" or "delta8-THC" or "8-THC").mp.	464
28	("delta-9-tetrahydrocannabinol" or "delta(9)-Tetrahydrocannabinol" or "delta9-tetrahydrocannabinol" or "9-tetrahydrocannabinol" or "delta(9)-THC" or "delta9-THC" or "Delta-9-THC" or "9-THC" or "(−)-trans-Δ9-tetrahydrocannabinol").mp.	6953
29	(Dexanabinol or HU-211).mp.	377
30	(cannabicyclol or cannabichromene or cannabigerol).mp.	338
31	((Mari#uan$ or cannabis or cannabid$ or cannabin$ or tetrahydrocannab$ or THC or CBD or hemp) and (capsule$ or spray$ or oil$ or vapo$ or transdermal or patch$ or inhal$ or smoke$)).tw.	6398
32	or/1-31	58160
33	exp Review/ or Systematic review/ or Meta-Analysis/ or exp Review Literature as Topic/ or Meta-Analysis as Topic/ or Systematic Reviews as Topic/	3171609
34	((systematic$ or methodologic$ or comprehensive or integrative or collaborative or "state-of-the-art" or scoping or umbrella or narrative or integrative or iterative or technolog$ or quantitat$ or qualitat$ or traditional or critical or rapid or mixed studies or mixed methods or thematic or pragmatic or realist or Cochrane or Campbell) adj2 (review$ or overview$ or bibliograph$ or report$ or summary or summaries)).tw.	394614

35	(literature review or "review of reviews" or "overview of reviews" or evidence synthes* or meta analy$ or meta-analy$ or metaanalys$ or meta-synthe$ or metasynth$ or metaregression or meta-regression or health technology assessment$ or "synthesis of evidence" or meta-summary or "mapping review" or "literature map" or systematic map$).mp.	392285
36	(Cochrane or systematic or technology assessment).jn,jw.	43877
37	(handsearch or data extraction or "risk of bias" or AMSTAR or AMSTAR2 or ROBIS or "AMSTAR 2" or ROB2 or "ROBINS-I" or "ROBINS-1").tw.	58323
38	(search$ adj2 (literature or strateg$ or electronic or hand or systematic or bibliographic or keyword$ or key term$ or Pubmed or Medline or Embase or Cochrane or Scopus or "Web of Science" or CINAHL)).mp.	215432
39	(search$ and (Pubmed or Medline or CINAHL or Embase or Cochrane or Scopus or "Web of Science")).tw.	239746
40	or/33-39	3377834
41	32 and 40	9252
42	Comment/ or Letter/ or Editorial/ or (Animals/ not (Animals/ and Humans/))	6976193
43	41 not 42	8891
44	limit 43 to yr="2010 - 2023"	6075

Ovid Embase

Database: Embase 1974 to 2022 June 08

Platform: Ovid

Search date: 09 Jun 2022

Search line	Search terms	Results
1	exp Medical Cannabis/	3363
2	exp Cannabis/	39829
3	exp "cannabis use"/	15432
4	exp Cannabinoid/	78433
5	exp Cannabinoid Receptor Modulators/	33184
6	exp "Cannabis (genus)"/	1334
7	(Mari#uan$ and (clinical$ or therap$ or medic$ or trial$ or patient$ or placebo$ or randomi$ or adminis$ or ameliorat$ or treat$ or manage$ or tolerat$ or intervention$ or prescrib$)).mp.	17114
8	(Cannabis$ and (clinical$ or therap$ or medic$ or trial$ or patient$ or placebo$ or randomi$ or adminis$ or ameliorat$ or treat$ or manage$ or tolerat$ or intervention$ or prescrib$)).mp.	47961
9	((Cannabid* or cannabin*) and (clinical$ or therap$ or medic$ or trial$ or patient$ or placebo$ or randomi$ or adminis$ or ameliorat$ or treat$ or manage$ or tolerat$ or intervention$ or prescrib$)).mp.	32466
10	Exocannabi*.mp.	38
11	(Tetrahydrocannabi$ and (clinical$ or therap$ or medic$ or trial$ or patient$ or placebo$ or randomi$ or adminis$ or ameliorat$ or treat$ or manage$ or tolerat$ or intervention$ or prescrib$)).mp.	11435
12	phytocannabi*.mp.	1207

13	((CBD not (cortical bone density or common bile duct$)) and (clinical$ or therap$ or medic$ or trial$ or patient$ or placebo$ or randomi$ or adminis$ or ameliorat$ or treat$ or manage$ or tolerat$ or intervention$ or prescrib$)).mp.	7955
14	((THC not (total hydrocarbons or telephonic health coaching or total hospital charge$)) and (clinical$ or therap$ or medic$ or trial$ or study or studies or patient$ or placebo$ or random$ or adminis$ or ameliorat$ or treat$ or manage$ or tolerat$ or intervention$ or prescrib$)).mp.	11339
15	THCVS.mp.	2
16	(("C.indica" or "C. sativa" or "C. ruderalis") not Camelina sativa).tw.	375
17	((((Hash or hashish) not (hash1 or "hash function" or hashtag$ or hash value or hashing or "hash code")) or Ganja or bhang or canabis) and (clinical$ or therap$ or medic$ or trial$ or patient$ or placebo$ or randomi$ or adminis$ or ameliorat$ or treat$ or manage$ or tolerat$ or intervention$ or prescrib$)).mp.	988
18	((hemp or Cannabac$) and (clinical$ or therap$ or medic$ or trial$ or patient$ or placebo$ or randomi$ or adminis$ or ameliorat$ or treat$ or manage$ or tolerat$ or intervention$ or prescrib$)).tw,hw,kf.	1091
19	((weed* or joint*) and (cannab* or marij*)).tw,hw,kf.	1258
20	(Dronabinol* or Marinol or Syndros).mp.	8939
21	(Nabiximol$ or Sativex or "GW 1000-02" or "GW-1000-02" or "GW 1000" or Tetranabinex or Nabidiolex or "SAB 378").mp.	1276
22	(Nabilone or Cesamet).mp.	1581
23	(Epidiolex or Epidyolex).mp.	377
24	(Tilray or Bedrobinol or Bedrocan or Bediol or Bedica or Bedrolite or Aurora Sedamen Softgels or Namisol or CannEpil).mp.	128
25	(maconha or dagga or marihuaanat or marihuwana or marigwana or mariuana or tshuaj maj or "marihuána" or "marijúana").mp.	61
26	("11-OH-THC" or "11-Hydroxy-THC" or "11-Hydroxy-delta9-tetrahydrocannabinol" or 11-Hydroxyhexahydrocannabinol or "11-OH-delta9-THC" or "11-Hydroxycannabinol (11-OH-CBN)").mp.	371
27	("delta-1-Tetrahydrocannabinol" or "delta(1)-Tetrahydrocannabinol" or "delta1-tetrahydrocannabinol" or "1-tetrahydrocannabinol" or "delta(1)-THC" or "delta1-THC" or "1-THC").mp.	241
28	("delta-8-tetrahydrocannabinol" or "delta(8)-tetrahydrocannabinol" or "delta8-tetrahydrocannabinol" or "8-tetrahydrocannabinol" or "delta(8)-THC" or "delta8-THC" or "8-THC").mp.	1325
29	("delta-9-tetrahydrocannabinol" or "delta(9)-Tetrahydrocannabinol" or "delta9-tetrahydrocannabinol" or "9-tetrahydrocannabinol" or "delta(9)-THC" or "delta9-THC" or "Delta-9-THC" or "9-THC" or "(−)-trans-Δ9-tetrahydrocannabinol").mp.	8369
30	(Dexanabinol or HU-211).mp.	1270
31	(cannabicyclol or cannabichromene or cannabigerol).mp.	712
32	((Mari#uan$ or cannabis or cannabid$ or cannabin$ or tetrahydrocannab$ or THC or CBD or hemp) and (capsule$ or spray$ or oil$ or vapo$ or transdermal or patch$ or inhal$ or smoke$)).tw.	9244
33	or/1-32	108417

34	exp Review/ or Systematic review/ or exp Meta-Analysis/ or "Meta-Analysis (Topic)"/ or "Systematic Review (Topic)"/	3066044
35	((systematic$ or methodologic$ or comprehensive or integrative or collaborative or "state-of-the-art" or scoping or umbrella or integrative or iterative or technolog$ or quantitat$ or qualitat$ or traditional or critical or rapid or mixed studies or mixed methods or thematic or pragmatic or realist or Cochrane or Campbell) adj2 (review$ or overview$ or bibliograph$ or summary or summaries)).tw.	430488
36	(literature review or "review of reviews" or "overview of reviews" or narrative review$ or evidence synthes$ or meta analy$ or meta-analy$ or metaanalys$ or meta-synthe$ or metasynth$ or metaregression or meta-regression or health technology assessment$ or "synthesis of evidence" or meta-summary or "mapping review" or "literature map" or systematic map$).tw.	475721
37	(Cochrane or systematic or technology assessment).jn,jx.	57952
38	(handsearch or data extraction or "risk of bias" or AMSTAR or AMSTAR2 or ROBIS or "AMSTAR 2" or ROB2 or "ROBINS-I" or "ROBINS-1").tw.	70016
39	(search$ adj2 (literature or strateg$ or electronic or hand or systematic or bibliographic or keyword$ or key term$)).tw.	174481
40	(search$ and (Pubmed or Medline or CINAHL or Embase or Cochrane or Scopus or "Web of Science")).tw.	297459
41	or/34-40	3370527
42	33 and 41	17861
43	(endocannabinoid$ not (cannabinoid$ or exocannabinoid$ or cannabidiol$ or cannabinol$ or cannabis or mari#uan#)).tw,hw,kf.	4458
44	42 not 43	16991
45	(exp animal/ or exp animal experiment/ or exp veterinary study/ or animal model/ or animal tissue/ or agriculture/ or drug manufacture/ or preclinical study/ or nonhuman/ or exp in vitro study/ or exp invertebrate/ or exp plant/ or exp fungus/ or human cell/ or (animal model or rat or rats or mice or mouse or murine or dog or dogs or canine or veterinar$ or nematod$ or cell line$ or "in vitro" or "in silico").tw.) not (exp Human/ or exp Miscellaneous named groups/ or (human$ or patient$ or participant$).tw.)	7005360
46	44 not 45	16291
47	limit 46 to yr="2010 - 2023"	10214

Ovid PsycINFO

Database: APA PsycINFO 1806 to June Week 1 2022

Platform: Ovid

Search date: 09 Jun 2022

Search line	Search terms	Search results
1	exp Medical Marijuana/	381
2	exp Marijuana/	3788
3	exp Marijuana Usage/	3277

4	exp Cannabinoids/	6397
5	Mari#uan$.mp.	16523
6	Cannabis$.mp.	14514
7	(Cannabid* or cannabin*).mp.	7473
8	Exocannabi*.mp.	5
9	Tetrahydrocannabi$.mp.	2831
10	Phytocannabi*.mp.	179
11	((CBD not cortical bone density) or common bile duct$).mp.	1178
12	(THC not (total hydrocarbons or telephonic health coaching or total hospital charge$)).mp.	2522
13	THCVS.mp.	0
14	(("C.indica" or "C. sativa" or "C. ruderalis") not Camelina sativa).tw.	12
15	(hemp or Cannabac$).tw.	99
16	(((Hash or hashish) not (hash1 or "hash function" or hashtag$ or hash value or hashing or "hash code")) or Ganja or bhang or canabis).mp.	605
17	((weed* or joint*) and (cannab* or marij*)).mp.	375
18	(Dronabinol* or Marinol or Syndros).mp.	1784
19	(Nabiximol$ or Sativex or "GW 1000-02" or "GW-1000-02" or "GW 1000" or Tetranabinex or Nabidiolex or "SAB 378").mp.	99
20	(Nabilone or Cesamet).mp.	98
21	(Epidiolex or Epidyolex).mp.	25
22	(Tilray or Bedrobinol or Bedrocan or Bediol or Bedica or Bedrolite or Aurora Sedamen Softgels or Namisol or CannEpil).mp.	7
23	(maconha or dagga or marihuaanat or marihuwana or marigwana or mariuana or tshuaj maj or "marihuána" or "marijúana").mp.	60
24	("11-OH-THC" or "11-Hydroxy-THC" or "11-Hydroxy-delta9-tetrahydrocannabinol" or 11-Hydroxyhexahydrocannabinol or "11-OH-delta9-THC" or "11-Hydroxycannabinol (11-OH-CBN)").mp.	38
25	("delta-1-Tetrahydrocannabinol" or "delta(1)-Tetrahydrocannabinol" or "delta1-tetrahydrocannabinol" or "1-tetrahydrocannabinol" or "delta(1)-THC" or "delta1-THC" or "1-THC").mp.	46
26	("delta-8-tetrahydrocannabinol" or "delta(8)-tetrahydrocannabinol" or "delta8-tetrahydrocannabinol" or "8-tetrahydrocannabinol" or "delta(8)-THC" or "delta8-THC" or "8-THC").mp.	61
27	("delta-9-tetrahydrocannabinol" or "delta(9)-Tetrahydrocannabinol" or "delta9-tetrahydrocannabinol" or "9-tetrahydrocannabinol" or "delta(9)-THC" or "delta9-THC" or "Delta-9-THC" or "9-THC" or "(−)-trans-Δ9-tetrahydrocannabinol").mp.	2145
28	(Dexanabinol or HU-211).mp.	6
29	(cannabicyclol or cannabichromene or cannabigerol).mp.	28
30	((Mari#uan$ or cannabis or cannabid$ or cannabin$ or tetrahydrocannab$ or THC or CBD or hemp) and (capsule$ or spray$ or oil$ or vapo$ or transdermal or patch$ or inhal$ or smoke$)).tw.	3064
31	or/1-30	31201
32	exp Literature Review/ or Systematic review/ or Meta-Analysis/	28546
33	("4600" or "4800" or "5000").dt.	121014
34	(systematic review or literature review or meta-analysis or metasynthesis).md.	196168

35	((systematic$ or methodologic or comprehensive or integrative or collaborative or "state-of-the-art" or scoping or umbrella or narrative or integrative or iterative or technolog$ or quantitat$ or qualitat$ or traditional or critical or mapping or rapid or mixed studies or mixed methods or thematic or pragmatic or realist or Cochrane or Campbell) adj2 (review$ or overview$ or literature or bibliograph$ or report$ or map or maps or mapping or summary or summaries)).mp.	153916
36	(literature review or "review of reviews" or "overview of reviews" or evidence synthes* or meta analy$ or meta-analy$ or metaanalys$ or meta-synthe$ or metasynth$ or metaregression or meta-regression or health technology assessment$ or "synthesis of evidence" or meta-summary).mp.	97247
37	(Cochrane or systematic or technology assessment).jn,jw.	344
38	(handsearch or data extraction or "risk of bias" or AMSTAR or AMSTAR2 or ROBIS or "AMSTAR 2" or ROB2 or "ROBINS-I" or "ROBINS-1").mp.	5454
39	(search$ adj2 (literature or strateg$ or electronic or hand or systematic or bibliographic or keyword$ or key term$ or Pubmed or Medline or Embase or Cochrane or Scopus or "Web of Science")).mp.	29655
40	or/32-39	443601
41	31 and 40	2618
42	limit 41 to yr="2010 - 2023"	1761
43	("2600" or "2800" or "3000" or "3800" or "4000" or "4200").dt.	213900
44	42 not 43	1691

EBSCO CINAHL Complete

Database: CINAHL Complete

Platform: EBSCO

Search date: 09 Jun 2022

Search line	Search terms	Search Options	Results
S1	(MH "Medical Marijuana")	Expanders - Apply equivalent subjects Search modes - Boolean/ Phrase	2,196
S2	(MH "Cannabis+")	Expanders - Apply equivalent subjects Search modes - Boolean/ Phrase	11,595
S3	(TI (Cannabis)) OR (AB (cannabis)) OR (SU (Cannabis))	Expanders - Apply equivalent subjects Search modes - Boolean/ Phrase	16,641
S4	(TI (Marijuana OR Marihuana)) OR (AB (Marijuana OR Marihuana)) OR (SU (Marijuana OR Marihuana))	Expanders - Apply equivalent subjects Search modes - Boolean/ Phrase	9,996

S5	(TI (Cannabid* OR Cannabin*)) OR (AB (Cannabid* OR Cannabin*)) OR (SU(Cannabid* OR Cannabin*))	Expanders - Apply equivalent subjects Search modes - Boolean/ Phrase	4,837
S6	(TX (Exocannabi*))	Expanders - Apply equivalent subjects Search modes - Boolean/ Phrase	10
S7	(TI (Tetrahydrocannab*)) OR (AB (Tetrahydrocannab*) OR (SU (Tetrahydrocannab*)	Expanders - Apply equivalent subjects Search modes - Boolean/ Phrase	767
S8	(TI (Phytocannab*)) OR (AB (Phytocannab*)) OR (SU (Phytocannab*))	Expanders - Apply equivalent subjects Search modes - Boolean/ Phrase	160
S9	((TI (CBD)) OR (AB (CBD)) OR (SU (CBD))) NOT (TX ("Cortical Bone Density" OR "Common Bile Duct" OR "Community-Based Distribution" OR "Central Business District"))	Expanders - Apply equivalent subjects Search modes - Boolean/ Phrase	1,414
S10	((TI (THC)) OR (AB (THC)) OR (SU (THC))) NOT (TX ("Total Hydrocarbons" OR "Telephonic Health Coaching" OR "Total Hospital Charges"))	Expanders - Apply equivalent subjects Search modes - Boolean/ Phrase	1,393
S11	(TI (THCVS)) OR (AB (THCVS)) OR (SU (THCVS))	Expanders - Apply equivalent subjects Search modes - Boolean/ Phrase	15
S12	(TI ("C.indica" OR "C. sativa" OR "C. ruderalis")) OR (AB ("C.indica" OR "C. sativa" OR "C. ruderalis")) OR (SU ("C.indica" OR "C. sativa" OR "C. ruderalis"))	Expanders - Apply equivalent subjects Search modes - Boolean/ Phrase	37
S13	(TI (Hemp OR Cannabac*)) OR (AB (Hemp OR Cannabac*)) OR (SU (hemp OR Cannabac*))	Expanders - Apply equivalent subjects Search modes - Boolean/ Phrase	459
S14	(TI (Hash OR Hashish OR Ganja OR Bhang OR Canabis)) OR (AB (Hash OR Hashish OR Ganja OR Bhang OR Canabis))	Expanders - Apply equivalent subjects Search modes - Boolean/ Phrase	262
S15	(TI (Dronabinol* OR Marinol* OR Syndros)) OR (AB (Dronabinol* OR Marinol* OR Syndros)) OR (SU (Dronabinol* OR Marinol* OR Syndros))	Expanders - Apply equivalent subjects Search modes - Boolean/ Phrase	165
S16	(TI (Nabiximol* OR Sativex OR "GW 1000-02" OR "GW-1000-02" OR "GW 1000" OR Tetranabinex OR Nabidiolex OR "SAB 378")) OR (AB (Nabiximol* OR	Expanders - Apply equivalent subjects	119

	Sativex OR "GW 1000-02" OR "GW-1000-02" OR "GW 1000" OR Tetranabinex OR Nabidiolex OR "SAB 378")) OR (SU (Nabiximol* OR Sativex OR "GW 1000-02" OR "GW-1000-02" OR "GW 1000" OR Tetranabinex OR Nabidiolex OR "SAB 378"))	Search modes - Boolean/ Phrase	
S17	(TI (Nabilone OR Cesamet)) OR (AB (Nabilone OR Cesamet)) OR (SU (Nabilone OR Cesamet))	Expanders - Apply equivalent subjects Search modes - Boolean/ Phrase	111
S18	(TI (Epidiolex OR Epidyolex)) OR (AB (Epidiolex OR Epidyolex)) OR (SU (Epidiolex OR Epidyolex))	Expanders - Apply equivalent subjects Search modes - Boolean/ Phrase	53
S19	(TI (Tilray OR Bedrobinol OR Bedrocan OR Bediol OR Bedica OR Bedrolite or "Aurora Sedamen Softgels" OR Namisol OR CannEpil)) OR (AB (Tilray OR Bedrobinol OR Bedrocan OR Bediol OR Bedica OR Bedrolite OR "Aurora Sedamen Softgels" OR Namisol or CannEpil)) OR (SU (Tilray OR Bedrobinol OR Bedrocan OR Bediol OR Bedica OR Bedrolite OR "Aurora Sedamen Softgels" OR Namisol OR CannEpil))	Expanders - Apply equivalent subjects Search modes - Boolean/ Phrase	10
S20	(TI (maconha OR dagga OR marihuaanat OR marihuwana OR marigwana OR mariuana OR "tshuaj maj" OR "marihuána" OR "marijúana")) OR (AB (maconha OR dagga OR marihuaanat OR marihuwana OR marigwana or mariuana OR "tshuaj maj" OR "marihuána" OR "marijúana")) OR (SU (maconha OR dagga OR marihuaanat OR marihuwana OR marigwana OR mariuana OR "tshuaj maj" OR "marihuána" OR "marijúana"))	Expanders - Apply equivalent subjects Search modes - Boolean/ Phrase	62
S21	(TI ("delta-1-Tetrahydrocannabinol" OR "delta(1)-Tetrahydrocannabinol" OR "delta1-tetrahydrocannabinol" OR "1-tetrahydrocannabinol" OR "delta(1)-THC" OR "delta1-THC" OR "1-THC")) OR (AB ("delta-1-Tetrahydrocannabinol" OR "delta(1)-Tetrahydrocannabinol" OR "delta1-tetrahydrocannabinol" OR "1-tetrahydrocannabinol" OR "delta(1)-THC" OR "delta1-THC" OR "1-THC")) OR (SU ("delta-1-Tetrahydrocannabinol" OR "delta(1)-Tetrahydrocannabinol" OR "delta1-tetrahydrocannabinol" OR "1-tetrahydrocannabinol" OR "delta(1)-THC" OR "delta1-THC" OR "1-THC"))	Expanders - Apply equivalent subjects Search modes - Boolean/ Phrase	0
S22	(TI ("delta-8-tetrahydrocannabinol" OR "delta(8)-tetrahydrocannabinol" OR "delta8-tetrahydrocannabinol" OR "8-tetrahydrocannabinol" OR "delta(8)-THC" or "delta8-THC" OR "8-THC")) OR (AB ("delta-8-tetrahydrocannabinol" OR "delta(8)-	Expanders - Apply equivalent subjects Search modes - Boolean/ Phrase	3

	tetrahydrocannabinol" OR "delta8-tetrahydrocannabinol" OR "8-tetrahydrocannabinol" OR "delta(8)-THC" OR "delta8-THC" OR "8-THC")) OR (SU ("delta-8-tetrahydrocannabinol" OR "delta(8)-tetrahydrocannabinol" OR "delta8-tetrahydrocannabinol" OR "8-tetrahydrocannabinol" OR "delta(8)-THC" OR "delta8-THC" OR "8-THC"))		
S23	(TI ("delta-9-tetrahydrocannabinol" OR "delta(9)-Tetrahydrocannabinol" OR "delta9-tetrahydrocannabinol" OR "9-tetrahydrocannabinol" OR "delta(9)-THC" OR "delta9-THC" or "Delta-9-THC" OR "9-THC" OR "(−)-trans-Δ9-tetrahydrocannabinol") OR AB ("delta-9-tetrahydrocannabinol" OR "delta(9)-Tetrahydrocannabinol" OR "delta9-tetrahydrocannabinol" or "9-tetrahydrocannabinol" or "delta(9)-THC" or "delta9-THC" or "Delta-9-THC" or "9-THC" or "(−)-trans-Δ9-tetrahydrocannabinol") OR SU ("delta-9-tetrahydrocannabinol" OR "delta(9)-Tetrahydrocannabinol" OR "delta9-tetrahydrocannabinol" OR "9-tetrahydrocannabinol" OR "delta(9)-THC" OR "delta9-THC" OR "Delta-9-THC" OR "9-THC" OR "(−)-trans-Δ9-tetrahydrocannabinol")	Expanders - Apply equivalent subjects Search modes - Boolean/ Phrase	382
S24	(TI (Dexanabinol or HU-211)) OR (AB (Dexanabinol or HU-211)) OR (SU (Dexanabinol or HU-211))	Expanders - Apply equivalent subjects Search modes - Boolean/ Phrase	8
S25	(TI (Cannabicyclol OR Cannabichromene OR Cannabigerol)) OR (AB (Cannabicyclol OR Cannabichromene OR Cannabigerol)) OR (SU (Cannabicyclol OR Cannabichromene OR Cannabigerol))	Expanders - Apply equivalent subjects Search modes - Boolean/ Phrase	45
S26	((TI (Marijuana OR Marihuana OR Cannabis OR Cannabid* OR Cannabin* OR Tetrahydrocannab* OR THC OR CBD OR Hemp)) AND (TI (Capsule* OR Spray* OR Oil* OR Vapo* OR Transdermal OR Patch* or Inhal* or Smoke*))) OR ((AB (Marijuana OR Marihuana OR Cannabis OR Cannabid* OR Cannabin* OR Tetrahydrocannab* OR THC OR CBD OR Hemp)) AND (AB (Capsule* OR Spray* OR Oil* OR Vapo* OR Transdermal OR Patch* or Inhal* or Smoke*)))	Expanders - Apply equivalent subjects Search modes - Boolean/ Phrase	2,456
S27	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26	Expanders - Apply equivalent subjects	25,277
S28	(MH "Literature Review+")	Expanders - Apply equivalent subjects	123,802
S29	(MH "Meta Analysis")	Expanders - Apply equivalent subjects	63,150

S30	(TI ("Systematic review" OR "Literature review" OR "Meta-analysis" or Metasynthesis)) OR (AB ("Systematic review" OR "Literature review" OR "Meta-analysis" OR Metasynthesis)) OR (SU ("Systematic review" OR "Literature review" OR "Meta-analysis" OR Metasynthesis))	Expanders - Apply equivalent subjects	236,214
S31	(TI ((systematic* OR methodologic OR comprehensive OR integrative OR collaborative OR "state-of-the-art" OR scoping OR umbrella OR narrative OR integrative OR iterative OR technolog* OR quantitat* OR qualitat* OR traditional OR critical OR mapping OR rapid OR “mixed studies” OR “mixed methods” OR thematic OR pragmatic OR realist OR Cochrane OR Campbell) N2 (review* OR overview* OR literature OR bibliograph* OR report* OR map OR maps OR mapping OR summary OR summaries))) OR (AB ((systematic* OR methodologic OR comprehensive OR integrative OR collaborative OR "state-of-the-art" OR scoping OR umbrella OR narrative OR integrative OR iterative OR technolog* OR quantitat* OR qualitat* OR traditional OR critical OR mapping OR rapid OR “mixed studies” OR “mixed methods” OR thematic OR pragmatic OR realist OR Cochrane OR Campbell) N2 (review* OR overview* OR literature OR bibliograph* OR report* OR map OR maps OR mapping OR summary OR summaries))) OR (SU ((systematic* OR methodologic OR comprehensive OR integrative OR collaborative OR "state-of-the-art" OR scoping OR umbrella OR narrative OR integrative OR iterative OR technolog* OR quantitat* OR qualitat* OR traditional OR critical OR mapping OR rapid OR “mixed studies” OR “mixed methods” OR thematic OR pragmatic OR realist OR Cochrane OR Campbell) N2 (review* OR overview* OR literature OR bibliograph* OR report* OR map OR maps OR mapping OR summary OR summaries)))	Expanders - Apply equivalent subjects	225,906
S32	(TI (literature review OR "review of reviews" OR "overview of reviews" OR evidence synthes* OR meta analy* OR meta-analy* OR metaanalys* OR meta-synthe* OR metasynth* OR metaregression OR meta-regression OR health technology assessment* OR "synthesis of evidence" OR meta-summary)) OR (AB (literature review OR "review of reviews" OR "overview of reviews" OR evidence synthes* OR meta analy* OR meta-analy* OR metaanalys* OR meta-synthe* OR metasynth* OR metaregression OR meta-regression OR health technology assessment* OR "synthesis of evidence" OR “meta-summary”)) OR (SU (literature	Expanders - Apply equivalent subjects	163,857

	review OR "review of reviews" OR "overview of reviews" OR evidence synthes* OR meta analy* OR meta-analy* OR metaanalys* OR meta-synthe* OR metasynth* OR metaregression OR meta-regression OR health technology assessment* OR "synthesis of evidence" OR meta-summary))		
S33	SO (Cochrane OR systematic OR "technology assessment")	Expanders - Apply equivalent subjects	11,769
S34	TI (handsearch or data extraction or "risk of bias" or AMSTAR or AMSTAR2 or ROBIS or "AMSTAR 2" or ROB2 or "ROBINS-I" or "ROBINS-1") OR AB (handsearch or data extraction or "risk of bias" or AMSTAR or AMSTAR2 or ROBIS or "AMSTAR 2" or ROB2 or "ROBINS-I" or "ROBINS-1") OR SU (handsearch or data extraction or "risk of bias" or AMSTAR or AMSTAR2 or ROBIS or "AMSTAR 2" or ROB2 or "ROBINS-I" or "ROBINS-1")	Expanders - Apply equivalent subjects	23,149
S35	TI (search* N2 (literature OR strateg$ OR electronic OR hand OR systematic OR bibliographic OR keyword* OR key term* OR Pubmed OR MEDLINE OR Embase OR Cochrane OR Scopus OR "Web of Science")) OR AB (search* N2 (literature OR strateg$ or electronic OR hand OR systematic OR bibliographic OR keyword* OR key term* OR Pubmed OR MEDLINE OR Embase OR Cochrane OR Scopus OR "Web of Science")) OR SU (search* N2 (literature OR strateg$ OR electronic OR hand OR systematic OR bibliographic OR keyword* OR key term* OR Pubmed OR MEDLINE OR Embase OR Cochrane OR Scopus OR “Web of Science”)	Expanders - Apply equivalent subjects	96,544
S36	S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35	Expanders - Apply equivalent subjects	324,483
S37	S27 AND S36	Limiters - Published Date: 20100101-20221231	1,103
S38	TI rat or rats or mouse or mice OR "in vitro"	Limiters - Published Date: 20100101-20221231	182,510
S39	TI S37 NOT S38	Limiters - Published Date: 20100101-20221231	1,103
S40	PT (Biography OR Book Review OR Care Plan OR Case Study OR Commentary OR Computer Program OR Consumer/Patient Teaching Materials OR Editorial OR Games OR Historical Material OR Interview OR Letter OR Nurse Practice Acts OR Nursing Diagnoses OR Obituary OR Pamphlet OR Poetry OR Practice Guidelines OR Teaching Materials)	Expanders - Apply equivalent subjects	1,460,579

S41	PT S39 NOT S40	Expanders - Apply equivalent subjects	1,045
S42	TI ("THC volume") AND TI ("THC volume") AND TI ("Cover and Front matter" OR "Cover and Back Matter")	Expanders - Apply equivalent subjects	66
S43	S41 NOT S42	Expanders - Apply equivalent subjects	979

EBSCO SocINDEX with Full Text

Database: SocIndex with Full Text

Platform: EBSCO

Search date: 09 Jun 2022

Search line	Search terms	Limits	Results
S1	DE "MARIJUANA" OR DE "HASHISH"		2,825
S2	TI cannabis OR AB cannabis OR SU cannabis OR KW cannabis	Expanders - Apply equivalent subjects	3,971
S3	TI marijuana OR AB marijuana OR SU marijuana OR KW marijuana	Expanders - Apply equivalent subjects	7,452
S4	TI marihuana OR AB marihuana OR SU marihuana OR KW marihuana	Expanders - Apply equivalent subjects	393
S5	TI (cannabid* OR cannabin*) OR AB (cannabid* or cannabin*) OR SU (cannabid* OR cannabin*) OR KW (cannabid* OR cannabin*)	Expanders - Apply equivalent subjects	355
S6	TI (exocannabi*) OR AB (exocanabi*) OR SU (exacannabi*) OR KW (exocannabi*)	Expanders - Apply equivalent subjects	0
S7	TI Tetrahydrocannab* OR AB Tetrahydrocannab* OR SU Tetrahydrocannab* OR KW Tetrahydrocannab*	Expanders - Apply equivalent subjects	138
S8	TX Phytocannab*	Expanders - Apply equivalent subjects	19
S9	(TI CBD OR AB CBD OR SU CBD OR KW CBD) NOT ((TX ("cortical bone density" or "common bile duct" OR "Community-Based Distribution" OR " central business district")))	Expanders - Apply equivalent subjects	138
S10	(TI THC OR AB THC OR SU THC OR KW THC) NOT ((TX ("total hydrocarbons" OR "telephonic health coaching" OR "total hospital charges"))	Expanders - Apply equivalent subjects	276
S11	TI THCVS OR AB THCVS OR SU THCVS OR KW THCVS	Expanders - Apply equivalent subjects	0
S12	TX ("C.indica" OR "C. sativa" OR "C. ruderalis")	Expanders - Apply equivalent subjects	6
S13	TI (hash OR hashish OR Ganja OR bhang OR canabis) OR AB (hash OR hashish OR Ganja OR bhang OR canabis) OR KW (hash OR hashish OR Ganja OR bhang OR canabis)	Expanders - Apply equivalent subjects	286

S14	TI ((Dronabinol* OR Marinol OR Syndros)) OR AB ((Dronabinol* OR Marinol OR Syndros)) OR SU ((Dronabinol* OR Marinol OR Syndros)) OR KW ((Dronabinol* OR Marinol OR Syndros))	Expanders - Apply equivalent subjects	14
S15	TI ((Nabiximol* OR Sativex OR "GW 1000-02" OR "GW-1000-02" OR "GW 1000" OR Tetranabinex OR Nabidiolex OR "SAB 378"))) OR AB ((Nabiximol* OR Sativex OR "GW 1000-02" OR "GW-1000-02" OR "GW 1000" OR Tetranabinex OR Nabidiolex OR "SAB 378"))) OR SU ((Nabiximol* OR Sativex OR "GW 1000-02" OR "GW-1000-02" OR "GW 1000" OR Tetranabinex OR Nabidiolex OR "SAB 378"))) OR KW ((Nabiximol* OR Sativex OR "GW 1000-02" OR "GW-1000-02" OR "GW 1000" OR Tetranabinex OR Nabidiolex OR "SAB 378")))	Expanders - Apply equivalent subjects	2
S16	TI ((Nabilone OR Cesamet)) OR AB ((Nabilone OR Cesamet)) OR SU ((Nabilone OR Cesamet)) OR KW ((Nabilone OR Cesamet))	Expanders - Apply equivalent subjects	11
S17	TI ((Epidiolex OR Epidyolex)) OR AB ((Epidiolex OR Epidyolex)) OR SU ((Epidiolex OR Epidyolex)) OR KW ((Epidiolex OR Epidyolex))	Expanders - Apply equivalent subjects	0
S18	TI ((Tilray OR Bedrobinol OR Bedrocan OR Bediol OR Bedica OR Bedrolite OR "AurORa Sedamen Softgels" OR Namisol OR CannEpil)) OR AB ((Tilray OR Bedrobinol OR Bedrocan OR Bediol OR Bedica OR Bedrolite OR "AurORa Sedamen Softgels" OR Namisol OR CannEpil)) OR SU ((Tilray OR Bedrobinol OR Bedrocan OR Bediol OR Bedica OR Bedrolite OR "AurORa Sedamen Softgels" OR Namisol OR CannEpil)) OR KW ((Tilray OR Bedrobinol OR Bedrocan OR Bediol OR Bedica OR Bedrolite OR "Aurora Sedamen Softgels" OR Namisol OR CannEpil))	Expanders - Apply equivalent subjects	1
S19	TI ((maconha OR dagga OR marihuaanat OR marihuwana OR marigwana OR mariuana OR "tshuaj maj" OR "marihuána" OR "marijúana")) OR AB ((maconha OR dagga OR marihuaanat OR marihuwana OR marigwana OR mariuana OR tshuaj maj OR "marihuána" OR "marijúana")) OR SU ((maconha OR dagga OR marihuaanat OR marihuwana OR marigwana OR mariuana OR “tshuaj maj” OR "marihuána" OR "marijúana")) OR KW ((maconha OR dagga OR marihuaanat OR marihuwana OR marigwana OR mariuana OR "tshuaj maj" OR "marihuána" OR "marijúana"))	Expanders - Apply equivalent subjects	12
S20	TI (("delta-1-Tetrahydrocannabinol" OR "delta(1)-Tetrahydrocannabinol" OR "delta1-tetrahydrocannabinol" OR "1-tetrahydrocannabinol" OR "delta(1)-THC" OR "delta1-THC" OR "1-THC")) OR AB (("delta-1-Tetrahydrocannabinol" OR "delta(1)-Tetrahydrocannabinol" OR "delta1-tetrahydrocannabinol" OR "1-tetrahydrocannabinol" OR "delta(1)-THC" OR "delta1-THC" OR "1-THC")) OR SU	Expanders - Apply equivalent subjects	0

	(("delta-1-Tetrahydrocannabinol" OR "delta(1)-Tetrahydrocannabinol" OR "delta1-tetrahydrocannabinol" OR "1-tetrahydrocannabinol" OR "delta(1)-THC" OR "delta1-THC" OR "1-THC"))		
S21	TI (("delta-8-tetrahydrocannabinol" OR "delta(8)-tetrahydrocannabinol" OR "delta8-tetrahydrocannabinol" OR "8-tetrahydrocannabinol" OR "delta(8)-THC" OR "delta8-THC" OR "8-THC")) OR AB (("delta-8-tetrahydrocannabinol" OR "delta(8)-tetrahydrocannabinol" OR "delta8-tetrahydrocannabinol" OR "8-tetrahydrocannabinol" OR "delta(8)-THC" OR "delta8-THC" OR "8-THC")) OR SU (("delta-8-tetrahydrocannabinol" OR "delta(8)-tetrahydrocannabinol" OR "delta8-tetrahydrocannabinol" OR "8-tetrahydrocannabinol" OR "delta(8)-THC" OR "delta8-THC" OR "8-THC"))	Expanders - Apply equivalent subjects	0
S22	TI (("delta-9-tetrahydrocannabinol" OR "delta(9)-Tetrahydrocannabinol" OR "delta9-tetrahydrocannabinol" OR "9-tetrahydrocannabinol" OR "delta(9)-THC" OR "delta9-THC" OR "Delta-9-THC" OR "9-THC" OR "(−)-trans-Δ9-tetrahydrocannabinol")) OR AB (("delta-9-tetrahydrocannabinol" OR "delta(9)-Tetrahydrocannabinol" OR "delta9-tetrahydrocannabinol" OR "9-tetrahydrocannabinol" OR "delta(9)-THC" OR "delta9-THC" OR "Delta-9-THC" OR "9-THC" OR "(−)-trans-Δ9-tetrahydrocannabinol")) OR SU (("delta-9-tetrahydrocannabinol" OR "delta(9)-Tetrahydrocannabinol" OR "delta9-tetrahydrocannabinol" OR "9-tetrahydrocannabinol" OR "delta(9)-THC" OR "delta9-THC" OR "Delta-9-THC" OR "9-THC" OR "(−)-trans-Δ9-tetrahydrocannabinol"))	Expanders - Apply equivalent subjects	52
S23	TI ((Dexanabinol or "HU-211")) OR AB ((Dexanabinol or "HU-211")) OR SU ((Dexanabinol or "HU-211")) OR KW ((Dexanabinol or "HU-211"))	Expanders - Apply equivalent subjects	0
S24	TI ((cannabicyclol OR cannabichromene OR cannabigerol)) OR AB ((cannabicyclol OR cannabichromene OR cannabigerol)) OR SU ((cannabicyclol OR cannabichromene OR cannabigerol)) OR KW ((cannabicyclol OR cannabichromene OR cannabigerol))	Expanders - Apply equivalent subjects	1
S25	TI (Marijuana OR marihuana OR cannabis OR cannabid* OR cannabin* OR tetrahydrocannab* OR THC OR CBD OR hemp) AND TI ((capsule* OR spray* OR oil* OR vapo* OR transdermal OR patch* OR inhal* OR smoke*)))	Expanders - Apply equivalent subjects	69
S26	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25	Expanders - Apply equivalent subjects	10,381

S27	TI (((systematic* OR methodologic OR comprehensive OR integrative OR collaborative OR "state-of-the-art" OR scoping OR umbrella OR narrative OR integrative OR iterative OR technolog* OR quantitat* OR qualitat* OR traditional OR critical OR mapping OR rapid OR mixed studies OR mixed methods OR thematic OR pragmatic OR realist OR Cochrane OR Campbell) N2 (review* OR overview* OR literature OR bibliograph* OR report* OR map OR maps OR mapping OR summary OR summaries))) OR AB (((systematic* OR methodologic OR comprehensive OR integrative OR collaborative OR "state-of-the-art" OR scoping OR umbrella OR narrative OR integrative OR iterative OR technolog* OR quantitat* OR qualitat* OR traditional OR critical OR mapping OR rapid OR mixed studies OR mixed methods OR thematic OR pragmatic OR realist OR Cochrane OR Campbell) N2 (review* OR overview* OR literature OR bibliograph* OR report* OR map OR maps OR mapping OR summary OR summaries))) OR SU (((systematic* OR methodologic OR comprehensive OR integrative OR collaborative OR "state-of-the-art" OR scoping OR umbrella OR narrative OR integrative OR iterative OR technolog* OR quantitat* OR qualitat* OR traditional OR critical OR mapping OR rapid OR mixed studies OR mixed methods OR thematic OR pragmatic OR realist OR Cochrane OR Campbell) N2 (review* OR overview* OR literature OR bibliograph* OR report* OR map OR maps OR mapping OR summary OR summaries))) OR KW (((systematic* OR methodologic OR comprehensive OR integrative OR collaborative OR "state-of-the-art" OR scoping OR umbrella OR narrative OR integrative OR iterative OR technolog* OR quantitat* OR qualitat* OR traditional OR critical OR mapping OR rapid OR mixed studies OR mixed methods OR thematic OR pragmatic OR realist OR Cochrane OR Campbell) N2 (review* OR overview* OR literature OR bibliograph* OR report* OR map OR maps OR mapping OR summary OR summaries)))	Expanders - Apply equivalent subjects	20,908
S28	TI ("systematic review" OR "literature review" OR "meta-analysis" OR metasynthesis) OR AB ("systematic review" OR "literature review" OR "meta-analysis" OR metasynthesis) OR SU ("systematic review" OR "literature review" OR "meta-analysis" OR metasynthesis) OR KW ("systematic review" OR "literature review" OR "meta-analysis" OR metasynthesis)	Expanders - Apply equivalent subjects	13,634
S29	TI (("literature review" OR "literature reviews" OR "review of reviews" OR "overview of reviews" OR "evidence synthesis" OR "evidence syntheses" OR "meta analysis" OR "meta-analysis" OR metaanalys* OR "meta-synthesis" OR	Expanders - Apply equivalent subjects	14,822

	"meta-syntheses" OR metasynth* OR metaregression OR "meta-regression" OR "health technology assessment" OR "synthesis of evidence" OR "meta-summary")) OR AB (("literature review" OR "review of reviews" OR "overview of reviews" OR "evidence synthesis" OR "evidence syntheses" OR "meta analysis" OR "meta-analysis" OR metaanalys* OR "meta-synthesis" OR "meta-syntheses" OR metasynth* OR metaregression OR "meta-regression" OR "health technology assessment" OR "synthesis of evidence" OR "meta-summary")) OR KW (("literature review" OR "literature reviews" OR "review of reviews" OR "overview of reviews" OR "evidence synthesis" OR "evidence syntheses" OR "meta analysis" OR "meta-analysis" OR metaanalys* OR "meta-synthesis" OR "meta-syntheses" OR metasynth* OR metaregression OR "meta-regression" OR health technology assessment* OR "synthesis of evidence" OR "meta-summary")) OR SU (("literature review" OR "literature reviews" OR "review of reviews" OR "overview of reviews" OR "evidence synthesis" OR "evidence syntheses" OR "meta analysis" OR "meta-analysis" OR metaanalys* OR "meta-synthesis" OR "meta-syntheses" OR metasynth* OR metaregression OR "meta-regression" OR "health technology assessment" OR "synthesis of evidence" OR "meta-summary"))		
S30	TI ((handsearch or data extraction or "risk of bias" or AMSTAR or AMSTAR2 or ROBIS or "AMSTAR 2" or ROB2 or "ROBINS-I" or "ROBINS-1")) OR AB ((handsearch or data extraction or "risk of bias" or AMSTAR or AMSTAR2 or ROBIS or "AMSTAR 2" or ROB2 or "ROBINS-I" or "ROBINS-1")) OR SU ((handsearch or data extraction or "risk of bias" or AMSTAR or AMSTAR2 or ROBIS or "AMSTAR 2" or ROB2 or "ROBINS-I" or "ROBINS-1")) OR KW ((handsearch or data extraction or "risk of bias" or AMSTAR or AMSTAR2 or ROBIS or "AMSTAR 2" or ROB2 or "ROBINS-I" or "ROBINS-1"))	Expanders - Apply equivalent subjects	569
S31	TI ((search* N2 (literature OR strateg$ OR electronic OR hand OR systematic OR bibliographic OR keyword* OR key term* OR Pubmed OR Medline OR Embase OR Cochrane OR Scopus OR "Web of Science"))) OR AB ((search* N2 (literature OR strateg$ OR electronic OR hand OR systematic OR bibliographic OR keyword* OR key term* OR Pubmed OR Medline OR Embase OR Cochrane OR Scopus OR "Web of Science"))) OR SU ((search* N2 (literature OR strateg$ OR electronic OR hand OR systematic OR bibliographic OR keyword* OR key term* OR Pubmed OR Medline OR Embase OR Cochrane OR Scopus OR "Web of Science"))) OR KW ((search* N2 (literature OR strateg$ OR electronic OR hand OR systematic OR bibliographic OR keyword* OR key term*	Expanders - Apply equivalent subjects	3,959

	OR Pubmed OR Medline OR Embase OR Cochrane OR Scopus OR "Web of Science")))		
S32	SO (Cochrane OR systematic OR"technology assessment")	Expanders - Apply equivalent subjects	29,236
S33	S27 OR S28 OR S29 OR S30 OR S31 OR S32	Expanders - Apply equivalent subjects	52,826
S34	(S26 AND S33)	Expanders - Apply equivalent subjects	263

LILACS

Database: LILACS

Platform: Virtual Health Library English interface https://lilacs.bvsalud.org/en/

Search date: 10 Jun 2022

Search line	Search terms	Results
1	"cannabis" [Subject descriptor] and review [Title words]	17
2	cannabis [Words] and review [Words]	119
3	marijuana [Words] and review [Words]	115
4	tetrahydrocannabinol [Words] and review [Words]	23
5	THC [Words] and review [Words]	24
6	cannabinoid [Words] and review [Words]	65
7	cannabidiol [Words] and review [Words]	20
8	phytocannabinoid [Words] and review [Words]	1
9	CBD [Words] and review [Words]	14
10	canabis OR marihuana [Words] and review [Words]	113
	Total	511

SciELO

Database: SciELO

Platform: https://www.scielo.org/

Search date: 10 Jun 2022

Date Limits: 2010-2024

Search line	Search terms	Results
1	(ab:(cannabis OR canabis)) AND (ab:(review))	68
2	(ab:(cannabis)) AND (ti:(review))	32
3	(ab:(marijuana)) AND (ti:(review))	9
4	(ab:(tetrahydrocannabinol)) AND (ti:(review))	6
5	(ab:(tetrahydrocannabinol)) AND (ab:(review))	14
6	(ab: (marijuana or marihuana)) and (ab:(review))	0
7	(ab:(THC)) AND (ab:(review))	12
8	(ti:(THC)) AND (ab:(review))	0

9	(ab:(THC)) AND (ti:(review))	5
10	(ab:(cannabinoid)) AND (ti:(review))	10
11	(ab:(cannabinoid)) AND (ab:(review))	31
12	(ab:(cannabidiol)) AND (ab:(review))	12
13	(ab:(cannabidiol)) AND (ti:(review))	1
14	(ab:(cbd)) AND (ti:(review))	2
15	(ab:(cbd)) AND (ab:(review))	10
	Total	212

Wiley Cochrane Library

Database: Cochrane Library

Platform: John Wiley & Sons Ltd. https://www.cochranelibrary.com/

Search Date: 09 Jun 2022

Search line	Search terms	Results
#1	MeSH descriptor: [Cannabis] explode all trees	366
#2	MeSH descriptor: [Medical Marijuana] explode all trees	26
#3	MeSH descriptor: [Marijuana Use] explode all trees	351
#4	MeSH descriptor: [Cannabinoids] explode all trees	970
#5	MeSH descriptor: [Cannabinoid Receptor Modulators] explode all trees	95
#6	(cannabis*):ti,ab,kw	2860
#7	(marijuana or marihuana):ti,ab,kw	2150
#8	(cannabid* or cannabin*):ti,ab,kw	1860
#9	(exocannabi*):ti,ab,kw	0
#10	(tetrahydrocannabi*):ti,ab,kw	1112
#11	(Phytocannabi*):ti,ab,kw	37
#12	(CBD):ti,ab,kw	1236
#13	(THC):ti,ab,kw	1288
#14	(THCVS):ti,ab,kw	0
#15	("C.indica" or "C. sativa" or "C. ruderalis"):ti,ab,kw	8
#16	(Hash or hashish or Ganja or bhang or canabis):ti,ab,kw	63
#17	(Dronabinol* or Marinol or Syndros):ti,ab,kw	988
#18	(Nabiximols or Sativex or "GW 1000-02" or "GW-1000-02" or "GW 1000" or Tetranabinex or Nabidiolex or "SAB 378"):ti,ab,kw	200
#19	(Nabilone or Cesamet or Canemes):ti,ab,kw	162
#20	(Epidiolex or Epidyolex):ti,ab,kw	130
#21	(Tilray or Bedrobinol or Transvamix or "VER-01" or Bedrocan or Bediol or Bedica or Bedrolite or Aurora Sedamen Softgels or Namisol or CannEpil):ti,ab,kw	59
#22	(maconha or dagga or marihuaanat or marihuwana or marigwana or mariuana or tshuaj maj or "marihuána" or "marijúana"):ti,ab,kw	2155
#23	("11-OH-THC"):ti,ab,kw	59
#24	("11-Hydroxy-THC"):ti,ab,kw	19
#25	("11-OH-delta9-THC"):ti,ab,kw	1
#26	("11-Hydroxy-delta9-tetrahydrocannabinol"):ti,ab,kw	1

	#27 ("11-Hydroxyhexahydrocannabinol"):ti,ab,kw	0
	#28 (("delta-1-Tetrahydrocannabinol" or "delta(1)-Tetrahydrocannabinol" or "delta1-tetrahydrocannabinol" or "1-tetrahydrocannabinol" or "delta(1)-THC" or "delta1-THC" or "1-THC")):ti,ab,kw	50
	#29 (("delta-8-tetrahydrocannabinol" or "delta(8)-tetrahydrocannabinol" or "delta8-tetrahydrocannabinol" or "8-tetrahydrocannabinol" or "delta(8)-THC" or "delta8-THC" or "8-THC")):ti,ab,kw	23
#30	("delta-9-tetrahydrocannabinol"):ti,ab,kw	466
#31	("delta(9)-Tetrahydrocannabinol"):ti,ab,kw	466
#32	("delta9-tetrahydrocannabinol"):ti,ab,kw	92
#33	("9-tetrahydrocannabinol"):ti,ab,kw	624
#34	("delta(9)-THC"):ti,ab,kw	85
#35	("delta9-THC"):ti,ab,kw	29
#36	("Delta-9-THC"):ti,ab,kw	85
#37	("9-THC"):ti,ab,kw	164
#38	("(−)-trans-Δ9-tetrahydrocannabinol"):ti,ab,kw	7
#39	(Dexanabinol or HU-211):ti,ab,kw	8
#40	(cannabicyclol or cannabichromene or cannabigerol):ti,ab,kw	19
#41	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40	5754 including 51 reviews
Date limit	2010-2022	42 reviews

Wiley Campbell Library

Database: Campbell Library

Platform: Wiley

Search date: 09 Jun 2022

Search terms	Results
Keyword search: cannabis Date limit: 01 Jan 2010 – 09 Jun 2022	6
Keyword search: marijuana Date limit: 01 Jan 2010 – 09 Jun 2022	3
Total	6

Epistemonikos

Database: Epistemonikos

Platform: https://www.epistemonikos.org

Date 09 Jun 2022

Search terms	Results
(title:(cannabis OR marijuana OR marihuana OR CBD OR THC) OR abstract:(cannabis OR marijuana OR marihuana OR CBD OR THC)) OR (title:(exocannabi* OR phytocannabi* OR	1331

tetrahydrocannabi* OR cannabid* OR cannabin*) OR abstract:(exocannabi* OR phytocannabi* OR tetrahydrocannabi* OR cannabid* OR cannabin*)) OR (title:(Dronabinol* OR Marinol OR Syndros OR Nabiximols OR Sativex OR "GW 1000-02" OR "GW-1000-02" OR "GW 1000" OR Tetranabinex OR Nabidiolex OR "SAB 378" OR Nabilone OR Cesamet OR Canemes OR Epidiolex OR Epidyolex OR Tilray OR Bedrobinol OR Transvamix OR "VER-01" OR Bedrocan OR Bediol OR Bedica OR Bedrolite OR Aurora Sedamen Softgels OR Namisol OR CannEpil OR Dexanabinol OR cannabicyclol OR cannabichromene OR cannabigerol) OR abstract:(Dronabinol* OR Marinol OR Syndros OR Nabiximols OR Sativex OR "GW 1000-02" OR "GW-1000-02" OR "GW 1000" OR Tetranabinex OR Nabidiolex OR "SAB 378" OR Nabilone OR Cesamet OR Canemes OR Epidiolex OR Epidyolex OR Tilray OR Bedrobinol OR Transvamix OR "VER-01" OR Bedrocan OR Bediol OR Bedica OR Bedrolite OR Aurora Sedamen Softgels OR Namisol OR CannEpil OR Dexanabinol OR cannabicyclol OR cannabichromene OR cannabigerol))

Date limit: 2010-2023
Publication limit: Systematic reviews

Agency for Healthcare Quality and Research Systematic Review Data Repository

Database/resource: Agency for Health Research and Quality Systematic Review Data Repository

Platform: https://srdrplus.ahrq.gov/searches

Search date: 09 Jun 2022

Search terms	Results
Name: Cannabis	1
Name: marijuana	0
Name: marihuana	0
Name: THC	0
Name: tetrahydrocannabinol	0
Name: cannabinoid	0
Name: phytocannabinoid	0
Name: cannabidiol	0
Description: Cannabis	2
Description: marijuana	0
Description: THC	Confounder: search was found to capture “healTHCare” for THC; therefore, after testing this term was not used here as a description search
Description: tetrahydrocannabinol	1
Description: cannabinoid	1
Description: phytocannabinoid	0
Description: cannabidiol	1
Total	2

Database of Abstracts of Reviews of Effects (DARE)

Database/Resource: Database of Abstracts of Reviews of Effects (DARE)

Interface: https://www.crd.york.ac.uk/CRDWeb/

Search date: 10 Jun 2022

Limits: No date limits were used but the CRD DARE interface no longer received new content after 2015, so a de facto limit is imposed.

Search terms	Results
Results for: Any Field (cannabis) FROM 2010 TO 2022	27 (1 duplicate)
cannabis [Words] and review [Words]	-
marijuana [Words] and review [Words]	-
tetrahydrocannabinol [Words] and review [Words]	-
THC [Words] and review [Words]	-
cannabinoid [Words] and review [Words]	-
cannabidiol [Words] and review [Words]	-
phytocannabinoid [Words] and review [Words]	-
CBD [Words] and review [Words]	-
canabis OR marihuana [Words] and review [Words]	-
Total	26

Database of promoting health effectiveness reviews (DoPHER)

Database/Resource: Dopher (EPPI Centre)

Interface: https://eppi.ioe.ac.uk/webdatabases4/Intro.aspx?ID=9

Search date: 10 Jun 2022

Search terms	Results
Freetext (All but Authors): cannabis	30
Freetext (All but Authors): marijuana	25
Freetext (All but Authors): tetrahydrocannabinol	1
Freetext (All but Authors): THC	0
Freetext (All but Authors): cannabinoid	1
Freetext (All but Authors): cannabidiol	0
Freetext (All but Authors): phytocannabinoid	0
Freetext (All but Authors): CBD	0
Total	57

Joanna Briggs Institute (JBI) Evidence Syntheses

Database/Resource: Joanna Briggs Institute Evidence Syntheses

Interface: https://journals.lww.com/jbisrir/pages/default.aspx

Search date: 10 Jun 2022

Search number	Search terms	Results
1	Title: Cannabis	1

2	Abstract: Cannabis	4
3	Title: Marijuana	0
4	Abstract: Cannabis	0
5	Title: Tetrahydrocannabinol	0
6	Abstract: Tetrahydrocannabinol	0
7	Title: THC	0
8	Abstract: THC	0
9	Title: CBD	0
10	Abstract: CBD	0
11	Title: cannabidiol	0
12	Abstract: cannabidiol	0
13	Title: cannabinoid	0
14	Abstract: cannabinoid	0
15	Title: phytocannabinoid	0
16	Abstract: phytocannabinoid	0
	Total	5

International Health Technology Assessment (HTA) database

Database: International HTA database

Platform/Interface: https://database.inahta.org/

Search date: 10 Jun 2022

Limit: 2010-2023

Search number	Search terms	Results
1	(cannabis)[Title] OR (cannabis)[abs] OR (cannabis)[Keywords] FROM 2010 TO 2023	15
2	(marijuana)[Title] OR (marijuana)[abs] OR (marijuana)[Keywords] FROM 2010 TO 2023	6
3	(tetrahydrocannabinol)[Title] OR (tetrahydrocannabinol)[abs] OR (tetrahydrocannabinol)[Keywords] FROM 2010 TO 2023	1
4	(THC)[Title] OR (THC)[abs] OR (THC)[Keywords] FROM 2010 TO 2023	3
5	(CBD)[Title] OR (CBD)[abs] OR (CBD)[Keywords] FROM 2010 TO 2023	4
6	(cannabidiol)[Title] OR (cannabidiol)[abs] OR (cannabidiol)[Keywords] FROM 2010 TO 2023	3
7	(cannabinoid)[Title] OR (cannabinoid)[abs] OR (cannabinoid)[Keywords] FROM 2010 TO 2023	5
8	(phytocannabinoid)[Title] OR (phytocannabinoid)[abs] OR (phytocannabinoid)[Keywords] FROM 2010 TO 2023	0
	Total	37

PROSPERO

Database/resource: PROSPERO (National Institute for Health Research)

Platform: https://www.crd.york.ac.uk/prospero/#searchadvanced

Search date: 11 Jun 2022

Search number	Search terms	Results
1	cannabis:TI,ER,FR,KW	339
2	Cannabis IV	327
3	Marijuana TI	127
4	marijuana:IV	83
5	THC: IV	53
6	THC: TI	9
7	tetrahydrocannab*:TI	9
8	tetrahydrocannab*:IV	49
9	CBD:TI	16
10	CBD IV	60
11	(cannabinoid):TI	25
12	(cannabinoid):IV	70
	Total	1167

Health Evidence (McMaster University)

Database/resource: Health Evidence

Platform: https://www.healthevidence.org/ by McMaster University

Search date: 11 Jun 2022

Search number	Search terms	Results
1	Results for: [cannabis OR marijuana OR THC OR tetrahydrocannabinol] AND Limit: Date = Published from 2010 to 2022	46

Search engine: DuckDuckgo.com

Database/resource: DuckDuckGo search engine

Platform: https://duckduckgo.com/

Search date: 11 Jun 2022

Search terms	Extracted results
cannabis AND "systematic review"	First 150
“marijuana" AND "systematic review"	First 150

Search engine: Google Scholar

Database/resource: Google Scholar

Platform: https://scholar.google.com/

Search date: 12 Jun 2022

Search number	Search terms	Quoted results	Downloaded results
1	allintitle “cannabis” "systematic review"	About 346 results (0.05 sec) Does not include patents or citations. The first 150 were downloaded.	150
2	allintitle “marijuana” “systematic review”	About 49 results (0.05 sec) (does not include patents or citations	49
3	allintitle “THC” “systematic review”	About 16 results (0.05 sec) (does not include patents or citations	16
4	allintitle tetrahydrocannabinol “systematic review”	About 15 results (0.05 sec) (does not include patents or citations	15
5	allintitle cannabidiol “systematic review”	About 52 results (0.05 sec) (does not include patents or citations	52
	Total		282

Search engine: BASE: Bielefeld Academic Search Engine

Database/resource: BASE: Bielefeld Academic Search Engine by Bielefeld University Library

Platform: https://www.base-search.net/

Search date: 10 Jun 2022

Search number	Search terms	Results
	tit:cannabis AND tit:review year:[2010 TO 2015]	246
	tit:cannabis AND tit:review year:[2016 TO 2020]	791
	tit:cannabis AND tit:review year:[2021 TO 2023]	504
	tit:Marijuana AND tit:review year:[2010 TO 2023]	261
	tit:tetrahydrocannabinol AND tit:review year:[2010 TO 2023]	82
	tit:THC AND tit:review year:[2010 TO 2023]	64
	tit:cannabinoid AND tit:review year:[2010 TO 2023]	231
	tit:CBD AND tit:review year:[2010 TO 2023]	88
	tit:phytocannabinoid AND tit:review year:[2010 TO 2023]	4
	tit:canabis AND tit:review year:[2010 TO 2023]	0
	tit:cannabidiol AND tit:review year:[2010 TO 2023]	239
	Total	2510

Preprint resource: MedRxiv/BioRxiv

Database/resource: MedRxiv and BioRxiv

Platform: https://www.medrxiv.org/search (Single search interface to search both MedRxiv and BioRxiv)

Search date: 11 Jun 2022

Search number	Search terms	Results
1	for abstract or title ""cannabis" "review"" (match all words) and posted between "01 Jan, 2010 and 11 Jun, 2022"	26

2	for abstract or title ""marijuana" "review"" (match all words) and posted between "01 Jan, 2010 and 11 Jun, 2022"	5
3	for abstract or title ""THC" "review"" (match all words) and posted between "01 Jan, 2010 and 11 Jun, 2022"	2
4	for abstract or title ""tetrahydrocannabinol" "review"" (match all words) and posted between "01 Jan, 2010 and 11 Jun, 2022"	1
5	for abstract or title ""cbd" "review"" (match all words) and posted between "01 Jan, 2010 and 06 Nov, 2022"	9
6	for abstract or title ""cannabidiol" "review"" (match all words) and posted between "01 Jan, 2010 and 11 Jun, 2022"	3
	Total exported	46

Preprint resource: Osf.io

Database/resource: OSF

Platform: https://osf.io/search/

Search date: 11 Jun 2022

Note: Results are broken down in OSF as files, projects, registrations, components and 'Share'. On examination, projects and registrations were the most useful overall units.

Search number	Search terms	Results	Exported Results
1	(Cannabis AND review) NOT (animal or veterinary)	77 results, of which 19 projects, 11 registrations	30
2	(Marijuana AND review) NOT (animal or veterinary)	9 results, of which 3 projects, 3 registrations	6
3	(Tetrahydrocannabinol AND review) NOT (animal or veterinary)	3 results, of which 1 project, 1 registration	2
4	(THC AND review) NOT (animal or veterinary)	2 results, of which 1 registration	1
5	(Cannabinoid AND review) NOT (animal or veterinary)	12 results, of which 7 projects, 4 registrations	11
6	(CBD AND review) NOT (animal or veterinary)	13 results, of which 4 projects, 2 registrations	6
	Total		56

Preprint resource: ResearchSquare

Database/resource: ResearchSquare

Platform: https://www.researchsquare.com/

Search date: 11 Jun 2022

Search number	Search terms	Results
1	Cannabis (Systematic reviews)	2
2	Marijuana (systematic reviews)	0
3	Tetrahydrocannabinol (systematic reviews)	0
4	THC (Systematic reviews)	0
5	Cannabinoid (Systematic reviews)	2
6	CBD (Systematic review)	0
	Total	4

Open access research aggregator: Core

Database/resource: Core

Platform: https://core.ac.uk/

Search date: 10 Jun 2022

Date limit: 2010-2021

	Search terms	Results	Downloaded results
	title:"Cannabis" AND title:"review"	375	100
	title:"Marijuana" AND title:"review"	62	62
	title:"THC" AND title:"review"	21	21
	title:"tetrahydrocannabinol" AND title:"review"	18	18
	title:"cannabidiol" and title:"review"	64	64
	title:"CBD" and title:"review"	25	25
	Total		290

Topic-specific resource: International Alliance for Cannabinoid Medicines

Database/resource: Association for Cannabinoid Medicines (IACM)

Platform: https://cannabis-med.org/

Search date: 12 Jun 2022

Search number	Search terms	Results
1	“Systematic review”	14
2	“Literature review”	15
3	“Evidence synthesis”	2
	Deduplicated and exported	16

Supplemental grey literature search

Appendix Table 5 Supplemental searches

Supplemental searches	Subtotal	Results
Ovid MEDLINE	1,276	
Cochrane Library	44	

Epistemonikos	500	
Google Scholar	194	
Total results		2014

Appendix Table 6 Reference/citation/protocol chasing

Reference/citation/protocol chasing	Subtotal	Results
Reference chasing of 53 reviews	3,433	
Citation chasing of 53 reviews	2,371	
Follow-up of protocols, meeting abstracts, posters, umbrella reviews from title/abstract screening	2,673	
Total supplemental search results		8,477
Total supplemental search results screened in EPPI Reviewer		5,571

Follow-up search strategies

Ovid MEDLINE

Database: MEDLINE

Platform: Ovid

Search date: 15 Jan 2023

Search line	Search terms	Results
1	Medical Marijuana/	2113
2	Cannabis/	12942
3	exp "Marijuana Use"/	6933
4	exp Cannabinoids/	17536
5	exp Cannabinoid Receptor Modulators/	13751
6	(Mari#uan* and (clinical$ or therap$ or medic$ or trial$ or patient$ or placebo$ or randomi$ or adminis$ or ameliorat$ or treat$ or manage$ or tolerat$ or intervention$ or prescrib$)).mp.	14503
7	(Cannabis and (clinical$ or therap$ or medic$ or trial$ or patient$ or placebo$ or randomi$ or adminis$ or ameliorat$ or treat$ or manage$ or tolerat$ or intervention$ or prescrib$)).mp.	16278
8	((Cannabid* or cannabin*) and (clinical$ or therap$ or medic$ or trial$ or patient$ or placebo$ or randomi$ or adminis$ or ameliorat$ or treat$ or manage$ or tolerat$ or intervention$ or prescrib$)).mp.	18183
9	Exocannabi*.mp.	28
10	(Tetrahydrocannabi$ and (clinical$ or therap$ or medic$ or trial$ or patient$ or placebo$ or randomi$ or adminis$ or ameliorat$ or treat$ or manage$ or tolerat$ or intervention$ or prescrib$)).mp.	5327
11	phytocannabi*.mp.	795
12	((CBD not (cortical bone density or common bile duct$)) and (clinical$ or therap$ or medic$ or trial$ or patient$ or placebo$ or randomi$ or adminis$ or ameliorat$ or treat$ or manage$ or tolerat$ or intervention$ or prescrib$)).mp.	3876

13	((THC not (total hydrocarbons or telephonic health coaching or total hospital charge$)) and (clinical$ or therap$ or medic$ or trial$ or study or studies or patient$ or placebo$ or random$ or adminis$ or ameliorat$ or treat$ or manage$ or tolerat$ or intervention$ or prescrib$)).mp.	6599
14	THCVS.mp.	1
15	(("C.indica" or "C. sativa" or "C. ruderalis") not Camelina sativa).tw.	259
16	((((Hash or hashish) not (hash1 or "hash function" or hashtag$ or hash value or hashing or "hash code")) or Ganja or bhang or canabis) and (clinical$ or therap$ or medic$ or trial$ or patient$ or placebo$ or randomi$ or adminis$ or ameliorat$ or treat$ or manage$ or tolerat$ or intervention$ or prescrib$)).mp.	496
17	((hemp or Cannabac$) and (clinical$ or therap$ or medic$ or trial$ or patient$ or placebo$ or randomi$ or adminis$ or ameliorat$ or treat$ or manage$ or tolerat$ or intervention$ or prescrib$)).tw,hw,kf.	572
18	((weed* or joint*) and (cannab* or marij*)).mp.	650
19	(Dronabinol* or Marinol or Syndros).mp.	8295
20	(Nabiximols or Sativex or "GW 1000-02" or "GW-1000-02" or "GW 1000" or Tetranabinex or Nabidiolex or "SAB 378").mp.	343
21	(Nabilone or Cesamet or Canemes).mp.	337
22	(Epidiolex or Epidyolex).mp.	115
23	(Tilray or Bedrobinol or Transvamix or "VER-01" or Bedrocan or Bediol or Bedica or Bedrolite or Aurora Sedamen Softgels or Namisol or CannEpil).mp.	33
24	(maconha or dagga or marihuaanat or marihuwana or marigwana or mariuana or tshuaj maj or "marihuána" or "marijúana").mp.	63
25	("11-OH-THC" or "11-Hydroxy-THC" or "11-Hydroxy-delta9-tetrahydrocannabinol" or 11-Hydroxyhexahydrocannabinol or "11-OH-delta9-THC" or "11-Hydroxycannabinol (11-OH-CBN)").mp.	264
26	("delta-1-Tetrahydrocannabinol" or "delta(1)-Tetrahydrocannabinol" or "delta1-tetrahydrocannabinol" or "1-tetrahydrocannabinol" or "delta(1)-THC" or "delta1-THC" or "1-THC").mp.	216
27	("delta-8-tetrahydrocannabinol" or "delta(8)-tetrahydrocannabinol" or "delta8-tetrahydrocannabinol" or "8-tetrahydrocannabinol" or "delta(8)-THC" or "delta8-THC" or "8-THC").mp.	446
28	("delta-9-tetrahydrocannabinol" or "delta(9)-Tetrahydrocannabinol" or "delta9-tetrahydrocannabinol" or "9-tetrahydrocannabinol" or "delta(9)-THC" or "delta9-THC" or "Delta-9-THC" or "9-THC" or "(−)-trans-Δ9-tetrahydrocannabinol").mp.	6544
29	(Dexanabinol or HU-211).mp.	374
30	(cannabicyclol or cannabichromene or cannabigerol).mp.	310
31	((Mari#uan$ or cannabis or cannabid$ or cannabin$ or tetrahydrocannab$ or THC or CBD or hemp) and (capsule$ or spray$ or oil$ or vapo$ or transdermal or patch$ or inhal$ or smoke$)).tw.	5716
32	or/1-31	54315
33	exp Review/ or Systematic review/ or Meta-Analysis/ or exp Review Literature as Topic/ or Meta-Analysis as Topic/ or Systematic Reviews as Topic/	2984098

34	((systematic$ or methodologic$ or comprehensive or integrative or collaborative or "state-of-the-art" or scoping or umbrella or narrative or integrative or iterative or technolog$ or quantitat$ or qualitat$ or traditional or critical or rapid or mixed studies or mixed methods or thematic or pragmatic or realist or Cochrane or Campbell) adj2 (review$ or overview$ or bibliograph$ or report$ or summary or summaries)).tw.	344154
35	(literature review or "review of reviews" or "overview of reviews" or evidence synthes* or meta analy$ or meta-analy$ or metaanalys$ or meta-synthe$ or metasynth$ or metaregression or meta-regression or health technology assessment$ or "synthesis of evidence" or meta-summary or "mapping review" or "literature map" or systematic map$).mp.	347693
36	(Cochrane or systematic or technology assessment).jn,jw.	42386
37	(handsearch or data extraction or "risk of bias" or AMSTAR or AMSTAR2 or ROBIS or "AMSTAR 2" or ROB2 or "ROBINS-I" or "ROBINS-1").tw.	54118
38	(search$ adj2 (literature or strateg$ or electronic or hand or systematic or bibliographic or keyword$ or key term$ or Pubmed or MEDLINE or Embase or Cochrane or Scopus or "Web of Science" or CINAHL)).mp.	191701
39	(search$ and (Pubmed or MEDLINE or CINAHL or Embase or Cochrane or Scopus or "Web of Science")).tw.	213334
40	or/33-39	3118856
41	32 and 40	8450
42	Comment/ or Letter/ or Editorial/ or (Animals/ not (Animals/ and Humans/))	6924019
43	41 not 42	8075
44	limit 43 to yr="2021 - 2023"	1276

Epistemonikos

Database: Epistemonikos

Platform: https://www.epistemonikos.org

Date: 15 Jan 2023

Search line	Search terms	Results
1	(title:(cannabis OR marijuana OR marihuana OR CBD OR THC) OR abstract:(cannabis OR marijuana OR marihuana OR CBD OR THC)) OR (title:(exocannabi* OR phytocannabi* OR tetrahydrocannabi* OR cannabid* OR cannabin*) OR abstract:(exocannabi* OR phytocannabi* OR tetrahydrocannabi* OR cannabid* OR cannabin*)) OR (title:(Dronabinol* OR Marinol OR Syndros OR Nabiximols OR Sativex OR "GW 1000-02" OR "GW-1000-02" OR "GW 1000" OR Tetranabinex OR Nabidiolex OR "SAB 378" OR Nabilone OR Cesamet OR Canemes OR Epidiolex OR Epidyolex OR Tilray OR Bedrobinol OR Transvamix OR "VER-01" OR Bedrocan OR Bediol OR Bedica OR Bedrolite OR Aurora Sedamen Softgels OR Namisol OR CannEpil OR Dexanabinol OR cannabicyclol OR cannabichromene OR cannabigerol) OR abstract:(Dronabinol* OR Marinol OR Syndros OR Nabiximols OR Sativex OR "GW 1000-02" OR "GW-1000-02" OR "GW 1000" OR Tetranabinex OR Nabidiolex OR "SAB 378" OR Nabilone OR Cesamet OR Canemes OR Epidiolex OR Epidyolex OR Tilray	500

	OR Bedrobinol OR Transvamix OR "VER-01" OR Bedrocan OR Bediol OR Bedica OR Bedrolite OR Aurora Sedamen Softgels OR Namisol OR CannEpil OR Dexanabinol OR cannabicyclol OR cannabichromene OR cannabigerol)) Date limit: 2021-2023 Publication limit: Systematic reviews

Wiley Cochrane Library

Database: Cochrane Library

Platform: John Wiley & Sons, Inc. Cochrane Library https://www.cochranelibrary.com/

Search date: 14 Jan 2023

Search line	Search terms	Results
#1	MeSH descriptor: [Cannabis] explode all trees	406
#2	MeSH descriptor: [Medical Marijuana] explode all trees	26
#3	MeSH descriptor: [Marijuana Use] explode all trees	355
#4	MeSH descriptor: [Cannabinoids] explode all trees	1014
#5	MeSH descriptor: [Cannabinoid Receptor Modulators] explode all trees	106
#6	(cannabis*):ti,ab,kw	3086
#7	(marijuana or marihuana):ti,ab,kw	2213
#8	(cannabid* or cannabin*):ti,ab,kw	2009
#9	(exocannabi*):ti,ab,kw	0
#10	(tetrahydrocannabi*):ti,ab,kw	1160
#11	(Phytocannabi*):ti,ab,kw	37
#12	(CBD):ti,ab,kw	1369
#13	(THC):ti,ab,kw	1363
#14	(THCVS):ti,ab,kw	0
#15	("C.indica" or "C. sativa" or "C. ruderalis"):ti,ab,kw	9
#16	(Hash or hashish or Ganja or bhang or canabis):ti,ab,kw	65
#17	(Dronabinol* or Marinol or Syndros):ti,ab,kw	1007
#18	(Nabiximols or Sativex or "GW 1000-02" or "GW-1000-02" or "GW 1000" or Tetranabinex or Nabidiolex or "SAB 378"):ti,ab,kw	213
#19	(Nabilone or Cesamet or Canemes):ti,ab,kw	165
#20	(Epidiolex or Epidyolex):ti,ab,kw	139
#21	(Tilray or Bedrobinol or Transvamix or "VER-01" or Bedrocan or Bediol or Bedica or Bedrolite or Aurora Sedamen Softgels or Namisol or CannEpil):ti,ab,kw	64
#22	(maconha or dagga or marihuaanat or marihuwana or marigwana or mariuana or tshuaj maj or "marihuána" or "marijúana"):ti,ab,kw	2218
#23	("11-OH-THC"):ti,ab,kw	61
#24	("11-Hydroxy-THC"):ti,ab,kw	19
#25	("11-OH-delta9-THC"):ti,ab,kw	1
#26	("11-Hydroxy-delta9-tetrahydrocannabinol"):ti,ab,kw	1

#27	("11-Hydroxyhexahydrocannabinol"):ti,ab,kw	0
#28	(("delta-1-Tetrahydrocannabinol" or "delta(1)-Tetrahydrocannabinol" or "delta1-tetrahydrocannabinol" or "1-tetrahydrocannabinol" or "delta(1)-THC" or "delta1-THC" or "1-THC")):ti,ab,kw	56
#29	(("delta-8-tetrahydrocannabinol" or "delta(8)-tetrahydrocannabinol" or "delta8-tetrahydrocannabinol" or "8-tetrahydrocannabinol" or "delta(8)-THC" or "delta8-THC" or "8-THC")):ti,ab,kw	24
#30	("delta-9-tetrahydrocannabinol"):ti,ab,kw	481
#31	("delta(9)-Tetrahydrocannabinol"):ti,ab,kw	481
#32	("delta9-tetrahydrocannabinol"):ti,ab,kw	91
#33	("9-tetrahydrocannabinol"):ti,ab,kw	643
#34	("delta(9)-THC"):ti,ab,kw	85
#35	("delta9-THC"):ti,ab,kw	29
#36	("Delta-9-THC"):ti,ab,kw	85
#37	("9-THC"):ti,ab,kw	168
#38	("(−)-trans-Δ9-tetrahydrocannabinol"):ti,ab,kw	7
#39	(Dexanabinol or HU-211):ti,ab,kw	8
#40	(cannabicyclol or cannabichromene or cannabigerol):ti,ab,kw	20
#41	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40	6135
	51 reviews of which 44 published 2009-2023	51
	44 reviews exported	44

Google Scholar

Database/Resource: Google Scholar

Platform: https://scholar.google.com/

Search date: 14 Jan 2023

Search line	Search terms	Results
1	allintitle: cannabis OR cannabinoid OR marijuana "systematic review" -recreational Limited to dates 2021-2023 (as supplemental to the original searches)	Actual results: Google described results: About 205 results (0.03 sec)'
2	allintitle: THC OR CBD OR cannabidiol OR tetrahydrocannabinol "systematic review" -recreational	Actual results: Google described results: 'About 40 results (0.07 sec)'
	Citations exported	194*

*Number of extractable citations was less than number of citations initially suggested by Google as results. A discrepancy between Google-described results and actual exportable results is not unusual.

Screening results

Stage 1 Deduplication of primary search results

Appendix Table 7 Stage 1: Deduplication of 25,888 search records

Category	Total results
Include for first stage of title/abstract screen	14,636
Exclude on duplicate	11,252

Stage 2a Title/abstract screening

Appendix Table 8 Stage 2a: Screening on Title/Abstract of 14,636 records

Category	Subcategory: Exclusions	Total results
Include on title & abstract		617
Exclude on date	8	
Exclude on study design	4,975	
Exclude on intervention	8,449	
Exclude on age	86	
Exclude on in scope protocol, conference abstract, poster	301	
Exclude on language out of scope	153	
Exclude on language in scope.	33	
Exclude on duplicate	13	
Total excluded citations		14,019

Stage 2b Title/abstract deduplication screening

Appendix Table 9 Stage 2b: Deduplication screening of 617 included records

Category	Total results
Include for second stage of title/abstract screen	590
Exclude on duplicate	27

Stage 2c Title/abstract screening

Appendix Table 10 Stage 2c: Second title/abstract screening of 590 records from stage 1

Category	Subcategory: Exclusions	Total results
Include on title/abstract		407
Exclude on study design	101	
Exclude on study design: In-scope conference abstract or poster	51	
Exclude on intervention	12	
Exclude on age	1	

Exclude on date (published before 2010)	2	
Exclude on language: In scope	15	
Exclude on language: Out of scope	1	
Total excluded citations		183

Stage 2d Title/abstract deduplication screening

Appendix Table 11 Stage 2d: Deduplication screening of 407 included records

Category	Total results
Include for full-text screen	392
Exclude on duplicate	15

Stage 3a Full-text screening

Appendix Table 12 Stage 3a: Full-text screening of 392 included records

Category	Subcategory; Exclusions	Total results
Include on full-text screening		119
Subcategory: Include (double blinded)		38
Subcategory: Include (mixed blinding)		76
Subcategory: Include (no blinding)		5
Exclude on intervention	11	
Exclude on outcome	1	
Exclude on methods: no/inadequate quality assessment/risk of bias assessment	82	
Exclude on methods: no search strategy	12	
Exclude on methods: Searched less than two databases	8	
Exclude on methods: Review contains unextractable studies	26	
Exclude on study design: General	50	
Exclude on study design: Empty review	11	
Exclude on study design: Relevant umbrella review	3	
Exclude on study design: In-scope protocol/ conference abstract/poster	42	
Exclude on age	15	
Exclude on language	11	
Exclude on date	1	
Total excluded citations		273

Stage 3b Full-text screening

Appendix Table 13 Stage 3b: Full text screening of 119 included records

Category	Double blinding	Mixed blinding	No blinding	Subtotal	Total results
Include	17	34	2		53
Exclude on methods: Inadequate search strategy	6	4	0	10	20

Exclude on age	4	10	0	14	28
Exclude: review not cannabis-specific	6	13	1	20	40
Exclude on age and inadequate search strategy	3	7	1	11	22
Exclude on age and review not cannabis-specific	0	1	0	1	2
Exclude on review not cannabis-specific and inadequate search strategy	1	2	0	3	6
Exclude on age, inadequate search strategy and review not cannabis-specific	1	4	1	6	12
Exclude on intervention	0	1	0	1	2
Total excluded citations	38	76	5		66

Stage 3c Full-text screening

Appendix Table 14 Stage 3c: Full-text screening of 53 included records

Category	Double blinding	Mixed blinding	No blinding	Final results
Include				40
Exclude on non-extractable studies	1	5	0	6
Exclude on search strategy	0	2	1	3
Exclude on not cannabis-specific review	1	1	0	2
Exclude on study design	1	0	0	1
Exclude on intervention	0	1	0	1
Total excluded citations	3	9	1	13

Stage 4 Deduplication of supplemental search results

Appendix Table 15 Stage 4: Supplemental screening deduplication of 8478 records

Category	Results
Include for screening	5571
Exclude on duplicate	2907

Stage 5 Title/abstract screening of supplement search results

Appendix Table 16 Stage 5: Supplemental search: Title/abstract screening of 5571 records

Category	Results
Include on title and abstract	57
Exclude on already included reviews	57
Exclude on date	487
Exclude on study design	2970
Exclude on intervention	1660
Exclude on age	70

Exclude on in scope protocols & other such formats	47
Exclude on language in scope	68
Exclude on Language out of scope	129
Exclude on duplicate	23
Exclude review on multiple interventions not specifically cannabis	3

Stage 6a Full-text screening of supplemental search results

Appendix Table 17 Stage 6a: Supplemental search: Full-text screening of 57 records

Category	Results
Include for final screening	11
Exclude on existing include	1
Exclude on study design	6
Exclude on intervention	6
Exclude on methods: Inadequate search	5
Exclude on methods: Inadequate risk of bias	4
Exclude on age	9
Exclude on not cannabis-specific review	3
Exclude on date	1
Exclude on unextractable studies	7
Exclude on outcome	3
Exclude as unavailable paper	1

Stage 6b Full-text screening of supplemental search results

Appendix Table 18 Stage 6b: Supplemental search: Full-text screening of 11 records

Category	Results
Include	8
Exclude on existing included review	1
Exclude on study design	1
Exclude on age	1

Stage 6c Full-text screening of supplemental search results

Appendix Table 19 Stage 6c: Supplemental search: Full-text screening of 8 records

Category	Results
Include	7
Exclude on methods: Inadequate literature search	1

Appendix C Excluded reviews

Citations excluded at full-text screening stages

Citations excluded from the primary search results at the full-text screening stage (3a)

(Total citations excluded at this stage n=273)

Appendix Table 20 Citations excluded from full-text screening stage 3a on intervention

Number	Full-text screening stage 3a: Citations excluded on intervention (n=11)
1.	Dalacorte RR, Rigo JC, Dalacorte A. Pain management in the elderly at the end of life. *N Am J Med Sci* 2011;**3**:348–54. doi:https://doi.org/10.4297/najms.2011.3348
2.	de Freitas LA. *The efficacy of cannabidiol in mitigating delta-9-tetrahydrocannabinol-induced harms: A systematic review*. 2020.http://hdl.handle.net/1807/100413
3.	Indraccolo U, Indraccolo SR, Mignini F. Micronized palmitoylethanolamide/trans-polydatin treatment of endometriosis-related pain: a meta-analysis. *Ann Ist Super Sanita* 2017;**53**:125–34. doi:https://doi.org/10.4415/ANN_17_02_08
4.	Jasemi SV, Khazaei H, Momtaz S, *et al.* Natural products in the treatment of pulmonary emphysema: Therapeutic effects and mechanisms of action. *Phytomedicine* 2022;**99**:153988. doi:https://doi.org/10.1016/j.phymed.2022.153988
5.	Jung F, Lee Y, Manzoor S, *et al.* Effects of perioperative cannabis use on bariatric surgical outcomes: a systematic review. *Obes Surg* 2021;**31**:299–306. doi:https://doi.org/10.1007/s11695-020-04962-x
6.	Landrigan J, Bessenyei K, Leitner D, *et al.* A systematic review of the effects of cannabis on cognition in people with multiple sclerosis. *Mult Scler Relat Disord* 2022;**57**:103338. doi:https://doi.org/10.1016/j.msard.2021.103338
7.	Liang AL, Gingher EL, Coleman JS. Medical cannabis for gynecologic pain conditions: A systematic review. *Obstet Gynecol* 2022;**139**:287–96. doi:https://doi.org/10.1097/AOG.0000000000004656
8.	Mejia-Gomez J, Phung N, Philippopoulos E, *et al.* The impact of cannabis use on vasomotor symptoms, mood, insomnia and sexuality in perimenopausal and postmenopausal women: a systematic review. *Climacteric* 2021;**24**:572–6. doi:https://doi.org/10.1080/13697137.2021.1898581
9.	Schaiquevich P, Riva N, Maldonado C, *et al.* Clinical pharmacology of cannabidiol in refractory epilepsy. *Farm Hosp* 2020;**44**:222–9. doi:https://doi.org/10.7399/fh.11390
10.	Turna J, Syan SK, Frey BN, *et al.* Cannabidiol as a novel candidate alcohol use disorder pharmacotherapy: A systematic review. *Alcohol Clin Exp Res* 2019;**43**:550–63. doi:https://doi.org/10.1111/acer.13964
11.	Yang M, Feng Y, Zhang YL, *et al.* Herbal formula MaZiRenWan (Hemp Seed Pill) for constipation: A systematic review with meta-analysis. *Phytomedicine* 2021;**82**:153459. doi:https://doi.org/10.1016/j.phymed.2021.153459

Appendix Table 21 Citations excluded from full-text screening stage 3a on methods: no/inadequate quality assessment/risk of bias assessment

Number	Full-text screening stage 3a: Citations excluded on methods: no/inadequate quality assessment/risk of bias assessment (n=82)
1.	Alvarado RIN, Sánchez RM del C, Salcedo VV. Therapeutic properties of cannabinoid drugs and marijuana in several disorders: A narrative review. Salud Ment (Mex) 2017;40:111–8. doi:https://doi.org/10.17711/SM.0185-3325.2017.014
2.	Andrzejewski K, Barbano R, Mink J. Cannabinoids in the treatment of movement disorders: A systematic review of case series and clinical trials. Basal Ganglia 2016;6:173–81. doi:https://doi.org/10.1016/j.baga.2016.06.001
3.	Bahji A, Mazhar MN. Treatment of cannabis dependence with synthetic cannabinoids: a systematic review. Can J Addict 2016;7:8. doi:https://doi.org/10.1097/02024458-201602000-00003
4.	Barnes MP, Barnes JC. Cannabis: the evidence for medical use. London: All-Party Parliamentary Group for Drug Policy Reform 2016. https://www.drugsandalcohol.ie/26086/
5.	Beedham W, Sbai M, Allison I, *et al.* Cannabinoids in the older person: a literature review. Geriatrics (Basel) 2020;5:2. doi:https://doi.org/10.3390/geriatrics5010002
6.	Blumenthal DE, Malemud CJ. Recent strategies for drug development in fibromyalgia syndrome. Expert Rev Neurother 2016;16:1407–11. doi:https://doi.org/10.1080/14737175.2016.1207531
7.	Bonaccorso S, Ricciardi A, Zangani C, *et al.* Cannabidiol (CBD) use in psychiatric disorders: A systematic review. Neurotoxicology 2019;74:282–98. doi:https://doi.org/10.1016/j.neuro.2019.08.002
8.	Boychuk DG, Goddard G, Mauro G, *et al.* The effectiveness of cannabinoids in the management of chronic nonmalignant neuropathic pain: a systematic review. J Oral Facial Pain Headache 2015;29:7–14. doi:https://doi.org/10.11607/ofph.1274
9.	Canadian Agency for Drugs and Technologies in Health. Cannabinoids as co-analgesics: review of clinical effectiveness. Canada: Canadian Agency for Drugs and Technologies in Health (CADTH) 2010. https://www.cadth.ca/sites/default/files/pdf/l0196_cannabinoids_co-analgesics_htis-2.pdf
10.	Canadian Agency for Drugs and Technologies in Health. Cannabinoids for the management of neuropathic pain: review of clinical effectiveness. Canada: Canadian Agency for Drugs and Technologies in Health (CADTH) 2010. https://www.cadth.ca/sites/default/files/pdf/l0197_cannabinoids_neuropathic_pain_htis-2.pdf
11.	Carvalho ACA de, Souza GA de, Marqui SV de, *et al.* Cannabis and canabidinoids on the inflammatory bowel diseases: going beyond misuse. Int J Mol Sci 2020;21:2940. doi:https://doi.org/10.3390/ijms21082940
12.	Cooper ZD, Abrams DI. Considering abuse liability and neurocognitive effects of cannabis and cannabis-derived products when assessing analgesic efficacy: a comprehensive review of randomized-controlled studies. Am J Drug Alcohol Abuse 2019;45:580–95. doi:https://doi.org/10.1080/00952990.2019.1669628
13.	Darkovska-Serafimovska M, Serafimovska T, Arsova-Sarafinovska Z, *et al.* Pharmacotherapeutic considerations for use of cannabinoids to relieve pain in patients

with malignant diseases. J Pain Res 2018;11:837–42. doi:https://doi.org/10.2147/JPR.S160556

14. Figura M, Koziorowski D, Sławek J. Cannabis in parkinson's disease - the patient's perspective versus clinical trials: a systematic literature review. Neurol Neurochir Pol 2022;56:21–7. doi:https://doi.org/10.5603/PJNNS.a2022.0004

15. First L, Douglas W, Habibi B, *et al.* Cannabis use and low-back pain: a systematic review. Cannabis Cannabinoid Res 2020;5:283–9. doi:https://doi.org/10.1089/can.2019.0077

16. Fu X, Wang Y, Wang C, *et al.* A mixed treatment comparison on efficacy and safety of treatments for spasticity caused by multiple sclerosis: a systematic review and network meta-analysis. Clin Rehabil 2018;32:713–21. doi:https://doi.org/10.1177/0269215517745348

17. Furgiuele A, Cosentino M, Ferrari M, *et al.* Immunomodulatory potential of cannabidiol in multiple sclerosis: a systematic review. J Neuroimmune Pharmacol 2021;16:251–69. doi:https://doi.org/10.1007/s11481-021-09982-7

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19. Gilmartin CGS, Dowd Z, Parker APJ, *et al.* Interaction of cannabidiol with other antiseizure medications: A narrative review. Seizure 2021;86:189–96. doi:https://doi.org/10.1016/j.seizure.2020.09.010

20. Gunawan C, Seneviratne U, D'Souza W. The effect of antiepileptic drugs on epileptiform discharges in genetic generalized epilepsy: A systematic review. Epilepsy & Behavior 2019;96:175–82. doi:https://doi.org/10.1016/j.yebeh.2019.04.030

21. Gupta AK, Talukder M, Bamimore MA. Natural products for male androgenetic alopecia. Dermatol Ther 2022;35:e15323. doi:https://doi.org/10.1111/dth.15323

22. Hill KP, Gold MS, Nemeroff CB, *et al.* Risks and benefits of cannabis and cannabinoids in psychiatry. Am J Psychiatry 2022;179:98–109. doi:https://doi.org/10.1176/appi.ajp.2021.21030320

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24. Huestis MA, Solimini R, Pichini S, *et al.* Cannabidiol adverse effects and toxicity. Curr Neuropharmacol 2019;17:974–89. doi:https://doi.org/10.2174/1570159X17666190603171901

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29. Khanna R, Kwatra SG. Cannabinoids for the treatment of refractory chronic pruritus. J Am Acad Dermatol 2019;81:AB29. doi:https://doi.org/10.1016/j.jaad.2019.06.145

30. Khoury JM, Neves M de CL das, Roque MAV, *et al.* Is there a role for cannabidiol in psychiatry? World J Biol Psychiatry 2019;20:101–16. doi:https://doi.org/10.1080/15622975.2017.1285049

31. Koppel BS, Brust JCM, Fife T, *et al.* Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2014;82:1556–63. doi:https://doi.org/10.1212/WNL.0000000000000363

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33. Laprevote V, Schwan R, Schwitzer T, *et al.* Is there a place for off-label pharmacotherapy in cannabis use disorder? A review on efficacy and safety. Curr Pharm Des 2015;21:3298–305. doi:https://doi.org/10.2174/1381612821666150619093940

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35. Malik A, Fatehi KS, Menon NN, *et al.* Review of medicinal use of cannabis derivatives and the societal impact of legalization. Indian J Palliat Care 2020;26:369–80. doi:https://doi.org/10.4103/IJPC.IJPC_19_20

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79.	Yarnell S. The use of medicinal marijuana for posttraumatic stress disorder: a review of the current literature. Prim Care Companion CNS Disord 2015;17:10.4088/PCC.15r01786. doi:https://doi.org/10.4088/PCC.15r01786
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81.	Zhornitsky S, Potvin S. Cannabidiol in humans—the quest for therapeutic targets. Pharmaceuticals (Basel) 2012;5:529–52. doi:https://doi.org/10.3390/ph5050529
82.	Ziffra M. Panic disorder: A review of treatment options. Ann Clin Psychiatry 2021;33:124–33. doi:https://doi.org/10.127788/acp.0014

Appendix Table 22 Citations excluded from full-text screening stage 3a on methods: no search strategy

Number	Full-text screening stage 3a: Citations excluded on methods: no search strategy (n=12)
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2.	Di Stefano G, De Stefano G, Di Lionardo A, *et al.* Pharmacotherapeutic options for managing pain in multiple sclerosis. CNS Drugs 2020;34:749–61. doi:https://doi.org/10.1007/s40263-020-00731-7
3.	Larsen C, Shahinas J. Dosage, efficacy and safety of cannabidiol administration in adults: a systematic review of human trials. J Clin Med Res 2020;12:129–41. doi:https://doi.org/10.14740/jocmr4090
4.	MacDonald E, Adams A. The use of medical cannabis with other medications: a review of safety and guidelines - an update. Ottawa: Canadian Agency for Drugs and Technologies in Health 2019. http://www.ncbi.nlm.nih.gov/books/NBK549545/
5.	MacDonald E, Farrah K. Medical cannabis use in palliative care: review of clinical effectiveness and guidelines – an update. Ottawa: Canadian Agency for Drugs and Technologies in Health 2019. http://www.ncbi.nlm.nih.gov/books/NBK551867/
6.	McGolrick D, Frey N. Nabilone for chronic pain management: a review of clinical effectiveness and guidelines – an update. Ottawa: Canadian Agency for Drugs and Technologies in Health 2018. http://www.ncbi.nlm.nih.gov/books/NBK538943/
7.	Millar SA, Stone N l., Bellman ZD, *et al.* A systematic review of cannabidiol dosing in clinical populations. Br J Clin Pharmacol 2019;85:1888–900. doi:https://doi.org/10.1111/bcp.14038
8.	Narain T, Farrah K. Nabilone for non-chemotherapy associated nausea and vomiting and weight loss due to medical conditions: a review of clinical effectiveness and guidelines. Ottawa: Canadian Agency for Drugs and Technologies in Health 2017. http://www.ncbi.nlm.nih.gov/books/NBK493532/
9.	Oliveira RAA de, Baptista AF, Sá KN, *et al.* Pharmacological treatment of central neuropathic pain: consensus of the Brazilian Academy of Neurology. Arq Neuropsiquiatr 2020;78:741–52. doi:https://doi.org/10.1590/0004-282X20200166

10.	Peprah K, McCormack S. Medical cannabis for the treatment of dementia: a review of clinical effectiveness and guidelines. Ottawa: Canadian Agency for Drugs and Technologies in Health 2019. http://www.ncbi.nlm.nih.gov/books/NBK546328/
11.	Prud'homme M, Cata R, Jutras-Aswad D. Cannabidiol as an intervention for addictive behaviors: a systematic review of the evidence. Subst Abuse 2015;9:SART.S25081. doi:https://doi.org/10.4137/SART.S25081
12.	Ružić Zečević D, Folić M, Tantoush Z, *et al.* Investigational cannabinoids in seizure disorders, what have we learned thus far? Expert Opin Investig Drugs 2018;27:535–41. doi:https://doi.org/10.1080/13543784.2018.1482275

Appendix Table 23 Citations excluded from full-text screening stage 3a on methods: no/inadequate quality assessment/risk of bias assessment

Number	Full-text screening stage 3a: Citations excluded on methods: Searched less than two databases (n=8)
1.	Cuménal M, Selvy M, Kerckhove N, *et al.* The safety of medications used to treat peripheral neuropathic pain, part 2 (opioids, cannabinoids and other drugs): Review of double-blind, placebo-controlled, randomized clinical trials. Expert Opin Drug Saf 2021;20:51–68. doi:https://doi.org/10.1080/14740338.2021.1842871
2.	Joseph D, Schulze J. Cannabinoid activity—is there a causal connection to spasmolysis in clinical studies? Biomolecules 2021;11:826. doi:https://doi.org/10.3390/biom11060826
3.	McClam TD, Marano CM, Rosenberg PB, *et al.* Interventions for neuropsychiatric symptoms in neurocognitive impairment due to alzheimer's disease: a review of the literature. Harv Rev Psychiatry 2015;23:377–93. doi:https://doi.org/0.1097/HRP.0000000000000097
4.	Shishko I, Oliveira R, Moore TA, *et al.* A review of medical marijuana for the treatment of posttraumatic stress disorder: Real symptom re-leaf or just high hopes? Ment Health Clin 2018;8:86–94. doi:10.9740/mhc.2018.03.086
5.	Skelley JW, Deas CM, Curren Z, *et al.* Use of cannabidiol in anxiety and anxiety-related disorders. J Am Pharm Assoc (2003) 2020;60:253–61. doi:https://doi.org/10.1016/j.japh.2019.11.008
6.	Stella F, Valiengo LCL, Paula VJR de, *et al.* Medical cannabinoids for treatment of neuropsychiatric symptoms in dementia: a systematic review. Trends Psychiatry Psychother 2021;43:243–55. doi:https://doi.org/10.47626/2237-6089-2021-0288
7.	Vecera L, Gabrhelik T, Prasil P, *et al.* The role of cannabinoids in the treatment of cancer. Bratisl Lek Listy 2020;121:79–95. doi:https://doi.org/10.4149/BLL_2020_012
8.	Wong E, Ranapurwala SI. Cardiovascular risk associated with medical use of opioids and cannabinoids: A systematic review. Curr Cardiovasc Risk Rep 2019;13:30. doi:https://doi.org/10.1007/s12170-019-0625-x

Appendix Table 24 Citations excluded from full-text screening stage 3a on methods: review contains unextractable studies

Number	Full-text screening stage 3a: Citations excluded on methods: Review contains unextractable studies (n=26)
1.	Akinyemi E, Randhawa G, Longoria V, *et al.* Medical marijuana effects in movement disorders, focus on Huntington disease; a literature review. J Pharm Pharm Sci 2020;23. doi:https://doi.org/10.18433/jpps30967

2. Bahji A, Breward N, Duff W, *et al.* Cannabinoids in the management of behavioral, psychological, and motor symptoms of neurocognitive disorders: a mixed studies systematic review. J Cannabis Res 2022;4:11. doi:https://doi.org/10.1186/s42238-022-00119-y

3. Bhagavan C, Kung S, Doppen M, *et al.* Cannabinoids in the treatment of insomnia disorder: A systematic review and meta-analysis. CNS Drugs 2020;34:1217–28. doi:https://doi.org/10.1007/s40263-020-00773-x

4. Breward NJB. A systematic review examining cannabis use for the treatment of multiple sclerosis. 2019.http://hdl.handle.net/10388/12360

5. Brown D, Watson M, Schloss J. Pharmacological evidence of medicinal cannabis in oncology: a systematic review. Support Care Cancer 2019;27:3195–207. doi:https://doi.org/10.1007/s00520-019-04774-5

6. Chan CJ. Efficacy of plant based cannabis in reducing pain in patients with chronic pain: A meta analysis. 2020.https://scholarworks.calstate.edu/downloads/qf85nd96q

7. Charoenporn V, Charernboon T, Mackie CJ. Medical cannabis as a substitute for prescription agents: A systematic review and meta-analysis. J Subst Use 2022;:13pp. doi:https://doi.org/10.1080/14659891.2022.2070870

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9. Ghabrash MF, Coronado-Montoya S, Aoun J, *et al.* Cannabidiol for the treatment of psychosis among patients with schizophrenia and other primary psychotic disorders: A systematic review with a risk of bias assessment. Psychiatry Res 2020;286:112890. doi:https://doi.org/10.1016/j.psychres.2020.112890

10. Hassan S. Cannabinoids for the treatment of chronic pain: A critical review of randomized controlled trials. J Pain Manag Med 2018;4:1–7. doi:https://doi.org/10.35248/2684-1320.18.4.131

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12. Hindocha C, Cousijn J, Rall M, *et al.* The effectiveness of cannabinoids in the treatment of posttraumatic stress disorder (PTSD): A systematic review. J Dual Diagn 2020;16:120–39. doi:https://doi.org/10.1080/15504263.2019.1652380

13. Jawahar R, Oh U, Yang S, *et al.* A systematic review of pharmacological pain management in multiple sclerosis. Drugs 2013;73:1711–22. doi:https://doi.org/10.1007/s40265-013-0125-0

14. Kuhathasan N, Dufort A, MacKillop J, *et al.* The use of cannabinoids for sleep: A critical review on clinical trials. Exp Clin Psychopharmacol 2019;27:383–401. doi:https://doi.org/10.1037/pha0000285

15.	Kurlyandchik I, Tiralongo E, Schloss J. Safety and efficacy of medicinal cannabis in the treatment of fibromyalgia: A systematic review. J Altern Complement Med 2021;27:198–213. doi:https://doi.org/10.1089/acm.2020.0331
16.	Madden K, van der Hoek N, Chona S, *et al.* Cannabinoids in the management of musculoskeletal pain: A critical review of the evidence. JBJS Rev 2018;6:e7. doi:https://doi.org/10.2106/JBJS.RVW.17.00153
17.	McBain C, Lawrie TA, Rogozińska E, *et al.* Treatment options for progression or recurrence of glioblastoma: a network meta-analysis. Cochrane Database Syst Rev 2021;5:CD013579. doi:https://doi.org/10.1002/14651858.CD013579.pub2
18.	Nabata KJ, Tse EK, Nightingale TE, *et al.* The therapeutic potential and usage patterns of cannabinoids in people with spinal cord injuries: A systematic review. Curr Neuropharmacol 2021;19:402–32. doi:https://doi.org/10.2174/1570159X18666200420085712
19.	Nugent SM, Morasco BJ, O'Neil ME, *et al.* The effects of cannabis among adults with chronic pain and an overview of general harms: A systematic review. Ann Intern Med 2017;167:319–31. doi:https://doi.org/10.7326/M17-0155
20.	Rehman Y, Saini A, Huang S, *et al.* Cannabis in the management of PTSD: a systematic review. AIMS Neurosci 2021;8:414–34. doi:https://doi.org/10.3934/Neuroscience.2021022
21.	Steardo L, Carbone EA, Menculini G, *et al.* Endocannabinoid system as therapeutic target of PTSD: A systematic review. Life 2021;11:214. doi:https://doi.org/10.3390/life11030214
22.	Suraev AS, Marshall NS, Vandrey R, *et al.* Cannabinoid therapies in the management of sleep disorders: A systematic review of preclinical and clinical studies. Sleep Med Rev 2020;53:101339. doi:https://doi.org/10.1016/j.smrv.2020.101339
23.	Taylor C, Birch B. Cannabinoids in urology. which benign conditions might they be appropriate to treat: A systematic review. Urology 2021;148:8–25. doi:https://doi.org/10.1016/j.urology.2020.10.024
24.	Werneck MA, Kortas GT, de Andrade AG, *et al.* A systematic review of the efficacy of cannabinoid agonist replacement therapy for cannabis withdrawal symptoms. CNS Drugs 2018;32:1113–29. doi:https://doi.org/10.1007/s40263-018-0577-6
25.	Zeraatkar D, Cooper MA, Agarwal A, *et al.* Long-term and serious harms of medical cannabis and cannabinoids for chronic pain: A systematic review of non-randomized studies. 2021;:2021.05.27.21257921. doi:https://doi.org/10.1101/2021.05.27.21257921
26.	Zhang S, Li M, Guo Z. Effect of cannabidiol on schizophrenia based on randomized controlled trials: A meta-analysis. Ann Med Psychol (Paris) 2022;180:630–8. doi:https://doi.org/10.1016/j.amp.2021.09.019

Appendix Table 25 Citations excluded from full-text screening stage 3a on study design: general

Number	Full-text screening stage 3a: Citations excluded on study design: General (n=50)
1.	Acosta L del CL, Ventura CAA. Scientific evidence on therapeutic marihuana use in individuals treated in health care services. SMAD Revista eletrônica saúde mental álcool e drogas 2017;13:167–74. doi:https://doi.org/10.11606/issn.1806-6976.v13i3p167-174

2. Akgün K, Essner U, Seydel C, *et al.* Daily practice managing resistant multiple sclerosis spasticity with delta-9-tetrahydrocannabinol: Cannabidiol oromucosal spray: a systematic review of observational studies. J Cent Nerv Syst Dis 2019;11:1179573519831997. doi:https://doi.org/10.1177/1179573519831997

3. Calapai F, Cardia L, Calapai G, *et al.* Effects of cannabidiol on locomotor activity. Life 2022;12:652. doi:https://doi.org/10.3390/life12050652

4. Canadian Agency for Drugs and Technologies in Health. Medical marijuana for post-traumatic stress disorder: A review of clinical effectiveness and guidelines. Canadian Agency for Drugs and Technologies in Health 2017. https://www.cadth.ca/medical-marijuana-post-traumatic-stress-disorder-review-clinical-effectiveness-and-guidelines

5. Castañeda Cardona C, Lasalvia P, Ferreiros A, *et al.* Cannabis in inflammatory bowel disease: a narrative summary. Revista colombiana de Gastroenterología 2020;35:104–13. doi:https://doi.org/10.22516/25007440.407

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10. Garcia JM, Shamliyan TA. Cannabinoids in patients with nausea and vomiting associated with malignancy and its treatments. Am J Med 2018;131:755-759.e2. doi:https://doi.org/10.1016/j.amjmed.2017.12.041

11. Gasparotto FM, Dos Reis Lívero FA, Tolouei Menegati SEL, *et al.* Herbal medicine as an alternative treatment in autism spectrum disorder: a systematic review. Curr Drug Metab 2018;19:454–9. doi:https://doi.org/10.2174/1389200219666171227202332

12. Haddad R, Denys P, Arlandis S, *et al.* Nocturia and nocturnal polyuria in neurological patients: from epidemiology to treatment. a systematic review of the literature. Eur Urol Focus 2020;6:922–34. doi:https://doi.org/10.1016/j.euf.2020.02.007

13. Hassan S, Zheng Q, Rizzolo E, *et al.* Does integrative medicine reduce prescribed opioid use for chronic pain? A systematic literature review. Pain Med 2020;21:836–59. doi:https://doi.org/10.1093/pm/pnz291

14. Jarjou'i A, Izbicki G. Medical cannabis in asthmatic patients. Isr Med Assoc J 2020;22:232–5.

15. Kaur S, Sharma N, Roy A. Role of cannabinoids in various diseases: a review. Curr Pharm Biotechnol 2022;23:1346–58. doi:https://doi.org/10.2174/1389201023666211223164656

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17. Kim SH, Yang JW, Kim KH, *et al.* A review on studies of marijuana for Alzheimer's disease - focusing on CBD, THC. J Pharmacopuncture 2019;22:225–30. doi:https://doi.org/10.3831/KPI.2019.22.030

18. Lim XY, Tan TYC, Rosli SHM, *et al.* Cannabis sativa subsp. sativa's pharmacological properties and health effects: A scoping review of current evidence. PLoS One 2021;16:e0245471. doi:https://doi.org/10.1371/journal.pone.0245471

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49.	Taneja S, Hoogenes J, Slaven M, *et al.* Use of cannabis in urological cancer patients: A review to evaluate risk for cancer development, therapeutic use, and symptom management. Can Urol Assoc J 2021;15:413–9. doi:https://doi.org/10.5489/cuaj.7198
50.	Tsai SHL, Lin C-R, Shao S-C, *et al.* Cannabinoid use for pain reduction in spinal cord injuries: A meta-analysis of randomized controlled trials. Front Pharmacol 2022;13:866235. doi:https://doi.org/10.3389/fphar.2022.866235

Appendix Table 26 Citations excluded from full-text screening stage 3a on study design: in-scope protocol/ conference abstract/poster

Number	Full-text screening stage 3a: Citations excluded on study design: in-scope protocol/ conference abstract/poster (n=42)
1.	Alharbi GS, Chen LC, Knaggs R. Efficacy of anticonvulsant, antidepressant and opioid in treating neuropathic pain - A systematic review and meta-analysis. Pharmacoepidemiol Drug Saf 2016;25:582. doi:https://doi.org/10.1002/pds.4070
2.	Alkabbani W, Friesen KJ, Janzen D, *et al.* The efficacy of pharmaceutical cannabinoids in the management of cannabis use disorder: A systematic review. J Popul Ther Clin Pharmacol 2019;26:e31–2. doi:https://jptcp.com/index.php/jptcp/article/view/654

3.	Asthana N, Sewell D. A systematic review of the novel applications of cannabinoids in dementia care: food refusal and neuropsychiatric symptoms. Am J Geriatr Psychiatry 2021;29:S60–1. doi:https://doi.org/10.1016/j.jagp.2021.01.052
4.	Bahji A, Meyyappan AC, Hawken E. Cannabis for anxiety: Systematic review and meta-analysis. 2020.https://www.researchgate.net/publication/328492852_Cannabis_for_Anxiety_Systematic_Review_and_Meta-analysis
5.	Banerjee S, McCormack S. Medical cannabis for the treatment of chronic pain: A review of clinical effectiveness and guidelines. Ottawa: Canadian Agency for Drugs and Technologies in Health 2019. https://www.ncbi.nlm.nih.gov/books/NBK546424/
6.	Belgers V, Röttgering JG, Douw L, *et al.* P12.07 The potential of cannabinoids to improve quality of life in glioma patients: A meta-analysis in patients with neurological and oncological disease. Neuro-Oncology 2021;23:ii32. doi:https://doi.org/10.1093/neuonc/noab180.109
7.	Black N, Stockings E, Tran LT, *et al.* Cannabis and cannabinoids for the treatment of mental disorders and symptoms: A systematic review and meta-analysis. Wiley 2019. S28. doi:https://espace.library.uq.edu.au/view/UQ:c05a195
8.	Boongmongkol T, Jitkritsadakul O, Bhidayasiri R. The systematic review on cannabinoids as a treatment of Parkinson's disease. Mov Disord Clin Pract 2019;6:S55-SS57. doi:https://doi.org/10.1002/mdc3.12744
9.	Busse J, Wang L, Kamal El Din M, *et al.* Opioids for chronic non-cancer pain: A systematic review of randomized controlled trials. Pain Pract 2018;18:54–5. doi:https://doi.org/10.1080/24740527.2017.1329323
10.	Canavan C, Power CK, Fullen BM. WIP18-0454 Adverse events and withdrawal rates in pharmacological trials for chronic spinal cord injury pain: A systematic review. Pain Pract 2018;18:56. doi:https://onlinelibrary.wiley.com/doi/pdf/10.1111/papr.12693
11.	Canavan C, Power CK, Fullen BM. WIP18-0455 The efficacy of medication for chronic spinal cord injury pain; A systematic review. Pain Pract 2018;18:56. doi:https://onlinelibrary.wiley.com/doi/pdf/10.1111/papr.12693
12.	Crathorne L, Campbell J, Vila Silván C, *et al.* Evidence for the efficacy of nabiximols oromucosal spray in the management of patients with spasticity: A systematic review. Mult Scler 2020;26:155–6. doi:https://doi.org/10.1177/1352458520974937
13.	Doeve B, Van Schaik F, Van De Meeberg M, *et al.* Cannabis and cannabinoids for the treatment of inflammatory bowel disease: A systematic review and meta-analysis. J Crohns Colitis 2019;13:S335–6. doi:https://academic.oup.com/ecco-jcc/article/13/Supplement_1/S335/5301046
14.	Gaisl T, Haile SR, Thiel S, *et al.* Efficacy of pharmacotherapy for OSA in adults: A systematic review and network meta-analysis. Eur Resp J 2019;54:PA4168. doi:https://doi.org/10.1183/13993003.congress-2019.PA4168
15.	Gaisl T, Haile SR, Thiel S, *et al.* P32 Efficacy of pharmacotherapy for obstructive sleep apnea in adults: A systematic review and network meta-analysis. Respiration 2019;97:604. doi:https://doi.org/10.1159/000499887

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24. Kung T, Hochman J, Sun Y, *et al.* C2–CC100. Efficacy and safety of cannabinoids for pain in musculoskeletal diseases: A systematic review and meta-analysis. Reumatologia Clinica Suplementos 2011;7:166.

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28. Linley W, Hawkins N, Schwenkglenks M, *et al.* Comparative effectiveness of fenfluramine vs cannabidiol for the treatment of seizures in Dravet syndrome (DS): A network meta-analysis (NMA). Epilepsia 2021;62:154. doi:https://doi.org/10.1111/epi.17079

29.	Linley W, Hawkins N, Schwenkglenks M, *et al.* Comparative effectiveness of fenfluramine vs cannabidiol for the treatment of seizures in Dravet syndrome (DS): A network meta-analysis (NMA). Dev Med Child Neurol 2022;64:30. doi:https://doi.org/10.1111/dmcn.15123
30.	McParland A, Daniel K, Bhatia A, *et al.* 695 Cannabinoids and sleep health in patients with chronic neuropathic pain: A systematic review and meta-analysis. Sleep 2021;44:A271–2. doi:https://doi.org/10.1093/sleep/zsab072.693
31.	Mejia-Gomez J, Phung N, Philippopoulos E, *et al.* Effect of cannabis use in peri- and post-menopausal women: a systematic review. J Obstet Gynaecol Can 2021;43:680–1. doi:https://doi.org/10.1016/j.jogc.2021.02.107
32.	Oberbarnscheidt T, Miller N. Marijuana-is it a medicine? Med Cannabis Cannabinoids 2020;3:123. doi:https://doi.org/10.1159/000505827
33.	Okpeku A, Goodin A. Review of medical marijuana use in HIV/AIDS. Med Cannabis Cannabinoids 2021;4:137. doi:https://doi.org/10.1159/000519038
34.	Ortiz AC, Gavioli A, Ortiz SR. Cannabinoids' neuroprotective effect as an alternative treatment for Parkinson's disease: A systematic review. J Neurol Sci 2021;429:119526. doi:10.1016/j.jns.2021.119526
35.	Oskarsson B, Katzberg H, Weber M. Treatment for cramps in amyotrophic lateral sclerosis/motor neuron disease: An updated Cochrane review. Amyotroph Lateral Scler Frontotemporal Degener 2017;18:54–5.
36.	Parsai S, Herman R, Johnson S. Systematic literature review of randomized controlled trials to evaluate the efficacy of medical marijuana for analgesia. Pharmacotherapy 2014;34:e287. doi:https://doi.org/10.1002/phar.1497
37.	Patel A. Pharmacological interventions for the management of paraneoplastic sweating in patients with advanced cancer: A systematic review of the literature. Palliat Med 2016;30:S24–5. doi:https://doi.org/10.1177/0269216316631462
38.	Pinho C, Leitao M, Oliveira AI. Cannabis sativa L. and inflammatory bowel disease. Viseu: Atencion Primaria 2016. 147.https://recipp.ipp.pt/handle/10400.22/22186
39.	Rosewall T, Feuz C, Bayley A. Cannabis and radiation therapy: A scoping review of human clinical trials. Radiother Oncol 2020;150:S61. doi:https://doi.org/10.1016/S0167-8140%2820%2931033-1
40.	Schloss J, Brown D, Steel A. Medicinal cannabis and cancer: A narrative systematic literature review. Asia Pac J Clin Oncol 2017;13:221. doi:https://doi.org/10.1111/ajco.12799
41.	Willis MA, Nichol KE, Hollenack KA. Systematic review of real-world evidence on the effect of nabiximols on pain and sleep impairment in persons with ms (pwms) experiencing spasticity. PM R 2021;13:S64. doi:https://doi.org/10.1002/pmrj.12735
42.	Yu M, Bega D. A systematic review of the clinical evidence for complementary and alternative medicine in Huntington's disease. Neurotherapeutics 2019;16:1388. doi:https://doi.org/10.1007/s13311-019-00788-3

Appendix Table 27 Citations excluded from full-text screening stage 3a on study design: empty review

Number	Full-text screening stage 3a: Citations excluded on study design: empty review (n=11)
1.	Andrade A, Kuah CY, Martin-Lopez JE, *et al.* Interventions for chronic pruritus of unknown origin. Cochrane Database Syst Rev Published Online First: 2020. doi:https://doi.org/10.1002/14651858.CD013128.pub2
2.	Ayati Z, Sarris J, Chang D, *et al.* Herbal medicines and phytochemicals for obsessive–compulsive disorder. Phytother Res 2020;34:1889–901. doi:https://doi.org/10.1002/ptr.6656
3.	Bohn E, Goren K, Switzer L, *et al.* Pharmacological and neurosurgical interventions for individuals with cerebral palsy and dystonia: a systematic review update and meta-analysis. Dev Med Child Neurol 2021;63:1038–50. doi:https://doi.org/10.1111/dmcn.14874
4.	Chinuck R, Dewar J, Baldwin DR, *et al.* Appetite stimulants for people with cystic fibrosis. Cochrane Database Syst Rev 2014;:CD008190. doi:https://doi.org/10.1002/14651858.CD008190.pub2
5.	Cutillo G, Tolba H, Hirsch LJ. Anti-seizure medications and efficacy against focal to bilateral tonic-clonic seizures: A systematic review with relevance for SUDEP prevention. Epilepsy & Behavior 2021;117:107815. doi:https://doi.org/10.1016/j.yebeh.2021.107815
6.	Harrison AM, Heritier F, Childs BG, *et al.* Systematic review of the use of phytochemicals for management of pain in cancer therapy. Biomed Res Int 2015;2015:506327. doi:https://doi.org/10.1155/2015/506327
7.	7 Kolber MR, Ton J, Thomas B, *et al.* PEER systematic review of randomized controlled trials: Management of chronic low back pain in primary care. Can Fam Physician 2021;67:e20–30. doi:https://doi.org/10.46747/cfp.6701e20
8.	Meyer MJ, Megyesi J, Meythaler J, *et al.* Acute management of acquired brain injury part II: an evidence-based review of pharmacological interventions. Brain Inj 2010;24:706–21. doi:https://doi.org/10.3109/02699051003692126
9.	Nageye F, Cortese S. Beyond stimulants: a systematic review of randomised controlled trials assessing novel compounds for ADHD. Expert Rev Neurother 2019;19:707–17. doi:https://doi.org/10.1080/14737175.2019.1628640
10.	Steiner L, Brunetti L, Roberts S, *et al.* A review of the efficacy of appetite stimulating medications in hospitalized adults. Nutr Clin Pract 2023;38:80–7. doi:https://doi.org/10.1002/ncp.10839
11.	Wagner M, Probst P, Haselbeck-Köbler M, *et al.* The problem of appetite loss after major abdominal surgery: A systematic review. Ann Surg 2022;276:256–69. doi:https://doi.org/10.1097/SLA.0000000000005379

Appendix Table 28 Citations excluded from full-text screening stage 3a on study design: relevant umbrella review

Number	Full-text screening stage 3a: Citations excluded on study design: Relevant umbrella review (n=3)
1.	Häuser W, Fitzcharles M-A, Radbruch L, *et al.* Cannabinoids in pain management and palliative medicine. Dtsch Arztebl Int 2017;114:627–34. doi:https://doi.org/10.3238/arztebl.2017.0627
2.	Kansagara D, O'Neil M, Nugent S, *et al.* Benefits and harms of cannabis in chronic pain or post-traumatic stress disorder: A systematic review. Washington (DC):

	Department of Veterans Affairs (US) 2017. https://www.hsrd.research.va.gov/publications/esp/cannabis.pdf
3.	van den Beuken-van Everdingen MHJ, de Graeff A, Jongen JLM, *et al.* Pharmacological treatment of pain in cancer patients: The role of adjuvant analgesics, a systematic review. Pain Pract 2017;17:409–19. doi:https://doi.org/10.1111/papr.12459

Appendix Table 29 Citations excluded from full-text screening stage 3a on language

Number	Full-text screening stage 3a: Citations excluded on language (n=11)
1.	Álvarez Pinzón A M, Maldonado J. Tratamiento farmacológico de dolor neuropático de tipo central en pacientes con esclerosis múltiple/. Rev salud bosque 2012;2:47–63. doi:https://doi.org/10.18270/rsb.v2i1.86
2.	Benze G, Geyer A, Alt-Epping B, *et al.* Behandlung von Übelkeit und Erbrechen mit 5HT3-Antagonisten, Steroiden, Antihistaminika, Anticholinergika, Somatostatinanaloga, Benzodiazepinen und Cannabinoiden bei Palliativpatienten. Schmerz 2012;26:481–99. doi:https://doi.org/10.1007/s00482-012-1235-4
3.	Bogaczewicz A, Sobow T, Bogaczewicz J, *et al.* Metaanaliza badań dotyczących stosowania leków działających na ośrodkowy układ nerwowy w terapii świądu mocznicowego. Dermatologia Kliniczna 2012;14:5–12.
4.	Kairuz Bernate MJF. Revisión sistemática de estudios clínicos sobre el consumo de cannabis con fines terapéuticos entre los años 2005-2015. 2015.https://repository.javeriana.edu.co/handle/10554/19110
5.	Maldonado J, Álvarez Pinzón AM, Rodríguez Martínez M. Efectividad y efectos secundarios del tratamiento con canabinoides en dolor neuropático de tipo central en pacientes con Escleriosis Múltiple. Revista Med 2010;18:77–83.
6.	Moreno Torres M del C. Eficacia y tolerabilidad de placebo y cannabinoides en esclerosis múltiple. 2015.https://www.tesisenred.net/bitstream/handle/10803/312333/fmct1de1.pdf
7.	Mücke M, Carter C, Cuhls H, *et al.* Cannabinoide in der palliativen Versorgung. Systematische Übersicht und Metaanalyse der Wirksamkeit, Verträglichkeit und Sicherheit. Schmerz 2016;30:25–36. doi:https://doi.org/10.1007/s00482-015-0085-2
8.	Pereira F de A, Torres AC, Philadelpho VO, *et al.* Efeitos do canabidiol na frequência das crises epilépticas: Uma revisão sistemática. Rev bras neurol psiq 2018;22:86–100.
9.	Petzke F, Enax-Krumova EK, Häuser W. Wirksamkeit, Verträglichkeit und Sicherheit von Cannabinoiden bei neuropathischen Schmerzsyndromen. Schmerz 2016;30:62–88. doi:https://doi.org/10.1007/s00482-015-0089-y
10.	Santos AB, Scherf JR, Mendes R de C. Eficácia do canabidiol no tratamento de convulsões e doenças do sistema nervoso central: revisão sistemática. Acta Brasiliensis 2019;3:30–4. doi:https://doi.org/10.22571/2526-4338131
11.	Volz MS, Siegmund B, Häuser W. Wirksamkeit, Verträglichkeit und Sicherheit von Cannabinoiden in der Gastroenterologie. Schmerz 2016;30:37–46. doi:https://doi.org/10.1007/s00482-015-0087-0

Appendix Table 30 Citations excluded from full-text screening stage 3a on age

Number	Full-text screening stage 3a: Citations excluded on age (n=15)

1.	Brigo F, Jones K, Eltze C, *et al.* Anti-seizure medications for Lennox-Gastaut syndrome. Cochrane Database Syst Rev 2021;4:CD003277. doi:https://doi.org/10.1002/14651858.CD003277.pub4
2.	Fusar-Poli L, Cavone V, Tinacci S, *et al.* Cannabinoids for people with ASD: A systematic review of published and ongoing studies. Brain Sci 2020;10:572. doi:https://doi.org/10.3390/brainsci10090572
3.	Kondo K, Morasco BJ, Nugent S, *et al.* Pharmacotherapy for the Treatment of Cannabis Use Disorder: A Systematic Review. Washington, DC: Department of Veterans Affairs 2019. https://www.hsrd.research.va.gov/publications/esp/pharmacotherapy-cud.pdf
4.	Lattanzi S, Brigo F, Cagnetti C, *et al.* Efficacy and safety of adjunctive cannabidiol in patients with Lennox–Gastaut syndrome: A systematic review and meta-analysis. CNS Drugs 2018;32:905–16. doi:https://doi.org/10.1007/s40263-018-0558-9
5.	Lattanzi S, Brigo F, Trinka E, *et al.* Efficacy and safety of cannabidiol in epilepsy: A systematic review and meta-analysis. Drugs 2018;78:1791–804. doi:https://doi.org/10.1007/s40265-018-0992-5
6.	Lattanzi S, Trinka E, Striano P, *et al.* Cannabidiol efficacy and clobazam status: A systematic review and meta-analysis. Epilepsia 2020;61:1090–8. doi:https://doi.org/10.1111/epi.16546
7.	Lattanzi S, Trinka E, Striano P, *et al.* Highly purified cannabidiol for epilepsy treatment: A systematic review of epileptic conditions beyond Dravet syndrome and Lennox-Gastaut syndrome. CNS Drugs 2021;35:265–81. doi:https://doi.org/10.1007/s40263-021-00807-y
8.	Moisset X, Bouhassira D, Avez Couturier J, *et al.* Pharmacological and non-pharmacological treatments for neuropathic pain: Systematic review and French recommendations. Rev Neurol (Paris) 2020;176:325–52. doi:https://doi.org/10.1016/j.neurol.2020.01.361
9.	Pringsheim T, Doja A, Gorman D, *et al.* Canadian guidelines for the evidence-based treatment of tic disorders: Pharmacotherapy. Can J Psychiatry 2012;57:133–43. doi:https://doi.org/10.1177/070674371205700302
10.	Saulino PA, Greenwald BD, Gordon DJ. The changing landscape of the use of medical marijuana after traumatic brain injury: a narrative review. Brain Inj 2021;35:1510–20. doi:https://doi.org/10.1080/02699052.2021.1978548
11.	Spanagel R, Bilbao A. Approved cannabinoids for medical purposes - Comparative systematic review and meta-analysis for sleep and appetite. Neuropharmacology 2021;196:108680. doi:https://doi.org/10.1016/j.neuropharm.2021.108680
12.	Stockings E, Zagic D, Campbell G, *et al.* Evidence for cannabis and cannabinoids for epilepsy: a systematic review of controlled and observational evidence. J Neurol Neurosurg Psychiatry 2018;89:741–53. doi:https://doi.org/10.1136/jnnp-2017-317168

13.	Tramèr MR, Carroll D, Campbell FA, *et al.* Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. BMJ 2001;323:16–21. doi:https://doi.org/10.1136/bmj.323.7303.16
14.	Watanabe AH, Navaravong L, Sirilak T, *et al.* A systematic review and meta-analysis of randomized controlled trials of cardiovascular toxicity of medical cannabinoids. J Am Pharm Assoc (2003) 2021;61:e1–13. doi:https://doi.org/10.1016/j.japh.2021.03.013
15.	Zhang L, Wang J, Wang C. Efficacy and safety of antiseizure medication for Lennox-Gastaut syndrome: a systematic review and network meta-analysis. Dev Med Child Neurol 2022;64:305–13. doi:https://doi.org/10.1111/dmcn.15072

Appendix Table 31 Citations excluded from full-text screening stage 3a on date

Number	Full-text screening stage 3a: Citations excluded on date (n=1)
1.	Martín-Sánchez E, Furukawa TA, Taylor J, *et al.* Systematic review and meta-analysis of cannabis treatment for chronic pain. Pain Med 2009;10:1353–68. doi:https://doi.org/10.1111/j.1526-4637.2009.00703.x

Appendix Table 32 Citations excluded from full-text screening stage 3a on outcome

Number	Full-text screening stage 3a: Citations excluded on outcome (n=1)
1.	Jahn F, Wörmann B, Brandt J, *et al.* The prevention and treatment of nausea and vomiting during tumor therapy. Dtsch Arztebl Int 2022;119:382–92. doi:https://doi.org/10.3238/arztebl.m2022.0093

Citations excluded from the primary search results at the full-text screening stage (3b)

(Total citations excluded at this stage: n=66)

Appendix Table 33 Citations excluded from full-text screening stage 3b on review not cannabis-specific

Number	Full-text screening stage 3b: Citations excluded on review not cannabis-specific (n=20)
1.	Advani SM, Advani PG, VonVille HM, *et al.* Pharmacological management of cachexia in adult cancer patients: a systematic review of clinical trials. BMC Cancer 2018;18:1174. doi:10.1186/s12885-018-5080-4
2.	Amaniti A, Sardeli C, Fyntanidou V, *et al.* Pharmacologic and non-pharmacologic interventions for HIV-neuropathy pain. A systematic review and a meta-analysis. Medicina (Kaunas) 2019;55:762. doi:https://doi.org/10.3390/medicina55120762
3.	Bacaro V, Buonanno C, Mancini F, *et al.* Efficacy of interventions for improving health in patients with multiple sclerosis on insomnia symptoms and sleep quality: A systematic review of randomized controlled trials. J Behav Cogn Ther 2021;31:137–45. doi:https://doi.org/10.1016/j.jbct.2020.12.001
4.	Baldinger R, Katzberg HD, Weber M. Treatment for cramps in amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database Syst Rev 2012;:CD004157. doi:https://doi.org/10.1002/14651858.CD004157.pub2

5.	Braud A, Boucher Y. Taste disorder's management: a systematic review. Clin Oral Investig 2020;24:1889–908. doi:https://doi.org/10.1007/s00784-020-03299-0
6.	Busse JW, Wang L, Kamaleldin M, *et al.* Opioids for chronic noncancer pain: A systematic review and meta-analysis. JAMA 2018;320:2448–60. doi:https://doi.org/10.1001/jama.2018.18472
7.	de Souza Nascimento S, DeSantana JM, Nampo FK, *et al.* Efficacy and safety of medicinal plants or related natural products for fibromyalgia: A systematic review. Efficacy and Safety of Medicinal Plants or Related Natural Products for Fibromyalgia: A Systematic Review 2013;2013:e149468. doi:https://doi.org/10.1155/2013/149468
8.	Ergul M, Nodehi Moghadam A, Soh R. The effectiveness of interventions targeting spasticity on functional clinical outcomes in patients with multiple sclerosis: a systematic review of clinical trials. Eur J Physiother 2022;24:21–9. doi:https://doi.org/10.1080/21679169.2020.1775888
9.	Finnerup NB, Attal N, Haroutounian S, *et al.* Pharmacotherapy for neuropathic pain in adults: A systematic review and meta-analysis. Lancet Neurol 2015;14:162–73. doi:https://doi.org/10.1016/S1474-4422(14)70251-0
10.	Kuspinar A, Rodriguez AM, Mayo NE. The effects of clinical interventions on health-related quality of life in multiple sclerosis: A meta-analysis. Mult Scler 2012;18:1686–704. doi:https://doi.org/10.1177/1352458512445201
11.	Langhorst J, Wulfert H, Lauche R, *et al.* Systematic review of complementary and alternative medicine treatments in inflammatory bowel diseases. J Crohns Colitis 2015;9:86–106. doi:https://doi.org/10.1093/ecco-jcc/jju007
12.	Ling H-Q, Chen Z-H, He L, *et al.* Comparative efficacy and safety of 11 drugs as therapies for adults with neuropathic pain after spinal cord injury: A Bayesian network analysis based on 20 randomized controlled trials. Front Neurol 2022;13:818522. doi:https://doi.org/10.3389/fneur.2022.818522
13.	McDonagh MS, Selph SS, Buckley DI, *et al.* Nonopioid pharmacologic treatments for chronic pain. Rockville (MD): Agency for Healthcare Research and Quality (US) 2020. https://effectivehealthcare.ahrq.gov/sites/default/files/related_files/nonopioid-chronic-pain.pdf
14.	Mena M, Dalbah L, Levi L, *et al.* Efficacy of topical interventions for temporomandibular disorders compared to placebo or control therapy: A systematic review with meta-analysis. J Dent Anesth Pain Med 2020;20:337–56. doi:https://doi.org/10.17245/jdapm.2020.20.6.337
15.	Merlin JS, Bulls HW, Vucovich LA, *et al.* Pharmacologic and non-pharmacologic treatments for chronic pain in individuals with HIV: A systematic review. AIDS Care 2016;28:1506–15. doi:https://doi.org/10.1080/09540121.2016.1191612
16.	Pourmohammadi A, Riahi R, Hosseini SM, *et al.* Pharmacological treatment of tremor in multiple sclerosis; a systematic review. Mult Scler Relat Disord 2022;60:103722. doi:https://doi.org/10.1016/j.msard.2022.103722
17.	Qureshi AR, Rana AQ, Malik SH, *et al.* Comprehensive examination of therapies for pain in Parkinson's disease: A systematic review and meta-analysis. Neuroepidemiology 2018;51:190–206. doi:https://doi.org/10.1159/000492221
18.	Richards BL, Whittle SL, Buchbinder R. Neuromodulators for pain management in rheumatoid arthritis. Cochrane Database Syst Rev 2012;:CD008921. doi:https://doi.org/10.1002/14651858.CD008921.pub2

19.	Snedecor SJ, Sudharshan L, Cappelleri JC, *et al.* Systematic review and comparison of pharmacologic therapies for neuropathic pain associated with spinal cord injury. J Pain Res 2013;6:539–47. doi:https://doi.org/10.2147/JPR.S45966
20.	Snedecor SJ, Sudharshan L, Cappelleri JC, *et al.* Systematic review and meta-analysis of pharmacological therapies for painful diabetic peripheral neuropathy. Pain Pract 2014;14:167–84. doi:https://doi.org/10.1111/papr.12054

Appendix Table 34 Citations excluded from full-text screening stage 3b on age

Number	Full-text screening stage 3b: Citations excluded on age (n=14)
1.	Amato L, Davoli M, Minozzi S, *et al.* Systematic reviews on therapeutic efficacy and safety of cannabis (including extracts and tinctures) for patients with multiple sclerosis, chronic neuropathic pain, dementia and Tourette syndrome, HIV/AIDS, and cancer receiving chemotherapy. Lazio, Italy: Department of Epidemiology, Lazio Regional Health Service 2016.
2.	Caputo MP, Rodriguez CS, Padhya TA, *et al.* Medical cannabis as adjunctive therapy for head and neck cancer patients. Cureus 2021;13:e18396. doi:https://doi.org/10.7759/cureus.18396
3.	Chow R, Valdez C, Chow N, *et al.* Oral cannabinoid for the prophylaxis of chemotherapy-induced nausea and vomiting-a systematic review and meta-analysis. Support Care Cancer 2020;28:2095–103. doi:https://doi.org/10.1007/s00520-019-05280-4
4.	Doeve BH, van de Meeberg MM, van Schaik FDM, *et al.* A systematic review with meta-analysis of the efficacy of cannabis and cannabinoids for inflammatory bowel disease: What can we learn from randomized and nonrandomized studies? J Clin Gastroenterol 2021;55:798–809. doi:https://doi.org/10.1097/MCG.0000000000001393
5.	Gloss D, Vickrey B. Cannabinoids for epilepsy. Cochrane Database Syst Rev 2014;:CD009270. doi:https://doi.org/10.1002/14651858.CD009270.pub3
6.	Grossman S, Tan H, Gadiwalla Y. Cannabis and orofacial pain: a systematic review. Br J Oral Maxillofac Surg 2022;60:e677–90. doi:https://doi.org/10.1016/j.bjoms.2021.06.005
7.	Johal H, Devji T, Chang Y, *et al.* Cannabinoids in chronic non-cancer pain: A systematic review and meta-analysis. Clin Med Insights Arthritis Musculoskelet Disord 2020;13:1179544120906461. doi:https://doi.org/10.1177/1179544120906461
8.	Lattanzi S, Brigo F, Trinka E, *et al.* Adjunctive cannabidiol in patients with Dravet syndrome: A systematic review and meta-analysis of efficacy and safety. CNS Drugs 2020;34:229–41. doi:https://doi.org/10.1007/s40263-020-00708-6
9.	Linde LD, Ogryzlo CM, Choles CM, *et al.* Efficacy of topical cannabinoids in the management of pain: a systematic review and meta-analysis of animal studies. Reg Anesth Pain Med 2022;47:183–91. doi:https://doi.org/10.1136/rapm-2021-102719
10.	Madden K, George A, van der Hoek NJ, *et al.* Cannabis for pain in orthopedics: a systematic review focusing on study methodology. Can J Surg 2019;62:369–80. doi:https://doi.org/10.1503/cjs.001018
11.	NICE Guideline Updates Team. Evidence review for chronic pain: Cannabis-based medicinal products: Evidence review B. London, UK: National Institute for Health and

	Care Excellence (NICE) 2019. https://www.nice.org.uk/guidance/ng144/evidence/b-chronic-pain-pdf-6963831759
12.	Rabgay K, Waranuch N, Chaiyakunapruk N, *et al.* The effects of cannabis, cannabinoids, and their administration routes on pain control efficacy and safety: A systematic review and network meta-analysis. J Am Pharm Assoc (2003) 2020;60:225-234.e6. doi:https://doi.org/10.1016/j.japh.2019.07.015
13.	Stockings E, Campbell G, Hall WD, *et al.* Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. Pain 2018;159:1932–54. doi:https://doi.org/10.1097/j.pain.0000000000001293
14.	Whiting PF, Wolff RF, Deshpande S, *et al.* Cannabinoids for medical use: A systematic review and meta-analysis. JAMA 2015;313:2456–73. doi:https://doi.org/10.1001/jama.2015.6358

Appendix Table 35 Citations excluded from full-text screening stage 3b on inadequate search strategy

Number	Full-text screening stage 3b: Citations excluded on search strategy (n=10)
1.	Aviram J, Samuelly-Leichtag G. Efficacy of cannabis-based medicines for pain management: A systematic review and meta-analysis of randomized controlled trials. Pain Physician 2017;20:E755–96.
2.	Bougea A, Koros C, Simitsi A-M, *et al.* Medical cannabis as an alternative therapeutics for Parkinsons' disease: Systematic review. Complement Ther Clin Pract 2020;39:101154. doi:https://doi.org/10.1016/j.ctcp.2020.101154
3.	Charernboon T, Lerthattasilp T, Supasitthumrong T. Effectiveness of cannabinoids for treatment of dementia: A systematic review of randomized controlled trials. Clin Gerontol 2021;44:16–24. doi:https://doi.org/10.1080/07317115.2020.1742832
4.	Deshpande A, Mailis-Gagnon A, Zoheiry N, *et al.* Efficacy and adverse effects of medical marijuana for chronic noncancer pain: Systematic review of randomized controlled trials. Can Fam Physician 2015;61:e372–81.
5.	Dykukha I, Malessa R, Essner U, *et al.* Nabiximols in chronic neuropathic pain: A meta-analysis of randomized placebo-controlled trials. Pain Med 2021;22:861–74. doi:https://doi.org/10.1093/pm/pnab050
6.	Gates PJ, Albertella L, Copeland J. The effects of cannabinoid administration on sleep: a systematic review of human studies. Sleep Med Rev 2014;18:477–87. doi:https://doi.org/10.1016/j.smrv.2014.02.005
7.	Senderovich H, Wagman H, Zhang D, *et al.* The effectiveness of cannabis and cannabis derivatives in treating lower back pain in the aged population: A systematic review. Gerontology 2022;68:612–24. doi:https://doi.org/10.1159/000518269
8.	Tallant J. Cannabinoids for the treatment of cancer-related pain: a systematic review. Cancer Nurs Practice 2020;22:37–42. doi:https://doi.org/10.7748/cnp.2020.e1669
9.	Wang J, Wang Y, Tong M, *et al.* Medical cannabinoids for cancer cachexia: A systematic review and meta-analysis. Biomed Res Int 2019;2019:2864384. doi:https://doi.org/10.1155/2019/2864384
10.	Wong SSC, Chan WS, Cheung CW. Analgesic effects of cannabinoids for chronic non-cancer pain: A systematic review and meta-analysis with meta-regression. J Neuroimmune Pharmacol 2020;15:801–29. doi:https://doi.org/10.1007/s11481-020-09905-y

Appendix Table 36 Citations excluded from full-text screening stage 3b on age and review not cannabis-specific

Number	Full-text screening stage 3b: Citations excluded on age and review not cannabis-specific (n=1)
1.	Mehta S, McIntyre A, Janzen S, *et al.* Systematic review of pharmacologic treatments of pain after spinal cord injury: An update. Arch Phys Med Rehabil 2016;97:1381-1391.e1. doi:https://doi.org/10.1016/j.apmr.2015.12.023

Appendix Table 37 Citations excluded from full-text screening stage 3b on age and inadequate search strategy

Number	Full-text screening stage 3b: Citations excluded on age and inadequate search strategy (n=11)
1.	Ahmed S, Roth RM, Stanciu CN, *et al.* The impact of THC and CBD in schizophrenia: A systematic review. Front Psychiatry 2021;12:694394. doi:https://doi.org/10.3389/fpsyt.2021.694394
2.	Bartoli F, Riboldi I, Bachi B, *et al.* Efficacy of cannabidiol for Δ-9-tetrahydrocannabinol-Induced psychotic symptoms, schizophrenia, and cannabis Use disorders: A narrative review. J Clin Med 2021;10:1303. doi:https://doi.org/10.3390/jcm10061303
3.	Chesney E, Oliver D, Green A, *et al.* Adverse effects of cannabidiol: a systematic review and meta-analysis of randomized clinical trials. Neuropsychopharmacol 2020;45:1799–806. doi:https://doi.org/10.1038/s41386-020-0667-2
4.	Gazendam A, Nucci N, Gouveia K, *et al.* Cannabinoids in the management of acute pain: A systematic review and meta-analysis. Cannabis Cannabinoid Res 2020;5:290–7. doi:https://doi.org/10.1089/can.2019.0079
5.	Goldenberg M, Reid MW, IsHak WW, *et al.* The impact of cannabis and cannabinoids for medical conditions on health-related quality of life: A systematic review and meta-analysis. Drug Alcohol Depend 2017;174:80–90. doi:https://doi.org/10.1016/j.drugalcdep.2016.12.030
6.	Lim K, See YM, Lee J. A systematic review of the effectiveness of medical cannabis for psychiatric, movement and neurodegenerative disorders. Clin Psychopharmacol Neurosci 2017;15:301–12. doi:https://doi.org/10.9758/cpn.2017.15.4.301
7.	Lynch ME, Ware MA. Cannabinoids for the treatment of chronic non-cancer pain: an updated systematic review of randomized controlled trials. J Neuroimmune Pharmacol 2015;10:293–301. doi:https://doi.org/10.1007/s11481-015-9600-6
8.	Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. Br J Clin Pharmacol 2011;72:735–44. doi:https://doi.org/10.1111/j.1365-2125.2011.03970.x
9.	Reis R de C, Almeida KJ, Lopes L da S, *et al.* Efficacy and adverse event profile of cannabidiol and medicinal cannabis for treatment-resistant epilepsy: Systematic review and meta-analysis. Epilepsy Behav 2020;102. doi:https://doi.org/10.1016/j.yebeh.2019.106635
10.	Serafimovska T, Darkovska-Serafimovska M, Stefkov G, *et al.* Pharmacotherapeutic considerations for use of cannabinoids to relieve symptoms of nausea and vomiting induced by chemotherapy. Folia Med (Plovdiv) 2020;62:668–78. doi:https://doi.org/10.3897/folmed.62.e51478

11.	Stevens AJ, Higgins MD. A systematic review of the analgesic efficacy of cannabinoid medications in the management of acute pain. Acta Anaesthesiol Scand 2017;61:268–80. doi:https://doi.org/10.1111/aas.12851

Appendix Table 38 Citations excluded from full-text screening stage 3b on inadequate search strategy and not a CDB-specific review

Number	Full-text screening stage 3b: Citations excluded on inadequate search strategy and review not cannabis-specific (n=3)
1.	Behm K, Morgan P. The effect of symptom-controlling medication on gait outcomes in people with multiple sclerosis: a systematic review. Disability and Rehabilitation 2018;40:1733–44. doi:10.1080/09638288.2017.1309581
2.	Canavan C, Inoue T, McMahon S, *et al.* The efficacy, adverse events, and withdrawal rates of the pharmacological management of chronic spinal cord injury pain: A systematic review and meta-analysis. Pain Med 2022;23:375–95. doi:https://doi.org/10.1093/pm/pnab140
3.	Hanson LC, Ersek M, Gilliam R, *et al.* Oral feeding options for people with dementia: a systematic review. J Am Geriatr Soc 2011;59:463–72. doi:https://doi.org/10.1111/j.1532-5415.2011.03320.x

Appendix Table 39 Citations excluded from full-text screening stage 3b on age, inadequate search strategy and review not cannabis-specific

Number	Full-text screening stage 3b: Citations excluded on age, inadequate search strategy and review not cannabis-specific (n=6)
1.	Devi N, Madaan P, Ameen R, *et al.* Short-term and long-term efficacy and safety of antiseizure medications in Lennox Gastaut syndrome: A network meta-analysis. *Seizure* 2022;99:164–75. doi:https://doi.org/10.1016/j.seizure.2022.04.004
2.	Ebrahimi F, Farzaei MH, Bahramsoltani R, *et al.* Plant-derived medicines for neuropathies: a comprehensive review of clinical evidence. *Rev Neurosci* 2019;30:671–84. doi:https://doi.org/10.1515/revneuro-2018-0097
3.	Farzaei MH, Shahpiri Z, Bahramsoltani R, *et al.* Efficacy and tolerability of phytomedicines in multiple sclerosis patients: A review. *CNS Drugs* 2017;31:867–89. doi:https://doi.org/10.1007/s40263-017-0466-4
4.	Gouveia DN, Guimarães AG, Santos WB da R, *et al.* Natural products as a perspective for cancer pain management: A systematic review. *Phytomedicine* 2019;58:152766. doi:https://doi.org/10.1016/j.phymed.2018.11.026
5.	Phillips TJC, Cherry CL, Cox S, *et al.* Pharmacological treatment of painful hiv-associated sensory neuropathy: A systematic review and meta-analysis of randomised controlled trials. *PLoS ONE* 2010;5:e14433. doi:https://doi.org/10.1371/journal.pone.0014433
6.	Pinto JV, Saraf G, Frysch C, *et al.* Cannabidiol as a treatment for mood disorders: A systematic review: Le cannabidiol comme traitement des troubles de l'humeur: une revue systématique. *Can J Psychiatry* 2020;65:213–27. doi:https://doi.org/10.1177/0706743719895195

Appendix Table 40 Citations excluded from full-text screening stage 3b on intervention

Number	Full-text screening stage 3b: Citations excluded on intervention (n=1)
1.	Imtiaz S, Roerecke M, Kurdyak P, *et al.* Brief interventions for cannabis use in healthcare settings: Systematic review and meta-analyses of randomized trials. J Addict Med 2020;14:78–88. doi:https://doi.org/10.1097/ADM.0000000000000527

Citations excluded from the primary search results at the full-text screening stage (3c)

(Total citations excluded at this stage: n=13)

Appendix Table 41 Citations excluded from full-text screening stage 3c on intervention

Number	Exclude on intervention (n=1)
1.	Thanabalasingam SJ, Ranjith B, Jackson R, *et al.* Cannabis and its derivatives for the use of motor symptoms in Parkinson's disease: a systematic review and meta-analysis. Ther Adv Neurol Disord 2021;14:17562864211018560. doi:https://doi.org/10.1177/17562864211018561

Appendix Table 42 Citations excluded from full-text screening stage 3c on review not cannabis-specific

Number	Exclude on review not cannabis-specific (n=2)
1.	Marshall K, Gowing L, Ali R, *et al.* Pharmacotherapies for cannabis dependence. Cochrane Database Syst Rev 2014;12:CD008940. doi:10.1002/14651858.CD008940.pub2
2.	McDonagh MS, Wagner J, Ahmed AY, *et al.* Living systematic review on cannabis and other plant-based treatments for chronic pain. Comparative effectiveness review no. 250. Agency for Healthcare Research and Quality (US) 2021. doi:10.23970/AHRQEPCCER250

Appendix Table 43 Citations excluded from full-text screening stage 3c on methods: review contains unextractable studies

Number	Exclude on methods: review contains unextractable studies (n=6)
1.	Bahji A, Meyyappan AC, Hawken ER. Cannabinoids for the neuropsychiatric symptoms of dementia: A systematic review and meta-analysis. Can J Psychiatry 2020;65:365–76. doi:https://doi.org/10.1177/0706743719892717
2.	Paulsingh CN, Mohamed MB, Elhaj MS, *et al.* The efficacy of marijuana use for pain relief in adults with sickle cell disease: A systematic review. Cureus 2022;14:e24962. doi:https://doi.org/10.7759/cureus.24962
3.	Ruthirakuhan M, Lanctôt KL, Vieira D, *et al.* Natural and synthetic cannabinoids for agitation and aggression in Alzheimer's disease: A meta-analysis. J Clin Psychiatry 2019;80:18r12617. doi:https://doi.org/10.4088/JCP.18r12617
4.	Sankaranarayanan A, Wilding H, Neill E, *et al.* A critical systematic review of evidence for cannabinoids in the treatment of schizophrenia. Psychiatric Annals 2018;48:214–23. doi:https://doi.org/10.3928/00485713-20180409-01
5.	Vivace BJ, Sanders AN, Glassman SD, *et al.* Cannabinoids and orthopedic surgery: a systematic review of therapeutic studies. J Orthop Surg Res 2021;16:57. doi:https://doi.org/10.1186/s13018-021-02205-y
6.	Wang L, Hong PJ, May C, *et al.* Medical cannabis or cannabinoids for chronic non-cancer and cancer related pain: A systematic review and meta-analysis of

randomised clinical trials. BMJ 2021;374:n1034. doi:https://doi.org/10.1136/bmj.n1034

Appendix Table 44 Citations excluded from full-text screening stage 3c on methods: inadequate search strategy

Number	Exclude on methods: inadequate search strategy (n=3)
1.	Abo Youssef N, Schneider MP, Mordasini L, *et al.* Cannabinoids for treating neurogenic lower urinary tract dysfunction in patients with multiple sclerosis: A systematic review and meta-analysis. BJU International 2017;119:515–21. doi:https://doi.org/10.1111/bju.13759
2.	Ayers C, Harrod C, Durbin S, *et al.* Cannabis for the management of symptoms of PTSD - update 1: A living systematic review. The Systematically Testing the Evidence on Marijuana Project. The Systematically Testing the Evidence on Marijuana Project 2021. https://doi.org/10.13140/rg.2.2.26267.75047
3.	Tateo S. State of the evidence: Cannabinoids and cancer pain-A systematic review. J Am Assoc Nurse Pract 2017;29:94–103. doi:https://doi.org/10.1002/2327-6924.12422

Appendix Table 45 Citations excluded from full-text screening stage 3c on study design

Number	Exclude on study design (n=1)
1.	Kafil TS, Nguyen TM, MacDonald JK, *et al.* Cannabis for the treatment of crohn's disease and ulcerative colitis: Evidence from cochrane reviews. Inflamm Bowel Dis 2020;26:502–9. doi:https://doi.org/10.1093/ibd/izz233

Citations excluded from the supplementary search results at the full-text screening stage (6a)

(Total citations excluded at this stage n=46)

Appendix Table 46 Citations excluded from full-text screening stage 6a on age

Number	Full-text supplemental search screening stage 6a: Citations excluded on age (n=9)
1.	Vinci A, Ingravalle F, Bardhi D, *et al.* Cannabinoid therapeutic effects in inflammatory bowel diseases: a systematic review and meta-analysis of randomized controlled trials. Biomedicines 2022;10:2439. doi:https://doi.org/10.3390/biomedicines10102439
2.	Bilbao A, Spanagel R. Medical cannabinoids: a pharmacology-based systematic review and meta-analysis for all relevant medical indications. BMC Med 2022;20:259. doi:https://doi.org/10.1186/s12916-022-02459-1
3.	Grossman S, Tan H, Gadiwalla Y. Cannabis and orofacial pain: a systematic review. Br J Oral Maxillofac Surg 2022;60:e677–90. doi:https://doi.org/10.1016/j.bjoms.2021.06.005
4.	Pinto JS, Martel F. Effects of cannabidiol on appetite and body weight: a systematic review. Clin Drug Investig 2022;42:909–19. doi:https://doi.org/10.1007/s40261-022-01205-y
5.	Campos DA, Mendivil EJ, Romano M, *et al.* A systematic review of medical cannabinoids dosing in human. Clin Ther 2022;44:e39–58. doi:https://doi.org/10.1016/j.clinthera.2022.10.003

6.	Wu J, Zhang L, Zhou X, *et al.* Efficacy and safety of adjunctive antiseizure medications for dravet syndrome: A systematic review and network meta-analysis. Front Pharmacol 2022;13:980937. doi:https://doi.org/10.3389/fphar.2022.980937
7.	Doppen M, Kung S, Maijers I, *et al.* Cannabis in palliative care: a systematic review of current evidence. J Pain Symptom Manage 2022;64:e260–84. doi:https://doi.org/10.1016/j.jpainsymman.2022.06.002
8.	Souza JDR, Pacheco JC, Rossi GN, *et al.* Adverse effects of oral cannabidiol: an updated systematic review of randomized controlled trials (2020–2022). Pharmaceutics 2022;14:2598. doi:https://doi.org/10.3390/pharmaceutics14122598
9.	Linley W, Schwenkglenks M, Hawkins N, *et al.* Comparative effectiveness of fenfluramine versus cannabidiol in their licensed indications for the treatment of seizures in Dravet Syndrome: a systematic review and network meta-analysis. 2022. doi:https://doi.org/10.1101/2022.07.01.22277155

Appendix Table 47 Citations excluded from full-text screening stage 6a on date

Number	Full-text supplemental search screening stage 6a: Citations excluded on date
1.	Krishnan S, Cairns R, Howard R. Cannabinoids for the treatment of dementia. Cochrane Database Syst Rev 2009;2009:CD007204. doi:https://doi.org/10.1002/14651858.CD007204.pub2

Appendix Table 48 Citations excluded from full-text screening stage 6a on existing include

Number	Full-text supplemental search screening stage 6a: Citations excluded on existing include
1.	AminiLari Mahmood. Medicinal cannabis, chronic pain and sleep: efficacy and safety, patients' perspectives, and patterns of use. 2021.https://macsphere.mcmaster.ca/handle/11375/27001

Appendix Table 49 Citations excluded from full-text screening stage 6a on inadequate risk of bias assessment

Number	Full-text supplemental search screening stage 6a: Citations excluded on inadequate risk of bias assessment
1.	Andrzejewski K, Barbano R, Mink J. Cannabinoids in the treatment of movement disorders: A systematic review of case series and clinical trials. Basal Ganglia 2016;6:173–81. doi:https://doi.org/10.1016/j.baga.2016.06.001
2.	Francisco AP, Lethbridge G, Patterson B, *et al.* Cannabis use in Attention – Deficit/Hyperactivity Disorder (ADHD): A scoping review. J Psychiatr Res 2023;157:239–56. doi:https://doi.org/10.1016/j.jpsychires.2022.11.029
3.	Nielsen S, Sabioni P, Trigo JM, *et al.* Opioid-sparing effect of cannabinoids: a systematic review and meta-analysis. Neuropsychopharmacol 2017;42:1752–65. doi:https://doi.org/10.1038/npp.2017.51
4.	Peng M, Khaiser M, Lam M, *et al.* Medical marijuana, cancer anorexia and cachexia. In: Cannabis: Medical Aspects. Nova Science Publishers, Inc. 2017. 113–28.https://novapublishers.com/shop/cannabis-medical-aspects/

Appendix Table 50 Citations excluded from full-text screening stage 6a on inadequate search

Number	Full-text supplemental search screening stage 6a: Citations excluded on inadequate search (n=5)
1.	Paulus V, Billieux J, Benyamina A, *et al.* Cannabidiol in the context of substance use disorder treatment: A systematic review. Addict Behav 2022;132:107360. doi:https://doi.org/10.1016/j.addbeh.2022.107360
2.	Holst M, Nowak D, Hoch E. Cannabidiol as a treatment for Covid-19 symptoms? A critical review. Cannabis Cannabinoid Res 2022;13:866235. doi:https://doi.org/10.1089/can.2021.0135
3.	Tsai SHL, Lin C-R, Shao S-C, *et al.* Cannabinoid use for pain reduction in spinal cord injuries: a meta-analysis of randomized controlled trials. Front Pharmacol 2022;13:866235. doi:https://doi.org/10.3389/fphar.2022.866235
4.	Oikonomou P, Jost WH. Randomized controlled trials on the use of cannabis-based medicines in movement disorders: a systematic review. J Neural Transm (Vienna) 2022;129:1247–56. doi:https://doi.org/10.1007/s00702-022-02529-x
5.	Alderman B, Hui D, Mukhopadhyay S, *et al.* Multinational Association of Supportive Care in Cancer (MASCC) expert opinion/consensus guidance on the use of cannabinoids for gastrointestinal symptoms in patients with cancer. Support Care Cancer 2022;31:39. doi:https://doi.org/10.1007/s00520-022-07480-x

Appendix Table 51 Citations excluded from full-text screening stage 6a on intervention

Number	Full-text supplemental search screening stage 6a: Citations excluded on intervention: general (n=2)
1.	Tourjman SV, Buck G, Jutras-Aswad D, *et al.* Canadian network for mood and anxiety treatments (canmat) task force report: a systematic review and recommendations of cannabis use in bipolar disorder and major depressive disorder. Can J Psychiatry 2022;:7067437221099769. doi:https://doi.org/10.1177/07067437221099769
2.	Caputo MP, Rodriguez CS, Padhya TA, *et al.* Medical cannabis as adjunctive therapy for head and neck cancer patients. Cureus 2021;13. doi:https://doi.org/10.7759/cureus.18396

Appendix Table 52 Citations excluded from full-text screening stage 6a on intervention (population)

Number	Full-text supplemental search screening stage 6a: Citations excluded on intervention: population (n=4)
1	Zhang S, Li M, Guo Z. Effect of cannabidiol on schizophrenia based on randomized controlled trials: A meta-analysis. Ann Med Psychol (Paris) 2022;180:630–8. doi:https://doi.org/10.1016/j.amp.2021.09.019
2	Scholfield CN, Waranuch N, Kongkaew C. Systematic review on transdermal/topical cannabidiol trials: a reconsidered way forward. Cannabis Cannabinoid Res Published Online First: 2022. doi:https://doi.org/10.1089/can.2021.0154
3	Tang Y, Tonkovich KL, Rudisill TM. The effectiveness and safety of cannabidiol in non-seizure-related indications: a systematic review of published randomized clinical trials. Pharmaceut Med 2022;36:353–85. doi:https://doi.org/10.1007/s40290-022-00446-8
4	Velzeboer R, Malas A, Boerkoel P, *et al.* Cannabis dosing and administration for sleep: a systematic review. Sleep 2022;45:zsac218. doi:https://doi.org/10.1093/sleep/zsac218

Appendix Table 53 Citations excluded from full-text screening stage 6a on review not cannabis-specific

Number	Full-text supplemental search screening stage 6a: Citations excluded on review not cannabis-specific (n=3)
1	Nielsen S, Gowing L, Sabioni P, *et al.* Pharmacotherapies for cannabis dependence. Cochrane Database Syst Rev 2019;1:CD008940. doi:https://doi.org/10.1002/14651858.CD008940.pub3
2	Bahji A, Meyyappan AC, Hawken ER, *et al.* Pharmacotherapies for cannabis use disorder: A systematic review and network meta-analysis. Int J Drug Policy 2021;97:103295. doi:https://doi.org/10.1016/j.drugpo.2021.103295
3	Skeie-Larsen M, Stave R, Grønli J, *et al.* The effects of pharmacological treatment of nightmares: a systematic literature review and meta-analysis of placebo-controlled, randomized clinical trials. Int J Environ Res Public Health 2023;20:777. doi:https://doi.org/10.3390/ijerph20010777

Appendix Table 54 Citations excluded from full-text screening stage 6a on outcome

Number	Full-text supplemental search screening stage 6a: Citations excluded on outcome (n=3)
1	Kwee CM, van Gerven JM, Bongaerts FL, *et al.* Cannabidiol in clinical and preclinical anxiety research. A systematic review into concentration–effect relations using the IB-de-risk tool. J Psychopharmacol 2022;36:1299–314. doi:10.1177/02698811221124792
2	Herzog S, Shanahan M, Grimison P, *et al.* Systematic Review of the Costs and Benefits of Prescribed Cannabis-Based Medicines for the Management of Chronic Illness: Lessons from Multiple Sclerosis. Pharmacoeconomics 2018;36:67–78. doi:10.1007/s40273-017-0565-6
3	Zeng L, Lytvyn L, Wang X, *et al.* Values and preferences towards medical cannabis among people living with chronic pain: a mixed-methods systematic review. BMJ Open 2021;11:e050831. doi:https://doi.org/10.1136/bmjopen-2021-050831

Appendix Table 55 Citations excluded from full-text screening stage 6a on study design

Number	Full-text supplemental search screening stage 6a: Citations excluded on study design (n=6)
1	Hoch E, Niemann D, von Keller R, *et al.* How effective and safe is medical cannabis as a treatment of mental disorders? A systematic review. Eur Arch Psychiatry Clin Neurosci 2019;269:87–105. doi:https://doi.org/10.1007/s00406-019-00984-4
2	Orsolini L, Chiappini S, Volpe U, *et al.* Use of medicinal cannabis and synthetic cannabinoids in post-traumatic stress disorder (PTSD): a systematic review. Medicina (Kaunas) 2019;55:525. doi:https://doi.org/10.3390/medicina55090525
3	Duda J, Reinert JP. Cannabidiol in refractory status epilepticus: A review of clinical experiences. Seizure 2022;103:115–9. doi:https://doi.org/10.1016/j.seizure.2022.11.006
4	Evans W, Durocher-Allen L, Daeninck P, *et al.* Cancer and the health effects of cannabis and cannabinoids: An update of the systematic review by the National Academies of Sciences, Engineering, and Medicine (2017) consensus study report.

	Program in Evidence-Based Care Evidence Summary No.: 23-2. Toronto, Ontario: Ontario Health (Cancer Care Ontario) 2020. https://www.cancercareontario.ca/en/file/55641/
5	Kansagara D, O'Neil M, Nugent S. Benefits and harms of cannabis in chronic pain or post-traumatic stress disorder: a systematic review. Washington D. C., United States: Department of Veterans Affairs (US) 2017. https://www.hsrd.research.va.gov/publications/esp/cannabis.pdf
6	Sherpa ML, Shrestha N, Ojinna BT, *et al.* Efficacy and safety of medical marijuana in migraine headache: a systematic review. Cureus 2022;14:e32622. doi:https://doi.org/10.7759/cureus.32622

Appendix Table 56 Citations excluded from full-text screening stage 6a on unavailable paper

Number	Full-text supplemental search screening stage 6a: Citations excluded on unavailable paper (n=1)
1	Gomes PMV. Insomnia in patients diagnosed with multiple sclerosis: the effect of medicinal cannabis - a systematic review. 2022.https://repositorio-aberto.up.pt/handle/10216/142145

Appendix Table 57 Citations excluded from full-text screening stage 6a on methods: review contains unextractable studies

Number	Full-text supplemental search screening stage 6a: Citations excluded on methods: review contains unextractable studies (n=7)
1	Longoria V, Parcel H, Toma B, *et al.* Neurological benefits, clinical challenges, and neuropathologic promise of medical marijuana: a systematic review of cannabinoid effects in multiple sclerosis and experimental models of demyelination. Biomedicines 2022;10:539. doi:https://doi.org/10.3390/biomedicines10030539
2	Zeraatkar D, Cooper MA, Agarwal A, *et al.* Long-term and serious harms of medical cannabis and cannabinoids for chronic pain: a systematic review of non-randomised studies. BMJ Open 2022;12:e054282. doi:https://doi.org/10.1136/bmjopen-2021-054282
3	Ranum RM, Whipple MO, Croghan I, *et al.* Use of cannabidiol in the management of insomnia: a systematic review. Cannabis Cannabinoid Res Published Online First: 2022. doi:https://doi.org/10.1089/can.2022.0122
4	Narayan AJ, Downey LA, Manning B, *et al.* Cannabinoid treatments for anxiety: A systematic review and consideration of the impact of sleep disturbance. Neurosci Biobehav Rev 2022;143:104941. doi:https://doi.org/10.1016/j.neubiorev.2022.104941
5	Okusanya BO, Asaolu IO, Ehiri JE, *et al.* Medical cannabis for the reduction of opioid dosage in the treatment of non-cancer chronic pain: a systematic review. Syst Rev 2020;9:167. doi:https://doi.org/10.1186/s13643-020-01425-3
6	Wieghorst A, Roessler KK, Hendricks O, *et al.* The effect of medical cannabis on cognitive functions: a systematic review. Syst Rev 2022;11:210. doi:https://doi.org/10.1186/s13643-022-02073-5
7	Jomy Jane. Harms associated with inhaled cannabis for management of chronic pain: a systematic review and meta-analysis of observational studies. 2022.https://macsphere.mcmaster.ca/handle/11375/27673

Citations excluded from the supplementary search results at the full-text screening stage (6b)

(Total citations excluded at this stage n=3)

Appendix Table 58 Citations excluded from full-text screening stage 6b on age

Number	Full-text supplemental search screening stage 6b: Citations excluded on age (n=1)
1	Doeve BH, van de Meeberg MM, van Schaik FDM, *et al.* A systematic review with meta-analysis of the efficacy of cannabis and cannabinoids for inflammatory bowel disease: what can we learn from randomized and nonrandomized studies? J Clin Gastroenterol 2021;55:798–809. doi:https://doi.org/10.1097/MCG.0000000000001393

Appendix Table 59 Citations excluded from full-text screening stage 6b on existing included citation

Number	Full-text supplemental search screening stage 6b: Citations excluded on existing included citation (n=1)
1	Quintero J-M, Pulido G, Giraldo L-F, *et al.* A systematic review on cannabinoids for neuropathic pain administered by routes other than oral or inhalation. Plants 2022;11:1357. doi:https://doi.org/10.3390/plants11101357

Appendix Table 60 Citations excluded from full-text screening stage 6b on study design

Number	Full-text supplemental search screening stage 6b: Citations excluded on study design (n=1)
1	Villanueva MRB, Joshaghani N, Villa N, *et al.* Efficacy, safety, and regulation of cannabidiol on chronic pain: a systematic review. Cureus 2022;14. doi:https://doi.org/10.7759/cureus.26913

Citations excluded from the supplementary search results at the full-text screening stage (6b)

(Total citations excluded at this stage n=1)

Appendix Table 61 Citations excluded from full-text screening stage 6c on methods: review contains unextractable studies

Number	Full-text supplemental search screening stage 6c: Citations excluded on methods: review contains unextractable studies
1	Dykukha I, Essner U, Schreiber H, *et al.* Effects of Sativex® on cognitive function in patients with multiple sclerosis: A systematic review and meta-analysis. Mult Scler Relat Disord 2022;68:104173. doi:https://doi.org/10.1016/j.msard.2022.104173

Appendix D HRB-adapted Joanna Briggs Institute data extraction form

Exclude paper if only one database was searched – fatal flaw

Exclude paper if no risk of bias assessment was completed for RCTs – fatal flaw

Please highlight any section in yellow if unclear/need to discuss with team member

Parameter	Extraction items
First author and year of publication	
Objectives **Report exact review question(s) and page number**	• **Study objectives:** • **Exact review question and page number:** • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** ➢ **Setting:** ➢ **Intervention:** ➢ **Comparison:** ➢ **Outcome:**
Participants (characteristics and numbers) The defining characteristics of the participants in studies included in the research syntheses/review should be detailed, for example this may include diagnostic criteria, age, or ethnicity.	**For whole sample and subgroups:** • **Number of participants:** • **Age:** • **Gender:** • **Details of clinical diagnosis/indications:**

Parameter	Extraction items
The total number of participants that inform the outcomes relevant to the umbrella review question from all studies included studies should be presented.	
Setting/context Details of the setting of interest such as acute care, primary health care, or the community or a geographical location should be included. For some umbrella reviews, particularly those that draw upon qualitative research syntheses, the context that underpins the review question will be important to clearly reveal to the reader and may include but is not limited to consideration of cultural factors such as geographic location and specific racial or gender based interests.	**Countries (alphabetic order):** **Setting (university, public or private clinic):** **Other relevant features of setting:**
Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** • **Dose and regimen:**

Parameter	Extraction items
Clear, succinct details of the interventions or phenomena of interest should be presented as described by systematic review author(s), including the type of intervention, the frequency, and/or intensity of the intervention. A statement of the phenomena of interest is also required where applicable.	• **Administration methods:** • **Comparator:** • **Treatment duration:** • **Timeframe for follow-up:**
Databases and sources searched The number of sources searched should be reported. Though this will have been considered during critical appraisal of the research synthesis, reporting to the reader of the review will allow rapid and easy comparison between differences across included reviews and also consideration of potential for publication bias in the event that no formal analysis has been conducted. Where possible the names	• **Number and names of databases:** • **Other sources:** • **Grey literature:** • **Reference chasing:** Yes/No • **Expert consultation:** Yes/No • **Dates:** • **Search limits:** • **Justifications for search limits:** • **Other searches:** • **Protocol prepared:** Yes/No • **If yes, published:** Yes/No, if yes, number and link: • **Search strategy/key words provided:**

Parameter	Extraction items
of databases and sources should be listed (i.e. if <5-10). The search range of each database should also be included.	• **Screening completed in duplicate:** Yes/No • **If yes, rate of agreement:** • **Extraction completed in duplicate:** Yes/No • **If Yes, rate of agreement:** • **Funding of review:** • **Conflicts of interest of review:** • **How conflicts of interest were managed:**
Date Range (years) of included studies The date range spanning from the earliest study that informs the included research synthesis to the latest should be reported. This is important information that allows for consideration of the currency of the evidence base not necessarily reflected in the year of publication of the research synthesis. If this is not readily identifiable in the table of study characteristics provided by the included synthesis, it should be discerned by scanning the date range	• **Exact years for included studies:**

Parameter	Extraction items
of publications through the results section of the included systematic review.	
Number of primary studies included in the systematic review Summary descriptive details of the included studies in the research synthesis should be reported. This includes the number of studies in the included research synthesis, the types of study designs included in the research synthesis, for example randomized controlled trials, prospective cohort study, phenomenology, ethnography etc., and also the country of origin of the included studies. The latter is important to allow the reader of the review to consider the external validity and generalizability of the results presented.	• **Number of studies:** • **Number of studies by study design:** • **Study years:** • **Funding of included studies:** • **Conflicts of interest of included studies:**
Types of studies included	**Planned study designs to be included:**

Parameter	Extraction items
	Reasons for including only RCTs/prospective cohort studies: **List of excluded studies at full text and reasons for exclusion:**
Appraisal instruments used The instrument or tool used to assess risk of bias, rigour or study quality should be reported along with some summary estimate of the quality of primary studies in the included research synthesis. For example, for umbrella reviews that use the Jadad Scale, a mean score for quality may be reported whereas for checklist appraisals, reporting of cut-off score or any ranking of quality should be reported. An example of the latter would be exclusion of studies that score <3/10, and inclusion of four moderate quality studies (4-6/10) and two high quality studies (7-10/10).	**Full name of tools used:** **<u>For RCTs, record Yes/No for appraisal instrument assessment of:</u>** • **Concealment of allocation:** • **Blinding of assessors:** • **Sequence allocation (individual vs group randomisation):** • **Selective reporting:** **<u>For prospective cohort studies:</u>** • **Confounding:** • **Selection bias:** • **Exposure and outcomes:** • **Selective reporting:**
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The authors did not provide an overall assessment of risk of bias for each trial. However, HRB notes that according to Cochrane's Collaboration tool, and graphical information

Parameter	Extraction items

	provided in the paper, the included trials appeared to have a high risk of bias (n=X), unclear risk of bias (n=x) and low risk of bias (n=x)
	• **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:**
	  ○ Overall: Low risk randomisation (); low risk outcome ascertainment ()
	  ○ Example 1 Pain intensity: Low risk randomisation (); low risk outcome ascertainment ()
	  ○ Example 2 Sleep: Low risk randomisation (); low risk outcome ascertainment ()
	• **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:**
	• **Graphical or statistical test for publication bias:**
	• **Authors' comments likelihood and magnitude of publication bias:**
	• **Authors' comment on how publication bias was dealt with:**
	• **Only low ROB RCTs included in review:** Yes/No
	• **Only low ROB RCTs included in meta-analysis:** Yes/No
	• **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:**

Method of analysis The type of research synthesis as stated by the authors of the included review should be detailed. The method of analysis or synthesis used by the included research synthesis	• **Description of method of analysis as per authors:** • **Justification for narrative synthesis or meta-analysis:** • **Justification for combining data in meta-analysis:**

<table>
<tr><th>Parameter</th><th>Extraction items</th></tr>
<tr><td>should be reported. For example, this may include narrative synthesis, vote counting, random effects meta-analysis, fixed effect meta-analysis, network meta-analysis, thematic synthesis, meta- aggregative synthesis, or meta-ethnography.</td><td></td></tr>
<tr><td>Outcome assessed
Included here should be the outcomes of interest to the umbrella review question reported on by the research synthesis, i.e. the names or labels of the outcomes (see below for presentation of results).</td><td>List of outcomes assessed and intended time frames:
Primary outcomes:
Secondary outcomes:
Intended timeframes:
Actual timeframes:</td></tr>
<tr><td>Results/findings
The relevant findings or results presented by the included research syntheses must be extracted. For quantitative reviews, this will ideally be an effect estimate with 95% Cis or measure from a presented meta-analysis. Measures of heterogeneity</td><td>Findings by outcome:
GRADE by outcome:
<table><tr><th>Outcome</th><th>Measure (no. studies)</th><th>GRADE</th></tr><tr><td></td><td></td><td></td></tr><tr><td></td><td></td><td></td></tr><tr><td></td><td></td><td></td></tr><tr><td></td><td></td><td></td></tr></table></td></tr>
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<tr><th>Parameter</th><th>Extraction items</th></tr>
<tr><td>should also be extracted where applicable. In the absence of this a statement indicating the key result relevant to an outcome may be inserted in the required field. For qualitative syntheses, the key synthesized finding should be extracted.</td><td>Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):
<table>
<tr><th>Outcome</th><th>No. studies (No. participants)</th><th>Summary estimate</th><th>P-value</th><th>I^2 (%)</th><th>Direction of effect</th></tr>
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Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:
Appropriate weighted technique used, adjusted for heterogeneity where necessary:
Separate summaries reported for RCTs and prospective cohort studies when included in the same review: Yes/No

For prospective cohort studies:

Combined effect estimates adjusted for confounding, rather than combining raw data:

Justification for combining raw data provided, where adjusted effect estimates unavailable:</td></tr>
<tr><td>Significance/direction</td><td>See above if results listed by outcome:</td></tr>
<tr><td>Heterogeneity</td><td>
See above if I^2 available:
Authors’ comment on potential impact of heterogeneity on results and quality of evidence:
</td></tr>
</table>

Parameter	Extraction items
	• **Causes of heterogeneity investigated:**
Comments There should be provision to extract and present in the table of included study characteristics any relevant details or comments on the included research synthesis by the authors of the Umbrella Review. These comments may be relevant details regarding the included research synthesis, for example, the congruence between the review results and conclusions, and for highlighting any potential methodological differences between the individual included reviews.	

Appendix E HRB-adapted AMSTAR 2 instrument

Having piloted the AMSTAR 2 intstrument and used it in a previous HRB evidence review, we have made a number of adjustments in order to ensure that all reviewers are making decisions using the same parameters:

- The scoring of Items 1, 4, and 8 has been adjusted to provide consistent and more stringent judgement of the parameters being scrutinised.
- For items 1-4, 8, 9, and 11-16, we have added text to further explain and clarify what is required for each parameter.
- References to non-randomised studies of interventions have been replaced by references to prospective cohort studies, as these are the only non-randomised studies included in our eligibility criteria.

The adapted instrument appears in Appendix Table 62. The notation for the HRB adapted version of AMSTAR 2 is as follows:

- **An asterisk** * following a number denotes a critical factor.
- **Text in red** indicates an exclusion factor.
- **Text in purple** indicates agreed adaptions and interpretation

These factors will be included in the screening criteria. Any systematic review that searched only one bibliographic database or has not completed any quality assessment or risk of bias assessment will be excluded.

Appendix Table 62 HRB-adapted AMSTAR 2 instrument

Item		Scoring	Extract (incl pg no)
1*	**Did the research questions and inclusion criteria for the review include the components of PICO?** Four of the five components must be in the Introduction or Methods to be awarded Yes: For Yes to PICO: ☐ Population ☐ Intervention ☐ Comparator ☐ Outcome ☐ Timeframe for follow-up	☐ Yes ☐ No	

2*	**Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? The protocol must be accessible to check that the parameters below are covered.**	☐ Yes ☐ Partial Yes ☐ No
	For Partial Yes: The protocol must be reported as prepared and accessible The authors state that they had a written protocol or guide that included ALL the following: ☐review question(s) ☐a search strategy ☐inclusion/exclusion criteria ☐a risk of bias assessment For 'full' Yes: Protocol must be registered and accessible As for partial yes, plus the protocol should be registered and should also have specified: ☐a meta-analysis/synthesis plan, if appropriate, and ☐a plan for investigating causes of heterogeneity ☐justification for any deviations from the protocol	
3	**Did the review authors explain their selection of the study designs for inclusion in the review?**	☐ Yes ☐ No
	Authors must have justified their rationale for selecting the study design to be awarded Yes If study design is provided a-priori but without an explanation, score No For Yes, the review should satisfy ONE of the following: ☐Explanation for including only RCTs ☐OR Explanation for including only prospective cohort studies	

	☐OR Explanation for including both RCTs and prospective cohort studies	
4*	**Did the review authors use a comprehensive literature search strategy?**	☐Yes ☐Partial Yes ☐No
	For Partial Yes (all of the following): ☐ searched at least two databases (relevant to research question) (Exclude if only one database was searched – fatal flaw) ☐ provided key word and/or search strategy ☐ justified publication restrictions (e.g., language and/or duration of search) For 'full' Yes (two or more of the following): ☐ searched the reference lists/bibliographies of included studies ☐ searched trial/study registries ☐ where relevant, searched for grey literature ☐ conducted search within 24 months of completion of the review ☐ included/consulted experts in the field	
5	**Did the review authors perform study selection in duplicate?**	☐ Yes ☐ No
	For Yes, either ONE of the following: ☐ at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include ☐ OR two reviewers selected a sample of eligible studies AND achieved good agreement (at least 80 per cent), with the remainder selected by one reviewer	
6	**Did the review authors perform data extraction in duplicate?**	☐ Yes ☐ No

	For Yes, either ONE of the following: ☐ at least two reviewers achieved consensus on which data to extract from included studies ☐ OR two reviewers extracted data from a sample of eligible studies AND achieved good agreement (at least 80 per cent), with the remainder extracted by one reviewer	
7	**Did the review authors provide a list of excluded studies and justify the exclusions?**	☐ Yes ☐ Partial Yes ☐ No
	For Partial Yes: ☐ provided a list of all potentially relevant studies that were read in full text form but excluded from the review For 'full' Yes, must also have: ☐ justified the exclusion from the review of each potentially relevant study	
8	**Did the review authors describe the included studies in adequate detail?**	☐ Yes ☐ Partial Yes ☐ No
	For Partial Yes (ALL the following): ☐ adequately described populations, including condition/clinical indication, age, gender where relevant ☐ adequately described interventions, including dosing regimen, cannabinoid profile, administration route ☐ described comparators ☐ described outcomes ☐ described research designs For 'full' Yes, should also have ALL the following: ☐ described study's setting ☐ timeframe for follow-up	

	(Removed points on detailed description due to overlap with criteria above)	
9*	**Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?**	**Randomised controlled trials or clinical trials:** ☐ Yes ☐ Partial Yes ☐ No ☐ Includes only prospective cohort studies **Non-randomised prospective cohort studies** ☐ Yes ☐ Partial Yes ☐ No ☐ Includes only randomised controlled trials / clinical trials
	Authors must complete quality or risk of bias assessment on primary studies using the correct instrument for the included study design (risk of bias assessment for RCTs and purposely designed tool for prospective cohort studies) (Exclude if absent – fatal flaw) Did the authors assess the relevant points (see below)? **Randomised controlled trials or clinical trials:** For Partial Yes, must have assessed RoB from ☐ unconcealed allocation (randomization and blinding combined when allocating the intervention), AND ☐ lack of blinding assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality or admission to hospital)	

For 'full' Yes, must have assessed RoB from:

☐ allocation sequence that was not truly random (individual randomisation versus group randomization), AND

☐ selection of the reported result from among multiple measurements or analyses of a specified outcome, known as selective reporting (using only the outcomes or measurements that provide the researchers with their desired answer and ignoring other outcomes that may contradict the desired findings)

Non-randomised epidemiological studies:

For Partial Yes, must have assessed RoB:

☐ from confounding, AND

☐ from selection bias

For Yes, must also have assessed RoB:

☐ methods used to ascertain exposures and outcomes, AND

☐ selection of the reported result from among multiple measurements or analyses of a specified outcome, known as selective reporting (using only the outcomes or measurements that provide the researchers with their desired answer and ignoring other outcomes that may contradict the desired findings)

10	**Did the review authors report on the sources of funding for the studies included in the review?**	☐ Yes ☐ No

For Yes,

☐ Must have reported on the sources of funding for individual studies included in the review

	(Note: Reporting that the reviewers looked for this information, but it was not reported by study authors also qualifies)	
11*	**If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?** **Randomised controlled trials or randomised clinical trials:** For Yes: ☐ The authors justified combining the data in a meta-analysis ☐ AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present ☐ AND investigated the causes of any heterogeneity conducted If heterogeneity present, appropriate investigations may include: completed feasibility analysis to decide what studies to include (PICO for clinical heterogeneity) and what type of meta-analysis to use (pairwise [2 arm trials and two competing interventions] versus network [three or more arm trials and more than two competing interventions]), used a random effects model if statistical heterogeneity is greater than an pre-agreed level (25%, 50% or 75%), estimated statistical heterogeneity (Q or I^2 test), determined influence of highly weighted studies (any one study influencing the outcome), high risk or unclear risk of bias studies (removed from analysis), or studies with different populations, comparators and intervention formats through sensitivity or sub-group analysis.	☐ Yes ☐ No ☐ No meta-analysis

Observational epidemiological studies prospective longitudinal studies:

For Yes:

- ☐ The authors justified combining the data in a meta-analysis
- ☐ AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present
- ☐ AND they statistically combined effect estimates from prospective cohort studies that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available
- ☐ AND they reported separate summary effect estimates for RCTs and prospective cohort studies separately when both were included in the review

If heterogeneity present, appropriate investigations may include: completed feasibility analysis to decide what studies to include (PICO for clinical heterogeneity) and used pairwise meta-analysis, used confounding adjusted risk or odds ratios, used a random effects model if statistical heterogeneity is greater than a pre-agreed level (25%, 50% or 75%), estimated statistical heterogeneity (Q or I^2 test), determined influence of highly weighted studies (any one study influencing the outcome), determined influence if low quality studies removed from analysis, determined influence if studies with low levels of control for confounding removed from analysis, and/or determined influence of studies with different populations, comparators and intervention formats. The influence should be determined through sensitivity or sub-group analysis.

12*	**If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?**	☐ Yes ☐ No ☐ No meta-analysis
	For Yes: ☐ included only low risk of bias RCTs (sensitivity analysis) Note: It is not good practice to combine RCT and prospective cohort studies; therefore, separate results should be provided and their similarities or differences discussed	
13*	**Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?**	☐ Yes ☐ No
	For Yes: ☐ included only low risk of bias RCTs in the review ☐ included only low risk of bias RCTs (in meta-analysis or a sensitivity analysis and discuss differences) ☐ OR, if RCTs with moderate or high RoB, or prospective cohort studies were included the review provided a discussion of the likely impact of RoB on the results and quality of evidence or limitations in conclusions or summary Note: Generally, non-randomised studies of interventions have more positive results that RCTs because of self-selection bias and lack of randomization and readers should be reminded of this. Confounding should be controlled for in the meta-analysis by using adjusted odds ratios. Loss to follow-up should be controlled for in the inclusion criteria. Loss to follow-up of over 20% introduces a serious bias to longitudinal studies. Risk of bias should also be discussed for narrative analysis	

	Risk of bias should concentrate on the areas that were scored high risk or unclear risk of bias and its effect on the direction of the results.	
14*	**Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?** For Yes: ☐ There was no significant heterogeneity in the results ☐ OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results (feasibility assessment, random effects model, sensitivity and sub-group analysis) AND discussed the impact of this heterogeneity on the results of the review and the quality of evidence If narrative analysis completed, the effects of clinical heterogeneity on the results and quality of evidence must be discussed.	☐ Yes ☐ No
15	**If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?** For Yes: ☐ performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias Publication bias occurs when results of published studies are systematically different from unpublished or grey literature studies. Publication bias is trying to estimate the influence of unpublished studies on the results of the systematic review. Publication bias can be controlled for through a good comprehensive search strategy that includes unpublished studies, yet to be published studies,	☐ Yes ☐ No ☐ No meta-analysis

	or studies published in grey literature and a wide selection of databases. Publication bias can be measured using a funnel plot and its p-value. A funnel plot is a scatter plot of estimates of the treatment effects of each study against the measure of its precision (1/Standard Error). In the absence of publication bias, plot will look like symmetric inverted funnel. A minimum of 10 studies are required to run the funnel plot analysis. The effect of publication bias should be considered in the GRADE quality of evidence.	
16	**Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?** For Yes: ☐ The authors reported no competing interests OR ☐ The authors described their funding sources and how they managed potential conflicts of interest In this case, the industry producing cannabis-based medicinal products is the main source of potential conflicts of interest.	☐ Yes ☐ No

Appendix Table 63 Summary flaws

Item	Flaws	Rationale
1*	Did the research questions and inclusion criteria for the review include the components of PICO?	
2*	Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	
3	Did the review authors explain their selection of the study designs for inclusion in the review?	
4*	Did the review authors use a comprehensive literature search strategy?	
5	Did the review authors perform study selection in duplicate?	
6	Did the review authors perform data extraction in duplicate?	
7	Did the review authors provide a list of excluded studies and justify the exclusions?	

8	Did the review authors describe the included studies in adequate detail?
9*	Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?
10	Did the review authors report on the sources of funding for the studies included in the review?
11*	If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?
12*	If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?
13*	Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?
14*	Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
15	If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?
16	Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?
Overall	

HRB-adapted AMSTAR 2 critical domains

We have selected eight rather than seven critical domains. Appendix Table 64 displays the critical domains selected by us and the original AMSTAR 2 authors, along with justifications for selection of critical domains.

Appendix Table 64 HRB-adapted AMSTAR 2 critical domains

Domain	Pollock *et al.* [24] AMSTAR critical domains	Shea *et al.* [17] AMSTAR 2 critical domains	HRB authors critical domains	Agreement or justification for selection of critical domains
Did the research questions and inclusion criteria for the review	Yes	No	Yes	We regard this item as critical, as overviews indicate that clarity in the PICO leads to a better research objective, search strategy,

include the components of PICO (item 1)?				clear inclusion and exclusion criteria, and a planned approach to analysis.
Protocol registered before commencement of the review (item 2)	No	Yes	Yes	We agree that this item is critical.
Adequacy of the literature search (item 4)	Yes	Yes	Yes	We agree that this item is critical. In addition, the inclusion of this item may help deal with excluding items 7 (excluded primary studies) and 15 (publication bias) as critical, and we agree that trials or cohort studies excluded at full text screening should be listed with a reason for exclusion.
Was there duplicate study selection and data extraction (item 5)?	Yes	No	No	We believe that this item is standard practice nowadays.
Justification for excluding individual studies (item 7)	Yes	Yes	No	We believe that this item overlaps with items 1 (PICO), 4 (search strategy), and 9 (risk of bias), and therefore does not need to be included as a critical domain.
Risk of bias and publication bias based on primary studies being included in the systematic review (item 9)	No	Yes	Yes	We agree that this item is critical.
If meta-analysis was performed, did the review authors assess the potential impact of risk of bias in individual studies on the results of the meta-analysis or other evidence synthesis (item 12)?	No	No	Yes	We believe that item 12 (risk of bias in doing meta-analysis) is critical. We think dealing with bias openly is key to avoiding misleading results.
Appropriateness of meta-analytical methods (item 11)	No	Yes	Yes	We agree that this item is critical.

Consideration of risk of bias when interpreting the results of the review (item 13)	No	Yes	Yes	We agree that this item is critical.
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review (item 14)?	No	No	Yes	We believe that clinical and statistical homogeneity or consistency (item 14) are key to a trustworthy analysis and must be dealt with the authors before and after meta-analysis.
Assessment of presence and likely impact of publication bias (item 15)	No	Yes	No	We regarded other items as more critical, and that this issue may be included under item 9.

Rating overall confidence in the results of individual systematic reviews

We allocated each included systematic review a confidence rating using the schema from Shea et al., shown in Appendix Table 65.

Appendix Table 65 Rating overall confidence in the results of individual systematic reviews

Score	Criteria
High	No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest
Moderate	More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review
Low	One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest
Critically low	More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies
*Downgrade	*Multiple non-critical weaknesses may diminish confidence in the review, and it may be appropriate to move the overall appraisal down from moderate to low confidence.

Source: Shea *et al.* (2017)

Appendix F Data extraction for included reviews

Abdallah *et al.* (2020): Analgesic efficacy of cannabinoids for acute pain management after surgery: a systematic review and meta-analysis

Parameter	Extraction items
First author and year of publication	Abdallah *et al.* (2020)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** To evaluate analgesic outcomes in patients receiving cannabis compounds for acute pain management in the surgical setting. • **Exact review question and page number:** "to evaluate analgesic outcomes in patients receiving cannabis compounds for acute pain management in the surgical setting" p509 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** Adult patients ≥18 years old ➢ **Setting:** Surgical setting ➢ **Intervention:** Cannabinoid or cannabinoid containing product ➢ **Comparison:** Control (standard opioid-based unimodal (opioids only) or multimodal (combination of opioids and other adjuvants) systemic analgesia) ➢ **Outcome:** Acute postoperative pain management
Participants (characteristics and numbers)	**For whole sample and subgroups:** N=5183 (RCT cannabinoid n=662; RCT cannabinoid receptor agonist n=262; observational n=4259) *The RCTs assessing cannabinoid receptor agonists and observational studies are excluded from the remainder of the extraction.

Parameter	Extraction items
	• **Number of participants:** N=662 • **Age:** Not reported • **Gender:** Not reported • **Details of clinical diagnosis/indications:** Acute fracture or trauma (n=56); renal surgery (n=100); elective abdominal hysterectomy (n=20); various major surgeries (n=41); radial prostatectomy (n=105); various elective surgeries (n=340)
Setting/context	**Countries (alphabetic order):** Not reported **Setting (university, public or private clinic):** Not reported **Other relevant features of setting:** Not reported

Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** Cannabinoid or cannabinoid containing product (RCT only)
	• **Dose and regimen:**
	  ○ Levonantradol (2 RCTs): 1-3 mg; one dose preoperative, one dose postoperative
	  ○ THC (2 RCTs): 5 mg; one dose postoperative day 2; one dose one hour preoperative, seven doses until 48 hours postoperative
	  ○ Nabilone (2 RCTs): 1 or 2 mg capsule orally, one dose an hour postoperative, one dose every 8 hours for 24 hours; 0.5 mg capsule prior to general anaesthesia
	• **Administration methods:** Orally (4 RCTs); intramuscular (2 RCTs)
	• **Comparator:** Control (not specified 6 RCTs). Additional active comparator arms include pethidine (1 RCT); ketoprofen (1 RCT)
	• **Treatment duration:** Between 1 hour prior to surgery to 2 days post-surgery
	• **Timeframe for follow-up:** Not specified

Parameter	Extraction items
Databases and sources searched	• **Number and names of databases:** 3; MEDLINE; the Cochrane Database of Systematic Reviews; EMBASE; inception-01/09/19 • **Other sources:** Clinical Trials Registry (www.clinicaltrials.gov) • **Grey literature:** Published abstracts of the following international meetings: American Society of Anesthesiologists (ASA) 2011–2018, American Society of Regional Anesthesia and Pain Medicine (ASRA) 2013–2018, the European Society of Regional Anaesthesia (ESRA) 2014–2018, and the European Society of Anaesthesiology (ESA) 2015–2018. • **Reference chasing:** Yes • **Expert consultation:** No • **Dates:** Inception-01/09/19 • **Search limits:** No • **Justifications for search limits:** Not applicable • **Other searches:** Not applicable • **Protocol prepared:** Yes • **If yes, published:** Not available • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Funding of review:** "Authors receives research time support from the Department of Anesthesiology and Pain Medicine, and the Ottawa Hospital Research Institute, University of Ottawa; and the Evelyn Bateman Cara Operations Endowed Chair in Ambulatory Anesthesia and Women's Health, Women's College Hospital, Toronto, Ontario, Canada." p518

Parameter	Extraction items
	• **Conflicts of interest of review:** None • **How conflicts of interest were managed:** Not applicable
Date Range (years) of included studies	• **Exact years for included studies:** 1981-2017
Number of primary studies included in the systematic review	• **Number of studies:** 6 RCTs • **Number of studies by study design:** 6 RCTs • **Study years:** 1981 (1 RCT); 1983 (1 RCT); 2003 (1 RCT); 2006 (2 RCTs); 2017 (1 RCT) • **Funding of included studies:** Not reported • **Conflicts of interest of included studies:** Not reported
Types of studies included	**Planned study designs to be included:** RCT and observational **Reasons for including only RCTs/prospective cohort studies:** Not reported **List of excluded studies at full text and reasons for exclusion:** Not reported
Appraisal instruments used	**Full name of tools used:** Cochrane Risk of Bias, GRADE **Risk of bias criteria for AMSTAR 2 assessment, for RCTs record Yes/No for:** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes

Parameter	Extraction items
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The authors did not provide an overall assessment of risk of bias for each trial. However, HRB notes that according to Cochrane's Collaboration tool, and graphical information provided in the paper, the included trials appeared to have an unclear risk of bias (6 RCTs). • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** o Overall: Low risk randomisation (2/6); low risk outcome ascertainment (3/6) *THC (nabilone, levonantradol, delta-9-THC) vs unspecified control* o Analgesic consumption: Low risk randomisation (1/2); low risk outcome ascertainment (1/2) o Rest pain severity: Low risk randomisation (1/2); low risk outcome ascertainment (1/2) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** Not discussed • **Graphical or statistical test for publication bias:** Assessed in the two co-primary outcomes of this review using the Egger's regression test and also by visual inspection of a funnel plot. • **Authors' comments likelihood and magnitude of publication bias:** "From a methodological perspective, we were unable to statistically pool across both of our primary outcomes (analgesic consumption and rest pain scores at 24 hours) due to limited reporting across all research articles. As a result, we were also unable to assess for risk of publication bias for our primary outcomes." p518 • **Authors' comment on how publication bias was dealt with:** Not applicable • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** No • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** Not reported

Parameter	Extraction items
Method of analysis	• **Description of method of analysis as per authors:** **Statistical analysis** "For all continuous outcomes in this review, a mean and [standard deviation] was extracted. In situations where these values were unavailable, the median and [interquartile range] were used as an approximation. If required for statistical pooling, all dichotomous data were converted to continuous data in the form of a mean and [standard deviation]. For instances where a 95% CI was reported, the value was converted to a [standard deviation]. The value of the [standard deviation] was imputed if a measure variation (i.e., standard deviation, confidence interval, or interquartile range) was not provided by the included study, and the median was used to approximate the mean in situation where the mean could not be derived. For all dichotomous outcomes in this review, data were converted to overall incidence numbers." **Meta-analysis** "Data were pooled only if available from three or more research articles; otherwise, we qualitatively summarized the results in situations when data from less than three articles were available. In situations when continuous data could be statistically pooled, we used the inverse variance method with random-effects modelling since we anticipated the presence of clinical heterogeneity between the included articles. Similarly, when dichotomous outcome data could be pooled, the Mantel-Haenszel random-effects model was used. For the primary outcomes of this review, namely cumulative oral morphine equivalent consumption (mg) and rest pain severity (VAS) at 24 hours postoperatively, a weighted mean difference (WMD) with a 95% CI was calculated. For the continuous secondary outcomes of this review, namely VAS pain scores in [post anesthesia care unit] (0–2hours), 6 and 12 hours, cumulative postoperative oral morphine equivalent (mg) during the [post anaesthesia care unit] stay and during the 24–48 hour time interval, patient satisfaction, and quality of recovery, a [weighted mean difference] with a 95% CI was also calculated. For the dichotomous secondary outcomes of this review, namely opioid related side-effects and cannabinoid-

Parameter	Extraction items
	related side effects, an OR with a 95%CI was calculated. For the two coprimary outcomes of this review, our threshold for significance was p<0.025. For the secondary outcomes of this review, p<0.05 was considered significant. All tests of significance were two-tailed." p511 • **Justification for narrative synthesis or meta-analysis:** Above • **Justification for combining data in meta-analysis:** Above
Outcome assessed	**List of outcomes assessed and intended timeframes** • Primary outcomes: Analgesic consumption, as measured by cumulative oral morphine equivalent consumption the first 24-hour time interval; Rest pain severity, as measured by Visual Analog Scale (VAS) pain scores, at 24 hours postoperatively. • Secondary outcomes: Cumulative postoperative oral morphine equivalent (mg) during the postoperative anaesthesia care unit stay and during the 24–48 hour time interval; postoperative rest pain severity (VAS) in [post anaesthesia care unit] (0–2hours), 6, and 12 hours. Safety outcomes: opioid-related side effects and cannabinoid-related side effects." • Intended timeframes: 0-48 hours postoperative • Actual timeframes: 0-12 hours postoperative
Results/findings	• **Findings by outcome:** PRIMARY OUTCOMES *Primary analgesic outcomes* ○ Cumulative oral morphine equivalent consumption at 24 hours postoperatively: Not possible to pool data. Two studies (n=153) reported no significant difference between nabilone (1 RCT) and THC (1 RCT) groups and control groups (placebo and active comparator) (no summary statistics reported).

Parameter	Extraction items

- Rest pain scores at 24 hours postoperatively using VAS pain score: Not possible to pool data. One study (n=105) reported no significant difference between THC and control groups (no summary statistics reported). One study (n=41) reported higher pain in nabilone compared with control groups (ketoprofen and placebo) (no summary statistics reported).

SECONDARY OUTCOMES

Secondary analgesic outcomes

- Interval rest pain severity scores: Three studies (n=460) reported no significant differences between cannabinoid and cannabis groups and control (pethidine, placebo) groups at post anaesthesia care unit stay (no summary statistics reported). Three studies (n=460) reported no significant differences between cannabinoid and cannabis groups and control (pethidine, placebo) groups at 6 hours (no summary statistics reported). One study (n=105) reported no significant differences between cannabis and placebo at 12 hours (no summary statistics reported).
- Oral morphine equivalent consumption during post anaesthesia care unit stay: Three studies (n=486) reported no significant difference between cannabinoid and cannabis groups and control (placebo and ketoprofen) groups (WMD 1.12, 95% Cl –4.71 to 6.94).

Safety outcomes adverse events (it is not possible to ascertain from article text whether intervention groups were cannabinoid or cannabis or cannabinoid receptor nor whether control groups were placebo or active comparator).

- **GRADE by outcome:**

Outcome	No. studies	GRADE
Oral morphine consumption at 2 hours (post-anaesthesia care unit)	3	Moderate

<table>
<tr><th>Parameter</th><th>Extraction items</th></tr>
<tr><td></td><td>

Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):
<table>
<tr><th>Outcome</th><th>No. studies (No. participants)</th><th>Summary estimate (95% CI)</th><th>P-value</th><th>I^2 (%)</th><th>Direction of effect</th></tr>
<tr><td colspan="6">Cannabinoid and cannabis vs mixed control (placebo, active)</td></tr>
<tr><td>Oral morphine consumption at 2 hours</td><td>3 (486)</td><td>MD 1.12 (-4.71 to 6.94)</td><td>0.71</td><td>91</td><td>No significant difference</td></tr>
</table>

Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available: Not reported
Appropriate weighted technique used, adjusted for heterogeneity where necessary: Yes
Separate summaries reported for RCTs and prospective cohort studies when included in the same review: Yes

</td></tr>
<tr><td>Significance/direction</td><td>See above if results listed by outcome: Above</td></tr>
<tr><td>Heterogeneity</td><td>

See above if I^2 available: Above
Authors' comment on potential impact of heterogeneity on results and quality of evidence: "Furthermore, outcomes that we were able to successfully pool were characterized by a high level of heterogeneity. These were likely due to (i) the variations in the cannabinoid compounds used, including the dose route and timing of administration and (ii) the variation in the surgical procedures performed." p518
Causes of heterogeneity investigated: Yes, random effects models used, I^2 calculated, sensitivity and subgroup analysis considered

</td></tr>
<tr><td>Comments</td><td>This systematic review includes 12 studies (6 RCTs assessing cannabinoid or cannabis, 2 RCTs assessing cannabinoid receptor agonists and 4 qualitative trials). Unless specified otherwise, the above information only reported on RCT studies assessing cannabinoid or cannabis as per the umbrella review inclusion criteria.</td></tr>
</table>

Parameter	Extraction items
	Although pain severity scores at post anaesthesia care unit (PACU) and six hours are labelled as RCT only, references on p515 indicate observational studies were included here. Therefore, this data is not reported in this form. In relation to 'SAFETY OUTCOMES ADVERSE EVENTS' findings it is not possible to ascertain from article text whether intervention groups were cannabinoid or cannabis or cannabinoid receptor nor whether control groups were placebo or active comparator.

AminiLari *et al.* (2022): Medical cannabis and cannabinoids for impaired sleep: a systematic review and meta-analysis of randomized clinical trials

Parameter	Extraction items
First author and year of publication	AminiLari *et al.* (2021)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "to explore the effectiveness of medical cannabis for impaired sleep" p1 • **Exact review question and page number:** "to explore the effectiveness of medical cannabis for impaired sleep" p1 • **PICO elements reported in Introduction/Methods:** • **Patient or population:** "patients aged 18 or older with impaired sleep" p2 ➢ **Setting:** Not specified ➢ **Intervention: "**medical cannabis or cannabinoids" p2 ➢ **Comparison:** Usual care, placebo or other non-cannabis therapeutic interventions. ➢ **Outcome:** Sleep quality, sleep disturbance, adverse events

Parameter	Extraction items
Participants (characteristics and numbers)	**For whole sample and subgroups:** N=5100 *One study exploring ultra-micronized palmitoylethanolamide (PEA) has been excluded from the remainder of this extraction. • **Number of participants:** n=5058 • **Age:** Mean/median age range 23.6-67.0 years • **Gender:** 53.3% female • **Details of clinical diagnosis/indications:** Chronic pain (n=2172); Cancer-related pain (n=1674); neuropathic pain (n=984); Parkinson's Disease (n=57); post-traumatic stress disorder (n=10); anorexia nervosa (n=11); HIV-associated neuropathic pain (n=34); multiple sclerosis (n=43); sleep apnoea (n=73)
Setting/context	**Countries (alphabetic order):** Not reported **Setting (university, public or private clinic):** Not reported **Other relevant features of setting:** Not applicable

Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** "Medical cannabis or cannabinoids" p2
	• **Dose and regimen:** Not specified
	  ○ Nabilone (7 RCTs): 1-240 mg; not reported
	  ○ Sativex (18 RCTs): 12.6-129.6 mg THC and 20-120 mg CBD; 4-48 sprays daily
	  ○ Dronabinol (3 RCTs): 2.5 mg, 10 mg, 20 mg; not reported
	  ○ Cannabis flowers (1 RCT): 75 mg; not reported
	  ○ Cannador (2 RCTs): 25 mg, 2.5 mg; not reported

Parameter	Extraction items
	○ Cannabis extract (4 RCTs): 25 mg, 30 mg, 120 mg, not reported; daily, twice daily, three times daily ○ Delta-9 THC (1 RCT): 30 mg; not reported ○ Whole plant extracts (1 RCT): 120 mg; daily • **Administration methods:** Orally (18 RCTs); Oromucosal spray (19 RCTs); Smoking (1 RCT) • **Comparator:** Placebo (35 RCTs); active comparator (3 RCTs) • **Treatment duration:** 2-16 weeks • **Timeframe for follow-up:** Median follow-up duration was 35 days (IQR, 28-56 days) (Range 14-105 days)
Databases and sources searched	• **Number and names of databases:** 4; MEDLINE, EMBASE, CENTRAL, and PsycINFO; inception-19/01/2021 • **Other sources:** Not reported • **Grey literature:** Not reported • **Reference chasing:** Yes • **Expert consultation:** Yes- academic librarian • **Dates:** Inception-19/01/21 • **Search limits:** No • **Justifications for search limits:** Not applicable • **Other searches:** Not applicable • **Protocol prepared:** Yes • **If yes, published:** CRD42018103266 https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=103266 • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Substantial (κ = 0.78)

Parameter	Extraction items
	• **Extraction completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Funding of review:** No funding was received to conduct this study • **Conflicts of interest of review:** The authors declared no conflict of interest • **How conflicts of interest were managed:** Not applicable
Date Range (years) of included studies	• **Exact years for included studies:** 1983-2020
Number of primary studies included in the systematic review	• **Number of studies:** 37 publications reporting 38 RCTs • **Number of studies by study design:** 37 publications reporting 38 RCTs • **Study years:** 1983 (1 RCT); 2003 (2 RCTs); 2004 (5 RCTs); 2005 (1 RCT); 2006 (1 RCT); 2007 (1 RCT); 2008 (1 RCT); 2010 (5 RCTs); 2011 (2 RCTs); 2012 (4 RCTs); 2013 (1 RCT); 2014 (1 RCT); 2015 (2 RCTs); 2016 (1 RCT); 2017 (1 RCT); 2018 (4 RCTs); 2019 (2 RCTs); 2020 (2 RCTs) • **Funding of included studies:** Industry funded (16 RCTs); non-industry funded (7 RCTs); not reported (2 RCTs); partially industry funded (13 RCTs) • **Conflicts of interest of included studies:** Not reported
Types of studies included	**Planned study designs to be included:** RCT **Reasons for including only RCTs/prospective cohort studies:** Not reported **List of excluded studies at full text and reasons for exclusion:** References not provided, reasons provided.
Appraisal instruments used	**Full name of tools used:** Modified Cochrane Risk of Bias tool

Parameter	Extraction items
	<u>Risk of bias criteria for AMSTAR 2 assessment, for RCTs record Yes/No for:</u> • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** No
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The authors did not provide an overall assessment of risk of bias for each trial. However, HRB notes that according to Cochrane's Collaboration tool, and graphical information provided in the paper, the included trials appeared to have a high risk of bias (37 RCTs); and low risk of bias (1 RCT). • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** o Overall: Low risk randomisation (30/38); low risk outcome ascertainment (37/38) *Mixed cannabinoid vs placebo* o Sleep quality: Low risk randomisation (12/16); low risk outcome ascertainment (16/16) o Sleep disturbance: Low risk randomisation (12/16); low risk outcome ascertainment (15/160) *Nabilone vs placebo* o PTSD nightmares: Low risk randomisation (0/1); low risk outcome ascertainment (0/1) o Sleep quality back and neck carcinomas: Low risk randomisation (1/1); low risk outcome ascertainment (1/1) *Dronabinol vs placebo* o Sleepiness sleep apnoea: Low risk randomisation (1/1); low risk outcome ascertainment (1/1) *Nabilone vs amitriptyline* o Insomnia: Low risk randomisation (1/1); low risk outcome ascertainment (1/1)

Parameter	Extraction items
	○ Restful sleep: Low risk randomisation (1/1); low risk outcome ascertainment (1/1) *Nabilone vs opioids only* ○ Sleep interruptions: Low risk randomisation (1/1); low risk outcome ascertainment (1/1) *Cannabis (delta-9-THC) vs diazepam only* ○ Sleep disturbance: Low risk randomisation (1/1); low risk outcome ascertainment (1/1) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** Not discussed • **Graphical or statistical test for publication bias:** Visual assessment of symmetry of funnel plot and Egger's test where there were at least 10 studies available for a given outcome • **Authors' comments likelihood and magnitude of publication bias:** No publication bias was detected in any included studies • **Authors' comment on how publication bias was dealt with:** Outlined in Table 1 (5 RCTs outcomes undetected; 5 RCTs uncertain bias) • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** RoB was assessed for adequate randomisation and allocation concealment. • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** Yes
Method of analysis	• **Description of method of analysis as per authors:** *"Data analysis* Other measures of sleep were converted to a 10cm [visual analog scale] as long as they had ≥4 categories. Measures were rescaled so higher scores indicated worse sleep quality. When possible, the authors pooled effects across trials using random-effects models and the DerSimonian-Laird method. For all meta-analyses, we used change scores from baseline to the end

Parameter	Extraction items
	of follow-up to account for interpatient variability. If change scores were not reported, we calculated them using the baseline and end-of-study scores and the associated standard deviation (SD) using a correlation coefficient derived from the largest trial at the lowest risk of bias that reported a change score *Continuous outcomes* The authors reported pooled effect estimates of continuous outcomes as both the weighted mean difference and, when possible, the modelled risk difference (RD) of achieving the minimally important difference (MID) to optimize interpretability *Binary outcomes* The authors We reported the pooled effects on binary outcomes as relative risks and [risk differences]." p2 • **Justification for narrative synthesis or meta-analysis:** Not reported • **Justification for combining data in meta-analysis:** Not reported
Outcome assessed	**List of outcomes assessed and intended timeframes** • Primary outcomes: Sleep quality, sleep disturbance, other sleep-related outcomes • Secondary outcomes: Adverse events • Intended timeframes: >2 weeks • Actual timeframes: 2-16 weeks
Results/findings	• **Findings by outcome:** PRIMARY OUTCOMES *Cannabinoids vs placebo only: Sleep*

Parameter	Extraction items
	○ Sleep quality: Pooled data from 16 studies (n=2052) reported a significantly improved sleep in cannabis and cannabinoid compared with placebo groups (WMD -0.43, 95% CI -0.18 to -0.67). Pooling data was not possible in four studies. One study (n=46) study reported more 'pleasant sleep' in cannabinoid compared with placebo groups (p=0.046). One study (n=630) reported significant improvement in sleep quality in cannabinoid compared with placebo groups (p=0.02). One study (n=34) reported the median of "good" nights for THC:CBD (55.4%, IQR 78-34.5, p<0.001), THC (42.9%, IQR 57.2, 35.7, p<0.001) and CBD (36.9%, IQR 47.9, 28.6, p<0.001) was significantly higher than placebo (17.0%, IQR 35.7, 3.6, p<0.001). ○ Sleep disturbance: Pooled data from 11 studies (n=906 participant with chronic non-cancer pain) reported significant improvement in cannabinoid compared with placebo groups (WMD -0.99, 95% CI-0.57 to -1.41). Pooled data from 5 studies (n=1249 participants with chronic cancer pain) reported significant improvement in cannabinoid compared with placebo groups (WMD -0.19, 95% CI -0.03 to -0.36). ○ Other sleep outcomes: "Low-certainty evidence from one trial (73 patients) suggests that nabilone, versus placebo, may reduce the frequency and intensity of nightmares among post-traumatic stress disorder patients (mean change in the clinician-administered [post-traumatic stress disorder scale], –3.6 ± 2.4 vs. –1.0 ± 2.1), but may provide no benefit for total sleep time or numbers of awakenings each night. Very low-certainty evidence from one trial (56 patients) suggests that nabilone, compared to placebo, may not improve sleep among patients undergoing radiotherapy for head and neck carcinomas. Low-certainty evidence from one trial (73 patients) suggests dronabinol, versus placebo, may reduce sleepiness among patients with moderate to severe obstructive sleep apnea at a dose of 10 mg/day (mean change in the Epworth Sleepiness Scale, 2.3 ±1.2, p = .05), but not at a lower dose of 2.5 mg/day." (p5-6) *Nabilone vs amitriptyline only*

Parameter	Extraction items
	○ Insomnia: One study (n=32) reported significantly improved insomnia in the nabilone compared with amitriptyline group (MD 3.25, 95% CI, 5.26 to 1.24). This study also reported significantly more restful sleep in the cannabinoid compared with amitriptyline groups (MD 0.48, 95% CI 0.01 to 0.95). *Nabilone vs opioids only* ○ Sleep interruptions: One study (n=96) reported no significant difference between nabilone and opioid groups (MD 0.2, 95% CI, –0.1 to 0.5, p=0.02) *Cannabis (delta-9-THC) vs diazepam only* ○ Sleep disturbance: One study (n=11) reported improvements in delta-9-THC compared with diazepam groups a (–2.09 vs. –1.91, p=0.004). SECONDARY OUTCOMES *Cannabinoids vs placebo only: Adverse events* ○ Nausea: Pooled data from 22 studies (n=3543) reported significantly increased risk in cannabinoid compared with placebo groups (RR 1.85, 95% Cl 1.47 to 2.32). ○ Dizziness: Pooled data from 24 studies (n=4305) reported significantly increased risk in cannabinoid compared with placebo groups (RR 2.66, 95% Cl 2.06 to 3.44). ○ Diarrhoea: Pooled data from 12 studies (n=1777) reported Increased pooled risk of diarrhoea in cannabinoid group (RR 1.74, 95% Cl 1.07 to 2.82). ○ Vomiting: Pooled data from nine studies (n=1538) reported significantly increased risk in cannabinoid compared with placebo groups (RR 1.56, 95% Cl 0.97 to 2.49). ○ Headache: Pooled data from 14 studies (n=1819) reported significantly increased risk in cannabinoid compared with placebo groups (RR 0.91, 95% Cl 0.67 to 1.24).

Parameter	Extraction items

- Fatigue: Pooled data from 13 studies (n=2087) reported significantly increased risk in cannabinoid compared with placebo groups (RR 1.86, 95% CI 1.36 to 2.54).
- Dry mouth: Pooled data from 15 studies (n=2734) reported significantly increased risk in cannabinoid compared with placebo groups (RR 2.11, 95% CI 1. 47 to 3.03).
- Disturbance in attention: Pooled data from 7 studies (n=1086) reported significantly increased risk of disturbance in attention in cannabinoid compared with placebo groups (RR 4.70, 95% CI 1.77 to 12.50).
- Somnolence: Pooled data from 14 studies (n=2753) reported significantly increased risk of somnolence in cannabinoid compared with placebo groups (RR 1.89, 95% CI 1.89 to 3.65 to 12.50).
- Constipation: Pooled data from 8 studies (n=1659) reported no difference in risk of constipation in cannabinoid compared with placebo groups (RR 0.86, 95% CI 0.56 to 1.32).

- **GRADE by outcome**

Outcome	No studies,	GRADE
Sleep quality	16	Moderate
Sleep disturbance non-cancer	11	High
Sleep disturbance cancer	5	Moderate
Adverse events		
Nausea ≥ 3 months	4	High
Nausea < 3 months	18	High
Dizziness ≥ 3 months	5	High
Dizziness < 3 months	19	High
Diarrhoea	12	High
Disturbance in attention	7	Moderate
Vomiting	9	Moderate
Headache	14	Moderate

Parameter	Extraction items

Fatigue	13	High
Dry mouth ≥ 3 months	5	High
Dry mouth < 3 months	10	Moderate
Somnolence	14	High
Constipation	8	Low

- **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):**

Outcomes	No. studies (No. participants)	Summary estimate (95% CI)	P-value	I^2 (%)	Direction of effect
Cannabinoids vs placebo only: Sleep					
Sleep quality	16 (2052)	WMD -0.43 (-0.67 to -0.18)	0.002	57.9	Cannabinoid
Sleep disturbance non-cancer	11 (906)	WMD -0.99 (-0.57 to -1.41)	NR	71.4	Cannabinoid
Sleep disturbance cancer	5 (1249)	WMD -0.19 (-0.03 to -0.36)	NR	0	Cannabinoid
Cannabinoids vs placebo only: Adverse events					
Nausea (all timeframes)	22 (3543)	RR 1.85 (1.47 to 2.32)	NR	0	Cannabinoid
Nausea ≥ 3 months	4 (1163)	RR 2.64 (1.83 to 3.80)	NR	0	Cannabinoid
Nausea < 3 months	18 (2380)	RR 1.49 (1.11 to 1.98)	NR	0	Cannabinoid
Dizziness (all times)	24 (4305)	RR 2.66 (2.06 to 3.44)	NR	48.6	Cannabinoid
Dizziness ≥3 months	5 (1824)	RR 4.28 (2.76 to 6.65)	NR	59.7	Cannabinoid
Dizziness <3 months	19 (2481)	RR 2.03 (1.60 to 2.58)	NR	0	Cannabinoid
Diarrhoea	12 (1777)	RR 1.74 (1.07 to 2.82)	NR	0	Cannabinoid
Disturbance in attention	7 (1086)	RR 4.70 (1.77 to 12.5)	NR	0	Cannabinoid
Vomiting	9 (1538)	RR 1.56 (0.97 to 2.49)	NR	0	Cannabinoid

Parameter	Extraction items

Headache	14 (1819)	RR 0.91 (0.67 to 1.24)	NR	0	No significant difference
Fatigue	13 (2087)	RR 1.86 (1.36 to 2.54)	NR	11	Cannabinoid
Dry mouth (all times)	15 (1588)	RR 2.11 (1.47 to 3.03)	NR	39.3	Cannabinoid
Dry mouth ≥ 3 months	5 (1829)	RR 2.77 (1.91 to 4.02)	NR	20.8	Cannabinoid
Dry mouth < 3 months	10 (905)	RR 1.48 (0.96 to 2.29)	NR	9.3	Cannabinoid
Somnolence	14 (2753)	RR 2.62 (1.89 to 3.65)	NR	0	Cannabinoid
Constipation	8 (1659)	RR 0.86 (0.56 to 1.32)	NR	0	No significant difference

- **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Not applicable
- **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Yes - Random effects model used, I^2
- **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable

Significance/direction

See above if results listed by outcome: Above

Heterogeneity

- **See above if I^2 available:** Above
- **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** Not reported
- **Causes of heterogeneity investigated:** Yes, random effects model, I^2 calculated, subgroup analysis conducted

Parameter	Extraction items
Comments	One study included in this review by AminiLari *et al.* (2021) explored ultra-micronized palmitoylethanolamide (PEA) versus usual care (Evangelista *et al.* 2019). As per our inclusion criteria, data from this study has not been included in this extraction form.

Andreae *et al.* (2015): Inhaled Cannabis for Chronic Neuropathic Pain: A Meta-analysis of Individual Patient Data

Parameter	Extraction items
First author and year of publication	Andreae *et al.* (2015)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** To perform a Bayesian responder meta-analysis of individual patient data to study whether inhaled cannabis provides relief for chronic neuropathic pain. • **Exact review question and page number:** "We performed a Bayesian responder meta-analysis of individual patient data to study whether inhaled cannabis provides relief for chronic neuropathic pain." p1222 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** Patients with neuropathic pain ➢ **Setting:** Not specified ➢ **Intervention:** Inhaled cannabis sativa ➢ **Comparison:** Placebo

Parameter	Extraction items
	➢ **Outcome:** Changes in pain
Participants (characteristics and numbers)	**For whole sample and subgroups** • **Number of participants:** N=189 (178 participants included in analysis) • **Age:** Mean age range 45.4-50 years • **Gender:** 25.9% female • **Details of clinical diagnosis/indications:** HIV (n=89); trauma or surgery (n=23); spinal cord injury, peripheral neuropathy, or nerve injury (n=38); reflex sympathetic dystrophy, peripheral neuropathy, postherpetic neuralgia, poststroke pain, multiple sclerosis, or spinal cord injury (n=39)
Setting/context	**Countries (alphabetic order):** Not reported **Setting (university, public or private clinic):** Not reported **Other relevant features of setting:** Not reported
Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** Inhaled cannabis sativa • **Dose and regimen:** THC: Range 10.32 mg-96 mg; three times daily; three times daily; four times daily; per session; per period • **Administration methods:** Inhaled (5 RCTs) • **Comparator:** Placebo (5 RCTs) – Whole plant with removal of cannabinoids/active ingredient; Ethanol capsule • **Treatment duration:** "Hours to days or weeks" p1225 • **Timeframe for follow-up:** Not reported
Databases and sources searched	• **Number and names of databases:** 4: AMED, MEDLINE, EMBASE, CENTRAL; Not reported-23/04/15

Parameter	Extraction items
	• **Other sources:** No • **Grey literature:** Hand search of conference abstracts from the Conference on Retroviruses and Opportunistic Infections 2011, the International AIDS Conference, and the World Congress of Pain 2010 • **Reference chasing:** Yes • **Expert consultation:** No • **Dates:** Not reported-23/04/15 • **Search limits:** No • **Justifications for search limits:** Not applicable • **Other searches:** Not reported • **Protocol prepared:** Yes • **If yes, published:** CRD42011001182 https://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42011001182 • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Unclear • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Funding of review:** National Center for Advancing Translational Sciences (NCATS), a component of the National Institutes of Health (NIH), through CTSA grant numbers UL1TR000086, TL1RR000087, and KL2TR000088), the Center for Drug Evaluation and Research (CDER) through grant number R01-AT005824 and in part by Grant 5R01AT5824 from the National Center for Complementary and Alternative Medicine (NCCAM). Supported by the University of California Center for Medicinal Cannabis Research and NIH Grant 5-MO1-RR00083. • **Conflicts of interest of review:** The authors declared no conflict of interest

Parameter	Extraction items
	• **How conflicts of interest were managed:** Not applicable
Date Range (years) of included studies	• **Exact years for included studies:** 2007-2013
Number of primary studies included in the systematic review	• **Number of studies:** 5 RCTs • **Number of studies by study design:** 5 RCTs • **Study years:** 2007 (1 RCT); 2008 (1 RCT); 2009 (1 RCT); 2010 (1 RCT); 2013 (1 RCT) • **Funding of included studies:** 5 RCTs publicly funded • **Conflicts of interest of included studies:** Not specified "all authors provided detailed conflicts of interest statements" p1225
Types of studies included	**Planned study designs to be included:** RCT **Reasons for including only RCTs/prospective cohort studies:** Not reported **List of excluded studies at full text and reasons for exclusion:** Yes - Provided in appendices
Appraisal instruments used	**Full name of tools used:** Cochrane Risk of Bias **Risk of bias criteria for AMSTAR 2 assessment, for RCTs record Yes/No for:** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The authors did not provide an overall assessment of risk of bias for each trial. However, HRB notes that according to Cochrane's Collaboration tool, and graphical information

Parameter	Extraction items
	provided in the paper, the included trials appeared to have high risk of bias (2 RCTs), unclear risk of bias (2 RCTs) and low risk of bias (1 RCT). • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** ○ Overall: Low risk randomisation (4/5); low risk outcome ascertainment (1/5) *Cannabis products (THC) vs placebo* ○ Chronic neuropathic pain 30% reduction: Low risk randomisation (4/5); low risk outcome ascertainment (1/5) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** "We characterized the risk of bias of the studies (Fig 2 and Supplementary Table 1). Randomization and allocation concealment were well described and suggested a low risk of bias. Ineffective participant blinding might have possibly resulted in performance bias in all studies; placebo effects are likely, when participants guessed their allocation, possibly leading them to overestimate the effect of inhaled cannabis on pain. Blinding of outcome observer was well described in 1 study, and the use of patient diaries as an outcome instrument led us to estimate the risk of detection bias as unclear in the remaining studies. Incomplete outcome data were well described in all studies and are detailed in Table 2. Withdrawals potentially related to treatment effects led to a high risk of bias in 1 study but did not seem to be associated with group allocation in all others. All the trials included reported their primary outcome as specified in the protocol." p1225 "Yet, our meta-analysis can only be as strong as the underlying data (Tables 1 and 2) and the methodological quality (Fig 2 and Supplementary Table 1); the small number of studies included, their small number of participants, and shortcomings in allocation concealment[42] and attrition (Table 2) limit our ability to draw firm conclusions." p1229 • **Graphical or statistical test for publication bias:** Yes • **Authors' comments likelihood and magnitude of publication bias:**

Parameter	Extraction items
	"We investigated publication bias in a funnel plot proposed by Egger et al, because with fewer studies than 10 studies, the power of the tests is insufficient to distinguish chance from real asymmetry." p1225 • **Authors' comment on how publication bias was dealt with:** Above • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** No • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** "we performed a sensitivity analysis (available on request) with regard to differences in the quality of studies, we found effect estimates and credible intervals to be robust regarding the inclusion or exclusion of any single study" p1227
Method of analysis	• **Description of method of analysis as per authors:** "We performed full Bayesian probability modelling of the population-averaged subject-specific effect as detailed in the statistical supplement (Supplementary Appendix 3). We pooled the treatment effects following a hierarchical random-effects Bayesian responder model. Kruschke provided an accessible introduction to Bayesian methods in health sciences. Ashby6 recently offered a chronological outline of applications in medicine, and Spiegelhalter et al compiled the first concise overview. Gelman et al described Bayesian hierarchical modeling approaches more formally. Supplementary boxes explain the basic concepts of Bayesian inference (Supplementary Boxes 1–3). The prior for the betweenstudy variability (Cauchy) and the pooled effect estimate (normal distribution) were centered at zero with a standard deviation of 100. We preferred the Cauchy distribution over the closely related t-distribution, because the Cauchy is more robust in accommodating outliers; these priors for our meta-analysis were uninformative and served to ensure computational convergence of the Markov chain Monte Carlo algorithm. Our priors were subsequently subjected to sensitivity analysis. Inference was implemented using a Gibbs sampling scheme to generate a computer simulation of a Monte Carlo sample from the posterior distribution in OpenBugs. Our OpenBugs program code is provided in Supplementary Appendix 4. We

Parameter	Extraction items
	have uploaded details on Monte Carlo Markov chain convergence, including graphs demonstrating mixing, as supplementary material (Supplementary Figs 1 and 2). Differences in the design and quality of the studies were the focus of a sensitivity analysis. We tested the sensitivity of our results for our Bayesian model and its assumptions. We investigated our choice of prior and model parameters and reanalyzed the individual patient responder data 1) in a frequentist random-effects meta-analysis and 2) controlling for cannabis dose as an explanatory variable of the between-study variability in a meta-regression (methods and data not shown but available on request).” p1223-1224 • **Justification for narrative synthesis or meta-analysis:** Above • **Justification for combining data in meta-analysis:** Above
Outcome assessed	**List of outcomes assessed and intended timeframes** • Primary outcome: Neuropathic pain • Secondary outcome: Adverse effects • Intended timeframe: Not specified • Actual timeframe: 5-6 hours to 2 weeks
Results/findings	• **Findings by outcome:** PRIMARY OUTCOME *30% reduction of neuropathic pain* ○ Five studies (N=178) reported that the cannabis group was significantly more likely to have more than 30% reduction in pain scores in response to inhaled cannabis compared with placebo for chronic painful neuropathy (OR 3.2, CRI 95% 1.59, 7.24). All 5 RCTs reported continuous patient-reported spontaneous pain intensity scales. SECONDARY OUTCOMES

Parameter	Extraction items

- Withdrawals due to adverse effects: One study (n=unclear) reported one withdrawal occurred in the placebo group (a case of psychosis) and two withdrawals in cannabis group (hypertension and increased pain) (no summary statistics reported).
- One study (n=38) reported short-term declines in attention, psychomotor performance, and learning and memory in the highest dose (7% tetrahydrocannabinol) group (no summary statistics reported).
- Statistically significant physiological changes (such as increases in heart rate) were observed in one study (n=31) but not in another study (n=23) after administration of medical cannabis (no summary statistics reported).
- Psychoactive effects (such as feeling ''high''): Two studies (n=89) reported significant increases in cannabis groups compared with placebo (no summary statistics reported).

- **GRADE by outcome:**

Outcome	Studies	GRADE
Neuropathic pain	5	Not reported

- **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):**

Outcome	No. studies (No. participants)	Summary estimate (95% CI)	P-value	I^2 (%)	Direction of effect
THC vs placebo					
Neuropathic pain (>30% reduction)	5 (178)	OR 3.22 (1.59 to 7.24)	Significant	0	Cannabis

- **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Not applicable

Parameter	Extraction items
	• **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Yes • **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable
Significance/direction	**See above if results listed by outcome:** Not applicable
Heterogeneity	• **See above if I^2 available:** Not applicable • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** "Even if the absence of evidence for heterogeneity constitutes no evidence for clinical homogeneity, the consistency and uniformity of the effect of inhaled cannabis on chronic neuropathic pain across different causes and populations, further enhances our confidence in the generalizability of our findings." p1228-1229 • **Causes of heterogeneity investigated:** Yes I^2, random effects model used, sensitivity analysis conducted
Comments	

Bahji *et al.* (2020): Efficacy and acceptability of cannabinoids for anxiety disorders in adults: A systematic review & meta-analysis

Parameter	Extraction items
First author and year of publication	Bahji *et al.* (2020)
Objectives	
Report exact review question(s) and page number	• **Study objectives**: "This systematic review and meta-analysis aimed to comprehensively appraise the evidence for the efficacy and acceptability of a range of cannabinoid and cannabis-preparations—including THC, CBD, and their synthetic analogues—in reducing symptoms associated with anxiety disorders." p258

Parameter	Extraction items
	• **Exact review question and page number:** "This systematic review and meta-analysis aimed to comprehensively appraise the evidence for the efficacy and acceptability of a range of cannabinoid and cannabis-preparations—including THC, CBD, and their synthetic analogues—in reducing symptoms associated with anxiety disorders." p258 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** "adults with a clinician diagnosed anxiety disorder (e.g., generalized anxiety disorder, post-traumatic stress disorder, social anxiety disorder, obsessive compulsive disorder)." p258 ➢ **Setting:** Psychiatric, non-psychiatric, community settings ➢ **Intervention:** "Any cannabis-based medications with the aim of reducing anxiety symptom" p258 ➢ **Comparison:** "Different pharmacotherapies, placebo, or no pharmacotherapy (i.e. supportive care)" p258 ➢ **Outcome:** "Outcomes included severity of anxiety symptoms, adverse effects, completion of treatment, and engagement in follow-up treatment." p258
Participants (characteristics and numbers)	**For whole sample and subgroups:** N=1548 (RCT n=533, cohort n=1015) The observational studies are excluded from the remainder of the extraction unless specified otherwise. • **Number of participants:** n=533 • **Age:** Mean age range 23.5-52.3 years • **Gender:** 32.8% female (not reported in one open-label study) • **Details of clinical diagnosis/indications:** Generalised anxiety disorder (n=323); post-traumatic stress disorder (n=176); social anxiety disorder (n=34)

Parameter	Extraction items
Setting/context	**Countries (alphabetic order):** Brazil (3 studies), Israel (1 study), North America (10 studies) (figures include full cohort- unable to extract separately for each study included) **Setting (university, public or private clinic):** Psychiatric, non-psychiatric, and community; not specified for individual studies **Other relevant features of setting:** Not reported

Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** Any cannabis-based medications with the aim of reducing anxiety symptom
	• **Dose and regimen:**
	  ○ Nabilone (4 RCTs): 0.5-6 mg; 1-3 times daily
	  ○ CBD (3 RCTs): 1 mg/kg; 400-600 mg; once daily
	  ○ THC (4 RCTs): 2-3 g, 23%, 5-10 mg; once daily
	• **Administration methods:** Orally (8 RCTs/open-label); Smoked (3 open-label)
	• **Comparator:** Placebo (5 RCTs); Not reported (6 RCTs/open-label)
	• **Treatment duration:** 1 to 104 weeks
	• **Timeframe for follow-up:** Not reported

Databases and sources searched	• **Number and names of databases:** 4; MEDLINE, EMBASE, PsycINFO, and Web of Science databases (inception – 12/2019) • **Other sources:** Ongoing trials (source not reported); Review articles examined for relevant primary studies • **Grey literature:** No • **Reference chasing:** Yes • **Expert consultation:** No • **Dates:** Inception-12/2019 • **Search limits:** English language, Humans

Parameter	Extraction items
	• **Justifications for search limits:** Not reported • **Other searches:** Not reported • **Protocol prepared:** Yes • **If yes, published:** https://osf.io/gjc5u • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Funding of review:** Not reported • **Conflicts of interest of review:** Not reported • **How conflicts of interest were managed:** Not applicable
Date Range (years) of included studies	• **Exact years for included studies:** 1981-2017
Number of primary studies included in the systematic review	• **Number of studies:** 11 • **Number of studies by study design:** 6 RCTs; 5 open-label • **Study years:** 1981 (2 RCTs); 1982 (1 RCT); 2009 (1 RCT); 2011 (4 RCTs); 2014 (1 RCT); 2015 (1 RCT); 2017 (1 RCT) • **Funding of included studies:** Not reported • **Conflicts of interest of included studies:** Not reported
Types of studies included	**Planned study designs to be included:** "Studies reporting the type and dose of cannabinoid medication used and the characteristics of participants treated were included" p258

Parameter	Extraction items
	Reasons for including only RCTs/prospective cohort studies: Not applicable **List of excluded studies at full text and reasons for exclusion:** Not applicable
Appraisal instruments used	**Full name of tools used:** Cochrane Risk of Bias **<u>Risk of bias criteria for AMSTAR 2 assessment, for RCTs record Yes/No for:</u>** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The authors did not provide an overall assessment of risk of bias for each trial. However, HRB notes that according to Cochrane's Collaboration tool, and graphical information provided in the paper, the included trials appeared to have a high risk of bias (6 RCTs/open-label) and low risk of bias (3 RCTs/open-label). • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment**: o Overall: Low risk randomisation (5/9); low risk outcome ascertainment (5/9) o Generalized anxiety disorder: Low risk randomisation (2/4); low risk outcome ascertainment (2/4) o Social anxiety disorder: Low risk randomisation (2/2); low risk outcome ascertainment (2/2) o Post-traumatic stress disorder: Low risk randomisation (2/4); low risk outcome ascertainment (2/4) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** "The quality of evidence among the primary and secondary outcomes was low to moderate (Appendices 2, 3), suffering from several serious methodological limitations, particularly blinding of the participants (owing to the subjective effects of cannabis

Parameter	Extraction items
	products). Randomization was not consistently done across studies as there were only three randomized controlled trials, with no single trial assessing all the outcomes of interest. This, in addition to high heterogeneity in the interventions of interest and anxiety disorder groups, contributed to great variability. The rate of attrition was not particularly high, and most studies discussed participant flow through the study. We found little evidence of selective reporting or selection bias." p260 • **Graphical or statistical test for publication bias:** Visual inspection of funnel plots, trim-and-fill method, rank correlation test, Egger's test • **Authors' comments likelihood and magnitude of publication bias:** "Risk of publication bias was assessed graphically using funnel plots, depicted in Fig. 3 and was deemed high owing to the grossly asymmetric appearance of the plots. Statistical tests for publication bias completed using the linear regression test of funnel plot asymmetry confirmed the gross asymmetry of the funnel plots (p=0.01) were statistically significant. Accordingly, the trim-and-fill method was applied, with an estimate of 6 missing studies required to correct the asymmetry in the funnel plot. Consequently, crude effect sizes were substantially inflated by publication bias; after correction, the overall effect of cannabinoids for anxiety disorder symptoms was no longer statistically significant" p262 • **Authors' comment on how publication bias was dealt with:** "However, publication bias was substantial, and after correction, the overall anxiolytic effect was not statistically significant" p257 • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** No • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** Not reported
Method of analysis	• **Description of method of analysis as per authors:**

Parameter	Extraction items
	"We used Cochrane's Review Manager (Version 5.3) for random-effects meta-analysis (The Cochrane Collaboration, 2014). For dichotomous outcomes, risk ratios were calculated with 95% confidence intervals. For continuous data, outcomes were expressed as standardized mean differences with 95% CI. If studies involved more than two treatment arms (e.g., two different active medications and placebo), the active medications, compared to placebo, were included in separate subgroups and the calculation of overall totals was suppressed thereby avoiding the unit of analysis error of double-counting participants. Clinically relevant heterogeneity was assessed by reviewing the variations between studies in terms of the characteristics of participants included, the interventions, and the reported outcomes. Statistical heterogeneity was measured using the Chi (American Psychiatric Association, 2013), tau, and I (American Psychiatric Association, 2013) statistics (DerSimonian and Laird, 2015) and by visual inspection of the forest plots (Kang *et al.*, 2016). A p-value of the Chi (American Psychiatric Association, 2013) test lower than 0.05 or an I^2 statistic of at least 50% indicated a significant statistical heterogeneity. To identify potential sources of heterogeneity, we considered sensitivity analyses, leave-out-one meta-analysis, comparisons with fixed-effects meta-analyses estimates, and subgroup analyses. For example, we stratified results from randomized controlled trials and quasi-experimental observational studies given the methodological differences in these study designs." p259 • **Justification for narrative synthesis or meta-analysis:** Above • **Justification for combining data in meta-analysis:** Above
Outcome assessed	**List of outcomes assessed and intended time frames:** • Primary outcomes: Generalised anxiety disorder (GAD); social anxiety disorder (SAD); post-traumatic stress disorder (PTSD); study discontinuation due to adverse events • Secondary outcomes: Adverse events • Intended timeframe: Not specified • Actual timeframes: 1 to 104 weeks

Parameter	Extraction items
Results/findings	○ **Findings by outcome:** PRIMARY OUTCOMES *Efficacy of cannabinoids for generalized anxiety disorder* ○ Pooled data from three studies (n=36) reported a significant improvement in anxiety symptoms in cannabinoid/cannabis group compared with placebo groups (SMD -1.77, 95% CI -2.44 to -1.10). ○ One study (n=20) identified a statistically significant improvement in anxiety symptoms in the nabilone group compared with the placebo group (p<0.001). ○ One study (n=8) found that cannabidiol attenuated THC-induced anxiety effects. ○ One study (n=8) did not find that nabilone had significant anxiolytic effects. ○ One additional open label study (n=287) reported nearly 30% (87/287) of participants receiving medical cannabis reported significant reductions in self-reported anxiety symptoms. *Efficacy of cannabinoids for social anxiety disorder* ○ Pooled data from two studies (n=34) reported a significant improvement in anxiety symptoms in cannabinoid (CBD) group compared with placebo groups (SMD -2.19, 95% -4.24 to -0.14). ○ Two studies (n=34) reported significantly lower anxiety symptoms in the CBD group compared with the placebo group (p=0.01). However, there was no difference between CBD-treated and healthy controls. *Efficacy of cannabinoids for post-traumatic stress disorder* ○ One study (n=10) reported significant improvement in nightmares, global functioning, but no improvement in sleep after nabilone treatment (no summary statistics reported).

Parameter	Extraction items

- One study (n=80) reported improvement in quality of life, pain, symptoms, and reduced analgesic use after THC treatment (smoked medical cannabis)(no summary statistics reported).
- One study (n=29) reported significant improvement in symptoms after THC (smoked cannabis) treatment (no summary statistics reported).
- One study (n=47) reported that nabilone was effective at reducing nightmare symptoms, sleep, flashbacks, and night sweats.

SECONDARY OUTCOMES

- No serious adverse events were reported by any study. “Dry mouth, dry eyes, headaches, presyncope, and drowsiness were reported more frequently in the nabilone users in 2 studies. However, the other two nabilone studies did not report any adverse events. CBD was relatively well-tolerated, with only one study reporting participants to experience more sleepiness” p262

- **GRADE by outcome:** Not reported
- **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):**

Outcome	No. studies (No. participants)	Summary estimate (95% CI)	P-value	I^2 (%)	Direction of effect
Anxiety (GAD)	3 (36)	SMD -1.77 (-2.44 to -1.10)	NR	0	Cannabinoid
Anxiety (SAD)	2 (34)	SMD -2.19 (-4.24 to -0.14)	NR	84	Cannabinoid

- **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Not applicable
- **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Yes
- **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Yes

Parameter	Extraction items
Significance/direction	**See above if results listed by outcome:** Above
Heterogeneity	• **See above if I^2 available:** Above • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** "Significant heterogeneity was identified, likely due to study-specific differences in the types of preparations used, the disorders considered, the duration of treatment, and the design of the component studies. This heterogeneity may account for significant variability across studies and undermines the quality of the evidence presented here." p262 "To that end, the short duration of some studies and very long duration of others makes arriving at a clear conclusion regarding optimal treatment timelines more challenging. As a result, the combination of such studies to create pooled estimates may appear to be a statistical violation at first glance—however, when we explored the contributions of study design and cannabinoid subtype to heterogeneity by way of subgroup analyses, we found minimal evidence for this, suggesting the decision to be inclusive was fair." p263 • **Causes of heterogeneity investigated:** Yes, I^2, random-effects model, sensitivity analysis considered
Comments	This systematic review includes 14 studies (6 RCTs, 5 open-label studies, and 3 cohort studies). Unless specified otherwise, the above information only reported on RCT studies as per the umbrella review inclusion criteria. Furthermore, Bahji reported on three anxiety disorders: generalised anxiety disorder (GAD); social anxiety disorder (SAD); and post-traumatic stress disorder (PTSD). Bahji conducted three meta-analyses by outcome. In GAD and SAD only RCTs are reported. However, PTSD synthesises open-label and cohort studies together. Therefore, only GAD and SAD meta-analysis outcomes are included in the current review of reviews. We would also like to highlight Table 1 and Figure 2 discrepancy: Massiah 2012 is not cited, named or described in paper but is included in PTSD meta-analysis.

Parameter	Extraction items
	There is a discrepancy between I^2 reported for SAD outcomes in the text "I^2 = 85.7%" and in Figure 2 “84%”. We have used the data from figure 2 in this extraction form.

Bajtel *et al.* (2022): The Safety of Dronabinol and Nabilone: A Systematic Review and Meta-Analysis of Clinical Trials

Parameter	Extraction items
First author and year of publication	Bajtel *et al.* (2022)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** “to prepare a systematic review of the literature in order to analyze the [adverse events] of dronabinol and nabilone based on the meta-analysis of placebo-controlled trials.” p2 • **Exact review question and page number:** “to prepare a systematic review of the literature in order to analyze the [adverse events] of dronabinol and nabilone based on the meta-analysis of placebo-controlled trials.” p2 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** Adult patients ➢ **Setting:** Not specified ➢ **Intervention:** Dronabinol or nabilone ➢ **Comparison:** Placebo ➢ **Outcome:** Frequency of adverse events
Participants (characteristics and numbers)	**For whole sample and subgroups** • **Number of participants:** N=1046 (N=903 completed trials) • **Age:** Mean age range 22.5-87 years

Parameter	Extraction items
	• **Gender:** 57.3% female (1 RCT n=16 did not report gender breakdown) ○ **Details of clinical diagnosis/indications:** Chemosensory perception (n=46); chest pain (n=19); dementia (n=89); fibromyalgia (n=40); gastrointestinal transit (n=66); hyperalgesia and other central nervous system symptoms (n=30); multiple sclerosis (n=699); older people (n=12); spasticity (n=13); spinal cord injury and spasticity (n=12); not reported (n=20)
Setting/context	**Countries (alphabetic order):** Austria/Germany (1); Canada (6); Denmark (1); Netherlands (3); UK (2); USA (3) **Setting (university, public or private clinic):** Not reported **Other relevant features of setting:** Not reported

Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** Dronabinol or nabilone
	• **Dose and regimen:**
	  ○ Nabilone (6 RCTs): 0.5-3 mg; 1-3 times daily
	  ○ Dronabinol (10 RCTs): 5-15 mg; 1-3 times daily
	Administration methods: Oral (16 RCTs) Not reported
	• **Comparator:** Placebo
	• **Treatment duration:** 2 days to 16 weeks
	• **Timeframe for follow-up:** Not specified

Databases and sources searched	• **Number and names of databases:** 3; EMBASE, PubMed, Cochrane Central Register of Controlled Trials; Inception to 21/02/2020

Parameter	Extraction items
	• **Other sources:** Web of Science • **Grey literature:** No • **Reference chasing:** No • **Expert consultation:** No • **Dates:** Inception to 21/02/21 • **Search limits:** No • **Justifications for search limits:** Not applicable • **Other searches:** Not reported • **Protocol prepared:** Yes • **If yes, published:** CRD42021240190 https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021240190 • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Full-text screening was completed in duplicate. It is unclear if title/abstract screening was completed in duplicate. • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Funding of review:** "ÚNKP-21-3-SZTE-262 New National Excellence Program of the Ministry for Innovation and Technology from the source of the National Research, Development and Innovation Fund" p13 • **Conflicts of interest of review:** Authors reported no conflict of interest • **How conflicts of interest were managed:** Not applicable
Date Range (years) of included studies	• **Exact years for included studies:** 2002-2019

Parameter	Extraction items
Number of primary studies included in the systematic review	• **Number of studies:** 16 RCTs • **Number of studies by study design:** 16 RCT • **Study years:** 2019 (1 RCT); 2017 (1 RCT); 2015 (1 RCT); 2014 (1 RCT); 2012 (2 RCTs); 2011 (1 RCT); 2010 (1 RCT); 2008 (2 RCTs); 2007 (1 RCT); 2006 (2 RCTs); 2004 (1 RCT); 2003 (1 RCT); 2002 (1 RCT) • **Funding of included studies:** Not reported • **Conflicts of interest of included studies:** Not reported
Types of studies included	**Planned study designs to be included:** Placebo-controlled RCT **Reasons for including only RCTs/prospective cohort studies:** Not reported **List of excluded studies at full text and reasons for exclusion:** Yes (Table S2)
Appraisal instruments used	**Full name of tools used:** Cochrane Risk of Bias tool **Risk of bias criteria for AMSTAR 2 assessment, for RCTs record Yes/No for:** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The authors did not provide an overall assessment of risk of bias for each trial. However, HRB notes that according to Cochrane's Collaboration tool, and graphical information provided in the paper, the included trials appeared to have a low risk of bias (3 RCTs), unclear risk of bias (6 RCTs) and high risk of bias (7 RCTs).

Parameter	Extraction items

	• **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:**
	  ○ Overall: Low risk randomisation (9/16); low risk outcome ascertainment (10/16)
	  ○ Adverse events: Low risk randomisation (9/16); low risk outcome ascertainment (10/16)
	• **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** "Overall, the methodical quality of the trials included in our final quantitative analysis was considered to be good, mostly with low or unclear risk of bias (Figure 2)." p7
	• **Graphical or statistical test for publication bias:** Yes
	• **Authors' comments likelihood and magnitude of publication bias:** "Publication bias was assessed by using Egger's test, and a funnel plot was utilized for visual assessment. The number of studies allowed this test only in case of headache in dronabinol studies. The inspection of the funnel plot and the significance of Egger's test (p=0.015) revealed a small study effect in case of this [adverse event] (Figure S1)." p8
	• **Authors' comment on how publication bias was dealt with:** Above
	• **Only low ROB RCTs included in review:** No
	• **Only low ROB RCTs included in meta-analysis:** No
	• **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** No

Method of analysis	• **Description of method of analysis as per authors:** "Pooled odds ratios (ORs) were calculated for dichotomous outcomes. A random-effect model was applied in all analyses with the DerSimonian–Laird estimation. Statistical heterogeneity was analyzed using the I^2 and χ^2 tests to gain probability values; $p < 0.10$ was defined to indicate significant heterogeneity. The I^2 test represents the percentage of total variability across studies because of heterogeneity. I^2 values of 30–60%, 50–90% and 75–100% corresponded to moderate, substantial and considerable heterogeneity, respectively, based on

Parameter	Extraction items
	Cochrane's handbook. Forest plots displayed the results of the meta-analysis. Sensitivity analyses were also carried out omitting one study and calculating the summary OR, weighted mean difference with the 95% CI to investigate the influence of a single study on the final estimation. Publication bias was assessed by performing Egger's test, and a funnel plot was utilized for visual assessment. A leave-one-out sensitivity analysis was performed by iteratively removing one study at a time to confirm that our findings were not driven by any single study. The statistical analyses were performed with Stata 16 SE (Stata Corp)" p13 • **Justification for narrative synthesis or meta-analysis:** Not reported • **Justification for combining data in meta-analysis:** Not reported
Outcome assessed	**List of outcomes assessed and intended time frames** • Primary outcomes: Adverse events • Secondary outcomes: None • Intended time frames: Not specified • Actual timeframes: 2 days to 16 weeks
Results/findings	• **Findings by outcome:** *Nabilone adverse events* ○ Summary adverse effects: Across six studies (n=154), 39 different adverse effects were reported. These adverse effects were categorized into three main categories: central nervous system, cardiovascular system and miscellaneous. Frequency of adverse events was higher in the nabilone group compared with the placebo groups (228 events vs 61 events).

Parameter	Extraction items
	○ Drowsiness: Pooled data from three studies (n=40) reported significantly increased likelihood in nabilone groups compared and placebo groups (OR 7.25, 95% CI 1.64 to 31.95). However, this effect was no longer significant if one study (n=20) was removed from meta-analysis. ○ Dizziness: Pooled data from three studies (n=89) reported significantly increased likelihood in nabilone groups compared and placebo groups (OR 21.14, 95% CI 2.92 to 152.75). However, this effect was no longer significant if one study (n=40) was removed from meta-analysis. ○ Dry mouth: Pooled data from four studies (n=102) reported significantly increased likelihood in nabilone groups compared and placebo groups (OR 17.23, 95% CI 4.33 to 68.55). Summary ORs remain stable in leave-one-out sensitivity analysis. ○ Frequency of headache: Pooled data from four studies (n=102) reported no significant difference between nabilone and placebo groups (OR 0.94, 95% CI 0.19 to 4.72). Summary ORs remain stable in leave-one-out sensitivity analysis. *Dronabinol adverse events* ○ Summary adverse events: Across ten studies (n=892), 97 different adverse effects were reported. These adverse effects were categorized into five main categories: central nervous system, respiratory system, musculoskeletal, gastrointestinal, urogenital and miscellaneous. Frequency of adverse events was higher in the dronabinol group compared with the placebo groups (325 events vs 142 events). ○ Dry mouth: Pooled data from six studies (n=741) reported significantly increased likelihood in dronabinol groups compared to placebo groups (OR 5.58, 95% CI 3.19 to 9.78). Summary ORs remain stable in leave-one-out sensitivity analysis. ○ Dizziness: Pooled data from nine studies (n=827) reported significantly increased likelihood in dronabinol groups compared to placebo groups (OR 4.60, 95% CI 2.39 to 8.83. Summary ORs remain stable in leave-one-out sensitivity analysis.

Parameter	Extraction items

- Headache: Pooled data from eight studies (n=473) reported significantly increased likelihood in dronabinol groups compared to placebo groups (OR 2.90, 95% CI: 1.07 to 7.85). However, this effect was no longer significant if one of four studies (n=46; n=24; n=19; n=12) were removed from meta-analysis.
- Nausea: Pooled data from five studies (n=325) reported no significant difference between dronabinol and placebo groups (OR 1.45, 95% CI: 0.38 to 5.43). Summary ORs remain stable in leave-one-out sensitivity analysis.
- Drowsiness: Pooled data from three studies (n=66) reported no significant difference between dronabinol and placebo groups (OR 3.77, 95% CI: 0.43 to 33.25). Summary ORs remain stable in leave-one-out sensitivity analysis.
- Fatigue: Pooled data from four studies (n=333) reported no significant difference between dronabinol and placebo groups (OR 2.00, 95% CI 0.82 to 4.88). Summary ORs remain stable in leave-one-out sensitivity analysis.

- **GRADE by outcome:** Not reported

- **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):**

Outcome	No. studies (No. participants)	Summary estimate (95% CI)	P-value	I^2 (%)	Direction of effect
Nabilone vs placebo					
Drowsiness	3 (40)	OR 7.25 (1.64 to 31.95)	Not reported	0	Nabilone
Dizziness	3 (89)	OR 21.14 (2.92 to 152.75)	Not reported	35.7	Nabilone
Dry mouth	4 (102)	OR 17.23 (4.33 to 68.55)	Not reported	0	Nabilone
Headache	4 (102)	OR 0.94 (0.19 to 4.72)	Not reported	33.9	Nabilone
Dronabinol vs placebo					

Parameter	Extraction items

Dry mouth	6 (741)	OR 5.58 (3.19 to 9.78)	Not reported	0	Dronabinol
Dizziness	8 (827)	OR 4.60 (2.39 to 8.83)	Not reported	41.9	Dronabinol
Headache	9 (473)	OR 2.90 (1.07 to 7.85)	Not reported	42.1	Dronabinol
Nausea	5 (325)	OR 1.45 (0.38 to 5.43)	Not reported	43.6	No significant difference
Drowsiness	3 (66)	OR 3.77 (0.43 to 33.25)	Not reported	77.4	No significant difference
Fatigue	4 (333)	OR 2.00 (0.82 to 4.88)	Not reported	0	No significant difference

- **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Not applicable
- **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Yes
- **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable

Significance/direction

See above if results listed by outcome: Above

Heterogeneity

- **See above if I^2 available:** Above
- **Authors' comment on potential impact of heterogeneity on results and quality of evidence:**

"In addition, sensitivity analyses by iteratively removing one study at a time showed similar and consistent results, thus indicating the robustness of our findings, except for headache, where in case of the removal of the results of either Brisbois *et al.* or Svendsen *et al.* or Malik *et al.* or Ahmed *et al.*, the risk of AEs in groups treated with dronabinol or placebo was not significantly different (Figure S3)" p10

- **Causes of heterogeneity investigated:** Random-effect model used, sensitivity analysis conducted

Parameter	Extraction items
Comments	

Belgers *et al.* (2023): Cannabinoids to Improve Health-Related Quality of Life in Patients with Neurological or Oncological Disease: A Meta-Analysis

Parameter	Extraction items
First author and year of publication	Belgers *et al.* 2023
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "we performed a meta-analysis of the current evidence on cannabinoid efficacy on HRQoL [health-related quality of life] and mental well-being in oncological and neurological patients" p1 • **Exact review question and page number:** "to assess the effects of cannabinoids on [health-related quality of life] in oncological patients and patients with [central nervous system] disease" p8 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** "patients had any oncological disease or any chronic [central nervous system] disease (such as [multiple sclerosis] or Parkinson's disease), or a history of an acute event such as stroke or traumatic brain injury with symptoms lasting > 3 months. Patients had to be 18 years of age or older" p3 ➢ **Setting:** Not specified ➢ **Intervention:** "Treatment consisted of cannabinoids in any form (synthetic or plant based), route of administration or dose, given for at least a week to establish a steady-state concentration of active substances. The active component could be THC, CBD, or a combination of both in any composition" p3 ➢ **Comparison:** Placebo or active control ➢ **Outcome:** Health-related quality of life; mental well-being

Parameter	Extraction items
Participants (characteristics and numbers)	**For whole sample and subgroups:** • **Number of participants:** N=2553 • **Age:** Not reported • **Gender:** Not reported • **Details of clinical diagnosis/indications:** Amyotrophic lateral sclerosis (n=27); Alzheimer's disease (n=42); cancer (n=747); Huntington's disease (n=26); multiple sclerosis (n=1620); Parkinson's disease (n=91)
Setting/context	**Countries (alphabetic order):** Not reported **Setting (university, public or private clinic):** Not reported **Other relevant features of setting:** Not reported
Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** "cannabinoids in any form (synthetic or plant based), route of administration or dose, given for at least a week to establish a steady-state concentration of active substances. The active component could be THC, CBD, or a combination of both in any composition" p3 • **Dose and regimen**: ○ Dronabinol (6 RCTs): 4.5, 5, 10 mg, max 10 mg, max 25 mg, max 28 mg; daily ○ Sativex (5 RCTs): 2.5 mg CBD and 2.7 mg THC per spray; 30 mg, max 30 mg, max 40 mg, max 75 mg, max 120 mg; daily ○ Nabilone capsule (2 RCTs): 1 mg THC, 2 mg THC; daily ○ Cannabis extract (2 RCTs): 2:5 mg (CBD:THC), max 25 mg; daily ○ CBD (2 RCTs): 75mg or 300mg, max 300 mg; daily

Parameter	Extraction items
	• **Administration methods:** Oromucosal (5 RCTs); oral (12 RCTs) • **Comparator:** Placebo (16 RCTs); megestrol acetate (1 RCT) • **Treatment duration:** Range 26 weeks – 36 months • **Timeframe for follow-up:** Not reported for any study
Databases and sources searched	• **Number and names of databases:** 3; PubMed (inception to 02/08/2021), EMBASE (inception to 02/08/2021), PsycINFO (inception to 03/08/2021) • **Other sources:** Clarivate Analytics/Web of Science Core Collection (inception to 03/08/2021); trial registration websites • **Grey literature:** Not reported • **Reference chasing:** Not reported • **Expert consultation:** Yes (experienced librarian) • **Dates:** Above • **Search limits:** No restrictions on publication date or language • **Justifications for search limits:** Not applicable • **Other searches:** Not reported • **Protocol prepared:** Yes • **If yes, published:** Not registered or published • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** No (verified by second reviewer) • **If yes, rate of agreement:** Not applicable

Parameter	Extraction items
	• **Funding of review:** "This meta-analysis has been funded by the (CCA2018-2-17)." p13 • **Conflicts of interest of review:** "Arrieta reports personal fees from Pfizer, grants and personal fees from Astra Zeneca, grants and personal fees from Boehringer Ingelheim, personal fees from Lilly, personal fees from Merck, personal fees from Bristol Myers Squibb, and grants and personal fees from Roche, outside the submitted work. The other authors declare no conflict of interests" p13 • **How conflicts of interest were managed:** Not reported
Date Range (years) of included studies	• **Exact years for included studies:** 2002-2021
Number of primary studies included in the systematic review	• **Number of studies:** 17 RCTs • **Number of studies by study design:** 17 RCTs • **Study years:** 2002 (1 RCT); 2003 (1 RCT); 2004 (2 RCTs); 2005 (1 RCT): 2006 (1 RCT); 2010 (1 RCT); 2011 (1 RCT); 2012 (2 RCTs); 2014 (1 RCT); 2015 (2 RCTs); 2016 (1 RCT); 2018 (1 RCT); 2020 (1 RCT); 2021 (1 RCT) • **Funding of included studies:** Industry funded (11 RCTs); non-industry funded (6 RCTs) • **Conflicts of interest of included studies:** Not reported
Types of studies included	**Planned study designs to be included:** RCT **Reasons for including only RCTs/prospective cohort studies:** "To limit assumptions and thereby risk of bias, only RCTs were included, and data were not imputed" p12 **List of excluded studies at full text and reasons for exclusion:** Not reported
Appraisal instruments used	**Full name of tools used:** Cochrane Risk of Bias Tool 2.0 **<u>Risk of bias criteria for AMSTAR 2 assessment, for RCTs, record Yes/No for:</u>** • **Concealment of allocation:** Yes

Parameter	Extraction items
	• **Blinding of assessors:** Yes • **Sequence allocation (individual vs group randomisation):** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The included trials appeared to have a high risk of bias (10 RCTs), unclear risk of bias (authors refer to as "some concerns") (2 RCTs) and low risk of bias (5 RCTs). • "Studies were considered low risk of bias if all domains were judged to be of low risk; if some domains raised some concerns, the study was judged to be of some concern; and when at least one domain was high risk, the study was believed to have a high risk of bias. Inconsistencies between reviewers were discussed with each other until consensus was achieved." p4 • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** *Cannabinoids vs placebo:* ○ Overall: Low risk randomisation (15/17); low risk outcome ascertainment (7/17) ○ General health-related quality of life: Low risk randomisation (11/13); low risk outcome ascertainment (6/13) ○ Mental wellbeing: Low risk randomisation (11/13); low risk outcome ascertainment (6/13) *CBD:THC vs placebo* ○ General health-related quality of life: Low risk randomisation (5/5); low risk outcome ascertainment (1/5) ○ Mental wellbeing: Low risk randomisation (5/5); low risk outcome ascertainment (2/5) *THC vs placebo* ○ General health-related quality of life: Low risk randomisation (5/6); low risk outcome ascertainment (3/6) ○ Mental wellbeing: Low risk randomisation (5/6); low risk outcome ascertainment (2/6) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** Not reported

Parameter	Extraction items
	• **Graphical or statistical test for publication bias:** Yes "We tested for publication bias by using Egger's formula, which tests the degree of funnel plot asymmetry." p4 • **Authors' comments likelihood and magnitude of publication bias:** In relation to general health-related quality of life outcomes "Egger's test did not indicate the presence of publication bias (p = 0.74)" p8. In relation to mental well-being outcomes "Egger's test did not indicate the presence of publication bias (p=0.20)" p8. • **Authors' comment on how publication bias was dealt with:** Not applicable • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** No • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** Not reported
Method of analysis	• **Description of method of analysis as per authors:** "Data were analyzed with Rstudio (version 4.0.2). We used the packages ''dmetar,'' ''effsize,'' ''meta,'' ''tidyverse,'' ''dplyr,'' and ''esc.''22–27 Risk of bias was visualized with the ''robvis'' package. In studies with multiple intervention groups, such as multiple doses or different forms of cannabinoids, data of intervention groups were pooled and new mean changes and SDs were calculated. We quantified the treatment effect by Hedges' g and its accompanying standard error. For crossover studies, we calculated the Hedges' g using the formula for paired data. Hedges' g corrects for small sample sizes and is calculated by dividing the differences in mean change from baseline by the pooled and weighted SD. A g < 0.2 represents a small effect, 0.5 < g < 0.8 a moderate effect, and g ‡ 0.8 a large effect. We used a random-effects model to account for heterogeneity between studies due to differences in disease, intervention, and study duration. We visualized the effect sizes with forest plots. Two-sided p-values < 0.05 were considered significant. We tested heterogeneity of study outcomes with I^2 ; < 25% was considered negligible and > 75% undeniable heterogeneity." p4

<table>
<tr><th>Parameter</th><th>Extraction items</th></tr>
<tr><td></td><td>• Justification for narrative synthesis or meta-analysis: Not reported
• Justification for combining data in meta-analysis: Not reported</td></tr>
<tr><td>Outcome assessed</td><td>List of outcomes assessed and intended timeframes
• Primary outcomes: Health-related quality of life; mental health
• Intended timeframes: >1 week
• Actual timeframes: 2 weeks-36 months treatment duration; follow-up period not reported for any study</td></tr>
<tr><td>Results/findings</td><td>• Findings by outcome:
General health-related quality of life
○ Pooled data from twelve studies (n=1171) reported no significant difference between cannabinoid and control (11 placebo, 1 megestrol acetate) groups (SMD -0.02, 95% CI -0.11 to 0.06). In subgroup analyses, neither population (cancer vs central nervous system disease) nor intervention method (THC:CBD vs THC) significantly effected health-related quality of life.
Mental well-being
○ Pooled data from twelve studies reported no significant difference between cannabinoid and placebo groups (SMD -0.02, 95% CI -0.16 to 0.13).
• GRADE by outcome: Not reported
• Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects): Random
<table>
<tr><th>Outcome</th><th>No. studies (No. participants)</th><th>Summary estimate (95% CI)</th><th>P-value</th><th>I^2 (%)</th><th>Direction of effect</th></tr>
<tr><td colspan="6">Cannabinoids vs placebo</td></tr>
<tr><td>General health-related quality of life</td><td>13 (1771)</td><td>SMD -0.02 (-0.11 to 0.06)</td><td>0.57</td><td>0</td><td>No significant difference</td></tr>
<tr><td>Mental well-being</td><td>13 (1613)</td><td>SMD -0.02 (-0.16 to 0.13)</td><td>0.81</td><td>23.7</td><td>No significant difference</td></tr>
</table>
</td></tr>
</table>

Parameter	Extraction items

THC:CBD vs placebo					
General health-related quality of life	5(1258)	SMD 0.03 (-0.07 to 0.13)	Not reported	0	No significant difference
Mental well-being	5(796)	SMD -0.09 (-0.27 to 0.09)	Not reported	0	No significant difference
THC vs placebo					
General health-related quality of life	6(462)	SMD -0.12 (-0.21 to -0.02)	Not reported	0	No significant difference
Mental well-being	6(798)	SMD 0.05 (-0.21 to 0.30)	Not reported	37	No significant difference

- **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Above
- **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Yes, I^2, random effects model, subgroup analysis
- **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable

Significance/direction

See above if results listed by outcome: Above

Heterogeneity

- **See above if I^2 available:** Above
- **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** "Considerably, heterogeneous patient populations, interventions, and outcome measures were included in this meta-analysis. The subgroup analyses, however, did not indicate differences between active intervention and control group in mental well-being or general [health-related quality of life], except for a difference between the effects of THC and CBD:THC on general [health-related quality of life], but not on mental well-being. CBD:THC did not decrease or increase [health-related quality of life], and THC had only a small, possibly futile negative effect on general HRQoL" p12
- **Causes of heterogeneity investigated:** Yes, I^2, random effects model, subgroup analysis

Parameter	Extraction items
Comments	There is a discrepancy between the article text and the forest plots in relation to the number of RCTs included in each meta-analysis of cannabinoids vs placebo. The text states that 12 RCTs were included in each meta-analysis, but the forest plots display 13 RCTs included in each. There is a corresponding discrepancy in the number of participants in each meta-analysis; the text states n=1771 (p8) and n=1613 (p8) respectively, but the total number of participants in the studies listed in the forest plot (based on the study characteristics listed in Table 1) is 1773 and 1620. Data has been extracted from article text p8 in this extraction form.

Bialas *et al.* (2022): Long-term observational studies with cannabis-based medicines for chronic non-cancer pain: A systematic review and meta-analysis of effectiveness and safety

Parameter	Extraction items
First author and year of publication	Bialas *et al.* (2022)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "to assess the long-term effectiveness, tolerability and safety of [cannabis-based medicines] in the management of chronic noncancer pain in patients of any age in long-term observational studies" p1222 • **Exact review question and page number:** "to assess the long-term effectiveness, tolerability and safety of [cannabis-based medicines] in the management of chronic noncancer pain in patients of any age in long-term observational studies" p1222 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** Patients with chronic non-cancer pain ➢ **Setting:** Not reported ➢ **Intervention:** "studies with cannabinoids (either phytocannabinoids such as herbal cannabis [hashish, marihuana], plant-based cannabinoids [cannabidiol, nabiximole] or pharmacological [synthetic] cannabinoids [e.g. dronabinol, levonantradol, nabilone]), at any dose, by any route, administered for the relief of [chronic non-cancer pain]" p1223

Parameter	Extraction items
	➢ **Comparison:** No comparison ➢ **Outcome:** Chronic non-cancer pain
Participants (characteristics and numbers)	**For whole sample and subgroups** • **Number of participants:** N=2686 (data extracted from table 1, discrepancy with N=2641 reported in main text) • **Age:** Mean age range 36-82 years • **Gender:** 50.6% female (n=1358) • **Details of clinical diagnosis/indications:** Neuropathic pain, musculoskeletal pain, other pain, visceral pain, headache, combinations (n=1045); fibromyalgia (n=102); musculoskeletal pain, neuropathic pain, lower back pain, other pain conditions, cancer (n=206); back pain, osteoarthritis, chronic headaches (n=751); fibromyalgia, cancer, post-traumatic stress disorder (n=367); nociceptive pain, neuropathic pain, other (n=215)
Setting/context	**Countries (alphabetic order):** Canada (2); Israel (2); Italy (2) **Setting (university, public or private clinic):** Clinical centres in Canada, Israel and Italy **Other relevant features of setting:** Not applicable
Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** "studies with cannabinoids (either phytocannabinoids such as herbal cannabis [hashish, marihuana], plant-based cannabinoids [cannabidiol, nabiximol] or pharmacological [synthetic]

Parameter	Extraction items

	cannabinoids [e.g. dronabinol, levonantradol, nabilone]), at any dose, by any route, administered for the relief of [chronic non cancer pain]" p1223
	• **Dose and regimen:**
	  ○ Medical cannabis (3 studies): THC/CBD, THC, THC and/or CBD, THC and CBD; 30-43.2 g/month, 1.5 g/day, 140 mg/day and 39 mg/day
	  ○ Bedrocan and Bediol (1 study): 22% THC/1% CBD, 6.3% THC/8% CBD; 10-200 drops/day
	• **Administration methods:** Smoking or inhaling (1 study); smoking, oral, vaporising (1 study); orally (1 study), Not reported (1 study)
	• **Comparator:** None
	• **Treatment duration:** 6-12 months
	• **Timeframe for follow-up:** Not reported for included studies

Databases and sources searched	• **Number and names of databases:** 3; CENTRAL, EMBASE and MEDLINE; inception to 22/12/21 • **Other sources:** US National Institutes of Health clinical trial register (www.ClinicalTrials.gov), European Union Clinical Trials Register (www.clinicaltrialsregister.eu), World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/). • **Grey literature:** No • **Reference chasing:** No • **Expert consultation:** No • **Dates:** Inception to 22/12/21 • **Search limits:** No • **Justifications for search limits:** Not applicable • **Other searches:** Not applicable

Parameter	Extraction items
	• **Protocol prepared:** Yes • **If yes, published:** CRD42021293251 https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=293251 • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** Yes • **If Yes, rate of agreement:** Not reported • **Funding of review:** The authors reported they received no funding for this review. • **Conflicts of interest of review:** "Patric Bialas has received one honorarium for an educational lecture by Spectrum cannabis. The other authors declare no financial conflicts with regards to the manuscript. Winfried Häuser was the head of EFIC's task force of a position paper on cannabis-based medicines and medical cannabis for chronic pain and member of the task force of the German Pain Society on the same topic. Mary-Ann Fitzcharles was the head of a task force of the Canadian Association of Rheumatology of a position paper on medical cannabis for rheumatic diseases." p1231 • **How conflicts of interest were managed:** Not reported
Date Range (years) of included studies	• **Exact years for included studies:** 2015-2021
Number of primary studies included in the systematic review	• **Number of studies:** 6 studies • **Number of studies by study design:** 6 prospective cohort studies • **Study years:** 2015 (1 study); 2016 (1 study); 2019 (1 study); 2020 (2 studies); 2021 (1 study) • **Funding of included studies:** Not reported (2 studies); cannabis-producing enterprise, by public funding (1 study); cannabis-producing enterprise (1 study); no funding (1 study)

Parameter	Extraction items
	• **Conflicts of interest of included studies:** "Two studies did not report on funding. One study each received public funding, by cannabis-producing enterprise, by public funding and by cannabis-producing enterprise and no funding. One author group did not declare their conflicts of interest. Three author groups declared that they have no conflicts of interest" p1226
Types of studies included	**Planned study designs to be included:** Prospective cohort design studies **Reasons for including only RCTs/prospective cohort studies:** "We included long-term (≥6months) prospective observational studies. We selected a trial duration of at least 6 months guided by the guideline on the clinical development of medicinal products intended for the treatment of pain by the European Medicines Agency." p1223 **List of excluded studies at full text and reasons for exclusion:** Yes
Appraisal instruments used	**Full name of tools used:** Methodological Index for Non-Randomised Studies (MINORS); GRADE system **<u>Risk of bias criteria for AMSTAR 2 assessment, for prospective cohort studies record Yes/No for:</u>** • **Confounding:** No • **Selection bias:** Yes (inclusion of consecutive patients) • **Exposure and outcomes:** No • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** Fair quality (6 studies) • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** Not applicable • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** Not reported • **Graphical or statistical test for publication bias:** "We planned to use the Egger intercept test (Egger *et al.*, 1997) and the Begg rank correlation test for funnel plot asymmetry (Begg & Mazumdar, 1994) at the significance level p<0.05" p1225

Parameter	Extraction items
	• **Authors' comments likelihood and magnitude of publication bias:** Not reported • **Authors' comment on how publication bias was dealt with:** Not reported • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** No • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** No
Method of analysis	• **Description of method of analysis as per authors:** "The mean difference of the continuous variable pain intensity, standardized to a 0–10 scale, and standardized mean differences of other continuous variables were calculated using means and standard deviations for each intervention using a random effects model. Pooled estimates of event rates of categorical data (e.g. drop out due to adverse events) were calculated using a random effects model. Confidence intervals (95% CI) were calculated for all summary data. We used the I^2 statistic to identify heterogeneity. Combined results with I^2>50% were considered substantially heterogeneous (Deeks *et al.*, 2021)." p123 • **Justification for narrative synthesis or meta-analysis:** Not reported • **Justification for combining data in meta-analysis:** Not reported
Outcome assessed	**List of outcomes assessed and intended timeframes:** • Primary outcomes: Pain intensity from baseline to follow-up, proportion of patients with pain relief of 50% or greater and 30% or greater, adverse events (drop-out due to adverse events and proportion of patients with serious adverse events), proportion of patients that completed study, proportion of patients that dropped out due to lack of efficacy, disability

Parameter	Extraction items
	• Secondary outcomes: Sleep, depression, anxiety, health-related quality of life, opioid cessation, adverse events (nervous system disorders, psychiatric disorders, gastrointestinal disorders, pulmonary disorders), aberrant drug behaviour • Intended timeframes: ≥6 months • Actual timeframes: 6-12 months
Results/findings	• **Findings by outcome** *Continuous outcomes (all studies used medical cannabis with varying levels of THC and CBD)* PRIMARY OUTCOMES o Mean pain intensity: Pooled data from six studies (n=2571) reported significant improvement in medical cannabis compared with placebo groups (WMD 1.75, 95% CI 0.72 to 2.78). SECONDARY OUTCOMES o Disability: Pooled data from five studies (n=2201) reported significant improvement in medical cannabis compared with placebo groups (SMD 0.45, 95% CI 0.05 to 0.88). o Sleep: Pooled data from five studies (n=2213) reported significant improvement in medical cannabis compared with placebo groups (SMD 0.56, 95% CI 0.33 to 0.80). o Depression: Pooled data from four studies (n=2007) reported significant improvement in medical cannabis compared with placebo groups (SMD 0.33, 95% CI 0.05 to 0.60). o Anxiety: Pooled data from two studies (n=1147) reported significant improvement in medical cannabis compared with placebo groups (SMD 0.36, 95% CI 0.26 to 0.46). o Health-related quality of life: Pooled data from two studies (n=1412) reported significant improvement in medical cannabis compared with placebo groups (SMD 1.05, 95% CI 0.20 to 1.89). *Dichotomous outcomes*

Parameter	Extraction items
	PRIMARY OUTCOMES ○ Pain relief of 50% or greater: Pooled prevalence reported in six studies (n=2686) was 20.8% (10.2 to 34.0) in cannabis compared with placebo groups. ○ Pain relief of 30% or greater: Pooled prevalence reported in six studies (n=2686) was 38.3% (95% CI, 21.2% to 57.1%). Pooled prevalence fell to 20.5% (95 % CI,18.3% to 22.9%) after sensitivity analysis removing four studies that had applied imputation methods. ○ Drop out due to lack of efficacy: Pooled prevalence reported in four studies (n=568) was 7.4% (95% CI, 1.8% to 16.1%). SECONDARY OUTCOMES ○ Retention rate: Pooled prevalence reported in six studies (n=2686) was 53.9% (95% CI, 26.8% to 79.9%). ○ Opioid cessation: Pooled prevalence reported in three studies (n=594) was 16.2% (95% CI, 6.2% to 29.8%). ○ Drop out due to adverse events: Pooled prevalence reported in three studies (n=1568) was 6.8% (95% CI, 4.3% to 9.7%). ○ Central nervous system adverse events: Pooled prevalence reported in three studies (n=1005) was 25.1% (95% CI, 9.8% to 44.6%). ○ Psychiatric adverse events: Pooled prevalence reported in four studies (n=1051) was 23.6% (95% CI, 10.9% to 39.3%). ○ Gastrointestinal adverse events: Pooled prevalence reported in four studies (n=1051) was 28.2% (95% CI, 12.8% to 46.9%). ○ Pulmonary adverse events: Pooled prevalence reported in three studies (n=500) was 17.8% (95% CI, 0.7% to 50.4%). ○ Serious adverse events: Pooled prevalence reported in three studies (n=1466) was 3.0% (95% CI, 0.02% to 12.8%). ○ Deaths: Pooled prevalence reported in five studies (n=1935) was 0.3% (95% CI, 0.09% to 0.60%).

Parameter	Extraction items

- **GRADE by outcome:** The authors state "the certainty of evidence was very low for all outcomes" p1226
- **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):** Random effects models

Indication	No. studies (No. participants)	Summary estimate (95% CI)	P-value	I^2 (%)	Direction of effect
Continuous outcome variables (mixed cannabinoid)					
Mean pain intensity	6 (2571)	WMD 1.75 (0.72 to 2.78)	0.0009	96.6	Cannabis
Disability	5 (2201)	SMD 0.45 (0.05 to 0.88)	0.03	95.5	Cannabis
Sleep problems	5 (2213)	SMD 056 (0.33 to 0.80)	<0.0001	84.4	Cannabis
Depression	4 (2007)	SMD 0.33 (0.05 to 0.60)	0.02	84.4	Cannabis
Anxiety	2 (1147)	SMD 0.36 (0.26 to 0.46)	<0.0001	0	Cannabis
Health-related quality of life	2 (1412)	SMD 1.05 (0.20 to 1.89)	0.02	98.2	Cannabis

Indication	No. studies (No. participants)	Proportion of sample % (95% CI)	I^2 (%)
Dichotomous outcome variables			
Pain relief of 50% or greater	6 (2686)	20.8 (10.2 to 34.0)	98.0
Pain relief of 30% or greater	6 (2686)	38.3 (21.2 to 57.1)	98.9
Opioid cessation	3 (594)	16.2 (6.2 to 29.8)	93.2
Drop out (lack of efficacy)	4 (1568)	7.4 (1.8 to 16.1)	95.3
Retention rate	6 (2686)	53.9 (26.8 to 79.9)	99.5
Adverse events			
Drop out due to adverse events	3 (1568)	6.8 (4.3 to 9.7)	68.0
Central nervous system	3 (1005)	25.1 (9.8 to 44.6)	97.5
Psychiatric	4 (1051)	23.6 (10.9 to 39.3)	96.2
Gastrointestinal	4 (1051)	28.2 (12.8 to 46.9)	97.1
Pulmonary	3 (500)	17.8 (0.7 to 50.4)	99.7
Serious adverse events	3 (1466)	3.0 (0.02 to 12.8)	97.3

Parameter	Extraction items
	Death | 5 (1935) | 0.3 (0.09 to 0.6) | 0
	• **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Above • **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** I^2, random effects model • **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable **For prospective cohort studies:** • **Combined effect estimates adjusted for confounding, rather than combining raw data:** Not reported **Justification for combining raw data provided, where adjusted effect estimates unavailable:** Not reported
Significance/direction	**See above if results listed by outcome:** Above
Heterogeneity	• **See above if I^2 available:** Above • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** "There was a high heterogeneity of all outcomes except for two probably due to the heterogeneity of the study samples and of the settings of the studies. Therefore, we have downgraded the certainty of evidence by one level due to inconsistency (high heterogeneity)" p1230 • **Causes of heterogeneity investigated:** Yes, I^2, random-effects model, sensitivity and subgroup analysis
Comments	There is a discrepancy between total participants reported on p1225 and p1227-1228 (table 1) (2641 vs 2686 respectively). Data from table 1 is used in this extraction form. Prospective cohort study (Aviram, Ware); prospective open label cohort (Haroutounian); prospective observational study (Giorgi, Safakish, Sagy).

Black *et al.* (2019): Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis

Parameter	Extraction items
First author and year of publication	Black *et al.* (2019)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "to examine the available evidence for all types of medicinal cannabinoids and all study designs (controlled and observational) to ascertain the impact of medicinal cannabinoids on remission from and symptoms of depression, anxiety, post-traumatic stress disorder, and psychosis, as well as symptoms of attention deficit hyperactivity disorder (ADHD) and Tourette syndrome, either as the primary disorder or secondary to other disorders; and the impact of medicinal cannabinoids on outcomes including global functioning, quality of life, and patient or caregiver impression of change. We also examined the safety of medicinal cannabinoids for mental health symptoms and disorders, including all-cause, serious, and treatment-related adverse events and study withdrawals." p997 • **Exact review question and page number:** As above **PICO elements reported in Introduction/Methods:** ➢ **Population:** Adults aged ≥ 18 years for the purpose of treating depression, anxiety, attention deficit hyperactivity disorder and Tic/Tourette syndrome, post-traumatic stress disorder and psychosis either as the primary condition or as secondary to other medical conditions ➢ **Intervention:** Any type and formulation of medicinal cannabinoid ➢ **Comparator:** Active comparator or placebo ➢ **Outcome:** "Remission from and symptoms of depression, anxiety, post-traumatic stress disorder, and psychosis, as well as symptoms of attention deficit hyperactivity disorder and Tourette syndrome, either as

Parameter	Extraction items
	the primary disorder or secondary to other disorders; and the impact of medicinal cannabinoids on outcomes including global functioning, quality of life, and patient or caregiver impression of change, safety of medicinal cannabinoids for mental health symptoms and disorders, including all-cause, serious, and treatment-related adverse events and study withdrawals." p997
Participants (characteristics and numbers)	**For whole sample and subgroups** n=3088 RCT; n=5481 observational/open label studies *The observational/open label studies are excluded from the remainder of the extraction. • **Number of participants:** N=3088 • **Age:** Median age range 23.6-61.2 years (three studies did not report age) • **Gender:** 53.96% female • **Details of clinical diagnosis/indications:** Depression (n=2551); anxiety (n=605); Tourette (n=36); attention deficit hyperactivity disorder (n=30); post-traumatic stress disorder (n=10); psychosis (n=281)
Setting/context	**Countries (alphabetic order):** Brazil (3 RCTs); Canada (4 RCTs); Germany (2 RCTs); Italy (2 RCT); Netherlands (2 RCTs); Spain (1 RCT); Switzerland (1 RCT); UK (8 RCTs); UK, Israel, Czech Republic (1 RCT); UK, Romania, Poland (1 RCT); UK, Spain, Poland, Czech Republic, Italy (1 RCT); USA (10 RCTs); USA, Europe, Latin America and South Africa (1 RCT) **Setting (university, public or private clinic):** Not reported **Other relevant features of setting:** Not applicable
Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** "We considered studies examining any type and formulation of medicinal cannabinoid: tetrahydrocannabinol; cannabidiol; combination tetrahydrocannabinol and cannabidiol; cannabis sativa; and other cannabinoids e.g. tetrahydrocannabinolic

Parameter	Extraction items
	acid, cannabidiolic acid, cannabidivarin, and the synthetic delta-9- tetrahydrocannabinol formulations nabilone and dronabinol. We categorised these into pharmaceutical grade THC (with or without CBD; labelled here as THC:CBD), pharmaceutical grade CBD, and medicinal cannabis." p997 • **Dose and regimen:** o Cannabis sativa (5 RCTs); 1-9.4% THC; daily o Nabiximols (8 RCTs): 2.7-120 mg THC and 2.5-120 mg CBD; daily o Dronabinol (6 RCTs): 9-24 mg; daily o Nabilone (6 RCTs): 0.25-4 mg; daily o THC extract (5 RCTs): 2.5-16 mg; daily o CBD extract (8 RCTs): 2.5-1000mg; daily o THC:CBD extract: (2 RCTs): 2.25mg THC and 2.5-12.5 mg CBD; daily • **Administration methods:** Intravenous (1 RCT); oral (21 RCTs); not recorded (1 RCT); oromucosal spray (8 RCTs); smoked (3 RCTs); sublingual spray (1 RCTs); vaporised (2 RCTs) • **Comparator:** Placebo (34 RCTs); amisulpride (1 RCT); dihydrocodeine (1 RCT); ibuprofen (1 RCT) • **Treatment duration:** Not specified (study duration range 1 day-156 weeks) • **Timeframe for follow-up:** Not reported for included RCTs
Databases and sources searched	• **Number and names of databases:** MEDLINE, Embase, PsycINFO, the Cochrane Central Register of Controlled Clinical Trials (CENTRAL), and the Cochrane Database of Systematic Reviews; 01/01/1980 to 30/04/2018 • **Other sources:** ClinicalTrials.gov, the EU Clinical Trials Register, the Australian and New Zealand Clinical Trials Registry • **Grey literature:** No • **Reference chasing:** Yes

Parameter	Extraction items

	• **Expert consultation:** No
	• **Dates:** 01/01/1980- 30/04/2018
	• **Search limits:** None
	• **Justifications for search limits:** Not applicable
	• **Other searches:** No
	• **Protocol prepared:** Yes
	• **If yes, published:** Yes
	  ○ Depression: CRD42017059376 https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=59376
	  ○ Anxiety: CRD42017059373 https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=59373
	  ○ Post-traumatic stress disorder: CRD42017064996 https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=64996
	  ○ Attention deficit hyperactivity disorder/Tourette syndrome: CRD42017059372 https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=59372
	  ○ Psychosis: CRD42018102977 https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=102977
	• **Search strategy/key words provided:** Yes
	• **Screening completed in duplicate:** Yes
	• **If yes, rate of agreement:** Not reported
	• **Extraction completed in duplicate:** Unclear
	• **If yes, rate of agreement:** Not reported

Parameter	Extraction items
	• **Funding of review:** "Therapeutic Goods Administration, Australia; Commonwealth Department of Health, Australia; Australian National Health and Medical Research Council; and US National Institutes of Health" p995 • **Conflicts of interest of review:** "MF and LD have been investigators on untied (ie, no control of the company over the conduct, reporting, or publication of study findings) investigator-driven educational grants funded by Reckitt Benckiser, Mundipharma, and Seqirus. MF, GC, and LD have been investigators on untied investigator-driven educational grants funded by Indivior. All other authors declare no competing interests" p1008 • **How conflicts of interest were managed:** "The funders had no role in study design, data collection, data analysis, data interpretation, the writing of the report, or the decision to submit the paper for publication." p999
Date Range (years) of included studies	• **Exact years for included studies:** 2001-2018
Number of primary studies included in the systematic review	• **Number of studies:** 36 RCTs; 46 observational studies (the 46 observational studies are excluded from the remainder of the extraction). • **Number of studies by study design:** RCT • **Study years:** 2001 (1 RCT); 2003 (2 RCTs); 2004 (2 RCTs); 2005 (2 RCTs); 2007 (1 RCT); 2008 (4 RCTs); 2009 (2 RCTs); 2010 (3 RCTs); 2011 (3 RCTs); 2012 (4 RCTs); 2013 (1 RCT); 2015 (3 RCTs); 2016 (1 RCT); 2017 (4 RCTs); 2018 (3 RCTs); unpublished (1 RCT) • **Funding of included studies:** Not reported

Parameter	Extraction items
	• **Conflicts of interest of included studies:** None (18 RCTs); potential conflict (18 RCTs); not reported (14 RCTs)
Types of studies included	**Planned study designs to be included:** "As per existing reviews examining the efficacy of medicinal cannabinoids for [chronic non-cancer pain] and epilepsy, we included both experimental and observational study designs, that is, randomised controlled trials (RCTs), non-RCTs, quasi-experimental, before and after studies, prospective and retrospective cohort studies, case control studies, analytical cross-sectional studies, observational studies, self-report, and N-of-1 studies." **Reasons for including only RCTs/prospective cohort studies:** "This approach allows researchers, clinicians, and policymakers to map current research activity and to identify knowledge gaps." p997 **List of excluded studies at full text and reasons for exclusion:** Yes
Appraisal instruments used	**Full name of tools used:** Cochrane Risk of Bias Tool; GRADE system **Risk of bias criteria for AMSTAR 2 assessment, for RCTs record Yes/No for:** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The authors did not provide an overall assessment of risk of bias for each trial. However, HRB notes that according to Cochrane's Collaboration tool, and graphical information provided in the paper, the included trials appeared to have a high risk of bias (16 RCTs) and unclear risk (21 RCTs).

Parameter	Extraction items
	• **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** ○ Overall: Low risk randomisation (16/37); low risk outcome assessment (19/37) *THC/CBD vs placebo* ○ Change in depressive symptoms: Low risk randomisation (5/12); low risk outcome assessment (4/12) ○ Change in anxiety symptoms: Low risk randomisation (1/7); low risk outcome assessment (1/7) ○ Change in ADHD symptoms: Low risk randomisation (1/1); low risk outcome assessment (1/1) ○ Change in tic severity: Low risk randomisation (0/2); low risk outcome assessment (0/2) ○ Positive symptoms of psychosis: Low risk randomisation (0/1); low risk outcome assessment (0/1) ○ Negative symptoms of psychosis: Low risk randomisation (0/1); low risk outcome assessment (0/1) *THC vs active* ○ Change in depressive symptoms: Low risk randomisation (1/1); low risk outcome assessment (1/1) ○ Change in anxiety symptoms: Low risk randomisation (1/1); low risk outcome assessment (1/1) *CBD vs placebo* ○ Change in anxiety symptoms: Low risk randomisation (0/2); low risk outcome assessment (1/2) ○ Change in psychosis symptoms: Low risk randomisation (1/2); low risk outcome assessment (1/2) ○ Positive symptoms of psychosis: Low risk randomisation (1/2); low risk outcome assessment (1/2) ○ Negative symptoms of psychosis: Low risk randomisation (1/2); low risk outcome assessment (1/2) *CBD vs active* ○ Change in psychosis symptoms: Low risk randomisation (0/1); low risk outcome assessment (0/1) ○ Positive symptoms of psychosis: Low risk randomisation (0/1); low risk outcome assessment (0/1) ○ Negative symptoms of psychosis: Low risk randomisation (0/1); low risk outcome assessment (0/1)

Parameter	Extraction items
	Plant vs placebo ○ Change in depressive symptoms: Low risk randomisation (1/1); low risk outcome assessment (1/1) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** "Nonetheless, our analyses and conclusions are limited by the small amount of available data, small study sizes, and heterogeneity of findings across studies. Small study sizes are of particular concern as effects have been identified to be larger in small studies of medicinal cannabinoids for chronic noncancer pain. Moreover, various independent analyses were done and hence might not retain significance if they are adjusted for multiple comparisons. However, no recommended approach exists for addressing multiplicity in systematic reviews, and we attempted to minimise this by choosing few primary outcomes, keeping subgroups to a minimum, and testing effects at a single time-point only" p1007 • **Graphical or statistical test for publication bias:** Not specified • **Authors' comments likelihood and magnitude of publication bias:** Not reported • **Authors' comment on how publication bias was dealt with:** Not reported • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** No • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** No
Method of analysis	• **Description of method of analysis as per authors:** "All analyses were conducted using Review Manager (RevMan) version 5.316. Meta-analyses included parallel and cross-over RCTs. Continuous and dichotomous outcomes were pooled as standardised mean differences and odds ratios, respectively, using random effects, generic inverse variance meta-analyses. A

Parameter	Extraction items
	common rule of thumb for interpreting SMDs is: 0.2, 0.5, and 0.8 represent small, medium, and large effects, respectively. Heterogeneity was assessed using the I^2 statistic. I^2 values of 0-39%, 40-74%, and 75-100% can be considered unimportant, moderate/substantial, and high levels of inconsistency across studies, respectively. Analyses were stratified by mental health condition, cannabinoid used (pharmaceutical THC:CBD, pharmaceutical CBD, medicinal cannabis), and comparator used (active, placebo). For each of these, we first pooled the evidence from all eligible RCTs, regardless of population studied. Where applicable (depression and anxiety studies only), we then conducted sensitivity analyses restricted to only those RCTs enrolling participants with the mental health disorder. Where heterogeneity was substantial and sample sizes were sufficient, we conducted exploratory analyses to examine potential reasons for the heterogeneity. Finally, we pooled the evidence across RCTs (regardless of mental health condition) on the incidence of adverse events and withdrawals. Narrative synthesis of results from observational studies was conducted by summarising key results from each study, using the same stratification as for RCTs where possible. For the interested reader, further details on the meta-analytic approach–including methods employed to manage variations in study design and avoid unit-of-analysis errors–are provided in Appendix (p 51).” p999 • **Justification for narrative synthesis or meta-analysis:** Not applicable • **Justification for combining data in meta-analysis:** Not reported
Outcome assessed	**List of outcomes assessed and intended timeframes** • Primary outcomes: Depression, anxiety, attention deficit hyperactivity disorder, Tourette syndrome, post-traumatic stress disorder, psychosis

Parameter	Extraction items
	• Secondary outcomes: Global functioning, quality of life, and patient or caregiver impression of change, safety of medicinal cannabinoids for mental health symptoms and disorders, including all-cause, serious, and treatment-related adverse events and study withdrawals • Intended timeframes: Not specified • Actual timeframes: 1 day-156 weeks
Results/findings	○ **Findings by outcome:** PRIMARY OUTCOMES *THC-CBD (THC with or without CBD)* ○ Depression: Pooled data from 12 studies (n=1656) reported no significant difference between THC-CBD and placebo groups (SMD –0.05, 95% CI –0.20 to 0.11). One study (n=52) reported no significant difference between THC-CBD and active comparator group (SMD 0.00, 95% CI –0.17 to 0.17). ○ Anxiety: Pooled data from seven studies (n=252) reported significant improvements in THC-CBD compared with placebo groups (SMD –0.25, 95% CI –0.49 to –0.01). One study (n=52) reported no difference between THC-CBD and active comparator groups (SMD –0·12, 95% CI –0·30 to 0·05). Two studies reported no significant difference between THC-CBD and placebo, one study reported significant improvement in THC-CBD compared with placebo (no summary statistics reported). ○ Attention deficit hyperactivity disorder: One study (n=30) reported no significant difference between THC-CBD and placebo groups in symptoms (SMD –0.67, 95% CI –1.41 to 0.07). ○ Tourette syndrome: Two studies (n=41) reported no significant difference between THC and placebo groups in symptoms (SMD –0.46, 95% CI –1.32 to 0.40).

Parameter	Extraction items
	○ Psychosis: One study (n=24) reported no significant difference between THC and placebo groups in relation to positive symptoms (SMD –0.20, 95% CI –0.45 to 0.06). This study (n=24) reported significant worsening in negative symptoms (SMD 0.36, 95% CI 0.10 to 0.62) in THC compared with placebo groups. *CBD* ○ Anxiety: Two studies (n=44) reported no significant difference between CBD and placebo groups (SMD–0·87, 95% CI –2·01 to 0·27). ○ Psychosis: ○ Total symptoms: Pooled analysis from two studies (n=122) reported no significant differences between CBD and placebo groups (SMD 0.05, 95% CI –0.50 to 0.61). One study (n=39) reported no significant differences between CBD and active comparator (SMD –0.02, 95% CI –0.65 to 0.60). ○ Positive symptoms: Pooled analysis from two studies (n=122) reported no significant differences between CBD and placebo groups in positive symptoms (SMD –0.17, 95% CI –0.69 to 0.35). One study (n=39) reported no significant differences between CBD and active comparator (SMD –0.10, 95% CI –0.73 to 0.53). ○ Negative symptoms: Pooled data from two studies (n=122) reported no significant differences between CBD and placebo groups (SMD 0.08, 95% CI –0.27 to 0.44). One study (n=39) reported no significant differences between CBD and active comparator (SMD –0.48, 95% CI –1.12 to 0.16) *Cannabis (plant-based)* ○ Depression: One study (n=42) reported no significant difference between cannabis and placebo groups (SMD -0.14, 95% CI -0.33 to 0.05).

Parameter	Extraction items
	SECONDARY OUTCOMES *THC-CBD* ○ Post-traumatic stress disorder: One study reported significant improvements in THC-CBD compared with placebo groups in global functioning (SMD –1.13, 95% CI –1.48 to –0.77) and change in nightmare frequency (SMD –1.11, 95% CI –1.46 to –0.76). This study (n=19) reported no significant difference between THC-CBD and placebo groups in sleep quality (SMD –0.10, 95% CI –0.38 to 0.18). ○ Tourette syndrome: Two studies (n=41) reported no significant difference between THC and placebo groups in global functioning (SMD –0.84, 95% CI –2.10 to 0.42). ○ Attention deficit hyperactivity disorder: One study (n=30) reported no significant difference between THC-CBD and placebo groups in global functioning (SMD 0.00, 95% CI –0.72 to 0.72) and weight change (SMD 0.14, 95% CI –0.58 to 0.85). ○ Psychosis: One study (n=24) reported significant worsening of cognitive function (SMD 1.08, 95% CI 0.71 to 1.45) in THC compared with placebo groups. ○ Adverse events (all cause): Pooled data from ten studies (n=1495) reported significantly increased likelihood in THC-CBD groups compared with placebo groups (OR 1.99, 95% CI 1.20 to 3.29). One study (n=60) reported no significant difference between THC-CBD and active comparator (OR 1.59, 95% 0.57 to 4.45). ○ Serious adverse events (all cause): Pooled data from four studies (n=954) reported no significant difference between THC-CBD and placebo groups (OR 1.29, 95% CI 0.94 to 1.77). ○ Treatment-emergent events (all cause): Pooled data from two studies (n=385) reported no significant difference between THC-CBD and placebo groups (OR 1.32, 95% CI 0.79 to 2.20).

Parameter	Extraction items
	○ Withdrawals all cause: Pooled data from fifteen studies (n=2299) reported no significant difference between THC-CBD and placebo groups (OR 1.51, 95% CI 0.96 to 2.36). Pooled data from two studies (n=252) reported no significant difference between THC-CBD and active comparator groups (OR 0.54, 95% CI 0.17 to 1.68). ○ Withdrawals due to adverse events: Pooled data from eleven studies (n=1621) reported significantly increased likelihood in THC-CBD groups compared with placebo groups OR 2.78 (1.59 to 4.86). *CBD* ○ Psychosis: ○ Emotional functioning: Pooled analysis from two studies (n=122) reported no significant differences between CBD and placebo groups (SMD 0.10, 95% CI–0.49 to 0.69). One study (n=39) reported no significant differences between CBD and active comparator (SMD 0.27, 95% CI–0.36 to 0.90). ○ Global functioning: One study (n=86) reported significant improvement in CBD compared with placebo groups (SMD –0.62, 95% CI –1.14 to –0.09). ○ Cognitive function: Pooled analysis from three studies (n=150) reported no significant differences between CBD and placebo groups (SMD –0.01, 95% CI–0.33 to 0.32). ○ Adverse events (all cause): One study (n=88) reported no significant difference between CBD and placebo groups (OR 0.97, 95% CI 0.40 to 2.33). ○ Serious adverse event (all cause): One study (n=88) reported no significant difference between CBD and placebo groups (OR 0.34, 95% CI 0.01 to 8.60). ○ Treatment-emergent events (all cause): One study (n=88) reported no significant difference between CBD and placebo groups (OR 1.06, 95% CI 0.39 to 2.87).

Parameter	Extraction items

- Withdrawals (all cause): One study (n=88) reported no significant difference between CBD and placebo groups (OR 1.61, 95% CI 0.26 to 10.16). One study (n=42) reported no significant difference between CBD and active comparator groups (OR 3.33, 95% CI 0.32 to 34.99).
- Withdrawals due to adverse events: One study (n=88) reported no significant difference between CBD and placebo group (OR 1.05, 95% CI 0.06 to 17.30).

Cannabis (plant-based)

- Withdrawals (all cause): Pooled data from three studies (n=209) reported no significant difference between cannabis and placebo groups (OR 1.41 (0.51 to 3.88)

- **GRADE by outcome:**

Outcome	No. studies	GRADE
THC-CBD		
Depression		
Change in depressive symptoms (active)	1	Very low
Change in depressive symptoms (placebo)	12	Very low
Anxiety		
Change in anxiety symptoms (placebo)	7	Very low
Change in anxiety symptoms (active)	1	Very low
ADHD		
Change in ADHD symptoms, any location (placebo)	1	Low
Change in global functioning (placebo)	1	Low
Weight change (placebo)	1	Low
Tourette syndrome		
Change in tic or Tourette symptoms (placebo)	2	Low
Change in global functioning (placebo)	2	Very low
Post-traumatic stress disorder		
Change in global functioning	1	Low
Change in sleep quality	1	Low

Parameter	Extraction items		
Change in nightmare frequency	1	Low
Psychosis		
Change in positive symptoms	1	Low
Change in negative symptoms	1	Low
Change in cognitive function	1	Low
Adverse events		
Adverse events all cause (active)	1	Very low
Adverse events all cause (placebo)	10	Low
Serious adverse events all cause (placebo)	4	Low
Treatment emergent events all cause (placebo)	2	Low
Withdrawals all cause (placebo)	15	Very low
Withdrawals all cause (active)	2	Low
Withdrawals due to adverse events (placebo)	11	Moderate
Cannabidiol		
Anxiety		
Change in anxiety symptoms (Placebo)	2	Very low
Psychosis		
Change in total symptoms (Active)	1	Low
Change in total symptoms (Placebo)	2	Low
Change in positive symptoms (Active)	1	Low
Change in positive symptoms (Placebo)	2	Low
Change in negative symptoms (Active)	1	Low
Change in negative symptoms (Placebo)	2	Moderate
Change in global functioning (placebo)	1	Low
Change in cognitive functioning (placebo)	3	Moderate
Change in emotional functioning (Active)	1	Low
Change in emotional functioning (Placebo)	2	Very low
Adverse events		
Adverse events all cause (placebo)	1	Low
Serious adverse events all cause (placebo)	1	Very low
Treatment emergent events all cause (placebo)	1	Low
Withdrawals all cause (placebo)	1	Very low
Withdrawals all cause (active)	1	Very low

Parameter	Extraction items

Withdrawals due to adverse events	1	Very low
Cannabis		
Adverse events		
Withdrawals all cause (placebo)	3	Very low

- **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):**

Indication	No. studies (No. participants)	Summary estimate (95% CI)	P-value	I^2 (%)	Direction of effect
THC-CBD					
Depression					
Change in depressive symptoms (active)	1 (52)	SMD 0.00 (–0.17 to 0.17)	NR	NA	No significant difference
Change in depressive symptoms (placebo)	12 (1656)	SMD –0.05 (–0.20 to 0.11)	NR	67%	No significant difference
Anxiety					
Change in anxiety symptoms (placebo)	1 (52)	SMD –0.12 (–0.30 to 0.05)	NR	NA	No significant difference
Change in anxiety symptoms (active)	7 (252)	SMD –0.25 (–0.49 to –0.01)	NR	65	THC-CBD
ADHD					
Change in ADHD symptoms, any location (placebo)	1 (30)	SMD –0.67 (–1.41 to 0.07)	NR	NA	No significant difference
Change in global functioning (placebo)	1 (30)	SMD 0.00 (–0.72 to 0.72)	NR	NA	No significant difference
Weight change (placebo)	1 (30)	SMD 0.14 (–0.58 to 0.85)	NR	NA	No significant difference
Tourette syndrome					
Change in tic or Tourette symptoms (placebo)	2 (41)	SMD –0.46 (–1.32 to 0.40)	NR	68	No significant difference
Change in global functioning (placebo)	2 (41)	SMD –0.84 (–2.10 to 0.42)	NR	68	No significant difference

Parameter	Extraction items					
	Post-traumatic stress disorder					
	Change in global functioning (placebo)	1 (19)	SMD –1.13 (–1.48 to –0.77)	NR	NA	THC-CBD
	Change in sleep quality (placebo)	1 (19)	SMD –0.10 (–0.38 to 0.18)	NR	NA	No significant difference
	Change in nightmare frequency (placebo)	1 (19)	SMD –1.11 (–1.46 to –0.76)	NR	NA	THC-CBD
	Psychosis					
	Change in positive symptoms (placebo)	1 (24)	SMD –0.20 (–0.45 to 0.06)	NR	NA	No significant difference
	Change in negative symptoms (placebo)	1 (24)	SMD 0.36 (0.10 to 0.62)	NR	NA	THC-CBD
	Change in cognitive function (placebo)	1 (24)	SMD 1.08 (0.71 to 1.45)	NR	NA	THC-CBD
	Adverse events					
	All cause (active)	1 (60)	OR 1.59 (0.57 to 4.45)	NR	NA	No significant difference
	All cause (placebo)	10 (1495)	OR 1.99 (1.20 to 3.29)	NR	59	THC-CBD
	Serious all cause (placebo)	4 (954)	OR 1.29 (0.94 to 1.77)	NR	0	No significant difference
	Treatment emergent all cause (placebo)	2 (385)	OR 1.32 (0.79 to 2.20)	NR	0	No significant difference
	Withdrawals all cause (placebo)	15 (2299)	OR 1.51 (0.96 to 2.36)	NR	42	No significant difference
	Withdrawals all cause (active)	2 (252)	OR 0.54 (0.17 to 1.68)	NR	0	No significant difference
	Withdrawals due to adverse events (placebo)	11 (1621)	OR 2.78 (1.59 to 4.86)	NR	22	THC-CBD
	Cannabidiol					
	Anxiety					
	Change in anxiety symptoms (placebo)	2 (44)	SMD –0.87 (–2.01 to 0.27)	NR	NA	No significant difference
	Psychosis					
	Change in total symptoms (active)	1 (39)	SMD –0.02 (–0.65 to 0.60)	NR	NA	No significant difference

Parameter	Extraction items					
	Change in total symptoms (placebo)	2 (122)	SMD 0.05 (–0.50 to 0.61)	NR	52	No significant difference
	Change in positive symptoms (active)	1 (39)	SMD –0.10 (–0.73 to 0.53)	NR	NA	No significant difference
	Change in positive symptoms (placebo)	2 (122)	SMD –0.17 (–0.69 to 0.35)	NR	47	No significant difference
	Change in negative symptoms (active)	1 (39)	SMD –0.48 (–1.12 to 0.16)	NR	NA	No significant difference
	Change in negative symptoms (placebo)	2 (122)	SMD 0.08 (–0.27 to 0.44)	NR	0	No significant difference
	Change in global functioning (placebo)	1 (86)	SMD –0.62 (–1.14 to –0.09)	NR	NA	CBD
	Change in cognitive functioning (placebo)	3 (150)	SMD –0.01 (–0.33 to 0.32)	NR	0	No significant difference
	Change in emotional functioning (active)	1 (39)	SMD 0.27 (–0.36 to 0.90)	NR	NA	No significant difference
	Change in emotional functioning (placebo)	2 (122)	SMD 0.10 (–0.49 to 0.69)	NR	57	No significant difference
	Adverse events					
	All cause (placebo)	1 (88)	OR 0.97 (0.40 to 2.33)	NR	NA	No significant difference
	Serious all cause (placebo)	1 (88)	OR 0.34 (0.01 to 8.60)	NR	NA	No significant difference
	Treatment emergent all cause (placebo)	1 (88)	OR 1.06 (0.39 to 2.87)	NR	NA	No significant difference
	Withdrawals all cause (active)	1 (42)	OR 3.33 (0.32 to 34.99)	NR	NA	No significant difference
	Withdrawals all cause (placebo)	1 (88)	OR 1.61 (0.26 to 10.16)	NR	NA	No significant difference
	Withdrawals due to adverse events	1 (88)	OR 1.05 (0.06 to 17.30)	NR	NA	No significant difference
	Cannabis					
	Adverse events					
	Withdrawals all cause (placebo)	3 (209)	OR 1.41 (0.51 to 3.88)	NR	7	No significant difference

Parameter	Extraction items
	• **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Above • **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Yes **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable
Significance/direction	**See above if results listed by outcome:** Above
Heterogeneity	• **See above if I^2 available:** Above • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** "Nonetheless, our analyses and conclusions are limited by the small amount of available data, small study sizes, and heterogeneity of findings across studies." p1007 • **Causes of heterogeneity investigated:** Yes I^2, random effects model, sensitivity analysis conducted
Comments	Black 2019 includes RCT, open-label and prospective cohort studies. RCTs are synthesised separately. However, open label and prospective cohort studies are synthesised together. Therefore, as per our inclusion criteria, only findings related to RCTs will be included in this umbrella review.

Boland *et al.* (2020): Cannabinoids for adult cancerrelated pain: systematic review and meta-analysis

Parameter	Extraction items
First author and year of publication	Boland *et al.* (2020)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** To determine the beneficial and adverse effects of cannabis/cannabinoids compared with placebo/other active agents for the treatment of cancer-related pain in adults.

Parameter	Extraction items
	• **Exact review question and page number: "**The aim was to determine the beneficial and adverse effects of cannabinoids compared with placebo or other active agents for the treatment of cancer-related pain in adults from RCTs." p15 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** Cancer-related pain in adults ➢ **Setting:** Not specified ➢ **Intervention:** Cannabinoids (THC/CBD, THC extract, nabiximols, Sativex, medical cannabis) ➢ **Comparison:** Placebo or other active agents ➢ **Outcome:** Pain
Participants (characteristics and numbers)	**For whole sample and subgroups** • **Number of participants:** N=1460 • **Age:** Not reported- adult population • **Gender:** Not reported • **Details of clinical diagnosis/indications:** Cancer (advanced cancer, patients with chemotherapy-induced neuropathic pain (n=18) and cancer-related pain) (n=1460)
Setting/context	**Countries (alphabetic order):** Not reported **Setting (university, public or private clinic):** Not reported **Other relevant features of setting:** Not reported

Parameter	Extraction items

Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors: "**Multiple doses of cannabinoids via any route, for pain cancer-related management (studies where only the minority of the exposed group received cannabis and cannabinoids were excluded)" p15
	• **Dose and regimen:** Multiple doses- single dose studies were excluded
	  ○ Nabiximols (3 RCTs): low dose 1-4 sprays/day; medium dose 6–10 sprays/day; high dose 11–16 sprays/day; max daily dose 10 sprays
	  ○ Sativex (2 RCTs): max daily dose 10 sprays
	  ○ THC:CBD extract, THC extract (1 RCT): not specified
	• **Administration methods:** Oromucosal spray (5 RCTs); not reported (1 RCT)
	• **Comparator:** Placebo (6 RCTs)
	• **Treatment duration:** 2-9 weeks
	• **Timeframe for follow-up:** Not reported for included studies

Databases and sources searched	• **Number and names of databases:** 5: Embase (1974 to 01/08/2019); Ovid MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (1946 to 01/08/2019); PsycInfo (1967 to 01/08/2019); Cochrane Database of Systematic Reviews (no date restrictions); Cochrane Central Register of Controlled Trials (no date restrictions) • **Other sources:** Conference Proceedings Citation Index– Science (Web Of Science; Thomson Reuters, New York City, NY); ClinicalTrials.gov (US NIH); ISRCTN registry (BMC) • **Grey literature:** Bielefeld Academic Search Engine (BASE) (https://www.basesearch.net/), OpenGrey (http://www.opengrey.eu/) and Mednar (https://mednar.com/) • **Reference chasing:** Yes

Parameter	Extraction items
	• **Expert consultation:** No • **Dates:** 1946/67/74 to 08/2018; updated search to 01/08/2019 • **Search limits:** No • **Justifications for search limits:** Not applicable • **Other searches:** Not reported • **Protocol prepared:** Yes • **If yes, published:** CRD42018107662 https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=107662 • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Funding of review:** "The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors." p23 • **Conflicts of interest of review:** The authors reported no conflicts of interest. • **How conflicts of interest were managed:** Not applicable
Date Range (years) of included studies	• **Exact years for included studies:** 2010-2018
Number of primary studies included in the systematic review	• **Number of studies:** 6 RCTs (5 RCTs included in meta-analysis) • **Number of studies by study design:** 6 RCTs

Parameter	Extraction items
	• **Study years:** 2010 (1 RCT); 2012 (1 RCT); 2014 (1 RCT); 2017 (2 RCTs); 2018 (1 RCT) • **Funding of included studies:** Not reported • **Conflicts of interest of included studies:** Not reported
Types of studies included	**Planned study designs to be included:** RCTs **Reasons for including only RCTs/prospective cohort studies:** Not reported **List of excluded studies at full text and reasons for exclusion:** Not reported
Appraisal instruments used	**Full name of tools used:** Cochrane Risk of Bias Tool **Risk of bias criteria for AMSTAR 2 assessment, for RCTs record Yes/No for:** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The authors reported the included trials had a low risk of bias (6 RCTs). "The studies included were at low risk of bias" p19 • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** ○ Overall: Low risk randomisation (6/6); low risk outcome ascertainment (6/6) *THC/CBD formulations (nabiximols, sativex and THC/CBD capsule) vs placebo* ○ Pain intensity: Low risk randomisation (5/5); low risk outcome ascertainment (5/5) *THC/CBD formulation (nabiximols) vs placebo* ○ 30% reduction in pain: Low risk randomisation (1/1); low risk outcome ascertainment (1/1)

Parameter	Extraction items
	• **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** "Studies with a low risk of bias showed that for adults with advanced cancer, the addition of cannabinoids to opioids did not reduce cancer pain compared with placebo." p21 • **Graphical or statistical test for publication bias:** Yes • **Authors' comments likelihood and magnitude of publication bias: "**The funnel plot (online supplementary figure 1) showed that distribution was roughly symmetrical, indicating that publication bias was not likely to be present." p19-20 • **Authors' comment on how publication bias was dealt with:** Above • **Only low ROB RCTs included in review:** Yes • **Only low ROB RCTs included in meta-analysis:** Yes • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** Not applicable
Method of analysis	• **Description of method of analysis as per authors: "**Data on the numbers of patients experiencing adverse events for each group, the OR and 95% CI were calculated for each study adverse event. The mean difference or ORs were pooled using a fixed-effect model or random effects model (the Mantel-Haenszel method) and the corresponding 95% CIs were calculated. Where the analysis indicated significant heterogeneity, a random-effects model was chosen, otherwise a fixed-effects model was applied. Statistical heterogeneity was assessed using Cochran's Q test. Cochran's Q tests the presence versus the absence of heterogeneity and the p value is stated. The I^2 index describes the percentage of variation across studies that is due to heterogeneity rather than chance. Interpretation is as follows: low, moderate and high to I^2 values of 25%, 50% and 75%, respectively." p16 • **Justification for narrative synthesis or meta-analysis:** Not reported • **Justification for combining data in meta-analysis:** Not reported

Parameter	Extraction items
Outcome assessed	**List of outcomes assessed and intended timeframes** • Primary outcomes: Absolute change in mean pain intensity • Secondary outcomes: Adverse events, dropouts • Intended timeframes: Not specified • Actual timeframes: 2-9 weeks
Results/findings	• **Findings by outcome:** PRIMARY OUTCOMES ○ Pain intensity (numeric rating scale, NRS): Pooled data from five studies (n=1745) reported no significant difference between nabiximol and placebo groups (MD −0.21, 95% CI −0.48 to 0.07). Sensitivity analysis including four phase III RCTs (n=1305) reported no significant difference between nabiximol and placebo groups (MD −0.02, 95% CI −0.21 to 0.16). ○ 30% reduction in pain: One study (n=360) reported no significant difference between nabiximol and placebo groups (p=0.59). SECONDARY OUTCOMES *Adverse events* ○ Dizziness: Pooled data from four studies (n=1095) reported increased likelihood in nabiximol compared with control groups (OR 1.58, 95% CI 0.99 to 2.51, p=0.05). ○ Nausea: Pooled data from four studies (n=1095) reported no significant difference in nabiximol compared with control groups (OR 1.41, 95% CI 0.97 to 2.05). ○ Vomiting: Pooled data from four studies (n=1095) reported no significant difference in nabiximol compared with control groups (OR 1.34, 95% CI 0.85 to 2.11).

Parameter	Extraction items

- Somnolence: Pooled data from four studies (n=904) reported increased likelihood in nabiximol compared with control groups (OR 2.69, 95% CI 1.54 to 4.71).
- Withdrawals: Pooled data from five studies (n=1281) reported no significant difference between nabiximol compared with placebo (OR 1.33, 95% CI 0.95 to 1.85).

- **GRADE by outcome:** Not reported
- **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):**

Indication	No. studies (No. participants)	Summary estimate (95% CI)	P-value	I^2 (%)	Direction of effect
Phase II and III studies (nabiximol and THC/CBD capsule vs placebo)					
Pain intensity	5 (1642)	WMD -0.21 (-0.48 to 0.07)	0.04	59	Nabiximol
Phase III studies (nabiximol vs placebo)					
Pain intensity	3 (796)	WMD -0.02 (-0.21 to 0.16)	0.42	0	No significant difference
Adverse events (nabiximol vs placebo)					
Dizziness	4 (1095)	OR 1.58 (0.99 to 2.51)	0.05	0	Nabiximol
Nausea	4 (1095)	OR 1.41 (0.97 to 2.05)	0.08	0	No significant difference
Vomiting	4 (1095)	OR 1.34 (0.85 to 2.11)	0.21	0	No significant difference
Somnolence	4 (904)	OR 2.69 (1.54 to 4.71)	0.0005	0	Nabiximol
Withdrawal	5 (1281)	OR 1.33 (0.95 to 1.85)	0.10	16	No significant difference

- **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Above
- **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** "Where the analysis indicated significant heterogeneity, a random-effects model was chosen, otherwise a fixed-effects model was applied" p16.

Parameter	Extraction items
	• **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable
Significance/direction	**See above if results listed by outcome:** Above
Heterogeneity	• **See above if I^2 available:** Above • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** "Although the same overall conclusions were attained, this systematic review and meta-analysis is based on additional methodological information and thus supported by higher quality evidence (as included studies were deemed to have lower risk of bias)" p21 • **Causes of heterogeneity investigated: "**Due to the heterogeneous nature of some of these studies (in study design, duration/dose of cannabinoid administered, timing of outcome measurement), five studies were included in a meta-analysis (representing a total of 1442 participants) and six studies in a narrative analysis (representing a total of 1460 participants)" p16-19
Comments	

Bosnjak-Kuharic *et al.* (2021): Cannabinoids for the treatment of dementia (Review)

Parameter	Extraction items
First author and year of publication	Bosnjak-Kuharic *et al.* (2021)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "To determine the efficacy and safety of cannabinoids for the treatment of dementia." p7 • **Exact review question and page number:** "The cannabinoids are one potential agent under investigation for the treatment of dementia. The purpose of this systematic review was to investigate whether cannabinoids could help people with dementia, and whether they have any potential harmful effects." p2 • **PICO elements reported in Introduction/Methods:**

Parameter	Extraction items
	➢ **Patient or population:** "People of any age and either sex diagnosed with Alzheimer's dementia, vascular dementia, mixed dementia or unspecified dementia of any severity and from any setting were included." p7 ➢ **Setting:** Any setting which included a "hospital, nursing home and outpatient clinic" p4 ➢ **Intervention:** "cannabinoids administered by any route, at any dose, for any duration" p8 ➢ **Comparison:** "placebo, no treatment, or any active control intervention" p8 ➢ **Outcome:** Primary outcomes: Changes in global and specific cognitive function; behavioural and psychological symptoms of dementia; adverse events. Secondary outcomes: activities for daily living (ADLs); overall dementia severity; objective sleep outcomes; changes in appetite; agitated or aggressive behaviour; mood; carer ratings of sleep; quality of life; other symptoms associated with dementia; carer burden and quality of life; treatment or research discontinuation/dropout; and mortality.
Participants (characteristics and numbers)	**For whole sample and subgroups** • **Number of participants:** N=126 • **Age:** ≥40 years (1 RCT); ≥ 55 years (1 RCT); ≥65 years (1 RCT); mean age 76.9 years • **Gender:** 37.9% female (n=87, 3 RCTs); not reported (1 RCT, n=39) • **Details of clinical diagnosis/indications:** People with dementia
Setting/context	**Countries (alphabetic order):** Canada (1 RCT); Netherlands (2 RCTs); USA (1 RCT) **Setting (university, public or private clinic):** Outpatient and long-term care setting (1 RCT); Community, outpatient and long-term care setting (1 RCT); hospital (2 RCTs)

Parameter	Extraction items
	Other relevant features of setting: Not applicable

Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** "cannabinoids administered by any route, at any dose, for any duration" p8
	• **Dose and regimen:**
	  ○ Nabilone (1 RCT): 0.25-2 mg; daily
	  ○ THC (2 RCT): 0.75-1.5 mg; twice daily; three times daily
	  ○ Dronabinol (1 RCT): 2.5 mg capsule; twice daily
	• **Administration methods:** Orally (4 RCTs)
	• **Comparator:** Placebo (4 RCTs)
	• **Treatment duration:** 3-14 weeks
	• **Timeframe for follow-up:** Not reported for 3 RCTs; two week follow-up for 1 RCT

Databases and sources searched	• **Number and names of databases**: 1; ALOIS - the Cochrane Dementia and Cognitive Improvement Group's Specialised Register. The register contains records from all major healthcare databases (the Cochrane Library, CENTRAL; MEDLINE, Embase, PsycINFO, CINAHL, LILACS); searched on 08/07/2021 • **Other sources:** ALOIS contains records from monthly searches of a number of trial registers: ISRCTN (Current Controlled Trials); UMIN (Japan's Trial Register); the World Health Organization (WHO) portal (ICTRP) (which covers ClinicalTrials.gov; ISRCTN; the Chinese Clinical Trials Register; the German Clinical Trials Register; the Iranian Registry of Clinical Trials, and the Netherlands National Trials Register, plus others). • **Grey literature:** ALOIS contains six-monthly searches of a number of grey literature sources including ISI Web of Knowledge Conference Proceeding

Parameter	Extraction items
	• **Reference chasing:** Yes • **Expert consultation:** Not reported • **Dates:** Inception – 08/07/2021 • **Search limits:** No • **Justifications for search limits:** Not applicable • **Other searches:** Google search engine and the Norml website • **Protocol prepared:** Yes • **If yes, published:** https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012820/full • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** Yes • **If Yes, rate of agreement:** Not reported • **Funding of review:** "This review was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to the Cochrane Dementia and Cognitive Improvement Group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service, or the Department of Health" p74 • **Conflicts of interest of review:** "The review authors have no conflict of interest to declare." p74 • **How conflicts of interest were managed:** Not applicable
Date Range (years) of included studies	• **Exact years for included studies:** 1997-2019

Parameter	Extraction items
Number of primary studies included in the systematic review	• **Number of studies:** 4 RCTs • **Number of studies by study design:** 4 RCTs • **Study years:** 1997 (1 RCT); 2014 (1 RCT); 2015 (1 RCT); 2019 (1 RCT) • **Funding of included studies:** Non-industry (public) (2 RCTs); public and industry (1 RCT); sponsors and collaborators (1 RCT) • **Conflicts of interest of included studies:** Not reported (2 RCTs); authors declared no conflict of interest (2 RCTs)
Types of studies included	**Planned study designs to be included:** RCT **Reasons for including only RCTs/prospective cohort studies:** Not reported **List of excluded studies at full text and reasons for exclusion:** Yes
Appraisal instruments used	**Full name of tools used:** Cochrane Risk of Bias tool **Risk of bias criteria for AMSTAR 2 assessment, for RCTs record Yes/No for:** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The authors did not provide an overall assessment of risk of bias for each trial. However, HRB notes that according to Cochrane's Collaboration tool, and graphical information provided in the paper, the included trials appeared to have an unclear risk of bias (2 RCTs) and low risk of bias (2 RCTs). • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:**

Parameter	Extraction items
	○ Overall: Low risk randomisation (3/4); low risk outcome ascertainment (3/4) *Nabilone vs placebo* ○ Cognitive function: Low risk randomisation (1/1); low risk outcome ascertainment (1/1) *THC vs placebo* ○ Behavioural and psychological symptoms of dementia: Low risk randomisation (3/3); low risk outcome ascertainment (3/3) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** "This review included four trials - three cross-over and one parallel group trial. All four trials were placebo-controlled randomised controlled trials (RCTs), and sample sizes in all four included trials were very small, ranging from 15 to 50 enrolled participants. Thus, we have a lot of uncertainty about their results. Using GRADE methods, we judged the certainty of evidence for primary outcomes to be low or very low due to risk of bias, inconsistency, indirectness, and imprecision of results." p21 • **Graphical or statistical test for publication bias:** None • **Authors' comments likelihood and magnitude of publication bias:** "We are unable to exclude the possibility of publication bias." p21 • **Authors' comment on how publication bias was dealt with:** Not reported • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** No • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** Yes
Method of analysis	• **Description of method of analysis as per authors:** "We used mean differences (MDs) or standardised mean differences (SMDs) with 95% confidence intervals (CIs) for continuous outcomes, and odds ratios (ORs) with 95% CIs for analysis of

Parameter	Extraction items
	dichotomous outcomes. We considered ordinal outcomes only if we could justifiably treat them as a continuous variable, or if they could be sensibly dichotomised by combining adjacent categories. Given that there are no definitive guidelines for handling these measurements, we reported on our decision, which was reached in a discussion that involved at least two review authors." p9 "We used meta-analysis for combining data if (i) at least two studies reported an estimated treatment effect, (ii) included studies appeared to have similar characteristics, (iii) studies had the same outcome measures, and (iv) each study reported the necessary data…. we analysed all efficacy study data using the generic inverse variance fixed-effect model to determine overall weighted treatment effects and their 95% CIs" p10 • **Justification for narrative synthesis or meta-analysis:** Not reported • **Justification for combining data in meta-analysis:** Not reported
Outcome assessed	**List of outcomes assessed and intended timeframes** • Primary outcomes: Cognitive function; behavioural and psychological symptoms of dementia; adverse events. • Secondary outcomes: Nervous system disorders; sedation; treatment induced sedation; psychiatric disorders; gastrointestinal disorders; change in functional outcomes; dementia severity; agitation/aggression; weight (kg); ini-nutritional assessment short-form; body mass index; Caloric intake; Cohen-Mansfield agitation inventory scale; quality of life-Alzheimer's Disease scale; carer burden; all-cause discontinuation; all-cause mortality • Intended timeframes: Not specified • Actual timeframes: 3-15 weeks
Results/findings	• **Findings by outcome:** PRIMARY OUTCOMES ○ Cognitive function: Global and specific cognitive function: One study (n=39) reported a small significant improvement in nabilone compared with placebo groups (MD 1.1 points, 95% CI 0.1 to 2.1).

Parameter	Extraction items
	○ Behavioural and psychological symptoms of dementia: Pooled data from three studies (n=111) reported little or no clinical effect of cannabinoid compared with placebo (MD -1.97, 95% CI -3.87 to -0.07). *Adverse events* ○ Nervous system disorders: One study (n=50) reported no significant difference between THC and placebo groups (OR 0.71, 95% CI 0.23 to 2.18). Related to sedation, one study (n=39) reported significant likelihood in nabilone compared with placebo groups (OR 2.83, 95% CI 1.07 to 7.48). Related to muscle spasms, one study (n=50) reported no significant difference between THC and placebo groups (OR 0.71, 95% CI 0.23 to 2.18). ○ Psychiatric disorders: One study (n=50) reported no significant difference in general psychiatric disorders between THC and placebo groups (OR 2.26, 95% CI 0.57 to 9.02). This study (n=50) also reported no significant difference in euphoria between THC and placebo groups ((OR 0.35, 95% CI 0.01 to 8.93). ○ Gastrointestinal disorders: One study (n=50) reported no significant difference between THC and placebo groups in general gastrointestinal disorders (OR 2.40, 95% CI 0.40 to 14.49). This study (n=50) also reported no significant difference in nausea between THC and placebo groups (OR 2.27, 95% CI 0.19 to 26.81). ○ Other adverse events: One study (n=50) reported no significant difference between THC and placebo groups in relation to fatigue (OR 0.70, 95% CI 0.11 to 4.58). ○ Overall adverse events: "Volicer 1997, which included 12 participants in a cross-over study, reported 67 adverse events among participants taking dronabinol and 58 adverse events among those given placebo; study authors did not report adverse events for separate study periods. van den Elsen NCT01302340, which included 22 participants in a cross-over study, reported 46 adverse events among participants taking Namisol and 48 adverse events among participants taking placebo during Period A (the first period of six weeks). There were 45 adverse events with Namisol and 45 adverse events with placebo during Period B (second period of six weeks).

Parameter	Extraction items
	Van den Elsen NCT01608217 reported 16 adverse events in the Namisol group (N = 24) and 14 adverse events in the placebo group (N = 26). Herrmann 2019, which included 39 patients in a cross-over study, reported treatment-emergent adverse events (TEAEs) in 38 patients, as 1 patient discontinued the study during the placebo run-in (Week 1) due to clinically significant delusions and was not included in the analysis; there were 31 TEAEs with nabilone and 14 TEAEs with placebo; the study did not report TEAEs for different study periods. Study authors reported the results of McNemar's test with P = 0.05." p17 SECONARY OUTCOMES ○ Agitation/aggression (NPI subscale agitation/aggression): Pooled data from three studies (n=100) reported little or no clinical effect of THC (cannabinoid compared with placebo (MD -0.63, 95% CI -1.08 to -0.18). ○ Cohen-Mansfield Agitation Inventory: Pooled data from three studies (n=100) reported significant improvement in cannabinoid compared with placebo groups (MD -2.35, 95% CI -4.10 to -0.60). ○ Quality of life-Alzheimer's Disease: One study (n=50) reported no significant difference between THC and placebo groups (MD -0.50, 95% CI -2.60 to 1.60). ○ Change in functional outcomes: One study (n=50) reported no significant difference between THC and placebo groups (MD 0.60, 95% CI -0.75 to 1.95). ○ Dementia severity: Pooled data from two studies (n=89) reported significant improvement in cannabinoid compared with placebo groups (OR 1.88, 95% CI 1.03 to 3.44). ○ Weight (KG): Pooled data from three studies (n=104) reported no significant difference between cannabinoid and placebo groups (MD 0.33, 95% CI -0.08 to 0.75). ○ Mini-nutritional assessment short-form: One study (n=39) reported no significant difference between nabilone and placebo groups (MD 0.20, 95% CI 0.02 to 0.38).

Parameter	Extraction items

- Body mass index: One study (n=39) reported no significant difference between nabilone and placebo group (MD -0.14, 95% CI -0.35 to 0.07).
- Caloric intake: One study (n=15) reported no significant difference between dronabinol and placebo groups (MD 19.00, 95% CI -508.74 to 546.74).
- Carer burden: Pooled data from two studies (n=61) reported no significant difference between cannabinoid and placebo groups (MD -0.12, 95% CI -0.38 to 0.13).
- All-cause discontinuation: Pooled data from two studies (n=89) reported no significant difference between cannabinoid and placebo groups (OR 1.02, 95% CI 0.33 to 3.13).
- All-cause mortality: Pooled data from two studies (n=54) reported no significant difference between cannabinoid and placebo groups (OR 0.59, 95% CI 0.07 to 4.62).

- **GRADE by outcome:**

Outcome	Measure (no. studies)	GRADE
Cognitive function	1	Very low
Behavioural and psychological symptoms of dementia	3	Low
Adverse effects		
General	3	Low
Nervous system disorders	1	Low
Psychiatric disorders	1	Low
Gastrointestinal disorders	1	Low

- **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):** Fixed effects model

Outcome	No. studies (No. participants)	Summary estimate (95% CI)	P-value	I^2 (%)	Direction of effect

Parameter	Extraction items					
	THC vs placebo					
	Cognitive function	1 (39)	MD 1.1 (0.10 to 2.10)	0.03	NA	Nabilone
	Behavioural and psychological symptoms of dementia	3 (110)	MD -1.97 (-3.87 to -0.07)	0.04	69	THC and nabilone
	Agitation/aggression (NPI scale)	3 (110)	MD -0.63 (-1.08 to -0.18)	0.006	65	THC and nabilone
	Cohen-Mansfield Agitation Inventory	3 (111)	MD -2.35 (-4.10 to -0.60)	0.009	62	THC and nabilone
	Quality of life- Alzheimer's Disease	1 (50)	MD -0.50 (-2.60 to 1.60)	0.64	NA	No significant difference
	Change in functional outcomes	1 (50)	MD 0.60 (-0.75 to 1.95)	0.38	NA	No significant difference
	Dementia severity (clinicians global assessment of change)	2 (89)	OR 1.88 (1.03 to 3.44)	0.04	81	THC and nabilone
	Weight (KG)	3 (104)	MD 0.33 (-0.08 to 0.75)	0.12	68	No significant difference
	Mini-nutritional assessment short-form	1 (39)	MD 0.20 (0.02 to 0.38)	0.03	NA	No significant difference
	Body mass index	1 (39)	MD -0.14 (-0.35 to 0.07)	0.20	NA	No significant difference
	Caloric intake	1 (15)	MD 19.00 (-508.74 to 546.74)	0.94	NA	No significant difference
	Carer burden	2 (61)	SMD -0.12 (-0.38 to 0.13)	0.34	48	No significant difference
	Adverse effects					
	Nervous system disorders	1 (50)	OR 0.71 (0.23 to 2.18)	0.56	NA	No significant difference
	Sedation	1 (39)	OR 2.83 (1.07 to 7.48)	0.04	NA	Nabilone
	Treatment induced sedation	1 (39)	OR 4.01 (0.40 to 40.56)	0.24	NA	No significant difference
	Psychiatric disorders	1 (50)	OR 2.26 (0.57 to 9.02)	0.25	NA	No significant difference
	Gastrointestinal disorders	1 (50)	OR 2.40 (0.40 to 14.49)	0.95	NA	No significant difference
	Other	1 (50)	OR 0.70 (0.11 to 4.58)	0.71	NA	No significant difference
	All-cause discontinuation	2 (89)	OR 1.02 (0.33 to 3.13)	0.97	0	No significant difference
	All-cause mortality	2 (54)	OR 0.59 (0.07 to 4.62)	0.61	0	No significant difference

Parameter	Extraction items
	○ **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Not applicable ○ **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Yes ○ **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable
Significance/direction	**See above if results listed by outcome:** Above
Heterogeneity	• **See above if I^2 available:** Above • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** "Included studies were underpowered, heterogeneity among them was considerable, and their results were inconsistent." p20 "Based on data from four small, heterogeneous, and short placebo-controlled trials, it is uncertain whether cannabinoids have any beneficial or harmful effects on dementia compared to placebo. If there are benefits of cannabinoids for people with dementia, the effects may be too small to be clinically meaningful." p22 • **Causes of heterogeneity investigated:** Yes, I^2 calculated, random effects model, sensitivity and subgroup analyses conducted.
Comments	On p2 the authors state "Three studies had low risk of bias across all domains; one study had unclear risk of bias for the majority of domains". However, figure three p15 illustrates two studies with at least one 'unclear' risk of bias domain. Data in this extraction form have been extracted from figure 3 on p15.

Butler *et al.* (2015): Medical Cannabis for Non-Cancer Pain: A Systematic Review

Parameter	Extraction items
First author and year of publication	Butler *et al.* (2015)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "This systematic review of medical cannabis use for treating chronic non-cancer pain was conducted to assist the Minnesota Department of Health (MDH) Intractable Pain Advisory Panel in its deliberations, to provide information to stakeholders, and to support MDH in its deliberations regarding extending the use of medical cannabis to chronic non-cancer pain patients." p2 • **Exact review question and page number:** "The review addresses the following key questions: 1) What are the benefits (short-term and long-term) of cannabis use for the treatment of non-cancer pain? 2) What are the harms (short-term and long-term) of cannabis use for the treatment of non-cancer pain?" p3 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** Children or adults experiencing chronic non-cancer pain ➢ **Setting:** Outpatient ➢ **Intervention:** Smokable marijuana; marijuana extraction products; dronabinol; nabilone; nabiximols ➢ **Comparison:** Placebo; active pain treatment ➢ **Outcome:** Pain measures (such as visual analog scales)
Participants (characteristics and numbers)	**For whole sample and subgroups:** RCT (n=1162); RCT open label extension (n=560); RCT open-label (n=42); case series (n=33) *The case series studies are excluded from the remainder of the extraction. • **Number of participants:** n=1764 • **Age:** Mean age range 39-62.8 years (not reported in one study) • **Gender:** 57.4% female (not reported in two studies)

Parameter	Extraction items
	• **Details of clinical diagnosis/indications:** Multiple sclerosis (n=549), fibromyalgia (n=72); rheumatoid arthritis (n=58); neuropathic pain (n=966); brachial plexus (n=48); overuse of headache medication (n=30); motor neuron syndrome (n=13); chronic non-cancer pain (n=28)
Setting/context	**Countries (alphabetic order):** Austria (1), Canada (3), Denmark (1), Italy (1), UK (6 RCT), USA (1); UK, Czech Republic, Spain France and Czech Republic (1); UK, Czech Republic, Romania, Belgium, Canada (1), UK, Czech Republic, Romania, Belgium, Canada (2); UK, Belgium (2) **Setting (university, public or private clinic):** Outpatient **Other relevant features of setting:** Not reported

Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** Smokable marijuana; marijuana extraction products; dronabinol; nabilone; nabiximols
	• **Dose and regimen:**
	  ○ Nabiximols (11 studies): dose not reported; 6-48 actuations (not reported one study); daily
	  ○ Whole plant THC extract (1 study): 27mg/ml; max 48 sprays daily
	  ○ Nabilone (7 studies): 0.5-2.5mg; daily (not reported two studies)
	  ○ Dronabinol (2 studies): 5-60 mg; daily
	• **Administration methods:** Not reported
	• **Comparator:** Placebo (17); amitriptyline (1 RCT); dihydrocodeine (1 RCT)
	• **Treatment duration:** 2-124 weeks
	• **Timeframe for follow-up:** Not specified

Parameter	Extraction items
Databases and sources searched	• **Number and names of databases:** 4; Ovid MEDLINE, EMBASE, AMED, Cochrane Central Register of Controlled Trials; inception to July 2015 • **Other sources:** Not reported • **Grey literature:** No • **Reference chasing:** Yes • **Expert consultation:** No • **Dates:** Inception to July 2015 • **Search limits:** English language only • **Justifications for search limits:** Yes • **Other searches:** No • **Protocol prepared:** No • **If yes, published:** Not applicable • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** No • **If yes, rate of agreement:** Not applicable • **Funding of review:** Not reported • **Conflicts of interest of review:** Not reported • **How conflicts of interest were managed:** Not applicable
Date Range (years) of included studies	• **Exact years for included studies:** 2004-2015

Parameter	Extraction items
Number of primary studies included in the systematic review	• **Number of studies:** 19 studies • **Number of studies by study design:** RCT (14); Open-label extension of RCT (4); Open-label extension with randomized withdrawal (1) • **Study years:** 2004 (2); 2005 (1); 2006 (2); 2007 (3); 2008 (3); 2010 (2); 2012 (1); 2013 (2); 2014 (1); 2015 (2) • **Funding of included studies:** Industry (17); not reported (1); no funding (1) • **Conflicts of interest of included studies:** Not reported
Types of studies included	**Planned study designs to be included:** Randomized controlled trials, controlled trials, prospective or retrospective cohort with comparators; case control, case series **Reasons for including only RCTs/prospective cohort studies:** Not applicable **List of excluded studies at full text and reasons for exclusion:** Yes
Appraisal instruments used	**Full name of tools used:** Cochrane Risk of Bias tool; GRADE system **<u>Risk of bias criteria for AMSTAR 2 assessment, for RCTs record Yes/No for:</u>** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** High risk of bias (12); moderate risk of bias (6); low risk of bias (1) • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:**

Parameter	Extraction items
	Nabiximols vs placebo ○ Overall: Low risk randomisation (not reported/19); low risk outcome ascertainment (not reported/19) ○ Pain intensity: Low risk randomisation (not reported/3); low risk outcome ascertainment (not reported/3) ○ >30% pain reduction: Low risk randomisation (not reported/3); low risk outcome ascertainment (not reported/3) ○ Neuropathic pain: Low risk randomisation (not reported/4); low risk outcome ascertainment (not reported/4) *Nabiximols and nabilone vs placebo* ○ Patient global impression of change: Low risk randomisation (not reported/2); low risk outcome ascertainment (not reported/2) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** Not reported • **Graphical or statistical test for publication bias:** Not reported • **Authors' comments likelihood and magnitude of publication bias:** Not applicable • **Authors' comment on how publication bias was dealt with:** Not applicable • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** No • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** Not reported
Method of analysis	• **Description of method of analysis as per authors:** "We summarized included study characteristics and outcomes in evidence tables and conducted qualitative synthesis on all comparisons. We emphasized patient-centered outcomes in the evidence synthesis. When comparisons could be pooled, we conducted meta-analyses using a random effects model. Data were analyzed in OpenMetaAnalyst. We calculated odds ratios (OR) with the corresponding 95% CI for binary primary outcomes. Weighted mean differences (WMD) with the corresponding 95% confidence intervals (CIs) were

Parameter	Extraction items
	calculated for continuous outcomes. We assessed the clinical and methodological heterogeneity and variation in effect size to determine appropriateness of pooling data. We assessed statistical heterogeneity with Cochran's Q test and measure magnitude with I^2 statistic." • **Justification for narrative synthesis or meta-analysis:** Not reported • **Justification for combining data in meta-analysis:** Not reported
Outcome assessed	**List of outcomes assessed and intended timeframes:** • Primary outcomes: Pain measures (visual analog scales, numeric rating scale etc) • Secondary outcomes: Sleep, anxiety, depression, quality of life, global patient satisfaction, neuropathic pain assessed across multiple sclerosis; fibromyalgia; rheumatoid arthritis; other painful conditions • Intended timeframe: Not specified • Actual timeframes: 2 weeks-48 months
Results/findings	○ **Findings by outcome:** *Meta-analysis: Primary outcomes* ○ Pain reduction >30%: Pooled data from three studies (n=493) reported no significant difference between nabiximols and placebo (OR 1.30, 0.89 to 1.89). ○ Pain numerical rating scale: Pooled data from three studies (n=530) reported no significant difference between nabiximols and placebo (WMD -0.62, 95% CI 1.63 to 0.40). ○ Neuropathic pain scale: Pooled data from four studies (n=467) reported significant improvement in nabiximols compared with placebo groups (WMD -5.18, 95% CI -8.24 to -2.12). *Meta-analysis: Secondary outcomes*

Parameter	Extraction items
	○ Patient global impression of change: Pooled data from two studies (n=81) reported significant improvement in nabiximols compared with placebo groups (OR 6.07, 95% CI 2.24 to 16.47). *Comparative effectiveness: Primary outcomes* ○ Neuropathic pain: One study (n=96) reported a significant improvement in dihydrocodeine compared with nabilone groups (no summary statistics reported). ○ McGill Pain Questionnaire: One study (n=32) reported no significant difference between nabilone and amitriptyline groups (no summary statistic reported). *Comparative effectiveness: Secondary outcomes* ○ Anxiety and depression: Sleep: One study (n=96) reported no significant difference between nabilone and dihyrocodeine groups (no summary statistic reported). ○ Sleep: One study (n=96) reported no significant difference in number of hours sleep between nabilone and dihyrocodeine groups (no summary statistic reported). One study (n=32) reported significant improvement in insomnia in nabilone compared with amitriptyline groups (adjusted difference -3.25, 95% CI -5.26, -1.24) but no significant difference in Leeds Sleep Evaluation Questionnaire scores (no summary statistic reported). ○ Fibromyalgia impact questionnaire: One study (n=32) reported no significant difference between nabilone and dihydrocodeine groups (no summary statistic reported). ○ Global Patient Satisfaction: One study (n=32) reported no significant difference between nabilone and dihydrocodeine groups (no summary statistic reported). ○ Adverse events: ○ One study (n=96) with nabilone and dihydrocodeine groups reported “Withdrawals by group equally well-tolerated (no statistical analysis presented). No serious [adverse events] reported. Most common side

Parameter	Extraction items
	effects: tiredness, sleeplessness, sickness, tingling, strangeness, nightmares, shortness of breath, headaches." p10 ○ One study (n=32) with nabilone and amitriptyline groups reported "Withdrawals: 1 from side effects, 1 for lack of effect, 1 protocol violation. 2 severe [adverse events] for amitriptyline: headache and insomnia 1 severe [adverse event] for nabilone: drowsiness. 91 [adverse events] for nabilone; 53 for amitriptyline. Most common [adverse events] for nabilone: dizziness, nausea, dry mouth, drowsiness, constipation, insomnia, vomiting" p11 *Multiple sclerosis: Primary outcomes* ○ Pain numerical rating scale: One study (n=66) reported significant improvements in nabiximol compared with placebo groups (MD -1.25, 95% CI -2.11 to -0.39). One study (n=24) reported significant improvement in pain relief (MD 2.5, 95% CI 0.5 to 4.5) and in spontaneous pain in dronabinol compared with placebo groups (MD -20.5%, 95% CI -37.5 to -4.5), but no significant difference in radiating pain between cannabinoid and placebo groups (MD -0.6, 95% CI -1.3 to 0). One study (n=42) reported significant improvement in VRS pain in nabiximol compared with placebo groups (MD -0.79, p=0.03). ○ Pain visual analog scale: One study (n=15) reported significant improvement in pain intensity in nabilone compared with placebo groups (p<0.001). However, this study reported no significant difference in pain impact between cannabinoid and placebo groups (no summary statistics reported). ○ ≥30% pain reduction: One study (n=339) reported no significant difference between nabiximol and placebo groups (no summary statistic reported). ○ Brief pain inventory: One study (n=339) reported no significant difference between nabiximol and placebo groups (no summary statistic reported).

Parameter	Extraction items
	○ Neuropathic pain scale: One study (n=42) reported no significant difference between nabiximol and placebo groups (no summary statistic reported). One study (n=66) reported significant improvements in nabiximol compared with placebo groups (MD -6.58, 95% CI -12.97 to -0.19). *Multiple sclerosis: Secondary outcomes* ○ Sleep: One study (n=339) reported no significant difference in sleep quality (numeric rating scale) between nabiximol and placebo groups (no summary statistic reported). One study (n=42) reported significant improvement in sleep quality in nabiximol compared with placebo groups (MD -0.99, p=0.02). One study (n=66) reported significant improvements in sleep disturbance in nabiximol compared with placebo groups (MD -1.39, 95% CI -2.27 to -0.50). ○ Patient global impression of change: One study (n=339) reported no significant difference between nabiximol and placebo groups (no summary statistic reported). One study (n=66) reported participants in nabiximol group were 3.9 times more likely to rate themselves in any improve category (no summary statistics reported). One study (n=15) reported significant improvement in nabilone groups (100%) compared with placebo (43%) (p<0.05). ○ Adverse events: ○ One study (n=339) with nabiximol and placebo groups reported "Withdrawals by group not different. Treatment 15, Control 12. Severe [adverse event] withdrawals: Treatment 5, Control 3, no difference. Withdrawal for treatment related [adverse events]: Treatment 12, Control 6. Severe emergent [adverse event]: Treatment 21, Control 14. Overall [adverse events]: Treatment 120, Control 106." p12 ○ One study (n=42) with nabiximol and placebo groups reported "Serious [adverse events]: Treatment 2 (disorientation, suicidal ideation) Control 1 (suicidal ideation). 6 patients stopped medication in open-label; all previously placebo group in RCT phase. Most common [adverse events]: dizziness, fatigue, somnolence, vertigo, nausea." p12

Parameter	Extraction items
	○ One study (n=66) with nabiximol and placebo groups reported “Withdrawals: 2 in treatment arm for serious [adverse event], one for agitation with tachycardia and hypertension after 4 sprays, one for paranoid ideation. 88% Treatment group vs. 69% control group developed at least one [adverse event]. Dizziness more likely in treatment group. Other common [adverse events]: dry mouth, somnolence, nausea, falls, weakness, dissociation” p13 ○ One study (n=63) with nabiximol and placebo groups reported “Withdrawals: 25% due to [adverse events]. Mean treatment duration for withdrawals was 162 days. 95% experienced one or more [adverse events]; 92% treatment-related; nausea, dizziness, intoxication. One patient hospitalized for ventricular bigeminy and circulatory collapse” p13 ○ One study (n=24) with dronabinol and placebo groups reported “Withdrawals: none. [adverse events] more common in treatment phase: Treatment 96% of patients, Control 46% of patients (p=0.001) 4 patients reduced treatment dosage due to intolerable [adverse event]. Most common [adverse events] in treatment group: dizziness, headache, tiredness, myalgia” p14 ○ One study (n=15) with nabilone and placebo groups reported “Withdrawals: 1 from treatment group due to headache. Most common [adverse events] in treatment group: dizziness, drowsiness, dry mouth.” p14 *Fibromyalgia: Primary outcomes* ○ Pain visual analog scale: One study (n=40) reported significant improvement in nabilone compared with placebo groups (MD 1.43, p<0.05). No differences noted at 4 weeks following treatment end” p15 *Fibromyalgia: Secondary outcome* ○ Fibromyalgia Impact Questionnaire: One study (n=40) reported significant improvement in nabilone compared with placebo groups (MD -10.76, p<0.01). "No differences noted at 4 weeks following treatment end” p15 ○ Fibromyalgia Impact Questionnaire anxiety subscale: One study (n=40) reported significant improvement in nabilone compared with placebo groups (MD –2.20, p<0.01). "No differences noted at 4 weeks following treatment end” p15

Parameter	Extraction items
	○ Adverse events: ○ One study (n=40) with nabilone and placebo groups reported “Withdrawals: 17.5% (Treatment 5, Control 2). No serious adverse events reported. Side effects more common in treatment group at 4 weeks (p<.05). Most common [adverse events] in treatment group: drowsiness, dry mouth, vertigo, ataxia” p15 *Rheumatoid arthritis: Primary outcomes* ○ Change in morning pain on movement (0-10 rating scales): One study (n=58) reported significant improvement in nabiximol compared with placebo groups (MD -0.95, 95% CI -1.83 to -0.02). ○ Change in morning pain at rest (0-10 rating scale): One study (n=58) reported significant improvement in nabiximol compared with placebo groups (MD -1.04, 95% CI -1.90 to -0.18). ○ Short-form McGill pain questionnaire pain rating: One study (n=58) reported no significant difference between nabiximol and placebo groups (no summary statistic reported). ○ Short-form McGill pain questionnaire visual analog scale: One study (n=58) reported no significant difference between nabiximol and placebo groups (no summary statistic reported). *Rheumatoid arthritis: Secondary outcomes* ○ Change in sleep quality: One study (n=58) reported significant improvement in nabiximols compared with placebo groups (MD -1.17, 95% CI -2.20 to -0.14). ○ Adverse events: ○ One study (n=58) with nabiximol and placebo groups reported “Withdrawals: 1 treatment (unrelated surgery), 3 placebo (adverse events). No serious [adverse events] leading to withdrawal reported in treatment group (3 in placebo). Most common side effects: Dizziness, light-headedness, dry mouth” p16 *Neuropathic pain: Primary outcomes*

Parameter	Extraction items
	○ ≥30% pain reduction: One study (n=246) reported significant likelihood of improvement in nabiximol compared with placebo groups (OR 1.97, 95% CI 1.05 to 3.70). One study (n=125) reported significant likelihood of improvement in cannabinoid compared with placebo groups (OR 1.9, 95% CI 0.80 to 4.75). ○ Pain numerical rating scale: One study (n=246) reported no significant difference between nabiximol and placebo groups (no summary statistics reported). One study (n=125) reported significant improvements in nabiximol compared with placebo groups (MD 0.96, 95% CI -1.59 to-0.32). ○ Pain disability index: One study (n=125) reported significant improvements in nabiximol compared with placebo groups (no summary statistic reported). ○ Neuropathic pain scale: One study (n=246) reported no significant difference between nabiximol and placebo groups (no summary statistics reported). One study (n=125) reported significant improvements in nabiximol compared with placebo groups (no summary statistic reported). One study (n=30) reported no significant difference between nabiximol and placebo groups (no summary statistics reported). ○ McGill pain questionnaire: One study (n=30) reported no significant difference between nabiximol and placebo groups (no summary statistics reported). ○ Brief pain inventory: One study (n=246) reported no significant difference between nabiximol and placebo groups (no summary statistics reported). *Neuropathic pain: Secondary outcomes* ○ Sleep: One study (n=246) reported significant improvement in sleep quality (numeric rating scale) in nabiximol compared with placebo groups (no summary statistics reported). One study (n=125) reported significant improvements in sleep disturbance in nabiximol compared with placebo groups (no summary statistic reported).

Parameter	Extraction items
	○ Patient Global Impression of Change: One study (n=246) reported no significant difference between nabiximol and placebo groups (no summary statistics reported). One study (n=125) reported significant improvements in nabiximol compared with placebo groups (no summary statistic reported). ○ Allodynia: One study (n=125) reported significant improvements in nabiximol compared with placebo groups (no summary statistic reported). ○ Quality of life: One study (n=30) reported no significant difference between nabiximol and placebo groups (no summary statistics reported). ○ Depression: One study (n=30) reported participant with depression were more likely to respond to the nabiximol intervention (no summary statistics reported). ○ Adverse events: ○ One study (n=246) with nabiximol and placebo groups reported "Withdrawal: 13% (another 9% stopped treatment but remained in study). 10 patients in treatment arm 'experienced [serious adverse events], none of which was considered to be treatment-related.' [Adverse events] were experienced more frequently by treatment arm: most common [adverse events]: dizziness, dysgeusia, nausea, fatigue" p16-17 ○ One study (n=380) with nabiximol and placebo groups reported "11% (n=40) patients had serious [adverse events], 1% (n=4) treatment related; amnesia (n=2), paranoia (n=1), suicide attempt (n=1). 23% patients dropped due to [adverse events]: 7% severe, 18% treatment related. 78% (n=295) experienced at least one [adverse event], 59% (n=224) treatment related. Mean intoxication score (0-10 numerical rating scale) 1.5 (+2.3)" p17 ○ One study (n=125) with nabiximol and placebo groups reported "Withdrawals: Treatment 13 (11 side effects, 1 lack of effect), Control 7 (2 side effects, 5 lack of effect). Protocol violators: Treatment 15, Control 5. Gastrointestinal [adverse events] more common (p=0.003) in treatment. Most common [adverse events]

Parameter	Extraction items
	(higher in treatment group): dizziness, nausea, fatigue, dry mouth, vomiting, feeling drunk, diarrhea, nasopharyngitis, anorexia, somnolence. Intoxication reported to remain low, marginally higher in treatment group." p18 ○ One study (n=89) with nabiximol and placebo groups reported "56 (63%) patients withdrew; 18 side effects, 16 lack of efficacy, 15 withdrew consent, 7 other reasons. 2 serious [adverse event]" p18 ○ One study (n=246) with nabiximol and placebo groups reported "Withdrawals: 6 (20%)" p18 *Other chronic pain conditions: Primary outcomes* ○ 11-point pain scale: One study (n=48) of patients with spinal cord injury reported significant improvement in nabiximols (6.1) and whole THC (6.3) compared with placebo (6.9). However, this was not considered to be clinically significant. One study (n=13) of patients with chronic upper motor neuron syndrome reported a 2-point decrease in pain with nabilone treatment compared with placebo (p=-0.05, no other data provided). ○ McGill pain questionnaire: One study (n=48) of patients with spinal cord injury reported significant improvements in cannabinoid compared with placebo groups (no summary statistic reported). ○ McGill pain questionnaire visual analog scale: One study (n=48) of patients with spinal cord injury reported significant improvements in cannabinoid compared with placebo groups (no summary statistic reported). *Other chronic pain conditions: Secondary outcomes* ○ 11-point sleep quality scale: One study (n=48) of patients with spinal cord injury reported significant improvement in nabiximols (5.9) and whole THC (6.0) compared with placebo (5.3). However, this was not considered to be clinically significant. ○ Pain disability index: One study (n=48) of patients with spinal cord injury reported no significant difference between cannabinoid and placebo groups (no summary statistic reported).

Parameter	Extraction items
	○ General health questionnaire-12: One study (n=48) of patients with spinal cord injury reported significant improvements in cannabinoid compared with placebo groups (no summary statistic reported). ○ Headache: One study (n=30) of patients with medication overuse headache reported significant reduction in daily analgesic intake and significant improvement in duration of pain in cannabinoid compared with placebo (no summary statistic reported). This study reports no significant difference on the 'headache impact test' in cannabinoid compared with placebo (no summary statistic reported). ○ Depression and Anxiety Scales: One study (n=30) of patients with medication overuse headache reported significant improvement in cannabinoid compared with placebo (no summary statistic reported). ○ Adverse events: ○ One study (n=48) of patients with spinal cord injury with cannabinoid and placebo groups reported "Withdrawals: 1 treatment (feeling faint), 2 placebo (nausea and vomiting, anxiety and paranoia). No serious [adverse events] reported. Most common side effects: dizziness, somnolence, bad taste, nausea, feeling drunk. Intoxication VAS (100 mm): placebo-1 mm, nabiximols – 5.9 mm, THC – 9.7 mm" p19-20 ○ One study (n=30) of patients with medication overuse headache with cannabinoid and placebo groups reported "Withdrawals: 2 per arm. 1 per arm for [adverse event]. Most common [adverse event]: Dizziness, sleep disorders, decreased appetite, vomiting, nausea, asthenia, gastric discomfort, dry mouth, loss of attention." p20 ○ One study (n=13) with cannabinoid and placebo groups reported "Withdrawals: 2 [motor neuron syndrome] patients from nabilone for acute relapse and exacerbation of lower limb weakness. No other severe side effects reported. Other [adverse events] reported: drowsiness, weakness in lower limbs." p21 *Other contributing studies: Primary outcomes*

Parameter	Extraction items

- Main outcomes: One study (n=28) of adults with chronic non-cancer pain reported "Average pain decreased each week over the 4-week period, using 0-10 scale. Patient satisfaction and pain relief increased by 1.7 and 1.8 respectively from 0-10 scale, pain bothersomeness decreased 0.74 from 0-10 scale. Also, improvements from baseline in Brief Pain Inventory sleep, RAND-36 Energy/Fatigue, Pain, and social Functioning scores, and MOS Sleep Scale for sleep disturbance, sleep problems, and sleep adequacy. No difference in Hamilton Depression Scale." p22

Other contributing studies: Secondary outcomes

- Adverse events:
  - One study (n=28) of adults with chronic non-cancer pain reported "4 of 28 withdrew – 1 believed dronabinol precipitated migraines; 1 due to side effects, 1 "pain unrelated to study," 1 lost to follow-up. Most common [adverse event]: dry mouth, tiredness, sleepiness, drowsiness, anxiety/nervousness, headache, dizziness, abdominal pain, nausea, forgetfulness" p22

- **GRADE by outcome:**

Outcome	No studies	GRADE
Comparative effectiveness		
Pain (nabilone vs. dihydrocodeine)	1	Insufficient
Pain outcomes (nabilone vs. amitriptyline)	1	Insufficient
Multiple sclerosis		
Pain outcomes (dronabinol vs. placebo)	1	Insufficient
Pain outcomes (nabilone vs. placebo)	1	Insufficient
Central neuropathic pain (sativex vs. placebo)	2	Low
Fibromyalgia		
Pain outcomes (sativex vs. placebo)	1	Insufficient
Rheumatoid Arthritis		
Pain reduction >30% (sativex vs. placebo)	1	Low

Parameter	Extraction items
	○ **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):**

Indication	No. studies (No. participants)	Summary estimate (95% CI)	P-value	I^2 (%)	Favours
Nabiximols vs placebo					
Pain reduction >30%	3 (493)	OR 1.30 (0.89 to 1.89)	NR	0	No significant difference
Pain numerical rating scale	3 (530)	WMD -0.62 (-1.63 to 0.40)	NR	89	No significant difference
Neuropathic pain scale	4 (467)	WMD -5.18 (-8.24 to -2.12)	NR	0	Cannabinoids
Patient global impression of change	2 (81)	OR 6.07 (2.24 to 16.47	NR	0	Cannabinoids

	○ **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Not applicable ○ **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Not applicable ○ **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable
Significance/direction	**See above if results listed by outcome:** Above
Heterogeneity	• **See above if I^2 available:** Above • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** Not applicable • **Causes of heterogeneity investigated:** Not applicable
Comments	Open label and RCT all synthesised together. The exception is 'Other Conditions', however no meta-analysis was conducted with this group.

Da Rovare *et al.* (2017): Cannabinoids for spasticity due to multiple sclerosis or paraplegia: A systematic review and meta-analysis of randomized clinical trials

Parameter	Extraction items
First author and year of publication	da Rovare *et al.* (2017)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "To summarize the effects of cannabinoids compared with usual care, placebo for spasticity due to multiple sclerosis (MS) or paraplegia." p170 • **Exact review question and page number:** "The aim of this systematic review and meta-analysis is to look into more detail on the use of cannabinoids for these particular conditions. The intent to highlight specifically spasticity is due to the recent regulation of 1:1 THC:CBD oromucosal spray as a prescription medication in Brazil for patients with multiple sclerosis resistant to the current existing treatment." p171 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** "Patients with spasticity due to [multiple sclerosis] or paraplegia" p171 ➢ **Setting:** Not reported ➢ **Intervention:** "cannabis plant, with any compounds such as delta-9- tetrahydrocannabinol (THC) and/or cannabidiol (CBD), regardless the type of extracts (e.g. oil, hash, tinctures)" p171 ➢ **Comparison:** "usual care, placebo or no intervention." p171 ➢ **Outcome:** "the primary outcomes were spasticity, and spasm frequency and severity. Secondary outcomes were pain measured by any validated scale, bladder function; cognitive function; ADLs; and occurrence of any adverse events (dizziness, somnolence, nausea, dry mouth)." p171 ➢ **Timeframe:** "Eligible studies followed patients for a minimum of two weeks." p171
Participants (characteristics and numbers)	**For whole sample and subgroups** • **Number of participants:** N=2597

Parameter	Extraction items
	• **Age:** Mean range 42.4- 58.6 years • **Gender:** Not reported • **Details of clinical diagnosis/indications:** Spasticity (n=55); multiple sclerosis (n=2246); spinal cord injury (n=127) motor neuron syndrome (n=13); neurological diagnosis (n=21); incontinence (n=135)
Setting/context	• **Countries (alphabetic order):** Europe (13 RCTs), USA (1 RCT), Canada (1 RCT), not reported (1 RCT) • **Setting (university, public or private clinic):** Not reported • **Other relevant features of setting:** Not applicable
Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** "cannabis plant, with any compounds such as delta-9-tetrahydrocannabinol (THC) and/or cannabidiol (CBD), regardless the type of extracts (e.g. oil, hash, tinctures)" p171 • **Dose and regimen:** ○ THC:CBD (11 RCTs): 2.7 mg THC and 0.8-2.5 mg CBD; 12-48 sprays, max 25 mg; daily ○ Cannabis (1 RCT): 4% delta-9-THC; regimen not reported ○ Nabilone (1 RCT): Not reported ○ Dronabinol or C. Sativa extract (1 RCT): 20 or 30% CBD and <5% other cannabinoids; Not reported • **Administration methods:** Spray (9 RCTs); Capsules (6 RCTs); Cigarette (1 RCT) • **Comparator:** Placebo (16 RCTs) • **Treatment duration:** 2-19 weeks • **Timeframe for follow-up:** Not specified
Databases and sources searched	• **Number and names of databases:** 4; MEDLINE, EMBASE, Cochrane Controlled Trials Register (CENTRAL), LILACS: Inception-20/03/2017

Parameter	Extraction items
	• **Other sources:** Not reported • **Grey literature:** Not reported • **Reference chasing:** Yes • **Expert consultation:** Yes, ”we consulted clinical specialists and contacted authors of included trials" p171 • **Dates:** Inception-20/03/2017 • **Search limits:** No • **Justifications for search limits:** Not applicable • **Other searches:** Not reported • **Protocol prepared:** No • **If yes, published:** Not applicable • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** K=0.65 • **Extraction completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Funding of review:** “Regina El Dib received a Brazilian Research Council National Counsel of Technological and Scientific Development scholarship (#310953/2015-4)” p184 • **Conflicts of interest of review:** “Regina El Dib received a Brazilian Research Council National Counsel of Technological and Scientific Development (CNPq) scholarship (#310953/2015-4)” p184 • **How conflicts of interest were managed:** Not reported
Date Range (years) of included studies	• **Exact years for included studies:** 2002-2013

Parameter	Extraction items
Number of primary studies included in the systematic review	• **Number of studies:** 16 RCTS (24 reports) • **Number of studies by study design:** RCT • **Study years:** 2002 (1 RCT); 2003 (2 RCTs); 2004 (3 RCTs); 2006 (1 RCT); 2007(1 RCT); 2009 (1 RCT); 2010 (3 RCTs); 2011 (1 RCT); 2012 (2 RCTs); 2013 (2 RCTs) • **Funding of included studies:** Not reported • **Conflicts of interest of included studies:** Conflict of interest reported in 68.7% of included studies
Types of studies included	**Planned study designs to be included:** RCT **Reasons for including only RCTs/prospective cohort studies:** Not reported **List of excluded studies at full text and reasons for exclusion:** Not reported
Appraisal instruments used	**Full name of tools used:** Modified Cochrane Risk of Bias tool; Grading of Recommendations Assessment, Development and Evaluation (GRADE) **<u>Risk of bias criteria for AMSTAR 2 assessment, for RCTs record Yes/No for:</u>** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The authors did not provide an overall assessment of risk of bias for each trial. However, HRB notes that according to Cochrane's Collaboration tool, and graphical information provided in the paper, the included trials appeared to have a high risk of bias (14 RCTs) and low risk of bias (2 RCTs).

Parameter	Extraction items
	• **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** ○ Overall: Low risk randomisation (7/16); low risk outcome ascertainment (9/16) *Cannabis and cannabinoids vs placebo* ○ Spasticity: Low risk randomisation (3/7); low risk outcome ascertainment (4/7) *Cannabinoids vs placebo* ○ Spasm frequency: Low risk randomisation (2/5); low risk outcome ascertainment (3/5) ○ Spasm severity: Low risk randomisation (1/3); low risk outcome ascertainment (0/3) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** "Potential limitations are related to the data available for this subject on the current literature. Trials often had outcomes reported incompletely, inadequate random sequence, and a failure of blinding due to the nature of the intervention, but for some studies also avoidable lack of blinding (outcome adjudication). Another limitation of this review is the fact that most of the patients are using others concurrent active drugs such as interferon beta 1-b, glatiramer, and corticoids which can introduce bias in the true effects of cannabinoids. The results of trials purporting beneficial effects of a new intervention could not ignore the effects of concurrent treatments. Although this review presents some limitations, the issue is whether one should dismiss these results entirely or consider them bearing in mind the limitations. The latter represent our view of the matter." p180-181 • **Graphical or statistical test for publication bias:** "We focused on publication bias through visual inspection of funnel plots for outcomes addressed in 10 or more studies." p172 • **Authors' comments likelihood and magnitude of publication bias:** "Undetectable" Table 3 • **Authors' comment on how publication bias was dealt with:** Not reported

Parameter	Extraction items
	• **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** No • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** "If results of the primary analysis achieved statistical significance, we planned to conduct sensitivity analyses to test the robustness of those results; however, we were not able to because the primary outcomes did not reach a statistical significance." p172
Method of analysis	• **Description of method of analysis as per authors:** "We calculated pooled risk ratios (RRs) for dichotomous outcomes and standardized mean differences (SMD) for continuous variables with the associated 95% CIs using random-effects models with the Mantel Haenszel statistical method. Absolute effects and 95% CI were calculated by multiplying pooled RRs and 95% CI by baseline risk estimates derived from the largest of included RCTs in the meta-analysis. For dealing with missing data, we used complete case as our primary analysis; that is, we excluded participants with missing data. If results of the primary analysis achieved statistical significance, we planned to conduct sensitivity analyses to test the robustness of those results; however, we were not able to because the primary outcomes did not reach a statistical significance. Results were assessed by each study using different scales. Variability in results across studies was undertaken by using I2 statistic and the P value obtained from the Cochrane chi square test." p172 • **Justification for narrative synthesis or meta-analysis:** Above • **Justification for combining data in meta-analysis:** Above
Outcome assessed	• **List of outcomes assessed and intended time frames:** ○ Primary outcomes: Spasticity, spasm frequency, spasm severity ○ Secondary outcomes: Pain, cognitive function, daily activities, motricity, bladder function, dizziness, somnolence, headache, nausea, dry mouth

Parameter	Extraction items
	○ Intended timeframes: Minimum 2 weeks ○ Actual timeframes: 2-19 weeks
Results/findings	• **Findings by outcome:** PRIMARY OUTCOMES ○ Spasticity: Pooled data from seven studies (n=550) reported no significant difference between intervention (cannabinoid and cannabis) and placebo groups (SMD 0.36, CI 95% −0.17 to 0.88). ○ Spasm frequency: Pooled data from six studies (n=520) reported no significant difference between cannabinoid and placebo groups (SMD 0.04, CI 95% −0.15 to 0.22). ○ Spasm severity: Pooled data from three studies (n=142) reported no significant difference between cannabinoid and placebo groups (SMD −0.14, CI 95% −0.63 to 0.36). SECONDARY OUTCOMES ○ Pain Results: Pooled data from five studies (n=665) reported no significant difference between intervention (cannabinoid and cannabis) and placebo groups (SMD −0.02, CI 95% −0.39 to 0.35). ○ Cognitive function: Pooled data from three studies (n=107) reported no significant difference between intervention (cannabinoid and cannabis) and placebo groups (SMD 0.55, CI 95% −3.33 to 4.43). ○ Daily activities: Pooled data from three studies (n=180) reported no significant difference between cannabinoid and placebo groups (SMD 0.01 CI 95%, −1.21 to 1.24). ○ Motricity: Pooled data from four studies (n=407) reported no significant difference between intervention (cannabinoid and cannabis) and placebo groups (SMD 0.34, CI 95% −0.60 to 1.27). ○ Bladder function: One study (n=160) reported no significant difference between THC/CBD and placebo groups (SMD −0.06 [CI 95% −19.13 to 19.01).

Parameter	Extraction items

- Dizziness: Pooled data from fourteen studies (n=2763) reported significantly increased likelihood in intervention (cannabinoid and cannabis) compared with placebo (RR 3.45, CI 95% 2.71–4.40).
- Somnolence: Pooled data from eleven studies (n=1808) reported significantly increased likelihood in cannabinoid compared with placebo (RR 2.90, CI 95% 1.98–4.23).
- Headache: Pooled data from twelve studies (n=1666) reported no significant differences between intervention (cannabinoid and cannabis) and placebo groups (RR 1.1, CI 95% 0.79–1.54).
- Nausea: Pooled data from eleven studies (n=1694) reported significantly increased likelihood in intervention (cannabinoid and cannabis) compared with placebo (RR 2.25, CI 95% 1.62–3.13).
- Dry mouth: Pooled data from ten studies (n=2287) reported significantly increased likelihood in cannabinoid compared with placebo groups (RR 2.82, CI 95% 2.06–3.85).

Other outcomes

"The cannabinoids in multiple sclerosis (CAMS) study was the largest study approaching cannabinoids versus placebo for spasticity; however there was no statistically significant difference regards improvement in spasticity between both studied groups (RR 1.47, CI 95% 0.99–1.28, 209 patients]). The study also reported the following non-statistically significant difference outcomes: spasm frequency (RR 1.29, CI 95% 0.92–1.80, 231 patients); daily activities (energy) (RR 1.02, CI 95% 0.69–1.51, 249 patients); and pain (RR 2.14, CI 95% 1.31 to 3.49, 178 patients" p179

- **GRADE by outcome:**

Outcome	No. studies	GRADE
Spasticity	7	Low
Spasm frequency	6	Moderate
Spasm severity	3	Moderate
Pain	5	Moderate
Cognitive function	3	Moderate

Parameter	Extraction items

Daily activities	2	Moderate
Motricity	4	Moderate
Bladder function	1	Moderate

Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I2, number of trials or studies, number of participants, random or fixed effects):

Indication	No. studies (No. participants)	Summary estimate (96% CI)	P-value	I^2 (%)	Direction of effect
Cannabinoids / cannabis vs placebo					
Spasticity	7 (550)	SMD 0.36 (−0.17 to 0.88)	0.18	88	No significant effect
Spasm frequency	6 (520)	SMD 0.04 (−0.15 to 0.22)	0.70	2	No significant effect
Spasm severity	3 (142)	SMD −0.14 (−0.63 to 0.36)	0.59	0	No significant effect
Pain	5 (665)	SMD −0.02 (−0.39 to 0.35)	0.90	0	No significant effect
Cognitive function	3 (107)	SMD 0.55 (−3.33 to 4.43)	0.78	0	No significant effect
Daily activities	2 (180)	SMD 0.01 (−1.21 to 1.24)	0.98	0	No significant effect
Motricity	4 (399)	SMD 0.34 (−0.60 to 1.27)	0.48	0	No significant effect
Bladder function	1 (160)	SMD −0.06 (−19.13 to 19.01)	0.99	NA	No significant effect
Dizziness (adverse event)	14 (2763)	RR 3.45 (2.71 to 4.40)	<0.00001	23	Cannabinoid and cannabis
Somnolence (adverse event)	11 (1808)	RR 2.90 (1.98 to 4.23)	<0.00001	0	Cannabinoid
Headache (adverse event)	12 (1666)	RR 1.10 (0.79 to 1.54)	0.57	7	No significant effect
Nausea (adverse event)	11 (1694)	RR 2.25 (1.62 to 3.13)	<0.00001	0	Cannabinoid and cannabis
Dry mouth (adverse event)	10 (2287)	RR 2.82 (2.06 to 3.85)	<0.00001	0	Cannabinoid

Parameter	Extraction items
	○ **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Above ○ **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Yes; random effects model used ○ **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable
Significance/direction	**See above if results listed by outcome:** Above
Heterogeneity	• **See above if I^2 available:** Not applicable • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** Not reported • **Causes of heterogeneity investigated:** Yes, I^2, random effects model, sensitivity analysis considered
Comments	Discrepancies exist between pain, cognitive function and daily activities summary estimates in text (p179) and figures 6, 7, 8. In this form, data has been extracted from text, as study and participant numbers correspond with those outlined in GRADE Table 3. On p179 daily activities findings state three RCTs were included in meta-analysis. Upon inspection only two RCTs are included in corresponding forest plot (figure 7).

De Aquino *et al.* (2022): Alleviation of opioid withdrawal by cannabis and delta-9-tetrahydrocannabinol: A systematic review of observational and experimental human studies

Parameter	Extraction items
First author and year of publication	de Aquino *et al.* (2022)

Parameter	Extraction items
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "conducting a systematic review of observational and experimental human studies investigating opioid withdrawal-alleviating effects of both cannabis and THC among opioid-dependent persons, regardless of [opioid use disorder] treatment status." p2 • **Exact review question and page number:** "conducting a systematic review of observational and experimental human studies investigating opioid withdrawal-alleviating effects of both cannabis and THC among opioid-dependent persons, regardless of [opioid use disorder] treatment status." p2 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** "human participants exposed to cannabis or THC, while experiencing opioid withdrawal" p2 ➢ **Setting:** No specified ➢ **Intervention:** "cannabis and THC" p2 ➢ **Comparison:** Not specified ➢ **Outcome:** "opioid withdrawal-alleviating effects of both cannabis and THC" p2 and as secondary outcomes: 1. Abuse potential and 2. Cardiovascular effects p3
Participants (characteristics and numbers)	**For whole sample and subgroups:** Observational (n=5252); RCT (n=72) The observational studies of interventions are excluded from the remainder of the extraction. • **Number of participants:** n=72 • **Age:** Not reported • **Gender:** Not reported • **Details of clinical diagnosis/indications:** Opioid dependence (n=12); opioid use disorder (n=60)

Parameter	Extraction items
Setting/context	**Countries (alphabetic order):** Not reported **Setting (university, public or private clinic):** Inpatient/outpatient (n=60); laboratory (n=12) **Other relevant features of setting:** Not reported
Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** "cannabis and THC" p2 • **Dose and regimen:** ○ Dronabinol (2 RCTs): 5 mg, 10 mg, 20 mg, 30 mg (regimen not reported); 30 mg (regimen not reported) • **Administration methods:** Not reported, however both RCTs report using Dronabinol (a synthetic form of THC given orally as a capsule) • **Comparator:** Placebo (2 RCTs) • **Treatment duration:** 8 days (1 RCT), 5 weeks (1 RCT) • **Timeframe for follow-up:** 8 weeks for 1 RCT, no follow-up period for 1 RCT
Databases and sources searched	• **Number and names of databases:** 4; MEDLINE (Ovid), Cochrane Central Register of Controlled Trials (Ovid), EMBASE, CINAHL, PsycArticles; inception-07/2022 • **Other sources:** clinicaltrials.gov • **Grey literature:** Open Dissertations (EBSCO). • **Reference chasing:** No • **Expert consultation:** Yes (consultation and search strategy design from a health professional with experience in information retrieval p2) • **Dates:** Inception-07/2022

Parameter	Extraction items
	• **Search limits:** No • **Justifications for search limits:** Not applicable • **Other searches:** Not reported • **Protocol prepared:** No • **If yes, published:** Not applicable • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** Not reported • **If yes, rate of agreement:** Not applicable • **Funding of review:** "JPD is supported by the National Institute on Drug Abuse (NIDA) Grants K23DA052682 and R21DA057240, and by the VISN 1 Mental Illness Research Education Clinical Center (MIRECC)." p11 • **Conflicts of interest of review:** The authors declared no conflict of interest • **How conflicts of interest were managed:** "Other than providing funding, NIDA and the VA had no role in the conception and conduction of this project, nor in the interpretation or reporting of its findings." p11
Date Range (years) of included studies	• **Exact years for included studies:** 2015-2016
Number of primary studies included in the systematic review	• **Number of studies:** 2 RCTs (reported in 3 articles) • **Number of studies by study design:** 2 RCTs • **Study years:** 2015 (1 RCT); 2016 (1 RCT) • **Funding of included studies:** Not reported

Parameter	Extraction items
	• **Conflicts of interest of included studies:** Not reported
Types of studies included	**Planned study designs to be included:** Experimental and observational studies **Reasons for including only RCTs/prospective cohort studies:** Not applicable **List of excluded studies at full text and reasons for exclusion:** Not reported
Appraisal instruments used	**Full name of tools used:** Revised Cochrane Tool for Assessing Risk of Bias in Randomized Trials (RoB 2) **<u>Risk of bias criteria for AMSTAR 2 assessment, for RCTs, record Yes/No for:</u>** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence allocation (individual vs group randomisation):** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The included trials are reported to have unclear risk of bias (2 RCTs). • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** ○ Overall: Low risk randomisation (0/2); low risk outcome ascertainment (2/2) *Dronabinol vs placebo* ○ Opioid withdrawal: Low risk randomisation (0/2); low risk outcome ascertainment (2/2) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** Not reported • **Graphical or statistical test for publication bias:** Not reported • **Authors' comments likelihood and magnitude of publication bias:** Not reported • **Authors' comment on how publication bias was dealt with:** Not reported

Parameter	Extraction items
	• **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** Not applicable • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** No
Method of analysis	• **Description of method of analysis as per authors:** "The primary outcome of interest was opioid withdrawal in response to exposure to cannabis or THC, indexed by either participant- and/or observer-rated instruments for observational and experimental studies, respectively. Data collected included: 1) The sample size of each study; 2) The dose and duration of the exposure to cannabis or THC, when available; 3) The presence of withdrawal and/or its severity, indexed by the reported outcome. In addition, when available in the included studies, we also examined secondary outcomes related to specific adverse effects of acute exposure to cannabis or THC, including: 1) Abuse potential, indexed by semi-structured questionnaires and visual analog scales (VAS); and 2) Cardiovascular effects, indexed by heart rate and blood pressure. When data was only available in plot format, efforts were made to contact the authors of primary studies. However, since significant study heterogeneity existed concerning study procedures, it was decided, a priori, that quantitative data pooling was inappropriate." p2-3 • **Justification for narrative synthesis or meta-analysis:** "However, since significant study heterogeneity existed concerning study procedures, it was decided, a priori, that quantitative data pooling was inappropriate." p3 • **Justification for combining data in meta-analysis:** Not applicable
Outcome assessed	**List of outcomes assessed and intended timeframes** • Primary outcomes: Opioid withdrawal in response to exposure to cannabis or THC • Secondary outcomes: Adverse events • Intended timeframes: Not specified

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- Actual timeframes: 5 weeks (1 RCT); treatment duration 8 days with follow-up at 8 weeks
- **Findings by outcome:**

PRIMARY OUTCOMES

Withdrawal symptoms

- One study (n=12) reported “Oxycodone was superior to dronabinol in reducing opioid withdrawal ($p < .05$)” p6
- One study (n=12) reported “Dronabinol 30 mg produced higher [visual analog scale] “good effects” than placebo (32.1 ± 7.2 vs. 5.5 ± 3.8) ($p < .001$), but still smaller than oxycodone 30 mg (31.8 ± 7.9) and 60 mg (48.0 ± 6.0).” p6
- One study (n=60) reported “32% of regular cannabis users during the outpatient phase had significantly lower ratings of insomnia and anxiety and were more likely to complete the 8- week trial. Trend for higher rates of induction onto XR IM naltrexone following the administration of dronabinol (66 %) compared to placebo (55 %) ($\chi 2\ 2 = 1.46$, $p = .23$)” p6-7

Adverse events

- One study (n=12) reported “dronabinol 20 mg and 30 mg produced heart rate increases compared to placebo (107.6 ± 6.2 vs. 112 ± 3.4 vs. 84.4 ± 2.3 beats per minute, respectively). A higher dose of dronabinol, 40 mg, was discontinued following sustained tachycardia and anxiogenic effects.” p6

- **GRADE by outcome:**

Outcome	No. studies	GRADE
Opioid withdrawal	2	Very low

- **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):** Not applicable

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<tr><td>Results/findings</td><td></td></tr>
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Parameter	Extraction items
	• **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Not applicable • **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Not applicable • **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Yes
Significance/direction	**See above if results listed by outcome:** Above
Heterogeneity	• **See above if I^2 available:** Not applicable • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** Yes, but not specific to RCT data • **Causes of heterogeneity investigated:** No
Comments	The observational studies of interventions are excluded from this extraction form as per umbrella review criteria.

Filippini *et al.* (2022): Cannabis and cannabinoids for symptomatic treatment for people with multiple sclerosis (Review)

Parameter	Extraction items
First author and year of publication	Filippini *et al.* (2022)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "To assess benefit and harms of cannabinoids including synthetic, or herbal and plant-derived cannabinoids, for symptomatic treatment in [multiple sclerosis]." p10 • **Exact review question and page number:** "To assess benefit and harms of cannabinoids including synthetic, or herbal and plant-derived cannabinoids, for symptomatic treatment in [multiple sclerosis]." p10 • **PICO elements reported in Introduction/Methods:**

Parameter	Extraction items
	➢ **Patient or population:** "males and females (18 years or older), diagnosed with [multiple sclerosis], and all types of [multiple sclerosis] such as relapsing-remitting [multiple sclerosis], secondary-progressive [multiple sclerosis], primary-progressive [multiple sclerosis] and progressive-relapsing [multiple sclerosis]" p10 ➢ **Setting:** Not reported ➢ **Intervention:** "Any cannabinoids including herbal cannabis (e.g. marijuana), cannabis flowers (Bedrocan, Bedrobinol, Bediol, Bedrolite, Bedica), plant-based cannabinoids (Nabiximols, Cannabidiol), or synthetic cannabinoids (Dronabinol, Nabilone), irrespective of dose, route, frequency, or duration of use." p10 ➢ **Comparison:** "We included as a comparison intervention placebo or any active comparator. We included concomitant interventions if they were used in all the comparison groups." p10 ➢ **Outcome:** Patient reported outcomes including: Spasticity; chronic neuropathic pain; treatment discontinuation to adverse events; patient global impression of change; health related quality of life; serious adverse events; adverse events; improvement in bladder functions; fatigue; improvement of mobility, balance, tremor, and daily functioning; sleep problems; anxiety and depression; caregiver global impression of change; reduced use of other symptomatic treatments.
Participants (characteristics and numbers)	**For whole sample and subgroups** • **Number of participants:** N=3763 • **Age:** Range 18-60 years old • **Gender:** Range 50%-88% female • **Details of clinical diagnosis/indications:** Multiple sclerosis

Parameter	Extraction items
Setting/context	**Countries (alphabetic order):** Canada (1 RCT); Czech Republic (1 RCT); UK (8 RCTs); Czech Republic and Austria (1 RCT); Denmark (1 RCT); Italy (2 RCTs); Germany (1 RCT); Netherlands (2 RCTs); Switzerland (1 RCT); UK, Belgium and Romania (1 RCT); UK, Canada, Spain, France and Czech Republic (1 RCT); UK and Czech Republic (1 RCT); UK and Romania (1 RCT); UK, Spain, Poland, Czech Republic and Italy (1 RCT); USA (2 RCTs) **Other relevant features of setting:** Not applicable
Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** "Any cannabinoids including herbal cannabis (e.g. marijuana), cannabis flowers (Bedrocan, Bedrobinol, Bediol, Bedrolite, Bedica), plant-based cannabinoids (Nabiximols, Cannabidiol), or synthetic cannabinoids (Dronabinol, Nabilone), irrespective of dose, route, frequency, or duration of use." p10 • **Dose and regimen:** o Sativex (13 RCTs): Max 12-48 sprays daily o Dronabinol (3 RCTs): 10 mg daily; 7.5-10 mg daily o Nabilone (1 RCT): 0.5 or 1 mg capsules o Namisol (1 RCT): 24 mg daily o Cannabis extract (5 RCTs): Max smoked (Not reported); 0.125 mg/kg THC capsule twice daily; max 5 mg THC daily; one cigarette daily; max 30 mg THC daily; max 25 mg THC daily • **Administration methods:** Oromucosal spray (13 RCTs); oral (8 RCTs); inhaled (1 RCT); mixed (3 RCTs) • **Comparator:** "We included as a comparison intervention placebo or any active comparator. We included concomitant interventions if they were used in all the comparison groups." p10 • **Treatment duration:** Not specified (study duration range 3 days-156 weeks) • **Timeframe for follow-up:** Not specified

Parameter	Extraction items
Databases and sources searched	• **Number and names of databases:** 5: Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Database of Systematic Reviews (inception to 27/12/21); MEDLINE (PubMed) (1966 to 31/12/21); EMBASE (1974 to 31/12/21); CINAHL (1981 to 27/12/21); LILACS (1982 to 27/12/21); Physiotherapy Evidence Database (PEDro) (1990 to 27 December 2021) • **Other sources:** Yes; WHO international Clinical Trials Registry Platform (ICTRP); CLINCALTRIALS.GOV; European Union Clinical Trials Register; International Association of Cannabinoid Medicines (IACM) databank • **Grey literature:** No • **Reference chasing:** Yes • **Expert consultation:** Yes (Cochrane Multiple Sclerosis and Rare Diseases of the Central Nervous System group's Information Specialist) • **Dates:** Above • **Search limits:** No • **Justifications for search limits:** Not applicable • **Other searches:** Not applicable • **Protocol prepared:** Yes • **If yes, published:** https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013444/full • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Funding of review:** Below

Parameter	Extraction items
	• **Conflicts of interest of review:** "GF: none, SM: none, FB: She received research grants from GW pharmaceuticals (Cambridge, UK) to perform preclinical studies on phytocannabinoids and intestinal diseases, and patents on phytocannabinoids and colorectal cancer or inflammatory bowel diseases, MC: none, KD: She is employed as statistical editor by Cochrane" Online supplementary materials • **How conflicts of interest were managed:** Not reported
Date Range (years) of included studies	• **Exact years for included studies:** 2002-2018
Number of primary studies included in the systematic review	• **Number of studies:** N=25 RCTs (54 reports) • **Number of studies by study design:** RCT • **Study years:** 2002 (1 RCT); 2003 (1 RCT); 2004 (4 RCTs); 2005 (1 RCT); 2007 (1 RCT); 2009 (1 RCT); 2010 (2 RCTs); 2011 (1 RCT); 2012 (3 RCTs); 2013 (2 RCTs); 2014 (1 RCT); 2015 (2 RCTs); 2016 (1 RCT); 2017 (2 RCTs); 2018 (1 RCT); Not reported ongoing (1 RCT) • **Funding of included studies:** Industry (15 RCTs); public funding (8 RCTs); mixed funding (2 RCTs) • **Conflicts of interest of included studies:** Funding reported above
Types of studies included	**Planned study designs to be included:** RCT **Reasons for including only RCTs/prospective cohort studies:** Not reported **List of excluded studies at full text and reasons for exclusion:** Yes
Appraisal instruments used	**Full name of tools used:** Cochrane Risk of Bias (RoB 2) **Risk of bias criteria for AMSTAR 2 assessment, for RCTs record Yes/No for:** • **Concealment of allocation:** Yes

Parameter	Extraction items
	• **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** Some concerns (20 RCTs); high risk (2 RCTs); not reported (3 RCTs) • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** ○ Overall: Low risk randomisation (8/22); low risk outcomes ascertainment (2/22) *Information not reported for three RCTs *THC:CBD vs placebo* ○ Spasticity >30% reduction: Low risk randomisation (0/5); low risk outcomes ascertainment (0/5) *Mixed cannabinoids vs placebo* ○ Spasticity (continuous variable): Low risk randomisation (0/7); low risk outcomes ascertainment (0/7) ○ Pain >50% reduction: Low risk randomisation (1/1); low risk outcomes ascertainment (0/1) ○ Pain (continuous variable): Low risk randomisation (0/8); low risk outcomes ascertainment (0/8) ○ Health-related quality of life: Low risk randomisation (0/8); low risk outcomes ascertainment (0/8) ○ Patient global impression of change: Low risk randomisation (0/8); low risk outcomes ascertainment (0/8) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** "The quality of the included studies was difficult to assess, because the majority of the risk of bias judgements were deemed 'some concerns'. In particular, we judged 'deviations from intended interventions' and 'measurement of outcome' with some concerns for most included studies. An important bias that may have occurred was in blinding procedures. Given that

Parameter	Extraction items
	most participants in the included studies had previous or current Cannabis experience and our outcomes of interest were patientreported outcomes, make it likely that participants and personnel could become unblinded during trials. Half of the cross-over trials was at high risk of carry-over effect, as they did not have an adequate washout period or their second period was not long enough for the carry-over effect to disappear. Furthermore, none of the cross-over studies considered period effect in the analysis. We are moderately confident in the effect estimate of an important reduction in spasticity in the cannabinoid group compared with the placebo group. The true effect is likely to be close to the estimate of the effect, but there is a possibility thatitis substantially different. With respect to chronic neuropathic pain relief, our confidence in the effect estimate is limited because of the small sample size available from only one small trial that reported the number of participants with pain relief of 50% or greater over baseline. Additional data provided by seven studies showed a reduction of mean chronic neuropathic pain intensity from baseline in cannabinoid-treated participants compared with placebo, but there was a wide variation in reporting across the included studies. The majority of the evidence was low or very low-certainty for SAEs, nervous system or psychiatric disorders and drug tolerance, due to most trials having at least" p23-24 "We assessed the certainty of evidence in the present review as low to very low for most critical and important outcomes, excluding spasticity and [patient global impression of change] (moderate certainty), according to GRADE. In order for robust conclusions to be drawn regarding the antispastic and analgesic effects of cannabinoids-based medicines for people with [multiple sclerosis], we need studies of a high methodological quality, with large sample sizes and longer follow-up periods. There is also a need for randomised studies which compare these medicines with other active anti-spasticity medications and analgesics, in order to draw reliable conclusions about comparative efficacy between treatments" p25

Parameter	Extraction items
	• **Graphical or statistical test for publication bias:** "We evaluated the possibility of non-reporting bias by means of contour-enhanced funnel plots, if a meta-analysis included at least 10 studies (Peters 2008)." p15 • **Authors' comments likelihood and magnitude of publication bias:** "We explored potential non-reporting bias by generating a funnel plot (Figure 3) which indicates, although not conclusively, a lack of bias for the outcome." p19 • **Authors' comment on how publication bias was dealt with:** Not applicable • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** No • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** Above
Method of analysis	• **Description of method of analysis as per authors:** "We used the Mantel-Haenszel method in random-effects meta-analysis to calculate odds ratios. For continuous outcomes, we calculated MD or SMD, if the outcome was measured on different scales (e.g. pain or quality of life), with 95% CIs. We used a random-effects model because we assumed that the studies were not all estimating the same intervention effect and were estimating intervention effects that follow a distribution across studies (DerSimonian 1986). We conducted analyses using RevMan Web (Review Manager Web). *Subgroup analysis and investigation of heterogeneity.* We did prespecify subgroup analyses of number of participants reporting spasticity or pain reduction over baseline for study design and duration of follow-up, baseline severity score, different cannabinoids and co-therapies, to assess whether treatment effects varied across subgroups. However, we did not conduct subgroup analyses for the following reasons. First, the variation in treatment effect on spasticity and pain tended to be explained by outlying single studies rather than variation across all the studies. Second, less than 10 studies for subgroup analyses as planned were available leading to imbalance in studies when defined by subgroups. Third, there was a predominance of parallel group studies and short duration of follow-up.

Parameter	Extraction items
	Sensitivity analysis In the protocol we had planned a sensitivity analysis on the exclusion of trials that we judged to be at high risk of bias or to raise some concerns in at least one domain of RoB 2. However, since we judged all included trials at high risk of bias or with some concerns we did not seek to conduct a sensitivity analysis" p15-16 • **Justification for narrative synthesis or meta-analysis:** Not reported • **Justification for combining data in meta-analysis:** Not reported
Outcome assessed	**List of outcomes assessed and intended timeframes** • Primary outcomes: Spasticity; chronic neuropathic pain; patient global impression of change; health-related quality of life • Secondary outcomes: Serious adverse events; adverse events; severity of spasms; fatigue; sleep problems; mobility; depression; anxiety; carer's global impression of change; reduced use of other treatments • Intended timeframes: Not specified • Actual timeframes: 2-48 weeks
Results/findings	○ **Findings by outcome:** PRIMARY OUTCOMES *Spasticity* ○ Spasticity 30% reduction: Pooled data from five studies (n=1143) reported significantly increased likelihood in cannabinoid compared with placebo groups (OR 2.51, 95% CI 1.56 to 4.04). ○ Spasticity (continuous outcome): Pooled data from seven studies (n=1262) reported significant improvements in cannabinoid compared with placebo groups (MD -0.55, 95% CI -0.94 to -0.17). *Pain*

Parameter	Extraction items
	○ Pain relief 50% or greater: One study (n=48) reported significant likelihood in dronabinol compared with placebo groups (OR 4.23, 95% CI 1.11 to 16.17). ○ Neuropathic pain (continuous outcome): Pooled data from eight studies (n=1451) reported significant improvement in cannabinoid compared with placebo groups (MD -0.54, 95% CI -0.91 to -0.18). *Health-related quality of life* ○ All measures: Pooled data from eight studies (n=1942) reported no significant difference between cannabinoid and cannabis compared with placebo groups (MD -0.08, 95% CI -0.17 to 0.02). *Patient global impression of change* ○ Pooled data from eight studies (n=1215) reported significant likelihood of improvement in cannabinoid compared with placebo groups (OR 1.80, 95% CI 1.37 to 2.36). SECONDARY OUTCOMES ○ Spasticity (Ashworth scale or Modified Ashworth Scale): Pooled data from eleven studies (n=1777) reported significant improvement in cannabinoids compared with placebo groups. (MD -0.23, 95% CI -0.44 to -0.03). ○ Physical functioning: Pooled data from five studies (n=727) reported no significant difference between cannabinoid and cannabis compared with placebo groups placebo groups (MD -0.13, 95% CI -2.05 to 1.80). ○ Role physical: Pooled data from three studies (n=686) reported no significant difference between nabiximol and placebo groups (MD -0.28, 95% CI -3.18 to 2.63). ○ Bodily pain: Pooled data from three studies (n=686) reported significant improvement in nabiximol compared with placebo groups (MD 4.24, 95% CI 0.07 to 8.40). ○ General health: Pooled data from three studies (n=686) reported no significant difference between nabiximol and placebo groups (MD -0.12, 95% CI -2.53 to 2.29).

Parameter	Extraction items
	○ Vitality: Pooled data from three studies (n=686) reported no significant difference between nabiximol and placebo groups (MD 1.38, 95% CI -2.85 to 5.62). ○ Social functioning: Pooled data from three studies (n=686) reported no significant difference between nabiximol and placebo groups (MD -1.39, 95% CI -6.78 to 4.01). ○ Role emotion: Pooled data from three studies (n=686) reported no significant difference between nabiximol and placebo groups (MD -2.09, 95% CI -5.50 to 1.32). ○ Mental health: Pooled data from five studies (n=727) reported no significant difference between cannabinoid and cannabis compared with placebo groups (MD 0.41, 95% CI -1.69 to 2.50). *Adverse events* ○ Withdrawals due to adverse events: Pooled data from 21 studies (n=3110) reported significant likelihood in cannabinoid and cannabis compared with placebo groups (OR 2.41, 95% CI 1.51 to 3.84). ○ Serious adverse events: Pooled data from twenty studies (n=3124) reported no significant difference between cannabinoid and cannabis compared with placebo groups (OR 1.38, 95% CI 0.96 to 1.99). ○ Nervous system adverse events: Pooled data from seven studies (n=1154) reported significant likelihood in cannabinoid compared with placebo groups (OR 2.61, 95% CI 1.53 to 4.44). ○ Psychiatric disorders: Pooled data from six studies (n=1122) reported significant likelihood in cannabinoid compared with placebo groups (OR 1.94, 95% CI 1.31 to 2.88). ○ Drug tolerance: Pooled data from two studies (n=458) reported no significant difference between nabiximol and placebo groups (OR 3.07, 95% CI 0.12 to 75.95). ○ Fatigue: Pooled data from four studies (n=928) reported no significant differences between cannabinoid and cannabis compared with placebo groups (SMD 0.04, 95% CI -0.26 to 0.34).

Parameter	Extraction items
	○ Sleep quality: Pooled data from seven studies (n=1205) reported significant improvements in nabiximol compared with placebo groups (MD -0.66, 95% CI -1.10 to -0.22). ○ Depression: Pooled data from three studies (n=495) reported no significant difference between cannabinoid and placebo groups (MD 0.17, 95% CI -0.90 to 1.24) using the Beck Depression Inventory scale. One study (n=66) reported no significant difference between nabiximol and placebo groups (MD 0.09, CI -1.06 to 1.23; 66 participants) using the Hospital Anxiety and Depression Scale. ○ Anxiety: One study (n=66) reported no significant difference between nabiximol and placebo groups (MD -0.64, CI -1.75 to 0.46). *Other outcomes* ○ Activities of daily living: Pooled data from five studies (n=1134) reported no significant difference between cannabinoid and placebo groups (MD -0.08, 95% CI -0.32 to 0.16). ○ Carer global impression of change: Pooled data from four studies (n=582) reported significant likelihood of improvements in nabiximol compared with placebo groups (OR 1.66, 95% CI 1.15 to 2.41). ○ Bladder symptoms: One study (n=335) reported no significant difference in daily number of urinary incontinence episodes between nabiximol and placebo groups (no summary statistic reported). This study reported significant improvement in number of episodes of nocturia (no summary statistic reported). ○ Use of analgesics: One parallel-group trial (n=339, nabiximols) and one cross-over study (n=48, dronabinol) reported that paracetamol was provided for rescue analgesic use during the study and no significant difference was reported between cannabinoid and placebo (no summary statistics reported). ○ Frequency and severity of muscle spasms: One study (n=160) reported no significant difference between nabiximol and placebo groups (no summary statistic reported. One study (n=277) reported significantly greater improvements in cannador group (30.8%) compared with the placebo group (13.4%) (p<0.002).

Parameter	Extraction items

- Tremor: One study (n=14) reported no significant difference between cannador and placebo groups (no summary statistics reported).
- **GRADE by outcome:**

Outcome	No. studies	GRADE
Spasticity	7	Moderate
Chronic neuropathic pain	1	Very low
Withdrawals due to AEs	21	Low
Patient global impression of change	8	Moderate
Health related quality of life	8	Low
Serious adverse events	20	Low
Nervous system adverse events	7	Low
Psychiatric disorders	6	Low
Drug tolerance	2	Very low

- **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):**

Indication	No. studies (No. participants)	Summary estimate (95% CI)	P-value	I^2 (%)	Direction of effect
Spasticity					
Spasticity reduction 30% or greater	5 (1143)	OR 2.51 (1.56 to 4.04)	0.02	67	Cannabinoids
Spasticity (continuous outcome)	7 (1262)	MD -0.55 (-0.94 to -0.17)	0.005	68	Cannabinoids
Spasticity (Ashworth scale)	11 (1777)	MD -0.23 (-0.44 to -0.03)	0.03	50	Cannabinoids
Pain					
Pain relief 50% or greater	1 (339)	OR 1.61 (1.01 to 2.57)	0.046	NA	Dronabinol
Pain (continuous outcome)	8 (1451)	MD -0.54 (-0.91 to -0.18)	0.004	62	Cannabinoids

Parameter	Extraction items

Health-related quality of life					
All measures	8 (1942)	SMD -0.08 (-0.17 to 0.02)	0.10	0	No significant difference
Physical functioning	5 (727)	MD -0.13 (-2.05 , 1.80)	0.9	0	No significant difference
Role physical	3 (683)	MD -0.28 (-3.18 , 2.63)	0.85	0	No significant difference
Bodily pain	3 (683)	MD 4.24 (0.07 to -8.40)	0.05	45	Nabiximol
General health	3 (683)	MD -0.12 (-2.53 to 2.29)	0.48	0	No significant difference
Vitality	3 (683)	MD 1.38 (-2.85 to 5.62)	0.52	49	No significant difference
Social functioning	3 (683)	MD -1.39 (-6.78 to 4.01)	0.61	60	No significant difference
Role emotion	3 (683)	MD -2.09 (-5.50 to 1.32)	0.23	0	No significant difference
Mental health	5 (727)	MD 0.41 (-1.69 to 2.50)	0.70	0	No significant difference
Adverse events					
Withdrawals due to adverse events	21 (3110)	OR 2.41 (1.51 to 3.84)	0.0002	17	Cannabinoid and cannabis
Serious adverse events	20 (3124)	OR 1.38 (0.96 to 1.99)	0.08	0	No significant difference
Nervous system	7 (1154)	OR 2.61 (1.53 to 4.44)	0.0004	64	Cannabinoids
Psychiatric disorders	6 (1122)	OR 1.94 (1.31 to 2.88)	0.001	0	Cannabinoids
Drug tolerance	2 (458)	OR 3.07 (0.12 to 75.95)	0.49	NR	No significant difference
Fatigue	4 (928)	SMD 0.04 (-0.26 to 0.34)	0.78	35	No significant difference
Sleep quality	7 (1205)	MD -0.66 (-1.10 to -0.22)	0.003	73	Nabiximol (improvement)
Depression	3 (495)	MD 0.17 (-0.90 to 1.24)	0.75	0	No significant difference
Activities of daily living	5 (1134)	MD -0.08 (-0.32 to 0.16)	0.49	0	No significant difference
Other outcomes					
Patient global impression of change	8 (1215)	OR 1.8 (1.37 to 2.36)	<0.0001	0	Cannabinoids
Carer global impression of change	4 (582)	OR 1.66 (1.15 to 2.41)	0.67	0	No significant difference

- **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Not applicable

Parameter	Extraction items
	○ **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Yes ○ **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable
Significance/direction	**See above if results listed by outcome:** Above
Heterogeneity	• **See above if I^2 available:** Above • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** "Several factors limit the applicability of the evidence in our review. First, the baseline level of spasticity or chronic neuropathic pain and their duration varied across participants, and when assessing severity of these symptoms at baseline authors used a number of different instruments. The included studies recruited a mixture of patients with different clinical manifestations of spasticity and chronic neuropathic pain. This led to significant clinical and statistical heterogeneity in the effect estimates that limited the applicability of the evidence to the wider population of people with [multiple sclerosis]." p23 • **Causes of heterogeneity investigated:** Yes I^2, random effects model, sensitivity analysis considered
Comments	Different summary statistics (e.g. MD or OR) are reported for the same outcome. For consistency all meta-analysis summary statistics have been extracted from forest plots p87-91. Risk of bias not reported for three RCTs: Corey Bloom *et al.* (2012); Fox *et al.* (2004); Kavia *et al.* (2010)

Fisher *et al.* (2021): Cannabinoids, cannabis, and cannabis-based medicine for pain management: a systematic review of randomised controlled trials

Parameter	Extraction items
First author and year of publication	Fisher *et al.* (2021)

Parameter	Extraction items
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "to provide a comprehensive summary of the evidence from primary randomised controlled trials (RCTs) of cannabinoids, cannabis, and [cannabis-based medicine] in clinical acute and chronic pain management, across the lifespan." pS46 • **Exact review question and page number:** "to provide a comprehensive summary of the evidence from primary randomised controlled trials (RCTs) of cannabinoids, cannabis, and [cannabis-based medicine] in clinical acute and chronic pain management, across the lifespan." pS46 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** People with acute or chronic pain ➢ **Setting:** Not reported ➢ **Intervention:** Any type of cannabinoid product, natural or synthetic, delivered by any route of administration ➢ **Comparison:** Any control, including placebo or active pain therapy, pharmacological or non-pharmacological. ➢ **Outcome:** Primary outcomes: proportion of people with at least 30% pain intensity reduction/moderate improvement; proportion of people with at least 50% pain intensity reduction/substantial improvement Secondary outcomes: Continuous assessments of pain intensity (e.g. using a numerical rating scale or visual analogue scale); proportion of people who experienced a decrease in pain from moderate/severe to mild; disability or physical functioning; emotional functioning (e.g. anxiety and depression); carer global impression of change; quality of life as defined by validated scales; the number of adverse events (AEs); requirement for rescue analgesia; sleep duration and quality; onset and duration of analgesic effects (when relevant in acute pain trials).
Participants (characteristics and numbers)	**For whole sample and subgroups:** N=5869 (cannabinoid RCTs); N=1348 (palmitoylethanolamide, two fatty acid amide hydrolase, cannabinoid receptor agonist RCTs)

Parameter	Extraction items
	*RCTs of three palmitoylethanolamide, two fatty acid amide hydrolase and two cannabinoid receptor agonists are excluded from the remainder of the extraction as per inclusion criteria. • **Number of participants:** n=5869 • **Age:** Mean age range: 39-63.5 years • **Gender:** 59.3% female (two RCTs n=403 did not report gender breakdown) • **Details of clinical diagnosis/indications:** Neuropathic pain (n=544); cancer (n=1406), acute pain after surgery (n=445); multiple sclerosis (n=2673); diabetes (n=595); spinal cord injury (n=158); brachial plexus avulsion (n=48)
Setting/context	**Countries (alphabetic order):** Not reported **Setting (university, public or private clinic):** Unknown (16 RCTs); home (5 RCTs); hospital (6 RCTs); outpatient (2 RCTs) **Other relevant features of setting:** Not applicable
Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** "Any type of cannabinoid product, natural or synthetic, delivered by any route of administration" pS47 • **Dose and regimen:** o Cannabis (5 RCTs): 1.29% -7% THC regimen not reported; max 25 mg capsule daily o CBD:THC (1 RCT): 2.5 vs 2.5mg, regimen not reported o THC (3 RCTs): 2.5-20 mg; regimen not reported o Dronabinol (2 RCTs): 7.5-28 mg; daily o Nabilone (2 RCTs): 0.5-2.0 mg, regimen not reported

Parameter	Extraction items
	○ Nabiximols (15 RCTs): 2.5:2.7 mg THC:CBD; 1-24 sprays (details not reported for four RCTs) • **Administration methods:** Oromuscular spray (16 RCTs); orally (9 RCTs); smoked (4 RCTs) • **Comparator:** Placebo (24 RCTs); piritramide (1 RCT); placebo and codeine (2 RCTs); placebo and ibuprofen (1 RCT); dihydrocodeine (1 RCT) • **Treatment duration:** Not specified (study duration range 18 hours- 15 weeks) • **Timeframe for follow-up:** Not reported for included studies
Databases and sources searched	• **Number and names of databases:** 3: PubMed, EMBASE, Cochrane CENTRAL; Inception to April 2019 • **Other sources:** Online trial registries: clinicaltrials.gov, EudracT • **Grey literature:** No • **Reference chasing:** No • **Expert consultation:** No • **Dates:** Inception to April 2019 • **Search limits:** No • **Justifications for search limits:** Not applicable • **Other searches:** "conducted a targeted search for RCTs in this area in January 2020 for any new studies" pS47 • **Protocol prepared:** Yes • **If yes, published:** CRD42019124714 https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=124714 • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** Yes

Parameter	Extraction items
	• **If Yes, rate of agreement:** No • **Funding of review:** "The International Association for the Study of Pain commissioned this work in the form of a Presidential Task Force and funded attendance for the authors at a working meeting in Washington, DC, November 2019." pS63 • **Conflicts of interest of review:** "C. Eccleston reports grants from vs Arthritis, MayDay Foundation, Cochrane, and NIHR outside of 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.S.C. Rice is a Council Member of IASP and Chair of the Presidential Task Force of the IASP, and 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 Theranexus. 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

Parameter	Extraction items
	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 reports personal fees from Insys, outside the submitted work. The remaining authors have conflicts of interest to declare" pS63 • **How conflicts of interest were managed:** Not reported
Date Range (years) of included studies	• **Exact years for included studies:** 1975-2019
Number of primary studies included in the systematic review	• **Number of studies:** 30 RCTs (reported in 29 studies) • **Number of studies by study design:** 30 RCTs • **Study years:** 1975 (1 RCT); 1978 (1 RCT); 2002 (1 RCT); 2003 (1 RCT); 2004 (1 RCT); 2005 (2 RCTs); 2006 (1 RCT); 2007 (1 RCT); 2008 (3 RCTs); 2010 (2 RCTs); 2012 (4 RCTs); 2013 (2 RCTs); 2014 (1 RCT); 2015 (2 RCTs); 2016 (1 RCT); 2017 (3 RCTs); 2018 (1 RCT); 2019 (1 RCT) • **Funding of included studies:** Industry (14 RCTs); non-industry (12 RCTs); not reported (3 RCTs) • **Conflicts of interest of included studies:** Yes
Types of studies included	**Planned study designs to be included:** Trials > 30 participants **Reasons for including only RCTs/prospective cohort studies: "**We used randomized trials because they typically provide the least biased estimate for treatment efficacy" pS46 **List of excluded studies at full text and reasons for exclusion:** Not reported
Appraisal instruments used	**Full name of tools used:** Cochrane Risk of Bias tool

Parameter	Extraction items
	<u>Risk of bias criteria for AMSTAR 2 assessment, for RCTs record Yes/No for:</u> • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** High risk of bias (22 RCTs); unclear risk of bias (8 RCTs) • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** o Overall: Low risk randomisation (10/30); low risk outcome ascertainment (14/30) *Cannabis vs placebo < 7 days* o >30% pain reduction: Low risk randomisation (2/2); low risk outcome ascertainment (2/2) *Cannabis vs placebo ≥ 7 days* o >30% pain reduction: Low risk randomisation (1/1); low risk outcome ascertainment (1/1) *THC (delta-9-THC and THC congener) vs placebo/codeine <7days* o >30% pain reduction: Low risk randomisation (0/1); low risk outcome ascertainment (0/1) o >50% pain reduction: Low risk randomisation (0/2); low risk outcome ascertainment (0/2) *Nabiximols vs placebo ≥ 7days* o >30% pain reduction: Low risk randomisation (2/6); low risk outcome ascertainment (2/6) o >50% pain reduction: Low risk randomisation (1/2); low risk outcome ascertainment (1/2)

Parameter	Extraction items
	THC vs placebo ≥ 7 days ○ >30% pain reduction: Low risk randomisation (1/2); low risk outcome ascertainment (1/2) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** "No study was rated as low risk of bias across all risk of bias domains; studies were rated as having unclear or high risk of bias in at least one domain, and typically in several domains. Risks of bias, high heterogeneity in some analyses, and the likelihood of selective reporting biases influenced our judgements of the quality of evidence. No outcomes achieved a higher than "low quality" rating. In fact, we rated most outcomes as very low quality of evidence, meaning we are very uncertain of the estimates of effect reported." pS62 • **Graphical or statistical test for publication bias:** Mentioned but not reported • **Authors' comments likelihood and magnitude of publication bias:** Not reported • **Authors' comment on how publication bias was dealt with:** Not applicable • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** No • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** Yes
Method of analysis	• **Description of method of analysis as per authors:** "Data synthesis We combined data in meta-analyses where sufficient data were available using Revman 5.0. We used MDs for continuous outcomes, and risk difference (RD) for dichotomous outcomes. We calculated number needed to treat to benefit (NNTB) where we were able. Heterogeneity was interpreted following the Cochrane Handbook. Adverse events were entered into meta-analyses and calculated using RDs and 95% CIs. Where possible, we described any assessment of possible causality of AEs. We conducted comparisons of cannabis vs control, and CBM (including individual cannabinoids) vs

Parameter	Extraction items
	control, for each of our named outcomes to determine efficacy. We conducted 4 primary analyses, which included all trials, conducted with a subgroup analysis by drug type, at 2 time-points: (1) Cannabis vs control at short-term follow-up (up to 7 days treatment duration) (2) Cannabis vs control at long-term follow-up (greater than or equal to 7 days treatment duration) (3) Cannabis-based medicine vs control at short-term follow-up (up to 7 days treatment duration) (4) Cannabis-based medicine vs control at long-term follow-up (greater than or equal to 7 days treatment duration). We planned to conduct sensitivity analyses where appropriate to investigate the impact of risk of bias and study quality." p49-50 • **Justification for narrative synthesis or meta-analysis:** Not reported • **Justification for combining data in meta-analysis:** Not reported
Outcome assessed	**List of outcomes assessed and intended timeframes** • Primary outcomes: 30% reduction in pain intensity; 50% reduction in pain intensity • Secondary outcomes: Pain intensity change scores; Physical functioning (change scores); Emotional functioning (change scores); sleep quality (change scores); participants with any adverse event • Intended timeframe: Not specified • Actual timeframe: 18 hours-60 days
Results/findings	• **Findings by outcome:** PRIMARY OUTCOMES *Cannabis (short-term up to seven days duration)* ○ ≥30% reduction in pain: Pooled data from two studies (n=231) reported significant improvements in cannabis compared with placebo groups (RD 0.33, 95% CI 0.20 to 0.46).

Parameter	Extraction items
	Cannabis vs control at long-term follow-up (greater than or equal to 7 days treatment duration) ○ ≥30% reduction in pain: One study (n=174) reported significant improvements in pain in cannabis compared with placebo groups (RD 0.19, 95% CI 0.07 to 0.30). However, when reporting mean pain intensity of the whole sample after treatment, no significant effect was reported. A separate study (n=657) reported a greater proportion of patients with undefined "improvement" in pain in oral cannabis extract groups compared with placebo groups (no summary statistics reported). *Other cannabinoids vs control at short-term follow-up (up to 7 days treatment duration)* ○ Cancer ≥30% reduction in pain: One study (n=105) reported significant improvement in THC congener compared with placebo/codeine groups (RD 0.11, 95% CI -0.09 to 0.32). ○ Cancer ≥50% reduction in pain: Pooled data from two studies (n=207) reported significant improvement in cannabinoid (THC congener and nabilone) compared with control groups (one placebo, one codeine) (RD 0.07, 95% CI -0.29 to 0.43). *Nabiximols vs placebo (greater than or equal to 7 days treatment duration)* ○ ≥30% reduction in pain: Pooled data from six studies (n=1484) reported significant improvement in nabiximol compared with placebo groups (RD 0.06, 95% CI 0.01 to 0.12). ○ ≥50% reduction in pain: Pooled data from two studies (n=464) reported no significant difference between nabiximol and placebo groups (RD 0.07, 95% CI -0.04 to 0.17). *THC vs placebo (greater than or equal to 7 days treatment duration)* ○ ≥30% reduction in pain: Pooled data from two studies (n=528) reported no significant difference between THC and placebo groups (RD -0.02, 95% CI -0.09 to 0.05). SECONDARY OUTCOMES *Cannabis (short-term up to seven days duration)*

Parameter	Extraction items
	○ Pain intensity: One study (n=37) reported no significant difference between cannabis and placebo groups (no summary statistics reported). ○ Emotional functioning: One study (n=37) reported no significant difference between cannabis and placebo groups (no summary statistics reported). *Cannabis (greater than or equal to 7 days treatment duration)* ○ Pain intensity: One study (n=174) reported no significant difference in pain in cannabis compared with placebo groups (no summary statistics reported). ○ Sleep: One study (n=279) reported no significant differences between cannabis and placebo groups (no summary statistic reported). *Cannabis adverse events* ○ Adverse events: Pooled data from two studies (n=750) reported no significant difference between cannabis and placebo groups (RD 0.08, 95% CI 2 0.10 to 0.25). One study (n=279) reported significantly higher treatment-related adverse events in cannabis compared with placebo groups (no summary statistics reported). ○ Serious adverse events: Pooled data from three studies (n=690) reported no significant difference between cannabis and placebo groups (RD -0.05, 95% CI -0.16 to 0.07). One study (n=120) reported treatment-related serious adverse events and also found no significant difference between cannabis and placebo groups (no summary statistics reported). ○ Withdrawals: Pooled data from two studies (n=605) reported no significant difference between cannabis and placebo groups related to all-cause withdrawals (RD 0.05, 95% CI -0.03 to 0.13). Pooled data from two studies (n=605) reported no significant differences between cannabis and placebo groups related to withdrawals due to adverse events (RD 0.08, 95% CI -0.08 to 0.25). *Other cannabinoids vs control at short-term follow-up (up to 7 days treatment duration)*

Parameter	Extraction items
	○ Pain intensity: One study (n=105) reported no significant difference between oral THC and piritramide (a synthetic opioid analgesic) groups (no summary statistic reported). One study (n=340) reported no significant difference between nabilone and placebo groups (no summary statistics reported). *Nabiximols (greater than or equal to 7 days treatment duration)* ○ Pain intensity: Pooled data from 12 studies (n=2497 patients) reported significant improvement in nabiximol compared with placebo groups (MD -0.34, 95% CI -0.54 to -0.14). ○ Quality of life: One study (n=177) reported no significant difference between nabiximol and placebo groups (no summary statistic reported). ○ Rescue medication usage: One study (n=70) reported significantly lower usage in nabiximol compared with placebo, however six trials (references not specified) reported no significant difference between groups. ○ Adverse events: Pooled data from 12 studies (n=2551) reported participants in the nabiximol group were more likely to have an adverse events compared to placebo group (RD 0.13, 95% CI 0.08 to 0.19). Similarly, participants in the nabiximol group were significantly more likely to report a treatment-related adverse events compared to placebo groups (RD 0.19, 95% CI 0.10 to 0.27). ○ Serious adverse events: Pooled data from 11 studies (n=2108) reported no significant differences between nabiximol and placebo groups) (RD 0.02, 95% CI -0.00 to 0.04). Pooled data from 5 studies (n=1418) reported no significant difference found for treatment-related serious adverse events between nabiximol and placebo groups (RD 0.01, 95% CI -0.02 to 0.04). ○ Withdrawals: Pooled data from 11 studies (n=2489 participants) reported all causes of withdrawals and no difference was found between nabiximol and placebo groups (RD 0.03, 95% CI -0.01 to 0.07). However, pooled data from 12 studies (n=2601) reported significantly more people withdrew from the nabiximol group due to adverse events compared with placebo groups (RD 0.04, 95% CI 0.01 to 0.06). Pooled data from nine studies (n=2001) reported no

Parameter	Extraction items
	significant difference between nabiximol and placebo groups related to withdrawals due to lack of efficacy (RD -0.01, 95% CI -0.02 to 0.00). Pooled data from 5 studies (n=729) reported no significant difference between groups for withdrawals due to serious adverse events (RD 0.00, 95% CI -0.01 to 0.02). *THC (greater than or equal to 7 days treatment duration)* ○ Pain intensity: Pooled data from four studies (n=795) reported no significant difference between THC and placebo groups (MD -0.15, 95% CI --0.48 to 0.17). ○ Sleep quality: Two studies reported no significant difference between groups (references not specified). ○ Adverse events: Pooled data from four studies (n=1168) reported significantly higher frequency of adverse events in THC compared with placebo groups (RD 0.15, 95% CI 0.05 to 0.24). One study (n=240) reported no significant difference related to treatment-related adverse events between THC and control groups (RD 0.24, 95% CI 0.12 to 0.36). ○ Serious adverse events: Pooled data from five studies (n=1012) reported no significant difference between THC and control groups (one dihydrocodeine, four placebo) (RD 0.00, 95% CI -0.02 to 0.02). One study (n=240) reported no significant difference related to treatment-related serious adverse events between THC and control groups (RD 0.01, 95% CI -0.01 to 0.03). ○ Withdrawals: Pooled data from six studies (n=1357) reported no significant difference between THC and control groups (one dihydrocodeine, four placebo) (RD 0.01, 95% CI -0.06 to 0.08). Pooled data from seven studies (n=1428) reported no significant differences relating withdrawals due to adverse events between THC and control (one dihydrocodeine, six placebo) (RD 0.02, 95% CI -0.01 to 0.05). Pooled data from four studies (n=979) reported no significant differences relating withdrawals due to serious adverse events between THC and control (one dihydrocodeine, three placebo) (RD 0.00, 95% CI -0.01 to 0.01. Pooled data from three studies (n=675) reported no

Parameter	Extraction items

significant differences relating withdrawals due to lack of efficacy between THC and placebo groups (RD 0.00, 95% CI -0.01 to 0.01).

- **GRADE by outcome:**

Outcome	Studies	GRADE
Cannabis		
≥30% reduction in pain <7 days	2	Very low
Emotional functioning <7 days	1	Very low
Mean sleep ≥7 days	1	Very low
Adverse events	2	Very low
Serious adverse events	3	Very low
Withdrawals (all causes)	2	Very low
Withdrawals due to adverse events	2	Very low
Other cannabinoids (THC congener benzopyran peridine and nabilone)		
≥30% reduction in pain <7 days	1	Very low
≥50% reduction in pain <7 days	2	Very low
Nabiximols ≥7 days		
≥30% reduction in pain	6	Low
≥50% reduction in pain	2	Very low
Pain mean change	12	Very low
Adverse events ≥7 days	12	Low
Treatment-related adverse events	7	Very low
Serious adverse events	11	Low
Treatment-related serious adverse events	5	Very low
Withdrawal (all causes)	11	Low
Withdrawals due to adverse events	12	Very low
Physical functioning	4	Very low

Parameter	Extraction items

Emotional functioning	4	Low
Quality of life	6	Very low
Sleep quality	13	Very low
THC		
≥30% reduction in pain	2	Very low
Pain mean change	4	Very low
Adverse events	4	Very low
Serious adverse events	5	Low
Treatment-related serious adverse events	1	Very low
Withdrawal (all causes)	6	Very low
Withdrawals due to adverse event	7	Very low quality
Withdrawals due to serious adverse event	4	Low quality
Sleep quality	2	Very low

- **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):** Random effects

Outcome	No. studies (No. participants)	Summary estimate (95% CI)	P-value	I^2 (%)	Direction of effect
Cannabis vs placebo					
≥30% reduction in pain <7 days	2 (231)	RD 0.33 (0.20 to 0.46)	<0.00001	0	Cannabis
Adverse events	2 (750)	RD 0.08 (-0.10 to 0.25)	0.4	96	No significant difference
Treatment-related adverse events	1 (278)	RD 0.18 (0.10 o 0.27)	<0.0001	NA	Cannabis
Serious adverse events	3 (690)	RD -0.05 (-0.16 to 0.07)	0.43	86	No significant difference

Parameter	Extraction items					
	Treatment-related serious adverse events	1 (120)	RD 0.00 (-0.04 to 0.04)	1	NA	No significant difference (No events)
	Withdrawals (all causes)	2 (605)	RD 0.05 (-0.03 to 0.13)	0.25	54	No significant difference
	Withdrawals due to adverse events	2 (605)	RD 0.08 (-0.08 to 0.25)	0.33	94	No significant difference
	THC/CBD (nabiximols) vs placebo					
	≥30% reduction in pain ≥7days	6 (1484)	RD 0.06 (0.01 to 0.12)	0.03	24	Nabiximol
	≥50% reduction in pain ≥7days	2 (464)	RD 0.07 (-0.04 to 0.17)	0.21	47	Nabiximol
	Pain mean change ≥7days	12 (2497)	MD -0.34 (-0.54 to -0.14)	0.0008	50	Nabiximol
	Adverse events	12 (2251)	RD 0.13 (0.08 to 0.19)	<0.0001	66	Nabiximol
	Treatment-related adverse events	6 (1746)	RD 0.19 (0.10 to 0.27)	<0.0001	74	Nabiximol
	Serious adverse events	11 (2109)	RD 0.02 (-0.00 to 0.04)	0.12	0	No significant difference
	Treatment-related serious adverse events	5 (1418)	RD 0.01 (-0.02 to 0.04)	0.47	75	No significant difference
	Withdrawal (all causes)	11 (2489)	RD 0.03 (0.01 to 0.07)	0.11	44	No significant difference
	Withdrawals due to adverse events	12 (2601)	RD 0.04 (0.01, 0.06)	0.008	60	Nabiximol
	Withdrawals due to serious adverse events	5 (729)	RD 0.00 (-0.01 to 0.02)	0.70	0	No significant difference
	Physical functioning	4 (364)	MD -2.84 (-5.21 to -0.47)	0.02	16	Nabiximol
	Emotional functioning	4 (561)	MD 0.38 (-0.74 to 1.50)	0.50	12	No significant effect
	Quality of life	6 (1025)	SMD 0.01 (-0.15 to 0.18)	0.87	32	No significant difference

Parameter	Extraction items

Sleep quality	13 (2758)	MD -0.36 (-0.57 to -0.14)	0.001	66	Nabiximol
THC vs placebo					
≥30% reduction in pain ≥7 days	2 (528)	RD -0.02 (-0.09 to 0.05)	0.53	0	No significant difference
Pain mean change ≥7days	4 (795)	MD -0.15 (-0.48 to 0.17)	0.36	46	No significant difference
Sleep quality	2 (176)	MD -0.50 (-1.23 to 0.23)	0.18	50	No significant difference
THC (THC congener and delta-9-THC) vs placebo/codeine					
≥30% reduction in pain <7 days	1 (105)	RD 0.11 (-0.09 to 0.32)	0.27	NA	No significant difference
≥50% reduction in pain <7 days	2 (207)	RD 0.07 (-0.29 to 0.43)	0.70	87	No significant difference
THC vs mixed control					
Adverse events	4 (1168)	RD 0.15 (0.05 to 0.24)	0.002	67	THC
Treatment-related adverse events	1(240)	RD 0.24 (0.12 to 0.36)	<0.0001	NA	THC
Serious adverse events	5 (1012)	RD 0.00 (-0.02 to 0.02)	0.89	28	No significant difference
Treatment-related serious adverse events	1 (240)	RD 0.01 (-0.01 to 0.03)	0.48	NA	No significant difference
Withdrawal (all causes)	6 (1357)	RD 0.01 (-0.06 to 0.08)	0.79	84	No significant difference
Withdrawals due to adverse events	7 (1428)	RD 0.02 (-0.01 to 0.05)	0.26	74	No significant difference
Withdrawals due to serious adverse events	4 (979)	RD 0.00 (-0.01 to 0.01)	0.55	0	No significant difference

- **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Above

Parameter	Extraction items
	○ **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Yes ○ **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable
Significance/direction	**See above if results listed by outcome:** Above
Heterogeneity	• **See above if I^2 available:** Above • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** "No study was rated as low risk of bias across all risk of bias domains; studies were rated as having unclear or high risk of bias in at least one domain, and typically in several domains. Risks of bias, high heterogeneity in some analyses, and the likelihood of selective reporting biases influenced our judgements of the quality of evidence. No outcomes achieved a higher than 'low quality' rating. In fact, we rated most outcomes as very low quality of evidence, meaning we are very uncertain of the estimates of effect reported" pS63 • **Causes of heterogeneity investigated:** Yes, I^2, random effects model, sensitivity and subgroup analysis considered
Comments	This systematic review includes 37 studies (30 RCTs of cannabis/cannabinoids and 7 RCTs of PEA, FAAH and cannabinoid receptor agonists). Unless specified otherwise, the information in this extraction for only reports on RCTs of cannabis/cannabinoids as per the umbrella review inclusion criteria. Data on participant and gender numbers has been extracted from appendix 9. On pS53 authors report RR summary statistics. Upon inspection of forest plots RD should have been reported. This typo has been corrected in this extraction form.

Fitzcharles *et al.* (2016a): Efficacy, Tolerability, and Safety of Cannabinoid Treatments in the Rheumatic Diseases: A Systematic Review of Randomized Controlled Trials

Parameter	Extraction items
First author and year of publication	Fitzcharles *et al.* (2016a)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "To assess the efficacy, tolerability, and safety of cannabinoids (phyto- and syntheto-) in the management of rheumatic diseases." p681 (abstract) • **Exact review question and page number:** "To assess the efficacy, tolerability, and safety of cannabinoids (phyto- and syntheto-) in the management of rheumatic diseases." p681 (abstract) • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** People with rheumatic diseases ➢ **Setting:** Not specified ➢ **Intervention:** Cannabinoids ➢ **Comparison:** Placebo or active control ➢ **Outcome:** Pain, sleep disturbance, quality of life
Participants (characteristics and numbers)	**For whole sample and subgroups:** N=203 *One study exploring PF-04457845 fatty acid amide hydrolase (FAAH) has been excluded from the remainder of this extraction. • **Number of participants:** N=129 • **Age:** Not reported • **Gender:** Not reported • **Details of clinical diagnosis/indications:** Rheumatoid arthritis (n=58); fibromyalgia (n=71)

Parameter	Extraction items
Setting/context	**Countries (alphabetic order):** Not reported **Setting (university, public or private clinic):** Not reported **Other relevant features of setting:** Not reported

Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** Cannabinoids
	• **Dose and regimen:**
	  ○ Nabilone (2 RCTs): 0.5-1mg; twice daily, not reported
	  ○ Nabiximols (1 RCT): Not reported
	• **Administration methods:** Oromucosal spray (1 RCT); not reported (2 RCTs)
	• **Comparator:** Placebo (2 RCTs); amitriptyline (1 RCT)
	• **Treatment duration:** 2-8 weeks
	• **Timeframe for follow-up:** Not reported for included studies

Databases and sources searched	• **Number and names of databases:** 7; Medline (1946-25/09/2013), PubMed (1946-26/09/2013), Embase Classic and Embase (1947-24/09/2013); CENTRAL (to issue 9 of 12, 2013), DARE (to issue 3 of 4, July 2013); CINAHL (to 29/09/2013), PsycINFO (1806-week 4, 09/2013); AMED (1985-09/2013). The literature search was further updated in January 2015. • **Other sources:** BIOSIS Previews (1969 to week 43, 2013), Web of Science (via Thomson Reuters from 1996 to September 29, 2013); Scopus (via Elsevier from 1996 to September 26, 2013), ClinicalTrials.gov (www.clinicaltrials.gov, 12/05/2013), International Clinical Trials Registry Platform (http://apps.who. int/trialsearch, 12/05/2013), Current Controlled Trials (http://www.controlled-trials.com, 05/12/2013), and Natural Medicines (https://naturalmedicines.therapeuticresearch. com, 12/05/2013), as well as various drug and device regulatory approval sites • **Grey literature:** Not reported

Parameter	Extraction items
	• **Reference chasing:** Yes • **Expert consultation:** Yes (working group of rheumatologists, academic librarian) • **Dates:** Above • **Search limits:** English and French language only • **Justifications for search limits:** Yes • **Other searches:** Not reported • **Protocol prepared:** No • **If yes, published:** Not applicable • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Not reported • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** Unclear • **If yes, rate of agreement:** Not reported • **Funding of review:** Canadian Rheumatology Association • **Conflicts of interest of review:** Not reported • **How conflicts of interest were managed:** Not applicable
Date Range (years) of included studies	• **Exact years for included studies:** 2006-2010
Number of primary studies included in the systematic review	• **Number of studies:** 3 RCTs • **Number of studies by study design:** 3 RCTs • **Study years:** 2006 (1 RCT); 2008 (1 RCT); 2010 (1 RCT)

Parameter	Extraction items
	• **Funding of included studies:** Not reported • **Conflicts of interest of included studies:** Not reported
Types of studies included	**Planned study designs to be included:** RCT **Reasons for including only RCTs/prospective cohort studies:** Not reported **List of excluded studies at full text and reasons for exclusion:** Yes
Appraisal instruments used	**Full name of tools used:** Cochrane Risk of Bias tool; GRADE system **<u>Risk of bias criteria for AMSTAR 2 assessment, for RCTs record Yes/No for:</u>** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The included trials have high risk of bias (3 RCTs). • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** ○ Overall: Low risk randomisation (1/3); low risk outcome ascertainment (1/3) *Nabiximol vs placebo* ○ Pain, sleep, tolerability, adverse events: Low risk randomisation (0/1); low risk outcome ascertainment (0/1) *Nabilone vs placebo* ○ Pain, tolerability, adverse events: Low risk randomisation (0/1); low risk outcome ascertainment (0/1) *Nabilone vs amitriptyline* ○ Pain, sleep, tolerability, adverse events): Low risk randomisation (1/1); Low risk outcome ascertainment (0/1)

Parameter	Extraction items
	• **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** "The conclusions of this systematic review for cannabinoid use in rheumatology practice are limited by the weakness of the evidence available. Although 4 RCTs were identified, the studies were extremely small, were of short duration, and only included patients with RA [rheumatoid arthritis], FM [fibromyalgia], and OA [osteoarthritis]. Small sample size introduces a high risk of bias for all 3 completed studies and represents the most important limiting factor for interpretation of the results." p687 • **Graphical or statistical test for publication bias:** Not reported • **Authors' comments likelihood and magnitude of publication bias:** Not applicable • **Authors' comment on how publication bias was dealt with:** Not applicable • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** Not applicable • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** Yes
Method of analysis	• **Description of method of analysis as per authors:** Narrative "Data were recorded on a standardized form by 2 of the authors (M-AF and PAS-M). The following information was recorded for each study: first author, year of publication, specific agent studied, study design, sample size, specific disease studied, and outcome measurements reported. Where possible, data on the following outcomes were recorded: pain intensity, sleep quality, and health-related quality of life. Adverse events reported for each study were recorded with attention to the following: somnolence, cognitive symptoms, and gastrointestinal symptoms. The number of patients dropping out due to adverse events (tolerability), as well as the total number of severe adverse events, including deaths (safety), was recorded for each study" p683 • **Justification for narrative synthesis or meta-analysis:** "There were 4 controlled studies that met the inclusion criteria, but because the studies included patients with different rheumatic diseases and different products were used as

Parameter	Extraction items
	treatments, the existing information did not allow for meta-analysis, and therefore is reported only as a qualitative (narrative) review." p685 • **Justification for combining data in meta-analysis:** Not applicable
Outcome assessed	**List of outcomes assessed and intended timeframes** • Primary outcomes: Pain, sleep disturbance, quality of life • Secondary outcomes: Tolerability, adverse effects, disease activity score • Intended timeframes: Not specified • Actual timeframes: 2-8 weeks
Results/findings	• **Findings by outcome:** *Nabiximols* PRIMARY OUTCOMES • Pain: One study (n=58) reported significant improvements in morning pain on movement and at rest in nabiximol compared with placebo groups (no summary statistics reported). No significant differences in pain intensity were reported between nabiximol and placebo groups (no summary statistics reported). • Sleep quality: One study (n=58) reported significant improvements in nabiximol compared with placebo groups (no summary statistics reported). SECONDARY OUTCOMES • Tolerability (drop-outs): One study (n=58) reported three participants dropped out of the placebo group due to adverse events. No participants dropped out of the nabiximol group due to adverse events. • Adverse events: One study (n=58) reported adverse events were more common in the nabiximol group including dizziness (26%), dry mouth (13%), light-headedness (11%), and nausea and falls (6%). There were also less frequent

Parameter	Extraction items
	reports of constipation, arthritis pain, and headache. Constipation and malaise were identified as severe for each of the two patients in the cannabinoid group reporting this adverse effect. • Disease activity score: One study (n=58) reported significant improvements in nabiximol compared with placebo groups (no summary statistics reported). *Nabilone* PRIMARY OUTCOMES • Pain: One study (n=40) reported significant improvement in the nabilone compared with placebo group (no summary statistics reported). One study (n=31) reported no significant differences between nabilone and amitriptyline groups (no summary statistic reported). • Quality of life: One study (n=40) reported significant improvement in the nabilone compared with placebo group (no summary statistics reported). One study (n=31) reported no significant differences between nabilone and amitriptyline groups (no summary statistic reported). • Sleep: One study (n=31) reported significant improvement in sleep in both nabilone and amitriptyline groups (no summary statistic reported. A marginal advantage was reported in the nabilone group when assessed with the Insomnia Severity Index but not for the Leeds Sleep Evaluation Questionnaire (no summary statistics reported) SECONDARY OUTCOMES • Tolerability (drop-outs): One study (n=40) reported four participants dropped out due to adverse events across nabilone (n=3) and placebo groups (n=1). One study (n=31) reported one participant dropped out due to adverse events across nabilone(n=1) and placebo groups (n=0). • Adverse events: One study (n=40) reported adverse events were more common in the nabilone compared with placebo groups including drowsiness (almost one-half), dry mouth (approx. 33%), vertigo and ataxia in (approx. 20%), and fewer reporting confusion, poor concentration, headache, anorexia, and dysphoria or euphoria. There were no

Parameter	Extraction items
	serious adverse events reported for the study (no summary statistics reported). One study (n=31) reported adverse events were more common in the nabilone with placebo groups including dizziness, drowsiness, nausea, and dry mouth (no summary statistics reported). No serious adverse events were reported in either study. • **GRADE by outcome:** "Based on the GRADE approach, there is low-quality evidence suggesting that cannabinoids may be associated with improvements in pain and sleep quality in [rheumatoid arthritis] and [fibromyalgia]" p686 • **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):** Not applicable • **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Not applicable • **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Not applicable • **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable
Significance/direction	**See above if results listed by outcome:** Above
Heterogeneity	• **See above if I^2 available:** Not applicable • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** Not reported • **Causes of heterogeneity investigated:** No
Comments	One study exploring PF-04457845 fatty acid amide hydrolase (FAAH) was excluded from this extraction.

Fitzcharles *et al.* (2016b): Efficacy, tolerability and safety of cannabinoids in chronic pain associated with rheumatic diseases (fibromyalgia syndrome, back pain, osteoarthritis, rheumatoid arthritis)

Parameter	Extraction items
First author and year of publication	Fitzcharles *et al.* (2016 B)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "we have examined the literature for evidence of the efficacy, tolerability, and safety of cannabinoids in chronic spinal pain, [fibromyalgia syndrome], [osteoarthritis], and [rheumatoid arthritis] pain." p48 • **Exact review question and page number:** "we have examined the literature for evidence of the efficacy, tolerability, and safety of cannabinoids in chronic spinal pain, [fibromyalgia syndrome], [osteoarthritis], and [rheumatoid arthritis] pain." p48 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** "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 [osteoarthritis]; neck and/or thoracic spine and/or low back) diagnosed by recognized diagnostic criteria (e.g., American College of Physicians); b. [rheumatoid arthritis] diagnosed by recognized diagnostic criteria (e.g., American College of Rheumatology, European League Against Rheumatism); c. Any [osteoarthritis] diagnosed by recognized diagnostic criteria (e.g., American College of Rheumatology); d. Fibromyalgia using the 1990 or 2010 criteria or the research criteria." p48 ➢ **Setting:** Not specified ➢ **Intervention:** "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" p48 See comments section at the end of the extraction form for details about authors errors in sentence above ➢ **Comparison:** Placebo or active comparator ➢ **Outcome:** Primary outcomes include: participant-reported pain relief of 50% or greater; patient global impression of change much or very much improved; withdrawal due to adverse events (tolerability); serious adverse events (safety).

Parameter	Extraction items
	Secondary outcomes include: participant-reported pain relief of 30% or greater; sleep problems; fatigue; depression; anxiety; disability; health related quality of life; specific adverse events; remission for inflammatory rheumatic disease
Participants (characteristics and numbers)	**For whole sample and subgroups** • **Number of participants:** N=160 • **Age:** Mean age range: 49-55 years • **Gender:** 82.9% female • **Details of clinical diagnosis/indications:** Fibromyalgia (n=72); chronic therapy-resistant pain caused by the skeletal and locomotor system (n=30); rheumatoid arthritis (n=58)
Setting/context	**Countries (alphabetic order):** Austria (1 RCT), Canada (2 RCTs), UK (1 RCT) **Setting (university, public or private clinic):** Outpatient (1 RCT); pain clinic (1 RCT); private clinic (1 RCT); Not reported (1 RCT) **Other relevant features of setting:** Not reported
Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** "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" p48 • **Dose and regimen:** ○ THC:CBD (1 RCT): 2.7 mg THC and 2.5 mg CBD; max 6 sprays daily ○ Nabilone (3 RCTs): 0.25 mg to 1 mg; daily, twice daily • **Administration methods:** Oromucosal spray (1 RCTs); Oral (3 RCTs)

Parameter	Extraction items
	• **Comparator:** Placebo (3 RCTs); amitriptyline (1 RCT) • **Treatment duration:** 2 – 5 weeks • **Timeframe for follow-up:** 7 days to 16 weeks
Databases and sources searched	• **Number and names of databases:** 2; Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE; Inception to 30/04/2015 • **Other sources:** Clinicaltrials.gov; International Association for Cannabinoid Medicinces databank (http://www.cannabis-med.org/ studies/study.php); WHO ICTTRP (http://apps.who.int/trialsearch/) • **Grey literature:** Not reported • **Reference chasing:** Yes • **Expert consultation:** Yes (contacted experts in the field) • **Dates:** Inception to 30/04/2015 • **Search limits:** No • **Justifications for search limits:** Not applicable • **Other searches:** Not reported • **Protocol prepared:** No • **If yes, published:** Not applicable • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported

Parameter	Extraction items
	• **Funding of review:** Canadian Rheumatology Association • **Conflicts of interest of review:** "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 speaking 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" p57 • **How conflicts of interest were managed:** Not reported
Date Range (years) of included studies	• **Exact years for included studies:** 2006-2010
Number of primary studies included in the systematic review	• **Number of studies:** 4 • **Number of studies by study design:** RCT • **Study years:** 2006 (2 RCTs); 2008 (1 RCT); 2010 (1 RCT) • **Funding of included studies:** Not reported (1 RCT); Valeant Canada and an HSC Medical Stuff Council Fellowship Fund (1 RCT); Valeant (Canada) and MC Gill University Health Center (1 RCT); GW pharmaceuticals (1 RCT) • **Conflicts of interest of included studies:** Not reported (3 RCTs); Reported (1 RCT)
Types of studies included	**Planned study designs to be included:** RCT **Reasons for including only RCTs/prospective cohort studies:** Not reported **List of excluded studies at full text and reasons for exclusion:** Not applicable (no studies excluded at full-text stage)
Appraisal instruments used	**Full name of tools used:** Cochrane Risk of Bias tool **<u>Risk of bias criteria for AMSTAR 2 assessment, for RCTs record Yes/No for:</u>**

Parameter	Extraction items
	• **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** "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." p50 Studies reported on are high risk of bias (3 RCTs) and unclear risk of bias (1 RCT). • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** ○ Overall: Low risk randomisation (1/4); low risk outcome ascertainment: (0/4) *Nabilone vs placebo* ○ Pain, adverse events, serious adverse events, withdrawal due to adverse events: Low risk randomisation (0/2); low risk outcome ascertainment (0/2) *Nabilone vs amitriptyline* ○ Pain, adverse events, serious adverse events, withdrawal due to adverse events: Low risk randomisation (1/1); low risk outcome ascertainment (0/1) *THC:CBD vs placebo*

Parameter	Extraction items
	○ Pain, adverse events, serious adverse events, withdrawal due to adverse events: Low risk randomisation (0/1); low risk outcome ascertainment (0/1) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** Not reported • **Graphical or statistical test for publication bias:** Yes "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" p51 • **Authors' comments likelihood and magnitude of publication bias:** Not applicable • **Authors' comment on how publication bias was dealt with:** Not applicable • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** Not applicable • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** No
Method of analysis	• **Description of method of analysis as per authors:** Uncertain, the authors provide in-depth information on how meta-analysis has been conducted, however only a narrative synthesis of findings is provided. This is also highlighted in Fig 1: PRISMA flow diagram. • **Justification for narrative synthesis or meta-analysis:** Not reported • **Justification for combining data in meta-analysis:** Not reported
Outcome assessed	**List of outcomes assessed and intended timeframes** • Primary outcomes: Patient-reported pain relief of 50% or greater; Patient global impression of change; Withdrawal due to adverse events; Serious adverse events; • Secondary outcomes: Health related quality of life; fatigue; depression; quality of sleep; participant-reported pain relief of >30%; anxiety; disability; adverse events

Parameter	Extraction items
	• Intended timeframes: > 2 weeks • Actual timeframes: 7 days to 16 weeks
Results/findings	○ **Findings by outcome:** PRIMARY OUTCOMES ○ Pain: One study (n=40) reported a significant improvement in pain in the nabilone group (mean 4.8, SD 2.2) compared with placebo (mean 5.7, SD 2.2) (p=0.02). One study (n=30) reported no significant difference between nabilone (median 0.9) and placebo groups (median 0.5) (p=0.20). One study (n=32) reported no significant difference in pain intensity between nabilone and amitriptyline (no summary statistics reported). One study (n=58) reported significant improvement in pain (morning at rest) in THC:CBD group (mean 3.1) compared with placebo (mean 4.1) (p=0.02). ○ Serious adverse events: Two studies (n=58; n=30) reported 0% vs 2%; and 3.3% vs 2% serious adverse events in THC:CBD compared with placebo groups and nabilone compared with placebo groups. One study (n=32) reported 0% vs 0% serious adverse events in nabilone compared with amitriptyline groups. ○ Withdrawal due to adverse events: Two studies (n=58; n=40) reported 0% vs 11%; and 15% vs 0% withdrawals in THC:CBD compared with placebo groups and nabilone compared with placebo groups. One (n=32) reported 3% vs 0% withdrawals in nabilone compared with amitriptyline groups. SECONDARY OUTCOMES *Efficacy* ○ Sleep: One study (n=58) reported significant improvement in THC:CBD group (mean 3.4) compared with placebo (mean 4.6) (p=0.03). One study (n=32) reported significant improvement in nabilone (mean 9, SD 10.8) compared with amitriptyline groups (mean 13, SD 10.8) (p-value not reported).

Parameter	Extraction items
	○ Activity (DAS-28): One study (n=58) reported significant improvement in THC:CBD group (mean 5) compared with placebo (mean 5.9) (p=0.002). ○ Fatigue: One study (n=40) reported no significant difference between nabilone and placebo groups (no summary statistics reported). ○ Depression: One study (n=40) reported no significant difference between nabilone and placebo groups (no summary statistics reported). ○ Anxiety: One study (n=40) reported a significant improvement in the nabilone group (mean 4.3, SD 1.8) compared with placebo (mean 4.9, SD 2.2) (p<0.01). ○ Health-related quality of life: One study (n=40) reported a significant improvement in the nabilone group (mean 54, SD 22.3) compared with placebo (mean 64, SD 13.4) (p<0.01). One study (n=30) reported no significant difference between nabilone (median 5.0) and placebo groups (median 2.0) (p=0.90). One study (n=32) reported no significant differences between nabilone and amitriptyline groups (no summary statistics provided). *Adverse events* ○ Adverse events: One study (n=58) reported the following adverse events: Dizziness (26% vs 4%), light-headedness (10% vs 4%), dry mouth (13% vs 0%), nausea (6% vs 4%), constipation (3% vs 4%), drowsiness (3% vs 4%), fall (6% vs 0%), headache (3% vs 4%), palpitations (0% vs 7%), vomiting (0% vs 7%) in THC:CBD compared with placebo groups. One study (n=30) reported fatigue (30% vs 13%), dry mouth (20% vs 3%) vertigo (33% vs 10%), sleep problems (17% vs 3%) in nabilone compared with placebo groups. One study (n=40) reported drowsiness (47% vs 6%), dry mouth (33% vs 6%), vertigo (27% v 0%), ataxia (20% vs 6%), confusion (13% vs 6%), decreased concentration (13% vs 6%) in nabilone compared with placebo groups.

Parameter	Extraction items
	One study (n=32) reported dizziness (32% vs 13%), headache (13% vs 19%), nausea (29% vs 3%), dry mouth (23% vs 10%), drowsiness (23% vs 3%), constipation (19% vs 3%), insomnia (10% vs 0%) in nabilone compared with amitriptyline groups. ○ **GRADE by outcome:** Not reported ○ **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):** Not applicable ○ **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Not reported ○ **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Not applicable ○ **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable
Significance/direction	**See above if results listed by outcome:** Above
Heterogeneity	• **See above if I^2 available:** Not applicable • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** Not applicable • **Causes of heterogeneity investigated:** Not applicable
Comments	"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." The authors created their own 'risk of bias' categorisation.

Parameter	Extraction items
	On p52 the authors state “three studies met the criteria of a low study quality (as reported) and one study of a high study quality”. However, these scores do not align with authors categorisation framework. Subsequently this has been corrected in this extraction form. Discrepancy between number of studies reported on versus what’s outlined in the flow diagram. Authors provide in-depth information on how meta-analysis was conducted. However, no meta-analysis appears to have been conducted. The authors describe cannabinoids on p48 of their review. There are errors in their descriptions of cannabinoids. Firstly, phytocannabinoid does not refer to “herbal cannabis” but to cannabinoids found in the plant. Second, plant-based cannabinoids and phyto-cannabinoids are synonyms and therefore it does not make sense to differentiate these. And finally, cannabidiol is not a synthetic cannabinoid as referred to by the authors. ➢ “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” p48

Giossi *et al.* (2022): Systematic Review and Meta-analysis Seem to Indicate that Cannabinoids for Chronic Primary Pain Treatment Have Limited Benefit

Parameter	Extraction items
First author and year of publication	Giossi *et al.* (2022)

Parameter	Extraction items
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "The aim of this systematic review and meta-analysis is to evaluate the efficacy and safety of cannabinoid administration in chronic primary pain" p1341 • **Exact review question and page number: "**we conducted a systematic review with a meta-analysis to investigate the role of cannabinoids in the treatment of [chronic primary pain], compared to placebo or other active compounds." p1344 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** Adult or pediatric patients with chronic primary pain ➢ **Setting:** Not reported ➢ **Intervention:** Any type and preparation of cannabinoid treatment ➢ **Comparison:** Placebo or any other active treatment ➢ **Outcome:** Primary outcome: pain reduction; Secondary outcomes: quality of life, appetite, anxiety, depression, and sleep
Participants (characteristics and numbers)	**For whole sample and subgroups:** • **Number of participants:** N=240 • **Age:** Mean age range 31-52 years • **Gender:** 83.75% female • **Details of clinical diagnosis/indications:** Fibromyalgia (n=115), chronic primary chest pain (n=19), irritable bowel syndrome (n=68), chronic regional pain syndrome (n=22), various chronic secondary pain conditions (n=16)
Setting/context	**Countries (alphabetic order):** Not reported **Setting (university, public or private clinic):** Not reported

Parameter	Extraction items
	Other relevant features of setting: Not reported

Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** Any type and preparation of cannabinoid treatment
	• **Dose and regimen:**
	  ○ THC-rich cannabis oil (1 RCT): 24.44 mg/mL THC + 0.51 mg/mL CBD daily; initial dose was one drop daily with subsequent increases according to symptoms
	  ○ Dronabinol (2 RCTs): 5 mg twice daily; 2.5 mg or 5 mg twice daily
	  ○ Nabilone (2 RCTs): 0.2-0.5 mg daily; 0.5-1.0 mg before bedtime
	  ○ CBD gums (1 RCT): 1-6 daily if pain score over 4; 5.3 – 6.5 gums consumed per week
	  ○ Bedrocan, Bediol, Bedrolite (1 RCT): Bedrocan (22% THC and 1% CBD) and Bediol (6.3% THC and 8% CBD) and Bedrolite (1% THC and 9% CBD)
	  ○ Delta-9-THC (1 RCT): 3.5% THC cigarettes; regimen not reported
	• **Administration methods:** Oral (5 RCTs), inhaled/vaporised (1 RCT), smoked (1 RCT), sublingual (1 RCT)
	• **Comparator:** Placebo (7 RCTs) and amitriptyline (1 RCT)
	• **Treatment duration:** Range of 2 days to 10 weeks
	• **Timeframe for follow-up:** No reported for included studies

Databases and sources searched	• **Number and names of databases:** 3; Pubmed, EMBASE and the Cochrane library (CENTRAL) form inception to 30/10/2021 • **Other sources:** Not reported • **Grey literature:** Not reported • **Reference chasing:** No • **Expert consultation:** No

Parameter	Extraction items
	• **Dates:** Inception to 30/10/2021 • **Search limits:** English language only • **Justifications for search limits:** None • **Other searches:** No reported • **Protocol prepared:** Yes • **If yes, published:** CRD42021281840 https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021281840 • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Funding of review: "**The study and the journal's Rapid Service Fee was funded by Postgraduate School of Clinical Pharmacology and Toxicology, Department of Medical Biotechnology and Translational Medicine, Universita degli Studi di Milano, Milan, Italy." p1355 • **Conflicts of interest of review: "**Riccardo Giossi received support for congress participation from Mylan and acted as a consultant for Daiichi-Sankyo; Federica Carrara received support for congress participation from Jazz Pharmaceuticals; Matteo Padroni has nothing to disclose; Maria Concetta Bilancio has nothing to disclose; Martina Mazzari has nothing to disclose; Silvia Enisci has nothing to disclose; Maria Silvia Romio has nothing to disclose; Gloria Boni has nothing to disclose; Federica Corru has nothing to disclose; Veronica Andrea Fittipaldo has nothing to disclose; Irene Tramacere has nothing to disclose; Arianna Pani has nothing to disclose; Diego Fornasari received fees in the last 2 years as speaker or member of Advisory Boards from the following companies: Alfasigma, Astellas, Bayer, Grunenthal, Lundbeck, Molteni,

Parameter	Extraction items
	SPA.; Francesco Scaglione received fees as speaker or member of Advisory Boards from Bayer, MSD, Angelini, and Dompe." p1355 • **How conflicts of interest were managed:** Not reported
Date Range (years) of included studies	• **Exact years for included studies:** 2008-2021
Number of primary studies included in the systematic review	• **Number of studies:** 8 • **Number of studies by study design:** 8 RCTs • **Study years:** 2008 (2 RCTs), 2010 (1 RCT), 2012 (1 RCT), 2017 (1 RCT), 2019 (1 RCT), 2020 (1 RCT), 2021 (1 RCT) • **Funding of included studies:** Not reported • **Conflicts of interest of included studies:** Not reported
Types of studies included	**Planned study designs to be included:** RCTs or observational, retrospective or prospective studies **Reasons for including only RCTs/prospective cohort studies:** Not reported **List of excluded studies at full text and reasons for exclusion:** Not included
Appraisal instruments used	**Full name of tools used:** Cochrane Risk of Bias 2 tool **<u>Risk of bias criteria for AMSTAR 2 assessment, for RCTs, record Yes/No for:</u>** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence allocation (individual vs group randomisation):** Yes • **Selective reporting:** Yes

Parameter	Extraction items
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** "Overall, we considered one study at low risk of bias; five studies had some concerns regarding risk of bias, and two studies were at high risk of bias" p1346 HRB notes that this assessment matches with our assessment according to Cochrane's Collaboration tool and graphical information provided in the paper • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** o Overall: Low risk randomisation (8/8); low risk outcome ascertainment (8/8) *Cannabinoids vs placebo* o Pain reduction: Low risk randomisation (6/6); low risk outcome ascertainment (6/6) *Nabilone vs amitriptyline* o Low risk randomisation (1/1); low risk outcome ascertainment (1/1) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** "In our study, the quality of evidence was in general low to very low, mainly for imprecision due to limited sample size and risk of bias. Indeed, risk of bias from unclear to high was observed also in previous systematic reviews on cannabinoids in various primary and secondary pain conditions, indicating the need for higher quality studies to better define cannabinoids' role in chronic pain treatment" p1354 • **Graphical or statistical test for publication bias:** Yes • **Authors' comments likelihood and magnitude of publication bias:** "We did not observe signs of possible publication bias" p1353 • **Authors' comment on how publication bias was dealt with:** Not applicable • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** No

Parameter	Extraction items
	• **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** Yes
Method of analysis	• **Description of method of analysis as per authors:** **"**A meta-analysis was performed when there were at least two included studies with available data for assessed outcomes. For continuous outcomes, the weighted generic inverse variance on mean difference (MD) method was used to estimate MD and 95% confidence intervals (95% CI). For studies reporting the same outcome measure with different scales (pain, anxiety, depression), we used the standardized MD (SMD) as the effect measure. We then re-expressed SMD to the corresponding MD units of the VAS scale for pain, the BAI for anxiety, and the BDI for depression. When studies did not report standard deviations, standard errors, or 95% CI, these were estimated from MD, study arm populations, and p values. For dichotomous outcomes, the Mantel–Haenszel method was used to calculate measures of effect as odds ratios (ORs) with 95% CI. Results were pooled using a random-effect meta-analysis. Heterogeneity was assessed with I-squared statistic. Analyses were performed comparing cannabinoids to placebo or any active comparator…. Publication bias was assessed through the creation of a funnel plot. The different forest plots and funnel plot are available in the Supplementary Material. Analyses were performed with the use of Cochrane RevMan 5.4 software." p1345 • **Justification for narrative synthesis or meta-analysis:** Not reported • **Justification for combining data in meta-analysis:** Not reported
Outcome assessed	**List of outcomes assessed and intended timeframes** • Primary outcome: Pain (chronic primary pain) reduction • Secondary outcomes: Quality of life, appetite, anxiety, depression and sleep, adverse events

Parameter	Extraction items
	• Intended timeframes: Not specified • Actual timeframes: Treatment duration 2 days to 10 weeks, described as follow-up; follow-up periods after treatment cessation not reported
Results/findings	• **Findings by outcome:** PRIMARY OUTCOMES ○ Pain reduction: "In a primary analysis, we assessed cannabinoids efficacy against placebo or any active comparator. When comparing cannabinoids to placebo the difference was non-significant (MD = -0.64, 95% CI -1.30 to 0.02). Nabilone and amitriptyline were not significantly different in pain reduction (MD = -0.19, 95% CI -0.58 to 0.19). When grouping included studies by study design (parallel or crossover) and by treatment duration (at least 4 weeks or less than 4 weeks), we observed a significant reduction of pain in parallel studies with more than 4 weeks of cannabinoid treatment compared to placebo (MD = -1.28; 95% CI -2.33 to -0.22). This difference was not significant for crossover studies with a treatment duration less than 4 weeks compared to placebo (MD = -0.34; 95% CI -1.1 to 0.42)."… In a subgroup analysis, we evaluated the efficacy of cannabinoids against placebo by different CPP conditions. No significant differences were observed in patients with fibromyalgia (MD = -0.70; 95% CI -1.54 to 0.12), chronic primary chest pain (MD = 0.00; 95% CI -2.19 to 2.19), and IBS (MD = 0.34; 95% CI -1.06 to 1.73), while we observed a significant reduction in patients with CRPS type I (MD = -1.62; 95% CI -3.01 to -0.26). However, a sensitivity analysis including studies on fibromyalgia showed that cannabinoids significantly reduced pain compared to placebo in parallel RCTs with more than 4 weeks of follow-up (MD = -0.82; 95% CI -1.41 to -0.24) while it was non-significant in crossover RCTs with less than 4 weeks of follow-up (MD = -0.01; 95% -0.52 to 0.50)." p1346-8 SECONDARY OUTCOMES

Parameter	Extraction items

- Quality of life: “We found statistically non-significant differences when comparing cannabinoids against placebo (MD = -21.69; 95% CI -46.20 to 2.82) or amitriptyline (MD = -0.70; 95% CI -7.30 to 5.90). Another crossover study comparing CBD to placebo reported [quality of life] data from 30 patients with IBS who completed the IBS-36 questionnaire. No significant differences were observed between CBD and placebo (MD = -1.0; 95% CI -6.8 to 4.9).” p1350
- Anxiety and depression: “A non-significant difference was observed for anxiety (MD = 95% CI -7.99 to 3.08) and depression (MD = 2.32; 95% CI -1.71 to 6.35)” p1352
- Sleep and appetite: “(one study) comparing nabilone to amitriptyline, showed that nabilone was superior to amitriptyline in improving the Insomnia Severity Index (MD = -3.25; 95% CI -5.26 to -1.24). Also, nabilone marginally improved restfulness assessed with the Leeds Sleep Evaluation Questionnaire, while other subscales showed no marked differences. Appetite was not evaluated.” p1352-3
- Safety: Across five RCTs (n=221) a non-significant difference was found between cannabinoids and placebo in discontinuation due to adverse events (OR = 2.15; 95% CI 0.44 to 10.65). No serious adverse events were reported.

- **GRADE by outcome:**

Outcome	No. studies	GRADE
Cannabinoids vs placebo		
Pain (overall chronic primary pain)	6	Low
Pain (overall chronic primary pain parallel RCT)	3	Low
Pain (overall chronic primary pain crossover RCT)	3	Low
Pain (fibromyalgia)	3	Low
Pain (fibromyalgia parallel RCT)	2	Low
Pain (fibromyalgia crossover RCT)	1	Very Low
Pain (chronic primary chest pain)	1	Very Low
Pain (chronic regional pain syndrome type I + chronic secondary pain)	1	Low
Pain (irritable bowel syndrome)	1	Low
Quality of life (fibromyalgia)	2	Low

Parameter	Extraction items

Quality of life (irritable bowel syndrome)	1	Low
Anxiety assessed with: Beck Anxiety Inventory	3	Very Low
Depression assessed with: Beck Depression Inventory	2	Low
Serious adverse events	5	Very Low
Discontinuation due to adverse events	6	Low

Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):

Outcome	No. studies (No. participants)	Summary estimate (95% CI)	P-value	I^2 (%)	Direction of effect
Cannabinoids vs placebo					
Pain (overall chronic primary pain)	6 (151)	SMD -0.32 (-0.65 to 0.01)	0.06	21	No significant difference
Pain (overall chronic primary pain parallel RCT)	3 (63)	SMD -0.64 (-1.16 to -0.11)	0.02	3	Favours cannabinoids
Pain (overall chronic primary pain crossover RCT)	3 (90)	SMD -0.17 (-0.55 to 0.21)	0.39	16	No significant difference
Pain (fibromyalgia)	3 (83)	SMD -0.35 (-0.77 to 0.06)	0.09	13	No significant difference
Pain (fibromyalgia parallel RCT)	2 (58)	SMD -21.69 (-46.20 to 2.82)	0.08	82	No significant difference
Pain (chronic primary chest pain)	1 (13)	SMD 0.00 (-1.09 to 1.09)	1.00	Not applicable	No significant difference
Pain (chronic regional pain syndrome type I + chronic secondary pain)	1 (38)	SMD -0.81 (-1.50 to -0.13)	0.02	Not applicable	Favours cannabinoids
Pain (irritable bowel syndrome)	1 (32)	SMD 0.17 (-0.53 to 0.86)	0.63	Not applicable	No significant difference
Quality of life (fibromyalgia)	2 (50)	MD -21.69 (-46.20 to 2.82)	0.08	82	No significant difference
Quality of life (IBS)	1 (30)	MD -1.0 (-6.8 to 4.9)	Not reported	Not applicable	No significant difference

Parameter	Extraction items

Anxiety assessed with: Beck Anxiety Inventory	3 (63)	SMD -0.33 (-1.09 to 0.42)	0.38	51	No significant difference
Depression assessed with: Beck Depression Inventory	2 (30)	SMD 0.42 (-0.31 to 1.15)	0.26	0	No significant difference
Discontinuation due to adverse events	6 (171)	OR 2.15 (0.44 to 10.65)	0.35	0	No significant difference
Cannabinoids (nabilone) vs amitriptyline					
Pain (overall chronic primary pain)	1 (32)	SMD -0.35 (-1.09 to 0.38)	0.35	0	No significant difference
Quality of life (fibromyalgia)	1 (32)	SMD -0.70 (-7.30 to 5.90)	0.84	0	No significant difference

- **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** As above
- **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Weighted mean difference shown above
- **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable

Significance/direction

See above if results listed by outcome: "Overall cannabinoid treatment in patients with CPP had limited benefit on pain relief, with generally low quality of evidence. Long-term administration studies showed limited evidence of efficacy of cannabinoids in pain reduction while crossover, short-term studies did not. This limited efficacy was present only in fibromyalgia and CRPS type I, while no beneficial effect was found for IBS and chronic primary chest pain. Our results confirm that cannabinoids might improve pain and FIQ in fibromyalgia with long-term administration. Cannabinoids displayed a safety profile comparable to placebo or amitriptyline. Good-quality evidence on use of cannabinoids is limited and lacking for the majority of CPP conditions, and large, well-designed RCTs—and importantly with a long-term follow-up—are urgently needed." p1355

Parameter	Extraction items
Heterogeneity	• **See above if I^2 available:** I^2 reported in studies where possible. Outline above in "findings by outcome" • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** No comment from authors. The state in the methods "Heterogeneity was assessed with I-squared statistic". • **Causes of heterogeneity investigated:** Not reported
Comments	The authors report their findings in the main text as MDs (mean difference), however these values do not correspond to the forest plots in the supplemental figures where weighted standard mean difference (SMD) is shown. The authors report the Chaves et al has n=18 participants in table 1. However, they also state that there were 17 females in the study and that this was 100% of the study population. No mention of drop-outs for this study is reported in the paper. Discrepancy in reporting of Skrabek et al, where table 1 says n=40 participants and n=47 female. HRB assumes this should state n=37 female, as the authors give a % of females in the study of 92.5%. The authors give an overview of all findings in Table 2. However, not all graphs/data could be found for these figures. Indeed, none of the actual figures could be found in the study at all as they were inputted as MDs, while all graphs in the paper are in SMDs.

Hammond *et al.* (2021): The Effect of Cannabis-Based Medicine in the Treatment of Cachexia: A Systematic Review and Meta-Analysis

Parameter	Extraction items
First author and year of publication	Hammond *et al.* (2021)

Parameter	Extraction items
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "to compare the effects of cannabis-based medicinal products against both placebo and active treatment in anorexia–cachexia syndrome for appetite stimulation, change in body mass, and [quality of life]." p475 • **Exact review question and page number:** "to compare the effects of cannabis-based medicinal products against both placebo and active treatment in anorexia–cachexia syndrome for appetite stimulation, change in body mass, and [quality of life]." p475 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** "patients with cachexia, from any underlying illness, as defined by official diagnostic criteria, having had a sustained weight loss > 5% (or body mass index < 20 kg/m^2) in less than 12 months with three of the five of the following characteristics: decreased muscle strength, fatigue, anorexia, low fat-free mass index, and abnormal biochemistry" p475 ➢ **Setting:** Not specified ➢ **Intervention:** "cannabis-based medicines or their synthetic analog" p475 ➢ **Comparison:** Placebo or active comparator ➢ **Outcome:** "chosen outcomes were objective measurements, such as weight gain and additionally subjective measurements such as patient-reported QoL and their change in appetite." p475
Participants (characteristics and numbers)	**For whole sample and subgroups** • **Number of participants:** N=934 • **Age:** Mean age 53 years old • **Gender:** "For four studies, the majority of patients were male with just the nabilone study on non-small cell lung cancer patients having a female majority" p477

Parameter	Extraction items
	• **Details of clinical diagnosis/indications:** AIDS patients with anorexia-associated weight loss (n=139); cancer-associated cachexia (n=712); HIV wasting syndrome (n=50); non-small cell lung cancer patients with anorexia (n=33)
Setting/context	**Countries (alphabetic order):** Not reported **Setting (university, public or private clinic):** Not reported **Other relevant features of setting:** Not applicable

Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** "cannabis-based medicines or their synthetic analog" p475
	• **Dose and regimen:**
	  ○ Dronabinol (3 RCTs): 2.5 mg; twice daily
	  ○ Cannabis extract and THC (1 RCT): 2.5 mg THC and 1 mg cannabidiol (CBD); twice daily
	  ○ Nabilone (1 RCT): 0.5-1 mg: once daily
	• **Administration methods:** Not reported
	• **Comparator:** Placebo (3 RCTs); megestrol acetate (2 RCTs)
	• **Treatment duration:** ≥4 weeks (range 4-12 weeks)
	• **Timeframe for follow-up:** Not reported for included studies

Databases and sources searched	• **Number and names of databases:** 3; Medline (inception to 02/03/2020); EMBASE (1947 to 02/03/2020); Cochrane Central Register of Controlled Trials (CENTRAL) (inception to 02/03/2020) • **Other sources:** Not reported • **Grey literature:** Web of Science Core Collection search strategy • **Reference chasing:** Yes

Parameter	Extraction items
	• **Expert consultation:** Yes (medical librarian) • **Dates:** Above • **Search limits:** No • **Justifications for search limits:** Not applicable • **Other searches:** Not reported • **Protocol prepared:** No • **If yes, published:** Not applicable • **Search strategy/key words provided:** No • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** Not reported • **If yes, rate of agreement:** Not reported • **Funding of review:** No funding was received • **Conflicts of interest of review:** No competing financial interests exist • **How conflicts of interest were managed:** Not applicable
Date Range (years) of included studies	• **Exact years for included studies:** 1995-2018
Number of primary studies included in the systematic review	• **Number of studies:** 5 • **Number of studies by study design:** 5 RCTs • **Study years:** 1995 (1 RCT); 1997 (1 RCT); 2002 (1 RCT); 2006 (1 RCT); 2018 (1 RCT) • **Funding of included studies:** Not reported

Parameter	Extraction items
	• **Conflicts of interest of included studies:** Not reported
Types of studies included	**Planned study designs to be included:** RCT **Reasons for including only RCTs/prospective cohort studies:** Not reported **List of excluded studies at full text and reasons for exclusion:** Reasons given, references not reported
Appraisal instruments used	**Full name of tools used:** Cochrane Risk of Bias; GRADE system **<u>Risk of bias criteria for AMSTAR 2 assessment, for RCTs record Yes/No for:</u>** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The authors reported the included trials as follows: High risk of bias (1 RCT), unclear risk of bias (4 RCTs). However, according to Cochrane's Collaboration tool, and graphical information provided in the paper, the included trials appear to have a high risk of bias (3 RCTs) and unclear risk of bias (2 RCTs). • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** ○ Overall: Low risk randomisation (3/5); low risk outcome ascertainment (4/5) *Cannabinoid vs placebo* ○ Change in appetite: Low risk randomisation (0/2); low risk outcome ascertainment (2/2) *Cannabinoid vs control(*megestrol acetate*)/placebo* ○ Change in weight: Low risk randomisation (1/2); low risk outcome ascertainment (1/2)

Parameter	Extraction items
	*Cannabinoid vs control(*megestrol acetate*)/placebo* ○ Quality of life: Low risk randomisation (1/3); low risk outcome ascertainment (3/3) *Dronabinol vs control(megestrol acetate)/placebo* ○ Acceptability of treatment: Low risk randomisation (3/5); low risk outcome ascertainment (4/5) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** "No statistically significant change in weight was observed in the three studies measuring weight change. However, the quality of evidence for this outcome was assessed as very low due to identified risk of bias in outcome measurement and a likelihood of high study heterogeneity." p482 "QoL data were pooled for three studies, but no statistically significant change was observed. The quality of evidence here was again considered low. The risk of bias in reporting outcomes was also high in one included study." p482 • **Graphical or statistical test for publication bias:** No • **Authors' comments likelihood and magnitude of publication bias:** Not applicable • **Authors' comment on how publication bias was dealt with:** Not applicable • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** No • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** Yes
Method of analysis	• **Description of method of analysis as per authors:** "For continuous outcomes, a pooled mean difference (MD) and 95% CI was calculated. However, in studies using different scales measuring appetite, pain, and nausea, the standardized MD and 95% CI were calculated. For studies that reported baseline and endpoint data, we calculated the standard deviation

Parameter	Extraction items
	(SD) of the mean change from the baseline according to reported CI. A decision was made not to pool studies together if considerable clinical heterogeneity exists. All data were calculated using the Review Manager (Cochrane, v5.3).” p476 • **Justification for narrative synthesis or meta-analysis:** Not reported • **Justification for combining data in meta-analysis:** Not reported
Outcome assessed	• **List of outcomes assessed and intended timeframes** o Outcomes: Change in appetite; Change in weight; Quality of life; Acceptability of treatment o Intended timeframe: ≥4 weeks o Actual timeframes: 4-12 weeks
Results/findings	• **Findings by outcome** PRIMARY OUTCOMES o Change in appetite: Pooled data from two studies (n=276) reported no significant difference between cannabinoid and placebo groups (MD -1.79, 95% CI -3.77 to 0.19). o Change in weight: Pooled data from two studies (n=55) reported no significant difference between cannabinoid and control (megestrol acetate; placebo) groups (MD-4.26, 95% CI -12.28 to 3.76). o Quality of life: Pooled data from four studies (n=487) reported no significant difference between cannabinoid and control (megestrol acetate; placebo) groups (MD -0.14, 95% CI -0.32 to 0.03). o Acceptability of treatment: One study (n=139) reported significantly increased frequency of adverse events in the dronabinol group (43%) compared with the placebo group (13%) ($p < 0.001$). Nervous system events (dizziness, euphoria, and drowsiness) were the most common adverse events seen (cannabinoid 35%; placebo 9%) ($p<0.001$).

Parameter	Extraction items

Two studies reported no significant difference in frequency of adverse events between dronabinol and control (megestrol acetate) groups. One of these studies reported significantly increased frequency of impotence in the megestrol acetate (18%) compared with dronabinol (4%) (p=0.002).

Three studies reported no significant difference frequency of adverse events in cannabinoid and placebo groups.

- **GRADE by outcome:**

Outcome	No. studies	GRADE
Change in appetite	2	Low
Change in weight	2	Very low
Quality of life	3	Low

- **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):**

Outcome	No. studies (No. participants)	Summary estimate	P-value	I^2 (%)	Direction of effect
Mixed cannabinoids vs placebo					
Change in appetite	2 (276)	MD -1.79 (-3.77 to 0.19)	0.08	0	No significant effect
THC (dronabinol, nabilone) vs mixed control					
Change in weight	2 (55)	MD -4.26 (-12.28 to 3.76)	0.30	95	No significant effect
Mixed cannabinoids vs mixed control (placebo, megestrol acetate)					
Quality of life	4 (587)	SMD 0.14 (-0.32 to 0.03)	0.11	0	No significant effect

- **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Not applicable
- **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Yes

Parameter	Extraction items
	• **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable
Significance/direction	**See above if results listed by outcome:** Above
Heterogeneity	• **See above if I^2 available:** Above • **Authors' comment on potential impact of heterogeneity on results and quality of evidence: "**No statistically significant change in weight was observed in the three studies measuring weight change. However, the quality of evidence for this outcome was assessed as very low due to identified risk of bias in outcome measurement and a likelihood of high study heterogeneity." p482 • **Causes of heterogeneity investigated:** Yes, I^2 reported, random effects model, subgroup analysis considered
Comments	Based on text (p476-478), the authors appear to have assessed sequence generation, allocation concealment, blinding of participants, blinding of outcome assessors, missing data. However, the authors do not explicitly state whether studies are assigned low, unclear or high risk on these domains. Therefore, this has been marked as 'not specified' in this form.

Häuser *et al.* (2019): Efficacy, tolerability and safety of cannabis-based medicines for cancer pain A systematic review with meta-analysis of randomised controlled trials

Parameter	Extraction items
First author and year of publication	Häuser *et al.* (2019)

Parameter	Extraction items
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "to update the literature and to assess the efficacy, tolerability, and safety of medical cannabis and cannabis-based medicines (plant-based, synthetic) compared to placebo or conventional drugs for cancer pain in patients of any age" p425 • **Exact review question and page number:** "How effective and safe are medical cannabis and cannabis-based medicines compared to controls in managing cancer pain in patients of any age?" Protocol p1 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** Patients of any age with any type of cancer with cancer pain; there will be no exclusion criteria of type of cancer. ➢ **Setting:** Not specified ➢ **Intervention:** "Medical cannabis (marihuana) and cannabis-based medicines (plant-based cannabinoids [dronabinol, nabiximols]), or pharmacological (synthetic) cannabinoids [nabilone], at any dose or by any route that were administered for the relief of cancer pain" p425 ➢ **Comparison:** Placebo or active comparator ➢ **Outcome:** Primary outcomes: Pain relief of 50% and greater; patient perceived global improvement; combined responder; tolerability; serious adverse events Secondary outcomes: Pain relief of 30% or more; mean pain intensity; sleep problems; psychological distress; daily opioid maintenance dosage; daily breakthrough opioid dosage; adverse events
Participants (characteristics and numbers)	**For whole sample and subgroups** • **Number of participants:** N=1567 (extracted from table 1) • **Age:** Mean age range 58-61 years old

Parameter	Extraction items
	• **Gender:** "There was a slight preponderance of male participants in all studies" p430 • **Details of clinical diagnosis/indications:** "All studies included only patients with moderate to severe cancer pain which had not adequately responded to opioids, with three studies specifically defining criteria for failure of opioid therapy" p430
Setting/context	**Countries (alphabetic order):** All studies were multi-centre. European (1 RCT); European, Asian and Middle East (2 RCTs); Europe and the USA (1 RCT); and Europe, USA, Latin America and South Africa (1 RCT) **Setting (university, public or private clinic):** Multi-centre **Other relevant features of setting:** Not reported
Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** "Medical cannabis (marihuana) and cannabis-based medicines (plant-based cannabinoids [dronabinol, nabiximols]), or pharmacological (synthetic) cannabinoids [nabilone], at any dose or by any route that were administered for the relief of cancer pain" p425 • **Dose and regimen:** Nabiximols (5 RCTs): 2.7 mg tetrahydrocannabinol and 2.5 mg cannabidiol; 1-16 sprays daily • **Administration methods:** Oromucosal spray (5 RCTs) • **Comparator:** Placebo (5 RCTs) • **Treatment duration:** >2 weeks (actual durations 2-5 weeks) • **Timeframe for follow-up:** Not reported for included studies
Databases and sources searched	• **Number and names of databases:** 3; Cochrane Central Register of Controlled Trials (CENTRAL) (inception to 28/12/2018); MEDLINE (1946 to 28/12/2018); SCOPUS (1974 to 28/12/2018). • **Other sources:** US National Institutes of Health clinical trial register (www.ClinicalTrials.gov), European Union Clinical Trials Register (www. clinicaltrialsregister.eu) and International Association for Cannabinoid Medicines (IACM) databank (www. cannabis-med.org/studies/study.php)

Parameter	Extraction items
	• **Grey literature:** No • **Reference chasing:** Yes • **Expert consultation:** No • **Dates:** Above • **Search limits:** No • **Justifications for search limits:** Not applicable • **Other searches:** No • **Protocol prepared:** Yes • **If yes, published:** CRD42019119414 https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=119414 • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Unclear • **If yes, rate of agreement:** Not applicable • **Extraction completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Funding of review:** Not reported • **Conflicts of interest of review:** "W. Häuser was reimbursed for travel and accommodation fees by Bioevents for organising a congress on controversies on cannabis-based medicines. He is the head of the steering committee of the European Pain Federation (EFIC) position paper on appropriate use of cannabis-based medicines and medical cannabis for chronic pain management. L. Radbruch is the president of the Geram Society for Palliative care. P. Welsch and P. Klose have no academic conflict of interests to declare. M.-A. Fitzcharles is the head of the steering committee of a position statement of the Canadian Rheumatology Association ("A Pragmatic Approach for Medical Cannabis and Patients with Rheumatic Diseases"). All authors declare that they have no financial conflicts of interest."

Parameter	Extraction items
	• **How conflicts of interest were managed:** Not reported
Date Range (years) of included studies	• **Exact years for included studies:** 2010-2018
Number of primary studies included in the systematic review	• **Number of studies:** 5 RCTS • **Number of studies by study design:** 5 RCTs • **Study years:** 2010 (1 RCT); 2012 (1 RCT); 2017 (2 RCTs); 2018 (1 RCT) • **Funding of included studies:** Industry funded (5 RCTs) • **Conflicts of interest of included studies:** Reported (4 RCTs); not reported (1 RCT)
Types of studies included	**Planned study designs to be included:** RCT **Reasons for including only RCTs/prospective cohort studies:** Not reported **List of excluded studies at full text and reasons for exclusion:** Yes
Appraisal instruments used	**Full name of tools used:** Criteria outlined in the Cochrane Handbook for Systematic Reviews of Intervention; GRADE system **<u>Risk of bias criteria for AMSTAR 2 assessment, for RCTs record Yes/No for:</u>** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes

Parameter	Extraction items
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** High risk of bias (3 RCTs) and unclear risk of bias (2 RCTs) (authors follow predefined criteria of the Cochrane RoB tool) • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** o Overall: Low risk randomisation (0/5); low risk outcome ascertainment (0/5) Parallel RCTs o Pain relief of 50% or greater: Low risk randomisation (0/4); low risk outcome ascertainment (0/4) o Loss of therapeutic response of patient impression to be much or very much improved: Low risk randomisation (0/2); low risk outcome ascertainment (0/2) o Combined responder (pain relief of 30% or greater and reduced opioid use): Low risk randomisation (0/1); low risk outcome ascertainment (0/1) o Withdrawal due to adverse events: Low risk randomisation (0/4); low risk outcome ascertainment (0/4) o Serious adverse events: Low risk randomisation (0/4); low risk outcome ascertainment (0/4) o Adverse events: Low risk randomisation (0/4); low risk outcome ascertainment (0/4) Enriched enrolment randomised withdrawal (EERW) RCTs o Loss of therapeutic response of patient impression to be much or very much improved: Low risk randomisation (0/1); low risk outcome ascertainment (0/1) o Withdrawal due to adverse events: Low risk randomisation (0/1); low risk outcome ascertainment (0/1) o Serious adverse events: Low risk randomisation (0/1); low risk outcome ascertainment (0/1) o Adverse events: Low risk randomisation (0/1); low risk outcome ascertainment (0/1)

Parameter	Extraction items
	• **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** "We report that the evidence for all outcomes is of very low quality for a number of reasons: limitations of study design (high risk of bias in majority of studies included); indirectness (people with hepatic and renal insufficiency excluded); and publication bias (all studies were sponsored by the manufacturer of the drug)." p434 • **Graphical or statistical test for publication bias:** "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" p428 • **Authors' comments likelihood and magnitude of publication bias:** "We assumed a potential publication bias if all studies were initiated and funded by the manufacturer of the drug" p428 "Two hundred participants would have to have been included in entirely negative (zero treatment effect) trials to breach the pre-set level of utility (a NNTB of 10 or more) for the patient impression to be much or very much improved." p432 • **Authors' comment on how publication bias was dealt with:** "We assumed a potential publication bias if all studies were initiated and funded by the manufacturer of the drug" p428 • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** No • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** Yes
Method of analysis	**Description of method of analysis as per authors:** "We calculated numbers needed to treat for an additional beneficial outcome (NNTB) as the reciprocal of the absolute risk reduction (ARR). For unwanted effects, we calculated the number needed to treat for an additional harmful outcome (NNTH) in the same manner. We used dichotomous data to calculate risk

Parameter	Extraction items
	differences (RD) with 95% confidence intervals (CIs) using a random-effect model. We set the threshold for a clinically relevant benefit or a clinically relevant harm for categorical variables by an NNTB or NNTH ≤10. We calculated standardised mean differences (SMD) with 95% CIs for continuous variables using a random-effect model. We used Cohen's categories to evaluate the magnitude of the effect size, calculated by SMD, with Hedges' g value of 0.2 = small, 0.5 = medium, and 0.8 = large. We labelled a g value less than 0.2 to be a "not substantial" effect size. We assumed a minimally important difference if the Hedges' g value was 0.2 or greater." p427-428 "We used a random-effects model using the inverse variance method in Review Manager 5 for meta-analysis because there was significant clinical heterogeneity due to the different types of cancer pain conditions included." p428 • **Justification for narrative synthesis or meta-analysis:** Not reported • **Justification for combining data in meta-analysis:** Not reported
Outcome assessed	• **List of outcomes assessed and intended timeframes:** ○ Primary outcomes: Pain relief of 50% or greater; Global impression to be much or very much improved; Drop out due to adverse events; Serious adverse events ○ Secondary outcomes: Pain relief of 30% or greater; Mean pain intensity; Sleep problems; Daily maintenance opioid dosage; Daily break-through opioid dosage; Nervous system disorder adverse events; Psychiatric disorder adverse events; Gastrointestinal disorder adverse events ○ Intended timeframes: >2 weeks ○ Actual timeframes: 2-5 weeks
Results/findings	• **Findings by outcome:** PRIMARY OUTCOMES *Pain relief of 50% or greater*

Parameter	Extraction items
	○ Parallel RCT: Pooled data from four studies (n=1333) reported no significant difference in likelihood of pain relief of 50% or greater between nabiximol and placebo groups (RD 0.00, 95% CI –0.03 to 0.04). *Global impression to be much or very much improved* ○ Parallel RCT: Pooled data from two studies (n=710) reported significantly improved likelihood in nabiximol groups (27.1%) compared with placebo groups (20.7%) (RD 0.06, 95% CI 0.00 to 0.13). ○ Enriched enrolment randomised withdrawal: One study (n=206) reported significantly better impression of change in the nabiximol group compared with the placebo group (–0.31, 95% CI –0.57, –0.04) (p=0.02). *Combined responder* ○ Parallel RCT: One study (n=397) reported no significant difference between the nabiximol and placebo groups (OR 1.40; p=0.11). *Drop out due to adverse events* ○ Parallel RCT: Pooled data from four studies (n=1332) reported significantly increased likelihood of drop out due to adverse events in nabiximol groups (15.2%) compared with placebo groups (9.7%) (RD 0.05, 95% CI 0.01 to 0.09). As per predefined categories, there was no clinically relevant harm by nabiximol. ○ Enriched enrolment randomised withdrawal: One study (n=206) reported significant differences in the nabiximol group (21/103) compared with the placebo group (13/103) (p=0.05). *Serious adverse events* ○ Parallel RCT: Pooled data from four studies (n=1330) reported no significant difference in likelihood of serious adverse events in nabiximol groups (23.9%) compared with placebo groups (21.2%) (RD 1.06, 95% CI 0.86 to 1.32). ○ Enriched enrolment randomised withdrawal: One study (n=206) reported no significant difference between the nabiximol (33/103) and placebo groups (16/103) (p=0.13).

Parameter	Extraction items
	SECONDARY OUTCOMES *Pain relief of 30% or greater* ○ Parallel RCT: Pooled data from four studies (n=1333) reported no significant difference between nabiximol (29.4%) and placebo groups (26.5%) (RD 0.03, 95% CI –0.02 to 0.08). *Mean pain intensity* ○ Parallel RCT: Pooled data from four studies (n=1331) reported no significant difference between nabiximol groups and placebo groups (SMD –0.11, 95% CI –0.25 to 0.02). ○ Enriched enrolment randomised withdrawal: One study (n=206) reported no significant difference between the nabiximol and placebo groups (0.12, 95% CI –0.18 to 0.42) (p=0.43). *Sleep problems* ○ Parallel RCT: Pooled data from three studies (n=971) reported no significant difference in nabiximol groups compared with placebo groups (SMD 0.04, 95% CI –0.09 to 0.17). ○ Enriched enrolment randomised withdrawal: One study (n=206) reported no significant difference between the nabiximol and placebo groups (0.06, 95% CI –0.28 to 0.39) (p=0.73). *Psychological distress* ○ Parallel RCT: One study (n=177) reported no significant differences between nabiximol and placebo groups (CBD/THC vs placebo treatment difference 6.73, p=0.08; THC vs placebo treatment difference 5.22, p=0.17). ○ One study (n=388) reported no significant difference between nabiximol and placebo groups across three dosage arms- 1-4 sprays daily (p=0.48); 6-10 sprays (p=0.15); 11-16 sprays (p=0.08). *Daily maintenance opioid dosage* ○ Parallel RCT: Pooled data from three studies (n=970) reported no significant difference between nabiximol and placebo groups (SMD 0.08, 95% CI –0.10 to 0.27).

Parameter	Extraction items
	○ Enriched enrolment randomised withdrawal: One study (n=206) reported no significant difference between nabiximol and placebo groups (–3.63, 95% CI –10.80 to 3.55) (p=0.32). *Daily break-through opioid dosage* ○ Parallel RCT: Pooled data from three studies (n=970) reported no significant difference between nabiximol and placebo groups (SMD –0.12, 95% CI –0.25 to 0.01). ○ Enriched enrolment randomised withdrawal: One study (n=206) reported no significant difference between the nabiximol and placebo groups (–4.17, 95% CI –8.76 to 0.42) (p=0.08). *Nervous system disorder adverse events* ○ Parallel RCT: Pooled data from four studies (n=1330) reported significantly increased likelihood in nabiximol groups (22.4%) compared with placebo groups (9.3%) (RD 0.10, 95% CI 0.04 to 0.15). As per predefined categories, there was a clinically relevant harm by nabiximol. ○ Enriched enrolment randomised withdrawal one study: One study (n=206) reported no significant difference between the nabiximol (1/103 cerebrovascular incident) and placebo groups (0/103 cerebrovascular incident) (p=0.32). This study reported no significant differences in reported dizziness and somnolence in the nabiximol group (6/103) compared with the placebo group (1/103) (p=0.06). *Psychiatric disorder adverse events* ○ Parallel RCT: Pooled data from four studies (n=1330) reported no significant difference between nabiximol (4.6%) and with placebo groups (1.6%) (RD 0.01, 95% CI –0.00 to 0.02). ○ Enriched enrolment randomised withdrawal: One study (n=206) reported no treatment-emergent suicidal ideations or behaviour in either group. *Gastrointestinal disorder adverse events*

Parameter	Extraction items

- Parallel RCT: Pooled data from four studies (n=1330) reported significantly increased likelihood in nabiximol groups (34.6%) compared with placebo groups (22.7%) (RD 0.09, 95% CI 0.03 to 0.15). As per predefined categories, there was no clinically relevant harm by nabiximol.
- Enriched enrolment randomised withdrawal: One study (n=206) reported no participant experienced nausea and vomiting in either group.

- **GRADE by outcome:**

Outcome	No. studies	GRADE
Parallel RCTs		
Pain relief of 50% or greater	4	Very low
Global impression to be much or very much improved	2	Very low
Drop out due to adverse events	4	Very low
Serious adverse events	4	Very low
Pain relief of 30% or greater	4	Very low
Mean pain intensity	4	Very low
Sleep problems	3	Very low
Daily maintenance opioid dosage	3	Very low
Daily break-through opioid dosage	3	Very low
Nervous system disorder adverse events	4	Very low
Psychiatric disorder adverse events	4	Very low
Gastrointestinal disorder adverse events	4	Very low

Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):

Outcome	No. studies (No. participants)	Summary estimate (95% CI)	P-value	I^2 (%)	Direction of effect
Parallel RCTs: Nabiximols vs placebo					

Parameter	Extraction items					
	Pain relief of 50% or greater	4 (1333)	RD 0.00 (-0.03 to 0.04)	0.82	0	No significant difference
	Global impression to be much or very much improved	2 (710)	RD 0.06 (0.00 to 0.13)	0.04	0	Nabiximol
	Drop out due to adverse events	4 (1332)	RD 0.05 (0.01 to 0.09)	0.03	0	Nabiximol
	Serious adverse events	4 (1330)	RD 1.06 (0.86 to 1.32)	0.58	0	No significant difference
	Pain relief of 30% or greater	4 (1333)	RD 0.03 (-0.02 to 0.08)	0.27	0	No significant difference
	Mean pain intensity	4 (1331)	SMD -0.11 (-025 to 0.02)	0.09	20	No significant difference
	Sleep problems	3 (971)	SMD 0.04 (-0.09 to 0.17)	0.52	1	No significant difference
	Daily maintenance opioid dosage	3 (970)	SMD 0.08 (-0.10 to 027)	0.38	42	No significant difference
	Daily break-through opioid dosage	3 (971)	SMD -0.12 (-025 to 0.01)	0.06	0	No significant difference
	Nervous system disorder adverse events	4 (1330)	RD 0.01 (0.04 to 0.15)	0.0004	36	Nabiximol
	Psychiatric disorder adverse events	4 (1330)	RD 0.01 (-0.00 to 0.02)	0.13	0	No significant difference
	Gastrointestinal disorder adverse events	4 (1330)	RD 0.09 (0.03 to 0.15)	0.004	31	Nabiximol

- **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Above
- **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Yes
- **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable

Significance/direction

See above if results listed by outcome: Above

Heterogeneity

- **See above if I^2 available:** Above

Parameter	Extraction items
	• **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** "There was no substantial (I^2 > 50%) heterogeneity in any comparison. Remarkably, I^2 in most comparisons was 0%." p432 • **Causes of heterogeneity investigated:** Yes, random effects models used, I^2 calculated, sensitivity and subgroup analyses considered
Comments	There is a discrepancy between total participant numbers reported in main text (N=1539) and Table 1 (N=1567). We have extracted total participant numbers from Table 1 in this extraction form.

Kafil *et al.* (2018a): Cannabis for the treatment of Crohn's disease (Review)

Parameter	Extraction items
First author and year of publication	Kafil *et al.* (2018a)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "The objectives were to assess the efficacy and safety of cannabis and cannabinoids for induction and maintenance of remission in people with Crohn's disease" p1 • **Exact review question and page number:** "The primary objective was to assess the efficacy and safety of cannabis for induction and maintenance of remission in people with Crohn's disease." p10 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** "Adults (≥18 years of age) with Crohn's disease (as defined by the included studies) were considered for inclusion." p10 ➢ **Setting:** ➢ **Intervention:** "Studies comparing any form of cannabis or its cannabinoid derivatives (natural or synthetic)" p10 ➢ **Comparison:** "placebo or an active therapy" p10

Parameter	Extraction items
	➢ **Outcome:** Primary outcomes included was remission at study endpoint for induction of remission studies (as defined by a Crohn's Disease Activity Index < 150) and relapse (e.g. Crohn's Disease Activity Index > 150) at study endpoint for maintenance studies. Secondary outcomes included clinical response; endoscopic remission; endoscopic improvement; histological response; quality of life; C-reactive protein and fecal calprotectin measurements; adverse events; serious adverse events; withdrawal due to adverse events; and cannabis dependence and withdrawal effects.
Participants (characteristics and numbers)	**For whole sample and subgroups:** • **Number of participants:** N=93 • **Age:** At least 20 years old (2 RCTs); not reported (1 RCT) • **Gender:** Not reported • **Details of clinical diagnosis/indications:** Crohn's disease (n=93)
Setting/context	**Countries (alphabetic order):** Not reported **Setting (university, public or private clinic):** Not reported **Other relevant features of setting:** Not reported
Description of Interventions/ phenomena of interest	➢ **Exact definition of the intervention as per authors:** "Studies comparing any form of cannabis or its cannabinoid derivatives (natural or synthetic)" p10 • **Dose and regimen** o Cannabis cigarettes (1 RCT): 115 mg of THC; twice daily o Cannabis oil (1 RCT): Cannabidiol 5%, 2 ml; twice daily

Parameter	Extraction items
	○ Cannabis oil (1 RCT): 15% cannabidiol and 4% THC; regimen not reported • **Administration methods:** Not reported • **Comparator:** Placebo (3 RCTs) • **Treatment duration:** 8 weeks (3 RCTs) • **Timeframe for follow-up:** 2 weeks (3 RCTs)
Databases and sources searched	• **Number and names of databases:** 6; MEDLINE, Embase, AMED (Allied & Alternative Medicine), PsycINFO, the Cochrane IBD Group Specialized Register, CENTRAL; inception-17/10/2018 • **Other sources:** ClinicalTrials.Gov, and the European Clinical Trials Register • **Grey literature:** "We searched abstracts from major gastroenterological meetings to identify research published in abstract form. We also contacted authors in this field for upcoming publications….Conference proceedings were searched to identify studies published in abstract form." p10 • **Reference chasing:** Yes • **Expert consultation:** No • **Dates:** Inception-17/10/2018 • **Search limits:** No • **Justifications for search limits:** Not applicable • **Other searches:** Not reported • **Protocol prepared:** Yes • **If yes, published:** https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012853/full • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported

Parameter	Extraction items
	• **Extraction completed in duplicate:** Yes • **If Yes, rate of agreement:** Not reported • **Funding of review:** "Funding for the Cochrane IBD Group (May 1, 2017 - April 30, 2022) has been provided by Crohn's and Colitis Canada (CCC)." p17 • **Conflicts of interest of review:** "Tahir S Kafil: None known-Tran M Nguyen: None known-John K MacDonald: None known-Nilesh Chande has received funds from AbbVie, Ferring, and Takdeda for consulting; and payment for lectures from Abbvie and Actavis. All of these financial activities are outside the submitted work." https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD012853.pub2/information#CD012853-sec-0073 • **How conflicts of interest were managed: Above**
Date Range (years) of included studies	• **Exact years for included studies:** 2013-2017
Number of primary studies included in the systematic review	• **Number of studies:** 3 RCTs • **Number of studies by study design:** RCT • **Study years:** 2013 (1 RCT); 2017 (2 RCTs) • **Funding of included studies:** Not reported • **Conflicts of interest of included studies:** Reported (1 RCT); not reported (2 RCTs)
Types of studies included	**Planned study designs to be included:** RCT **Reasons for including only RCTs/prospective cohort studies:** Not reported **List of excluded studies at full text and reasons for exclusion:** Yes
Appraisal instruments used	**Full name of tools used:** Cochrane risk of bias tool

Parameter	Extraction items
	<u>For RCTs, record Yes/No for appraisal instrument assessment of:</u> • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The authors did not provide an overall assessment of risk of bias for each trial. However, HRB notes that according to Cochrane's Collaboration tool, and graphical information provided in the paper, the included trials appeared to have a high risk of bias (2 RCTs) and unclear risk of bias (1 RCT). • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** o Overall: Low risk randomisation (2/3); low risk outcome ascertainment (3/3) *THC (cannabis cigarette) vs placebo* o Clinical remission rates: Low risk randomisation (0/1); low risk outcome ascertainment (1/1) *CBD (cannabis oil 5%) vs placebo* o Clinical remission rates: Low risk randomisation (1/1); low risk outcome ascertainment (1/1) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence**: "Our assessment based on GRADE analyses suggests that the certainty of the evidence supporting the outcomes in this review is low to very low. As a result of this uncertainty no firm conclusions regarding the efficacy and safety of cannabis for Crohn's can be drawn." p17 • **Graphical or statistical test for publication bias:** "If there were more than 10 included studies in a pooled analysis, we planned to investigated publication bias by constructing funnel plots (Egger 1997)." p11 • **Authors' comments likelihood and magnitude of publication bias:** Not reported

Parameter	Extraction items
	• **Authors' comment on how publication bias was dealt with:** Not reported • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** "We planned to perform a sensitivity analysis based on risk of bias. However, there were no studies were pooled for analysis because of differences in the interventions." p12 • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** Yes
Method of analysis	• **Description of method of analysis as per authors:** "We planned to combine data from individual trials when the interventions, patient groups and outcomes were sufficiently similar (determined by consensus). When pooling studies was not possible, we narratively summarized the results of individual trials. For dichotomous outcomes, we planned to calculate the pooled RR and 95% CI using a fixed-effect model. For continuous outcomes, we planned to calculate the pooled MD and corresponding 95% CI. For continuous outcomes that utilized different scales to measure the same underlying construct, we planned to calculate the standardized mean difference (SMD) and corresponding 95% CI." p11 • **Justification for narrative synthesis or meta-analysis:** "Data from the three included studies were not pooled due to the different routes of administration and formula composition for the two studies that used cannabis oil." p15 • **Justification for combining data in meta-analysis:** Not applicable
Outcome assessed	**List of outcomes assessed and intended timeframes** • Primary outcomes: Clinical remission rates • Secondary outcomes: Clinical response, C-reactive protein, quality of life, adverse events, serious adverse events • Intended timeframes: Not specified • Actual timeframes: 10 weeks for all studies (8weeks treatment, 2 weeks follow-up)
Results/findings	• **Findings by outcome:**

Parameter	Extraction items
	PRIMARY OUTCOMES *Clinical remission rates* • One study (n=21) reported no significant difference in clinical remission rates at eight weeks were in the cannabis (45.5%) compared with placebo (10%) groups (RR 4.55, 95% CI 0.63 to 32.56). • One study (n=19) reported no significant difference clinical remission rates at eight weeks in cannabis oil (40%) compared with placebo (33.3%) groups (RR 1.20, 95% CI 0.36 to 3.97). SECONDARY OUTCOMES *Clinical response* • One study (n=21) reported statistically significant clinical response in cannabis (90.9%) compared with placebo (40%) groups (RR 2.27, 95% CI 1.04 to 4.97) • One study (n=39) reported significantly improved Crohn's Disease Activity Index score in cannabidiol oil compared with placebo groups (MD -94.00, 95%CI -148.86 to -39.14) *C-reactive protein* • One study (n=21) reported no significant difference in serum C-reactive protein between cannabis and placebo groups at end of treatment (RR 1.36, 95% CI 0.28 to 6.56). *Quality of life* • One study (n=22) reported a difference between cannabis and placebo groups (no summary statistics reported). "There was an increase in the quality of life scores in the treatment group compared to the placebo group. There was an increase of 28 points in the treatment group from baseline to week 8, compared to a difference of 5 points in the placebo group from baseline to week 8." p15

Parameter	Extraction items

- One study (n=38) reported significant improvement in cannabidiol oil compared with placebo groups (MD 16.40, 95% CI 5.72 to 27.08, low-certainty evidence).

Adverse events

- One study (n=21) reported significantly higher frequency in cannabis (82%) and placebo groups (20%) (RR 4.09, 95% CI 1.15 to 14.57). However, these adverse events were considered to be mild in nature and included sleepiness, nausea, difficulty with concentration, memory loss, confusion and dizziness.
- One study (n=19) reported no significant difference between cannabis oil and placebo groups (no summary statistics reported).

Serious adverse events

- One study (n=19) reported no significant difference between cannabis oil (10%) and placebo (11%) groups (RR 0.90, 95% CI 0.07 to 12.38). In both cases the serious adverse event was worsening Crohn's disease that required rescue intervention.

Other outcomes

- One study (n=21) reported improvements in pain, appetite and satisfaction in cannabis compared with placebo groups (no summary statistics reported).

- **GRADE by outcome:**

Outcome	No. studies	GRADE
Cannabis cigarettes (115 mg THC) compared to placebo cigarettes		
Clinical remission	1	Very low
Clinical response	1	Very low
C-reactive protein	1	Low
Adverse events	1	Very low
Cannabis oil (5% cannabidiol sublingual oil) compared to placebo oil		
Clinical remission	1	Very low
Serious adverse events	1	Very low

Parameter	Extraction items
	<table><tr><td colspan="3">Cannabis oil (15% cannabidiol and 4% THC) compared to placebo oil</td></tr><tr><td>Quality of life</td><td>1</td><td>Low</td></tr></table> • **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):** Not applicable • **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Above • **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Not applicable • **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable
Significance/direction	**See above if results listed by outcome:** Above
Heterogeneity	• **See above if I^2 available:** Not applicable • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** Not reported • **Causes of heterogeneity investigated:** "Overall, there were sparse data and heterogenous outcomes. Each study used a different dose of cannabis or cannabidiol formula." p16
Comments	

Kafil *et al.* (2018b): Cannabis for the treatment of ulcerative colitis (Review)

Parameter	Extraction items
First author and year of publication	Kafil *et al.* (2018b)
Objectives	• **Study objectives:** "To assess the efficacy and safety of cannabis and cannabinoids for the treatment of patients with [ulcerative colitis]." p1

Parameter	Extraction items
Report exact review question(s) and page number	• **Exact review question and page number:** "To assess the efficacy and safety of cannabis and cannabinoids for the treatment of patients with [ulcerative colitis]." p8 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** Adult patients (> 18 years of age) with ulcerative colitis ➢ **Setting:** Not specified ➢ **Intervention:** "Studies comparing any form of cannabis or cannabinoid derivatives to placebo or an active therapy for [ulcerative colitis] were included. We included studies that utilized any dosage and method of administration" p8 ➢ **Comparison:** Placebo or active therapy ➢ **Outcome:** Primary: For induction of remission studies the outcome was clinical remission and for maintenance of remission studies the outcome was relapse at study endpoint; Secondary: Clinical response, endoscopic remission; endoscopic response, histological response, quality of life, C-reactive protein and fecal calprotectin measurements, symptom improvement, adverse events, serious adverse events, withdrawal due to adverse events, psychotropic adverse events, cannabis dependence and withdrawal effects
Participants (characteristics and numbers)	**For whole sample and subgroups** • **Number of participants:** N=92 • **Age:** 18-65 years (1 RCT); Not reported (1 RCT) • **Gender:** Not reported • **Details of clinical diagnosis/indications:** Ulcerative colitis
Setting/context	**Countries (alphabetic order):** Czech Republic (1 RCT); Not reported (1 RCT)

Parameter	Extraction items
	Setting (university, public or private clinic): Not reported **Other relevant features of setting:** Not applicable

Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** "Studies comparing any form of cannabis or cannabinoid derivatives to placebo or an active therapy for [ulcerative colitis] were included." p8
	• **Dose and regimen:**
	  ○ CBD containing up to 4.7% THC and other compounds: 50 mg to 250 mg; twice daily
	  ○ 0.5 g of cannabis, corresponding to 11.5 mg THC; twice daily
	• **Administration methods:** Capsule (1 RCT); cigarette (1 RCT)
	• **Comparator:** Placebo (2 RCTs)
	• **Treatment duration:** 8-10 weeks
	• **Timeframe for follow-up:** No follow-up period reported for any study. The authors note "We included all short-term and long-term outcome time points" p8

Databases and sources searched	• **Number and names of databases:** 5: MEDLINE (Ovid); Embase (Ovid); WHO ICTRP; AMED (Allied & Alternative Medicine); PsycINFO; CENTRAL; Inception to 02/01/2018 • **Other sources:** ClinicalTrials.Gov; European Clinical Trials Register; The Cochrane IBD Group Specialized Register • **Grey literature:** "Conference proceedings were also searched to identify additional studies. We also contacted authors in this field for more information and upcoming abstracts or studies." p8 • **Reference chasing:** Yes • **Expert consultation:** Yes • **Dates:** Inception to 02/01/2018 • **Search limits:** No

Parameter	Extraction items
	• **Justifications for search limits:** Not applicable • **Other searches:** No • **Protocol prepared:** Yes • **If yes, published:** https://doi.org/10.1002/14651858.CD012954 • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Funding of review:** "Cochrane [irritable bowel disease] Group (May 1, 2017 - April 30, 2022) has been provided by Crohn's and Colitis Canada (CCC)" p15 • **Conflicts of interest of review:** "Tahir S Kafil: None known; Tran M Nguyen: None known; John K MacDonald: None known; Nilesh Chande has received funds from AbbVie, Ferring, Takeda, Pfizer, and Lupin for consulting; and payment for lectures from AbbVie, Allergan, Takeda, and Shire." p29 • **How conflicts of interest were managed:** Not reported
Date Range (years) of included studies	• **Exact years for included studies:** 2018
Number of primary studies included in the systematic review	• **Number of studies:** 2 RCTs • **Number of studies by study design:** 2 RCTS • **Study years:** 2018 (2 RCTS) • **Funding of included studies:** Industry (1 RCT); Not reported (1 RCT)

Parameter	Extraction items
	• **Conflicts of interest of included studies:** Not reported
Types of studies included	**Planned study designs to be included:** RCT **Reasons for including only RCTs/prospective cohort studies:** Not reported **List of excluded studies at full text and reasons for exclusion:** Yes
Appraisal instruments used	**Full name of tools used:** Cochrane Risk of Bias tool; GRADE system **Risk of bias criteria for AMSTAR 2 assessment, for RCTs record Yes/No for:** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The authors did not provide an overall assessment of risk of bias for each trial. However, HRB notes that according to Cochrane's Collaboration tool, and graphical information provided in the paper, the included trials appeared to have a high risk of bias (1 RCT) and unclear risk of bias (1 RCT). • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** ○ Overall: Low risk randomisation (2/2); low risk outcome ascertainment (2/2) *Cannabinoid capsules vs placebo* ○ Clinical remission: Low risk randomisation (1/1); low risk outcome ascertainment (1/1) *Cannabis cigarettes vs placebo* ○ All outcomes: Low risk randomisation (1/1); low risk outcome ascertainment (1/1) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** "The overall risk of bias for the Irving 2018 study is low. Although the Naftali 2018 study used placebo cannabis cigarettes, we rated this study as

Parameter	Extraction items
	high risk of bias for blinding of participants and personnel because unmasking of treatment assignment was very likely given the psychotropic nature of cannabis. GRADE analyses suggest that the overall certainty of evidence supporting the outcomes in this review ranges from low to moderate. For cannabidiol, we rated the overall quality of the evidence supporting the outcomes clinical remission, clinical response, serious adverse events and withdrawal due to adverse events as low quality. The overall certainty of the evidence supporting the outcomes quality of life, [C-reactive protein] and adverse events was rated as moderate. More research is needed before firm conclusions can be drawn regarding the efficacy and safety of cannabidiol in [ulcerative colitis]. For cannabis cigarettes, we rated the overall certainty of the evidence supporting the outcome [C-reactive protein] as low. Overall, we are uncertain about the benefits and harms of cannabis cigarettes in people with active [ulcerative colitis]. More research is needed before firm conclusions can be drawn about the use of cannabis cigarettes in [ulcerative colitis]." p15 • **Graphical or statistical test for publication bias:** Planned but not conducted "If a sufficient number of studies are included in the pooled analysis (i.e. >10), we will construct a funnel plot to assess the potential for publication bias (Egger 1997)." p10 • **Authors' comments likelihood and magnitude of publication bias:** "Irving 2018 was rated as low risk of bias for selective reporting. The Naftali 2018 study was rated as unclear risk of bias for selective reporting." p13 • **Authors' comment on how publication bias was dealt with:** Not reported • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** No • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** Yes
Method of analysis	• **Description of method of analysis as per authors:** "We planned to pool data from individual studies for meta-analysis when the outcomes, patient groups and interventions were similar enough to justify pooling (determined by consensus).

Parameter	Extraction items
	When pooling studies was not possible, we narratively summarized the results of individual trials. For dichotomous outcomes, we planned to calculate the pooled RR and 95% CI using a fixed-effect model. For continuous outcomes, we planned to calculate the pooled MD and corresponding 95% CI. However, if the continuous outcomes utilize different scales to measure the same underlying construct (e.g. for quality of life), we planned to calculate the standardized mean difference (SMD) and corresponding 95% CI. If significant heterogeneity was identified, a random-effects model would be used to pool data. We would not pool data for meta-analysis if a high degree of heterogeneity was detected (e.g. I^2 > 75%).” p10 • **Justification for narrative synthesis or meta-analysis: “**When pooling studies was not possible, we narratively summarized the results of individual trials.” p10 • **Justification for combining data in meta-analysis:** Not reported
Outcome assessed	**List of outcomes assessed and intended timeframes:** o Primary outcomes: For remission studies, clinical remission at study endpoint; for maintenance of remission studies, clinical relapse at study endpoint o Secondary outcomes: Clinical response; C-reactive protein; Quality of life; Adverse events; serious adverse events; withdrawal due to adverse events o Intended timeframe: “We included all short-term and long-term outcome time points” p8 o Actual timeframe: Treatment duration 8-10 weeks; no follow-up period reported for any study
Results/findings	• **Findings by outcome:** *Cannabidiol capsules (100 mg to 500 mg/day with up to 4.7% THC) versus placebo capsules at 10 weeks* PRIMARY OUTCOME • Clinical remission: One study (n=60) reported no significant difference between cannabidiol and placebo groups (RR 0.94, 95% CI 0.39 to 2.25).

Parameter	Extraction items
	SECONDARY OUTCOMES • Clinical response: One study (n=60) reported no significant risk difference between cannabidiol and placebo groups (RR 1.37, 95% CI 0.59 to 3.21). • C-reactive protein: One study (n=59) reported no significant difference between cannabidiol and placebo groups at ten weeks (MD 1.79, 95% CI -5.67 to 9.25). • Quality of life: One study (n=53) reported no significant difference between cannabidiol and placebo groups (MD 17.40, 95% CI -3.45 to 38.25). • Pain: One study (n=57) reported no significant difference between cannabidiol and placebo groups (MD 0.32, 95% CI -0.51 to 1.15). • Irritable Bowel Syndrome Questionnaire: One study (n=53) reported no significant difference between cannabidiol and placebo groups (MD -17.4, 95% CI -3.45 to 38.25). • Stool frequency: One study (n=59) reported no significant difference between cannabidiol and placebo groups (MD 0.00, 95% CI -0.35 to 0.35). • Rectal bleeding: One study (n=57) reported no significant difference between cannabidiol and placebo groups (MD -0.09, 95% CI -0.47 to 0.29). • Adverse events: One study (n=60) reported significant risk in the cannabidiol group (29/29) compared with the placebo group (24/31) (RR 1.28, 95% CI 1.05 to 1.56). “Adverse events were considered to be mild or moderate in severity. Common adverse events reported in the cannabidiol group included dizziness, somnolence, disturbance in attention, headache, memory impairment, nausea, dry mouth, vomiting, lower respiratory tract infection, disorientation and fatigue. Common adverse events reported in the placebo group include dizziness, headache, nausea, abdominal pain, worsening ulcerative colitis, abdominal distention, constipation, fatigue, back pain and rash.” p13

Parameter	Extraction items

- Serious adverse events: One study (n=60) reported no significant risk in the cannabidiol group (0/29) compared with the placebo group (3/31) (RR 0.15, 95% CI 0.01 to 2.83). “Serious adverse events in the placebo group were related to worsening of disease and one complicated pregnancy. None of the serious adverse events were thought to be treatment-related.” p13
- Withdrawal due to adverse events: One study (n=60) reported no significant risk in the cannabidiol group (10/29) compared with the placebo group (5/31) (RR 2.14, 95% CI 0.83 to 5.51). “Withdrawals in the [cannabidiol] group were mostly due to dizziness. Withdrawals in the placebo group were due to worsening ulcerative colitis.” p5

Cannabis cigarettes (23 mg THC/day) versus placebo cigarettes at 8 weeks

- Mean disease activity: One study (n=28) reported significant improvement in cannabis group compared with placebo group (MD -4.00, 95% CI -5.98 to -2.02).
- C-reactive protein at 8 weeks: One study (n=28) reported no significant difference between cannabis and placebo groups (MD -0.30, 95% CI -1.35 to 0.75).
- Fecal calprotein levels: One study (n=28) reported no significant difference between cannabis and placebo groups (MD -114.00, 95% CI -246.01 to 18.01).
- Serious adverse events: One study (n=32) reported no significant risk in the cannabis group (0/17) compared with the placebo group (0/15).

GRADE by outcome:

Outcome	No. studies	GRADE
Cannabidiol capsules versus placebo capsules at 10 weeks		
Clinical remission	1	Low
Clinical response	1	Low
C-reactive protein	1	Moderate
Quality of life	1	Moderate

Parameter	Extraction items

Adverse events	1	Moderate
Serious adverse events	1	Low
Adverse events withdrawal	1	Low
Cannabis cigarettes versus placebo at 8 weeks		
C-reactive protein	1	Low

Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I2, number of trials or studies, number of participants, random or fixed effects): Not conducted

- **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:**

Outcome	No. studies (No. participants)	Summary estimate	P-value	Direction of effect
Cannabidiol capsules versus placebo capsules at 10 weeks				
Clinical remission	1 (90)	RR 0.94 (0.39 to 2.25)	NR	No significant difference
Clinical response	1 (90)	RR 1.37 (0.59 to 3.21)	NR	No significant difference
C-reactive protein	1 (90)	MD 1.79 (-5.67 to 9.25)	NR	No significant difference
Quality of life	1 (90)	MD 17.40 (-3.45 to 38.25)	NR	No significant difference
Adverse events	1 (90)	RR 1.28 (1.05 to 1.56)	NR	Cannabidiol
Serious adverse events	1 (90)	RR 0.15 (0.01 to 2.83)	NR	No significant difference
Withdrawal due to adverse events	1 (90)	RR 2.14 (0.83 to 5.51)	NR	No significant difference
Cannabis cigarettes versus placebo at 8 weeks				
Clinical remission	1 (28)	MD -4.00 (-5.98 to -2.02)	NR	Cannabis
C-reactive protein	1 (32)	MD -0.30 (-1.35 to 0.75)	NR	No significant difference
Fecal calprotein	1 (28)	MD -114.00 (-246.01 to 18.01)	NR	No significant difference

Parameter	Extraction items
	• **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Not applicable • **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable
Significance/direction	**See above if results listed by outcome:** Above
Heterogeneity	• **See above if I^2 available:** Not applicable • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** Not applicable • **Causes of heterogeneity investigated:** Not applicable
Comments	

Kopelli *et al.* (2020): The role of cannabidiol oil in schizophrenia treatment. a systematic review and meta-analysis

Parameter	Extraction items
First author and year of publication	Kopelli *et al.* (2020)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "to conduct a systematic review and meta-analysis focusing only on RCTs in patients with schizophrenia or other types of schizophrenia-like psychoses that assessed the efficacy of CBD oil compared to placebo or any antipsychotic drug either as monotherapy or add-on therapy" p2 • **Exact review question and page number:** "to conduct a systematic review and meta-analysis focusing only on RCTs in patients with schizophrenia or other types of schizophrenia-like psychoses that assessed the efficacy of CBD oil compared to placebo or any antipsychotic drug either as monotherapy or add-on therapy" p2 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** Patients with schizophrenia or other types of schizophrenia-like psychoses

Parameter	Extraction items
	➢ **Setting:** Not specified ➢ **Intervention:** Cannabidiol oil ➢ **Comparison:** Placebo or any antipsychotic drug either as monotherapy or add-on therapy ➢ **Outcome:** "Primary outcomes were a) the overall efficacy of cannabidiol oil treatment as measured by rating scales such as the Positive and Negative Syndrome Scale (Kay *et al.*, 1987) and the Brief Psychiatric Rating Scale (Beller and Overall, 1984) or any other validated scale and b) the assessment of cognition as measured by the Brief Assessment of Cognition in Schizophrenia (Keefe *et al.*, 2004), the MATRICS Consensus Cognitive Battery Composite Score (August *et al.*, 2012) or any other validated scale. Secondary outcomes were, clinically important response to treatment, defined as at least 50% reduction of rating scales such as the [Positive and Negative Syndrome Scale] or the [Brief Psychiatric Rating Scale], or at least "much improved" on the Clinical Global Impressions Scale (Guy, 1976) or as defined by study authors; negative symptoms measured by rating scales such as the [Positive and Negative Syndrome Scale] negative subscale, or the Scale for the Assessment of Negative Symptoms (Andreasen, 1989); positive symptoms measured by rating scales such as the [positive and negative syndrome scale] positive subscale; functioning measured by rating scales such as the Global Assessment of Functioning scale (Aas, 2010); quality of life (QoL); dropouts due to any cause and due to side-effects; the total number of patients with side-effects; and important individual side-effects such as weight gain, prolactin levels, extrapyramidal symptoms, sedation and sexual side-effects." p2
Participants (characteristics and numbers)	**For whole sample and subgroups** • **Number of participants:** N=166 • **Age:** Mean age range 30.1-47.4 years • **Gender:** Not reported

Parameter	Extraction items
	• **Details of clinical diagnosis/indications:** Acute paranoid schizophrenia (1 RCT); stable chronic schizophrenia (1 RCT); schizophrenia or a related psychotic disorder (1 RCT)
Setting/context	**Countries (alphabetic order):** Not reported **Setting (university, public or private clinic):** Not reported **Other relevant features of setting:** Not applicable
Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** Cannabidiol oil • **Dose and regimen:** 200-1000 mg/daily • **Administration methods:** Orally (3 RCTS) • **Comparator:** Placebo (2 RCTs); active comparator amisulpride (antipsychotic) (1 RCT) • **Treatment duration:** >2 week (study duration range 4-6 weeks) • **Timeframe for follow-up:** Not reported for included RCTs
Databases and sources searched	• **Number and names of databases:** 3; EMBASE, PubMed, Cochrane Central Register of Controlled Trials (CENTRAL); inception to 24/04/2020 • **Other sources:** ClinicalTrials.gov; WHO International Clinical Trials Registry Platform (ICTRP) • **Grey literature:** Not applicable • **Reference chasing:** Yes • **Expert consultation:** No • **Dates:** Inception to 24/04/2020 • **Search limits:** None

Parameter	Extraction items
	• **Justifications for search limits:** Not applicable • **Other searches:** No • **Protocol prepared:** Yes • **If yes, published:** CRD42020157146 https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=157146 • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Funding of review:** "This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors." p6 • **Conflicts of interest of review:** "The authors declare that they have no conflicts of interest." p6 • **How conflicts of interest were managed:** Not reported
Date Range (years) of included studies	• **Exact years for included studies:** 2012-2018
Number of primary studies included in the systematic review	• **Number of studies:** 3 RCTS • **Number of studies by study design:** 3 RCTs • **Study years:** 2012 (1 RCT); 2018 (2 RCTs) • **Funding of included studies:** Not reported • **Conflicts of interest of included studies:** Not reported
Types of studies included	**Planned study designs to be included:** RCT

Parameter	Extraction items
	Reasons for including only RCTs/prospective cohort studies: Not reported **List of excluded studies at full text and reasons for exclusion:** Not reported
Appraisal instruments used	**Full name of tools used:** Name not specified **<u>Risk of bias criteria for AMSTAR 2 assessment, for RCTs record Yes/No for:</u>** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The authors did not provide an overall assessment of risk of bias for each trial. However, HRB notes that according to Cochrane's Collaboration tool, and graphical information provided in the paper, the included trials appeared to have a high risk of bias (3 RCTs). • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** o Overall: Low risk randomisation (2/3); low risk outcome ascertainment (0/3) *Cannainoid vs amisulpride* o Efficacy: Low risk randomisation (1/1); low risk outcome ascertainment (0/1) *Cannabinoid vs placebo* o Efficacy (cannabinoid vs. placebo): Low risk randomisation (1/2); low risk outcome ascertainment (0/2) o Cognition (cannabinoid vs. placebo): Low risk randomisation (1/2); low risk outcome ascertainment (0/2) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** Not reported

Parameter	Extraction items
	• **Graphical or statistical test for publication bias:** "As we had only 3 studies available, we could not use funnel plots to assess publication bias." p3 • **Authors' comments likelihood and magnitude of publication bias:** Not applicable • **Authors' comment on how publication bias was dealt with:** Not applicable • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** No • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** Not reported
Method of analysis	• **Description of method of analysis as per authors:** "Meta-analytic calculations were done with Review Manager 5.3. We employed a random-effects model for analysis. Endpoint values were preferred to change whenever possible since calculation of change needs two assessments (baseline and endpoint) which can be difficult in unstable and difficult-to-measure conditions such as schizophrenia. All analyses were on a per protocol basis whenever possible. The effect size for dichotomous outcomes was Risk Ratios (RR). The effect size for continuous outcomes was weighted mean difference (MD); if different scales were used, the effect size was calculated as Hedge's adjusted g standardized mean difference (SMD) (Higgins *et al.*, 2019). Effect sizes were presented along with their 95% confidence intervals (CIs). Chi-square and I-squared statistics were considered to investigate statistical heterogeneity between trials." p2 • **Justification for narrative synthesis or meta-analysis:** Not applicable • **Justification for combining data in meta-analysis:** Not applicable
Outcome assessed	**List of outcomes assessed and intended timeframes** ○ Primary outcomes: Efficacy; cognitive function

Parameter	Extraction items
	○ Secondary outcomes: Extrapyramidal symptoms; weight gain; prolactin increase; response to treatment; positive symptoms; negative symptoms; adverse events ○ Intended timeframe: >2 weeks ○ Actual timeframe: 4-6 weeks
Results/findings	• **Findings by outcome:** *Primary outcomes: Comparison- cannabidiol treatment versus amisulpride treatment (monotherapy)* ○ Efficacy: One study (n=35) reported no significant difference between cannabidiol and amisulpride control groups (MD −0.40, 95% CI −14.22 to 13.42, p=0.95). *Secondary outcomes: Comparison- cannabidiol treatment versus amisulpride treatment (monotherapy)* ○ Cognitive assessment: No data available ○ Extrapyramidal symptoms: One study (n=42) reported significantly fewer symptoms in the cannabidiol group compared with the amisulpride control group (MD −0.22, 95% CI −0.40 to −0.04, p=0.01). ○ Weight gain: One study (n=42) reported significantly lower weight gain in the cannabidiol group compared with the amisulpride control group (MD −3.40, 95% CI −5.76 to −1.04, p=0.005). ○ Prolactin increase: One study (n=42) reported significantly lower prolactin increase in the cannabidiol group compared with the amisulpride control group (MD −75.00, 95% CI −109.12 to −40.88, p<0.0001). ○ Response to treatment: One study (n=39) reported no significant difference between cannabidiol and amisulpride control (RR 1.02, 95%CI 0.70 to 1.47, p=0.93). ○ Positive symptoms: One study (n=35) reported no significant difference between cannabidiol and amisulpride control (MD -0.60. 95% CI -5.12 to 3.92, p=0.79). ○ Negative symptoms: One study (n=35) reported no significant difference between cannabidiol and amisulpride control (MD -2.70, 95% CI -6.32 to 0.92, 9=0.14).

Parameter	Extraction items
	○ Treatment withdrawal: One study (n=42) reported no significant difference between cannabidiol and amisulpride control (RR 1.33, 95% CI 0.34 to 5.24). ○ No data were available for the assessment of functioning, quality of life, the total number of patients with side-effects, sedation and sexual side-effects. *Primary outcomes: Comparison- cannabidiol treatment versus placebo treatment (add-on therapy)* ○ Efficacy: Pooled data from two studies (n=122) reported no difference between cannabidiol and placebo groups (MD −1.07, 95% CI −2.64 to 0.49). ○ Cognition: Pooled data from two studies (n=121) reported no difference between cannabidiol and placebo groups (SMD 0.09, 95% CI −0.27 to 0.45). *Secondary outcomes: Comparison- cannabidiol treatment versus placebo treatment (add-on therapy)* ○ Negative symptoms: Pooled data from two studies (n=122) reported no significant difference between cannabidiol and placebo groups (MD 0.51, 95% CI -0.13 to 1.14). ○ Positive symptoms: Pooled data from two studies (n=122) reported significant improvements in cannabidiol compared with placebo (MD −1.62, 95% CI −2.14 to −1.09). ○ Extrapyramidal symptoms: One study (n=41) reported no significant difference between cannabidol and placebo groups (RR 2.86, 95% CI 0.12 to 66.44, p=0.051) ○ Response to treatment: One study (n=86) reported no significant difference between cannabidiol and placebo groups (MD 2.10, 95% CI 0.87 to 5.07). ○ Functioning: One study (n=86) reported no significant difference between cannabidiol and placebo groups (MD 4.10, 95% CI -0.66 to 8.86). ○ Withdrawals due to any reason: Pooled data from two studies (n=129) reported no significant difference between cannabidiol and placebo groups (MD 1.50, 95% CI-0.45 to 5.01, p=0.68).

Parameter	Extraction items

- Total adverse events: Pooled data from two studies (n=129) reported no significant difference between cannabidiol and placebo groups (RR 0.84, 95% CI 0.62 to 1.14).
- Weight gain: One study (n=41) reported no significant difference between cannabidiol and placebo groups (RR 0.32, 95% CI 0.01 to 7.38, p=0.48).
- Sedation: Pooled data from two studies (n=129) reported no significant difference between cannabidiol and placebo groups (RR 0.89, 95% CI 0.04 to 21.75).
- Sexual side effects: One study (n=41) reported no significant difference between cannabidiol and placebo groups (RR 0.48, 95% CI 0.05 to 4.85, p=0.53).

- **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):**

Outcome	No. studies (No. participants)	Summary estimate	P-value	I^2 (%)	Direction of effect
Comparison: cannabidiol treatment versus placebo treatment (add-on therapy)					
Efficacy	2 (122)	MD −1.07 (−2.64 to 0.49)	0.18	0	No significant difference
Cognition	2 (121)	SMD 0.09 (−0.27 to 0.45)	0.62	0	No significant difference
Positive symptoms	2 (122)	MD −1.62 (−2.14 to −1.09)	<0.00001	0	Cannabidiol
Negative symptoms	2 (122)	MD 0.51 (-0.13 to 1.14)	0.12	5	No significant difference
Response to treatment	2 (122)	MD 2.10 (0.87 to 5.07)	0.10	NA	No significant difference
Treatment withdrawal due to any reason	2 (129)	RR 1.50 (0.45 to 5.01)	0.51	0	No significant difference
Total adverse events	2 (129)	RR 0.84 (0.62 to 1.14)	0.26	0	No significant difference
Sedation	2 (129)	RR 0.89 (0.04 to 21.75)	0.94	68	No significant difference

Parameter	Extraction items
	• **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Above • **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Yes • **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable
Significance/direction	**See above if results listed by outcome:** Above
Heterogeneity	• **See above if I^2 available:** Above • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** Not reported • **Causes of heterogeneity investigated:** Yes I^2, random-effects model, sensitivity and subgroup analyses considered
Comments	

Longo *et al.* (2021): Cannabis for Chronic Pain: A Rapid Systematic Review of Randomized Control Trials

Parameter	Extraction items
First author and year of publication	Longo *et al.* (2021)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "to evaluate the effectiveness and secondary effects of cannabinoids for chronic pain management in response to the epidemic of inadequately treated chronic pain conditions" p142 • **Exact review question and page number:** "in adults with chronic pain, what is the effect of cannabis on pain intensity?" p142 • **PICO elements reported in Introduction/Methods:**

Parameter	Extraction items
	➢ **Patient or population:** Adults with chronic pain ➢ **Setting:** Not specified ➢ **Intervention:** "cannabis of any formulation" p142 ➢ **Comparison:** Control group ➢ **Outcome:** Efficacy and secondary effects in chronic pain conditions
Participants (characteristics and numbers)	**For whole sample and subgroups** • **Number of participants:** N=1764 randomised (n=1352 completed) • **Age:** Not reported • **Gender:** Not reported • **Details of clinical diagnosis/indications:** Advanced cancer with chronic pain unalleviated by opioids (n=1539); chronic abdominal pain as a result of pancreatitis (n=25); chronic neuropathic pain (n=38); chronic neuropathic pain caused by chemotherapy (n=18); fibromyalgia (n=57); surgery/chronic pancreatitis (n=65); spinal cord injury (n=7); multiple sclerosis (n=15)
Setting/context	**Countries (alphabetic order):** Variety of countries but details not specified **Setting (university, public or private clinic):** Not reported **Other relevant features of setting:** Not reported
Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** • **Dose and regimen:** o Nabilone (2 RCTs); dosage and regimen not reported

Parameter	Extraction items
	○ Dronabinol (1 RCT); dosage and regimen not reported ○ THC/CBD (5 RCTs): 1.7 mg/2.5 mg; regimen not reported ○ THC only (2 RCTs); dosage and regimen not reported ○ 8mg THC (2 RCTs); 8 mg; regimen not reported ○ Bedrocan (1 RCT); 22.4 mg THC, <1 mg CBD; regimen not reported ○ Bediol (1 RCT); 13.4 mg THC, 17.8 mg CBD); regimen not reported ○ Bedrolite (1 RCT); 18.4 mg CBD, <1 mg THC; regimen not reported ○ Smoked THC (1 RCT); 2.5%, 6.0% and 9.4%; three times daily ○ Sublingual THC oil (1 RCT); dosage and regimen not reported • **Administration methods:** Spray (6 RCTs); Oral (5 RCTs); Inhaled (2 RCTs) • **Comparator:** Placebo (10 RCTs); amitriptyline (1 RCT); diazepam (1 RCT); diphenhydramine (1 RCT) • **Treatment duration:** 1-18 weeks • **Timeframe for follow-up:** Not reported in included RCTs.
Databases and sources searched	• **Number and names of databases:** 4; Embase, Cochrane, PubMed, CINAHL; 01/01/2009-21/11/2019 • **Other sources:** No • **Grey literature:** No • **Reference chasing:** No • **Expert consultation:** No • **Dates:** 01/01/2009-21/11/2019 • **Search limits:** Timeframe • **Justifications for search limits:** “This timeframe was selected to prioritize current evidence and is reflective of medicinal cannabis being legalized fairly recently in most countries that have done so.” p142

Parameter	Extraction items
	• **Other searches:** No • **Protocol prepared:** No • **If yes, published:** Not applicable • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Not reported • **If yes, rate of agreement:** Not applicable • **Extraction completed in duplicate:** Not reported • **If yes, rate of agreement:** Not applicable • **Funding of review:** Not reported • **Conflicts of interest of review:** Not reported • **How conflicts of interest were managed:** Not applicable
Date Range (years) of included studies	• **Exact years for included studies:** 2010-2019
Number of primary studies included in the systematic review	• **Number of studies:** 13 RCTs • **Number of studies by study design:** 13 RCTs • **Study years:** 2010 (4 RCTs); 2012 (1 RCT); 2014 (1 RCT); 2015 (2 RCTs); 2017 (2 RCTs); 2018 (2 RCTs); 2019 (1 RCT) • **Funding of included studies:** Not reported • **Conflicts of interest of included studies:** Not reported
Types of studies included	**Planned study designs to be included:** RCT

Parameter	Extraction items
	Reasons for including only RCTs/prospective cohort studies: Yes "Studies included in this review were limited to RCTs, because RCTs demonstrate the highest levels of reliability and validity in providing evidence for cause-and-effect relationships" p142 **List of excluded studies at full text and reasons for exclusion:** Reasons reported but full-text references not reported
Appraisal instruments used	**Full name of tools used:** Jadad scale **<u>Risk of bias criteria for AMSTAR 2 assessment, for RCTs record Yes/No for:</u>** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** No
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** High methodological quality (13 RCTs), mean Jadad score was 4.23. • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** ○ Overall: Low risk randomisation (10/13); low risk outcome ascertainment (8/13) *Cannabinoids vs active control:* ○ Pain intensity: Low risk randomisation (3/3); low risk outcome ascertainment (blinding) (3/3) *Cannabinoids vs placebo:* ○ Pain intensity: Low risk randomisation (7/10); low risk outcome ascertainment (blinding) (5/10) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** "all articles included in this review received a high-quality Jadad score, which increases the validity of the review results."

Parameter	Extraction items
	"The Jadad scale may be overly simplistic and not as comprehensive as other evaluation methods, which may underestimate the risk for bias in individual studies included in this review." p147 • **Graphical or statistical test for publication bias:** Not applicable • **Authors' comments likelihood and magnitude of publication bias:** Not applicable • **Authors' comment on how publication bias was dealt with:** Not applicable • **Only low ROB RCTs included in review:** Yes • **Only low ROB RCTs included in meta-analysis:** Not applicable • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** Yes
Method of analysis	• **Description of method of analysis as per authors:** Not reported (appears to be narrative synthesis). • **Justification for narrative synthesis or meta-analysis:** Not reported • **Justification for combining data in meta-analysis:** Not applicable
Outcome assessed	**List of outcomes assessed and intended timeframes** • Primary outcomes: Reduction in pain intensity, pain impact, pain quality • Secondary outcomes: Mood, quality of life, opioid use, patient global impression of change, subject global impression of change, sleep, adverse events • Intended timeframes: Not specified • Actual timeframes: 1-18 weeks
Results/findings	• **Findings by outcome:** *Primary outcome measures*

Parameter	Extraction items
	○ Pain intensity: Eight studies found no significant differences between cannabinoids and control groups. Of these, three studies found no difference between cannabinoids and active control (THC vs diazepam, n=25; nabilone vs amitriptyline, n=32; dronabinol vs diphenhydramine, n=7). Four of the studies found no significant difference between cannabinoid and placebo (THC tablet, n=65; oral mucosal cannabis spray, n=397, n=360, n=18). One study (n=399) found a significant difference between oral mucosal cannabis spray and placebo only for U.S. patients <65 years of age. No summary statistics were reported for any study. Five studies reported significantly reduced pain with cannabinoids compared to placebo. Findings in favour cannabinoids were reported for inhaled cannabis with mostly THC and cannabis with THC and CBD (n=25), THC oil (n=15), high-content THC inhalation treatment (n=23), THC:CBD oral mucosal spray (n=177) (but not for THC only in the same study), and nabilone (n=15). No summary statistics were reported for any study. *Secondary outcome measures* ○ Sleep: Three studies (n=415) all reported significant sleep improvements in cannabinoid compared with placebo groups. One study (n=360) reported significant sleep improvements in oral mucosal cannabis spray compared with placebo groups. One study (n=32) reported significant sleep improvements in nabilone compared with amitriptyline groups. One study (n=23) reported significant sleep improvements in cannabis compared with placebo groups. No summary statistics were reported. ○ Patient global impression of change: Three studies (n=1017) reported significant improvements in cannabinoid compared with placebo groups. ○ Subject global impression of change: Two studies (n=1002) reported significant improvements in cannabinoid compared with placebo groups. ○ Other: There were no significant improvements found in mood, quality of life, and opioid use.

Parameter	Extraction items
	○ Adverse events: "The most commonly reported adverse events were dizziness, nausea, and dry mouth. Adverse events were mostly mild or moderate in severity. A total of seven severe adverse events related to the cannabis treatment were reported across all studies. Severe adverse events included constipation, moderate disorientation, severe drowsiness, hallucinations, syncope, and abdominal discomfort." p146 • **GRADE by outcome:** Not reported • **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):** Not applicable • **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Not reported • **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Not applicable • **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable
Significance/direction	**See above if results listed by outcome:** Above
Heterogeneity	• **See above if I^2 available:** Not applicable • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** "The heterogeneity of studies included in this review indicate the need for more consistent research in terms of sample size, route of intervention, dosage, and control agents used." p147 • **Causes of heterogeneity investigated:** Not applicable
Comments	

Lutge *et al.* (2013): The medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS (Review)

Parameter	Extraction items
First author and year of publication	Lutge *et al.* (2013)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "This review aims to objectively assess the studies that have examined the medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS." p3 • **Exact review question and page number:** "This review aims to objectively assess the studies that have examined the medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS." p3 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population: "**Adults with HIV-1 or HIV-2 infection" p4 ➢ **Setting:** "Hospital, outpatient clinic, or home care setting" p4 ➢ **Intervention:** "Smoked marijuana, ingested marijuana, smoked hashish, ingested hashish, ingested THC (dronabinol,or any other pharmaceutically produced form)" p4 ➢ **Comparison:** "Placebo, no drug, other form of cannabis" p4 ➢ **Outcome:** Primary outcomes: Mortality (HIV-related; all-cause); morbidity (frequency, type and duration of episodes of opportunistic infections; malignancies; incidence of AIDS (as defined by each study); hospital admissions; and other illness types as measured in the studies). Secondary outcomes: Appetite (subjective); nausea (subjective); mood (subjective); pain (subjective); quality of life (subjective); appetite (objective); anthropometry and measures of body composition; haematological nutrition markers; indices of viral load; markers of effect on immune system; cognitive function; respiratory function (if cannabis is smoked); effect of pharmacokinetics of antiretroviral treatment; development of dependence or sociological effects; adverse events functional assessments of learning, memory, vigilance and psychomotor performance; and adverse events

Parameter	Extraction items
	incidence of cannabis-related effects, such as anxiety, hypertension, hypotension and tachycardia, euphoria, dizziness, altered thinking.
Participants (characteristics and numbers)	**For whole sample and subgroups** • **Number of participants:** N=330 • **Age:** Not reported (5 RCTs); age range 21-50 (2 RCTs) • **Gender:** Not reported • **Details of clinical diagnosis/indications:** HIV (N=330)
Setting/context	**Countries (alphabetic order):** Not reported **Setting (university, public or private clinic):** Not reported **Other relevant features of setting:** Not reported
Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** "any cannabis intervention, in any form, and administered by any route, in adults with HIV or AIDS" p4 • **Dose and regimen:** o Dronabinol (5 RCTs): 0-30 mg; twice daily, twice daily, three times daily, four times daily, not reported o Delta-9-THC (5 RCTs): 1-8%; three times daily, four times daily, four times daily, not reported Note: Some of the above RCTs used Dronabinol and THC in the studies • **Administration methods:** Smoked (5 RCTs); Oral (5 RCTs) • **Comparator:** Placebo (7 RCTs) • **Treatment duration:** Not specified (study duration 21-84 days)

Parameter	Extraction items
	• **Timeframe for follow-up:** Not reported for included RCTs
Databases and sources searched	• **Number and names of databases:** 3; Cochrane, PubMed, EMBASE; 1980-30/07/2012 • **Other sources:** ClinicalTrials.gov, AEGIS, AIDsearch, Gateway, WHO ICTRP • **Grey literature:** Conference proceedings (International AIDS Conference; International Conference on HIV/ AIDS in Africa (ICASA); Consultative Group meetings, International Association of physicians in AIDS care (IAPAC); International Conference on Retroviruses and Opportunistic infections) • **Reference chasing:** Yes • **Expert consultation:** No • **Dates:** 1980-30/07/2012 • **Search limits:** No • **Justifications for search limits:** Not applicable • **Other searches:** No • **Protocol prepared:** Yes • **If yes, published:** Yes https://doi.org/10.1002/14651858.CD005175 • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Funding of review:** The Cochrane HIV/AIDS Mentoring Programme, South Africa. • **Conflicts of interest of review:** None

Parameter	Extraction items
	• **How conflicts of interest were managed:** Not applicable
Date Range (years) of included studies	• **Exact years for included studies:** 1993-2009
Number of primary studies included in the systematic review	• **Number of studies:** 7 RCTs • **Number of studies by study design:** 7 RCTs • **Study years:** 1993 (1 RCT); 1995 (1 RCT); 2003 (1 RCT); 2005 (1 RCT); 2007 (2 RCTs); 2009 (1 RCT) • **Funding of included studies:** Not reported • **Conflicts of interest of included studies:** Not reported
Types of studies included	**Planned study designs to be included:** RCT **Reasons for including only RCTs/prospective cohort studies:** Not reported **List of excluded studies at full text and reasons for exclusion:** Yes
Appraisal instruments used	**Full name of tools used:** Cochrane Risk of Bias **Risk of bias criteria for AMSTAR 2 assessment, for RCTs record Yes/No for:** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes

Parameter	Extraction items

Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The authors did not provide an overall assessment of risk of bias for each trial. However, HRB notes that according to Cochrane's Collaboration tool, and graphical information provided in the paper, the included trials appeared to have a high risk of bias (5 RCTs) and unclear risk of bias (2 RCTs).
	• **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:**
	  ○ Overall: Low risk randomisation (1/7); low risk outcome ascertainment (0/7)
	  ○ Mortality: No studies reported on this outcome
	  ○ Morbidity: No studies reported on this outcome
	• **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** "Comprehensive searches of journal and conference databases, including all languages, were conducted. Data extraction and the assessment of the methodological quality were done by at least two researchers, which minimised potential bias in the review. Extracting data from the report of the complex within-subject, staggered, double-dummy design used by Haney 2007 and Haney 2005 was very difficult and precluded the pooling of data from these studies. This limited the contribution of these trials to possible meta-analysis and the findings of this review. Many of the outcomes investigated in the trials were subjective in nature; given that blinding is unlikely to have been effective in these trials, our confidence in these subjective outcomes was low. This in itself is a subjective judgement however and another researcher may have felt differently." p12
	• **Graphical or statistical test for publication bias:** No
	• **Authors' comments likelihood and magnitude of publication bias:** Not reported
	• **Authors' comment on how publication bias was dealt with:** Not applicable
	• **Only low ROB RCTs included in review:** No
	• **Only low ROB RCTs included in meta-analysis:** Not applicable

Parameter	Extraction items
	• **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** Not applicable
Method of analysis	• **Description of method of analysis as per authors:** "Data analysis was conducted using Review Manager (RevMan) version 5.0.15 (2008). Outcome measures for dichotomous data (e.g. death, virologic suppression) were calculated as a relative risk with 95% confidence intervals. Where available, means were used as the unit for comparison for the following continuous outcomes. However, if the distribution of the data was not normal (for example in small studies), or medians were used for reporting, these could not be analysed in RevMan." p5 • **Justification for narrative synthesis or meta-analysis:** "Although it was our original intention to do a meta-analysis on the included studies, this was not possible because the outcomes measured by the studies were too different, because insufficient data was supplied in the study articles and because measurements were often expressed in terms of medians, which could not be used in RevMan." p6 • **Justification for combining data in meta-analysis:** Not applicable
Outcome assessed	• **List of outcomes assessed and intended timeframes** ○ Primary outcomes: Mortality, morbidity ○ Secondary outcomes: Change in weight; change in body fat; change in appetite; change in food and caloric intake; change in nausea and vomiting; change in performance; change in mood; subjective experience of drug effects; effect on peripheral neuropathy; effect on pharmacokinetics of protease inhibitors; effect on viral load and CD4 count; physiological measures; adverse events ○ Intended timeframes: Not specified ○ Actual timeframes: 21-84 days

Parameter	Extraction items
Results/findings	• **Findings by outcome:** PRIMARY OUTCOMES ○ Mortality: No primary studies reported on this outcome ○ Morbidity: No primary studies reported on this outcome SECONDARY OUTCOMES ○ Change in weight (measured in grams/kilograms/pounds/ ounces): One study (n=62) reported significant weight gain in cannabis and cannabinoid groups compared with placebo. The cannabis group gained a median of 3.0 kg (range -0.75 to 0.86 kg; p=0.021), those using dronabinol gained a median of 3.2 kg (range -1.4 to 7.6 kg; p = 0.004) while those in the placebo group gained a median of 1.1kg (range -1.4 to 5.2 kg). One study (n=10) reported significant weight gain in dronabinol and cannabis groups with higher strength marijuana and higher dronabinol dosage compared to lower doses (p<0.01). One study (n=5) found no significant difference between dronabinol and placebo groups (median gain of 0.5 kg versus median loss of 0.7 kg from baseline). One study (n=139) no significant difference between dronabinol and placebo groups (mean gain of 0.1 kg versus mean loss of 0.4 kg from baseline, p=0.14). ○ Change in body fat (measured as a percentage of total body weight): One study (n=5) reported significant increase in body fat in dronabinol compared with placebo group (gained 1.0% body fat versus 0.06% gain, p=0.04). ○ Change in appetite (measured on a visual analogue scale): One study (n=139) reported significant increase in appetite in dronabinol compared with placebo group (37% versus 17%, p=0.05). One study (n=5) reported no significant difference between dronabinol and placebo groups (no summary statistic reported). ○ Change in food and caloric intake (measured in kcals/kg/24hr): One study (n=10) reported “marijuana and higher doses of dronabinol significantly increased the number of daily eating occasions (p<0.005 and p<0.01 respectively), as well as the total calories consumed per day (p<0.005 for higher doses of marijuana and dronabinol and p<0.01 for lower doses)” p10. One study (n=30) reported significant increase in caloric consumption in dronabinol (p<0.01) and

Parameter	Extraction items
	cannabis (p<0.01) groups for participants with significant weight loss due to HIV. However, caloric consumption in participants with HIV who were of normal weight was not affected by cannabinoids. One study (n=5) reported no significant difference between dronabinol and placebo groups (median 3.48kcal/kg versus 0.84kcal/kg). ○ Change in nausea and vomiting (measured on a visual analogue scale): One study (n=139) reported significantly decreased likelihood in dronabinol compared with placebo groups (RR 4.96, 95% CI 1.51 to 16.27). ○ Change in performance (Karnofsky performance score or specific tests for memory and dexterity): One study (n=30) reported significant decreases in numbers of correct digits recalled and speed in dronabinol and cannabis groups compared with placebo groups (p<0.01 in each case). One study (n=10) reported neither cannabis or dronabinol (of any strengths or concentrations) significantly affected performance on any tasks, which included measures of learning, memory, vigilance, psychomotor ability (no summary statistics reported). One study (n=139) reported no significant difference between dronabinol compared with placebo group (-2.5 point change versus 0 point change, p = 0.18). ○ Change in mood (measured on a visual analogue scale): One study (n=139) reported no significant difference between dronabinol and placebo groups (RR 4.96, 95% CI 1.51 to 16.27, p=0.16). ○ Subjective experiences of drugs: One study (n=10) reported "Ratings of 'good drug effect', 'high', 'mellow' 'stimulated', 'friendly', and 'self-confident' were significantly increased by dronabinol (10 mg) and both active marijuana doses (2.0% and 3.0% THC) (p<0.005). The dronabinol group reported significant ratings of 'can't concentrate' (p<0.01) and the lower strength marijuana cigarette (2.0%) reported increased ratings of 'anxious'. One study (n=30) reported significantly increased rating of good effect in cannabis compared with placebo (p<0.01). ○ Effect on peripheral neuropathy: One study (n=50) reported a significantly greater proportion of participants achieving than 30% reduction in pain from baseline to the end of treatment in cannabis compared with placebo groups (52% vs 24%, p=0.04). One study (n=34) reported the proportion of participants achieving pain reduction of

Parameter	Extraction items
	30% or more was significantly greater in cannabis compared with placebo (0.46 versus 0.18, p=0.043). The same study found a significant difference in pain reduction between cannabis and placebo (p=0.016). ○ Effect on viral load and CD4 count: One study (n=62) reported no significant difference between viral load in log 10 copies per ml in marijuana and placebo groups (MD -0.06, 95% CI -0.26 to 0.13) and dronabinol and placebo (MD -0.07, 95% CI -0.24 to 0.06). This study reported increased CD4 in the THC group compared with placebo (p=0.025) but no significant difference between dronabinol and placebo (p=0.064). CD4 count is an indicator of immune system health, with higher counts indicating better health. ○ Physiological measures: One study (n=10) reported resting heart rate was significantly increased by both marijuana and dronabinol at all concentrations and doses (except for the lower dose of dronabinol which did not have a significant effect in the morning) (no summary statistic reported). Skin temperature was increased by high dose marijuana in the morning (p<0.01) and by both doses of marijuana in the afternoon (p<0.01). ○ Adverse events: One study (n=139) reported a significant increase in adverse events in dronabinol (43%) compared with placebo (13%) groups, 8.3% of events were severe in the dronabinol group. Three studies (n=142) reported no adverse events in cannabis, cannabinoid or placebo groups. ○ Drop-out: One study (n=139) reported no difference in drop-out rates between dronabinol and placebo groups (p=0.29). One study (n=34) reported one drop-out due to an acute, cannabis-induced psychosis, and one drop-out due to an intractable, smoking-related cough. In one study, 2 of the 12 eligible patients withdrew early because of intolerance of cannabis (mood-altering effects and sedation). • **GRADE by outcome:** Not applicable • **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):** Not applicable

Parameter	Extraction items
	• **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Above • **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Not applicable • **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable
Significance/direction	**See above if results listed by outcome:** Above
Heterogeneity	• **See above if I^2 available:** Not applicable • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** Not reported • **Causes of heterogeneity investigated:** No
Comments	Struwe 1993 reports two withdrawals of 12 eligible study participants. However, only five participants were reported in this study, all reporting no treatment limiting adverse events. Only data related to these five participants has been extracted.

McDonagh *et al.* (2022): Cannabis-Based Products for Chronic Pain - A Systematic Review

Parameter	Extraction items
First author and year of publication	McDonagh *et al.* (2022)
Objectives **Report exact review question(s) and page number**	• **Study objectives: "**To evaluate the benefits and harms of cannabinoids for chronic pain." p1143 • **Exact review question and page number: "**The purpose of this systematic review is to evaluate the benefits and harms of cannabinoids to treat chronic pain, using a novel categorization scheme for the amount of THC versus CBD in cannabis products." p1143 • **PICO elements reported in Introduction/Methods:**

Parameter	Extraction items
	➢ **Patient or population:** Patients with chronic pain ➢ **Setting:** Not specified ➢ **Intervention:** Cannabis products for at least four weeks of treatment or follow-up ➢ **Comparison:** Placebo or no treatment (usual care) ➢ **Outcome:** "Primary outcomes were measures of pain, physical or general functioning, and adverse events. Adverse events of interest were serious adverse events, adverse events leading to study withdrawal, nausea, dizziness, sedation, psychosis, development of cannabis use disorder, and cognitive deficits. Secondary outcomes were quality of life, mental health, sleep, and effect on opioid use" p1144
Participants (characteristics and numbers)	**For whole sample and subgroups:** RCT (n=1636); observational (n=13392) (figures extracted from appendix table 2) *Any non-prospective cohort design studies are excluded from the remainder of the extraction unless specified otherwise. **RCT STUDIES** • **Number of participants:** n=1636 (figures extracted from appendix table 2) • **Age:** Mean age range across THC-to-CBD categories: 50-65 years (extracted from table 2, p1146) • **Gender:** 67.4% female (extracted from table 2, p1146) • **Details of clinical diagnosis/indications:** Fibromyalgia (n=50); visceral pain— chronic pancreatitis and postsurgical abdominal pain (n=62); neuropathic pain-multiple sclerosis (n=963); neuropathic pain-diabetes (n=55); rheumatoid arthritis (n=58); chemotherapy-induced neuropathic pain (n=16); neuropathic pain mixed (n=400); HIV (n=32) (extracted from appendix table 1) **COHORT STUDIES** • **Number of participants:** n=2580 (figures extracted from appendix table 2)

Parameter	Extraction items
	• **Age:** Unable to extract • **Gender:** 59% female (extracted from table 2, p1146) • **Details of clinical diagnosis/indications:** Neuropathic pain mixed (n=156); chronic non-cancer pain mixed (n=1945); mixed (primarily musculoskeletal) (n=46); HIV (n=433) (figures extracted from appendix table 2)
Setting/context	**Countries (alphabetic order):** Not reported **Setting (university, public or private clinic):** Not reported **Other relevant features of setting:** Not reported
Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** Not specified • **Dose and regimen:** RCT o THC:CBD: 1.2 mg of THC/0.02 mg CBD (1 RCT); mean 3.6 drops daily; sublingual oral o THC capsule (7 RCTs): 2-24 mg; daily o THC:CBD (7 RCTs): 2.7 mg THC/2.5 mg CBD (not reported 1 RCT); mean of 5.4-10.9 sprays daily orally o CBD cream (1 RCT): 250 mg/3 oz; four times daily o CBD oil (1 RCT): Not reported; not reported o CBDV (1 RCT): 400 mg; daily Prospective cohort studies

Parameter	Extraction items
	○ Nabilone (1 prospective cohort study); 3.05 mg; daily or Gabapentin (anticonvulsant medication) and THC capsule (nabilone) mean dose, not reported and 3.02 mg THC; daily ○ Marijuana (1 prospective cohort study): Daily to monthly use of marijuana, unknown THC concentration ○ Cannabis (1 prospective cohort studies): self-reported frequent cannabis use of at least 20 days, dose and regimen not specified ○ Mixed cannabis products (1 prospective cohort study): THC 13.3 mg, CBD 28.9 mg; daily ○ Cannabis (1 prospective cohort study): THC 12.5 ± 1.5% herbal cannabis; median dose, 2.5 g; daily • **Administration methods:** Orally (16 RCTs; 1 prospective cohort), topical (2 RCTs); not reported (1 RCT; 4 prospective cohort) • **Comparator:** Placebo (18 RCTs); gabapentin (1 prospective cohort); no treatment (2 prospective cohort); usual care (2 prospective cohort) • **Treatment duration:** ○ RCT: 4-16 weeks ○ Prospective cohort studies: Not specified (study duration range (12-208 weeks) • Timeframe for follow-up ○ RCT: Not reported ○ Prospective cohort studies: 52 weeks (1 study)
Databases and sources searched	• **Number and names of databases:** 3: Ovid MEDLINE® (1946 to 21/01/22); EBM Reviews – Cochrane Central Register of Controlled Trials (inception- 03/01/22); APA PsycINFO (18–6 – second week of January 2022); Elsevier Embase (inception – 16/01/22); Elsevier Scopus (inception – 17/01/22) • **Other sources:** Posted request to Federal Register • **Grey literature:** Not reported

Parameter	Extraction items
	• **Reference chasing:** Yes • **Expert consultation:** Yes • **Dates:** Above • **Search limits:** English language • **Justifications for search limits:** Not reported • **Other searches:** Not reported • **Protocol prepared:** Yes • **If yes, published:** CRD42021229579 https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=229579 • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** No (completed by one review, verified by a second reviewer) • **If yes, rate of agreement:** Not reported • **Funding of review:** Agency for Healthcare Research and Quality (AHRQ), U.S Department of Health and Human Services under contract number 75Q80120D00006. • **Conflicts of interest of review:** The authors declared no conflict of interest. https://rmed.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M21-4520 • **How conflicts of interest were managed:** "The [Agency for Healthcare Research and Quality] did not directly participate in the literature search, determination of study eligibility criteria, data analysis, interpretation, or decision to submit this manuscript" p1145
Date Range (years) of included studies	• **Exact years for included studies:** 2005-2021

Parameter	Extraction items
Number of primary studies included in the systematic review	• **Number of studies:** 23 studies • **Number of studies by study design:** 18 RCTs; 5 prospective cohort studies • **Study years:** 2005 (1 RCT); 2006 (2 RCTs); 2007 (1 RCT); 2008 (1 RCT); 2010 (1 RCT); 2011 (1 prospective cohort); 2012 (2 RCTs); 2013 (1 RCT); 2014 (2 RCTs); 2015 (1 RCT, 1 prospective cohort); 2017 (2 RCTs); 2018 (1 prospective cohort); 2019 (1 prospective cohort); 2020 (2 RCTs); 2021 (2 RCT, 1 prospective cohort) • **Funding of included studies:** Not reported • **Conflicts of interest of included studies:** Not reported
Types of studies included	**Planned study designs to be included:** RCT and cohort studies **Reasons for including only RCTs/prospective cohort studies:** Not applicable **List of excluded studies at full text and reasons for exclusion:** Not reported
Appraisal instruments used	**Full name of tools used:** Two investigators independently assessed risk of bias for each study as low, moderate, or high using the Cochrane Back Pain Group's version of the Cochrane guidance for randomised trials and criteria developed by the U.S. Preventive Services Task Force for observational studies. **<u>Risk of bias criteria for AMSTAR 2 assessment, for RCTs record Yes/No for:</u>** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** No **<u>Risk of bias criteria for AMSTAR 2 assessment, for prospective cohort studies record Yes/No for:</u>**

Parameter	Extraction items
	• **Confounding:** Yes • **Selection bias:** Yes • **Exposure and outcomes:** Yes • **Selective reporting:** No
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The authors reported risk of bias for the included studies as follows: RCT (4 low risk, 10 moderate, 4 high); Cohort (3 moderate, 4 high). The authors use a modified Cochrane risk of bias tool which does not assess selective reporting. • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** o Overall: Low risk randomisation (8/18 RCT); low risk outcome ascertainment (10/18 RCT) *High THC-to-CBD ratio products (synthetic)* o Pain severity: Low risk randomisation (4/6 RCT); low risk outcome ascertainment (5/6 RCT) o ≥30% pain improvement: Low risk randomisation (1/1 RCT); low risk outcome ascertainment (1/1 RCT) o Overall function or disability: Low risk randomisation (2/2 RCT); low risk outcome ascertainment (2/2 RCT) *High THC-to-CBD ratio products (extracted)* o Pain severity: Low risk randomisation (2/2 RCT); low risk outcome ascertainment (2/2 RCT) o Overall function or disability: Low risk randomisation (1/1 RCT); low risk outcome ascertainment (1/1 RCT) *High THC-to-CBD ratio products (whole)* o Pain severity: Low risk randomisation (not reported); low risk outcome ascertainment (not reported) *Comparable THC-to-CBD ratio products* o Pain severity: Low risk randomisation (2/7 RCT); low risk outcome ascertainment (2/7 RCT) o ≥30% pain improvement: Low risk randomisation (1/4 RCT); low risk outcome ascertainment (1/4 RCT)

Parameter	Extraction items
	○ Overall function or disability: Low risk randomisation (1/6 RCT); low risk outcome ascertainment (1/6 RCT) *Low THC-to-CBD ratio products (CBD alone)* ○ Pain severity: Low risk randomisation (1/1 RCT); low risk outcome ascertainment (0/1 RCT) ○ ≥30% pain improvement: Low risk randomisation (1/1 RCT); low risk outcome ascertainment (0/1 RCT) *CBDV vs. placebo* ○ Pain severity: Low risk randomisation (1/1 RCT); low risk outcome ascertainment (1/1 RCT) ○ ≥30% pain improvement: Low risk randomisation (1/1 RCT); low risk outcome ascertainment (1/1 RCT) *Prospective cohort studies (cannabis products)* ○ Pain severity: Low risk randomisation (1/1 RCT); low risk outcome ascertainment (0/1 RCT) ○ Pain interference: Low risk randomisation (1/1 RCT); low risk outcome ascertainment (0/1 RCT) ○ Overall function or disability: Low risk randomisation (1/1 RCT); low risk outcome ascertainment (0/1 RCT) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** Not discussed • **Graphical or statistical test for publication bias:** Authors indicate yes (funnel plots and the Egger test), however results were not reported • **Authors' comments likelihood and magnitude of publication bias:** Not reported • **Authors' comment on how publication bias was dealt with:** Not reported • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** No • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** No
Method of analysis	• **Description of method of analysis as per authors: "**After examining clinical and methodological heterogeneity to determine the appropriateness of quantitative synthesis, we conducted meta-analyses using the profile likelihood

Parameter	Extraction items
	random-effects model. If topical products clearly were intended to have systemic effects, they were analyzed with oral and sublingual products but evaluated separately if intended to have local effects or if it was unclear if they were systemic. We analyzed studies according to the THC-to-CBD ratio category and source (synthetic vs. extracted). Heterogeneity was assessed using the I^2 statistic and the Cochran Q statistic x2 test (21). All meta-analyses were done using the metan and admetan commands in Stata/SE, version 16.1 (StataCorp). Sensitivity analyses were done by excluding studies rated as high risk of bias, excluding the trial of Namisol that was grouped with synthetic THC, and by repeating analyses using the Bartlett correction to the profile likelihood method to reduce potential deviation from the null distribution when the number of studies is small" p1144 • **Justification for narrative synthesis or meta-analysis:** Not applicable • **Justification for combining data in meta-analysis:** Above
Outcome assessed	**List of outcomes assessed and intended timeframes** • Primary outcomes: Pain severity, ≥30% pain improvement, overall function or disability, adverse events, withdrawal due to adverse events, serious adverse events • Secondary outcomes: Quality of life, mental health, sleep, and effect on opioid use • Intended timeframes: ≥ 4 weeks • Actual timeframes: 4-208 weeks
Results/findings	○ **Findings by outcome:** *High THC-to-CBD ratio products (synthetic)* ○ Pain severity: Pooled data from six RCTs (n=390) reported significant improvement in synthetic cannabinoid compared with placebo groups (MD -1.15, 95% CI -1.99 to -0.54).

Parameter	Extraction items
	○ ≥30% pain improvement: One RCT (n=26) reported significantly increased likelihood in cannabinoid compared with placebo groups (85% vs. 38%; RR 2.2, 95% CI 1.06 to 4.55). ○ Overall function or disability: Pooled data from two RCTs (n=40) reported no significant difference between cannabinoid and placebo groups (MD -0.35, 95% CI -1.90 to 0.94). One study (n= 13) reported that there was no difference in function between groups but did not provide data for the meta-analysis (no summary statistic reported). ○ Sedation (adverse event): Pooled data from three RCTs (n=335) reported significantly increased likelihood in cannabinoid compared with placebo groups (19% vs. 10%; RR 1.73, 95% CI 1.03 to 4.63). ○ Dizziness: Pooled data from two RCTs (n=302) reported significantly increased likelihood in dronabinol compared with placebo groups (32% vs. 11%; RR 2.74, 95% CI 1.47 to 6.86). ○ Nausea: Pooled data from two RCTs (n=302) reported no significant difference between dronabinol and placebo groups (RR 2.19, 95% CI 0.77-5.39). ○ Withdrawal due to adverse events: Pooled data from four RCTs (n=357) reported no significant difference between cannabinoid and placebo groups (RR 1.72, 95% CI 0.9 to 4.13). *High THC-to-CBD ratio products (extracted)* ○ Pain severity: Pooled data from two RCTs (n=294) reported no significant difference between high THC-CBD extracted products and placebo groups (MD -1.97, 95% CL -5.91 to 1.21). ○ Function/disability: One RCT (n=17) reported no significant difference between high THC-CBD extracted products and placebo groups (MD 1.75, 95% CI -0.46 to 3.98).

Parameter	Extraction items
	○ Quality of life: One RCT (n=17) reported significant improvement in high THC-CBD extracted products compared with placebo groups (Fibromyalgia Impact Questionnaire 1-100, MD 36.0; p= 0.005). However, these analyses were not adjusted for potentially important differences between groups in baseline scores. ○ Depression and anxiety: One RCT (n=17) reported no significant difference between high THC-CBD extracted products and placebo groups (no summary statistic reported). ○ Withdrawal due to adverse events: One study (n=277) reported significantly higher risk in high THC-CBD extracted products compared with placebo (RR 3.12, 95% CI 1.54 to 6.33). ○ Serious adverse events: One RCT (n=277) reported no significant difference between high THC-CBD extracted products and placebo groups (RR 2.19, 95% CI 0.58 to 8.28) ○ Dizziness adverse event: One RCT (n=277) reported significantly more withdrawals in high THC-CBD extracted product compared with and placebo groups (RR 8.34, 95% CI 4.53 to 15.34) *Comparable THC-to-CBD ratio products* ○ Pain severity: Pooled data from seven RCTs (n=702) reported significant improvements in cannabinoid compared with placebo groups (MD -0.54, 95% CI -0.95 to -0.19). ○ Overall function: Pooled data from six RCTs (n=616) reported significant improvement in cannabinoid compared with placebo groups (MD -0.42, 95% CI -0.73 to -0.16). ○ ≥30% improvement in pain: Pooled data from four RCTs (n=733) reported no significant difference between cannabinoids and placebo groups (RR 1.18, 95% CI 0.93 to 1.71). ○ Dizziness: Pooled data from six RCTs (n= 866) reported significantly increased likelihood in cannabinoid compared with placebo (30% vs. 8%, RR 3.57, 95% CI 2.42 to 5.60).

Parameter	Extraction items
	○ Sedation: Pooled data from six RCTs (n= 866) reported significantly increased likelihood in cannabinoid compared with placebo groups (8% vs. 1.2%; RR 5.04, 95% CI 2.10 to 11.89) ○ Nausea: Pooled data from six RCTs (n= 866) reported significantly increased likelihood in cannabinoid compared with placebo groups (13% vs. 7.5%, RR 1.79, 95% CI 1.19 to 2.77). ○ Withdrawal due to adverse events: Pooled data from four RCTs (n=834) reported no significant difference between cannabinoid and placebo groups (RR 1.14, 95% CI 0.65 to 3.02). ○ Sleep outcomes: Four RCTs reported significantly better sleep outcomes in the comparable THC to CBD ratio groups versus placebo groups (24, 27, 29, 30, 33). ○ Quality of life was not different between groups (number of RCTs and summary statistics not reported). Changes in depression and anxiety were not reported. *Low THC-to-CBD ratio products (CBD alone) and other cannabinoids* "In the short term, low THC-to-CBD ratio products (CBD topical and oral) had insufficient evidence to draw conclusions based on one 4-week, high risk of bias RCT (n= 29) of patients with neuropathic pain. A single moderate risk of bias RCT (n= 31) of a cannabinoid other than THC and CBD (cannabidivarin) was also insufficient to draw conclusions." *Prospective cohort studies (cannabis products)* ○ Pain intensity: One prospective cohort study (n=156) reported a significant improvement in cannabinoid compared with gabapentin groups (MD -5.8, 95% CI -10.18 to -1.42) but no significant difference between the cannabinoid group and the combined cannabinoid/gabapentin group (MD -5.1, 95% CI -11.48 to 1.28). One prospective cohort study (n=1514) reported no significant difference between cannabis and no treatment groups (Beta 0.37, 95% CI -

Parameter	Extraction items
	0.23 to 1.10), p=0.20). One prospective cohort study (n=46) reported no significant difference between cannabis and usual care groups (MD -14.71, 95% CI -32.71 to 3.29). ○ Pain interference: One prospective cohort study (n=156) reported no significant improvement in cannabinoid compared with gabapentin groups (MD -0.1, 95% CI -0.99 to 0.79) or between the cannabinoid group and the combined cannabinoid/gabapentin group (MD 0.00, 95% CI -0.88 to 0.88). One prospective cohort study (n=1514) reported no significant difference between cannabis and no treatment groups (Beta -0.63 95% CI -1.46 to 0.19, p=0.13). ○ Overall function: One prospective cohort study (n=156) reported no significant improvement in cannabinoid compared with gabapentin groups (MD 1.80, 95% CI -8.53 to 12.13) or between the cannabinoid group and the combined cannabinoid/gabapentin group (MD 4.60, 95% CI -5.83 to 15.03). One prospective cohort study (n=46) reported no significant difference between cannabis and usual care groups on 10 pain disability scale (MD -1.09, 95% CI -10.33 to 8.16) or the SF-36 function scale (MD 0.56, 95% CI -17.17 to 18.29). ○ Withdrawal due to adverse events: One prospective cohort study (n=156) reported no significant difference between cannabinoid and gabapentin groups (RR 0.44, 95% CI 0.17 to 1.16) or between the cannabinoid group and the combined cannabinoid/gabapentin group (RR 1.13, 95% CI 0.35 to 3.65). One prospective cohort study (n=431) reported increased prevalence in cannabis (4.65%) and usual care (not reported, assumed 0) groups. ○ Dizziness: One prospective cohort study (n=156) reported no significant difference between cannabinoid and gabapentin groups (RR 0.85, 95% CI 0.50 to 1.44) or between the cannabinoid group and the combined cannabinoid/gabapentin group (RR 0.99, 95% CI 0.57 to 1.73). One prospective cohort study (n=431) reported no significant difference between cannabis and usual care (RR 1.29, 95% CI 0.75 to 2.21).

Parameter	Extraction items

- Sedation: One prospective cohort study (n=156) reported significantly lower likelihood in cannabinoid compared with gabapentin groups (RR 0.58, 95% CI 0.37 to 0.91). One prospective cohort study (n=431) reported significantly increased frequency in cannabis compared with usual care groups (RR,2.91, 95% CI 1.46 to 5.83).
- Nausea: One prospective cohort study (n=431) reported significantly increased frequency in cannabis compared with usual care groups (RR, 1.72, 95% CI 1.04 to 2.85).
- Serious adverse events: One prospective cohort study (n=156) reported no significant difference between cannabinoid and gabapentin groups (RR 1.06, 95% CI 0.21 to 52.41). One prospective cohort study (n=431) reported significantly higher likelihood in cannabis compared with usual care (RR 2.39, 95% CI 1.20 to 4.80).
- Cognitive deficit: One prospective cohort study (n=431) reported no significant difference between groups (no summary statistic reported).

- **GRADE by outcome:**

Outcome	Studies	GRADE (Strength of Evidence)
Synthetic high THC-to-CBD vs Placebo		
≥30% pain improvement	1	Low
Pain severity	6	Low
Function/disability	2	Low
Withdrawal due to adverse events	4	Low
Serious adverse events	1	Insufficient
Dizziness	2	Moderate
Nausea	2	Low
Sedation	3	Low
Extracted high THC-to-CBD vs Placebo		
Pain severity	2	Insufficient
Function/disability	1	Insufficient
Withdrawal due to adverse events	1	Low
Serious adverse events	1	Insufficient
Dizziness	1	Low

Parameter	Extraction items

Whole plant high THC-to-CBD vs Placebo		
Pain severity	1	Insufficient
Withdrawal due to adverse events	1	Insufficient
Serious adverse events	1	Insufficient
Dizziness	1	Insufficient
Nausea	1	Insufficient
Sedation	1	Insufficient
Cognitive disorder	1	Insufficient
Comparable THC-to-CBD ratio vs. placebo		
≥30% pain improvement	4	Low
Pain severity	7	Moderate
Function/disability	6	Moderate
Withdrawal due to adverse events	5	Low
Serious adverse events	3	Low
Dizziness	6	Low
Nausea	6	Low
Sedation	6	Low
Low THC-to-CBD (topical) ratio vs. placebo		
Pain severity	1	Insufficient
Low THC-to-CBD (oral) ratio vs. placebo		
≥30% pain improvement	1	Insufficient
CBDV vs. placebo		
≥30% pain improvement	1	Insufficient
Pain severity	1	Insufficient

- **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):**

Outcome	No. studies (no. participants)	Summary estimate (95% CI)	P-value	I^2 (%)	Direction of effect
Synthetic high THC-to-CBD vs. placebo					
≥30% pain improvement	1 (26)	RR 2.20 (1.06 to 4.55)	NR	NA	No significant difference
Pain severity	6 (390)	MD -1.15 (-1.99 to -0.54)	0.084	48.5	Cannabinoid
Function/disability	2 (41)	MD -0.35(-1.90 to 0.94)	NR	72	No significant difference

Parameter	Extraction items					
	Withdrawal due to adverse events	4 (357)	RR 1.72 (0.90 to 4.13)	NR	0	No significant difference
	Serious adverse events	1 (240)	RR 1.60 (0.65 to 3.93)	NR	NA	No significant difference
	Dizziness	2 (302)	RR 2.74 (1.47 to 6.86)	NR	40	Cannabinoid
	Nausea	2 (302)	RR 2.19 (0.77 to 5.39)	NR	0	No significant difference
	Sedation	3 (335)	RR 1.73 (1.03 to 4.63)	NR	28	Cannabinoid
	Extracted high THC-to-CBD vs. placebo					
	Pain severity	2 (294)	MD -1.97 (-5.91 to 1.21)	NR	84.6	No significant difference
	Function/disability	1 (17)	MD 1.75 (-0.46 to 3.98)	NR	NA	No significant difference
	Withdrawal due to adverse events	1 (277)	RR 3.12 (1.54 to 6.33)	NR	NA	Cannabinoid
	Serious adverse events	1 (277)	RR 2.19 (0.58 to 8.28)	NR	NA	No significant difference
	Dizziness	1 (277)	RR 8.34 (4.53 to 15.34)	NR	NA	Cannabinoid
	Whole plant high THC-to-CBD vs. usual care					
	Pain severity	1 (431)	MD -1.10 (-1.56 to -0.72)	NR	NA	Cannabinoid
	Withdrawal due to adverse events	1 (431)	RR 21.10 (1.24 to 357.80)	NR	NA	Cannabinoid
	Serious adverse events	1 (431)	OR 0.64 (0.38 to 1.04)	NR	NA	No significant difference
	Dizziness	1 (431)	RR 1.29 (0.75 to 2.21)	NR	NA	No significant difference
	Nausea	1 (431)	RR 1.72 (1.04 to 2.85)	NR	NA	Cannabinoid
	Sedation	1 (431)	RR 2.91 (1.46 to 5.83)	NR	NA	Cannabinoid
	Cognitive disorder	1 (431)	RR 3.12 (1.54 to 6.33)	NR	NA	Cannabinoid
	Comparable THC-to-CBD ratio vs. placebo					
	≥30% pain improvement	4 (733)	RR, 1.18 (0.93 to 1.71)	NR	36	No significant difference
	Pain severity	7 (878)	MD -0.63 (-1.15 to -0.24)	NR	52	Cannabinoid
	Function/disability	6 (616)	MD -0.42, (-0.73 to -0.16)	0.193	32	Cannabinoid
	Withdrawal due to adverse events	5 (834)	RR 1.19 (0.60 to 3.72)	NR	54	No significant difference
	Serious adverse events	3 (866)	RR 1.18 (0.26 to 3.4)	NR	0	No significant difference
	Dizziness	6 (866)	RR 3.57 (2.42 to 5.60)	NR	0	Cannabinoid
	Nausea	6 (866)	RR 1.79 (1.19 to 2.77)	NR	0	Cannabinoid
	Sedation	6 (866)	RR 5.04 (2.10 to 11.89)	NR	0	Cannabinoid
	Low THC-to-CBD (topical) ratio vs. placebo					
	Pain severity	1 (29)	MD -0.75 (NR)	0.009	NA	Cannabinoid
	Low THC-to-CBD (oral) ratio vs. placebo					
	≥30% pain improvement	1 (136)	RR 1.01 (0.66 to 1.55)	NR	NA	No significant difference
	CBDV vs. placebo					
	≥30% pain improvement	1 (31)	RR 0.46 (0.24 to 0.91)	NR	NA	Cannabinoid
	Pain severity	1 (31)	MD 0.62 (-0.05 to 1.32)	NR	NA	No significant difference

Parameter	Extraction items
	○ **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Above ○ **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Yes ○ **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Yes **For prospective cohort studies:** Above ○ **Combined effect estimates adjusted for confounding, rather than combining raw data:** Not reported ○ **Justification for combining raw data provided, where adjusted effect estimates unavailable:** Not reported
Significance/direction	**See above if results listed by outcome:** Above
Heterogeneity	• **See above if I^2 available:** Above • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** **"**There was a high degree of heterogeneity in this combined estimate, making the finding insufficient to draw conclusions. Pain response (the proportion with ≥30% improvement in pain) was not reported." p1148 **'**Although both studies of extracted products with high THC-to-CBD ratios found statistically significant improvement in pain severity, the limitations of the individual studies, degree of heterogeneity, and marked imprecision due to limited evidence suggests that uncertainty remains about the exact magnitude and statistical significance of a possible treatment effect.' p1149 • **Causes of heterogeneity investigated:** Yes, I^2 calculated, random effects model, sensitivity analysis conducted
Comments	Characteristics of Vela *et al.* (2021) study is not outlined in table 2 in the appendices. This may account for discrepancies between participant numbers reported in table 2 p1146 and table 2 in appendices.

Parameter	Extraction items
	The protocol for the systematic review also covers a living systematic review published here: https://effectivehealthcare.ahrq.gov/products/plant-based-chronic-pain-treatment/living-review Conflicting results are reported in relation to 'cognitive deficit' outcomes. Publication text reports text reports 'Cognitive deficits were also reported, using 2 subsets each of the Wechsler Memory Scale and the Wechsler Adult Intelligence Scale, with a non-statistically significant difference between groups' on p1148. However, a supplementary table indicates a large effects in favour of the cannabis compared with usual care groups '13.9% vs. 5.7%; RR, 3.12 (CI, 1.54 to 6.33)'. Review of the original RCT article (Ware et al., 2016) indicated no significant difference between cannabis and usual care groups. This article indicates improvement in cannabis and control groups in follow-up compared with baseline which may explain the large effect stated in text. As per umbrella review criteria we are primarily interested in cannabis compared with a control group, we have reported no significant difference between groups in the main report.

McKee *et al.* (2021): Potential therapeutic benefits of cannabinoid products in adult psychiatric disorders: A systematic review and meta-analysis of randomised controlled trials

Parameter	Extraction items
First author and year of publication	McKee *et al.* (2021)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "The aim of this systematic review and meta-analyses is to not only offer the most recent examination of the literature in this area, but as well approach the clinical indications for [cannabinoid-based products] in mental health from the lens of a health regulatory board; to review high-level evidence in a systematic review/meta-analyses process." p268

Parameter	Extraction items
	• **Exact review question and page number:** "The aim of this systematic review and meta-analyses is to not only offer the most recent examination of the literature in this area, but as well approach the clinical indications for [cannabinoid-based products] in mental health from the lens of a health regulatory board; to review high-level evidence in a systematic review/meta-analyses process." p268 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** Adults with a primary diagnosis of a psychiatric disorder, defined by recognised diagnostic criteria ➢ **Setting:** Not specified ➢ **Intervention:** "A single, or repeated administration of a cannabinoid or [cannabinoid-based products]" p268 ➢ **Comparison:** Placebo or active comparator ➢ **Outcome: "**Primary outcome measures: reduction (i.e., change from baseline) in symptom frequency, or severity. Secondary outcome measures: changes related to quality of life, adherence to treatment regime, length of remission intervals, global impression of change" p268
Participants (characteristics and numbers)	**For whole sample and subgroups:** n=993 (cannabinoid RCTs); n=2281 (rimonabant RCTs) The RCTs assessing rimonabant have been excluded from the remainder of the extraction. • **Number of participants:** N=993 • **Age:** Not reported • **Gender:** Not reported • **Details of clinical diagnosis/indications:** Attention deficit hyperactivity disorder (n=30); anorexia nervosa (n=48); anxiety (n=54); cannabis use disorder (n=483); obsessive compulsive disorder (n=12); opioid use disorder (n=120); schizophrenia (n=176); post-traumatic stress disorder (n=10); tobacco use disorder (n=24); Tourette's syndrome (n=36)

Parameter	Extraction items
Setting/context	**Countries (alphabetic order):** Not reported **Setting (university, public or private clinic):** Not reported **Other relevant features of setting:** Not reported

Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** "Treatment was defined as single, or repeated administration of a cannabinoid or [cannabinoid-based products] with the intention of reducing one, or more, psychiatric symptoms. All routes of cannabinoid administration were considered for inclusion." p268
	• **Dose and regimen:**
	  ○ Nabiximols (5 RCTs): Range 37.8 mg THC + 35 mg CBD - 113.4 mg THC + 105 mg CBD; not reported
	  ○ Dronabinol (10 RCTs): Range 2.5 mg-240 mg; not reported, two-three times daily
	  ○ Cannabidiol (7 RCTs): Range 400 mg -1000 mg, 400 µg CBD dissolved in absolute ethanol; not reported
	  ○ Nabilone (3 RCTs): 2-3 mg; 1 mg three times daily, 2 mg daily, not reported
	  ○ Cannabis (THC/CBD) (1 RCT): 0.4% THC/10.4% CBD, not reported
	  ○ Epidiolex (1 RCT): 400 mg or 800 mg; three times daily
	  ○ Delta-9-THC (1 RCT): 2.5-5 mg; not reported
	• **Administration methods:** Spray (5 RCTs); orally (19 RCTs); not reported (2 RCTs); inhalation (1 RCT); intravenous (1 RCT)
	• **Comparator:** Placebo (25 RCTs); amisulpride (1 RCT); motivational enhancement/cognitive behavioural therapy (1 RCT); not reported (1 RCT)
	• **Treatment duration:** Not specified (actual duration 1-16 weeks)
	• **Timeframe for follow-up:** One RCT reported a 28 day follow up, follow-up was not reported for the other RCTs

Parameter	Extraction items
Databases and sources searched	• **Number and names of databases:** 10; Academic Search Premier, PubMed, Ovid MEDLINE, Web of Science, PsycARTICLES, PsycINFO, CINAHL (Nursing and Allied Health), Scopus, the Cochrane Library, Joanna Briggs Institute; inception-09/2020 • **Other sources:** No • **Grey literature:** No • **Reference chasing:** Yes • **Expert consultation:** No • **Dates:** Inception-09/2020 • **Search limits:** No • **Justifications for search limits:** Not applicable • **Other searches:** Not applicable • **Protocol prepared:** No • **If yes, published:** Not applicable • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** No • **If yes, rate of agreement:** Not applicable • **Funding of review:** Not reported • **Conflicts of interest of review:** "RWL has received honoraria for ad hoc speaking or advising/ consulting, or research funds, from Allergan, Asia-Pacific Economic Cooperation, BC Leading Edge Foundation, Canadian Network for Mood and Anxiety Treatments, Healthy Minds Canada, Janssen, Lundbeck, Lundbeck Institute, Michael Smith Foundation for Health Research, MITACS, Myriad Neuroscience, Ontario Brain Institute, Otsuka, Pfizer, Unity Health, and VGH Foundation. JHM

Parameter	Extraction items
	reports grants from Sanofi, and Janssen. KJA has received honoraria for ad hoc speaking or advising/ consulting, or research funds from Alberta Children's Hospital Foundation, Alberta Innovates, Canada-American Foundation for Addiction Research, Canada Foundation for Innovation, Janssen Inc., Lundbeck Canada, Mental Health Centre - Beyond the Capital Scope Research Program, Otsuka Canada Pharmaceuticals Inc., and non-financial support from HLS Therapeutics. She serves as a member of the AMH Research Hub, Alberta Cannabis Research and Innovation Network, Cannabis Scientific Research Group, Campus Alberta Neuroscience Advisory Committee, Clinical Pharmacogenetics Implementation Consortium (CPIC), Neuroscience and Mental Health Institute Operations Committee, Pharmacogene Variation Consortium, Schizophrenia Society of Alberta, and is a Board Member for the Canadian Consortium for Early Intervention in Psychosis. She is a co-author of Haplotype Translators for CYP2D6 & CYP2C19. PGT reports grants, personal fees and is an advisory board member for Janssen Inc. Reports personal fees and is an advisory board member for Otsuka Lundbeck alliance. All remaining authors have no disclosures or conflicts of interest to report." p279 • **How conflicts of interest were managed:** Not specified
Date Range (years) of included studies	• **Exact years for included studies:** 1981-2020
Number of primary studies included in the systematic review	• **Number of studies:** 28 RCTs • **Number of studies by study design:** 28 RCTs • **Study years:** 2020 (2 RCTs); 2019 (2 RCTs); 2018 (4 RCTs); 2017 (2 RCTs); 2016 (2 RCTs); 2015 (4 RCTs); 2014 (2 RCTs); 2013 (2 RCTs); 2012 (1 RCT); 2011 (3 RCTs); 2005 (1 RCT); 2003 (1 RCT); 2002 (1 RCT); 1981 (1 RCT) • **Funding of included studies:** Not reported • **Conflicts of interest of included studies:** Not reported
Types of studies included	**Planned study designs to be included:** RCT

Parameter	Extraction items
	Reasons for including only RCTs/prospective cohort studies: Not reported **List of excluded studies at full text and reasons for exclusion:** Not reported
Appraisal instruments used	**Full name of tools used:** "Cochrane collaboration revised guidelines (Higgins *et al.* 2016)" p269 **PARALLEL RCTS** **<u>Risk of bias criteria for AMSTAR 2 assessment, for RCTs record Yes/No for:</u>** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes **CROSSOVER RCTS** **<u>Risk of bias criteria for AMSTAR 2 assessment, for RCTs record Yes/No for:</u>** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence allocation (individual vs group randomisation):** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** High risk of bias (5 RCTs), unclear risk of bias (12) and low risk of bias (11 RCTs) • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:**

Parameter	Extraction items
	Overall ○ Parallel RCTs: Low risk randomisation (10/15); low risk outcome ascertainment was not explicitly reported data extracted under 'measurement of the outcome' domain (9/15) ○ Crossover RCTs: Low risk randomisation (6/13); low risk outcome ascertainment was not explicitly reported data extracted under 'blinding' domain (6/13) *THC vs placebo* ○ Anxiety symptoms: Low risk randomisation (0/1); low risk outcome ascertainment (0/1) ○ PTSD related nightmares: Low risk randomisation (0/1); low risk outcome ascertainment (0/1) ○ Positive, negative and cognitive symptoms of schizophrenia: Low risk randomisation (0/1); low risk outcome ascertainment (0/1) ○ Body weight anorexia nervosa: Low risk randomisation (1/1); low risk outcome ascertainment (1/1) ○ Tourette disorder tic severity: Low risk randomisation (2/2); low risk outcome ascertainment (1/2) ○ Opioid use disorder withdrawal symptoms: Low risk randomisation (1/2); low risk outcome ascertainment (1/2) ○ Cannabis use disorder reduction in cannabis use/craving: Low risk randomisation (0/2); low risk outcome ascertainment (1/2) ○ Cannabis use disorder withdrawal discomfort: Low risk randomisation (0/2); low risk outcome ascertainment (0/2) *THC (dronabinol, nabilone) and motivational enhance/relapse prevention therapy vs motivational enhance/relapse prevention therapy* ○ Cannabis use disorder cannabis consumed/abstinence/treatment retention: Low risk randomisation (1/1); low risk outcome ascertainment (1/1) ○ Cannabis use disorder withdrawal discomfort: Low risk randomisation (0/2); low risk outcome ascertainment (0/2) *CBD vs placebo*

Parameter	Extraction items
	○ Social anxiety: Low risk randomisation (1/2); low risk outcome ascertainment (0/2) ○ Positive and negative symptoms scale (PANSS): Low risk randomisation (2/2); low risk outcome ascertainment (1/2) ○ Cognitive function: Low risk randomisation (1/1); low risk outcome ascertainment (0/1) ○ Tobacco use disorder reduction in tobacco use/craving: Low risk randomisation (0/1); low risk outcome ascertainment (0/1) ○ Opioid use disorder craving: Low risk randomisation (1/1); low risk outcome ascertainment (1/1) *CBD vs amisulpride* ○ Positive and negative symptoms scale (PANSS): Low risk randomisation (1/1); low risk outcome ascertainment (1/1) *THC/CBD vs placebo* ○ ADHD cognitive performance/activity level: Low risk randomisation (1/1); low risk outcome ascertainment (1/1) ○ Cannabis use disorder withdrawal discomfort: Low risk randomisation (4/4); low risk outcome ascertainment (3/3) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** Overall, the evidence base for the use of cannabinoids to treat psychiatric disorders was assessed as moderate-to low-quality, and below that required to meet Level-1 evidence." p278 • **Graphical or statistical test for publication bias:** No • **Authors' comments likelihood and magnitude of publication bias:** Not reported • **Authors' comment on how publication bias was dealt with:** Not reported • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** Not applicable • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** "Overall,

Parameter	Extraction items
	the evidence base for the use of cannabinoids to treat psychiatric disorders was assessed as moderate-to low-quality, and below that required to meet Level-1 evidence." p278
Method of analysis	• **Description of method of analysis as per authors:** "Where sufficient data allowed, studies evaluating the same cannabinoid-based intervention for the same psychiatric disorder (using statistically comparable outcome measures) were pooled and evaluated using meta-analysis. Continuous data were extracted as means and standard deviations (SDs) (where necessary, Results reporting Standard Error [SE] were converted to SD). Pooled results for each disorder of interest were compared using a random-effects model. Heterogeneity between studies was assessed using the χ^2 test and I^2 statistic. If data were missing, attempts were made to contact study authors. With the aim of providing clinically relevant information concerning the effectiveness of specific CBPs, study authors did not feel it was appropriate to pool studies trialling dissimilar cannabinoids for the purpose of meta- analysis" p269 • **Justification for narrative synthesis or meta-analysis:** "For brevity, detailed statistics will only be reported for outcomes where the [cannabinoid-based products] in question was found to be more efficacious than the included control condition. Otherwise, comparisons will be discussed narratively. Importantly, due to incomplete reporting of outcome data in addition to the wide variety of study outcomes and statistical approaches encountered, the majority of studies captured in this review could not be meaningfully compared quantitively, and therefore, were synthesized narratively. As highlighted by Higgins *et al.* the assumption of the random-effects model is violated when there are differences in core study characteristics." p269 • **Justification for combining data in meta-analysis:** Above
Outcome assessed	**List of outcomes assessed and intended time frames:** • Primary outcomes: Change in symptom frequency or severity for attention deficit hyperactivity disorder; anorexia nervosa; anxiety; cannabis use disorder; obsessive compulsive disorder; opioid use disorder; schizophrenia; post-traumatic stress disorder; tobacco use disorder; Tourette's syndrome

Parameter	Extraction items
	• Secondary outcomes: None • Intended timeframes: Not specified • Actual timeframes: 3 days to 16 weeks
Results/findings	• **Findings by outcome:** *Narrative synthesis* ○ Anxiety: Three studies (n=54) reported significant improvements in the cannabinoid (2 studies CBD, 1 study nabilone) group compared with the placebo group (<0.001; p=0.002; p<0.001). ○ Post-traumatic stress disorder: One study (n=10) reported 3.6 ± 2.4 and -1.0 ± 2.1 (CAPS Recurring and Distressing Dream scores) respectively in the nabilone and placebo groups, indicating a significant reduction in severity with nabilone treatment compared with placebo (p=0.03). Significant improvements in general well-being and mean global improvements were reported in the nabilone group compared with the placebo group (no summary statistics reported). ○ Schizophrenia: One study (n=36) reported no significant improvement in cognition or positive/negative psychotic symptomology in CBD compared with placebo groups (no summary statistic reported). One study (n=88) reported significant improvement in positive/negative psychotic symptomology (treatment difference -1.4, 95% CI -2.5 to -0.2) in the CBD group compared with placebo. However, there was no clinically significant improvement differences between groups (≥20% improvement) (no summary statistic reported). One study (n=39) reported comparable clinically significant improvement on positive/negative psychotic symptomology and the brief psychiatric rating scale between CBD and active comparator groups (amisulpride) (no summary statistic reported). One study (n=13) reported short-term worsening of the positive, negative and cognitive symptoms of schizophrenia with administration of THC, compared with placebo and with the observed effects in healthy controls.

Parameter	Extraction items
	○ Anorexia nervosa: One RCT (n=24) reported significant increase in body weight (0.7 ± 1.4 kg) in dronabinol compared with placebo groups (p=0.03). A separate RCT with the same sample of participants (n=24) examined levels of physical activity but results were not reported in the review for this RCT. ○ Cannabis use disorder: Note: One study (Freeman et al, 2020) is listed in the table of characteristics, which examined abstinence from cannabis and RHC-COOH:creatinine ratio. However, McKee et al present no results from this study. Withdrawal symptoms/discomfort: Pooled findings from four studies (n=186) reported no significant difference in withdrawal symptoms between nabiximols and placebo (SMD -0.21 (-0.52 to 0.11), p=0.2). One of these studies (n=51) reported significantly improved withdrawal symptoms (and treatment retention) in nabiximols compared with placebo groups. However, the observed maintenance effects were not observed beyond three days after cessation of treatment. Pooled findings from two studies (n=52) reported significant improvement in withdrawal symptoms with dronabinol compared to placebo (SMD -1.28 (-1.89 to -0.67), p<0.0001). An additional study (n=156) reported improved withdrawal symptoms in dronabinol compared with placebo group (p=0.02) in combination with motivational enhancement and relapse prevention therapy. Cravings: Two studies (n=56) reported no significant difference in cravings between nabiximol and placebo groups. Treatment retention/abstinence: One study (n=156) found no significant difference in abstinence achievement of two weeks between dronabinol and placebo groups (dronabinol: 17.7%; placebo 15.6%) in combination with motivational enhancement and relapse prevention therapy. However, the same study reported improved treatment retention at week eight with dronabinol compared with placebo (77% vs 61%, p=0.02).

Parameter	Extraction items
	Maintenance (reduction in use and reduction in cravings): Three RCTs (n=40) reported that dronabinol produced positive maintenance effects compared with placebo (no summary statistics provided). Mixed findings for nabiximols were observed in three studies. One RCT (n=40) reported no significant difference in abstinence rates between nabiximols and placebo. One RCT (n=16) reported no significant difference in treatment retention between nabiximols and placebo (in combination with cognitive behavioural therapy). One RCT (n=51) reported significantly improved treatment retention in nabiximols compared with placebo groups. However, the observed maintenance effects were not observed beyond three days after cessation of treatment. Cannabis consumption (amounts): One study (n=128) reported significantly lower cannabis use in nabiximol group compared with placebo group in combination with motivational enhancement/cognitive behavioural therapy. One study (n=18) reported no significant difference in self-reported cannabis use between nabilone and placebo groups. One RCT (n=156) found no significant difference in the amount of cannabis consumed between dronabinol and placebo groups receiving treatment in combination with motivational enhancement and relapse prevention therapy. ○ Opioid use disorder: One study reported (n=60) reported improvement in withdrawal symptoms in dronabinol compared with placebo but no improvements in treatment retention. One study (n=18) reported weak (and short-lived) opioid withdrawal suppression in the dronabinol group compared with the placebo group. One study (n=42) reported significantly fewer anxiety (F=5.15, df=2, 78, p=0.0079) and craving responses (F=5.74, df=2, 78, p=0.0047) to drug cues, compared with exposure to a neutral cue in Epidiolex group compared with placebo group.

Parameter	Extraction items
	○ Tobacco use disorder: One study (n=24) reported significant reduction in cigarettes smoked by 40% during the one-week treatment period (p=0.002) in the CBD group compared with the placebo group; with a non-significant trend suggesting continued partial reduction in cigarette use at 14-day follow-up. Nicotine craving in both groups significantly fell during the treatment phase but was not maintained at follow-up. ○ Attention-Deficit/Hyperactivity Disorder: One study (n=30) reported no significant differences on cognitive performance and activity levels between nabiximol and placebo groups. ○ Tourette's disorder: One study (n=12) reported dronabinol was effective in treating global tic scores (p=0.026). One study (n=24) reported significant improvements in tic frequency and severity in dronabinol group compared with the placebo group (p<0.05) on ten treatment days. ○ Obsessive-compulsive disorder: One study (n=12) reported no significant effect of high-THC or high-CBD variants of cannabis on symptomatology. Participants administered the placebo had lower anxiety scores 20 minutes after smoking cannabis than participants administered high-THC cannabis (p=0.002) and high-CBD cannabis (p=0.039). *Meta analysis* ○ Withdrawal symptoms (opioid use disorder): Pooled analysis from two studies (n=81) reported no significant difference between dronabinol and placebo groups (SMD -0.18, 95% CI -1.12 to 0.76). ○ Withdrawal symptoms (cannabis use disorder): Pooled analysis from two studies (n=52) reported significantly lower withdrawal symptoms in dronabinol compared with placebo groups (SMD -1.28, 95% CI -1.89 to -0.67). ○ Withdrawal symptoms (cannabis use disorder): Pooled analysis from four studies (n=186) reported no significant difference between nabiximols and control groups (3 placebo controlled; 1 motivational enhancement/cognitive behavioural therapy controlled) (SMD -0.21, 95% CI -0.52 to 0.11). • **GRADE by outcome:** Not reported

<table>
<tr><th>Parameter</th><th>Extraction items</th></tr>
<tr><td></td><td>

Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects): Random effects model

<table>
<tr><th>Outcome</th><th>No. studies (No. participants)</th><th>Summary estimate (95% CI)</th><th>P-value</th><th>I^2 (%)</th><th>Direction of effect</th></tr>
<tr><td colspan="6">THC (dronabinol) vs placebo</td></tr>
<tr><td>Withdrawal symptoms opioid use disorder</td><td>2 (81)</td><td>SMD -0.18 (-1.12 to 0.76)</td><td>0.71</td><td>69</td><td>No significant difference</td></tr>
<tr><td>Withdrawal symptoms cannabis use disorder</td><td>2 (52)</td><td>SMD -1.28 (-1.89 to -0.67)</td><td><0.0001</td><td>0</td><td>Dronabinol</td></tr>
<tr><td colspan="6">Nabiximols vs placebo</td></tr>
<tr><td>Withdrawal symptoms cannabis use disorder</td><td>4 (186)</td><td>SMD -0.21 (-0.52 to 0.11)</td><td>0.2</td><td>0</td><td>No significant difference</td></tr>
</table>

Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available: Above
Appropriate weighted technique used, adjusted for heterogeneity where necessary: Yes
Separate summaries reported for RCTs and prospective cohort studies when included in the same review: Not applicable

</td></tr>
<tr><td>Significance/direction</td><td>See above if results listed by outcome: Above</td></tr>
<tr><td>Heterogeneity</td><td>

See above if I^2 available: Above
Authors' comment on potential impact of heterogeneity on results and quality of evidence: Not reported for narrative synthesis. No significant heterogeneity in meta-analyses.
Causes of heterogeneity investigated: Not discussed in relation to narrative synthesis or meta-analysis.

</td></tr>
<tr><td>Comments</td><td></td></tr>
</table>

McParland *et al.* (2023): Evaluating the impact of cannabinoids on sleep health and pain in patients with chronic neuropathic pain: a systematic review and meta-analysis of randomized controlled trials

Parameter	Extraction items
First author and year of publication	McParland *et al.* (2023)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "The objectives of this systematic review and meta-analysis were to determine the effect of cannabinoids on sleep quality, pain intensity, and patient impression of treatment efficacy in patients with neuropathic pain." p1 • **Exact review question and page number:** "to evaluate the impact of therapeutic cannabinoids on sleep quality, analgesic efficacy, and adverse effects in patients with neuropathic pain syndromes." p2 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** "human subjects over the age 18 years with central or peripheral neuropathic pain for at least 3 months" p2 ➢ **Setting:** Not specified ➢ **Intervention:** "synthetic and natural cannabinoids for a neuropathic pain state through both inhaled and oral routes" p2 ➢ **Comparison:** Placebo ➢ **Outcome:** Primary outcomes included sleep health (patient reported sleep quality and daytime somnolence). Secondary outcomes included pain intensity, patient global impression of change, the Euro-Quol 5-D index for quality of life, and common adverse effects of cannabinoids.
Participants (characteristics and numbers)	**For whole sample and subgroups:** N=10,000 *The non-randomised studies of interventions are excluded from the remainder of the extraction. • **Number of participants:** N=1011 (extracted from table 1) • **Age:** Mean 51.1 years

Parameter	Extraction items
	• **Gender:** 62.2% female (gender data could not be extracted from three studies: n=22, n=125, n=26) • **Details of clinical diagnosis/indications:** Multiple sclerosis (n=429); brachial plexus chronic neuropathic pain (n=48); any neuropathic pain (n=125); any peripheral neuropathic pain (n=246); diabetic peripheral neuropathy (n=26); post-traumatic or post-operative neuropathic pain (n=22)
Setting/context	**Countries (alphabetic order):** Canada (2 RCTs); Netherlands (1 RCT); UK (3 RCTs); UK, Czech Republic, Romania, Belgium, Canada (1 RCT); UK, Czech Republic, Canada, Spain, France (1 RCT) **Setting (university, public or private clinic):** Not specified **Other relevant features of setting:** Not specified

Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** "synthetic and natural cannabinoids for a neuropathic pain state through both inhaled and oral routes" p2
	• **Dose and regimen:**
	  ○ THC:CBD (5 RCTs): THC dose range 1–130mg, CBD dosage range 2.5–120mg; daily; max of 48 sprays per day
	  ○ Nabilone (1 RCT): 1-4 mg; daily
	  ○ THC inhaled (1 RCT): 25mg of 2.5%, 6%, and 9.4% THC; three times daily
	  ○ THC tablet (1 RCT): 16 mg; daily
	• **Administration methods:** Oromucosal spray (5 RCTs); Inhaled (1 RCT); oral (2 RCTs)
	• **Comparator:** Placebo (8 RCTs)
	• **Treatment duration:** Study duration 2-15 weeks
	• **Timeframe for follow-up:** Not reported for included studies

Parameter	Extraction items
Databases and sources searched	• **Number and names of databases:** Medline, Medline in-process/ epubs, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and Scopus (Elsevier) and PubMed (NLM); 1995-26/03/2021 • **Other sources:** Biosys Previews; Web of Science (Clarivate Analytics); ClinicalTrials.Gov (NIH); WHO ICTRP • **Grey literature:** "we reviewed eligible reports, prior systematic reviews for corroboration of search, professional international guidelines, and leading experts in the field for possible gaps in our search." P2 • **Reference chasing:** No • **Expert consultation:** Yes (medical Information Specialist) • **Dates:** 1995-26/03/2021 • **Search limits:** English; human subjects only; • **Justifications for search limits:** "This date range was chosen due to a paucity of literature on the topic prior to 1995." P2 • **Other searches:** Not reported • **Protocol prepared:** Yes • **If yes, published:** CRD42017074255 https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=74255 • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Funding of review:** "Departmental funds were used for the conducted for this study. MS, AB, RB, and HC are supported by the Merit Awards program of Department of Anesthesia and Pain Medicine, University of Toronto. MS is also supported by the Canadian Anesthesiologists' Society Career Scientist Award. CD is supported by the Clinician Investigator Program, Department of Anesthesia and Pain Medicine, University of Toronto." P11

Parameter	Extraction items
	• **Conflicts of interest of review:** The authors declared no conflict of interest • **How conflicts of interest were managed:** Not applicable
Date Range (years) of included studies	• **Exact years for included studies:** 2004-2017
Number of primary studies included in the systematic review	• **Number of studies:** 8 RCTs • **Number of studies by study design:** RCT • **Study years:** 2004 (1 RCT); 2005 (1 RCT); 2007 (1 RCT); 2010 (1 RCT); 2012 (1 RCT); 2013 (1 RCT); 2014 (1 RCT); 2017 (1 RCT) • **Funding of included studies:** GW Pharma (5 RCTs); Echo pharmaceuticals (1 RCT); Valeant Canada (1 RCT); Canadian Institutes of Health Research (1 RCT) • **Conflicts of interest of included studies:** Not reported
Types of studies included	**Planned study designs to be included:** RCT **Reasons for including only RCTs/prospective cohort studies:** Not reported **List of excluded studies at full text and reasons for exclusion:** Yes (supplemental material)
Appraisal instruments used	**Full name of tools used:** Cochrane Risk of Bias Assessment Instrument RoB 2; GRADE system **<u>Risk of bias criteria for AMSTAR 2 assessment, for RCTs, record Yes/No for:</u>** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence allocation (individual vs group randomisation):** Yes • **Selective reporting:** Yes

Parameter	Extraction items
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The authors reported included trials appeared to have a low risk of bias (8 RCTs) • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** o Overall: Low risk randomisation (8/8); low risk outcome ascertainment (8/8) o Sleep quality: Low risk randomisation (6/6); low risk outcomes ascertainment (6/6) o Daytime somnolence: Low risk randomisation (7/7); low risk outcomes ascertainment (7/7) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** "given the substantial sample sizes, absence of clear methodological sources of bias, and analysis of small-study effects risk, the overall risk of bias was not considered to be serious. All studies ranged from moderate to high certainty of evidence (table 4)" p7-8 • **Graphical or statistical test for publication bias:** "Small-study effects were investigated based on the criterion of an LFK index value of +1, between +1and +2, and >+2 (indicating no, minor and major asymmetry, respectively). Further analysis was pursued using the Hartung-Knapp-Sidik Jonkman methodology. Standard visualizations (forest plots and funnel plots) are included as well as doi plots/LFK indices (online supplemental table 3, online supplemental figure 3) to assess small study effects, as advocated by Furuya-Kanamori *et al.* and implemented in the metasens package" p3 • **Authors' comments likelihood and magnitude of publication bias:** "Based on the criterion of an LFK index value of +1, between+1and +2, and >+2, which describe no asymmetry, minor asymmetry and major asymmetry, respectively, five out of seven outcomes failed (sleep quality, pain NRS, nausea, PGIC and EQ-5D), which warranted the use of the Hartung-Knapp-Sidik-Jonkman methodology (online supplemental table 3). The doi plot and LFK index sign (+ or −) are representative of small study effects and publication bias. For example, for the outcome EQ-5D, the doi plot was skewed to the left, with an LFK index of 3.11, this indicated the possibility of publication bias to a large effect seen due to one study showing a very large effect, thereby resulting in a higher chance to get published. There may have been studies

Parameter	Extraction items
	with smaller sample sizes or effect sizes that were not published, and, hence, could not be included in the systematic review. Similarly, the doi plot for outcome nausea was skewed to the right, with an LFK index of −2.82, indicating publication of results with relatively fewer patients reporting nausea as a side effect, and, hence, a higher likelihood of getting published." P7 • **Authors' comment on how publication bias was dealt with:** Above • **Only low ROB RCTs included in review:** Yes • **Only low ROB RCTs included in meta-analysis:** Yes • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** Not applicable
Method of analysis	• **Description of method of analysis as per authors:** "Primary meta-analyses were performed using the random effects model. For continuous outcomes, standardized mean difference (SMD) and 95% Cis were computed. For binary outcomes, Ors with 95%CI were computed. SMD and OR were utilized due to variability with reported sleep and pain scores throughout the manuscript.9 Previously established thresholds for the I^2 were used (between 0% and 40%: might not be important; 30% and 60%: may represent moderate inconsistency; 50% and 90%: may represent substantial inconsistency; 75% and 100%: considerable inconsistency). We performed leave-one-out sensitivity analyses for each meta-analysis and meta-regression to assess for influential studies. All analyses were performed using R-4.1.2. using the metafor package and are interpreted using α=0.05 as the threshold for statistical significance. For all outcomes (except [patient global impression of change] due to reduced number of studies) we fit multilevel random effects meta-analyses/meta-regressions via restricted maximum likelihood estimation, using the rma.mv function. The Hartung-Knapp-Sidik-Jonkman adjustment for small study effects was then applied to the resulting estimates following the procedure detailed by IntHout *et al.* The [patient global impression of change] outcome did not include any studies with

Parameter	Extraction items
	multiple treatment arms; therefore, random effects meta-analyses/meta-regressions were fit using the rma.uni function via the Sidik-Jonkman estimator and adjusted using the in-built HKSJcorrection option. For each outcome, the overall meta-analysis was reported as an aggregate treatment effect based on the Ors or SMDs (Hedge's G) extracted from each study (table 2). We report a 95% CI for the estimate and a p value against a null treatment effect. Furthermore, we report a 95% prediction interval (PI) for the true treatment effect from a hypothetical future study, as recommended by IntHout *et al.* Standard visualizations (forest plots and funnel plots) are included as well as doi plots andLuis Furuya-Kanamori (LFK) indices (online supplemental table 3) to assess small study effects, as advocated by Furuya-Kanamori *et al.* and implemented in the metasens package. Inconsistency is quantified using Cochran's Q, τ 2 and I^2 (online supplemental tables 1 and 2). Subgroup analyses were conducted for covariates that were determined to have a significant moderator effect in the meta regression models, namely, treatment dose (high vs low dose), presence of CBD (CBD vs no CBD) and risk of bias (high risk vs low risk) (table 3)." P3 • **Justification for narrative synthesis or meta-analysis:** Not reported • **Justification for combining data in meta-analysis:** Not reported
Outcome assessed	**List of outcomes assessed and intended timeframes** • Primary outcomes: Sleep quality; daytime somnolence • Secondary outcomes: Pain scores; EuroQol 5-D quality of life; patient global impression of change; adverse events • Intended timeframes: Not specified • Actual timeframes: 2-15 weeks
Results/findings	• **Findings by outcome:**

Parameter	Extraction items
	Primary outcomes meta-analysis ○ Sleep quality: Pooled data from six studies (n=744) reported significant improvement in cannabinoid compared with placebo groups (SMD 0.40, 95% CI 0.19 to 0.61). ○ Daytime somnolence: Pooled data from seven studies (n=867) reported significantly higher likelihood in cannabinoid compared with placebo groups (SMD 2.23, 95% CI 1.32 to 3.74). *Secondary outcomes meta-analysis* ○ Pain score: Pooled data from eight studies (n=893) reported significant improvement in cannabinoid compared with placebo groups (SMD -0.55, 95% CI -0.69 to -0.19). ○ Patient global impression of change: Pooled data from six studies (n=800) reported significantly higher likelihood of improved scores in cannabinoid compare with placebo groups (OR 4.20, 95% CI 1.37 to 12.87). ○ EuroQol 5-D quality of life: Pooled data from four studies (n=632) reported no significant difference between cannabinoid and placebo groups (SMD 0.22, 95% CI -0.25 to 0.68). ○ Nausea adverse event: Pooled data from seven studies (n=867) reported significantly higher likelihood in cannabinoid compared with placebo groups (OR 1.66, 95% CI 1.22 to 2.27). ○ Dizziness adverse event: Pooled data from seven studies (n=867) reported significantly higher likelihood in cannabinoid compared with placebo groups (OR 3.80, 95% CI 2.52 to 5.73). *Meta-regression* ○ There is statistical evidence that the high-dosage treatment groups had a greater improvement in sleep quality relative to controls, when compared with low-dosage treatment groups (SMD 0.37, 95% CI 0.03 to 0.71, p=0.038). ○ Studies with a high risk of bias had a statistically significant reduction in the incidence of nausea (OR 0.18, 95% CI 0.1 to 0.33, p<0.001). *Sensitivity analysis*

Parameter	Extraction items

- In total, 149/153 (97.4%) of the sensitivity analyses were consistent with the primary meta-analysis and meta-regression findings (i.e. fell within the 95% CI). In each of the four sensitivity analyses not consistent with primary meta-analysis and meta-regression findings, the sensitivity analyses were in the same direction as the primary estimates but confidence intervals were larger in magnitude, when omitting that particular study

- **GRADE by outcome:**

Outcome	No. studies	GRADE
Sleep quality	6	Moderate
Daytime somnolence	7	High
Daily pain score	8	Moderate
Patient global impression of change	6	Moderate
EuroQol 5-D quality of life	4	Moderate
Nausea adverse event	7	High
Dizziness adverse events	7	High

- **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):**

Outcome	No. studies (No. participants)	Summary estimate (95% CI)	P-value	I^2 (%)	Direction of effect
Cannabinoid vs placebo					
Sleep quality	6 (744)	SMD 0.40 (0.19 to 0.61)	0.002	55.26	Cannabinoid
Daytime somnolence	7 (867)	OR 2.23 (1.32 to 3.74)	0.007	8.23	Cannabinoid
Pain score	8 (893)	SMD -0.44 (-0.69 to -0.19)	0.003	82.49	Cannabinoid
Patient global impression of change	6 (800)	OR 4.20 (1.37 to 12.87)	0.031	Not reported	Cannabinoid
EuroQol 5-D quality of life	4 (632)	SMD 0.22 (-0.25 to 0.68)	0.287	95.66	No significant difference
Nausea adverse event	7 (867)	OR 1.66 (1.22 to 2.27)	0.005	0	Cannabinoid

Parameter	Extraction items

Dizziness adverse event	7 (867)	OR 3.80 (2.52 to 5.73)	<0.001	6.23	Cannabinoid

- **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Not applicable
- **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Yes
- **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable

Significance/direction

See above if results listed by outcome: Above

Heterogeneity

- **See above if I^2 available:** Above
- **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** "There was a wide variety between-study I^2 , with sleep quality outcomes falling near the middle of the spectrum (I^2 =55.26%). For studies with multiple treatment arms, the within-study consistency was high (I^2 =0.00%) across all outcomes (I^2 reported with each outcome measure in results) (online supplemental table 2). Pain NRS, EQ-5D, and Sleep Quality show statistically significant heterogeneity at alpha=0.05 (online supplemental table 2)" p7
- **Causes of heterogeneity investigated:** Yes, I^2, random-effects model, sensitivity analysis

Comments

One study Toth *et al.* (2012) reported N=26 participants. In relation to gender data, Toth *et al.* (2012) reported 23 male and 51 female. As these figures do not add up, we excluded Toth *et al.* (2012) from our extraction on gender data.

One study Nurmikko *et al.* (2007) reported N=125 participants. In relation to gender data, Nurmikko *et al.* (2007) reported 125 male and 75 female. As these figures do not add up, we excluded Nurmikko *et al.* (2007) from our extraction on gender data.

Parameter	Extraction items
	One study Ware *et al.* (2010) reported N=22 participants. In relation to gender data, Ware *et al.* (2010)) reported 11 male and 12 female. As these figures do not add up, we excluded Ware *et al.* (2010) from our extraction on gender data. Table one references a study as Mark *et al.* in Table 1. This is a typo and should be referenced as Ware *et al.* The authors full name is Mark Ware and the corresponding reference is "Ware MA, Wang T, Shapiro S, *et al.* Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ 2010;182:E694–701."

Meng *et al.* (2017): Selective Cannabinoids for Chronic Neuropathic Pain: A Systematic Review and Meta-analysis

Parameter	Extraction items
First author and year of publication	Meng *et al.* (2017)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "to determine the analgesic efficacy of selective cannabinoids compared with conventional management or placebo for chronic [neuropathic pain] after at least 2 weeks after commencement of treatment." p1639 • **Exact review question and page number:** "to determine the analgesic efficacy of selective cannabinoids compared with conventional management or placebo for chronic [neuropathic pain] after at least 2 weeks after commencement of treatment." p1639 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** "human subjects above 18 years of age that had [neuropathic pain] for at least 3 months were included in this [systematic review meta analysis]. Intensity of pain had to be moderate or severe (4 or higher on a 0–10 numerical rating score or ≥40/100 for visual analog scale for pain)" p1639 ➢ **Setting:** Not specified ➢ **Intervention:** "administration of any of the 3 prescription selective cannabinoids (dronabinol, nabilone, and nabiximols)" p1639

Parameter	Extraction items
	➢ **Comparison:** Placebo or usual care ➢ **Outcome:** The primary outcome of interest was pain intensity. The secondary outcomes included: reduction in pain scores by ≥30%; quality of life; physical function; psychological function; sleep; overall patient satisfaction; and adverse effects incidence.
Participants (characteristics and numbers)	**For whole sample and subgroups** • **Number of participants:** N=1033 (1219 participants if cross-over control is double-counted) • **Age:** mean range 46-60.8 years • **Gender:** 60.3% female • **Details of clinical diagnosis/indications:** Multiple sclerosis (n=444); brachial plexus root aversion (n=48); multiple aetiologies (n=467); diabetes (n=56); chemotherapy induced (n=18)
Setting/context	**Countries (alphabetic order):** Not reported **Setting (university, public or private clinic):** Not reported **Other relevant features of setting:** Not applicable
Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** "administration of any of the 3 prescription selective cannabinoids (dronabinol, nabilone, and nabiximols)" p1639 • **Dose and regimen:** o Dronabinol (1 RCT): 2.5-10mg; daily o THC-CBD (7 RCTs): 4-10.9 mean sprays; daily o Nabilone (3 RCTs): 1-4mg; daily

Parameter	Extraction items
	• **Administration methods:** Orally (4 RCTs); oromucosal spray (7 RCTs) • **Comparator:** Placebo (10 RCTs); dihydrocodeine (1 RCT) • **Treatment duration:** >2 weeks (study duration range 2-15 weeks) • **Timeframe for follow-up:** Not reported for included RCTs
Databases and sources searched	• **Number and names of databases:** 3; EMBASE 1947-11/03/2016, MEDLINE, 1946-11/03/2016, MEDLINE In-Process and Other Non-Indexed Citations (all using the OvidSP Platform); and Cochrane Database of Systematic Reviews • **Other sources:** PROSPERO, Cochrane Central Register of Controlled Trials, Google Scholar, Clinicaltrials.gov • **Grey literature:** Proceedings of the major annual meetings of anesthesiology and pain societies (American Society of Anesthesiologists, European Society of Anaesthesiology, International Association for the Study of Pain, American Society of Regional Anesthesia and Pain Medicine, European Society of Regional Anesthesia and Pain Therapy, and World Institute of Pain) in the preceding 2 years. • **Reference chasing:** Yes • **Expert consultation:** Yes (experts with clinical and research experience on the role of selective cannabinoids for neuropathic pain were also consulted) • **Dates:** 1946-11/03/2016 • **Search limits:** English language, humans • **Justifications for search limits:** Yes • **Other searches:** No • **Protocol prepared:** Yes • **If yes, published:** Yes https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=36310 • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes

Parameter	Extraction items
	• **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** Unclear • **If yes, rate of agreement:** Not reported • **Funding of review:** "Department of Anesthesia and Pain Management at Toronto Western Hospital" p1638 • **Conflicts of interest of review:** "The authors declare no conflicts of interest." p1638 • **How conflicts of interest were managed:** Not applicable
Date Range (years) of included studies	• **Exact years for included studies:** 2004-2015
Number of primary studies included in the systematic review	• **Number of studies:** 11 RCTs • **Number of studies by study design:** 11 RCTs • **Study years:** 2004 (2 RCTs); 2005 (1 RCT); 2007 (1 RCT); 2008 (1 RCT); 2010 (1 RCT); 2012 (1 RCT); 2013 (1 RCT); 2014 (2 RCTs); 2015 (1 RCT) • **Funding of included studies:** Not reported • **Conflicts of interest of included studies:** Not reported
Types of studies included	**Planned study designs to be included:** RCT **Reasons for including only RCTs/prospective cohort studies:** Not reported **List of excluded studies at full text and reasons for exclusion:** Not reported
Appraisal instruments used	**Full name of tools used:** Cochrane Risk of bias tool **<u>Risk of bias criteria for AMSTAR 2 assessment, for RCTs record Yes/No for:</u>** • **Concealment of allocation:** Yes

Parameter	Extraction items
	• **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The authors reported the included trials as follows: High risk of bias (1 RCT) and low risk of bias (10 RCTs) using their own classification strategy as follows "A decision to classify "overall bias" as low, unclear, or high was made by the reviewers using the following method: • High: any trial with a high risk of bias listed on 3 or more domains. • Unclear: any trial with a high risk of bias listed on more than 1 but less than 3 domains. • Low: any trial with a high risk of bias on none or 1 domain and with no significant methodologic concerns that may have affected the study results." p1640 However, according to Cochrane's Collaboration tool classification guide, and graphical information provided in the paper, the included trials appear to have a high risk of bias (3 RCTs), unclear risk of bias (1 RCT), and low risk of bias (7 RCTs). • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** ○ Overall: Low risk randomisation (10/11); low risk outcome ascertainment (10/11) ○ Pain scores (all): Low risk randomisation (9/10); low risk outcome ascertainment (9/10) ○ Pain scores (dronabinol): Low risk randomisation (1/1); low risk outcome ascertainment (1/1) ○ Pain scores (nabilone): Low risk randomisation (3/3); low risk outcome ascertainment (3/3) ○ Pain scores (nabiximols): Low risk randomisation (5/6); low risk outcome ascertainment (5/6) ○ Central neuropathic pain: Low risk randomisation (5/5); low risk outcome ascertainment (5/5)

Parameter	Extraction items
	○ Peripheral neuropathic pain: Low risk randomisation (3/4); low risk outcome ascertainment (3/4) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** • **Graphical or statistical test for publication bias:** Yes • **Authors' comments likelihood and magnitude of publication bias:** "The funnel plot was asymmetrical suggesting the possibility of publication bias. Although other causes including clinical heterogeneity could be responsible for this finding, we decided to perform Begg's and Egger tests for publication bias but the P values for publication bias were nonsignificant (P = .371 and .103, respectively). This suggests that there was no publication bias." p1648 • **Authors' comment on how publication bias was dealt with:** Not applicable • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** No • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** Yes. Sensitivity analysis conducted with only low risk studies. "We performed a sensitivity analysis by removing the 1 trial with a high risk of bias. This trial also reported a significant effect of depression on [neuropathic pain] scores with patients in both arms who had more depression also had a more pronounced response to the study treatments. Meta-analysis of data from the other 9 trials on selective cannabinoids that had a low risk of bias (ie, after excluding 1 trial with a high risk of bias) showed that the significant but clinically small reduction in pain [numeric rating scale] in patients with [neuropathic pain] remained" p1647
Method of analysis	• **Description of method of analysis as per authors:** "We expected heterogeneity because of diverse populations with [neuropathic pain] and doses of selective cannabinoids administered, and therefore, we used DerSimonian and Laird random effects meta-analysis models. Heterogeneity was assessed with the Q test, and Higgins I^2 statistic was used to quantify it (I^2 >50% indicates substantial heterogeneity). The estimated mean effect of each study of these outcomes

Parameter	Extraction items
	was calculated with the respective 95% CI, and the pooled effect was then assessed. A P value of < .05 was considered significant for the analysis of the primary outcome (difference between pain scores). Bonferroni adjustment for multiple testing was not performed as per recommendations in the Cochrane Handbook. The Mantel-Haenszel method was used for calculating the pooled relative risk (risk ratio) with corresponding 95% CI. Investigation of sources of heterogeneity was based on analysis of prespecified subgroups for the primary outcome including type of selective cannabinoid (THC-CBD versus THC) and quality of trials (high versus unclear or low risk of bias). We performed random effects meta-regression of the standardize mean difference (effect size) using both a restricted maximal likelihood approach, which assumes a normal distribution, and the DerSimonian and Laird method, which assumes a non-normal distribution, for between-study variance" p1640 • **Justification for narrative synthesis or meta-analysis:** Not reported • **Justification for combining data in meta-analysis:** Not reported
Outcome assessed	**List of outcomes assessed and intended time frames:** ○ Primary outcomes: Pain scores ○ Secondary outcomes: Quality of life, physical function, sleep, anxiety, patient satisfaction, quantitative sensory testing profile ○ Intended timeframes: >2 weeks ○ Actual timeframes: 2-15 weeks
Results/findings	• **Findings by outcome:** PRIMARY OUTCOMES ○ Pain intensity: Pooled data from ten studies (n=973) reported a small reduction in pain scores with cannabinoids when compared to control (placebo and dihydrocodeine) (MD −0.65; 95% CI, −1.06 to −0.23 points).

Parameter	Extraction items
	○ Dronabinol pain scores: One study (n=24) reported significant improvements in pain in dronabinol vs placebo groups. ○ Nabilone pain scores: Pooled data from three studies (n=133) reported no significant difference in pain scores with nabilone compared to control (placebo and dihydrocodeine) (MD −1.22 points; 95% CI, −2.79 to 0.36 points). ○ Nabiximols (THC:CBD) pain scores: Pooled data from six studies (n=392) reported a small reduction in pain scores with nabiximols when compared to placebo (MD −0.50; 95% CI, −0.89 to −0.12). ○ Central neuropathic pain scores: Pooled data from five studies (n=564) reported a small reduction in pain scores with cannabinoids compared to placebo (−0.73; 95% CI, −1.26 to −0.20). ○ Peripheral neuropathic pain score: Pooled data from four studies (n=181) reported no significant difference in pain scores with selective cannabinoids compared to placebo (MD −0.72; 95% CI, −2.04 to 0.59). SECONDARY OUTCOMES ○ Quality of life: Five studies (n=533) reported significantly improved quality of life in cannabinoid compared with placebo groups (no summary statistics reported). Two studies (n=48) reported no significant differences between cannabinoid and placebo groups (no summary statistics reported). ○ Physical function: One study (n=125) reported significantly improved physical function in THC/CBD compared with placebo groups (no summary statistics reported). Two studies (n=72) study reported no significant differences between cannabinoid and placebo groups (no summary statistics reported). ○ Sleep: Six studies (n=850) reported significantly improved sleep in cannabinoid compared with placebo groups (no summary statistics reported). One study (n=96) reported no significant differences between nabilone and placebo groups (no summary statistics reported). ○ Anxiety: One study (n=66) reported significantly improved anxiety in THC/CBD compared with placebo groups (no summary statistics reported). Two studies (n=122) reported no significant difference between nabilone groups and placebo and dihydrocodeine groups (no summary statistics reported).

Parameter	Extraction items

- Quantitative sensory testing profile: Three studies (n=395) reported improvement in cannabinoid compared with placebo groups (no summary statistics reported). One study (n=18) reported no significant differences between THC/CBD and placebo groups (no summary statistics reported).
- Adverse effects: "The majority of reported adverse effects with selective cannabinoids were mild to moderate. The most common adverse effects with selective cannabinoids were dizziness/light-headedness, somnolence, and dry mouth. Adverse effects usually occurred at the onset of treatment and subsided over time, indicating development of tolerance (Table 2). We also assessed reports of severe adverse effects requiring withdrawal from the trials. These included confusion in 2 patients and headaches in 1 patient on nabilone. In a study with a crossover design, 4 participants (out of 96) on nabilone withdrew from the trial due to intolerance whereas 8 participants on dihydrocodeine ceased taking this medication. Two patients developed severe adverse events from selective cannabinoids (agitation and paranoid ideation). In another study, 11 (18%) patients withdrew from the nabiximols group because of adverse effects compared to 2 (3%) in the placebo group. All other studies demonstrated similar patient withdrawal rates between the trial arms." p1646

- **GRADE by outcome:**

Outcome	No. studies	GRADE
Pain scores (all)	10	Moderate
Central neuropathic pain	5	Moderate
Peripheral neuropathic pain	4	Low

- **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):**

Outcome	No. studies (No. participants)	Summary estimate	P-value	I^2 (%)	Direction of effect
Mixed cannabinoids vs mixed control					
Pain scores	10 (973)	MD -0.65 (−1.06 to −0.23)	0.002	60	Cannabinoid

Parameter	Extraction items

Mixed cannabinoids vs placebo					
Central neuropathic pain	5 (564)	MD −0.73 (−1.26 to −0.20)	0.007	51	Cannabinoid
Peripheral neuropathic pain	4 (181)	MD −0.72 (−2.04 to 0.59)	0.28	75	No significant effect
Nabilone vs mixed control					
Pain scores	3 (133)	MD −1.22 (−2.79 to 0.36)	0.13	85	No significant effect
Nabiximol vs placebo					
Pain scores	6 (392)	MD −0.50 (−0.89 to −0.12)	0.01	43	Nabiximol

- **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Not reported
- **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Yes
- **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable

Significance/direction

See above if results listed by outcome: Above

Heterogeneity

- **See above if I^2 available:** Above
- **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** "For the primary outcome, the I^2 statistic was 60% for the meta-analysis of pain [numeric rating scale] from all selective cannabinoid RCTs, it was 85% for comparison of mean postintervention pain scores for trials on nabilone, and 43% for comparison of mean postintervention pain scores for trials on nabiximols. These results indicate moderate to high heterogeneity. Several characteristics of these studies may have contributed to heterogeneity in our review including types of patient populations, timing of assessing primary outcome, and variations in dose." p1647
- **Causes of heterogeneity investigated:** "To explore heterogeneity, we conducted subgroups using meta-regression and a sensitivity analysis and found no significant difference based on central versus peripheral and on risk of bias. We

Parameter	Extraction items
	performed meta-regression analysis to assess whether there was a significant interaction between location of pain (central versus peripheral) and treatment effects of selective cannabinoids. We found no significant difference in effect size between studies on selective cannabinoids that enrolled participants with central pain compared to studies that enrolled participants with peripheral pain (P = .998 and .958 when assessed using normal and non-normal distribution assumptions, respectively). We performed a sensitivity analysis by removing the 1 trial with a high risk of bias." p1647
Comments	Authors reported 1219 participants. This figure includes double counting of cross-over control. Number of unique participants in 1033 according to Table 1. Unless specified otherwise, participant figures in this form do not double count cross-over control. Risk of bias was assessed as follows: "A decision to classify "overall bias" as low, unclear, or high was made by the reviewers using the following method: • High: any trial with a high risk of bias listed on 3 or more domains. • Unclear: any trial with a high risk of bias listed on more than 1 but less than 3 domains. • Low: any trial with a high risk of bias on none or 1 domain and with no significant methodologic concerns that may have affected the study results". Differs from scoring used by Cochrane. Discrepancy: Results state 5/8 studies report significant improvement in Qol in cannabinoid vs placebo. Discussion states 5/7 studies report significant improvement in Qol in cannabinoid vs placebo. Table 2 identifies seven studies, so data from discussion has been extracted.

Mücke *et al.* (2018a): Systematic review and meta-analysis of cannabinoids in palliative medicine

Parameter	Extraction items
First author and year of publication	Mücke *et al.* (2018a)

Parameter	Extraction items
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "to evaluate the efficacy, tolerability, and safety of cannabinoids as an adjunct or complementary therapy in palliative medicine." p221 • **Exact review question and page number:** "to evaluate the efficacy, tolerability, and safety of cannabinoids as an adjunct or complementary therapy in palliative medicine." p221 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** "participants of any age, diagnosed with any advanced or end-stage medical disease" p221 ➢ **Setting:** Not specified ➢ **Intervention:** "Herbal cannabis, plant based or synthetic cannabinoids in every form of application and dose" p221 ➢ **Comparison:** Placebo or active comparator ➢ **Outcome:** ○ Efficacy: responder (pain reduction ≥30%), body weight, appetite, caloric intake, and nausea/vomiting (primary endpoints); sleeping dysfunction, fatigue, mood disorders, and health-related quality of life (secondary endpoints) at the end of each medication phase. ○ Tolerability: Number of patients, who discontinued the study because of adverse events; dizziness, mental health symptoms, and cognitive dysfunction. ○ Safety: Number of serious adverse; deaths during medication.
Participants (characteristics and numbers)	**For whole sample and subgroups** • **Number of participants:** N=1544 • **Age:** Cancer (age range 58–66); HIV (age range 39–43); Alzheimer's Disease (age range 65–82); not reported (n=537) • **Gender:** 9.2% female • **Details of clinical diagnosis/indications:** Cancer (n=1275); HIV/AIDS (n=254); Alzheimer's Disease (n=15)

Parameter	Extraction items
Setting/context	**Countries (alphabetic order):** North America (7 RCTs); Great Britain (1 RCT); Europe (1 RCT) **Setting (university, public or private clinic):** Not reported **Other relevant features of setting:** "6 of the included studies were conducted as multicentre studies…,one (study) was split up in 2 study centres and another 2 studies were each conducted at a single centre" p225

Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** "Herbal cannabis, plant based or synthetic cannabinoids in every form of application and dose, were considered in comparison to a placebo or active control." p221
	• **Dose and regimen:**
	  ○ Dronabinol (3 RCTs): 2.5-20 mg; daily
	  ○ Combination megestrol and dronabinol (2 RCTs): 250-800 mg and 5 mg; daily
	  ○ THC:CBD (2 RCTs): 2.7 and 2.5 mg, max 1-48 sprays; daily
	  ○ THC (1 RCT): 2.7 mg max 48 sprays; daily
	  ○ Delta-9-THC (1 RCT): 0.9 g and 3.95%; 1-3 daily
	• **Administration methods:** Oromucosal spray (2 RCTs), Oral (5 RCTs); Inhaled (1 RCT)
	• **Comparator:** Placebo (8 RCTs)
	• **Treatment duration:** 16 days-12 weeks
	• **Timeframe for follow-up:** Not reported for included studies

Databases and sources searched	• **Number and names of databases:** 5; Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, PsycINFO, PubMed, and Scopus; Inception -15/03/2017 • **Other sources:** Clinicaltrials.gov and the International Association for Cannabinoid Medicines • **Grey literature:** Not reported

Parameter	Extraction items
	• **Reference chasing:** Yes • **Expert consultation:** No • **Dates:** Inception – 15/03/2017 • **Search limits:** No • **Justifications for search limits:** Not applicable • **Other searches:** Not reported • **Protocol prepared:** No • **If yes, published:** Not applicable • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Unclear • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Funding of review:** "Funding for MW, JC and LD was received from the Commonwealth Department of Health, the NSW Government Centre for Medicinal Cannabis Research and Innovation, the Victorian Department of Health and Human Services and the Queensland Department of Health. LD is supported by NHMRC research fellowship #1041472. The National Drug and Alcohol Research Centre at the University of NSW is supported by funding from the Australian Government under the Substance Misuse Prevention and Service Improvements Grant Fund" p233 • **Conflicts of interest of review:** "The authors declare that there is no conflict of interest." p233 • **How conflicts of interest were managed:** Not applicable
Date Range (years) of included studies	• **Exact years for included studies:** 1995-2012

Parameter	Extraction items
Number of primary studies included in the systematic review	• **Number of studies:** 9 RCTs • **Number of studies by study design:** 9 RCTs • **Study years:** 1995 (1 RCT); 1997 (2 RCTs); 2002 (1 RCT); 2003 (1 RCT); 2006 (1 RCT); 2010 (1 RCT); 2011 (1 RCT); 2012 (1 RCT) • **Funding of included studies:** Not reported (authors indicate this information was extracted, however it is not reported p223). • **Conflicts of interest of included studies:** Not reported (authors indicate this information was extracted, however it is not reported p223).
Types of studies included	**Planned study designs to be included:** "Double-blind or open label randomized controlled trials with parallel or crossover design and a duration of ≥2 weeks and ≥10 patients per study arm were included." p221 **Reasons for including only RCTs/prospective cohort studies:** Not reported **List of excluded studies at full text and reasons for exclusion:** Yes
Appraisal instruments used	**Full name of tools used:** "seven aspects of bias recommended by the Cochrane Collaboration" p223; GRADE system **Risk of bias criteria for AMSTAR 2 assessment, for RCTs record Yes/No for:** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The authors reported risk of bias in the included trials as follows: High risk of bias (6 RCTs) and moderate risk of bias (3 RCTs) using their own classification strategy as follows

Parameter	Extraction items
	"Studies were defined qualitatively as being high quality if they had six to seven factors with low risk of bias, as moderate quality if they had three to five factors with low risk of bias, and as low quality if only zero to two factors of the seven were classified as low risk of bias." p223 However, according to Cochrane's Collaboration tool classification guide, and graphical information provided in the paper, the included trials appear to have a high risk of bias (5 RCTs) and unclear risk of bias (4 RCTs). • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** o Overall: Low risk randomisation (2/9); low risk outcome ascertainment (1/9) *Efficacy: Cancer and HIV (cannabinoid vs. placebo)* o Weight loss/gain: Low risk randomisation (1/3); low risk outcome ascertainment (1/3) o Caloric intake: Low risk randomisation (1/1); low risk outcome ascertainment (1/1) o Appetite: Low risk randomisation (2/4); low risk outcome ascertainment (2/4) o Nausea and vomiting: Low risk randomisation (1/3); low risk outcome ascertainment (1/3) o Pain reduction >30%: Low risk randomisation (0/2); low risk outcome ascertainment (0/2) o Sleeping disorder: Low risk randomisation (1/2); low risk outcome ascertainment (0/2) *Efficacy: Alzheimer's disease (cannabinoid vs. placebo)* o Weight gain: Low risk randomisation (0/1); low risk outcome ascertainment (0/1) o Caloric intake: Low risk randomisation (0/1); low risk outcome ascertainment (0/1) o Mood disorders: Low risk randomisation (0/1); low risk outcome ascertainment (0/1) *Cancer efficacy (CBM vs. megestrol acetate)*

Parameter	Extraction items
	○ Appetite: Low risk randomisation (0/1); low risk outcome ascertainment (0/1) *HIV efficacy (CBM vs. megestrol acetate)* ○ Weight gain: Low risk randomisation (0/1); low risk outcome ascertainment (0/1) ○ Health-related quality of life: Low risk randomisation (0/1); low risk outcome ascertainment (0/1) ○ Nausea and vomiting: Low risk randomisation (0/1); low risk outcome ascertainment (0/1) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** "When studies were evaluated against the seven Cochrane criteria for possible methodical flaws, five studies were judged to be at high risk of an attrition bias, one was at high risk of a performance bias, and another one was at high risk of a selection bias (Figure 2). Overall, three of the studies were judged to be of moderate quality, and six were judged to be of low methodological quality (Figure 3)" p225 • **Graphical or statistical test for publication bias:** No • **Authors' comments likelihood and magnitude of publication bias:** Not reported • **Authors' comment on how publication bias was dealt with:** Not reported • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** No • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** "Following the GRADE methodology, no recommendations can be made for the use of cannabinoids in palliative care treatment for cancer, HIV–AIDS, or dementia. In view of this finding, further research is urgently needed to identify the efficacy and safety of cannabinoids as adjunctive or complementary therapies and to provide evidence-based recommendations on their clinical utility in palliative care." p232

Parameter	Extraction items
Method of analysis	• **Description of method of analysis as per authors:** "Standardized mean value differences of continuous variables were calculated for each intervention using MW and SD. A risk difference was determined for dichotomous variables. A random-effect model (inverse variance method) was used to examine the combined results because it is more conservative than the fixed-effects model and still accounts for both intra- and inter-study variance. The pooled estimates of event rates of categorical data, such as dropout rates because of serious adverse events, were calculated using a random effects model. Ninety-five percent confidence intervals were determined for all aggregated data. Heterogeneity was determined by the I^2 test. We dealt with clinical heterogeneity by combining studies that examined similar conditions. We assessed statistical heterogeneity visually and using the I^2 statistic. When the I^2 value was greater than 50%, we considered possible reasons for this. Probability value of 0.05 and <0.10 were evaluated as a statistical trend." p224 • **Justification for narrative synthesis or meta-analysis:** Not reported • **Justification for combining data in meta-analysis:** Not reported
Outcome assessed	**List of outcomes assessed and intended timeframes** • Primary outcomes: Efficacy including responder (pain reduction >30%), body weight, appetite, caloric intake, and nausea/vomiting (primary endpoints); sleeping dysfunction, fatigue, mood disorders, and health-related quality of life (secondary endpoints) at the end of each medication phase. • Secondary outcomes: Tolerability including number of patients, who discontinued the study because of adverse events; dizziness, mental health symptoms, and cognitive dysfunction; safety including number of serious adverse; deaths during medication. • Intended timeframes: > 2 weeks • Actual timeframes: 16 days – 12 weeks

Parameter	Extraction items
Results/findings	• **Findings by outcome:** PRIMARY OUTCOMES *Cannabis and cannabinoids compared with placebo: All conditions* ○ Appetite: Pooled data from four studies (n=517) reported no significant difference between cannabinoid and placebo groups (SMD 0.65, 95% CI -0.82 to 2.12). ○ Nausea and vomiting: Pooled data from two studies (n=307) reported a significant increase in THC/CBD groups compared with placebo groups (SMD 0.20, 95% CI -0.03 to 0.44). ○ Mental health (adverse event): Pooled data from five studies (n=799) reported no significant difference between cannabinoid and cannabis groups and placebo groups (SMD 0.01, 95% CI -0.02 to 0.04). ○ Health-related quality of life: Pooled data from four studies (n=570) reported no significant difference between cannabinoid and placebo groups (SMD 0.00, 95% CI -0.19 to 0.18). *Cannabis and cannabinoids compared with placebo: Cancer* ○ Weight gain: One study (n=243) reported no significant difference between THC/CBD and placebo groups (no summary statistic reported). ○ Caloric intake: One study (n=21) reported no significant difference dronabinol and placebo between groups (SMD 0.2, 95% CI -0.66 to 1.06). ○ Appetite: Pooled data from three studies (n=441) reported no significant difference between cannabinoid and placebo groups (SMD 0.81, 95% CI -1.14 to 2.75). ○ Nausea and vomiting: Pooled data from two studies (n=177) reported no significant difference between THC/CBD and placebo groups (SMD 0.21, 95% CI -0.1 to 0.53). ○ Pain reduction ≥ 30%: Pooled data from two studies (n=537) reported significantly increased likelihood of pain reduction in the THC/CBD group compared with the placebo group (RD 0.07, 95% CI -0.01 to 0.16).

Parameter	Extraction items
	○ Sleep: Pooled data from two studies (n=203) reported no significant difference in promoting sleep between cannabinoid and placebo groups (SMD -0.09, 95% CI -0.62 to 0.43). ○ Dizziness: Pooled data from four studies (n=823) reported no significant difference between cannabinoid and placebo groups (SMD 0.03, 95% CI -0.02 to 0.08). ○ Mental health (adverse event): Pooled data from three studies (n=528) reported no significant difference between cannabinoid and placebo groups. (SMD -0.01, 95% CI -0.04 to 0.03). ○ Health-related quality of life: Pooled data from two studies (n=420) reported no significant difference between cannabinoid and placebo groups (SMD 0.09, 95% CI -0.13 to 0.30). *Cannabis and cannabinoids compared with placebo: HIV* ○ Weight gain: Pooled data from two studies (n=192) reported significantly increased weight gain in the dronabinol and cannabis group compared with the placebo group (SMD 0.57, 95% CI 0.22 to 0.92). ○ Appetite: One study (n=139) reported significantly increased appetite in the dronabinol group compared with the placebo group (SMD 0.57, 95% CI 0.11 to 1.03). ○ Nausea: One study (n=139) reported no significant difference between dronabinol and placebo groups (SMD 0.20, 95% CI -0.15 to 0.54). ○ Mental health (adverse event): Two studies (n=206) reported significant increase in the development of mental health symptoms in the dronabinol and cannabis group (SMD 0.05, 95% CI 0.00 to 0.10). ○ Health-related quality of life: One study (n=139) reported no significant difference between dronabinol and placebo groups (SMD -0.24, 95% CI -0.58 to 0.11). *Cannabinoids (dronabinol) vs. placebo: Alzheimer's disease* ○ Weight gain: One crossover study (n=15) reported significantly increased weight gain in the dronabinol phase compared with the placebo phase (+3.95 kg vs +3.13 kg, p=0.017).

Parameter	Extraction items
	○ Caloric intake: One crossover study (n=15) reported no change in caloric intake in either the dronabinol or placebo phase. ○ Negative affect (anger, anxiety sadness): One crossover study (n=15) reported significantly greater decreases in negative affect in the dronabinol phase compared with the placebo phase (p=0.004). *Cannabis and cannabinoids vs. megestrol acetate: Cancer* ○ Appetite: One study (n=469) reported significantly improved appetite in the megestrol acetate group compared with the dronabinol group (49% to 75%; p = 0.0001). ○ Weight gain: One study (n=469) reported significantly greater weight gain in the megestrol acetate group compared with the dronabinol group (3% to 11%, p=0.02). ○ Health-related quality of life: One study (n=469) reported significantly improved health-related quality of life in the megestrol acetate group compared with the dronabinol group (p=0.03). *Cannabis and cannabinoids vs. megestrol acetate: HIV* ○ Weight gain: One study (n=48) reported significantly increased weight gain the megestrol acetate group (6.5 ± 1.1 kg) compared with the dronabinol group (-2 ± 1.3 kg)(p=0.0001). ○ Health-related quality of life: One study (n=48) reported no significant differences between dronabinol and megestrol acetate groups (no summary statistics reported). ○ Nausea and vomiting: One study (n=48) reported no significant differences between megestrol acetate and dronabinol groups (no summary statistics reported). ○ Depressive mood: One study (n=48) reported no significant differences between megestrol acetate and dronabinol groups (no summary statistics reported). *Herbal cannabis vs. plant-derived THC: HIV*

Parameter	Extraction items
	○ Weight gain: One study (n=45) reported significantly increased weight gain the herbal cannabis group (3.0 kg, range 0.75–8.6 kg) compared with the plant-derived THC group (3.2 kg, range -1.4–7.6 kg). SECONDARY OUTCOMES *Cannabis and cannabinoids compared with placebo: All conditions* ○ Tolerability (drop-outs): Pooled data from six studies (n=1031) reported a significant increase in cannabinoid and cannabis groups compared with placebo groups SMD 0.04 (0.00 to 0.08). ○ Safety (serious adverse events): Pooled data from six studies (n=1031) reported a significant increase in cannabinoid and cannabis groups compared with placebo groups (SMD 0.06, 95% CI 0.01 to 0.10). *Cannabis and cannabinoids compared with placebo: Cancer* ○ Tolerability (drop-outs): Pooled data from four studies (n=825) reported no significant difference between cannabinoid and placebo groups (RD 0.04, 95% CI -0.01 to 0.09). ○ Safety (serious adverse events): Pooled data from four studies (n=825) reported no significant difference between cannabinoid and placebo groups (RD 0.05, 95% CI -0.02 to 0.11). *Cannabis and cannabinoids compared with placebo: HIV* ○ Tolerability (drop-outs): Pooled data from two studies (n=206) reported no significant difference between dronabinol and cannabis groups and placebo groups (RD 0.05, 95% CI -0.02 to 0.11). ○ Safety (serious adverse events): Pooled data from two studies (n=206) reported significantly increased likelihood in dronabinol and cannabis groups compared with placebo groups (RD 0.06, 95% CI 0.01 to 0.12). *Cannabinoids (dronabinol) vs. placebo: Alzheimer's disease* ○ Tolerability (drop-outs): One crossover study (n=15) reported that one patient dropped out due to adverse events and two dropped out due to serious infections.

Parameter	Extraction items

Cannabis and cannabinoids vs. megestrol acetate: Cancer

- Tolerability (drop-outs): One study (n=469) reported significantly lower drop-outs in the megestrol acetate group compared with the dronabinol group (58% to 45%; p=0.03).
- Safety (serious adverse events): One study (n=469) reported no significant difference between megestrol acetate and dronabinol groups (15% to 22%; p=0.12).

Cannabis and cannabinoids vs. megestrol acetate: HIV

- Tolerability (drop-outs): One study (n=48) reported no significant differences between megestrol acetate and dronabinol groups (no summary statistics reported).
- Safety (serious adverse events): One study (n=48) reported no significant differences between megestrol acetate and dronabinol groups (no summary statistics reported).

Herbal cannabis vs. plant-derived THC: HIV

- Tolerability (drop-outs): One study (n=45) reported no significant differences between drop-out in the marijuana (9.5%) and dronabinol (8.3%) groups.
- Safety (serious adverse events): One study (n=45) reported no serious adverse events in either group.

- **GRADE by outcome:**

Outcome	No. studies	GRADE
Overall		
Weight gain	2	Very low
Weight gain (Strasser 2006)	1	Low
Caloric intake	1	Very low
Appetite	4	Very low
Nausea and vomiting	2	Very low
Pain reduction	2	Low
Sleep	2	Very low
Dizziness	4	Very low
Mental health (adverse event)	5	Very low

Parameter	Extraction items		
	Health-related quality of life	4	Very low
	Tolerability (drop-outs)	6	Very low
	Safety (serious adverse events)	6	Very low
	Cancer		
	Weight loss/gain	1	Low
	Caloric intake	1	Very low
	Appetite	3	Very low
	Nausea and vomiting	1	Low
	Pain reduction	2	Low
	Sleep	2	Very low
	Dizziness	4	Very low
	Mental health (adverse event)	3	Very low
	Health-related quality of life	3	Very low
	Tolerability (drop-outs)	4	Very low
	Safety (serious adverse events)	4	Very low
	HIV/AIDs		
	Weight gain	2	Very low
	Appetite	1	Very low
	Nausea	1	Very low
	Mental health (adverse event)	2	Very low
	Health-related quality of life	1	Very low
	Tolerability (drop-outs)	2	Very low
	Safety (serious adverse events)	2	Very low
	Alzheimer's Disease		
	Weight gain	1	Very low
	Mood disorders (anger, anxiety sadness):	1	Very low
	Tolerability	1	Very low
	Safety	1	Very low

- **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):**

Parameter	Extraction items

Outcome	No. studies (No. participants)	Summary estimate (95% CI)	P-value	I^2 (%)	Direction of effect
Overall (all conditions)					
Mixed cannabinoid vs placebo					
Appetite	4 (517)	SMD 0.65 (-0.82 to 2.12)	0.39	97	No significant difference
Health-related quality of life	4 (570)	SMD 0.00 (-0.19 to 0.18)	0.98	0	No significant difference
THC/CBD vs placebo					
Nausea and vomiting	2 (307)	SMD 0.20 (-0.03 to 0.44)	0.09	0	THC/CBD
Mixed cannabinoid and cannabis vs placebo					
Mental health (adverse event)	5 (799)	RD 0.01 (-0.02 to 0.04)	0.42	0	No significant difference
Tolerability (drop-outs)	6 (1031)	RD 0.04 (0.00 to 0.08)	0.04	0	Cannabinoid and cannabis
Safety (serious adverse events)	6 (1031)	RD 0.06 (0.01 to 0.10)	0.009	0	Cannabinoid and cannabis
Cancer					
Mixed cannabinoid vs placebo					
Appetite	3 (441)	SMD 0.81 (-1.14 to 2.75)	0.42	98	No significant difference
Sleep disorders	2 (198)	SMD -0.09 (-0.62 to 0.43)	0.72	63	No significant difference
Dizziness	4 (823)	RD 0.03 (-0.02 to 0.08)	0.23	0	No significant difference
Mental health (adverse event)	3 (582)	RD -0.01 (-0.04 to 0.03)	0.69	0	No significant difference
Health related quality of life	3 (431)	SMD 0.09 (-0.13 to 0.30)	0.42	0	No significant difference
Tolerability (drop-outs)	4 (825)	RD 0.04 (-0.01 to 0.09)	0.13	0	No significant difference
Safety (serious adverse events)	4 (825)	RD 0.05 (-0.02 to 0.11)	0.15	0	No significant difference
THC/CBD vs placebo					

Parameter	Extraction items

Pain reduction ≥30%	2 (537)	RD 0.7 (-0.01 to 0.16)	0.07	0	THC/CBD
HIV					
Cannabinoid and cannabis vs placebo					
Weight gain	2 (192)	SMD 0.57 (0.22 to 0.92)	0.001	15	Dronabinol
Tolerability (drop-outs)	2 (206)	RD 0.05 (-0.02 to 0.11)	0.16	0	No significant difference
Safety (serious adverse events)	2 (206)	RD 0.06 (0.01 to 0.12)	0.03	0	Dronabinol

- **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Above
- **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Yes
- **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable

Significance/direction

See above if results listed by outcome: Above

Heterogeneity

- **See above if I^2 available:** Above
- **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** No
- **Causes of heterogeneity investigated:** "We assessed statistical heterogeneity visually and using the I^2 statistic." p224

Comments

Text states a total of 1561 participants, however Table 1 only adds up to 1544 participants. Text states 251 participants with HIV/AIDs in text but 258 in table 1. Data has been extracted from table 1 in this form.

Appendix 2 includes the same study multiple times in meta-analyses of weight gain, appetite, nausea and vomiting, pain reduction, sleeping disorders, dizziness, mental health, health-related quality of life, tolerability and safety.

Parameter	Extraction items
	There are a number of discrepancies between the figures reported in the text and in the forest plots. These discrepancies related to outcomes 'Cancer—quality of life' p227, 'Cancer—tolerability' p227, 'Cancer—safety' p227, 'HIV—tolerability' p229, 'HIV—safety' p229. The corresponding forest plots are in appendix 2 '9. Health-related quality of life', '10. Tolerability: Drop out due to adverse events', and '11. Safety: Serious adverse events'. Based on the summary statistics reported Table 2 p228, we suspect these may have been minor typos (labelled as RD instead of RR). We have extracted information from Table 2 based on this assumption.

Mücke *et al.* (2018b): Cannabis-based medicines for chronic neuropathic pain in adults (Review)

Parameter	Extraction items
First author and year of publication	Mücke *et al.* (2018b)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "To assess the efficacy, tolerability, and safety of cannabis-based medicines (herbal, plant-based, synthetic) compared to placebo or conventional drugs for conditions with chronic neuropathic pain in adults" p7 • **Exact review question and page number:** "To assess the efficacy, tolerability, and safety of cannabis-based medicines (herbal, plant-based, synthetic) compared to placebo or conventional drugs for conditions with chronic neuropathic pain in adults" p7 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** "adults aged 18 years and above with one or more chronic (three months and more) neuropathic pain condition including (but not limited to): 1. cancer-related neuropathy; 2. central neuropathic pain (e.g. multiple sclerosis); 3. complex regional pain syndrome (CRPS) Type II; 4. HIV neuropathy; 5. painful diabetic neuropathy; 6. peripheral polyneuropathy of other aetiologies, for example toxic (alcohol, drugs); 7. phantom limb pain; 8. postherpetic

Parameter	Extraction items
	neuralgia; 9. postoperative or traumatic peripheral nerve lesions; 10. spinal cord injury; 11. nerve plexus injury; 12. trigeminal neuralgia." p8 ➢ **Setting:** Not specified ➢ **Intervention:** "Cannabis-based medicines, either herbal cannabis (hashish, marihuana), plant-based cannabinoids (dronabinol: nabiximols), or pharmacological (synthetic) cannabinoids (e.g. levonantradol, nabilone), at any dose, by any route, administered for the relief of neuropathic pain" p8 ➢ **Comparison: "**placebo or any active comparator" p8 ➢ **Outcome:** Primary outcomes include participant-reported pain relief of 50% or greater; patient global impression of change; withdrawals due to adverse events (tolerability); and serious adverse events (safety). Secondary outcomes include participant-reported pain relief of 30% or greater, mean pain intensity, health-related quality of life, sleep problems, fatigue, psychological distress, withdrawals due to lack of efficacy, any adverse event, specific adverse events, particularly nervous system (e.g. dizziness, somnolence, headache) and psychiatric disorders (e.g. confusion state; paranoia, psychosis, substance dependence).
Participants (characteristics and numbers)	**For whole sample and subgroups:** • **Number of participants:** N=1798 • **Age:** Mean 34-61 years • **Gender:** 47.2% female • **Details of clinical diagnosis/indications:** Plexus root avulsion (n=48); HIV (n=34); chronic central and peripheral neuropathic pain (n=96); chemotherapy-induced neuropathic pain (n=18); diabetes (n=353); spinal cord injury (n=116); pain and allodynia (n=125); post-herpetic neuralgia, peripheral neuropathy, focal nerve lesion,

Parameter	Extraction items
	radiculopathy or complex regional pain syndrome (n=246); non-HIV neuropathy (n=23); multiple sclerosis and other neurological conditions (n=70); multiple sclerosis (n=669)
Setting/context	**Countries (alphabetic order):** Canada (3 RCTs); Denmark (outpatient) (1 RCT); Germany (1 RCT); UK (5 RCTs); UK, Belgium (1 RCT); UK, Canada, Spain, France, Czech Republic (1 RCT); UK, Czech Republic, Romania, Belgium, Canada (1 RCT); UK, Czech Republic, Romania (1 RCT); UK, Romania (1 RCT); USA (1 RCT) **Setting (university, public or private clinic):** Outpatient (1 RCT); Not reported (15 RCTs) **Other relevant features of setting:** Nine studies were single centre and seven were multicentre p13
Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** "Cannabis-based medicines, either herbal cannabis (hashish, marihuana), plant-based cannabinoids (dronabinol: nabiximols), or pharmacological (synthetic) cannabinoids (e.g. levonantradol, nabilone), at any dose, by any route, administered for the relief of neuropathic pain" p8 • **Dose and regimen:** ○ THC (1 RCT): 4-8% cigarettes; four smoking sessions in eight hours ○ Delta-9-THC (1 RCT): Inhaled THC in three arms 2.5%, 6%, 9.4%; daily (dose estimate: 0, 1.625, 3.9 and 5.85 mg daily) ○ Nabilone (2 RCTs): 0.25-2 mg, dose adjusted every week (twice the first week); 1-5 mg daily ○ Dronabinol (1 RCT): 2.5-10 mg; daily ○ Not reported (1 RCT): 7.5-15 mg; regimen not reported

Parameter	Extraction items
	○ Sativex (2 RCTs): 27 mg/ml THC, 25 mg/ml CBD four sprays daily; 65 mg/ml THC, 60 mg/ml CBD daily ○ THC or THC:CBD (1 RCT): 27 mg/ml THC or 27 mg/25 mg/ml CBD; maximum 48 sprays per day ○ THC:CBD (7 RCTs): 2.5 mg - 2.7 mg THC and 2.5 mg CBD; 12-48 sprays daily • **Administration methods:** Oromucosal spray (8 RCTs); inhalation (2 RCT); sublingual (1 RCT); sublingual and oro-pharyngeal (1 RCT); oral (1 RCT); not reported (2 RCTs); • **Comparator: "**placebo or any active comparator (dihydrocodeine, 1 RCT)" p8 • **Treatment duration:** Not specified (2-26 weeks) • **Timeframe for follow-up:** Not reported for included studies
Databases and sources searched	• **Number and names of databases:** 3; CENTRAL, EMBASE, MEDLINE; inception-07/11/2017 • **Other sources:** US National Institutes of Health clinical trial register (www.ClinicalTrials.gov), European Union Clinical Trials Register (www.clinicaltrialsregister.eu), World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/), and International Association for Cannabinoid Medicines (IACM) databank (www.cannabis-med.org/ studies/study.php) • **Grey literature:** Not reported • **Reference chasing:** Yes • **Expert consultation:** Yes "The protocol followed the agreed template for neuropathic pain, which was developed in collaboration with Cochrane Musculoskeletal and Cochrane Neuromuscular Diseases." p23 • **Dates:** Inception-07/11/2017 • **Search limits:** No • **Justifications for search limits:** Not applicable • **Other searches:** Not reported • **Protocol prepared:** Yes

Parameter	Extraction items
	• **If yes, published:** https://doi.org/10.1002/14651858.CD012182 • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Funding of review:** "this project was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to Cochrane Pain, Palliative and Supportive Care (PaPaS). The views and opinions expressed therein are those of the review authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health." p23 • **Conflicts of interest of review:** "MM: none known; MM is a specialist in palliative care who treats patients with chronic neuropathic pain. TP: none known; TP is a specialist pain physician and manages patients with neuropathic pain. LR: none known; PR is a specialist in palliative care who treats patients with chronic neuropathic pain. FP is a specialist in pain medicine who treats patients with chronic neuropathic pain. He has received speaking fees for one educational lecture for Janssen-Cilaq (2015) on fibromyalgia and participated in an advisory board for the same company focusing on an unrelated product (2015). WH is a specialist in general internal medicine, psychosomatic medicine and pain medicine, who treats patients with fibromyalgia and chronic neuropathic pain. He is a member of the medical board of the German Fibromyalgia Association. He is the head of the steering committee of the German guideline on fibromyalgia and a member of the steering committee of the European League Against Rheumatism (EULAR) update recommendations on the management of fibromyalgia. He received speaking fees for one educational lecture from Grünenthal (2015) on pain management." p90 • **How conflicts of interest were managed:** Not reported

Parameter	Extraction items
Date Range (years) of included studies	• **Exact years for included studies:** 2004-2017
Number of primary studies included in the systematic review	• **Number of studies:** 16 RCTs • **Number of studies by study design:** 16 RCTs • **Study years:** 2004 (2 RCTs); 2005 (1 RCT); 2006 (1 RCT); 2007 (1 RCT); 2008 (1 RCT); 2009 (1 RCT); 2010 (2 RCTs); 2012 (1 RCT); 2013 (1 RCT); 2014 (2 RCTs); 2017 (1 RCT); not reported (2 RCTs) • **Funding of included studies:** Public funding (3 RCTs); no external funding (1 RCT); industry funded (12 RCTs) • **Conflicts of interest of included studies:** No conflict of interest (4 RCTs); not reported (6 RCTs); potential conflicts of interest by honoraria and/or funding received by the manufacturer of the drug (6 RCTs)
Types of studies included	**Planned study designs to be included:** RCT **Reasons for including only RCTs/prospective cohort studies:** Not reported **List of excluded studies at full text and reasons for exclusion:** Yes "Characteristics of excluded studies" in appendix
Appraisal instruments used	**Full name of tools used:** Cochrane Risk of bias; GRADE system **<u>Risk of bias criteria for AMSTAR 2 assessment, for RCTs, record Yes/No for:</u>** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence allocation (individual vs group randomisation):** Yes • **Selective reporting:** Yes

Parameter	Extraction items
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The authors did not provide an overall assessment of risk of bias for each trial. However, HRB notes that according to Cochrane's Collaboration tool, and graphical information provided in the paper, the included trials appeared to have a high risk of bias (10 RCTs) and unclear risk of bias (6 RCTs). • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** o Overall: Low risk randomisation (10/16); low risk outcome ascertainment (2/16) *RCT Mixed cannabinoids vs placebo* o 50% reduction in pain: Low risk randomisation (6/8); low risk outcome ascertainment (2/8) o Patient global impression much or very much improved: Low risk randomisation (3/6); low risk outcome ascertainment (1/6) *EERW Nabilone vs placebo* o 50% reduction in pain: Low risk randomisation (1/1); low risk outcome ascertainment (0/1) o Patient global impression much or very much improved: Low risk randomisation (1/1); low risk outcome ascertainment (0/1) *EERW THC:CBD vs placebo* o 50% reduction in pain: Low risk randomisation (1/1); low risk outcome ascertainment (0/1) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** "In view of the accumulating evidence regarding potential bias in small studies, the quality of the evidence for cannabis-based medicines for treating neuropathic pain cannot be relied upon." p21 • **Graphical or statistical test for publication bias:** "The planned assessment of publication bias was not possible because the NNTB (number needed to treat for an additional, beneficial outcome) of all cannabis-based medicines pooled

Parameter	Extraction items
	together versus placebo for all dichotomous primary and secondary outcomes surpassed the pre-set level of an NNTB of 10 or less." p19 • **Authors' comments likelihood and magnitude of publication bias:** Above • **Authors' comment on how publication bias was dealt with:** "We added publication bias (all studies funded by the manufacturer of the drug) into the GRADE rating of the quality of evidence, and described our approach to assigning 'very low quality' in some circumstances." p90 • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** No • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** Yes "Quality of the evidence" p21
Method of analysis	• **Description of method of analysis as per authors:** "We calculated numbers needed to treat for an additional beneficial outcome (NNTB) as the reciprocal of the absolute risk reduction (ARR; McQuay 1998). For unwanted effects, the NNTB becomes the number needed to treat for an additional harmful outcome (NNTH) and is calculated in the same manner. We used dichotomous data to calculate risk differences (RD) with 95% CIs using a fixed-effect model unless we found significant statistical or clinical heterogeneity (see below). We set the threshold for a clinically relevant benefit or a clinically relevant harm for categorical variables by an NNTB or NNTH less than 10 (Moore 2008). We calculated standardised mean differences (SMD) with 95% CIs for continuous variables using a fixed-effect model unless we found significant statistical or clinical heterogeneity. We used Cohen's categories to evaluate the magnitude of the effect size, calculated by SMD, with Hedges' g value of 0.2 = small, 0.5 = medium, and 0.8 = large (Cohen 1988). We labelled a g value less than 0.2 to be a 'not substantial' effect size. We assumed a minimally important difference if the Hedges' g value was 0.2 or greater (Fayers 2014)." p10

Parameter	Extraction items
	"We intended to use a fixed-effect model for meta-analysis. We used a random-effects model using the inverse variance method in Review Manager 5 for meta-analysis (RevMan 2014) because there was significant clinical heterogeneity due to the different types of neuropathic pain conditions included" p10 • **Justification for narrative synthesis or meta-analysis:** Not reported • **Justification for combining data in meta-analysis:** Not reported
Outcome assessed	**List of outcomes assessed and intended timeframes** • Primary outcomes: Participant-reported pain relief of 50% or greater; patient global impression of change much or very much improved; withdrawals due to adverse event; and serious adverse events • Secondary outcomes: Participant-reported pain relief of 30% or greater; participant-reported pain relief of 30% greater; mean pain intensity; health -related quality of life; sleep problems; fatigue; psychological distress; withdrawals due to lack of efficacy; any adverse event; specific adverse events • Intended timeframes: Not specified • Actual timeframes: 2-26 weeks
Results/findings	• **Findings by outcome:** PRIMARY OUTCOMES *Pain relief of 50% or greater* ○ Pooled data from eight RCTs (n=1001) reported statistically significant improvement in cannabinoid compared with placebo groups (RD 0.05, 95% 0.00 to 0.09). The authors noted this effect was not clinically relevant. ○ One study with an enriched enrolment randomised withdrawal design (n=42) reported significant improvement in THC:CBD compared with placebo groups (24% versus 57%; p=0.04).

Parameter	Extraction items
	○ One study with an enriched enrolment randomised withdrawal design (n=26) reported no significant difference between nabilone and placebo groups (31% vs 8%; p=0.12). *Patient global impression of change* ○ Pooled data from six studies (n=1092) reported significant improvement in cannabinoid compared with placebo groups (RD 0.09, 95% CI 0.01 to 0.17). The authors noted this effect was not clinically relevant. ○ One study (n=26) with an enriched enrolment randomised withdrawal design reported significant improvement in nabilone (6/13 participants) compared with placebo (1/13 participants) groups (p=0.04). *Withdrawals due to adverse event* ○ Pooled data from thirteen studies (n=1848) reported significantly increased likelihood in cannabinoid and cannabis groups compared with placebo groups (RD 0.04, 95% CI 0.02 to 0.07). The authors noted there was no clinically relevant harm associated with cannabinoids in their analysis. ○ One study (n=42) with an enriched enrolment randomised withdrawal design reported no significant difference in THC:CBD (0/21 participants) and placebo (1/21 participants) groups. ○ One study (n=26) with an enriched enrolment randomised withdrawal design reported no significant difference in nabilone (0/13 participants) and placebo (0/13 participants) groups. ○ One study (n=73) reported no significant difference between nabilone and dihydrocodeine groups (p=0.23). *Serious adverse events* ○ Pooled data from thirteen studies (n=1876) reported no significant difference between cannabinoid and cannabis groups compared with placebo groups (RD 0.01, 95% CI -0.01 to 0.03). ○ One study (n=42) with an enriched enrolment randomised withdrawal design reported no significant difference in THC/CBD (3/21 participants) and placebo (1/21 participants) groups.

Parameter	Extraction items
	○ One study (n=26) with an enriched enrolment randomised withdrawal design reported no significant difference in nabilone (0/13 participants) and placebo (0/13 participants) groups. SECONDARY OUTCOMES *Pain relief of 30% or greater* ○ Pooled data from ten studies (n=1586) reported significant improvement in cannabinoid and cannabis compared with placebo groups (RD 0.09, 95% CI 0.03 to 0.15). The authors noted this effect was not clinically relevant. ○ One study (n=26) with an enriched enrolment randomised withdrawal design reported significant improvement in nabilone compared with placebo groups (85% vs 38%; p=0.006). *Mean pain intensity* ○ Pooled data from fourteen studies (n=1837) reported significant improvement in cannabinoid and cannabis compared with placebo groups (SMD -0.35, 95% CI -0.60 to -0.09). The authors noted this effect was clinically relevant. ○ One study (n=42) with an enriched enrolment randomised withdrawal design reported significant improvement in THC/CBD compared with placebo groups (treatment difference -0.79, p=0.03). ○ One study (n=26) with an enriched enrolment randomised withdrawal design reported significant improvement in nabilone (mean 3.5, SD 1.3) compared with placebo (mean 5.4, SD 1.7) groups (p=0.05). ○ One study (n=73) reported no significant difference between nabilone (mean 59.93, SD 24.42) and dihydrocodeine groups (mean 58.58, SD 24.08). *Health-related quality of life* ○ Pooled data from nine studies (n=1284) reported no significant difference between cannabinoid and cannabis groups compared with placebo groups (SMD 0.02, 95% CI -0.10 to 0.13).

Parameter	Extraction items
	○ One study (n=42) with an enriched enrolment randomised withdrawal design reported no significant difference between THC/CBD and placebo groups (treatment difference 1.94, p=0.18). ○ One study (n=26) with an enriched enrolment randomised withdrawal design reported significant improvement in the nabilone (mean 0.74, SD 0.03) compared with placebo (mean 0.06, SD 0.8) groups (p<0.05). ○ One study (n=73) reported no significant difference between nabilone and dihydrocodeine groups (treatment difference 8.9, p=0.48). *Sleep problems* ○ Pooled data from eight studies (n=1386) reported significant improvement in cannabinoid and cannabis compared with placebo groups (SMD -0.47, 95% CI -0.90 to -0.04). The authors noted this effect was clinically relevant. ○ One study (n=42) with an enriched enrolment randomised withdrawal design reported significant improvement in THC/CBD compared with placebo groups (treatment difference -0.99, p=0.02). ○ One study (n=26) with an enriched enrolment randomised withdrawal design reported significant improvement in the nabilone (mean 27.1, SD 2.1) compared with placebo (mean 33.0, SD 2.6) groups (p<0.05). ○ One study (n=73) reported no significant difference between nabilone and dihydrocodeine groups (treatment difference 0.2, p=0.28). *Fatigue* ○ One study (n=42) assessed fatigue, however no summary statistics were reported. *Psychological distress* ○ Pooled data from seven studies (n=779) reported significant improvement in cannabinoid and cannabis compared with placebo groups (SMD -0.32, 95% CI -0.61 to -0.02). The authors noted this effect was clinically relevant. ○ One study (n=42) with an enriched enrolment randomised withdrawal design reported no significant difference between THC/CBD and placebo groups (treatment difference -0.56, p=0.73).

Parameter	Extraction items
	○ One study (n=73) reported no significant difference between nabilone and dihydrocodeine groups (treatment difference 2.5, p=0.35). *Withdrawal due to lack of efficacy* ○ Pooled data from nine studies (n=1576) reported no significant difference between cannabinoid and cannabis groups compared with placebo groups (RD -0.00, 95% CI -0.02 to 0.01). ○ One study (n=42) with an enriched enrolment randomised withdrawal design reported no withdrawals due to lack of efficacy in THC/CBD or placebo groups. *Any adverse event* ○ Pooled data from seven studies (n=1356) reported significantly increased likelihood in cannabinoid groups compared with placebo groups (RD 0.19, 95% CI 0.12 to 0.27). The authors noted there was no clinically relevant harm associated with cannabinoids in their analysis. ○ One study (n=42) with an enriched enrolment randomised withdrawal design reported 10% participants in THC/CBD compared with 24% participants in placebo groups reported an adverse event (no summary statistic reported). ○ One study (n=26) with an enriched enrolment randomised withdrawal design reported 54% in nabilone compared with 46% in placebo groups reported an adverse event (p=1.0). ○ One study (n=73) reported no significant difference between nabilone (333 adverse events reported) and dihydrocodeine (305 adverse events reported) groups (no summary statistics reported). *Specific adverse event: Nervous system disorder* ○ Pooled data from nine studies (n=1304) reported significantly increased likelihood in cannabinoid and cannabis groups compared with placebo groups (RD 0.38, 95% CI 0.18 to 0.58). The authors noted there was clinically relevant harm associated with cannabinoids in their analysis.

Parameter	Extraction items

- One study (n=42) with an enriched enrolment randomised withdrawal design reported no participants in THC/CBD or placebo groups reported this specific adverse event.

Specific adverse event: Psychiatric disorder

- Pooled data from nine studies (n=1314) reported significantly increased likelihood in cannabinoid groups compared with placebo groups (RD 0.10, 95% CI 0.06 to 0.15). The authors noted there was no clinically relevant harm associated with cannabinoids in their analysis.
- One study (n=42) with an enriched enrolment randomised withdrawal design reported participants in THC/CBD (5% participants) or placebo (5% participants) groups reported this specific adverse event.

- **GRADE by outcome:**

Outcome	No. studies	GRADE
Mixed cannabinoids vs placebo		
Pain relief of 50% or greater	8	Low
Patient global impression of change	6	Very low
Withdrawals due to adverse event	13	Moderate
Serious adverse events	13	Low
Pain relief of 30% or greater	10	Moderate
Mean pain intensity	14	Low
Health-related quality of life	9	Low
Sleep problems	8	Low
Psychological distress	7	Low
Withdrawals due to lack of efficacy	9	Low
Any adverse event	7	Low
Specific adverse event: Nervous system disorder	9	Low
Specific adverse event: Psychiatric disorder	9	Low

The quality of evidence of the three studies synthesised qualitatively (n=26; n=42; n=73) was low.

Parameter	Extraction items

- **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):**

Outcome	No. studies (No. participants)	Summary estimate (95% CI)	P-value	I^2 (%)	Direction of effect
Mixed cannabinoids vs placebo					
Pain relief of 50% or greater	8 (1001)	RD 0.05 (0.00 to 0.09)	0.04	29	Cannabinoid
Patient global impression of change	6 (1092)	RD 0.09 (0.01 to 0.17)	0.02	58	Cannabinoid
Any adverse event	7 (1356)	RD 0.19 (0.12 to 0.27)	0.0001	64	Cannabinoid
Withdrawal due to lack of efficacy	9 (1576)	RD -0.00 (-0.02 to 0.01)	0.79	0	No significant difference
Cannabinoid and cannabis vs placebo					
Withdrawals due to adverse event	13 (1848)	RD 0.04 (0.02 to 0.07)	0.0009	25	Cannabinoid and cannabis
Serious adverse events	13 (1876)	RD 0.01 (-0.01 to 0.03)	0.29	0	No significant difference
Pain relief of 30% or greater	10 (1586)	RD 0.09 (0.03 to 0.15)	0.004	34	Cannabinoid and cannabis
Mean pain intensity	14 (1837)	SMD -0.35 (-0.60 to -0.09)	0.008	84	Cannabinoid and cannabis
Health-related quality of life	9 (1284)	SMD 0.02 (-0.10 to 0.13)	0.79	0	No significant difference
Sleep problems	8 (1386)	SMD -0.47 (-0.90 to -0.04)	0.03	92	Cannabinoid and cannabis
Psychological distress	7 (779)	SMD -0.32 (-0.61 to -0.02)	0.04	66	Cannabinoid and cannabis
Specific adverse event: Nervous system disorder	9 (1304)	RD 0.38 (0.18 to 0.58)	0.0003	94	Cannabinoid and cannabis
Specific adverse event: Psychiatric disorder	9 (1314)	RD 0.10 (0.06 to 0.15)	0.0001	54	Cannabinoid and cannabis

- **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Above

Parameter	Extraction items
	• **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Yes • **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable
Significance/direction	**See above if results listed by outcome:** Above
Heterogeneity	• **See above if I^2 available:** Above • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** "I^2 was less than 50% except for Patient Global Impression of Change (I^2 = 58%), mean pain intensity (I^2 = 55%), sleep problems (I^2 = 92%), psychological distress (I^2 = 66%), any adverse event (I^2 = 64%), nervous system disorders as adverse event (I^2 = 94%) and psychiatric disorders as adverse event (I^2 = 54%). We did not find clinical explanations for heterogeneity." p20 • **Causes of heterogeneity investigated:** Yes, I^2, random effects models, subgroup analysis
Comments	

Noori *et al.* (2021): Opioid-sparing effects of medical cannabis or cannabinoids for chronic pain: a systematic review and meta-analysis of randomised and observational studies

Parameter	Extraction items
First author and year of publication	Noori *et al.* (2021)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "to explore the impact of adding medical cannabis on opioid dose, other patient-important outcomes and related harms in patients with chronic pain using prescribed opioid therapy." p2 • **Exact review question and page number:** "to explore the impact of adding medical cannabis on opioid dose, other patient-important outcomes and related harms in patients with chronic pain using prescribed opioid therapy." p2 • **PICO elements reported in Introduction/Methods:**

Parameter	Extraction items
	➢ **Patient or population:** People living with chronic pain (pain symptoms had persisted for ≥3 months) using prescribed opioids ➢ **Setting:** Not specified ➢ **Intervention:** Medical cannabis ➢ **Comparison:** Prescribed opioids ➢ **Outcome:** Chronic pain
Participants (characteristics and numbers)	**For whole sample and subgroups:** n=1540 RCT; n=1578 observational studies The observational studies are excluded from the remainder of the extraction. • **Number of participants:** n=1540 • **Age:** Mean age range 58.0-61.5 years • **Gender:** 45.6% female • **Details of clinical diagnosis/indications:** Chronic cancer pain (n=1540)
Setting/context	**Countries (alphabetic order):** Not reported **Setting (university, public or private clinic):** Multicentre trial (5 RCTS) **Other relevant features of setting:** Not reported
Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** "adding medical cannabis (ie, phytocannabinoids, endocannabinoids or synthetic cannabinoids) on the use of prescription opioids among people living with chronic pain" p2 • **Dose and regimen:**

Parameter	Extraction items
	○ THC:CBD (including nabiximols and THC:CBD extract) (5 RCTs): 2.5-27 mg THC and 2.5-25 mg CBD; 1-48 sprays; daily • **Administration methods:** Oromucosal spray (5 RCTS) • **Comparator:** Opioids (5 RCTS) (*Note: Table 1 states all RCTs are placebo controlled. However, text and appendix forest plots indicate all RCTs use opioid as a control). • **Treatment duration:** Not specified (study duration range: 2-5 weeks) • **Timeframe for follow-up:** Not reported for included RCTs
Databases and sources searched	• **Number and names of databases:** 3; Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE and MEDLINE; inception-03/2020 • **Other sources:** Clinicaltrials.gov • **Grey literature:** Not reported • **Reference chasing:** Yes • **Expert consultation:** Yes (medical librarian) • **Dates:** Inception-03/2020 • **Search limits:** No • **Justifications for search limits:** Not applicable • **Other searches:** Not reported • **Protocol prepared:** Yes • **If yes, published:** Yes CRD42018091098 https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=91098 • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported

Parameter	Extraction items
	• **Extraction completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Funding of review:** "The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors." p10 • **Conflicts of interest of review:** None declared • **How conflicts of interest were managed:** Not applicable
Date Range (years) of included studies	• **Exact years for included studies:** 2010-2017
Number of primary studies included in the systematic review	• **Number of studies:** 5 RCTs (4 publications) • **Number of studies by study design:** 5 RCTs (4 publications) • **Study years:** 2010 (1 RCT); 2012 (1 RCT); 2017 (3 RCTs) • **Funding of included studies:** Industry (5 RCTS) • **Conflicts of interest of included studies:** Not reported
Types of studies included	**Planned study designs to be included:** RCT and observational **Reasons for including only RCTs/prospective cohort studies:** Not reported **List of excluded studies at full text and reasons for exclusion:** Not reported
Appraisal instruments used	**Full name of tools used:** Modified Cochrane risk of bias tool; GRADE system **Risk of bias criteria for AMSTAR 2 assessment, for RCTs record Yes/No for:** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes

Parameter	Extraction items
	• **Sequence generation (individual vs group randomisation):** No • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The authors reported the included trials as follows: High risk of bias (3 RCTs) and low risk of bias (2 RCTs) using their own classification strategy. However, according to Cochrane's Collaboration tool classification guide, and graphical information provided in the paper, the included trials appear to have a high risk of bias (5 RCTs). • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** o Overall: Low risk randomisation (0/5); low risk outcome ascertainment (0/5) *THC:CBD formulation (THC:CBD capsule, nabiximols) and opioid vs opioid* o Opioid dose reduction: Low risk randomisation (0/4); low risk outcome ascertainment (0/4) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** None • **Graphical or statistical test for publication bias:** Not reported for RCTs due to < 10 studies • **Authors' comments likelihood and magnitude of publication bias:** Not reported • **Authors' comment on how publication bias was dealt with:** Not applicable • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** No • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** Yes
Method of analysis	• **Description of method of analysis as per authors:** "All continuous measures for pain intensity and sleep disturbance were converted to a 10cm [visual analog scale]; the minimally important difference (MID) for both was 1cm. All continuous outcomes that were reported by more than one study were pooled to derive the weighted mean difference

Parameter	Extraction items
	(WMD) and associated 95%CI. We pooled binary outcomes (adverse events) as relative risks (RRs) and risk differences (RDs) and their associated 95% CIs. We conducted all meta-analyses with random-effects models and the DerSimonian-Laird method." p2-3 • **Justification for narrative synthesis or meta-analysis:** Above • **Justification for combining data in meta-analysis:** Above
Outcome assessed	**List of outcomes assessed and intended timeframes** • Primary outcomes: Opioid dose reduction • Secondary outcomes: Pain relief; sleep disturbance; emotional and physical functioning; adverse events • Intended timeframes: Not reported • Actual timeframes: 2-5 weeks study duration, follow-up periods not reported
Results/findings	• **Findings by outcome:** PRIMARY OUTCOME o Opioid dose reduction: Pooled data from four studies (n=1176) reported no significant difference between cannabinoid/opioid and opioid groups (WMD −3.4, 95% CI −12.67 to 5.86). SECONDARY OUTCOMES o Pain relief: Pooled data from five studies (n=1536) reported no significant difference between cannabinoid/opioid and opioid groups (WMD −0.18, 95% CI −0.38 to 0.02). o Sleep disturbance: Pooled data from five studies (n=1536) reported significant improvements in cannabinoid/opioid groups compared with opioid groups (WMD −0.22, 95% CI −0.39 to −0.06). o Emotional functioning: One study (n=177) reported no significant difference between cannabinoid/opioid group and opioid groups (THC:CBD p=0.084, THC p=0.174).

Parameter	Extraction items

- Physical functioning: One study (n=177) reported no significant difference between cannabinoid/opioid group and opioid groups (THC:CBD p=0.108, THC p=0.631).
- Nausea (adverse event): Pooled data from four studies (n=1330) reported significantly higher risk of nausea in cannabinoid/opioid groups compared with opioid group (RR 1.43, 95% CI 1.04 to 1.96).
- Vomiting: Pooled data from four studies (n=1330) reported significantly higher risk of vomiting in cannabinoid/opioid groups compared with opioid group (RR 1.5, 95% CI 1.01 to 2.24).
- Constipation: Pooled data from three studies (n=1153) reported no significant difference between nabiximol/opioid and opioid groups (RR 0.85, 95% CI 0.54 to 1.35).

- **GRADE by outcome:**

Outcome	Measure (no. studies)	GRADE
Opioid dose reduction	4	Very low
Pain relief	5	High
Sleep disturbance	5	High
Physical functioning	1	Moderate
Emotional functioning	1	Moderate
Nausea (adverse event)	4	Moderate
Vomiting (adverse event)	4	Moderate
Constipation (adverse event)	3	Low

- **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):**

Outcome	No. studies (No. participants)	Summary estimate (95% CI)	P-value	I^2 (%)	Direction of effect
THC/CBD formulation (nabiximols and THC/CBD capsule) and opioid vs opioid					
Opioid dose reduction	4 (1176)	WMD −3.4 (−12.67 to 5.86).	NR	40.4	No significant effect

Parameter	Extraction items

Pain relief	5 (1536)	WMD −0.18 (−0.38 to 0.02	NR	28.1	No significant effect
Sleep disturbance	5 (1536)	WMD −0.22 (−0.39 to −0.06)	NR	0	THC/CBD
Nausea (adverse event)	4 (1330)	RR 1.43 (1.04 to 1.96)	NR	0	THC/CBD
Vomiting (adverse event)	4 (1330)	RR 1.50 (1.01 to 2.24)	NR	0	THC/CBD
Constipation (adverse event)	3 (1153)	RR 0.85 (0.54 to 1.35)	NR	0	No significant effect

- **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Above
- **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Yes
- **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Yes (only RCT included in extraction form).

Significance/direction

See above if results listed by outcome: Above

Heterogeneity

- **See above if I^2 available:** Above
- **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** "Studies included in our review administered different formulations of cannabis and cannabinoid products; however, pooled effects of outcomes reported in RCTs showed no important heterogeneity." p9
- **Causes of heterogeneity investigated:** "When we had at least two studies in each subgroup, we explored sources of heterogeneity with five prespecified subgroup hypotheses, assuming greater benefits with: (1) shorter versus longer duration of follow-up; (2) higher versus lower risk of bias; (3) enriched versus non-enriched study design; (4) chronic non-cancer versus chronic cancer-related pain and (5) higher versus lower THC content." p3

Parameter	Extraction items
Comments	This study included 18 studies (5 RCT, 13 observational studies). It was possible to extract data from RCT studies separately, unless stated otherwise, the information in this form relates to the 5 RCT studies (4 publications). The 13 observational studies included in Noori *et al.* 2021 included one retrospective cohort study. However, synthesis of this retrospective cohort study was combined with the other observational studies. There, it was not possible to extract this data. Risk of bias assessment were rated as "DYes: definitely yes; DNo: definitely no; PYes: probably yes; PNo: probably no DYes/PYes= low risk of bias; DNo/PNo=high risk of bias." Appendices p27. This study states all RCTs are placebo controlled. However, forest plots in the appendices and article text suggest that all RCTs use an active comparator (opioids) control rather than a placebo control. "Although RCT results do not support reduction in opioid dose by adding medical cannabis for opioids, the evidence is also very low certainty, primarily because investigators instructed patients to maintain their current opioid dose" p9

Oordt *et al.* (2021): Medical cannabis for treating various symptoms in Switzerland

Parameter	Extraction items
First author and year of publication	Oordt *et al.* (2021)
Objectives	• **Study objectives:** "The overall aim of this HTA report was to investigate the efficacy, effectiveness, safety, cost-effectiveness, and budget impact of medical cannabis use in chronic pain and spasticity in Switzerland." p2

Parameter	Extraction items
Report exact review question(s) and page number	• **Exact review question and page number:** "What is the efficacy, effectiveness, and safety, as well as the cost-effectiveness and budget impact of medical cannabis compared to placebo, no treatment, or standard of care, in patients of all ages with one of the four pre-specified symptoms chronic pain, spasticity, unintentional weight loss, or nausea and vomiting related to cancer treatment?" p22 "Footnote: Efficacy is the extent to which a specific health technology produces a beneficial, reproducible result under study conditions compared with alternative technologies (i.e. internal validity). Effectiveness is the extent to which a specific health technology, when applied in real world circumstances in the target group, does what it is intended to do for a diagnostic or therapeutic purpose regarding the benefits compared with alternative technologies (i.e. external validity). Safety is a judgement of the harmful effects and their severity using the health technology. Relevant adverse events are those that result in death, are life-threatening, require inpatient hospitalisation or cause prolongation of existing hospitalisation (i.e. serious adverse events) and those that occur repetitively and the most frequent (highest rate)." p22 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population: "**1. Patients (all ages) with the symptom chronic pain with any underlying cause 2. Patients (all ages) with the symptom treatment-resistant residual spasticity with any underlying cause" p32 ➢ **Setting:** Not specified ➢ **Intervention:** "Medical cannabis, prescribed as standalone treatment or add-on treatment" p33 ➢ **Comparison:** "Placebo/No treatment for chronic pain or spasticity/Standard of care according to the treatment guidelines (i.e. conventional drugs for the chronic pain condition or spasticity)" p33 ➢ **Outcome:** ➢ 1. "Efficacy/effectiveness of medical cannabis; chronic pain ○ a. Clinically relevant patient-reported pain relief ○ b. Withdrawal due to lack of pain relief efficacy of medical cannabis

Parameter	Extraction items
	○ c. Improvement in health-related quality of life ➢ 2. Efficacy/effectiveness of medical cannabis; spasticity ○ a. Clinically relevant improvement in a specific spasticity aspect ○ b. Withdrawal due to lack of anti-spasticity efficacy of medical cannabis ○ c. Improvement in [health-related quality of life] ➢ 3. Safety of medical cannabis: ○ a. Occurrence of cannabis-associated serious adverse event ○ b. Withdraw of treatment due to adverse effects of medical cannabis" p33 ➢ Additional health economic outcomes
Participants (characteristics and numbers)	**For whole sample and subgroups** • **Number of participants:** ○ Number analysed: Chronic pain 1863, spasticity 1178, total 3041. ○ Intention to treat: Chronic pain 1870, spasticity 1215, total 3085. ○ Please note that two studies of spasticity (Zajicek 2003 and Zajicek 2005) share a cohort (n=630 and n=502 respectively), and we have used only the n=630 cohort in our calculations here to avoid double-counting participants. • **Age:** Mean range 47.1- 62.8 years • **Gender:** 60.7% female based on 8 RCTs reporting gender breakdown • **Details of clinical diagnosis/indications:** Separate analyses for chronic pain (advanced cancer n=796, multiple sclerosis n=644 analysed, n=645 intention to treat, allodynia n=365 analysed, n=371 intention to treat, rheumatoid arthritis n=58) and spasticity (multiple sclerosis n=1119 analysed, n=1156 intention to treat, motor neuron disease n=59)

Parameter	Extraction items
Setting/context	**Countries (alphabetic order):** Australia, Belgium, Bulgaria, Canada, Czech Republic, Estonia, France, Germany, Hungary, India, Israel, Italy, Latvia, Lithuania, Poland, Romania, Spain, Taiwan, UK, USA **Setting (university, public or private clinic):** Not reported **Other relevant features of setting:** Not reported

Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** "Medical cannabis, prescribed as standalone treatment or add-on treatment" p33
	• **Dose and regimen:**
	• Chronic pain:
	  ○ THC:CBD spray 100 µl containing: 2.7 mg THC and 2.5 mg CBD; self-titration to optimal dose; maximum dosage ranged 6-48 sprays per day
	  ○ Dronabinol (THC) daily dose 7.5-15.0 mg/day
	• Spasticity:
	  ○ THC:CBD spray 100 µl containing: 2.7 mg THC and 2.5 mg CBD; self-titration to optimal dose; maximum dosage ranged 12-48 sprays per day
	  ○ Dronabinol (THC) daily dose 7.5-15.0mg/day
	  ○ THC:CBD capsules with 2.5 mg THC, 1.25 mg CBD, <5% other cannabinoids; dose based on body-weight, max. of 25 mg daily
	• **Administration methods:** Oromucosal spray (10 studies), capsules (2 studies), not reported (1 study)
	• **Comparator:** Chronic pain: Matching placebo capsules, solution, or spray with same excipients plus colourant
	• **Treatment duration:** Range 3-14 weeks

Parameter	Extraction items
Databases and sources searched	• **Timeframe for follow-up:** 12 studies had no follow-up, 1 study 12 months • **Number and names of databases:** 3: Medline (Pubmed), Embase, NHS Economic Evaluation Database (used for economic literature searches only, not included in this extraction) • **Other sources:** Search of websites of health technology assessment agencies • **Grey literature:** Not reported • **Reference chasing:** Yes • **Expert consultation:** Yes; information specialist • **Dates:** 1980 - 22 January 2020 • **Search limits:** Date, Language (English, French, German, Dutch), no animal studies, no reviews and meta-analyses • **Justifications for search limits:** Yes "Since a large amount of medical cannabis studies was published in the eighties and nineties, a time horizon of forty years was chosen" p36 • **Other searches:** Not reported • **Protocol prepared:** No • **If yes, published:** Not applicable • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Partially; 30% screened in duplicate • **If yes, rate of agreement:** Min 98% agreement title and abstract at 30% mark; Min 95% agreement full-text at 10% mark • **Extraction completed in duplicate:** Not reported • **If yes, rate of agreement:** Not applicable • **Funding of review:** Review carried out by Swiss Federal Office of Public Health • **Conflicts of interest of review:** Not reported

Parameter	Extraction items
	• **How conflicts of interest were managed:** Not reported
Date Range (years) of included studies	• **Exact years for included studies:** 2003-2019
Number of primary studies included in the systematic review	• **Number of studies:** 13 (8 RCTs of chronic pain, 5 RCTs of spasticity) • **Number of studies by study design:** 13 RCTs • **Study years:** 2003 (1 RCT), 2005 (2 RCTs), 2006 (1 RCT), 2007 (2 RCTs), 2010 (1 RCT), 2013 (1 RCT), 2014 (1 RCT), 2017 (2 RCTs), 2018 (1 RCT), 2019 (1 RCT) • **Funding of included studies:** 10 (8 chronic pain, 2 spasticity) RCTs funded by industry; funding sources for remaining 3 RCTs not specified • **Conflicts of interest of included studies:** Not reported
Types of studies included	**Planned study designs to be included:** RCTs, open-label extension studies of RCTs **Reasons for including only RCTs/prospective cohort studies:** Not specified **List of excluded studies at full text and reasons for exclusion:** Yes (appendix 15.2)
Appraisal instruments used	**Full name of tools used:** Key criteria from GRADE assessment **<u>For RCTs, record Yes/No for appraisal instrument assessment of:</u>** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** No • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:**

Parameter	Extraction items
	• The review authors describe 11/13 studies as moderate risk and 2/13 as high risk. HRB notes that according to Cochrane's Collaboration tool, and graphical information provided in the paper, the included trials appeared to have a high risk of bias (13/13) • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** o Overall: Low risk randomisation (6/13); Low risk outcome ascertainment (0/13) *THC:CBD spray vs placebo:* o Worst pain: Low risk randomisation (0/2); Low risk outcome ascertainment (0/2) o Pain score: Low risk randomisation (2/3); Low risk outcome ascertainment (2/3) o Neuropathic pain: Low risk randomisation (2/4); Low risk outcome ascertainment (0/4) o 30% reduction in pain: Low risk randomisation (2/4); Low risk outcome ascertainment (0/4) o 50% reduction in pain: Low risk randomisation (2/4); Low risk outcome ascertainment (0/4) o Quality of life: Low risk randomisation (2/4); Low risk outcome ascertainment (0/4) o Morning pain at rest: Low risk randomisation (0/1); Low risk outcome ascertainment (0/1) o 30% reduction in spasticity: Low risk randomisation (0/3); Low risk outcome ascertainment (0/3) o Spasticity scores: Low risk randomisation (0/2); Low risk outcome ascertainment (0/2) o Observer-rated spasticity: Low risk randomisation (2/2); Low risk outcome ascertainment (1/2) o Withdrawals due to adverse events: Low risk randomisation (6/11); Low risk outcome ascertainment (0/11) *Dronabinol vs placebo:* o Worst pain: Low risk randomisation (0/1); Low risk outcome ascertainment (0/1) o Neuropathic pain: Low risk randomisation (0/1); Low risk outcome ascertainment (0/1) o Quality of life: Low risk randomisation (0/1); Low risk outcome ascertainment (0/1)

Parameter	Extraction items
	○ Observer-rated spasticity: Low risk randomisation (1/1); Low risk outcome ascertainment (0/1) ○ Withdrawals due to adverse events: Low risk randomisation (1/2); Low risk outcome ascertainment (0/2) **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** "Furthermore, multiple factors increase the risk of bias in studies on medical cannabis, however the extent as well as the direction of the potential bias are difficult to comprehend. Although it was possible to calculate pooled estimates for part of the safety outcomes and some patient populations, the issues highlighted for efficacy also apply to safety, resulting in an incomplete safety profile of medical cannabis use for chronic pain and spasticity." p67 • **Graphical or statistical test for publication bias:** Not reported • **Authors' comments likelihood and magnitude of publication bias:** Not applicable • **Authors' comment on how publication bias was dealt with:** Not applicable • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** Not applicable • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** "Heterogeneity between studies in outcomes and outcome measures, data skewness, and incompleteness of study results (i.e. studies omitting to report detailed results such as treatment effects in the intervention and placebo arms or measures of variability) precluded the calculation of pooled estimates for efficacy data for the stratified pain and spasticity populations. Overall, the efficacy data on medical cannabis use for chronic pain and spasticity was inconsistent (i.e. studies with comparable patient populations and similar type of medical cannabis did not show consistent results) and inconclusive (i.e. none of the studies was able to draw a definitive conclusion on the efficacy of medical cannabis). Furthermore, multiple factors increase the risk of bias in studies on medical cannabis, however the extent as well as the direction of the potential bias are difficult to comprehend. Although it was possible to calculate pooled estimates for

Parameter	Extraction items
	part of the safety outcomes and some patient populations, the issues highlighted for efficacy also apply to safety, resulting in an incomplete safety profile of medical cannabis use for chronic pain and spasticity." p67
Method of analysis	• **Description of method of analysis as per authors:** "Pooled estimates were calculated and a GRADE assessment for the certainty of the evidence on outcome level was made, when 1) two or more studies within the above mentioned stratifications reported on the same outcome, and 2) sufficient data were reported in the studies (i.e. for efficacy data: mean change from baseline and standard deviation in the treatment arms; or number of patients with an outcome and total number of patients in the treatment arms; plus treatment difference between the treatment arms; for safety data: number of patients with an outcome and total number of patients in the treatment arms). This could be done for two outcomes: mortality and withdrawal of treatment due to adverse events. Pooling of data were done with the number of patients provided in the articles (i.e. for safety the data based on the number of randomised patients) and an unadjusted risk ratio was calculated. Considering the heterogeneity in the data, a random-effects model (DerSimonian & Laird) was used for the analyses. All analyses were conducted using the MetaXL (www.epigear.com) add-in for Microsoft Excel. The evidence on these outcomes was summarised in GRADE evidence profiles. For most efficacy and safety outcomes it was, however, not possible to calculate pooled estimates and implement a GRADE assessment: "for the efficacy outcomes clinically relevant patient-reported pain relief, improvement in a specific spasticity aspect, withdrawal due to lack of efficacy of medical cannabis, and improvement in [health-related quality of life]; and for the safety outcome occurrence of cannabis-associated [serious adverse events]. These outcomes were presented in summary tables and descriptively summarised per outcome measure." p42 • **Justification for narrative synthesis or meta-analysis:** As above • **Justification for combining data in meta-analysis:** Not reported
Outcome assessed	**List of outcomes assessed and intended timeframes**

Parameter	Extraction items
	• Primary outcomes: Efficacy for chronic pain (patient-rated pain score, worst pain score, percentage treatment responders, quality of life); efficacy for spasticity (Ashworth scale (observer-rated spasticity), patient-rated NRS spasticity score, quality of life, percentage treatment responders); safety (serious adverse events, withdrawal due to adverse events). • Secondary outcomes: Not reported • Intended timeframes: >2 weeks • Actual timeframes: 3- 16 weeks (12 month follow-up for one study)
Results/findings	• **Findings by outcome:** *Efficacy* ○ Cancer pain: One RCT (n=399) found no statistically significant treatment differences in worst pain scores between THC:CBD spray and placebo for cancer pain (adjusted treatment difference 0.11, 95% CI -0.21 to 0.44, p=0.496). One RCT (n=397) found no statistically significant treatment differences in worst pain scores between THC:CBD spray and placebo for cancer pain (adjusted treatment difference -0.06, 95% CI -0.36 to 0.24, p=0.678). ○ Neuropathic pain: Two RCTs found statistically significant treatment differences in favour of THC:CBD spray compared to placebo in pain scores (pain score adjusted treatment difference -1.25, 95% CI -2.11 to -0.39, p=0.005, n=65; neuropathic pain score adjusted treatment difference -0.96, 95% CI -1.59 to -0.32, p=0.004, n=125). Two RCTs reported no significant difference between of THC:CBD spray compared to placebo on metrics of pain reduction (pain scores, treatment difference -0.17, 95% CI -0.62– to 0.29, p=0.47, n=339; neuropathic pain scores, adjusted treatment difference -0.34, 95% CI -0.79 to 0.11, p=0.139, n=240). The unadjusted pooled estimates for a ≥30% and ≥50% reduction in pain with THC:CBD spray compared to placebo were OR 1.36 (95% CI 0.92 to 2.00) and OR 1.59 (0.62 to 4.04) respectively, neither of which were statistically significant.

Parameter	Extraction items
	One RCT (n=240) reported a significantly higher proportion of treatment responders in the treatment (THC:CBD spray) arm versus the control arm (28% vs 16%, OR 1.97, 95% CI 1.05, 3.70, p=0.034). One RCT (n=240) found no statistically significant difference in pain scores between dronabinol and placebo (-1.92 vs -1.81, p=0.676). ○ Quality of life in neuropathic pain: One RCT (n=125) found a statistically significant change in quality of life measures for patients receiving THC:CBD spray compared to placebo, with an improvement in the pain disability index (treatment difference -5.85, 95% CI -9.62 to -2.09, p=0.003). Two RCTs found no statistically significant difference in quality of life between THC:CBD spray and placebo (n=339, p=0.396 for EQ-5D health state index, p=0.383 for EQ-5D health status VAS; n=240, p=0.760.) One RCT (n=240) found no statistically significant difference in quality of life between dronabinol and placebo (summary statistics not reported). ○ Musculoskeletal pain: One RCT (n=58) found a statistically significant treatment difference between THC:CBD spray and placebo in morning pain at rest for patients with chronic pain caused by rheumatoid arthritis (treatment difference -1.04, 95% CI -1.90 to -0.18, p=0.018). ○ Spasticity: Pooled data from two studies (n=489) reported no significant difference between THC:CBD and placebo for a ≥ 30% reduction in spasticity (OR 1.70, 95% CI 0.99 to 2.92). One RCT (n=184) reported statistically significant treatment differences in spasticity in patients with multiple sclerosis (treatment difference -0.52, 95% CI -1.029 to -0.004, p=0.048). One RCT (n=305) reported no significant treatment differences in spasticity in participants with multiple sclerosis between THC:CBD and placebo arms (treatment difference -0.23, p=0.219).

Parameter	Extraction items
	One RCT (n=362) found a small significant effect for change in observer-rated spasticity for participant with multiple sclerosis receiving dronabinol at 52 weeks follow-up compared to placebo (n=362, treatment difference 2.05, p=0.01), but no effect for THC:CBD capsules (MD 0.32, 95% CI -1.04 to 1.67). One RCT (n=59) reported improvement in observer-rated spasticity in participant with motor-neurone disease after six weeks with THC:CBD spray compared to placebo (treatment difference -0.32, 95% CI -0.57 to -0.07, p=0.013), but no change in patient-rated spasticity (treatment difference -0.49, 95% CI -1.48 to 0.50, p=0.324) nor in proportion of responders for ≥30% reduction or ≥50 reduction in spasticity. ○ Quality of life in spasticity: One RCT (n=305) reported no significant difference between THC:CBD spray and placebo arms for any measure of quality of life (p=0.175 for EQ-5D health state index, p=0.538 for EQ-5D health status VAS). *Safety* ○ Cancer pain: Pooled data from two RCTs (n=796) reported no statistically significant effect of THC:CBD spray on occurrence of deaths (RR 0.90; 95% CI 0.62-1.30) or withdrawal from treatment due to adverse events (RR 1.21; 95% CI 0.90-1.63). ○ Neuropathic pain: In two RCTs on THC:CBD spray (n=305), did not report on number of deaths in treatment or placebo groups. Pooled data from four RCTs reported significantly increased withdrawals from treatment due to adverse events were observed in THC:CBD groups compared to placebo groups (13.3% vs 5.5%, RR 2.45; 95% CI 1.23-4.87). One RCT on dronabinol reported no deaths and withdrawal of 9.7% of participants due to adverse events in treatment arm compared to 0.9% in placebo arm. ○ Musculoskeletal pain: No deaths were reported in one RCT (n=58) on THC:CBD spray. No withdrawals due to adverse events were reported in the treatment arm, with 11.1% reported in the placebo arm.

Parameter	Extraction items

- Spasticity due to multiple sclerosis: Pooled analysis of two RCTs (n=526) showed no difference between THC:CBD spray and placebo arms in withdrawals from treatment due to adverse events (5.2% vs 3.0%, RR 1.75; 95% CI 0.72-4.23).

  One RCT on dronabinol, THC:CBD capsules and placebo reported seven, two, and zero participants withdrawing from treatment due to adverse events in the respective arms. Incomplete reporting on death outcomes; two deaths reported in THC:CBD capsules treatment arm.
- Spasticity due to motor neuron disease: One RCT (n=59) on THC:CBD spray reported no withdrawals in treatment or placebo arms.

- **GRADE by outcome:** GRADE assessment only carried out for outcomes for which two or more studies reported on the same outcome for the same patient group and sufficient data was reported in the studies.

Outcome	No. studies	GRADE
Adverse events: Mortality (cancer pain)	2	High
Adverse events: Withdrawal from treatment due to adverse events (cancer pain)	2	Moderate
Adverse events: Withdrawal from treatment due to adverse events (neuropathic pain)	4	Moderate
Adverse events: Withdrawal from treatment due to adverse events (spasticity due to multiple sclerosis)	2	Moderate

- **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):**

Outcome	No. studies (No. participants)	Summary estimate (95% CI)	P-value	I^2 (%)	Direction of effect
THC:CBD spray vs placebo					
≥30% reduction in pain (neuropathic pain)	4 (769 intention to treat)	OR 1.36 (0.92 to 2.00)	Not reported	Not reported	No significant difference

Parameter	Extraction items

≥50% reduction in pain (neuropathic pain)	4 (769 intention to treat)	OR 1.59 (0.62 to 4.04)	Not reported	Not reported	No significant difference
≥30% reduction in spasticity (multiple sclerosis)	2 (489)	OR 1.70 (0.99 to 2.92)	Not reported	Not reported	No significant difference
Adverse events: Cancer pain mortality	2 (796)	RR 0.90 (0.62 to 1.30)	Not reported	Not reported	No significant difference
Withdrawal due to adverse events (cancer pain)	2 (796)	RR 1.21 (0.90 to 1.63)	Not reported	Not reported	No significant difference
Withdrawal due to adverse events (neuropathic pain)	4 (776)	RR 2.45 (1.23 to 4.87)	Not reported	Not reported	Withdrawals significantly more likely with THC:CBD spray than placebo
Withdrawal due to adverse events (multiple sclerosis)	2 (526)	RR 1.75 (0.72 to 4.23)	Not reported	Not reported	No significant difference

- **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Meta-analysis results as above
- **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Yes; random effects model used
- **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable

Significance/direction

See above if results listed by outcome: Above

Heterogeneity

- **See above if I^2 available:** Not reported
- **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** "Heterogeneity between studies in outcomes and outcome measures, data skewness, and incompleteness of study results (i.e. studies omitting to report detailed results such as treatment effects in the intervention and placebo arms or measures of variability) precluded the calculation of pooled estimates for efficacy data for the stratified pain and spasticity populations...resulting in an incomplete safety profile of medical cannabis use for chronic pain and spasticity." p67
- **Causes of heterogeneity investigated:** Not reported

Parameter	Extraction items
Comments	"Overall, the efficacy data on medical cannabis use for chronic pain and spasticity was inconsistent (i.e. studies with comparable patient populations and similar type of medical cannabis did not show consistent results) and inconclusive (i.e. none of the studies was able to draw a definitive conclusion on the efficacy of medical cannabis). Furthermore, multiple factors increase the risk of bias in studies on medical cannabis" p67

Paunescu *et al.* (2020): A Systematic Review of Clinical Studies on the Effect of Psychoactive Cannabinoids in Psychiatric Conditions in Alzheimer Dementia

Parameter	Extraction items
First author and year of publication	Paunescu *et al.* (2020)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "To draw conclusions regarding the efficacy and safety of psychotropic cannabinoids in Alzheimer dementia agitation and aggression." p251 Table 1 • **Exact review question and page number:** "Which is the level of evidence, from quantitative and qualitative point of view, concerning the efficacy and safety of the treatment with psychotropic cannabinoids of neuropsychiatric symptoms in [Alzheimer's Disease]?" p249 (abstract • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** People with agitation/aggression in Alzheimer disease or other dementia ➢ **Setting:** Not specified ➢ **Intervention:** A natural or synthetic cannabinoid ➢ **Comparison:** Not specified ➢ **Outcome:** Efficacy (neuropsychiatric symptoms) and safety

Parameter	Extraction items
Participants (characteristics and numbers)	**For whole sample and subgroups** • **Number of participants:** N=238 (see notes for discrepancy) • **Age:** Mean age range 22.6-87.0 years • **Gender:** 34.1% female (not reported in 1 RCT) • **Details of clinical diagnosis/indications:** Alzheimer's Disease (n=41); Alzheimer's Disease, vascular dementia, mixed dementia (n=82); vascular and mixed dementia (n=18); major neurocognitive disorder due to Alzheimer's Disease or Alzheimer's Disease and major vascular neurocognitive disorder (n=77)
Setting/context	**Countries (alphabetic order):** Not reported **Setting (university, public or private clinic):** Hospital (1 RCT); Institutions of dementia care (1 RCT); Not reported (7 RCTs) **Other relevant features of setting:** Not reported

Description of Interventions/ phenomena of interest	➢ **Exact definition of the intervention as per authors:** A natural or synthetic cannabinoid
	• **Dose and regimen:**
	  ○ Dronabinol THC (8 RCTs): 0.75-2.5 mg; twice daily, three times daily, not reported
	  ○ Nabilone (1 RCT): 1.6 mg; not reported
	• **Administration methods:** Not reported
	• **Comparator:** Placebo (9 RCTs)
	• **Treatment duration:** 3 days to 7 weeks
	• **Timeframe for follow-up:** Not reported

Parameter	Extraction items
Databases and sources searched	• **Number and names of databases:** 3; PubMed, EMBASE, Cochrane Database of Systematic Reviews; inception-31/03/2019 • **Other sources:** Google Scholar Data, and Clinicaltrials.gov • **Grey literature:** Not reported • **Reference chasing:** Yes • **Expert consultation:** No • **Dates:** Inception-31/03/2019 • **Search limits:** English language • **Justifications for search limits:** Not applicable • **Other searches:** Not applicable • **Protocol prepared:** No • **If yes, published:** Not applicable • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Not reported • **If yes, rate of agreement:** Not applicable • **Extraction completed in duplicate:** Not reported • **If yes, rate of agreement:** Not applicable • **Funding of review:** Not reported • **Conflicts of interest of review:** "The authors have no conflicts of interest to declare." p249 • **How conflicts of interest were managed:** Not applicable
Date Range (years) of included studies	• **Exact years for included studies:** 1997-2019

Parameter	Extraction items
Number of primary studies included in the systematic review	• **Number of studies:** 6 RCTs (9 reports) • **Number of studies by study design:** 6 RCTs (9 reports) • **Study years:** 1997 (1 RCT); 2007 (1 RCT); 2011 (1 RCT); 2015 (3 RCTs); 2017 (1 RCT); 2018 (1 RCT); 2019 (1 RCT) • **Funding of included studies:** Not reported • **Conflicts of interest of included studies:** Not reported
Types of studies included	**Planned study designs to be included:** RCT, interventional products **Reasons for including only RCTs/prospective cohort studies:** Not reported **List of excluded studies at full text and reasons for exclusion:** List reported, reasons not reported
Appraisal instruments used	**Full name of tools used:** Name not specified (indicate Cochrane on p266) **Risk of bias criteria for AMSTAR 2 assessment, for RCTs record Yes/No for:** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The authors did not provide an overall assessment of risk of bias for each trial. However, HRB notes that according to Cochrane's Collaboration tool, and graphical information provided in the paper, the included trials appeared to have a high risk of bias (5) and unclear risk of bias (4). • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** ○ Overall: Low risk randomisation (1/9); low risk outcome ascertainment (4/9)

Parameter	Extraction items
	○ Neuropsychiatric symptoms (aggression/agitation in dementia): Low risk randomisation (1/7); low risk outcome ascertainment (3/7) ○ Adverse events: Low risk randomisation (1/8); low risk outcome ascertainment (4/9) ○ Drop-out due to adverse events: Low risk randomisation (0/1); low risk outcome ascertainment (1/1) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** "The sources of bias in the analyzed studies can be considered numerous, and, at least in the category Table 4. "Other bias," two elements have greatly disrupted the obtaining of conclusive results: (1) polypragmazia, a major role being played by the use of established or less established psychotropic drugs (other than cannabinoids) in an effort to reduce agitation and aggressive behavior of patients, and (2) a large number of concomitant symptoms, for example, pain (very commonly causing anxiety and agitation). Considering all of the above, from the clinical trials analyzed, no clear conclusion can be drawn on the effectiveness of psychoactive cannabinoids in the treatment of psychiatric manifestations, in particular, agitation and aggression from [Alzheimer's Disease]." p266-267 • **Graphical or statistical test for publication bias:** Not reported • **Authors' comments likelihood and magnitude of publication bias:** Not reported • **Authors' comment on how publication bias was dealt with:** Not reported • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** No • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** "The sources of bias in the analyzed studies can be considered numerous, and, at least in the category Table 4. "Other bias," two elements have greatly disrupted the obtaining of conclusive results: (1) polypragmazia, a major role being played by the use of established or less established psychotropic drugs (other than cannabinoids) in an effort to reduce agitation

Parameter	Extraction items
	and aggressive behavior of patients, and (2) a large number of concomitant symptoms, for example, pain (very commonly causing anxiety and agitation). Considering all of the above, from the clinical trials analyzed, no clear conclusion can be drawn on the effectiveness of psychoactive cannabinoids in the treatment of psychiatric manifestations, in particular, agitation and aggression from [Alzheimer's Disease]." p266-267
Method of analysis	• **Description of method of analysis as per authors:** Not reported • **Justification for narrative synthesis or meta-analysis:** "Pooled analysis of patients from the clinical studies included could not be performed. One reason was the inclusion of patients with other types of dementia, for example, vascular or mixed [Alzheimer's Disease] plus vascular, another one was the dementia's gravity that was extremely diverse from Mini-Mental Status Examination=0 to [Mini-Mental Status Examination]=18.5." p256 • **Justification for combining data in meta-analysis:** Not applicable
Outcome assessed	**List of outcomes assessed and intended time frames:** • Primary outcomes: Neuropsychiatric symptoms, adverse events, drop-outs • Secondary outcomes: None reported • Intended timeframes: Not reported • Actual timeframes: 3 days-7 weeks
Results/findings	• **Findings by outcome:** ○ Neuropsychiatric symptoms/agitation and aggression: Four studies report a possible beneficial effect of cannabinoids on aggression. Of these, one study (n=38) reported a significant improvement in nabilone group compared with placebo groups (b=-4, CI -6.5 to -1.5, p=0.003) and three studies (n=15; n=44; n=2) reported significant improvements in dronabinol groups compared with placebo groups (no summary statistics reported). Two studies (n=72) reported no significant difference between dronabinol and placebo groups.

Parameter	Extraction items
	○ Safety: One study (n=38) reported increased sedation in nabilone groups compared with placebo (45% vs 16%, p=0.02) but treatment-limiting sedation was not significant. One study (n=50) reported no significant difference in total adverse events between dronabinol (66.7%) and placebo (53.8%) groups (p=0.36). One study (n=18) reported no significant differences in mobility, dizziness, somnolence, and balance disorders between dronabinol and placebo groups. Three studies (n=72) indicated data on adverse events was collected, however the direction of effect (if any) cannot be ascertained from synthesis (no summary statistics reported). ○ Tolerability: One study (n=22) reported one dropout in THC group and one dropout in placebo group (no summary statistics reported). • **GRADE by outcome:** Not reported • **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):** Not applicable • **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Not applicable • **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Not applicable • **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable
Significance/direction	**See above if results listed by outcome:** Above
Heterogeneity	• **See above if I^2 available:** Above • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** "Risk of bias across studies and heterogeneity were very high due to the difference of study population, design, inclusion criteria, outcomes, and safety issues." p256

Parameter	Extraction items
	• **Causes of heterogeneity investigated:** Not reported
Comments	Authors report total of 422 participants. This figure was calculated by "multiplying selected patients with the number of psychoactive cannabinoid treatments in crossover studies, namely studies of Van den Elsen et al, using tetrahydrocannabinol (THC) and Herrmann et al, in which nabilone was used)" p250. In this form, participant figures have been extracted from Table 2.

Price *et al.* (2022): The Efficacy of Cannabis in Reducing Back Pain: A Systematic Review

Parameter	Extraction items
First author and year of publication	Price *et al.* (2022)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "To critically analyze the evidence and efficacy of cannabis to treat surgical and nonsurgical back pain via a Systematic Review" p343 • **Exact review question and page number:** "to evaluate the efficacy of medical cannabis in reducing pain in patients following spine surgery, for patients suffering from chronic low back or neck pain, and patients affected by previous spinal cord injury pain" p345 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** "Adults undergoing spinal surgery (acute pain), those with chronic low back or neck pain (chronic defined as ≥12 weeks), and those with chronic neuropathic pain following a spinal cord injury." p345 ➢ **Setting:** Not specified ➢ **Intervention:** "comparing medical cannabinoid use, any dose, and any administration" p345 ➢ **Comparison:** "to any non-cannabinoid treatment." p345

Parameter	Extraction items
	➢ **Outcome:** Pain
Participants (characteristics and numbers)	**For whole sample and subgroups:** n=79 (RCT); n=31 (observational) The observational study is excluded from the remainder of the extraction. • **Number of participants:** n=79 • **Age:** Mean age range 46.4-50.1 years • **Gender:** 45.4% female • **Details of clinical diagnosis/indications:** Back pain (disc herniation, foraminal stenosis, scoliosis, spondylarthrosis, osteochondrosis) (n=30); spinal cord injury (n=7); spinal cord injury and multiple sclerosis (n=42)
Setting/context	**Countries (alphabetic order):** Austria (1 RCT); USA (2 RCTs) **Setting (university, public or private clinic):** Not reported **Other relevant features of setting:** Not reported
Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** • **Dose and regimen:** ○ Nabilone (1 RCT): 0.25 mg; 1-4 times daily ○ Dronabinol (1 RCT): 20 mg; daily ○ Delta 9-THC (1 RCT): 2.9-6.7%; 12-20 puff; per eight-hour session • **Administration methods:** Oral (2 RCTs); Inhalation (1 RCT, 1 prospective cohort)

Parameter	Extraction items
	• **Comparator:** Placebo (1 RCT); diphenhydramine (1 RCT); mannitol (1 RCT) • **Treatment duration:** Not specified (study duration range: 4-12 weeks) • **Timeframe for follow-up:** Not reported for included RCTs
Databases and sources searched	• **Number and names of databases:** 4: MEDLINE (PubMed), EMBASE (Ovid), Cochrane Central Register of Controlled Trials (CENTRAL), and Cochrane Database of Systematic Reviews (CDSR); Inception to 31/12/2020 • **Other sources:** Not reported • **Grey literature:** Not reported • **Reference chasing:** Yes • **Expert consultation:** No • **Dates:** Inception to 31/12/2020 • **Search limits:** No • **Justifications for search limits:** Not applicable • **Other searches:** Not reported • **Protocol prepared:** Not reported • **If yes, published:** Not applicable • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported

Parameter	Extraction items
	• **Funding of review:** "The author(s) received no financial support for the research, authorship, and/or publication of this article" p351 • **Conflicts of interest of review:** "The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article" p351 • **How conflicts of interest were managed:** Not applicable
Date Range (years) of included studies	• **Exact years for included studies:** 2006-2016
Number of primary studies included in the systematic review	• **Number of studies:** 3 RCTs • **Number of studies by study design:** 3 RCTs • **Study years:** 2006 (1 RCT); 2010 (1 RCT); 2016 (1 RCT) • **Funding of included studies:** Not reported • **Conflicts of interest of included studies:** Not reported
Types of studies included	**Planned study designs to be included:** Any comparative trial **Reasons for including only RCTs/prospective cohort studies:** Not applicable **List of excluded studies at full text and reasons for exclusion:** Yes
Appraisal instruments used	**Full name of tools used:** Criteria and methods developed by the Cochrane Back Review Group; GRADE system **<u>Risk of bias criteria for AMSTAR 2 assessment, for RCTs record Yes/No for:</u>** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes

Parameter	Extraction items
	• **Selective reporting:** Yes **<u>Risk of bias criteria for AMSTAR 2 assessment, for prospective cohort studies record Yes/No for:</u>** • **Confounding:** Yes • **Selection bias:** Yes • **Exposure and outcomes:** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The included RCTs had fair risk of bias (2 RCTs) and low risk of bias (1 RCT). • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** o Overall: Low risk randomisation (2/3); low risk outcome ascertainment (3/3) *THC (nabilone) + mannitol vs mannitol* o Pain intensity: Low risk randomisation (0/1); low risk outcome ascertainment (1/1) *THC (dronabinol) vs diphenhydramine* o Pain intensity: Low risk randomisation (1/1); low risk outcome ascertainment (1/1) *Delta-9-THC (cannabis) vs placebo* o Pain intensity post-surgery: Low risk randomisation (1/1); low risk outcome ascertainment (1/1) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** "Overall, the studies were well-performed. No studies demonstrated excessive or outright bias." p349 • **Graphical or statistical test for publication bias:** Not reported • **Authors' comments likelihood and magnitude of publication bias:** Not applicable

Parameter	Extraction items
	• **Authors' comment on how publication bias was dealt with:** Not applicable • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** No • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** No
Method of analysis	• **Description of method of analysis as per authors:** Not reported • **Justification for narrative synthesis or meta-analysis:** "Given the heterogeneity of the included studies, a meta-analysis of cannabis efficacy for treating back pain could not be performed." p350 • **Justification for combining data in meta-analysis:** Not applicable
Outcome assessed	**List of outcomes assessed and intended time frames** • Primary outcomes: Efficacy in assessing pain following spinal surgery; efficacy in assessing pain in patients with chronic low back or neck pain; efficacy in assessing pain in patients with chronic pain post spinal cord injury; adverse events • Secondary outcomes: Quality of life • Intended timeframes: Not specified • Actual timeframes: 4-12 weeks
Results/findings	○ **Findings by outcome:** PRIMARY OUTCOMES ○ Efficacy in assessing pain in patients with chronic low back or neck pain: One RCT (n=30) reported a statistically significant decrease in reported spinal pain intensity at the end of the study in both the intent-to-treat and the per-protocol analysis in cannabinoid (nabilone) group compared with placebo group (0.6 v

Parameter	Extraction items

0, p=0.006; 2.0 vs 0, p=0.004). This study also reported no significant difference in average spinal pain intensity between cannabinoid and active control (mannitol) groups. One RCT study reported (n=42) reported significant improvements in both THC dose groups (2.9%, 6.7%) compared with the placebo group (1 hr 4.4 v 3.4 v 2.8; 2 hr 4.2 v 3.7 v 3.0; 3hr 4.3 v 3.4 v 3.2 dose response, p<0.01). There was no significant difference between THC dose groups.

- Efficacy in assessing pain in patients with chronic pain post spinal cord injury: One RCT study (n=7) reported no significant difference between cannabinoid (dronabinol) and active control (diphenhydramine) groups (20 ±.84 vs -1.80 ±2.49, p=0.102).

SECONDARY OUTCOMES

- Quality of life: One study (n=30) also reported no significant difference in quality of life and average spinal pain intensity between cannabinoid and active control (mannitol) groups.
- Adverse events: One RCT study (n=30) reported no significant difference in the frequency of adverse events in the cannabinoid (dronabinol)/mannitol group compared with the active control (mannitol) (Fatigue 30% v 13%, p=0.227; Dry mouth 20% v 3%, p=0.125; Vertigo 33% v 10% , p=0.039; insomnia 17% v 3%, p=0.125). The other three studies also reported on adverse events; however, it was not possible to ascertain the significance of these findings.

- **GRADE by outcome:**

Outcome	No. studies	GRADE
Chronic back or neck pain	2	Very low
Chronic pain post spinal cord injury (1-3 hours)	1	Low
Chronic pain post spinal cord injury (7 weeks)	1	Very low

Parameter	Extraction items
	○ **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):** Not applicable ○ **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Above ○ **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Not applicable ○ **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Yes **For prospective cohort studies:** ○ **Combined effect estimates adjusted for confounding, rather than combining raw data:** Not applicable ○ **Justification for combining raw data provided, where adjusted effect estimates unavailable:** Not applicable
Significance/direction	**See above if results listed by outcome:** Above
Heterogeneity	• **See above if I^2 available:** Above • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** Not reported • **Causes of heterogeneity investigated:** The authors identified administration, synthetic compounds and study length as potential sources of heterogeneity.
Comments	This systematic review includes four studies (3 RCTs and 1 observational study). Unless specified otherwise, the information in this extraction for only reports on RCTs as per the umbrella review inclusion criteria.

Quintero *et al.* (2022): A Systematic Review on Cannabinoids for Neuropathic Pain Administered by Routes Other than Oral or Inhalation

Parameter	Extraction items
First author and year of publication	Quintero *et al.* (2022)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "we aimed at evaluating the safety and effectiveness of cannabinoids used by routes other than oral or inhalation for neuropathic pain compared to placebo or other medications in terms of pain relief, quality of life and adverse events" p3 • **Exact review question and page number:** "we aimed at evaluating the safety and effectiveness of cannabinoids used by routes other than oral or inhalation for neuropathic pain compared to placebo or other medications in terms of pain relief, quality of life and adverse events" p3 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** People with neuropathic pain ➢ **Setting:** Not specified ➢ **Intervention:** Cannabinoids used by routes other than oral or inhalation ➢ **Comparison:** Usual care, placebo, or no treatment ➢ **Outcome:** Pain relief, quality of life and adverse effects
Participants (characteristics and numbers)	**For whole sample and subgroups** • **Number of participants:** N=29 • **Age:** Mean 68 years; range 35-79 years • **Gender:** 37.9% female • **Details of clinical diagnosis/indications:** Peripheral neuropathy secondary to diabetes mellitus, idiopathic peripheral neuropathy, drug-related neuropathy (n=29)

Parameter	Extraction items
Setting/context	**Countries (alphabetic order):** Not reported **Setting (university, public or private clinic):** Not reported **Other relevant features of setting:** Not reported
Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** Cannabinoids used by routes other than oral or inhalation • **Dose and regimen:** CBD oil containing 250 mg/3 fl. oz; not reported; not reported • **Administration methods:** Topical (1 RCT) • **Comparator:** Placebo (1 RCT) • **Treatment duration:** Not specified (study duration: 4 weeks) • **Timeframe for follow-up:** Not reported for included RCT
Databases and sources searched	• **Number and names of databases:** 3; PubMed, SCOPUS, LILACS; inception-04/04/22 • **Other sources:** Not reported • **Grey literature:** Not reported • **Reference chasing:** No • **Expert consultation:** No • **Dates:** Not reported • **Search limits:** No • **Justifications for search limits:** Not applicable • **Other searches:** Not reported • **Protocol prepared:** No

Parameter	Extraction items
	• **If yes, published:** Not applicable • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Funding of review:** "This research was funded by Universidad de La Sabana, grant number MED-296-2020." p9 • **Conflicts of interest of review:** "The authors declare no conflict of interest." p9 • **How conflicts of interest were managed:** "The authors declare no conflict of interest." p9
Date Range (years) of included studies	• **Exact years for included studies:** 2020
Number of primary studies included in the systematic review	• **Number of studies:** 1 RCT • **Number of studies by study design:** RCT • **Study years:** 2020 (1 RCT) • **Funding of included studies:** Not reported • **Conflicts of interest of included studies:** Not reported
Types of studies included	**Planned study designs to be included:** RCTs and observational studies (with either a cohort design, case-series or a case–control design) that compared cannabinoids with usual care, placebo, or no treatment were eligible. **Reasons for including only RCTs/prospective cohort studies:** Not applicable **List of excluded studies at full text and reasons for exclusion:** Yes
Appraisal instruments used	**Full name of tools used:** Cochrane Risk of Bias tool

Parameter	Extraction items
	Risk of bias criteria for AMSTAR 2 assessment, for RCTs record Yes/No for: • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The authors did not provide an overall assessment of risk of bias for each trial. However, HRB notes that according to Cochrane's Collaboration tool, and graphical information provided in the paper, the included trial appeared to have a high risk of bias (1 RCT). • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** Low risk randomisation (0/1); low risk outcome ascertainment (0/1) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** "Higher quality, long-term, randomized controlled trials are needed to examine whether cannabinoids administered by routes other than inhalation and oral routes may have a role in the treatment of neuropathic pain." p9 • **Graphical or statistical test for publication bias:** Not reported • **Authors' comments likelihood and magnitude of publication bias:** Not reported • **Authors' comment on how publication bias was dealt with:** Not reported • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** Not applicable • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** No

Parameter	Extraction items
Method of analysis	• **Description of method of analysis as per authors:** "For dichotomous data, we calculated the relative risk (RR), odds ratio (OR), inverse variance method and 95% Confidence Interval (CI). Continuous outcomes would be pooled using standardized mean differences and inverse variance method. In case of non-significant heterogeneity, the fixed-effect model would be used; otherwise, the random effects model would be used. Results (mean difference, 95% CIs, and p values) from the between-group statistical analyses reported by the study were also extracted. The significance level was set at a $p < 0.05$ (two-tailed)." p9 • **Justification for narrative synthesis or meta-analysis:** Not reported • **Justification for combining data in meta-analysis:** Not reported
Outcome assessed	**List of outcomes assessed and intended timeframes** • Primary outcomes: Pain relief, adverse events • Secondary outcomes: None • Intended timeframe: Not specified • Actual timeframe: 4 weeks
Results/findings	• **Findings by outcome:** o Pain relief: One study (n=29) reported significant ($p<0.05$) decreases in intense (-1.24 vs -0.59) and cold (-1.63 vs -0.43) sensations in favour of CBD oil compared with placebo. One study (n=29) reported significant ($p<0.05$) decreases in sharp (-0.76 vs -0.91) and itchy (0.1 vs -0.79) sensations in favour of placebo compared with CBD oil. o Adverse events: One study (n=29) reported no adverse events in either CBD oil or placebo groups. • **GRADE by outcome:** Not applicable

Parameter	Extraction items
	• **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):** Not applicable • **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Above • **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Not applicable • **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable
Significance/direction	**See above if results listed by outcome:** Above
Heterogeneity	• **See above if I^2 available:** Not applicable • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** Not applicable • **Causes of heterogeneity investigated:** Not applicable
Comments	Only one study met the inclusion criteria for Quintero 2022's review. The authors include summaries of excluded studies in their article, data from these excluded studies has not been extracted.

Razmovski-Naumovski *et al.* (2022): Efficacy of medicinal cannabis for appetite-related symptoms in people with cancer: A systematic review

Parameter	Extraction items
First author and year of publication	Razmovski-Naumovski *et al.* (2022)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "to systematically review the evidence on the efficacy of medicinal cannabis for improving appetite-related symptoms in people with cancer, considering variability in outcomes and interventions." p913

Parameter	Extraction items
	• **Exact review question and page number:** "to systematically review the evidence on the efficacy of medicinal cannabis for improving appetite-related symptoms in people with cancer, considering variability in outcomes and interventions." p913 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** Adults with cancer of any type and stage ➢ **Setting:** Not specified ➢ **Intervention:** "Cannabis – for example, natural/synthetic cannabinoids, botanical/extract, formulation and any dose" p514 Table 1 ➢ **Comparison:** Placebo; any intervention other than a cannabinoid ➢ **Outcome:** Anorexia, cachexia, weight gain/loss/maintenance or body mass index, food intake, appetite, hunger, food-related sensory experience, satiety, food enjoyment, food preferences
Participants (characteristics and numbers)	**For whole sample and subgroups** • **Number of participants:** N=847 • **Age:** Mean age range 52.6-67.0 years • **Gender:** 38.4% female (4 RCTs); not reported (1 RCT) • **Details of clinical diagnosis/indications:** Advanced palliative cancer (n=791); head and neck cancer (n=56)
Setting/context	**Countries (alphabetic order):** Mexico (1 RCT); Canada (2 RCTs); Germany, Switzerland and the Netherlands (1 RCT); USA (1 RCT)

Parameter	Extraction items
	Setting (university, public or private clinic): Outpatient (1 RCT); radiology department (1 RCT); homecare or outpatient clinic (1 RCT); clinic not specified (1 RCT); medical centres (1 RCT) **Other relevant features of setting:** Not specified

Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** "Cannabis-for example, natural/synthetic cannabinoids, botanical/extract, formulation and any dose" p514 Table 1
	• **Dose and regimen:**
	  ○ Nabilone (2 RCTs): 0.5-1 mg: daily, twice daily
	  ○ Dronabinol (2 RCTs): 2.5-20 mg daily; 2.5 mg twice daily
	  ○ THC (1 RCT): Not reported; twice daily
	  ○ Cannabis extract (1 RCT): Not reported; twice daily
	• **Administration methods:** Oral (5 RCTs)
	• **Comparator:** Placebo (4 RCTs); megestrol acetate (1 RCT)
	• **Treatment duration:** Not specified (evaluation 21 days to 8 weeks)
	• **Timeframe for follow-up:** Not reported for included RCTs

Databases and sources searched	• **Number and names of databases:** 3: MEDLINE, CINAHL and CENTRAL: inception-01/2019 • **Other sources:** International Association for Cannabinoid Medicines; clinician trial registries (not specified) • **Grey literature:** Not reported • **Reference chasing:** Yes • **Expert consultation:** No • **Dates:** Inception-01/2019 • **Search limits:** English language; RCT; peer reviewed

Parameter	Extraction items
	• **Justifications for search limits:** Yes • **Other searches:** Not reported • **Protocol prepared:** Yes • **If yes, published:** No • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** No • **If yes, rate of agreement:** Not applicable • **Funding of review:** "The author(s) received no financial support for the research, authorship, and/or publication of this article." p925 • **Conflicts of interest of review:** "The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article." p925 • **How conflicts of interest were managed:** Not applicable
Date Range (years) of included studies	• **Exact years for included studies:** 2002-2018
Number of primary studies included in the systematic review	• **Number of studies:** 5 RCTs • **Number of studies by study design:** 5 RCTs • **Study years:** 2002 (1 RCT); 2006 (1 RCT); 2011 (1 RCT); 2016 (1 RCT); 2018 (1 RCT) • **Funding of included studies:** Not reported • **Conflicts of interest of included studies:** Not reported

Parameter	Extraction items
Types of studies included	**Planned study designs to be included:** RCT **Reasons for including only RCTs/prospective cohort studies:** Not reported **List of excluded studies at full text and reasons for exclusion:** Not reported
Appraisal instruments used	**Full name of tools used:** Cochrane risk of bias tool **Risk of bias criteria for AMSTAR 2 assessment, for RCTs record Yes/No for:** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The authors did not provide an overall assessment of risk of bias for each trial. However, HRB notes that according to Cochrane's Collaboration tool, and graphical information provided in the paper, the included trials appeared to have a high risk of bias (3 RCTs) and unclear risk of bias (2 RCTs). • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** ○ Overall: Low risk randomisation (2/5); low risk outcome ascertainment (0/5) *THC (dronabinol, nabilone, THC vs placebo)* ○ Appetite: Low risk randomisation (2/4); low risk outcome ascertainment (0/4) ○ Chemosensory perception: Low risk randomisation (1/1); low risk outcome ascertainment (0/1) ○ Food intake: Low risk randomisation (1/2); low risk outcome ascertainment (0/2) ○ Satiety: Low risk randomisation (1/1); low risk outcome ascertainment (0/1) *CBD/THC (cannabis extract vs placebo)*

Parameter	Extraction items
	○ Appetite: Low risk randomisation (1/1); low risk outcome ascertainment (0/1) *THC (dronabinol) vs THC/megestrol acetate vs megestrol acetate* ○ Appetite: Low risk randomisation (0/1); low risk outcome ascertainment (0/1) ○ Weight: Low risk randomisation (0/1); low risk outcome ascertainment (0/1) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** Not reported • **Graphical or statistical test for publication bias:** Not reported • **Authors' comments likelihood and magnitude of publication bias:** Not reported • **Authors' comment on how publication bias was dealt with:** Not reported • **Only low ROB RCTs included in review:** Yes • **Only low ROB RCTs included in meta-analysis:** Yes • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** No
Method of analysis	• **Description of method of analysis as per authors:** "A meta-analysis was planned where studies were sufficiently homogenous and reported necessary details on outcomes. Where meta-analysis was not possible, a narrative approach to synthesis using tabulation and textual summaries was employed.30 The synthesis was structured according to sample characteristics (e.g. cancer type/ stages), study design, outcome measures and characteristics of the interventions and comparators. The goal of the synthesis was to organise findings and describe patterns across the studies in terms of the both the nature and direction of the effects and harms, the approaches used to measure these and whether justification of their choice was provided." p914-915 • **Justification for narrative synthesis or meta-analysis:** Above • **Justification for combining data in meta-analysis:** Above

Parameter	Extraction items
Outcome assessed	**List of outcomes assessed and intended timeframes** • Primary outcomes: Anorexia, cachexia, weight gain/loss/maintenance or body mass index, food intake, appetite, hunger, food-related sensory experience, satiety • Secondary outcomes: Quality of life, adverse events • Intended timeframe: Not specified • Actual timeframe: 21 days-8 weeks
Results/findings	• **Findings by outcome:** PRIMARY OUTCOMES ○ Appetite: Five RCTs examined appetite (three as a primary outcome) using a variety of measures. Two RCTs found no significant difference in appetite between nabilone and placebo (n=56, p=0.33; n=33, p=0.929 on FAACT measure and p not reported on NCCTG measure); one of these RCTs found that appetite improved from baseline within the nabilone group (n=33, p=0.006). One RCT found no significant difference in appetite between dronabinol and placebo (n=46, p=0.7); however, this study did find that appetite improved from baseline within the dronabinol group (p=0.05) and that pre-meal appetite was improved in the dronabinol group compared with the placebo group (p=0.05). One RCT (n=311) reported a significant improvement in appetite with megestrol acetate compared with dronabinol (75% vs 49%, p=0.0001 on NCCTG measure and p=0.003 on FAACT measure). This study reported no significant difference between a combination treatment (megestrol acetate and dronabinol) compared with megestrol acetate alone (n=317, p=0.3). One study found no significant difference between THC and placebo (n=148); the same study additionally found no significant difference between cannabis extract and placebo (n=195) (p=0.068).

Parameter	Extraction items
	○ Weight: Two studies (n=89) reported no significant difference between cannabinoid (nabilone) and placebo groups (p=0.724; p=0.1454). One study (n=243) reported no significant difference between cannabinoid (cannabis extract and THC) and placebo groups (summary statistics not reported). One study (n=469) reported no significant difference between a combination treatment (megestrol acetate and dronabinol) compared with megestrol acetate alone (summary statistics not reported). ○ Body mass index: One study (n=33) reported no significant difference between nabilone and placebo groups (p=0.854). ○ Calories per day: Two studies (n=33, n=46) reported no significant difference between cannabinoid and placebo groups (p=0.123; p=0.637 for dronabinol). ○ Protein per day: One study (n=33) reported no significant difference between nabilone and placebo groups (p=0.551). One study (n=46) reported a significant increase in proportion of kcal consumed as protein in dronabinol compared with placebo groups (p=0.008), however overall increase in protein intake was not significant (p=0.121). ○ Carbohydrates per day: One study (n=46) reported no significant difference between dronabinol and placebo groups (p=0.546). One study (n=33) reported a significant increase in cannabinoid compared with placebo groups (p=0.040). ○ Fats per day: Two studies (n=33, n=46) reported no significant difference between nabilone and placebo groups (p=0.193; p=0.126). ○ Iron per day: One study (n=33) reported no significant difference between nabilone and placebo groups (p=0.319). ○ Chemosensory perception (taste and smell): One study (n=46) reported significant improvements in cannabinoid (dronabinol) compared with placebo (Enhanced perception p=0.018; Improved scores p=0.026). ○ Satiety: One study (n=46) reported increased satiety relative to baseline (p=0.03) and placebo (p=0.05) for the dronabinol group.

Parameter	Extraction items
	SECONDARY OUTCOMES ○ Quality of life: Two studies (n=56; n=46) reported no significant difference between nabilone and placebo groups (p=0.4279)and between dronabinol and placebo groups (p=0.7). ○ Adverse events: One study (n=46) reported significantly better patient perceptions of sleep and relaxation in cannabinoid (dronabinol) compared with placebo groups (p=0.043, p=0.046). One study (n=46) reported no significant difference between cannabinoid (dronabinol) and placebo groups (p=0.622). One study (n=56) reported no significant difference between cannabinoid (nabilone) and placebo for drowsiness (p=0.3166), anxiety (p=0.9163), and xerostomia (p=0.8341). One study (n=469) reported no significant difference between dronabinol and placebo for nausea, vomiting, neurocortical dysfunction, oedema, ascites, pleural effusion and thromboembolic phenomena (p>0.05). One study (n=469) reported significantly increased impotence in megestrol acetate (control group) compared with cannabinoid (dronabinol) (p=0.002). One study (n=243) reported no significant difference between cannabinoid (cannabis extract and THC) groups for dizziness, feeling good, feeling high, hallucinations, heart beating, panic attacks, feeling active, or walking insecurely (summary statistics not reported). ○ Serious Adverse Events: One study (n=46) reported no significant difference between cannabinoid (dronabinol) and placebo groups (p=0.244). ○ Study drop-out: Five studies reported on drop-out in cannabinoid compared with placebo: 36% vs 32% (nabilone, n=33); 32% vs 54% (nabilone, n=56); 54% vs 55% (dronabinol, n= 46); 31% vs 35% vs 32% (cannabis extract, THC, n=43); 55% across all arms (n=469). • **GRADE by outcome:** Not applicable

Parameter	Extraction items
	• **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):** Not applicable • **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Only p-values reported, outlined above. • **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Not applicable • **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable
Significance/direction	**See above if results listed by outcome:** Above
Heterogeneity	• **See above if I^2 available:** Not applicable • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** Not reported • **Causes of heterogeneity investigated:** Not reported
Comments	

Rosager *et al.* (2021): Treatment studies with cannabinoids in anorexia nervosa: a systematic review

Parameter	Extraction items
First author and year of publication	Rosager *et al.* (2021)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "To identify all randomized controlled clinical trials that have exposed patients with anorexia nervosa to cannabinoids and assessed the effects on (1) weight and (2) other outcomes, in [anorexia nervosa]" p407" p408 • **Exact review question and page number:** "to identify all randomized controlled clinical trials that have exposed patients with anorexia nervosa to cannabinoids and assessed the effects on (1) weight and (2) other outcomes" p408 • **PICO elements reported in Introduction/Methods:**

Parameter	Extraction items
	➢ **Patient or population:** "Participants (of any age) diagnosed with anorexia nervosa according to DSM IV/V or ICD10 or to corresponding diagnostic criteria." p409 ➢ **Setting:** Not specified ➢ **Intervention:** "cannabinoids or similar products or analogues as intervention." p409 ➢ **Comparison:** "All types of control conditions." p409 ➢ **Outcome:** "(1) weight and (2) other outcomes" p408
Participants (characteristics and numbers)	**For whole sample and subgroups** • **Number of participants:** N=35 • **Age:** Not reported (>18 years old) • **Gender:** 100% female • **Details of clinical diagnosis/indications:** Anorexia (n=35)
Setting/context	**Countries (alphabetic order):** Not reported **Setting (university, public or private clinic):** Not reported **Other relevant features of setting:** Not reported
Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** "cannabinoids or similar products or analogues as intervention." p409 • **Dose and regimen:** ○ Dronabinol (1 RCT): 2.5 mg; twice daily ○ Delta-9-THC (1 RCT): 7.5-30 mg; daily

Parameter	Extraction items
	• **Administration methods:** Oral (2 RCTs) • **Comparator:** Placebo (2 RCTs) (*table 1 reports diazepam in control group, unclear if usual care or active comparator). • **Treatment duration:** Not specified (study duration range: 4-7 weeks) • **Timeframe for follow-up:** Not reported for included studies
Databases and sources searched	• **Number and names of databases:** 3; Pubmed, EMBASE, PsycInfo; Inception – 17/01/2020 • **Other sources:** EU clinical trial register, clinicaltrials.gov • **Grey literature:** Published protocols search • **Reference chasing:** No • **Expert consultation:** No • **Dates:** Inception to 17/01/2020 • **Search limits:** Animal studies • **Justifications for search limits:** Yes • **Other searches:** Not reported • **Protocol prepared:** Yes • **If yes, published:** CRD42019141293 https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=141293 • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** Not reported • **If yes, rate of agreement:** Not reported

Parameter	Extraction items
	• **Funding of review:** "support from Mental Health Center Ballerup and Mental Health Services in the Capital Region of Denmark." P414 • **Conflicts of interest of review:** "All the authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript." P414 • **How conflicts of interest were managed:** Not applicable
Date Range (years) of included studies	• **Exact years for included studies:** 1983-2015
Number of primary studies included in the systematic review	• **Number of studies:** 2 RCTs (4 reports) • **Number of studies by study design:** 2 RCTs • **Study years:** 1983 (1 RCT); 2014 (1 RCT); 2015 (2 RCTs) • **Funding of included studies:** Not reported • **Conflicts of interest of included studies:** Not reported
Types of studies included	**Planned study designs to be included:** RCT **Reasons for including only RCTs/prospective cohort studies:** Not reported **List of excluded studies at full text and reasons for exclusion:** Not reported
Appraisal instruments used	**Full name of tools used:** Cochrane Risk of Bias tool **<u>Risk of bias criteria for AMSTAR 2 assessment, for RCTs record Yes/No for:</u>**

Parameter	Extraction items
	• **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The authors did not provide an overall assessment of risk of bias for each trial. However, HRB notes that according to Cochrane's Collaboration tool, and graphical information provided in the paper, the included trials appeared to have a high risk of bias (1 RCT) and low risk of bias (1 RCT). • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** o Overall: Low risk randomisation (1/2); low risk outcome ascertainment (1/2) *THC (dronabinol) vs placebo* o Weight: Low risk randomisation (1/1); low risk outcome ascertainment (1/1) *Cannabis vs. diazepam* o Weight: Low risk randomisation (0/1); low risk outcome ascertainment (0/1) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** Not reported • **Graphical or statistical test for publication bias:** Not reported • **Authors' comments likelihood and magnitude of publication bias:** Not reported • **Authors' comment on how publication bias was dealt with:** Not reported • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** Not applicable • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** Yes

Parameter	Extraction items
Method of analysis	• **Description of method of analysis as per authors:** "After data extraction, the data were synthesized in Table 1 to enable an analysis of the effects on the outcomes (1) weight gain and (2) other outcomes. Results are also summarized in a narrative review below." p409 • **Justification for narrative synthesis or meta-analysis:** Not reported • **Justification for combining data in meta-analysis:** Not applicable
Outcome assessed	**List of outcomes assessed and intended timeframes** • Primary outcomes: Weight • Secondary outcomes: Adverse events, physical activity, other • Intended timeframes: Not specified • Actual timeframes: 4-7 weeks
Results/findings	• **Findings by outcome:** PRIMARY OUTCOME ○ Weight: One study (n=24) reported significant 1 kg weight gain in cannabinoid (dronabinol) compared with placebo groups (p=0.03). One study (n=11) reported no significant difference between cannabis and diazepam groups. SECONARDY OUTCOMES ○ Adverse events: One study (n=11) reported significantly increased somatization (p=0.012), increased interpersonal sensitivity (p=0.039), increased sleep disturbance (p=0.004), increased systolic blood pressure (p=0.005), and decreased diastolic blood pressure (p=0.041) in the cannabis group compared with the diazepam group. ○ Physical activity: One study (n=24) reported significantly increases in intensity (p=0.02), intensity among inpatients (p=0.04), duration of moderate to hard physical activity (p=0.04), increased duration of moderate to hard physical

Parameter	Extraction items
	activity among outpatients (p=0.02), and increased energy expenditure (p=0.01) in cannabinoid (dronabinol) groups compared with placebo. ○ Other: One study (n=24) reported urine free cortisol decreased with 18%, no effect on leptin, IGF-I or IGFBP-3, and minor reduction in adiponectin in cannabinoid compared with placebo groups (no summary statistics reported). • **GRADE by outcome:** Not reported • **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):** Not applicable • **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Not applicable • **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Not applicable • **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable
Significance/direction	**See above if results listed by outcome:** Above
Heterogeneity	• **See above if I^2 available:** Not applicable • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** "The level of evidence is low since there are only two RCTs having dissimilar designs, types of cannabinoids and levels of exposure." p414 • **Causes of heterogeneity investigated:** "The level of evidence is low since there are only two RCTs having dissimilar designs, types of cannabinoids and levels of exposure." p414
Comments	On p409 authors state all RCTs are placebo-controlled. However, on p413 the authors indicate one study (Gross *et al.* 1983) uses an 'active placebo' diazepam. In this extraction form, we have relabelled the 'active placebo' as an 'active control'.

Sainsbury *et al.* (2021): Efficacy of cannabis-based medications compared to placebo for the treatment of chronic neuropathic pain: a systematic review with meta-analysis

Parameter	Extraction items
First author and year of publication	Sainsbury *et al.* (2021)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "to evaluate the effectiveness of cannabis-based medications, including herbal cannabis (marijuana), plant-based cannabinoid compounds (THC/CBD, dronabinol), and pharmacological synthetic cannabinoids (e.g., nabilone, CT-3), as therapeutic agents compared to placebo intervention (i.e., cigarettes with 0% cannabis) in patients with chronic [neuropathic pain]" p482 • **Exact review question and page number:** "to evaluate the effectiveness of cannabis-based medications, including herbal cannabis (marijuana), plant-based cannabinoid compounds (THC/CBD, dronabinol), and pharmacological synthetic cannabinoids (e.g., nabilone, CT-3), as therapeutic agents compared to placebo intervention (i.e., cigarettes with 0% cannabis) in patients with chronic [neuropathic pain]" p482 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** "Individuals diagnosed with [neuropathic pain] (central [neuropathic pain], cancer-related neuropathy, painful diabetic neuropathy, complex regional pain syndrome type II, postherpetic neuralgia, peripheral polyneuropathy of other etiologies, trigeminal neuralgia; HIV neuropathy, spinal cord injury; postoperative or traumatic peripheral nerve lesions due to trauma; nerve plexus injury and phantom limb pain)." p482 ➢ **Setting:** "Orofacial pain clinic, university hospital, or clinical care center" p482 ➢ **Intervention:** "Cannabis-based medications, either herbal forms of cannabis (marijuana), plant-based cannabinoid compounds (THC/CBD, dronabinol), or pharmacological (synthetic) cannabinoid formulations (e.g., nabilone, CT-3). Any route of administration (i.e., smoking, vaping, oral administration)" p482 ➢ **Comparison:** Placebo

Parameter	Extraction items
	➢ **Outcome:** "Primary outcomes: [neuropathic pain] intensity and spontaneous pain intensity at baseline and post-treatment or reduction post-treatment. • Secondary outcomes: Other pain outcomes, quality of life, cognitive decline assessment, sleep quality, qualitative testing, disability status, rescue medications, and adverse events or side effects." p482
Participants (characteristics and numbers)	**For whole sample and subgroups** • **Number of participants:** N=861 • **Age:** Age range: 21-77 years • **Gender:** 41.7% female • **Details of clinical diagnosis/indications:** HIV (n=121); complex regional pain syndrome (n=27); avulsed brachial plexus injury (n=48); hyperalgesia and allodynia (n=21); unilateral peripheral neuropathic pain and allodynia (n=125); chronic painful diabetic peripheral neuropathy (n=29); allodynia (n=246); multiple sclerosis (n=24); neurological disorder (n=20); diabetes mellitus (n=16); neuropathic pain (n=62); spinal cord injury (n=122)
Setting/context	**Countries (alphabetic order):** Europe and UK (8 RCTs); Israel (1 RCT); USA (8 RCTs) **Setting (university, public or private clinic):** Pain clinical research centres (3 RCTs); university hospitals (8 RCTs); medical schools (3 RCTs) **Other relevant features of setting:** Not reported
Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** • **Dose and regimen:** o Cannabidivarin (1 RCT): 400 mg; daily

Parameter	Extraction items
	○ THC cigarettes (2 RCTs): 1-8%; three to five times daily, not reported ○ CT-3 (1 RCT): 10 mg; not reported ○ Sativex (3 RCTs): THC 2.7 mg and CBD 2.5 mg; not reported ○ Dronabinol (1 RCT): 2.5 mg; not reported ○ THC:CBD (1 RCT): 2.5 mg/2.5mg; not reported ○ THC spray (1 RCT): 2.5 mg; not reported ○ CBD spray (1 RCT): 2.5 mg; not reported ○ Vaporised cannabis (1 RCT): 1-7%; not reported ○ THC (5 RCTs): 1.29-9.4%, 0.5-1 mg; not reported • **Administration methods:** Inhaled (9 RCTs); oral (3 RCTs); oromucosal spray (5 RCTs) • **Comparator:** Placebo (17 RCTs) • **Treatment duration:** 3x150 minute sessions – 14 weeks • **Timeframe for follow-up:** Not reported for included RCTs
Databases and sources searched	• **Number and names of databases:** 4; EMBASE, MEDLINE through PubMed, Web of Science, and Cochrane; Inception to 02/01/21. • **Other sources:** "The reference sections of all literature reviews, systematic reviews, meta-analyses, and clinical guidelines in addition to all eligible RCTs were then scanned by three authors" p482 • **Grey literature:** Not reported • **Reference chasing:** Yes • **Expert consultation:** No • **Dates:** Inception to 02/01/21 • **Search limits:** English language, humans only

Parameter	Extraction items
	• **Justifications for search limits:** Yes • **Other searches:** Not reported • **Protocol prepared:** Yes • **If yes, published:** CRD42021234766 https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=234766 • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes (in triplicate) • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** Yes (in triplicate) • **If yes, rate of agreement:** Not reported • **Funding of review:** "The authors declare no funding for this study." p502 • **Conflicts of interest of review:** "The authors have no conflicts of interest." p502 • **How conflicts of interest were managed:** Not reported
Date Range (years) of included studies	• **Exact years for included studies:** 2002-2020
Number of primary studies included in the systematic review	• **Number of studies:** 17 RCTs • **Number of studies by study design:** 17 RCTs • **Study years:** 2002 (1 RCT); 2003 (1 RCT); 2004 (2 RCTs); 2007 (2 RCTs); 2008 (1 RCT); 2009 (1 RCT); 2010 (2 RCTs); 2013 (2 RCTs); 2015 (1 RCT); 2016 (2 RCTs); 2020 (2 RCTs) • **Funding of included studies:** Industry funded (7 RCTs); not reported (10 RCTs) • **Conflicts of interest of included studies:** Not reported
Types of studies included	**Planned study designs to be included:** RCT only

Parameter	Extraction items
	Reasons for including only RCTs/prospective cohort studies: Not reported **List of excluded studies at full text and reasons for exclusion:** Not reported
Appraisal instruments used	**Full name of tools used:** Guidelines in the Cochrane Handbook; GRADE system **<u>Risk of bias criteria for AMSTAR 2 assessment, for RCTs record Yes/No for:</u>** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** High risk of bias (8 RCTs); unclear risk of bias (9 RCTs) • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** o Overall: Low risk randomisation (14/17); low risk outcome ascertainment (5/17) *THC/CBD* o Change in pain intensity from baseline: Low risk randomisation (5/6); low risk outcome ascertainment (2/6) o Difference in percent reduction from baseline: Low risk randomisation (2/2); low risk outcome ascertainment (1/2) *THC* o Change in pain intensity from baseline: Low risk randomisation (4/5); low risk outcome ascertainment (0/5) *CBD* o Change in pain intensity from baseline: Low risk randomisation (1/1); low risk outcome ascertainment (0/1) *CBDV* o Change in pain intensity from baseline: Low risk randomisation (1/1); low risk outcome ascertainment (0/1)

Parameter	Extraction items
	CT-3 ○ Change in pain intensity from baseline: Low risk randomisation (1/1); low risk outcome ascertainment (0/1) *Synthetic (dronabinol)* ○ Change in pain intensity from baseline: Low risk randomisation (1/1); low risk outcome ascertainment (1/1) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** "This systematic review and meta-analyses demonstrated low to moderate quality of evidence due to high or unclear risk of bias, small number of studies, and limited duration. The quality of the evidence was low to moderate because of the unclear blinding of samples. Some studies received funding from drug companies, while others had co-interventions. However, a few studies have not completely reported the outcome data. In conclusion, a high overall risk of bias was assigned to six studies, and an unclear overall risk of bias was assigned to eight studies." p500 • **Graphical or statistical test for publication bias:** Not conducted • **Authors' comments likelihood and magnitude of publication bias:** Not reported • **Authors' comment on how publication bias was dealt with:** Not reported • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** No • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** Yes
Method of analysis	• **Description of method of analysis as per authors:** "Means and standard deviations (SD) were calculated based on reported medians (m) and interquartile range (IQR) = (q1, q3), with q1 = 25% quartile, and q3 = 75% quartile, as: mean = (q1 + m + q3)/3; SD = (q3 – q1)/ 1.35. SD was calculated based on the reported standard error of the mean (SEM) as follows: SD = SEM × sqrt (N), where N is the total sample size in the intervention group… Cochran's Q test [43] and the I^2

Parameter	Extraction items
	statistic [44] were used to test for heterogeneity. A random-effects model was employed when there was heterogeneity (Q-test P ≤ .05).” p483 • **Justification for narrative synthesis or meta-analysis:** Above • **Justification for combining data in meta-analysis:** Above
Outcome assessed	**List of outcomes assessed and intended timeframes** • Primary outcomes: Neuropathic pain intensity and spontaneous pain intensity at baseline and post-treatment, or baseline NP pain and reduction from baseline at post-treatment. • Secondary outcomes: Adverse events, neuropathic pain intensity (%), responders with a 30% or more reduction in pain intensity; 50% or more reduction in pain intensity, quality of life, general health, patient global impression change, cognitive decline, sleep quality, expanded disability status, profile of mood states, qualitative testing (allodynia, cold/hot threshold). • Intended timeframes: Not specified • Actual timeframes: 3x150 minute sessions – 14 weeks
Results/findings	○ **Findings by outcome:** PRIMARY OUTCOMES *THC:CBD vs placebo* ○ Pain intensity from baseline: Pooled data from five studies (n=522) reported a significant improvement in pain for baselines in THC:CBD compared with placebo groups (RD -6.624, 95% CI -9.154 to -4.094). *THC vs placebo*

Parameter	Extraction items
	○ Pain intensity from baseline visual analog scale: Pooled data from seven studies (n=332) reported a significant improvement in pain from baseline in THC compared with placebo groups (MD -8.681, 95% CI -10.975 to -6.387). ○ Percent reduction of pain: Two studies (n=87) reported a significant reduction in THC compared with placebo groups (MD -21.046 95% CI -35.827 to -6.265). *CBD vs placebo* ○ Pain intensity from baseline: One study (n=20) reported no significant difference between CBD and placebo (p=0.55). *CBDV vs placebo* ○ Pain intensity from baseline: One study (n=32) reported no significant difference between CBDV and placebo (p=1.00). *Synthetic cannabis vs placebo* ○ Pain intensity from baseline: One study (n=21) reported no significant differences between CT-3 and placebo groups (p=0.31). One study (n=24) reported a significant improvement in dronabinol compared with placebo groups (p=0.04). SECONDARY OUTCOMES *THC:CBD vs placebo* ○ 30% reduction in pain intensity: Pooled data from two studies (n=359) reported that participants were significantly more likely to experience 30% or more reduction in pain in THC:CBD spray compared with placebo (RR 1.756, 95% CI 1.161 to 2.656). ○ 50% or more reduction in pain: One study (n=125) reported no significant differences between THC:CBD spray and placebo groups (p=0.37).

Parameter	Extraction items
	○ Pain disability index: Pooled data from two studies (n=219) reported no significant differences between THC:CBD spray and placebo (MD -3.646, 95% CI -7.380 to 0.087). ○ Brief pain inventory: One study (n=246) reported no significant difference in pain intensity (p=0.29) and pain inference (p=0.184) between THC:CBD spray and placebo groups. ○ McGill VAS pain scale: Pooled data from two studies (n=71) reported no significant difference between THC:CBD spray and placebo groups (RD 1.005, 95% CI -19.137 to 21.147). One study (n=29) reported no significant difference in present pain intensity (p=0.19), sensory scale (p=0.46), or affective scale (p=0.67) between THC:CBD spray and placebo groups. One study (n=48) reported no significant difference in MPQ total score (p=0.08) between in THC:CBD spray and placebo groups. ○ SF-36 questionnaire: One study (n=29) reported no significant difference between THC:CBD spray and placebo groups (p=0.37). *THC vs placebo* ○ 30% reduction in pain intensity: Pooled data from six studies (n=353) reported THC participants were significantly more likely to experience 30% or more reduction in pain compared with placebo (RR 1.917, 95% CI 1.529 to 2.404). ○ Pain disability index: One study (n=48) reported no significant differences between THC and placebo groups (p=0.82). ○ McGill Pain Questionnaire: Pooled data from two studies (n=137) reported significant improvement in THC compared with placebo groups (MD -2.197, 95% CI -4.219 to -0.176). One study (n=48) reported significant improvement in post-treatment pain score in THC compared with placebo (p=0.02). One study (n=23) reported no significant difference in post-treatment present pain intensity (p=0.40), sensory scale (p=0.59), and affective scale (p=0.60) between THC and placebo groups. *CBDV vs placebo*

Parameter	Extraction items

- 30% reduction in pain: One study (n=32) reported CBDV participants were 53.8% less likely to achieve a 30% reduction in pain compared to patients receiving placebo (p=0.07).
- 50% reduction in pain: One study (n=32) reported CBDV participants were 88.9% less likely to achieve a 50% reduction in pain compared to patients receiving placebo (p=0.03).
- Brief Pain Inventory scale: One study (n=32) reported no significant differences in pain intensity score (p=0.65) or pain interference score between the CBDV and placebo groups (p=0.36).

Synthetic cannabis vs placebo

- 50% pain reduction: One study (n=24) reported no significant differences between dronabinol and placebo groups (p=0.13)
- SF-36: One study (n=24) reported significant improvements in mental health scores (p<0.001), physical functioning (p<0.001), and social functioning (p=0.04) in dronabinol compared with placebo groups.

All groups

- Adverse events: Twelve studies (n=694) reported adverse events including, but not limited to, anxiety, sedation, dizziness, nausea, and fatigue. Two studies (n=84) reported no serious side effects. One study (n=32) reported adverse events in 91.2% of participants (diarrhoea and dry mouth of mild severity were the most common) and one withdrawal due to an adverse event (cough) during CBDV treatment. One study (n=30) reported six withdrawals due to adverse events (withdrawal from dronabinol or placebo groups not specified).

- **GRADE by outcome:**

Outcome	No. studies	GRADE
THC:CBD vs placebo		
Pain intensity	5	Moderate
30% pain reduction	2	Low
Pain disability index	2	Low

Parameter	Extraction items

McGill Pain Questionnaire	2	Low
THC vs placebo		
Pain intensity	7	Moderate
Percent reduction of pain	2	Low
30% reduction in pain intensity	6	Moderate
McGill Pain Questionnaire	2	Low

- **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):** Fixed effects models

Outcome	No. studies (No. participants)	Summary estimate	P-value	I^2 (%)	Direction of effect
THC:CBD vs placebo					
Change in pain intensity from baseline	5 (522)	RD-6.624, 95% CI -9.154 to -4.094	<0 .001	NR	Cannabinoid
30% pain reduction	2 (359)	RR 1.756, 95% CI 1.161 to 2.656	0.008	NR	Cannabinoid
Pain disability index	2 (219)	MD -3.646, 95% CI -7.380 to 0.087	0.06	NR	No significant difference
McGill Pain Questionnaire	2 (71)	RD 1.005, 95% CI -19.137 to 21.147	0.92	NR	No significant difference
THC vs placebo					
Change in pain intensity from baseline	7 (332)	MD -8.681, 95% CI -10.975 to -6.387	<0.001	NR	THC
Percent reduction of pain	2 (87)	MD -21.046 95% CI -35.827 to -6.265	0.005	NR	THC
30% reduction in pain intensity	6 (353)	RR 1.917, 95% CI 1.529 to 2.404	<0.001	NR	THC
McGill Pain Questionnaire	2 (137)	MD -2.197, 95% CI -4.219 to -0.176	0.03	NR	THC

Parameter	Extraction items
	○ **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Above ○ **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** "A random-effects model was employed when there was heterogeneity (Q-test p<.10); otherwise, a fixed-effect model was used." p483 ○ **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable
Significance/direction	**See above if results listed by outcome:** Above
Heterogeneity	• **See above if I^2 available:** Not reported • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** "This systematic review included only RCTs comparing cannabis-based medications with a placebo. There was heterogeneity in terms of the intervention (THC/CBD, CBD, CBDV, synthetic cannabis), for which the review authors conducted subgroup analyses. Review authors conducted subgroup analyses with similarly reported outcomes. Different types of cannabis were utilized in the included studies, with varied mechanisms of action, routes of administration, dosages, and schedule. The route of administration of cannabis varied from smoked, inhaled, vaping, spray, and oil. The minimum and maximum doses of THC were 1% and 9.4%, respectively. [Neuropathic pain] types varied from HIV distal sensory predominant polyneuropathy, CRPS II, diabetic peripheral neuropathy, post-herpetic neuralgia, trigeminal neuralgia, focal nerve lesion, radiculopathy, multiple sclerosis, injury and disease of the spinal cord, nerve plexus injury, and postoperative or traumatic peripheral nerve lesions due to trauma. The diagnosis of [neuropathic pain] was based on clinical symptoms and various tools depending on the diagnosis (see Results section)." p500 • **Causes of heterogeneity investigated:** I^2 not reported however "A random-effects model was employed when there was heterogeneity (Q-test P<.10); otherwise, a fixed-effect model was used" p484, subgroup analysis completed

Parameter	Extraction items
Comments	

Simon *et al.* (2022): Cannabinoid interventions for improving cachexia outcomes in cancer: a systematic review and meta-analysis

Parameter	Extraction items
First author and year of publication	Simon *et al.* (2022)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "This review aimed to consider [non-randomised studies of interventions] alongside RCTs for a comprehensive approach to the available evidence on cannabinoid interventions in [cancer-associated cachexia or severe loss of weight and muscle mass], in order to inform clinical decisions and future investigations." p24 • **Exact review question and page number:** As above • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** "adult (>18 years) cancer patients, whose baseline characteristics were judged to describe cachexia, were eligible, including individuals of any gender, ethnicity, disease stage in any care setting, and undergoing chemotherapy or radiotherapy. Individuals with an eating disorder, undergoing treatment for appetite and weight loss, or with a history or current habit of marijuana use were excluded." p24-25 ➢ **Setting:** “any care setting” p25 ➢ **Intervention:** "Cannabinoid-based interventions included any smoked or ingested medical marijuana, plant-based cannabinoids (THC and CBD) and synthetic cannabinoids (dronabinol, nabilone, or any other pharmaceutical form)." p25 ➢ **Comparison:** "No restrictions on the comparisons were applied to allow inclusion of qualitative evidence. Treatment comparisons were any active or inactive control. Active control included nutritional interventions administered orally

Parameter	Extraction items
	(food fortification, snacks, and nutrient/caloric supplementation), while pharmacological interventions and co-interventions involved the use of active drugs (appetite stimulants, anticytokines [therapies to reduce inflammatory action of targeting cytokine proteins], and metabolic mediators), and other forms of cannabis. Inactive control included placebo, standard care or no treatment." p25 ➢ **Outcome:** "Primary outcomes included changes in weight and appetite and secondary outcomes included performance status [measure of ability to perform activities of daily living], quality of life, adverse events, treatment-related side effects, and mortality." p25
Participants (characteristics and numbers)	**For whole sample and subgroups** *The non-randomised studies of interventions are excluded from the remainder of the extraction. • **Number of participants:** n=647 • **Age:** Mean ages reported for subgroups or total samples, ranging 52.6 – 67 years • **Gender:** For 4 RCTs reporting full gender breakdown for n=608 participants, n=354 male (58.2%) and n=254 female (41.8%) • **Details of clinical diagnosis/indications:** Cancer ("advanced cancer" 3 RCTs, non-small cell lung cancer 1 RCT), with cachexia/weight loss/decreased foot intake/anorexia/malnourishment defined in various ways, including performance status scores
Setting/context	**Countries (alphabetic order):** Canada, Germany, Mexico, United Kingdom, all 1 RCT each **Setting (university, public or private clinic):** Not reported

Parameter	Extraction items
	Other relevant features of setting: Not reported
Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** "Cannabinoid-based interventions included any smoked or ingested medical marijuana, plant-based cannabinoids (THC and CBD) and synthetic cannabinoids (dronabinol, nabilone, or any other pharmaceutical form)." p25 • **Dose and regimen:** THC: 2.5 mg THC once daily for 3 days, twice daily on fourth day, option to increase to 20 mg/day (1 RCT, n =24 received THC, total n=46); THC: 2.5 mg THC twice daily (1 RCT, n=100 received THC, total n=243) Dronabinol: 2.5 mg dronabinol capsules twice daily plus liquid placebo (1 RCT, n=152 received dronabinol, total n=311) Cannabis extract: 2.5 mg:1 mg THC:CBD capsules twice daily (1 RCT, n=95 received cannabis extract, total n=243) Nabilone: 0.5 mg nabilone for 2 weeks, then 1mg nabilone for 6 weeks (1 RCT, n=14 received nabilone, total n=47) • **Administration methods:** Oral • **Comparator:** Equivalent placebo capsules (4 RCTs); 800 mg megestrol acetate (progesterone-based appetite stimulant) liquid suspension daily plus capsule placebos (1 RCT, n=159) • **Treatment duration:** 18 days (1 RCT), 6 weeks (1 RCT), 8 weeks (1 RCT), open-ended continued treatment monitored by healthcare provider (1 RCT) • **Timeframe for follow-up:** 30 days (1 RCT, n=46), 6 weeks (1 RCT, n=243), 8 weeks (1 RCT, n=47 randomised, n=33 included in analysis), open-ended continued treatment monitored by healthcare provider (1 RCT, n=311)
Databases and sources searched	• **Number and names of databases:** 3: Medline, Embase, Pubmed • **Other sources:** PROSPERO, ISRCTN, ClinicalTrials.gov • **Grey literature:** None reported • **Reference chasing:** Yes

Parameter	Extraction items
	• **Expert consultation:** None reported • **Dates:** Inception to May 2020 • **Search limits:** No • **Justifications for search limits:** Not applicable • **Other searches:** None reported • **Protocol prepared:** Yes • **If yes, published:** No • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** No; only uncertainties were discussed with another investigator • **If yes, rate of agreement:** Not applicable • **Extraction completed in duplicate:** No • **If yes, rate of agreement:** Not applicable • **Funding of review:** "The submission charges were funded by [University College London] Library" • **Conflicts of interest of review:** "The authors declare no potential conflicts of interest" p39 • **How conflicts of interest were managed:** Not applicable
Date Range (years) of included studies	• **Exact years for included studies:** 2002-2018
Number of primary studies included in the systematic review	• **Number of studies:** 4 RCTs • **Number of studies by study design:** 4 RCTs • **Study years:** 2002 (1 RCT), 2006 (1 RCT), 2011 (1 RCT), 2018 (1 RCT) • **Funding of included studies:** Not reported

Parameter	Extraction items
	• **Conflicts of interest of included studies:** Not reported
Types of studies included	**Planned study designs to be included:** "All RCTs and [non-randomised studies of interventions] were included" p25; this extraction form reports only on data from 4 included RCTs **Reasons for including only RCTs/prospective cohort studies:** "No restrictions on study design were applied to permit a comprehensive evaluation of the outcomes in a population of advanced cancer patients, in which ethical concerns complicate methodological implementation, such as randomization or blinding." p15 **List of excluded studies at full text and reasons for exclusion:** Not provided
Appraisal instruments used	**Full name of tools used:** Cochrane Risk of Bias (ROB2) **<u>Risk of bias criteria for AMSTAR 2 assessment, for RCTs, record Yes/No for:</u>** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes

Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The authors did not provide an overall assessment of risk of bias for each trial. However, HRB notes that according to Cochrane's Collaboration tool, and graphical information provided in the paper, the included trials appeared to have a high risk of bias (1/4 RCTs) and unclear risk of bias (3/4 RCTs).
	• **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:**
	  ○ Overall: Low risk randomisation (3/4); low risk outcome ascertainment (1/4)
	  ○ Weight: Low risk randomisation (2/3); low risk outcome ascertainment (1/3)

Parameter	Extraction items
	○ Appetite: Low risk randomisation (3/4); low risk outcome ascertainment (1/4) ○ Adverse events: Low risk randomisation (2/2); low risk outcome ascertainment (1/2) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** No comment • **Graphical or statistical test for publication bias:** Not carried out due to low number of studies • **Authors' comments likelihood and magnitude of publication bias:** Not applicable • **Authors' comment on how publication bias was dealt with:** Not applicable • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** No • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** Not discussed by review authors
Method of analysis	• **Description of method of analysis as per authors:** "Studies were grouped according to their design (RCTs or [non-randomised studies of interventions]). Outcome data and trends were described in terms of the number of studies, relevant effects, and statistical significance ($p < 0.05$) reported on the outcome. Results were combined narratively or by meta-analysis where possible. Studies only reported sufficient data to conduct meta-analyses for QoL and appetite, which were pooled using Review Manager (RevMan version 5.4; The Nordic Cochrane Center) using a continuous, inverse variance, random effects analysis. A random effects model was used because of variability in both study design and participants, and interventions… The standardized mean difference was used to account for differences in tools or methods of data collection for similar outcomes. The inconsistency (I^2) statistic was used to assess heterogeneity, which was subsequently classified as $I^2 < 40\%$—low; 30 to 60%—moderate; 50 to 90%—substantial and >75%—considerable." p26 • **Justification for narrative synthesis or meta-analysis:** Not explained by review authors

Parameter	Extraction items
	• **Justification for combining data in meta-analysis:** Not explained by review authors
Outcome assessed	**List of outcomes assessed and intended timeframes** • Primary outcomes: Weight; Appetite • Secondary outcomes: Performance status; Quality of life; Adverse events; Mortality • Intended timeframes: Not specified • Actual timeframes: 18 days (1 RCT), 6 weeks (1 RCT), 8 weeks (1 RCT), open-ended continued treatment monitored by healthcare provider (1 RCT); Follow-ups 30 days (1 RCT), 6 weeks (1 RCT), 8 weeks (1 RTC), open-ended continued treatment monitored by healthcare provider (1 RCT)
Results/findings	• **Findings by outcome:** PRIMARY OUTCOMES Weight ○ One RCT (n=311) found that standard treatment (megestrol acetate) resulted in greater weight gain than dronabinol, for both self-reported weight gain (3% patients with dronabinol vs 11% with megestrol acetate, p=0.02) and physician-reported weight gain (5% vs 14%, p=0.009). One other RCT (n=35) reported no difference in mean change in weight for groups receiving nabilone or placebo (mean change in bodyweight -1.4kg (SD 1.6) with nabilone vs -1.09 (SD 2.6) with placebo, p=0.724). Appetite ○ The findings from three RCTs (n = 297) were pooled in a meta-analysis. "There was no difference in change in appetite in groups receiving cannabinoid treatment compared with groups receiving placebo, standard mean difference: -0.02 [95% CI: -0.51, 0.46; P = 0.93]. Heterogeneity was substantial (I^2 = 63%, P = 0.04). A sensitivity analysis revealed that when the study favouring intervention was excluded, I^2 was reduced to 0% and there remained no difference

Parameter	Extraction items
	between groups." p32 One additional study reported significantly greater appetite in the group receiving megestrol acetate compared with the cannabinoid (dronabinol) intervention group. SECONDARY OUTCOMES Performance status ○ No RCTs reported data on performance status. Quality of life ○ The findings on global quality of life from four RCTs (n = 545) were pooled in a meta-analysis. "There was a small and significantly greater improvement in [global quality of life] in groups receiving either active (megestrol acetate) or inactive (placebo) control compared with groups receiving cannabinoids, suggesting that cannabinoid treatment was less efficacious, SMD: -0.25 (95% CI: -0.43, -0.07); P = 0.007). There was no heterogeneity (I^2 = 0%, P = 0.58)." p34 Adverse events ○ **"**Two of the RCTs [n=359] showed no significant difference for the number or severity of [adverse events] and serious [adverse events], or the incidence of side effects, in the intervention compared with the control group. One [n=48] reported four [adverse events] and one [serious adverse events] were possibly related to treatment. The other two RCTs [n=276] showed no significant effect, although one [n=243] reported more [adverse events] in the intervention compared with the control group… [However,] the intervention group was twice as numerous as the control group." p35 Mortality ○ "Three RCTs [n=587] reported on mortality noting that more participants died in the intervention group compared with the control group [22% vs 15%]. In one RCT [n=311], participants in the intervention group lived longer overall than participants in the control group. The number of deaths in each study was small, and the quality of evidence for this outcome was very low." p35

<table>
<tr><th>Parameter</th><th>Extraction items</th></tr>
<tr><td></td><td>

GRADE by outcome: GRADE assessment was carried out including four RCTs and six non-randomised studies of interventions; therefore, it has not been extracted here
Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):
<table>
<tr><th>Outcome</th><th>No. studies (No. participants)</th><th>Summary estimate (95% CI)</th><th>P-value</th><th>I^2 (%)</th><th>Direction of effect</th></tr>
<tr><td colspan="6">Mixed cannabinoids (THC, THC:CBD) vs placebo</td></tr>
<tr><td>Appetite</td><td>3 (297)</td><td>SMD -0.02 (-0.051 to 0.46)</td><td>0.93</td><td>64%</td><td>No significant difference</td></tr>
<tr><td colspan="6">Mixed cannabinoids (THC, THC:CBD) vs mixed control (placebo, megestrol acetate)</td></tr>
<tr><td>Global Quality of Life</td><td>4 (545)</td><td>SMD -0.25 (-0.43 to -0.07)</td><td>0.007</td><td>0%</td><td>Control (3 placebo, 1 megestrol acetate)</td></tr>
</table>

Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available: See above (Findings by outcome)
Appropriate weighted technique used, adjusted for heterogeneity where necessary: Yes; standardised mean difference and random effects model used
Separate summaries reported for RCTs and prospective cohort studies when included in the same review: Yes

</td></tr>
<tr><td>Significance/direction</td><td>See above if results listed by outcome: Evidence from four RCTs suggested that cannabinoids compared with control provided no significant benefits for appetite or weight gain and were significantly less efficient than active or inactive control for quality of life. The incidence of adverse events appears unrelated to treatment with cannabinoids.</td></tr>
<tr><td>Heterogeneity</td><td>

See above if I^2 available: As above; heterogeneity was substantial in meta-analysis on appetite but no heterogeneity was observed in meta-analysis on quality of life.
Authors' comment on potential impact of heterogeneity on results and quality of evidence: No discussion by authors
Causes of heterogeneity investigated: Yes, I^2, random-effects models, sensitivity analysis conducted

</td></tr>
</table>

Parameter	Extraction items
Comments	This systematic review includes 10 studies (4 RCTs and 6 non-randomised studies). Unless specified otherwise, the above information only reported on RCT studies as per the umbrella review inclusion criteria. Patient-reported observations from non-randomised studies of interventions suggested improvements in appetite, contrary to findings from RCTs; however, this could be due to self-selection bias. The authors state that the benefits of cannabinoids for quality of life are elusive across both RCTs and non-randomised studies.

Smith *et al.* (2015): Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy (Review)

Parameter	Extraction items
First author and year of publication	Smith *et al.* (2015)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "To evaluate the effectiveness and tolerability of cannabis-based medications for chemotherapy-induced nausea and vomiting in adults with cancer." p10 • **Exact review question and page number:** "To evaluate the effectiveness and tolerability of cannabis-based medications for chemotherapy-induced nausea and vomiting in adults with cancer." p10 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** "Adults aged 18 years and over presenting with any type of cancer and receiving chemotherapeutic treatment, independent of gender and clinical setting." p10 ➢ **Setting:** Any clinical setting ➢ **Intervention:** "licensed pharmacological interventions based on cannabinoids derived from cannabis: nabilone and dronabinol used either as monotherapy or adjunct to conventional dopamine antagonists." p10 ➢ **Comparison:** "placebo or conventional dopamine antagonists" p10 ➢ **Outcome:** "**Primary outcomes**

Parameter	Extraction items
	Complete control of nausea and vomiting (absence of episodes of nausea and vomiting without use of rescue medication) in the acute phase (within 24 hours of treatment with chemotherapy) and in the delayed phase (after 24 hours' treatment with chemotherapy) of nausea and vomiting. Complete control of vomiting (absence of episodes of vomiting without use of rescue medication) in the acute and delayed phases of nausea and vomiting. Complete control of nausea (absence of episodes of nausea without use of rescue medication) in the acute and delayed phases of nausea and vomiting. **Secondary outcomes** Withdrawal due to adverse effects of anti-emetic. Withdrawal due to any anti-emetic-related reason. Withdrawal due to lack of anti-emetic efficacy. Cross-over studies only: participant preference for one or other of the interventions (cannabis or control). Incidence of particular adverse effects: 'feeling high', sedation, euphoria, dizziness, heightened sense of anxiety or agitation (dysphoria), depression, hallucinations, paranoia, hypotension, focal dystonia, extrapyramidal effects and oculogyric crisis." P10
Participants (characteristics and numbers)	**For whole sample and subgroups** • **Number of participants:** n=1326 • **Age:** Medians/means reported for 17/23 RCTs, ranged 24-61 • **Gender:** Gender breakdown reported for 15/23 RCTs, n=972 participants total, n=547 male (56.3%), n=425 female (43.7%)

Parameter	Extraction items
	• **Details of clinical diagnosis/indications:** "The RCTs included people with a variety of cancers undergoing different chemotherapy regimens ranging from moderate to high anti-emetic potential, except for one of low emetic potential; five were unclassifiable as reporting of chemotherapy regimen was unclear" p14
Setting/context	**Countries (alphabetic order):** Not reported **Setting (university, public or private clinic):** Clinical settings, not otherwise described **Other relevant features of setting:** Not reported
Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** "licensed pharmacological interventions based on cannabinoids derived from cannabis: nabilone and dronabinol used either as monotherapy or adjunct to conventional dopamine antagonists." p10 • **Dose and regimen:** "Cannabinoids were also given as co-therapy with another anti-emetic agent compared with an antiemetic agent alone in two RCTs. Two different cannabis-based medications were tested: nabilone in 12 RCTs and dronabinol in 11 RCTs. Dosing schedules varied across trials. Nabilone when given as monotherapy was administered most commonly as a fixed dose of 2 mg twice daily with lower doses administered when given as co-therapy. Dronabinol was mainly given at doses according to body surface area and ranged from 10 mg/m^2 twice daily to 15 mg/m^2 six times daily." p14 • **Administration methods:** Both nabilone and dronabinol "were given as oral formulations. In two trials, oral dronabinol was replaced with cannabis-based cigarettes if the participants vomited." p14

Parameter	Extraction items
	• **Comparator:** "Nine RCTs compared cannabinoids given as monotherapy compared with placebo, with another anti-emetic agent (prochlorperazine) in 11 RCTs, metoclopramide in two RCTs, domperidone in one RCT, and chlorpromazine in one RCT." p14 • **Treatment duration**: Not clearly reported for 7 RCTs; reported as day of chemotherapy for 6 RCTs, 24 hours after chemotherapy for 5 RCTs, 3 days for 2 RCTs, 4 days for 1 RCT, 5 days for 1 RCT, and 2 cycles for 1 RCT. • **Timeframe for follow-up:** Follow-up periods not reported for any study; efficacy assessed at end of treatment period.
Databases and sources searched	• **Number and names of databases:** 5: Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, PsycINFO, LILACS • **Other sources:** "Related articles" feature on PubMed; hand search of key textbooks and previous systematic reviews and reports of conferences • **Grey literature:** Search of metaRegister, Physicians Data Query, www.clinicaltrials.gov, and www.cancer.gov/clinicaltrials for ongoing trials; conference proceedings and abstracts searched through ZETOC and WorldCat Dissertations • **Reference chasing:** Yes • **Expert consultation:** No • **Dates:** Database searches carried out January 2015 • **Search limits:** No • **Justifications for search limits:** Not applicable • **Other searches:** Not reported • **Protocol prepared:** Yes • **If yes, published:** Yes, available at Cochrane, https://doi.org/10.1002/14651858.CD009464 • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported

Parameter	Extraction items
	• **Extraction completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Funding of review: "**National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to the Cochrane Gynaecological, Neuro-oncology and Orphan Cancer Group" p20 • **Conflicts of interest of review:** "The authors have no conflicts of interest" p82 • **How conflicts of interest were managed:** Not applicable
Date Range (years) of included studies	• **Exact years for included studies:** 1975-1991
Number of primary studies included in the systematic review	• **Number of studies:** 23 • **Number of studies by study design:** 23 RCTs (19 crossover, 4 parallel) • **Study years:** 1975 (2 RCTs), 1979 (4 RCTs), 1980 (1 RCT), 1981 (3 RCTs), 1982 (7 RCTs), 1983 (3 RCTs), 1984 (1 RCT), 1985 (1 RCT), 1986 (2 RCTs), 1988 (1 RCT), 1991 (1 RCT) • **Funding of included studies:** Not reported • **Conflicts of interest of included studies:** Not reported
Types of studies included	**Planned study designs to be included:** RCTs **Reasons for including only RCTs/prospective cohort studies:** Not reported **List of excluded studies at full text and reasons for exclusion:** Yes
Appraisal instruments used	**Full name of tools used:** Cochrane Risk of Bias **<u>Risk of bias criteria for AMSTAR 2 assessment, for RCTs, record Yes/No for:</u>** • **Concealment of allocation:** Yes

Parameter	Extraction items
	• **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The authors did not provide an overall assessment of risk of bias for each trial. However, HRB notes that according to Cochrane's Collaboration tool, and graphical information provided in the paper, the included trials appeared to have a high risk of bias (12 RCTs), unclear risk of bias (9 RCTs) and low risk of bias (2 RCTs) ○ **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** ○ Overall: Low risk randomisation (3/23); low risk outcome ascertainment (22/23) *Cannabinoids versus placebo* ○ Complete absence of nausea: Low risk randomisation (0/2); low risk outcome ascertainment (2/2) ○ Complete absence of vomiting: Low risk randomisation (0/3); low risk outcome ascertainment (3/3) ○ Complete absence of nausea and vomiting: Low risk randomisation (1/3); low risk outcome ascertainment (3/3) *Cannabinoids versus other anti-emetic agent* ○ Complete absence of nausea: Low risk randomisation (1/5); low risk outcome ascertainment (5/5) ○ Complete absence of vomiting: Low risk randomisation (1/4); low risk outcome ascertainment (4/4) ○ Complete absence of nausea and vomiting: Low risk randomisation (1/4); low risk outcome ascertainment (3/4) *Cannabinoids plus other anti-emetic agent compared with other anti-emetic monotherapy* ○ Complete absence of nausea: Low risk randomisation (0/1); low risk outcome ascertainment (1/1) ○ Complete absence of vomiting: Low risk randomisation (0/2); low risk outcome ascertainment (2/2)

Parameter	Extraction items
	○ Complete absence of nausea and vomiting: Low risk randomisation (0/1); low risk outcome ascertainment (1/1) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** "Overall, the trials were of variable quality (very low to moderate by Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach). Strengths included the use of blinding by using double-dummy preparations by the majority of the trials. However, it is possible that the trials were at risk of observer bias, due to the characteristic adverse effect profile of cannabinoids. The risk of bias from selective reporting of the primary outcome was low. The majority of the trials were unclear with respect to methods used to generate randomisation sequence and whether randomisation was concealed, so may be at risk of selection bias. A major weakness lies in the fact that a large proportion of the trials were of cross-over design, and we were unable to adjust the data to take into account the paired data, which will result in narrower CIs around effect estimates. Another weakness was high risk of bias from attrition from the trials. This was largely due to participants being excluded from analyses in the cross-over trials if they did not complete all cross-over periods... The quality of the evidence for most outcomes was generally of low quality. The main reasons were due to risk of bias, imprecise results due to few studies or few events (or both) and unexplained heterogeneity. The impact of the downgrading decisions means that further research is likely to influence the confidence in our estimates of effects and may change the estimates." p19 • **Graphical or statistical test for publication bias:** Visual inspection of funnel plots corresponding to meta-analysis of primary outcome, if there were at least 10 trials included in meta-analysis. • **Authors' comments likelihood and magnitude of publication bias:** "In order to avoid publication bias, we searched for ongoing trials in clinical trial registry databases; however, we identified no further trials." p19 • **Authors' comment on how publication bias was dealt with:** Not reported • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** No

Parameter	Extraction items
	• **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** "The quality of the evidence for most outcomes was generally of low quality. The main reasons were due to risk of bias, imprecise results due to few studies or few events (or both) and unexplained heterogeneity. The impact of the downgrading decisions means that further research is likely to influence the confidence in our estimates of effects and may change the estimates." p19
Method of analysis	• **Description of method of analysis as per authors:** "Where we judged the trials sufficiently similar, we pooled their results in a meta-analysis. For dichotomous outcomes, we combined the RR for each study. We used random-effects models with inverse variance weighting for all meta-analyses due to the clinical and methodological diversity of the studies. If trials had multiple treatment groups, we divided the 'shared' comparison group into the number of treatment groups and treated comparisons between each treatment group and the split comparison group as independent comparisons. We conducted the following subgroup analyses for the primary outcome if sufficient trials were available: • history of cannabis use, naive users versus prior users of cannabis; • history of exposure to chemotherapy, chemotherapy naïve versus prior chemotherapy treatment; • type of cannabinoid agent, nabilone versus dronabinol. Sensitivity analysis We carried out sensitivity analyses for the primary outcome, if sufficient trials were available, excluding trials at high risk of bias and trials of a cross-over design. We also analysed the influence of the following factors on estimates of treatment effect: • repeating the analysis excluding trials where chemotherapeutic regimens had low or low-moderate emetic potential, or the emetic potential was unclassifiable;

Parameter	Extraction items
	• repeating the analysis excluding trials where the primary outcome data were gathered after more than 24 hours of chemotherapeutic treatment." p11-12 • **Justification for narrative synthesis or meta-analysis:** Not reported • **Justification for combining data in meta-analysis:** "Where we judged the trials sufficiently similar, we pooled their results in a meta-analysis." p11
Outcome assessed	**List of outcomes assessed and intended timeframes** • Primary outcomes: Absence of nausea; Absence of vomiting; Absence of nausea and vomiting • Secondary outcomes: Adverse events: Depression, Dysphoria, 'Feeling high', Paranoia, Sedation; Withdrawal due to adverse event • Intended timeframes: Not reported • Actual timeframes: Treatment duration not clearly reported for 7 RCTs; reported as day of chemotherapy for 6 RCTs, 24 hours after chemotherapy for 5 RCTs, 3 days for 2 RCTs, 4 days for 1 RCT, 5 days for 1 RCT, and 2 cycles for 1 RCT. Follow-up periods not reported for any study; efficacy assessed at end of treatment period.
Results/findings	• **Findings by outcome:** PRIMARY OUTCOMES Absence of nausea ○ No significant difference between cannabinoids and placebo (RR 2.0; 95% CI 0.19 to 21) (2 RCTs, n=96). ○ No significant difference between cannabinoids and prochlorperazine (RR 1.5; 95% CI 0.67 to 3.2) (5 RCTs, n=258) with substantial heterogeneity (I^2 = 58%, Tau^2 = 0.33, Chi^2 test for heterogeneity p = 0.05). ○ No significant difference between cannabinoid plus other anti-emetic agent versus other antiemetic agent monotherapy (RR 11; 95% CI 0.61 to 182) (1 RCT, n=41).

Parameter	Extraction items
	○ Trials comparing cannabinoids versus metoclopramide (2 RCTs), cannabinoids versus domperidone (1 RCT) and cannabinoids versus chlorpromazine (1 RCT) did not report data for this outcome. Absence of vomiting ○ Greater chance of reporting complete absence of vomiting with cannabinoids compared to placebo (RR 5.7; 95% CI 2.6 to 13) (3 RCTs, n=168) with unimportant heterogeneity (I^2 = 0%, Tau^2 = 0.0, Chi^2 test for heterogeneity p = 0.33). ○ No significant difference between cannabinoids and prochlorperazine (RR 1.1; 95% CI 0.86 to 1.4) (2 RCTs, n=209) with unimportant heterogeneity (I^2 = 0%, Tau^2 = 0.0, Chi^2 test for heterogeneity p = 0.53). ○ No significant difference between cannabinoid plus other anti-emetic agent versus other antiemetic agent monotherapy (RR 1.5; 95% CI 0.69 to 3.1) (2 RCTs, n=89). ○ Trials comparing cannabinoids versus metoclopramide (2 RCTs), cannabinoids versus domperidone (1 RCT) and cannabinoids versus chlorpromazine (1 RCT) did not report data for this outcome. Absence of nausea and vomiting ○ Greater chance of reporting complete absence of nausea and vomiting with cannabinoids compared to placebo (RR 2.9; 95% CI 1.8 to 4.7) (3 RCTs, n=288) with unimportant heterogeneity (I^2 = 0%, Tau^2 = 0.0, Chi^2 test for heterogeneity p = 0.50). ○ No significant difference between cannabinoids and prochlorperazine (RR 2.0; 95% CI 0.74 to 5.4) (4 RCTs, n=414) with substantial heterogeneity (I^2 = 60%, Tau^2 = 0.51, Chi^2 test for heterogeneity p = 0.06). “Sensitivity analysis, where the two parallel group trials were pooled after removal of the five cross-over trials, had an RR of 1.1 (95% CI 0.70 to 1.7) with no heterogeneity (I^2 = 0%, Tau^2 = 0.0, Chi^2 test for heterogeneity p = 0.56)." p17 ○ No significant difference between cannabinoid plus other anti-emetic agent versus other antiemetic agent monotherapy (RR 1.6; 95% CI 0.68 to 3.6) (1 RCT, n=37).

Parameter	Extraction items
	○ Trials comparing cannabinoids versus metoclopramide (2 RCTs), cannabinoids versus domperidone (1 RCT) and cannabinoids versus chlorpromazine (1 RCT) did not report data for this outcome. SECONDARY OUTCOMES Withdrawal (all cause): ○ One study (n=33) reported no significant difference between cannabinoid and placebo groups (RR 0.31; 95% CI 0.01 to 7.21). ○ One study (n=42) reported significantly higher likelihood in cannabinoid compared with prochlorperazine groups (RR 3.5; 95% CI 1.4 to 8.9). ○ One study (n=41) reported no significant difference between cannabinoid plus other anti-emetic agent compared with other antiemetic agent monotherapy (RR 1.3; 95% CI 0.41 to 4.2). Withdrawal due to lack of efficacy ○ One study (n=42) reported significantly higher chance in cannabinoid compared with compared with prochlorperazine groups (RR 3.5; 95% CI 1.4 to 8.9). ○ One study (n=38) reported no significant difference between cannabinoid and domperidone groups (RR 0.14; 95% CI 0.01 to 2.7). ○ One study (n=41) reported no significant difference between cannabinoid plus other anti-emetic agent compared with other antiemetic agent monotherapy (RR 0.12; 95% CI 0.01 to 2.0). Withdrawal due to adverse events ○ Greater chance of withdrawing due to an adverse event with cannabinoids compared to placebo (RR 6.9; 95% CI 2.0 to 24) (2 RCTs, n=226).

Parameter	Extraction items
	○ Greater chance of withdrawing due to an adverse event with cannabinoids compared to prochlorperazine (RR 3.9; 95% CI 1.3 to 12) with unimportant heterogeneity (I^2 = 17%, Tau^2 = 0.31, Chi^2 test for heterogeneity p = 0.31) (5 RCTs, n=664). ○ No significant difference between cannabinoids versus domperidone (RR 0.14; 95% CI 0.01 to 2.7), based on very low event rates (1 RCT, n=76). ○ No significant difference between cannabinoid plus other anti-emetic agent versus other antiemetic agent monotherapy (RR 7.0; 95% CI 0.88 to 55) (2 RCTS, n=105). Adverse event: 'Feeling high' ○ Greater chance of reporting 'feeling high' with cannabinoids compared to placebo (RR 31; 95% CI 6.4 to 152) (3 RCTs, n=137) with unimportant heterogeneity (I^2 = 0%, Tau^2 = 0.0, Chi^2 test for heterogeneity p = 0.95). ○ Greater chance of reporting 'feeling high' with cannabinoids versus prochlorperazine (RR 6.2; 95% CI 3.5 to 11) (4 RCTs; n=389) with unimportant heterogeneity (I^2 = 0%, Tau^2 = 0.0, Chi^2 test for heterogeneity p = 0.75). ○ No significant difference between cannabinoids versus metoclorpramide in one RCT (n=30) (RR 3.0; 95% CI 0.35 to 26). Adverse event: Depression ○ No significant difference between cannabinoids versus placebo in 1 RCT (n=16) (RR 3.8; 95% CI 0.18 to 80). ○ No significant difference between cannabinoids versus prochlorperazine (RR 0.81; 95% CI 0.51 to 1.3 (3 RCTs, n=317) with unimportant heterogeneity (I^2 = 0%, Tau^2 = 0.0, Chi^2 test for heterogeneity p = 0.47). ○ No significant difference between cannabinoid plus other anti-emetic agent versus other antiemetic agent monotherapy (no participants reporting depression in either group) (1 RCT, n=41). Adverse event: Dysphoria ○ No significant difference between cannabinoids versus placebo (RR 9.0; 95% CI 0.50 to 161) (2 RCTs, n=96).

Parameter	Extraction items
	○ Greater chance of reporting dysphoria with cannabinoids compared with prochlorperazine (RR 7.2; 95% CI 1.3 to 39) (3 RCTs, n=192) with unimportant heterogeneity: (I^2 = 0%, Tau^2 = 0.0, Chi^2 test for heterogeneity p = 0.75). ○ No significant difference between cannabinoid plus other anti-emetic agent versus other antiemetic agent monotherapy (RR 7.3; 95% CI 0.40 to 134) (1 RCT, n=41). Adverse event: Paranoia ○ No significant difference between cannabinoids versus placebo in 1 RCT (n=64) (RR 3.0; 95% CI 0.13 to 71). ○ No significant difference between cannabinoids versus prochlorperazine in 1 RCT (n=42) (RR 3.0; 95% CI 0.13 to 70). ○ No significant difference between cannabinoid plus other anti-emetic agent versus other antiemetic agent monotherapy (RR 5.2; 95% CI 0.27 to 103) (1 RCT, n=41). Adverse event: Sedation ○ No significant difference between cannabinoids versus placebo (RR 4.5; 95% CI 0.35 to 58) (2 RCTs, n=139). ○ Greater chance of reporting sedation with received cannabinoids compared with prochlorperazine (RR 1.4; 95% CI 1.2 to 1.8) (8 RCTs, n=947) with moderate heterogeneity (I^2= 31%, Tau^2 = 0.02, Chi^2 test for heterogeneity p = 0.18). ○ No significant difference between cannabinoids versus metoclorpramide in 1 RCT (n=30) (RR 0.93; 95% CI 0.73 to 1.2). ○ No significant difference between cannabinoids versus domperidone (RR 1.2; 95% CI 0.66 to 2.3). ○ No significant difference between cannabinoids versus chlorpromazine in 1 RCT (n=40) (RR 1.7; 95% CI 0.85 to 3.4), with few events giving rise to wide CIs around the point estimates. ○ No significant difference between cannabinoid plus other anti-emetic agent versus other antiemetic agent monotherapy (RR 1.8; 95% CI 0.48 to 6.4) (1 RCT, n=41). Adverse event: Dizziness

Parameter	Extraction items
	○ Greater chance of reporting dizziness with cannabinoids compared with prochlorperazine (RR 2.4; 95% CI 1.8 to 3.1) (7 RCTs, n=675) with unimportant heterogeneity: I^2 = 12%, Tau^2 = 0.02, Chi^2 test for heterogeneity p = 0.34). ○ Greater chance of reporting dizziness with cannabinoids compared with metoclorpramide in 1 RCT (n=30) (RR 12; 95% CI 1.8 to 81). ○ Greater chance of reporting dizziness with cannabinoids compared with domperidone (RR 2.8; 95% CI 1.1 to 7.1) (1 RCT, n=38). ○ No significant difference between cannabinoid plus other anti-emetic agent versus other antiemetic agent monotherapy (RR 2.1; 95% CI 0.21 to 21) (1 RCT, n=41). Adverse event: Euphoria ○ Greater chance of reporting dysphoria with cannabinoids compared with prochlorperazine (RR 18; 95% CI 2.4 to 133) (2 RCTs, n=280) with unimportant heterogeneity (I^2 = 0%, Tau^2 = 0.00, Chi^2 test for heterogeneity p = 0.47). ○ No significant difference between cannabinoids versus domperidone (RR 5.0; 95% CI 0.26 to 98) (1 RCT, n=38). ○ No significant difference between cannabinoids versus chlorpromazine in 1 RCT (n=40) (RR 3.0; 95% CI 0.13 to 70), with few events giving rise to wide CIs around the point estimates. Adverse event: Hallucinations ○ No significant difference between cannabinoids versus prochlorperazine (RR 5.4; 95% CI 0.66 to 44) (2 RCTs, n=144) with unimportant heterogeneity (I^2 = 0%, Tau^2 = 0.0, Chi^2 test for heterogeneity p = 0.80). Adverse event: Postural hypotension ○ No significant difference between cannabinoids versus prochlorperazine (RR 1.2; 95% CI 0.52 to 2.9) (3 RCTs, n=305) with moderate heterogeneity (I^2 = 41%, Tau^2 = 0.29, Chi^2 test for heterogeneity p = 0.18). ○ Greater chance of reporting postural hypotension with cannabinoids versus metoclorpramide in 1 RCT (n=30) (RR 17; 95% CI 1.1 to 270).

Parameter	Extraction items

- No significant difference between cannabinoids versus domperidone (RR 4.0; 95% CI 0.49 to 33) (1 RCT, n=38).
- No significant difference between cannabinoids versus chlorpromazine in 1 RCT (n=40) (RR 7.0; 95% CI 0.95 to 52), with few events giving rise to wide CIs around the point estimates.

Adverse event: Dystonia

- Neither one of two trials comparing cannabinoids versus metoclorpramide reported dystonic reactions (no summary statistics reported).

- **GRADE by outcome:**

Outcome	Measure (no. studies)	GRADE
Cannabinoids versus placebo		
Absence of nausea	2	Low
Absence of vomiting	3	Low
Absence of nausea and vomiting	3	Moderate
Withdrawal due to adverse events	2	Very low
Cannabinoids versus other anti-emetic agent		
Absence of nausea	5	Low
Absence of vomiting	4	Moderate
Absence of nausea and vomiting	4	Low
Withdrawal due to adverse events	6	Low
Cannabinoids plus other anti-emetic agent compared with other anti-emetic monotherapy		
Absence of nausea	1	Very low
Absence of vomiting	2	Low
Absence of nausea and vomiting	1	Low
Withdrawal due to adverse events	2	Very low

- **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):**

Outcome	No. studies (No. participants)	Summary estimate (95% CI)	P-value	I^2 (%)	Direction of effect

Parameter	Extraction items					
	Cannabinoids versus placebo					
	Absence of nausea	2(96)	RR 2.0 (0.2, 21)	0.56	Not applicable	No significant difference
	Absence of vomiting	3(168)	RR 5.7 (2.6, 12.6)	<0.0001	0	Favours cannabinoids
	Absence of nausea and vomiting	3(288)	RR 2.9 (1.8, 4.7)	<0.0001	0	Favours cannabinoids
	Withdrawal due to adverse events	2(276)	RR 6.9 (1.96, 24.0)	0.003	0	More common with cannabinoids compared to placebo
	Cannabinoids versus other anti-emetic agent					
	Absence of nausea	5 (258)	RR 1.46 (0.67, 3.15)	0.34	58	No significant difference
	Absence of vomiting	4 (209)	RR 1.1 (0.86, 1.4)	0.43	0	No significant difference
	Absence of nausea and vomiting	4 (414)	RR 2.0 (0.74, 5.4)	0.17	60	No significant difference
	Withdrawal due to adverse events	6(740)	RR 3.2 (1.3, 8.0)	0.01	0	More common with cannabinoids compared to other anti-emetic agent
	Cannabinoids plus other anti-emetic agent compared with other anti-emetic monotherapy					
	Absence of nausea	1(37)	RR 10 (0.61, 183)	Not reported	Not reported	No significant difference
	Absence of vomiting	2(89)	RR 1.5 (0.69, 3.1)	0.32	Not reported	No significant difference
	Absence of nausea and vomiting	1(37)	RR 1.6 (0.68, 3.6)	Not reported	Not reported	No significant difference

Parameter	Extraction items

Withdrawal due to adverse events	2(105)	RR 6.97 (0.88, 55.19)	0.07	0	No significant difference

Findings from additional meta-analyses for specific adverse events and subgroup analyses for cannabinoids versus specific anti-emetic agents are detailed above in 'Findings by outcome'.

- **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Not applicable
- **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Yes; "We used random-effects models with inverse variance weighting for all meta-analyses due to the clinical and methodological diversity of the studies" p11
- **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable

Significance/direction

See above if results listed by outcome: Findings were generally favourable towards cannabinoids; participants had greater chance of reporting complete absence of vomiting and complete absence of vomiting and nausea when receiving cannabinoids compared with placebo. However, cannabinoids were also associated with higher risk of withdrawal due to adverse events and higher risk of 'feeling high'. There was no evidence of a difference between cannabinoids and other anti-emetics in efficacy, though cannabinoids were associated with higher risk of a number of adverse events. The quality of evidence was generally low.

Heterogeneity

- **See above if I^2 available:** As above
- **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** "The quality of the evidence for most outcomes was generally of low quality. The main reasons were due to risk of bias, imprecise results due to few

Parameter	Extraction items
	studies or few events (or both) and unexplained heterogeneity. The impact of the downgrading decisions means that further research is likely to influence the confidence in our estimates of effects and may change the estimates." p19 • **Causes of heterogeneity investigated:** Subgroup analyses were carried out where sufficient trials were available to investigate possible reasons for heterogeneity. History of cannabis use, history of exposure to chemotherapy, and type of cannabinoid agent (nabilone versus dronabinol) were investigated for efficacy outcomes, but generally did not explain observed heterogeneity.
Comments	The quality of evidence was generally low and the review authors acknowledge that the included studies are generally older (pre-1991) and do not reflect current chemotherapy regimes and newer anti-emetic drugs. Further research is likely to modify the conclusions.

Thomas *et al.* (2022): A scoping review on the effect of cannabis on pain intensity in people with spinal cord injury

Parameter	Extraction items
First author and year of publication	Thomas *et al.* (2022)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "to examine the scientific evidence in [spinal cord injury] by mapping the current literature and identifying gaps in this growing area of research." p657 • **Exact review question and page number:** ""What is the current level of evidence on the effect of cannabis/cannabinoids upon pain intensity in [spinal cord injury]?" p657 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** People with pain related to spinal cord injury ➢ **Setting:** Not specified

Parameter	Extraction items
	➢ **Intervention:** "a cannabinoid preparation, applied by any route of administration or dose, and could involve synthetic cannabinoids (dronabinol, nabilone), whole-plant extracts, isolated or combined cannabinoid preparations (THC only, CBD only, THC-CBD)." p658 ➢ **Comparison:** Not specified ➢ **Outcome:** Pain intensity
Participants (characteristics and numbers)	**For whole sample and subgroups:** N=165 (RCT); N=22 (trial without comparator group); N=1 (case study) The trial without a comparator and the case study is excluded from the remainder of the extraction. • **Number of participants:** N=165 • **Age:** Mean range: 46.4-50.1 years • **Gender:** 24.1% female • **Details of clinical diagnosis/indications:** Chronic neuropathic pain at least three levels below the spinal cord lesion (n=7); central neuropathic pain (n=158)
Setting/context	**Countries (alphabetic order):** Not reported **Setting (university, public or private clinic):** Not reported **Other relevant features of setting:** Not reported
Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** "a cannabinoid preparation, applied by any route of administration or dose, and could involve synthetic cannabinoids (dronabinol, nabilone), whole-plant extracts, isolated or combined cannabinoid preparations (THC only, CBD only, THC:CBD)." p658 • **Dose and regimen:** ○ THC oral (1 RCT): 5 mg oral; regimen not reported

Parameter	Extraction items
	○ THC vaporised (1 RCT): 2.9% or 6.7% delta-9-THC; 4 puffs after baseline; then 4–8 puffs after 240 min ○ Dronabinol (1 RCT): 5 mg starting dose titrated up to maximum of 20 mg per day; regimen not reported ○ Nabiximols (1 RCT): Each puff delivered 100 µl; maximum permitted dose was eight puffs in any 3-hour period and 48 puffs in any 24-hour period. • **Administration methods:** Oral (1 RCT); vaporised (1 RCT); oromucosal spray (1 RCT); capsule (1 RCT) • **Comparator:** diphenhydramine (1 RCT); placebo (2 RCTs) • **Treatment duration:** Three 8-hour sessions – 5 months • **Timeframe for follow-up:** Not reported for included RCTs
Databases and sources searched	• **Number and names of databases:** 4; PubMed, Scopus, EMBASE, and CINAHL; inception-05/02/2020 • **Other sources:** clinicaltrials.gov • **Grey literature:** Not reported • **Reference chasing:** Yes • **Expert consultation:** No • **Dates:** "The initial search took place on August 29th 2019 and an updated search was completed on February 5th 2020." p657 • **Search limits:** "only studies written in English were included in this review" p658 • **Justifications for search limits:** Yes • **Other searches:** Not reported • **Protocol prepared:** No • **If yes, published:** Not applicable • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes

Parameter	Extraction items
	• **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** No, however the authors state "a single reviewer extracted data, while another monitored the process to ensure accuracy" p658 • **If yes, rate of agreement:** Not reported • **Funding of review:** The authors report no funding. • **Conflicts of interest of review:** The authors declare no conflicts of interest. • **How conflicts of interest were managed:** Not applicable
Date Range (years) of included studies	• **Exact years for included studies:** 2010-2016
Number of primary studies included in the systematic review	• **Number of studies:** 4 RCTs (2 RCTs sharing a single cohort) • **Number of studies by study design:** 4 RCTs (2 RCTs sharing a single cohort) • **Study years:** 1990 (1 RCT); 2010 (1 RCT); 2012 (1 RCT); 2016 (1 RCT) • **Funding of included studies:** Not reported • **Conflicts of interest of included studies:** Not reported
Types of studies included	**Planned study designs to be included:** "Eligible studies could include randomized controlled trials (RCTs), controlled trials, prospective open-label studies, and case studies." p658 **Reasons for including only RCTs/prospective cohort studies:** Not applicable **List of excluded studies at full text and reasons for exclusion:** Not reported
Appraisal instruments used	**Full name of tools used:** Physiotherapy Evidence Database (PEDro) scale

Parameter	Extraction items
	Note: The authors did not report on the domains of the PEDro scale. For this extraction form we used information about the scale from https://pedro.org.au/english/resources/pedro-scale/ **Risk of bias criteria for AMSTAR 2 assessment, for RCTs, record Yes/No for:** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence allocation (individual vs group randomisation):** Yes • **Selective reporting:** No
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The authors reported PEDro scores as follows: 5/11; 6/11; 10/11; 8/11 • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** o Overall: Low risk randomisation (cannot extract X/11); low risk outcome ascertainment (3/11) *THC vs placebo:* o Pain intensity: Low risk randomisation (cannot extract X/1); low risk outcome ascertainment (cannot extract X/1) *THC/CBD vs placebo* o Pain intensity: Low risk randomisation (cannot extract X/1); low risk outcome ascertainment (cannot extract X/1) *THC (dronabinol vs diphenhydramine* o Pain intensity: Low risk randomisation (cannot extract X/1); low risk outcome ascertainment (cannot extract X/1) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** Not reported • **Graphical or statistical test for publication bias:** Not reported • **Authors' comments likelihood and magnitude of publication bias:** Not reported

Parameter	Extraction items
	• **Authors' comment on how publication bias was dealt with:** Not reported • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** Not applicable • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** No
Method of analysis	• **Description of method of analysis as per authors:** "A data charting form was developed by the first and second author, this was informed by the Joanna Briggs Institute data extraction template. Microsoft Excel was used to chart and store data. A single reviewer extracted data, while another monitored the process to ensure accuracy. We contacted the principal investigators for permissions and data (if not publicly available) for studies identified through clincaltrials.gov." p658 …"We calculated effect size (Cohen's d) and percentages for which data is available. We provide estimates of effect size for studies which reported information on number needed to treat (NNT); estimates were calculated using a conversion table p659" • **Justification for narrative synthesis or meta-analysis:** Not reported • **Justification for combining data in meta-analysis:** Not reported
Outcome assessed	**List of outcomes assessed and intended time frames:** • Primary outcome: Pain • Secondary outcome: Adverse events • Intended timeframes: Not specified • Actual timeframes: three 8-hour sessions- 5 months
Results/findings	• **Findings by outcome:**

Parameter	Extraction items
	PRIMARY OUTCOME *Pain outcomes* ○ One study (n=7) reported no significant difference in pain (numeric rating scale) between dronabinol and diphenhydramine groups (p=0.102). ○ One study (n=116) reported no significant difference between nabiximol and placebo groups (SMD 0.039, p=0.708). ○ One study (n=42) reported significant improvement difference in pain (neuropathic pain scale) between lower THC and placebo groups (SMD 0.7, p<0.05) and between higher THC and placebo groups (SMD 1.0, p<0.05). SECONDARY OUTCOME *Adverse events* ○ One study (n=7) reported seven participants experienced side effects (dry mouth 71%, constipation 71%, fatigue 57%, drowsiness 57%), and two withdrawals in the dronabinol group. In the dihydramine group, five participants experienced side effects (fatigue 100%, dry mouth 60%, constipation 60%, drowsiness 60%) and zero withdrawals. ○ One study (n=116) reported 46 participants experienced side effects (dizziness 30%, disgeusia 20%, urinary tract infection 17%, somnolence 15%, nausea 13%, headache 11%), three participants reported adverse events (anemia 33%, fall 33%, infections 33%, tibia fracture 33%, confusion 33%, paranoia 33%) and two withdrawals in the nabiximols group. In the placebo group 29 participants reported side effects (dizziness 17%, disgeusia 14%, urinary tract infection 14%, nausea 10%, oral pain 10%; alanine aminotransferase increase 10%, gamma glutamyltransferase increase 10%), two participants reported adverse events (fall 50%, bladder infection 50%, pneumonia 50%, upper limb fracture 50%, dizziness 50%, contusion 50%) and one withdrawal. ○ One study (n=42) reported one participant experienced an adverse event (syncopy 100%) and zero withdrawals. • **GRADE by outcome:** Not reported

Parameter	Extraction items
	• **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):** Not applicable • **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Above • **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Not applicable • **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Yes
Significance/direction	**See above if results listed by outcome:** Above
Heterogeneity	• **See above if I^2 available:** Not applicable • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** "A number of methodological weaknesses limit what can be concluded from the existing body of research. Type, dosage and route of administration of cannabinoids was highly variable across studies. There was a dearth of parallel group designs and studies were underpowered to detect anticipated effects. Pain assessments were often non-standard and inconsistent across investigations. Important procedural elements such as randomization, blinding, and concealment were not adequately described. Participant retention was poor" p662 • **Causes of heterogeneity investigated:** No
Comments	"Two articles covering the same study were included in the current review because they presented different aspects of the research." p656 Note: The authors did not report on the domains of the PEDro scale. For this extraction form we used information from https://pedro.org.au/english/resources/pedro-scale/ as follows: PEDro scale: 1. eligibility criteria were specified; 2. subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received); 3. allocation was concealed; 4. the groups were similar at baseline regarding the most important prognostic

Parameter	Extraction items
	indicators; 5. there was blinding of all subjects; 6. there was blinding of all therapists who administered the therapy; 7. there was blinding of all assessors who measured at least one key outcome; 8. measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups; 9. all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by “intention to treat”; 10. the results of between-group statistical comparisons are reported for at least one key outcome; 11. the study provides both point measures and measures of variability for at least one key outcome Two studies Hagenbach *et al.* (1990) (no control group) and Maurer *et al.* (2007) (case study) have not been included in this extraction form as per umbrella review criteria.

Torres-Moreno *et al.* (2018): Assessment of Efficacy and Tolerability of Medicinal Cannabinoids in Patients With Multiple Sclerosis. A Systematic Review and Meta-analysis

Parameter	Extraction items
First author and year of publication	Torres-Moreno *et al.* (2018)
Objectives	• **Study objectives:** "to evaluate the therapeutic efficacy and tolerability of medicinal cannabinoids to treat the symptoms of spasticity, pain, and bladder dysfunction in patients with [multiple sclerosis]" p2

Parameter	Extraction items
Report exact review question(s) and page number	• **Exact review question and page number:** "to evaluate the therapeutic efficacy and tolerability of medicinal cannabinoids to treat the symptoms of spasticity, pain, and bladder dysfunction in patients with [multiple sclerosis]" p2 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** "adult patients with [multiple sclerosis]" p2 ➢ **Setting:** Not reported in PICO ➢ **Intervention:** "medicinal cannabinoids by oral or oromucosal route" p2 ➢ **Comparison:** Placebo ➢ **Outcome:** "symptoms of spasticity, pain, or bladder dysfunction" p2
Participants (characteristics and numbers)	**For whole sample and subgroups** • **Number of participants:** 3161 unique participants (two pairs of studies shared cohorts) • **Age:** Age for total sample reported for 15 studies, median or mean age ranged 45.5-54.9 years • **Gender:** 16 studies (n=3145) reported gender breakdown, n=1156 male (36.8%), n=1989 female (63.2%) • **Details of clinical diagnosis/indications:** Patients with multiple sclerosis with a range of symptoms, including spasticity, various types of pain, spasms, bladder problems, tremor, and muscle stiffness
Setting/context	**Countries (alphabetic order):** Canada (1 study), Czech Republic (1 study), Denmark (1 study), Italy (2 studies), Switzerland (1 study), UK (5 studies); UK, Belgium and Romania (1 study); UK and Czech Republic (1); UK, Czech Republic, Canada, Spain and France (1 study); UK and Romania (1); UK, Spain, Poland, Czech Republic and Italy (1); not reported (1 study) **Setting (university, public or private clinic):** Not reported **Other relevant features of setting:** Not reported

Parameter	Extraction items

Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** "medicinal cannabinoids by oral or oromucosal route" p2
	• **Dose and regimen:**
	  ○ Cannabis extract capsules (THC:CBD): 4 studies (n=427), all 2.5mg THC and range 0.9-1.25mg or 20-30% CBD, dose range 2-12 caps/day
	  ○ Nabiximols (THC:CBD): 9 studies (n=843), oromucosal spray, all 2.7mg THC + 2.5mg CBD/spray, dose most commonly self-titrated and ranged 1-48 sprays/day
	  ○ Dronabinol capsules (THC): 4 studies (n=575), capsules containing 2.5mg/capsule (3 studies) or 3.5mg/capsule (1 study), dose ranged 2-8 capsules/day
	  ○ Nabilone (THC): 1 study (n=8), 1-2 capsule/day (0.5-1mg THC/capsule)
	• **Administration methods:** Capsules, spray
	• **Comparator:** Placebo, mean dose ranged 2-9.6 caps/day or 8.9-19.1 sprays/day
	• **Treatment duration:** Range 2 weeks – 5 years
	• **Timeframe for follow-up:** Not reported for included studies

Databases and sources searched	• **Number and names of databases:** 2: MEDLINE, Cochrane Library Plus • **Other sources:** ClinicalTrials.gov • **Grey literature:** Books, monographs, reports • **Reference chasing:** Yes • **Expert consultation:** None reported • **Dates:** 26/07/2016 • **Search limits:** No • **Justifications for search limits:** Not applicable • **Other searches:** None reported

Parameter	Extraction items
	• **Protocol prepared:** Yes • **If yes, published:** CRD42014015391 https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=15391 • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** Not reported • **If yes, rate of agreement:** Not applicable • **Funding of review:** "Funded in part by grants from the Ministerio de Sanidad, Servicios Sociales e Igualdad (Plan Nacional sobre Drogas-PNSD, 2015I054); MINECO/Instituto de Salud Carlos III (ISCIII, FIS-FEDER, PI14/00715); and MINECO/ISCIII (Red de Trastornos Adictivos-RTA, RD12/0028/0009, RD16/0017/0003, and RD16/0017/0010)." p13 • **Conflicts of interest of review: "**None reported" p13 • **How conflicts of interest were managed:** Funders had no role in design and conduct of review.
Date Range (years) of included studies	• **Exact years for included studies:** 2002-2015
Number of primary studies included in the systematic review	• **Number of studies:** 17 studies, reported in 19 articles (two pairs of studies shared cohorts) • **Number of studies by study design:** 17 RCTs (5 crossover trials, 12 parallel trials) • **Study years:** 2002 (1 study), 2003 (1 study), 2004 (3 studies), 2005 (1 study), 2006 (1 study), 2007 (1 study), 2009 (1 study), 2010 (2 studies), 2011 (1 study), 2012 (1 study), 2013 (1 study), 2014 (2 studies), 2015 (3 studies) • **Funding of included studies:** 7 studies of cannabis extract and dronabinol funded by independent grants, 10 studies of nabilone and nabiximols funded by pharmaceutical companies • **Conflicts of interest of included studies:** Not reported

Parameter	Extraction items
Types of studies included	**Planned study designs to be included:** "randomized, placebo-controlled, double-blind, and parallel or crossover designed trials [with] a minimum length of treatment of 2 weeks" p2 **Reasons for including only RCTs/prospective cohort studies:** Not reported **List of excluded studies at full text and reasons for exclusion:** List of excluded studies provided, reasons reported only in PRISMA flow diagram, not for individual studies
Appraisal instruments used	**Full name of tools used:** Cochrane Risk of Bias tool **<u>Risk of bias criteria for AMSTAR 2 assessment, for RCTs, record Yes/No for:</u>** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The authors did not provide an overall assessment of risk of bias for each trial. However, HRB notes that according to Cochrane's Collaboration tool, and graphical information provided in the paper, the included trials appeared to have a high risk of bias (7 studies) and unclear risk of bias (10 studies). • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** ○ Overall: Low risk randomisation (4/17); low risk outcome ascertainment (4/17) *Cannabis extract vs placebo* ○ Spasticity (Ashworth/Modified Ashworth): Low risk randomisation (2/4); low risk outcome ascertainment (4/4)

Parameter	Extraction items
	○ Spasticity (subjective): Low risk randomisation (2/3); low risk outcome ascertainment (2/3) ○ Pain: Low risk randomisation (2/3); low risk outcome ascertainment (2/3) ○ Bladder dysfunction: Low risk randomisation (2/3); low risk outcome ascertainment (3/3) ○ Total adverse events: Low risk randomisation (2/5); low risk outcome ascertainment (5/5) ○ Serious adverse events: Low risk randomisation (2/3); low risk outcome ascertainment (2/3) ○ Withdrawal due to adverse events: Low risk randomisation (2/4); low risk outcome ascertainment (3/4) *Nabiximols vs placebo* ○ Spasticity (Ashworth/Modified Ashworth): Low risk randomisation (0/8); low risk outcome ascertainment (1/8) ○ Spasticity (subjective): Low risk randomisation (0/9); low risk outcome ascertainment (1/9) ○ Pain: Low risk randomisation (0/6); low risk outcome ascertainment (1/6) ○ Bladder dysfunction: Low risk randomisation (0/4); low risk outcome ascertainment (1/4) ○ Total adverse events: Low risk randomisation (0/11); low risk outcome ascertainment (1/11) ○ Serious adverse events: Low risk randomisation (0/8); low risk outcome ascertainment (1/8) ○ Withdrawal due to adverse events: Low risk randomisation (0/9); low risk outcome ascertainment (1/9) *Dronabinol vs placebo* ○ Spasticity (Ashworth/Modified Ashworth): Low risk randomisation (2/3); low risk outcome ascertainment (3/3) ○ Spasticity (subjective): Low risk randomisation (3/3); low risk outcome ascertainment (2/3) ○ Pain: Low risk randomisation (4/4); low risk outcome ascertainment (2/4) ○ Bladder dysfunction: Low risk randomisation (3/3); low risk outcome ascertainment (2/3) ○ Total adverse events: Low risk randomisation (4/5); low risk outcome ascertainment (3/5) ○ Serious adverse events: Low risk randomisation (4/4); low risk outcome ascertainment (2/4)

Parameter	Extraction items
	○ Withdrawal due to adverse events: Low risk randomisation (3/3); low risk outcome ascertainment (2/3) *Nabilone vs placebo* ○ Pain: Low risk randomisation (1/1); low risk outcome ascertainment (0/1) ○ Withdrawal due to adverse events: Low risk randomisation (1/1); low risk outcome ascertainment (0/1) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** Not reported • **Graphical or statistical test for publication bias:** Yes; funnel plot • **Authors' comments likelihood and magnitude of publication bias:** "Publication bias was detected both for and against cannabinoids" p4 • **Authors' comment on how publication bias was dealt with:** Not reported • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** No • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** No reported
Method of analysis	• **Description of method of analysis as per authors:** "In efficacy, high heterogeneity was clearly demonstrated in the format by which results were obtained (eg, F statistic, mean difference between groups, or odds ratio), making a direct comparison nonviable. As a consequence, standardization to the SMD, which is expressed in standard deviation units, was calculated in order to allow comparison. The SMD used was Hedges g... Calculations of the SMD were carried out on an intention-to-treat (ITT) basis by extrapolation of the missing data. Crossover studies were treated as parallel design... Data pooling was carried out by the simple averages of the SMDs and their standard errors. For tolerability, data were analyzed in the form of the rate ratio (RR). The meta-analysis was performed with RevMan software using the inverse-of-variance method. The random-effects model was used on an ITT basis. For efficacy, SMDs and their standard errors

Parameter	Extraction items
	were analyzed. For tolerability outcomes, the natural logarithm (ln) of the RRs and its respective standard errors were introduced. The heterogeneity of the results was evaluated by means of the I^2 statistic. After the systematic review, we conducted a sensitivity analysis of the results obtained to ascertain whether the findings were strong enough to reaffirm the methods used. With this objective, the meta-analyses were repeated, changing the parameters that could be affected by our decisions: (1) use of the fixed-effects model instead of random effects; (2) exclusion of crossover studies; (3) exclusion of studies with a sample size of 50 patients or fewer; (4) exclusion of studies with a length of treatment of 4 weeks or less; and (5) exclusion of studies with a high risk of bias in any of the evaluated domains. Furthermore, to reaffirm our calculations, other parallel secondary estimations for SMDs were performed with data from the studies." p3-4 • **Justification for narrative synthesis or meta-analysis:** Not reported • **Justification for combining data in meta-analysis:** Not reported
Outcome assessed	**List of outcomes assessed and intended timeframes** • Primary outcomes: Spasticity (Ashworth Scale and subjective), pain, bladder dysfunction • Secondary outcomes: Tolerability (adverse events) • Intended timeframes: >2 weeks • Actual timeframes: Treatment duration 2 weeks – 3 years; follow-up not described
Results/findings	• **Findings by outcome:** PRIMARY OUTCOMES *Spasticity* ○ Spasticity was evaluated separately for objective measures scored by an observer on the Ashworth and Modified Ashworth scales and for subjective spasticity measures scored by patients. No effects of cannabinoids in any form

Parameter	Extraction items

on the Ashworth and Modified Ashworth scales were observed. Statistically significant differences in favour of cannabis extract and nabiximols, but not dronabinol, versus placebo were observed in subjective measures of spasticity.

Pain

- Statistically significant differences in favour of cannabis extract and nabilone, but not nabiximols or dronabinol, were observed.

Bladder dysfunction

- Statistically significant differences in favour of cannabis extract but not nabiximols or dronabinol were observed.

SECONDARY OUTCOMES

Tolerability

- There was a higher risk of total adverse events in nabiximols, dronabinol and cannabinoids compared to placebo, and a higher risk of withdrawals due to adverse events in cannabis extract, nabiximols, dronabinol, and cannabinoids, but not in nabilone. No statistically significant difference was found in the meta-analysis of serious adverse events. A higher risk in cannabinoids was observed regarding dizziness or vertigo, dry mouth, fatigue, feeling drunk, impaired balance or ataxia, memory impairment, and somnolence.

- **GRADE by outcome:** No GRADE assessment carried out
- **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):**

Intervention	No. studies (No. participants)	Summary estimate (95% CI)	P-value	I^2 (%)	Direction of effect
Cannabis extract vs placebo					
Spasticity (Ashworth, modified Ashworth)	3 (456)	SMD 0.1 (-0.18 to 0.20)	0.90	0%	Favours cannabis extract against placebo

Parameter	Extraction items					
	Spasticity (subjective)	2 (595)	SMD -0.27 (-0.44 to -0.09)	0.003	0%	Favours cannabis extract against placebo
	Pain	2 (595)	SMD -0.33 (-0.50 to -0.16)	0.0002	0%	Favours cannabis extract against placebo
	Bladder dysfunction	2 (432)	SMD -0.29 (-0.50 to -0.09)	0.005	0%	Favours cannabis extract against placebo
	Total adverse events	4 (733)	RR 1.51 (0.87 to 2.63)	Not reported	Not reported	No significant difference
	Serious adverse events	2 (595)	RR 0.99 (0.26 to 3.74)	Not reported	Not reported	No significant difference
	Withdrawals due to adverse events	3 (709)	RR 3.11 (1.54 to 6.28)	Not reported	Not reported	Higher risk of withdrawals due to adverse events with cannabis extract against placebo
	Adverse event: Dizziness or vertigo	4 (733)	RR 2.51 (0.84 to 7.47)	Not reported	Not reported	No significant difference
	Adverse event: Dry mouth	4 (733)	RR 3.17 (1.91 to 5.25)	Not reported	Not reported	Higher risk of dry mouth with cannabis extract against placebo
	Adverse event: Fatigue	1 (277)	RR 2.60 (1.22 to 5.58)	Not reported	Not reported	Higher risk of fatigue with cannabis extract against placebo
	Adverse event: Impaired balance or ataxia	1 (24)	RR 3.50 (0.18 to 67.77)	Not reported	Not reported	No significant difference
	Adverse event: Somnolence	3 (456)	RR 1.32 (0.95 to 1.83)	Not reported	Not reported	No significant difference
	Nabiximols vs placebo					
	Spasticity (Ashworth, modified Ashworth)	7 (1170)	SMD -0.11 (-0.22 to 0.01)	0.07	0%	No significant difference

Parameter	Extraction items					
	Spasticity (subjective)	8 (1509)	SMD -0.29 (-0.47 to -0.12)	0.001	62%	Favours nabiximols against placebo
	Pain	6 (1229)	SMD -0.07 (-0.26 to 0.12)	0.49	61%	No significant difference
	Bladder dysfunction	4 (971)	SMD -0.07 (-0.22 to 0.08)	0.36	27%	No significant difference
	Total adverse events	10 (1710)	RR 1.80 (1.53 to 2.12)	Not reported	Not reported	Higher risk of adverse events with nabiximols against placebo
	Serious adverse events	8 (1608)	RR 1.43 (0.66 to 3.09)	Not reported	Not reported	No significant difference
	Withdrawals due to adverse events	9 (1674)	RR 2.20 (1.34 to 3.59)	Not reported	Not reported	Higher risk of withdrawals due to adverse events with nabiximols against placebo
	Adverse event: Dizziness or vertigo	10 (1710)	RR 3.33 (2.55 to 4.34)	Not reported	Not reported	Higher risk of dizziness/vertigo with nabiximols against placebo
	Adverse event: Dry mouth	8 (1489)	RR 2.30 (1.42 to 3.73)	Not reported	Not reported	Higher risk of dry mouth with nabiximols against placebo
	Adverse event: Fatigue	9 (1624)	RR 1.64 (1.17 to 2.28)	Not reported	Not reported	Higher risk of fatigue with nabiximols against placebo
	Adverse event: Feeling drunk	3 (361)	RR 3.70 (0.70 to 19.55)	Not reported	Not reported	No significant difference
	Adverse event: Impaired balance or ataxia	5 (1025)	RR 2.93 (1.04 to 8.27)	Not reported	Not reported	Higher risk of impaired balance/ataxia with nabiximols against placebo
	Adverse event: Memory impairment	3 (595)	RR 4.93 (1.07 to 22.70)	Not reported	Not reported	Higher risk of memory

Parameter	Extraction items					
						impairment with nabiximols against placebo
	Adverse event: Somnolence	10 (1710)	RR 3.47 (2.10 to 5.73)	Not reported	Not reported	Higher risk of somnolence with nabiximols against placebo
	Dronabinol vs placebo					
	Spasticity (Ashworth, modified Ashworth)	2 (336)	SMD -0.16 (-0.38 to 0.07)	0.18	0%	No significant difference
	Spasticity (subjective)	2 (805)	SMD -0.13 (-0.46 to 0.20)	0.44	76%	No significant difference
	Pain	3 (853)	SMD -0.23 (-0.55 to 0.09)	0.15	71%	No significant difference
	Bladder dysfunction	2 (805)	SMD -0.06 (-0.27 to 0.16)	0.62	50%	No significant difference
	Total adverse events	4 (877)	RR 1.62 (1.12 to 2.34)	Not reported	Not reported	Higher risk of adverse events with dronabinol against placebo
	Serious adverse events	3 (853)	RR 1.21 (0.89 to 1.63)	Not reported	Not reported	No significant difference
	Withdrawals due to adverse events	2 (805)	RR 4.12 (2.39 to 7.11)	Not reported	Not reported	Higher risk of withdrawals due to adverse events with dronabinol against placebo
	Adverse event: Dizziness or vertigo	4 (877)	RR 4.00 (2.43 to 6.58)	Not reported	Not reported	Higher risk of dizziness/vertigo with dronabinol against placebo
	Adverse event: Dry mouth	3 (384)	RR 4.32 (2.12 to 8.81)	Not reported	Not reported	Higher risk of dry mouth with dronabinol against placebo
	Adverse event: Fatigue	2 (541)	RR 1.09 (0.74 to 1.60)	Not reported	Not reported	No significant difference

Parameter	Extraction items					
	Adverse event: Feeling drunk	1 (48)	RR 11.00 (0.61 to 198.93)	Not reported	Not reported	No significant difference
	Adverse event: Impaired balance or ataxia	2 (541)	RR 1.28 (0.90 to 1.81)	Not reported	Not reported	No significant difference
	Adverse event: Somnolence	2 (336)	RR 0.55 (0.06 to 4.74)	Not reported	Not reported	No significant difference
	Nabilone vs placebo					
	Pain	1 (15)	SMD -1.40 (-2.78 to -0.03)	0.05	NA	Favours nabilone against placebo (borderline statistical significance)
	Withdrawals due to adverse events	1 (15)	RR 2.63 (0.11 to 64.44)	Not reported	Not reported	No significant difference
	Total cannabinoids vs placebo					
	Spasticity (Ashworth, modified Ashworth)	10 (1962)	SMD 0.09 (-0.18 to 0.00)	0.06	0%	No significant difference
	Spasticity (subjective)	11 (2909)	SMD -0.25 (-0.38 to -0.13)	<0.0001	59%	Favours cannabinoids against placebo
	Pain	11 (2692)	SMD -0.17 (-0.31 to -0.03)	0.01	63%	Favours cannabinoids against placebo
	Bladder dysfunction	7 (2208)	SMD -0.11 (-0.22 to 0.00)	0.05	34%	Favours cannabinoids against placebo (borderline statistical significance)
	Total adverse events	16 (3320)	RR 1.72 (1.46 to 2.02)	Not reported	Not reported	Higher risk of adverse events with cannabinoids against placebo
	Serious adverse events	12 (3056)	RR 1.23 (0.82 to 1.85)	Not reported	Not reported	No significant difference
	Withdrawals due to adverse events	14 (3203)	RR 2.95 (2.14 to 4.07)	Not reported	Not reported	Higher risk of withdrawals due to

Parameter	Extraction items					
						adverse events with cannabinoids against placebo
	Adverse event: Dizziness or vertigo	16 (3320)	RR 3.40 (2.55 to 4.53)	Not reported	Not reported	Higher risk of dizziness/vertigo with cannabinoids against placebo
	Adverse event: Dry mouth	13 (2606)	RR 2.94 (2.15 to 4.03)	Not reported	Not reported	Higher risk of dry mouth with cannabinoids against placebo
	Adverse event: Fatigue	12 (2442)	RR 1.61 (1.18 to 2.21)	Not reported	Not reported	Higher risk of fatigue with cannabinoids against placebo
	Adverse event: Feeling drunk	4 (409)	RR 4.85 (1.15 to 20.53)	Not reported	Not reported	Higher risk of feeling drunk with cannabinoids against placebo
	Adverse event: Impaired balance or ataxia	8 (1590)	RR 1.40 (1.01 to 1.95)	Not reported	Not reported	Higher risk of impaired balance/ataxia with cannabinoids against placebo
	Adverse event: Memory impairment	3 (595)	RR 4.93 (1.07 to 22.70)	Not reported	Not reported	Higher risk of memory impairment with cannabinoids (nabiximols) against placebo
	Adverse event: Somnolence	13 (2502)	RR 1.87 (1.24 to 2.81)	Not reported	Not reported	Higher risk of somnolence with cannabinoids against placebo-

Parameter	Extraction items
	• **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** As above • **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Standard mean difference, random effects model • **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable
Significance/direction	**See above if results listed by outcome:** Findings indicate that cannabinoids offer a limited reduction of subjective spasticity, pain, and bladder dysfunction in patients with MS, but no change in objectively measured spasticity. Cannabinoids were associated with higher risk of some adverse events, but not serious adverse events.
Heterogeneity	• **See above if I^2 available:** As above • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** "The sensitivity analysis showed no relevant differences affecting the results obtained. We can thus consider our results to have a high level of certainty." p12 • **Causes of heterogeneity investigated:** Random effects model and sensitivity analysis conducted
Comments	None

Urbi *et al.* (2022): Effects of Cannabis in Parkinson's Disease: A Systematic Review and Meta-Analysis

Parameter	Extraction items
First author and year of publication	Urbi *et al.* (2022)

Parameter	Extraction items
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "The aim of this review was to interrogate the published and unpublished literature for evidence of treatment effects of cannabis in [Parkinson's disease]. We have focused on the potential effects on [Parkinson's disease] severity and progression, as well as effects on motor and non-motor symptoms." p496 • **Exact review question and page number:** "The aim of this review was to interrogate the published and unpublished literature for evidence of treatment effects of cannabis in [Parkinson's disease]. We have focused on the potential effects on [Parkinson's disease] severity and progression, as well as effects on motor and non-motor symptoms." p496 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** "Patients with [Parkinson's disease]" p496 ➢ **Setting:** Not reported in PICO ➢ **Intervention:** "Cannabis or cannabis-based treatment included any agent considered a cannabinoid whether used alone or combined with other cannabinoids or other agents, whether synthetic or a direct cannabis extract" p496 ➢ **Comparison:** Not reported in PICO ➢ **Outcome:** "any motor and/or non-motor symptom of [Parkinson's disease]" p496
Participants (characteristics and numbers)	**For whole sample and subgroups** The observational studies are excluded from the remainder of the extraction. • **Number of participants:** 108 • **Age:** Not reported • **Gender:** Not reported • **Details of clinical diagnosis/indications:** Patients with Parkinson's disease (n=82, 3 studies), patients with Parkinson's disease and levodopa-induced dyskinesia (n=26, 2 studies)

Parameter	Extraction items
Setting/context	**Countries (alphabetic order):** Not reported **Setting (university, public or private clinic):** Not reported **Other relevant features of setting:** Not reported
Description of Interventions/ phenomena of interest	➢ **Exact definition of the intervention as per authors:** "Cannabis or cannabis-based treatment included any agent considered a cannabinoid whether used alone or combined with other cannabinoids or other agents, whether synthetic or a direct cannabis extract" p496 • **Dose and regimen:** ○ CBD capsule (n=44, 2 RCTs): 75 mg or 300 mg per day ○ Canador capsule (THC:CBD) (n=17, 1 RCT): ~11.5 mg:~5.75 mg per day ○ Nabilone capsule (THC) (n=47, 1 RCT): 0.3 mg/kg or 0.75 mg per day • **Administration methods:** Capsule (n=108, 5 RCTs) • **Comparator:** Placebo (n=108, 5 RCTs) • **Treatment duration:** Ranged 4-6 weeks for 3 RCTs, treatment administered once and twice in two RCTs respectively • **Timeframe for follow-up:** Follow-up periods not reported for any study
Databases and sources searched	• **Number and names of databases:** 7; MEDLINE, EMBASE, CINAHL, PsycINFO, Scopus, Proquest Dissertations, CENTRAL • **Other sources:** ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform, Web of Science • **Grey literature:** Not reported • **Reference chasing:** Yes • **Expert consultation:** Not reported

Parameter	Extraction items
	• **Dates:** Searches conducted 14 June 2021 • **Search limits:** No • **Justifications for search limits:** Not applicable • **Other searches:** Review papers assessed for additional studies • **Protocol prepared:** Yes • **If yes, published:** CRD42019124256 https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=124256 • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** Not reported • **If yes, rate of agreement:** Not applicable • **Funding of review:** No funding reported • **Conflicts of interest of review:** Conflicts disclosed for three authors, including roles as investigators for trials for BOD Australia, a pharmaceutical company that manufactures medical cannabis. • **How conflicts of interest were managed:** No management processes described
Date Range (years) of included studies	• **Exact years for included studies:** 2001-2020
Number of primary studies included in the systematic review	• **Number of studies:** 5 • **Number of studies by study design:** 5 RCTs • **Study years:** 2001 (1 RCT), 2004 (1 RCT), 2014 (1 RCT), 2020 (2 RCT) • **Funding of included studies:** Not reported

Parameter	Extraction items
	• **Conflicts of interest of included studies:** Not reported
Types of studies included	**Planned study designs to be included:** "Randomized controlled trials and non-randomized studies such as open label studies, before and after, case reports, chart reviews, surveys that evaluated therapeutic effects of cannabis or cannabis-based treatment in patients with [Parkinson's disease] were considered." p496 **Reasons for including only RCTs/prospective cohort studies:** Not reported **List of excluded studies at full text and reasons for exclusion:** Reasons given in PRISMA flow diagram but individual excluded studies and reasons not provided
Appraisal instruments used	**Full name of tools used:** Cochrane Risk of Bias tool **Risk of bias criteria for AMSTAR 2 assessment, for RCTs, record Yes/No for:** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The authors did not provide an overall assessment of risk of bias for each trial. However, HRB notes that according to Cochrane's Collaboration tool, and graphical information provided in the paper, the included trials appeared to have unclear risk of bias (4/5 RCTs) and low risk of bias (1/5 RCT). • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** ○ Overall: Low risk randomisation (4/5 RCTs); low risk outcome ascertainment (2/5 RCTs) ○ Total Unified Parkinson's Disease Rating Scale: Low risk randomisation (2/2 RCTs); low risk outcome ascertainment (1/2 RCTs)

Parameter	Extraction items
	○ Movement Disorder Society Unified Parkinson's Disease Rating Scale: Low risk randomisation (1/1 RCT); low risk outcome ascertainment (0/1 RCT) ○ Parkinson's Disease Questionnaire: Low risk randomisation (2/2 RCTs); low risk outcome ascertainment (1/2 RCTs) ○ Dyskinesia: Low risk randomisation (1/2 RCTs); low risk outcome ascertainment (0/1 RCTs) ○ Tremor: Low risk randomisation (1/1 RCTs); low risk outcome ascertainment (1/1 RCTs) ○ Sleep quality: Low risk randomisation (1/1 RCTs); low risk outcome ascertainment (1/1 RCTs) ○ Pain: Low risk randomisation (2/2 RCTs); low risk outcome ascertainment (1/2 RCTs) ○ Adverse events: Low risk randomisation (4/5 RCTs); low risk outcome ascertainment (2/5 RCTs) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** "The overall quality of the five randomized studies was considered high due to low risk of bias" p498 • **Graphical or statistical test for publication bias:** Not reported • **Authors' comments likelihood and magnitude of publication bias:** Not discussed by authors • **Authors' comment on how publication bias was dealt with:** Not discussed by authors • **Only low ROB RCTs included in review:** No, 4 RCTs with unclear risk of bias also included • **Only low ROB RCTs included in meta-analysis:** No, 1 RCT with unclear risk of bias also included • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** No discussion by authors
Method of analysis	• **Description of method of analysis as per authors:** "Where available, for randomized studies, treatment effects were measured as differences (treatment-control) in mean total UPDRS scores and meta-analyzed as weighted mean differences (WMD) utilizing a range of random effects models. The MDS-UPDRS was used in one RCT and is reported separately as it was determined that UPDRs and MDS-UPDRS scores could not be meaningfully combined...Data that

Parameter	Extraction items
	could not be meta-analyzed due to heterogeneity in outcome measures and study designs have been presented in descriptive terms." p497 • **Justification for narrative synthesis or meta-analysis:** "Data that could not be meta-analyzed due to heterogeneity in outcome measures and study designs have been presented in descriptive terms." p497 • **Justification for combining data in meta-analysis:** Not reported
Outcome assessed	**List of outcomes assessed and intended timeframes** • Primary outcomes assessed in RCTs: Total Unified Parkinson's Disease Rating Scale (UPDRS), Motor UPDRS, Parkinson's Disease Questionnaire (PDQ-39), Dyskinesia, tremor, sleep quality, pain, adverse events • Intended timeframes: Not specified • Actual timeframes: Treatment duration 4-6 weeks, no follow-up periods reported
Results/findings	• **Findings by outcome:** PRIMARY OUTCOMES ○ Total Unified Parkinson's Disease Rating Scale: "The overall estimate of the treatment effect was a marginal worsening of total UPDRS with a weighted mean difference of 0.39 (95% CI –4.52, 5.29; p = 0.877)… There was no evidence of an effect with regards to UPDRS Parts I, II, III, and IV." (Based on 2 RCTs of cannabinoid treatments, n=38) p498 ○ Movement Disorder Society Unified Parkinson's Disease Rating Scale: One RCT (n=38) reported significantly less deterioration in non-motor symptoms measured by MDS-UPDRS Part I in the nabilone group compared with placebo, but no significant difference was found for other subscales examining motor experiences of daily living, motor examination, and motor complications.

Parameter	Extraction items
	○ Tremor: “One randomized study demonstrated a decrease of tremor amplitude after administering a single CBD 300 mg dose compared to placebo (p = 0.022).” p498 ○ Levodopa-induced dyskinesia: "One randomized study showed that THC at a dose of 0.3 mg/kg alleviated dyskinesia (p = 0.05) while another randomized study using ∼11.5 mg THC and ∼5.75 mg CBD total dose reported no significant difference between cannabis and placebo groups (p = 0.09)... The sample sizes for both randomized studies were small (n = 26) and both used a crossover design in which THC psychoactive effects may have made it difficult to blind patients and to some extent, investigators and outcome assessors." p502 ○ Anxiety: "Data from a randomized study [n=23] indicated that a single CBD administration reduced anxiety in [Parkinson’s disease] patients who underwent the simulated public speaking test (SPST) compared to control as evaluated by the visual analog mood scales anxiety factor (p = 0.021). As this study used only a single CBD administration and induced anxiety experimentally, its results are not easily generalizable. Also, in another RCT [n=38], participants from a THC treated group reported reduction of their anxiety levels compared to placebo as measured by MDS-UPDRS Item 1.4 (p = 0.044)." p503 ○ Sleep quality: "A randomized double-blind trial [n=38] of nabilone reported fewer sleep problems in the treated group compared to placebo (p = < 0.001)." p503 ○ Pain: Two RCTs (n=55) reported no significant reduction in pain using Canador or nabilone compared with placebo (no summary statistics reported reported). ○ Quality of life: One RCT (n=21) reported that "treatment with CBD, 300 mg/day for 6 weeks, reduced feelings of stigma associated with [Parkinson’s disease] (p = 0.038) and improved overall activity of daily living (p = 0.022) positively affecting overall quality of life... No effect was noted at a dose of 75 mg/day for 6 weeks." Another study (n=17) reported no improvement in quality of life with treatment of ∼11.5 mg THC+ ∼5.75 mg CBD/day.

Parameter	Extraction items

- Adverse events: “Higher incidence of adverse events associated with higher cannabis dosing, especially products with THC. For cannabis products with THC, psychological side effects were common such as drowsiness, forgetfulness, insomnia and nightdreams.” p504 No significant safety events were reported in any study and adverse events were noted as being generally mild.

- **GRADE by outcome:** No GRADE assessment carried out
- **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):**

Outcome	No. studies (No. participants)	Summary estimate (95% CI)	P-value	I^2 (%)	Direction of effect
Mixed cannabinoid (cannador THC:CBD capsule, CBD capsule) vs. placebo					
Total Unified Parkinson’s Disease Rating Scale (UPDRS)	2 (38)	WMD 0.39 (-4.52 to 5.29)	0.877	Not reported	No significant difference
UPDRS Part I (Non-motor experiences of daily living)	2 (38)	WMD -0.14 (-0.67 to 0.38)	0.596	Not reported	No significant difference
UPDRS Part II (Motor experiences of daily living)	2 (38)	WMD 0.39 (-1.55 to 2.33)	0.692	Not reported	No significant difference
UPDRS Part III Motor examination	2 (38)	WMD 1.40 (-0.78 to 3.58)	0.209	Not reported	No significant difference
UPDRS Part IV Motor complications	2 (38)	WMD -0.13 (-1.86 to 1.59)	0.880	Not reported	No significant difference

- **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** As above (Findings by outcome)

Parameter	Extraction items
	• **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Yes: weighted mean difference, random effects model • **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Yes
Significance/direction	**See above if results listed by outcome:** Authors conclude that the review found no strong evidence for the beneficial use of cannabinoids in [Parkinson's disease] patients. Relatively few RCTs were identified with small sample sizes and substantial methodological heterogeneity, and none found clinically significant improvements in the overall symptoms of Parkinson's disease using standardised measures.
Heterogeneity	• **See above if I^2 available:** Not reported • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** No comment on impact; heterogeneity described: "Relatively few RCTs were identified. These had small sample sizes and were highly heterogeneous in the cannabinoids investigated, their methods of measurement, and study design." p505 • **Causes of heterogeneity investigated:** No
Comments	This systematic review includes 23 studies (5 RCTs and 18 non-randomised studies). Unless specified otherwise, the above information only reported on RCT studies as per the umbrella review inclusion criteria. Authors highlight that non-randomised studies reported more favourable findings that contrasted with the equivocal or absence of effect observed in the RCTs, and suggest that this indicates bias.

Van den Elsen *et al.* (2014): Efficacy and safety of medical cannabinoids in older subjects: A systematic review

Parameter	Extraction items
First author and year of publication	van den Elsen *et al.* (2014)

Parameter	Extraction items
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "This systematic review aims to integrate the evidence on indications, efficacy, safety and pharmacokinetics of medical cannabinoids in older subjects" p56 (abstract) • **Exact review question and page number:** "In the current systematic review we aimed to provide broader evidence on the safety and efficacy of medical cannabinoids in older subjects, independent of the reasons for prescription or the patients' cognitive status" p57 • **PICO elements reported in Introduction/Methods:** ➢ **Patient or population:** "Older subjects (defined as ≥65 years)" p57 ➢ **Setting:** Not reported in PICO ➢ **Intervention:** "medical cannabinoids administered by any route, at any dose and for any duration" p57 ➢ **Comparison:** Not reported in PICO ➢ **Outcome:** Not reported in PICO
Participants (characteristics and numbers)	**For whole sample and subgroups** • **Number of participants:** 267 • **Age:** Mean age ranged 47-78 years • **Gender:** 118/241 female participants (49.0%) in 3 studies reporting gender breakdown • **Details of clinical diagnosis/indications:** Chemotherapy-induced nausea and vomiting in a wide variety of neoplasms (n=214, 1 study), food refusal and disturbed behaviour (n=15, 1 study) and agitation (n=2, 1 study) in Alzheimer's disease, levodopa-induced dyskinesia (involuntary movement induced by levodopa, a first-line treatment for Parkinson's motor symptoms) in Parkinson's disease (n=25, 1 study), CO2 induced breathlessness in COPD (n=11, 1 study)

Parameter	Extraction items
Setting/context	**Countries (alphabetic order):** Not reported **Setting (university, public or private clinic):** Not reported **Other relevant features of setting:** Not reported
Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** "medical cannabinoids administered by any route, at any dose and for any duration" p57 • **Dose and regimen:** THC (oral/enteral): 2.5mg once or twice daily (n=17, 2 RCTs), 7.5-12.5mg five times daily (n=214, 1 RCT) THC:CBD (oral/enteral): 0.034-0.25mg THC/kg daily or 2.5gm twice daily (n=25, 1 RCT) THC:CBD (oral/sublingual): 2.7:2.5mg once to four times daily (n=11, 1 RCT) • **Administration methods:** Oral/enteral or oral/sublingual • **Comparator:** Placebo (n=53, 4 RCTs) or Prochlorperazine for nausea and vomiting (n=214, 1 RCT) • **Treatment duration:** Treatment cycle duration 1-42 days • **Timeframe for follow-up:** Follow-up periods not reported for any study
Databases and sources searched	• **Number and names of databases:** 4: PubMed, EMBASE, CINAHL, Cochrane Library • **Other sources:** Not reported • **Grey literature:** Not reported • **Reference chasing:** Not reported • **Expert consultation:** Not reported • **Dates:** Inception to 07/10/2013 • **Search limits:** English language • **Justifications for search limits:** No explanation provided

Parameter	Extraction items
	• **Other searches:** None reported • **Protocol prepared:** Yes • **If yes, published:** Not reported • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** Not reported • **If Yes, rate of agreement:** Not applicable • **Funding of review:** European Regional Development Fund • **Conflicts of interest of review:** Authors provide no declaration on conflicts • **How conflicts of interest were managed:** Funder "had no role in study design, collection, analysis, interpretation of the data or writing of the report" p63
Date Range (years) of included studies	• **Exact years for included studies:** 1982-2011
Number of primary studies included in the systematic review	• **Number of studies:** 5 • **Number of studies by study design:** 5 RCTs, with one preceded by an open-label study • **Study years:** 1982 (1 RCT), 1997 (1 RCT), 2004 (1 RCT), 2011 (2 RCTs) • **Funding of included studies:** Not reported • **Conflicts of interest of included studies:** Not reported
Types of studies included	**Planned study designs to be included:** "Prospective, controlled intervention trials" p57 **Reasons for including only RCTs/prospective cohort studies:** Not reported

Parameter	Extraction items
	List of excluded studies at full text and reasons for exclusion: Not reported
Appraisal instruments used	**Full name of tools used:** Modified Effective Practice and Organization of Care form **<u>Risk of bias criteria for AMSTAR 2 assessment, for RCTs, record Yes/No for:</u>** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** "Four out of five included studies showed a moderate to high risk of bias in several relevant domains. The study of Volicer *et al.* was judged to have a high risk of bias" p60 However, HRB notes that according to Cochrane's Collaboration tool, and graphical information provided in the paper, the included trials appeared to have a high risk of bias (5/5). • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** o Overall: Low risk randomisation (3/5); low risk outcome ascertainment (2/5) *THC vs prochlorperazine* o Nausea and vomiting (7-point nausea and vomiting score, global impression of change of appetite and food intake): Low risk randomisation (0/1); low risk outcome ascertainment (0/1) *Dronabinol vs placebo* o Food refusal (body weight, skin fold thickness, caloric intake): Low risk randomisation (0/1); low risk outcome ascertainment (0/1)

Parameter	Extraction items
	○ Disturbed behaviour (Cohen Mansfield Agitation Inventory, Lawton Observed Affect Scale-Past): Low risk randomisation (0/1); low risk outcome ascertainment (0/1) ○ Agitation (neuropsychiatric inventory, nocturnal motor activity): Low risk randomisation (1/1); low risk outcome ascertainment (1/1) *THC:CBD vs placebo* ○ Levodopa-induced dyskinesia (unified Parkinson's disease rating scale (UPDRS) Part IV (32–34), UPDRS total score): Low risk randomisation (1/1); low risk outcome ascertainment (1/1) ○ CO2 induced breathlessness (minute ventilation, PetCO2, Visual Analog Scale): Low risk randomisation (0/1); low risk outcome ascertainment (0/1) *Mixed cannabinoids vs control* ○ Adverse events: Low risk randomisation (3/5); low risk outcome ascertainment (2/5) ○ Serious adverse events: Low risk randomisation (2/4); low risk outcome ascertainment (2/4) ○ Drop out due to adverse events: Low risk randomisation (2/4); low risk outcome ascertainment (2/4) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** "Although only prospective and controlled intervention trials were included for analysis in this review, four out of five included trials still had a moderate to high risk of bias. This raises the question whether these studies are methodologically deficient and could just have been performed better, or whether research on these frail subjects is too difficult and complex in practice to meet the high quality methodological criteria. This is an important and general paradox in the quest for high quality evidence in frail older subjects: the methods needed for high quality evidence are often themselves interventions these subjects can no longer stand or comply to. It is therefore highly relevant to carefully adapt the study methods (including design, inclusion criteria and outcome measures) to the frailty of the target population." p62 • **Graphical or statistical test for publication bias:** Not reported

Parameter	Extraction items
	• **Authors' comments likelihood and magnitude of publication bias:** Not reported • **Authors' comment on how publication bias was dealt with:** Not applicable • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** Not applicable • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** "Although only prospective and controlled intervention trials were included for analysis in this review, four out of five included trials still had a moderate to high risk of bias. This raises the question whether these studies are methodologically deficient and could just have been performed better, or whether research on these frail subjects is too difficult and complex in practice to meet the high quality methodological criteria. This is an important and general paradox in the quest for high quality evidence in frail older subjects: the methods needed for high quality evidence are often themselves interventions these subjects can no longer stand or comply to. It is therefore highly relevant to carefully adapt the study methods (including design, inclusion criteria and outcome measures) to the frailty of the target population." p62
Method of analysis	• **Description of method of analysis as per authors:** "Qualitative, descriptive summaries" p58 • **Justification for narrative synthesis or meta-analysis:** "It was not feasible to conduct a meta-analysis, due to the high clinical and methodological diversity. Results of the included studies were therefore analyzed by making qualitative, descriptive summaries." p58 • **Justification for combining data in meta-analysis:** Not applicable
Outcome assessed	**List of outcomes assessed and intended timeframes** • Primary outcomes: Nausea and vomiting (7-point nausea and vomiting score, global impression of change of appetite and food intake); food refusal (body weight, skin fold thickness, caloric intake); disturbed behaviour (Cohen Mansfield

Parameter	Extraction items
	Agitation Inventory, Lawton Observed Affect Scale-Past); levodopa-induced dyskinesia (unified Parkinson's disease rating scale (UPDRS) Part IV (32–34), UPDRS total score); CO2 induced breathlessness (minute ventilation, PetCO2, Visual Analog Scale); agitation (neuropsychiatric inventory, nocturnal motor activity) • Intended timeframe: Not reported • Actual timeframe: Treatment cycle duration 1-42 days
Results/findings	• **Findings by outcome:** No inferential statistics reported for any outcome. PRIMARY OUTCOMES *Efficacy* o Nausea and vomiting: One study (n=214) reported THC did not improve chemotherapy related nausea and vomiting compared to prochlorperazine, with no difference in efficacy across age groups, for patients with a wide variety of neoplasms. o Global impression of change in appetite and food intake: One study (n=214) reportedly investigated this outcome; however, no data were presented in the review. o Breathlessness in COPD: One study (n=11) reported THC:CBD did not result in statistically significant improvement compared to placebo. o Dyskinesia in Parkinson's diseases: One study (n=25) reported THC:CBD did not result in statistically significant improvement compared to placebo. o Behavioural disturbances in Alzheimer's disease: No statistical analysis on neuropsychiatric inventory (nocturnal motor activity) scores was conducted due to very small sample size (n=2) in one study. In another study (n=15), disturbed behaviour (Cohen Mansfield Agitation Inventory) decreased during treatment with dronabinol and this persisted during the following placebo period. Positive affect was similar during both treatment periods, but negative affect decreased over the entire study period, decreasing more during treatment with dronabinol.

Parameter	Extraction items
	○ Food refusal in dementia: One study (n=15) reported greater weight gain for participants who received dronabinol (7.0 ± 1.5 lb) compared to placebo (4.6 ± 1.3 lb). Caloric intake did not change across the study period. Triceps skin fold thickness increased during the total study period but was not affected by treatment or order of treatment. *Safety* ○ Overall, adverse events were inconsistently assessed and the review reports only on the most frequently reported adverse events. Cannabinoid treatment was associated with more adverse effects than placebo or prochlorperazine (266 vs 133). Symptoms of sedation/drowsiness were most frequently reported in the cannabinoid group. Two older COPD participants developed cardiac arrythmias and another developed symptoms of mild intoxication after receiving THC:CBD. None of the studies reported severe adverse events associated with cannabinoid treatment. One study (n=214) reported more frequent adverse events with cannabinoids compared with placebo: sedation (78 vs 56, p<0.01), physiological adverse events (62 vs 24, p<0.01), and psychological adverse events (59 vs 10, p<0.01). Across four studies, 6/46 participants dropped out due to adverse events during cannabinoid treatment. • **GRADE by outcome:** No GRADE assessment carried out • **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):** No meta-analysis conducted • **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** None reported • **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Not applicable • **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable

Parameter	Extraction items
Significance/direction	**See above if results listed by outcome:** Limited evidence that THC may be useful in treatment of food refusal and behavioural symptoms in dementia. Adverse events were more commonly associated with cannabinoid treatment and were most frequently sedation-like treatment.
Heterogeneity	• **See above if I^2 available:** Not applicable • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** "[Due to] a high heterogeneity among the included studies, the absence of reported means and standard deviations per treatment group, and the generally very small sample sizes... only qualitative and descriptive summaries could be provided." p63 • **Causes of heterogeneity investigated:** No
Comments	Inadequate or no washout periods reported for some studies, no inferential statistics reported ("It was not feasible to report summary outcome measures as most studies did not report means and standard deviations per treatment group or study samples were too small to provide a reliable effect size." p60)

Votrubec *et al.* (2022): Cannabinoid therapeutics in orofacial pain management: a systematic review

Parameter	Extraction items
First author and year of publication	Votrubec *et al.* (2022)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "to explore the published evidence regarding effectiveness of cannabinoids in orofacial pain management in a dental setting" p315 • **Exact review question and page number:** "Are cannabinoid therapeutics effective in (acute and chronic) orofacial pain management, when compared to other pharmacological or placebo treatments'?" p315 • **PICO elements reported in Introduction/Methods:**

Parameter	Extraction items
	➢ **Patient or population:** Adult humans (>18 years) with orofacial pain (acute or chronic) as diagnosed by a dentist or dental therapist in the general or specialist dental setting ➢ **Setting:** "dental setting" p315 ➢ **Intervention:** "cannabinoids (natural and synthetic)" p315 ➢ **Comparison:** "other pharmacological treatments or placebos" p315 ➢ **Outcome:** "improved pain management" p315
Participants (characteristics and numbers)	**For whole sample and subgroups:** n=126 (cannabinoid RCTs); n=274 (cannabinoid receptor agonist RCTs) The RCTs assessing cannabinoid receptor agonists have been excluded from the remainder of the extraction unless specified otherwise. • **Number of participants:** N=126 • **Age:** Range 18-80 years old • **Gender:** Not reported • **Details of clinical diagnosis/indications:** Radiotherapy for head and neck carcinoma (n=56); surgical removal of molar (n=10); temporomandibular disorder (n=60)
Setting/context	**Countries (alphabetic order):** Canada (1 RCT); Poland (1 RCT); USA (1 RCT) **Setting (university, public or private clinic):** Not reported **Other relevant features of setting:** Radiotherapy (1 RCT); surgery (1 RCT); not reported (1 RCT)

Parameter	Extraction items

Description of Interventions/ phenomena of interest	➢ **Exact definition of the intervention as per authors:** "cannabinoids (natural and synthetic)" p315
	• **Dose and regimen:**
	  ○ Nabilone (1 RCT): Orally, 1 pill (0.5 mg) daily for first week, 2 pills daily for second week, maximum 4 pills daily from third week until end of radiotherapy
	  ○ CBD (1 RCT): Transdermal formulation containing 30% CBD, topically twice daily for 14 day
	  ○ THC (1 RCT): Single intravenous dose (0.22-0.44 mg/kg)
	• **Administration methods:** Oral (1 RCTs); topical (1 RCT); intravenous (1 RCT)
	• **Comparator:** Placebo (2 RCTs); placebo and diazepam (1 RCT)
	• **Treatment duration:** Every 7 days during intervention and 28 days after intervention (1 RCT); 14 days after intervention (1 RCT); at midpoint and 30 minutes post intervention, then at 24 hours and one month (1 RCT)
	• **Timeframe for follow-up:** Above

Databases and sources searched	• **Number and names of databases:** 2; PubMed (MEDLINE), Scopus; inception to 11/07/2021 • **Other sources:** Ovid (MEDLINE), clinicaltrials.gov, Cochrane Trials Library • **Grey literature:** No • **Reference chasing:** Yes • **Expert consultation:** No • **Dates:** Inception to 11/07/2021 • **Search limits:** English language • **Justifications for search limits:** Yes • **Other searches:** Not reported • **Protocol prepared:** Yes

Parameter	Extraction items
	• **If yes, published:** CRD42022274854 https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022274854 • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Funding of review:** Not reported • **Conflicts of interest of review:** The authors declare no conflict of interest. • **How conflicts of interest were managed:** Not applicable
Date Range (years) of included studies	• **Exact years for included studies:** 1977-2019
Number of primary studies included in the systematic review	• **Number of studies:** 3 RCTs • **Number of studies by study design:** 3 RCTs • **Study years:** 1977 (1 RCT); 2016 (1 RCT); 2019 (1 RCT) • **Funding of included studies:** Canadian Institutes of Health Research; Fond de recherche en sante du Quebec; ICN Valeant Pharmaceutical (1 RCT); MedycynaCBD and Maciej Pawlowski for material support (1 RCT); National Institute of Dental Research; Division of Research Facilities and Resources (1 RCT) • **Conflicts of interest of included studies:** Not reported
Types of studies included	**Planned study designs to be included:** RCT **Reasons for including only RCTs/prospective cohort studies:** Not reported **List of excluded studies at full text and reasons for exclusion:** Yes

Parameter	Extraction items
Appraisal instruments used	**Full name of tools used:** Cochrane risk-of-bias tool (RoB 2) **<u>Risk of bias criteria for AMSTAR 2 assessment, for RCTs, record Yes/No for:</u>** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence allocation (individual vs group randomisation):** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The authors judged included trials to have a high risk of bias (1 RCT), unclear risk of bias (1 RCTs) and low risk of bias (1 RCT) • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** ○ Overall: Low risk randomisation (2/3); low risk outcome ascertainment (3/3) *Nabilone versus placebo* ○ Pain, adverse events: Low risk randomisation (0/1); low risk outcome ascertainment (1/1) *CBD versus placebo* ○ Pain, adverse events: Low risk randomisation (1/1); low risk outcome ascertainment (1/1) *THC versus placebo* ○ Pain, adverse events: Low risk randomisation (1/1); low risk outcome ascertainment (1/1) • **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** "Generally, a low-quality evidence supporting the use of cannabinoids to treat pain and inflammation exist, with a lack of consistent and compelling high-quality evidence pertaining to its effectiveness in orofacial pain. Although one study in this review

Parameter	Extraction items
	reports positive effects, insufficient evidence exists to support a tangible clinical benefit of natural and synthetic cannabinoids in managing orofacial pain, especially for drugs delivered into systemic circulation" p323 • **Graphical or statistical test for publication bias:** Not reported • **Authors' comments likelihood and magnitude of publication bias:** Not reported • **Authors' comment on how publication bias was dealt with:** Not reported • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** Not applicable • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** Not reported
Method of analysis	• **Description of method of analysis as per authors:** "Data were extracted and compiled into a spreadsheet using a customized data form. A calibration process was used for six reviewers. Data were extracted independently from each included article by two different reviewers. Results and rationale were then reviewed by all six extractors and any disagreements were resolved by discussion and consensus was reached. The following data items were extracted: author(s); year of publication; location of study; funding source, if identifiable; study design; sampling characteristics; measured outcome and methodology of measuring scale/device used; initial recording of measurement; follow-up periods; adverse events and final outcomes." p316 • **Justification for narrative synthesis or meta-analysis:** Not reported • **Justification for combining data in meta-analysis:** Not reported
Outcome assessed	**List of outcomes assessed and intended timeframes** • Primary outcomes: Pain

Parameter	Extraction items
	• Secondary outcomes: Adverse events • Intended timeframes: Not specified • Actual timeframes: Every 7 days during intervention and 28 days after intervention (1 RCT);14 days after intervention (1 RCT); at midpoint and 30 minutes post intervention, then at 24 hours and one month (1 RCT)
Results/findings	• **Findings by outcome:** PRIMARY OUTCOMES *Pain* ○ One study (n=56) reported no significant difference in pain (visual analog scale) between nabilone and placebo groups (no summary statistics reported). ○ One study (n=60) reported significant improvement in pain intensity (visual analog scale) in CBD (70.2% reduction) and was not significant in the placebo group (9.81% reduction). ○ One study (n=10) reported no significant analgesic effect in pain tolerance in THC compared to placebo groups (no summary statistics reported). SECONDARY OUTCOMES *Adverse events* ○ One study (n=56) reported no significant difference between nabilone and placebo groups in adverse effects such as nausea, sleep and mood changes, drowsiness, anxiety and xerostomia (no summary statistics reported). ○ One study (n=60) reported no adverse events across CBD and placebo groups (no summary statistics reported). ○ One study (n=10) reported no participants experienced true clinical psychosis, however anxiety and some dysphoria were noted on administration of THC (0.022mg/kg) in six subjects. “One subject became so anxious after receiving THC (0.022 mg/kg) that surgery had to be terminated; however this subject used hashish for the previous 18 months while on active duty in Vietnam, and declared that THC recalled frightening wartime experiences.” p320

Parameter	Extraction items
	• **GRADE by outcome:** Not reported • **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):** Not applicable • **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** Above • **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Not applicable • **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable
Significance/direction	**See above if results listed by outcome:** Above
Heterogeneity	• **See above if I^2 available:** Not applicable • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** "Although all the included studies in the analysis were human studies, variations in sample populations, gender differences in study population, type of cannabinoid, routes of administration, and outcome measurements contributed to the heterogeneity of included studies. This presents difficulties when attempting to draw direct comparisons between studies to formulate concise conclusions." p321 • **Causes of heterogeneity investigated:** Above
Comments	Two studies Kalliomäki *et al.* (2013) (cannabinoid receptor agonist AZD1940) and Ostenfeld *et al.* (2011) (cannabinoid receptor agonist GW842166) have not been included in this extraction form as per umbrella review criteria.

Walitt *et al.* (2016): Cannabinoids for fibromyalgia (Review)

Parameter	Extraction items
First author and year of publication	Walitt *et al.* (2016)
Objectives **Report exact review question(s) and page number**	• **Study objectives:** "To assess the efficacy, tolerability and safety of cannabinoids for fibromyalgia symptoms in adults." p4 • **Exact review question and page number:** "To assess the efficacy, tolerability and safety of cannabinoids for fibromyalgia symptoms in adults." p4 • **PICO elements reported in Introduction/Methods:** • **Patient or population:** "Adults aged 18 years and above, diagnosed with fibromyalgia using the 1990 or 2010 criteria" p4 • **Setting:** Not reported in PICO; included studies were conducted in a rehabilitation clinic and pain clinic • **Intervention:** "Cannabinoids (either phytocannabinoids such as herbal cannabis (hashish, marihuana), plant-based cannabinoids (nabiximole) or pharmacological (synthetic) cannabinoids (e.g. cannabidiol, dronabinol, levonantradol, nabilone)), at any dose, by any route, administered for the relief of fibromyalgia symptoms" p4-5 • **Comparison:** "Placebo or any active comparator" p5 • **Outcome:** "Primary outcomes 1. Participant-reported pain relief of 50% or greater. 2.[Patient global impression of change] 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 hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is

Parameter	Extraction items
	an 'important medical event' that may jeopardise the person, or may require an intervention to prevent one of the above characteristics/consequences. Secondary outcomes 1. Participant-reported pain relief of 30% or greater. 2. Sleep problems. 3. Fatigue. 4. Depression. 5. Anxiety. 6. Health-related quality of life. 7. Disability. 8. Withdrawals due to lack of efficacy. 9. Participants experiencing any adverse event. 10.Other specific adverse events, particularly somnolence, dizziness and drug prescription abuse (addiction).” p5
Participants (characteristics and numbers)	**For whole sample and subgroups** • **Number of participants:** 72 • **Age:** Range 26-76 (mean age range 49-50) • **Gender:** 87.6% female • **Details of clinical diagnosis/indications:** Fibromyalgia, diagnosed according to the ACR 1990 classification criteria
Setting/context	**Countries (alphabetic order):** Canada (2 RCTs)

Parameter	Extraction items
	Setting (university, public or private clinic): Rehabilitation clinic (1 RCT), pain clinic (1 RCT) **Other relevant features of setting:** Single centre studies
Description of Interventions/ phenomena of interest	• **Exact definition of the intervention as per authors:** "Cannabinoids (either phytocannabinoids such as herbal cannabis (hashish, marihuana), plant-based cannabinoids (nabiximole), at any dose, by any route, administered for the relief of fibromyalgia symptoms and compared to placebo or any active comparator" p4-5 • **Dose and regimen:** Nabilone 0.5-1 mg/day twice per day, 0.5 or 1 mg/day flexible, in both studies (n=72 total, n=29 received nabilone) • **Administration methods:** Oral • **Comparator:** Placebo (1 parallel study, n=40 total, n=20 participants in placebo group), active comparator amitriptyline (a tricyclic antidepressant) oral flexible 10 or 20 mg/day (1 crossover study, n=32, n=29 received active comparator) • **Treatment duration:** 6 weeks (including 2-week washout period) and 4 weeks (treatment duration and follow-up for 1 parallel trial) • **Timeframe for follow-up:** No follow-up periods after treatment reported for any study
Databases and sources searched	• **Number and names of databases:** 3: Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 3 of 12, 2016), MEDLINE (to 26/04/2016), EMBASE (to 26/04/2016) • **Other sources:** ClinicalTrials.gov, International Association for Cannabinoid Medicines databank, World Health Organization International Clinical Trials Registry Platform, bibliographies of review articles • **Grey literature:** No other searches reported • **Reference chasing:** Yes • **Expert consultation:** Yes; "known experts in the field" p5 • **Dates:** to 26/04/2016

Parameter	Extraction items
	• **Search limits:** Animal studies excluded • **Justifications for search limits:** Yes • **Other searches:** None reported • **Protocol prepared:** Yes • **If yes, published:** https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011694/full • **Search strategy/key words provided:** Yes • **Screening completed in duplicate:** Yes • **If yes, rate of agreement:** Not reported • **Extraction completed in duplicate:** Yes • **If Yes, rate of agreement:** Not reported • **Funding of review:** "The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane Pain, Palliative and Supportive Care Group" p13 • **Conflicts of interest of review:** No statement on conflicts of interest • **How conflicts of interest were managed:** No statement on conflicts of interest
Date Range (years) of included studies	• **Exact years for included studies:** 2008-2010
Number of primary studies included in the systematic review	• **Number of studies:** 2 • **Number of studies by study design:** 2 RCTs (1 parallel, 1 cross-over) • **Study years:** 2008, 2010 • **Funding of included studies:** Both partially funded by the manufacturer of nabilone

Parameter	Extraction items
	• **Conflicts of interest of included studies:** The authors report no declaration of interest of primary investigators (1 RCT, p18); declaration of interest of primary investigators included (1 RCT, p20)
Types of studies included	**Planned study designs to be included: "**Randomised double-blind controlled trials of at least four weeks' duration" p4 **Reasons for including only RCTs/prospective cohort studies:** Not reported **List of excluded studies at full text and reasons for exclusion:** List of studies provided but reasons for exclusion not provided for individual studies
Appraisal instruments used	**Full name of tools used:** Cochrane Risk of Bias tool (Cochrane Handbook for Systematic Reviews of Interventions) **<u>Risk of bias criteria for AMSTAR 2 assessment, for RCTs, record Yes/No for:</u>** • **Concealment of allocation:** Yes • **Blinding of assessors:** Yes • **Sequence generation (individual vs group randomisation):** Yes • **Selective reporting:** Yes
Appraisal ratings	• **Number of studies by high risk of bias, medium and low:** The review authors designated the methodological quality of both studies as moderate (2/2). HRB notes that according to Cochrane's Collaboration tool, and graphical information provided in the paper, the included trials appeared to have a high risk of bias (2/2). • **Number of studies out of total number of studies that were at low risk of bias for randomization and at low risk of bias for outcome ascertainment:** ○ Overall: Low risk randomisation (1/2); low risk outcome ascertainment (2/2) ○ Withdrawal due to adverse events: Low risk randomisation (1/2); low risk outcome ascertainment (2/2) ○ Serious adverse events: Low risk randomisation (1/2); low risk outcome ascertainment (2/2)

Parameter	Extraction items
	• **Authors' exact comments on risk of bias and how it affected analysis and quality of evidence:** No direct comment on effect of risk of bias on analysis and quality of evidence. "Clinical trial evidence on the use of cannabis products in fibromyalgia was limited to two small studies with short-term duration. No convincing, unbiased evidence suggests that nabilone is of value in treating people with fibromyalgia." p12 • **Graphical or statistical test for publication bias:** No; only two studies included • **Authors' comments likelihood and magnitude of publication bias:** "The absence of publication bias (unpublished trials showing no benefit of cannabinoids over placebo) can never be proved. We carried out a broad search of studies and felt it was unlikely that significant amounts of relevant data remain unknown to us." p12 • **Authors' comment on how publication bias was dealt with:** Not applicable • **Only low ROB RCTs included in review:** No • **Only low ROB RCTs included in meta-analysis:** Not applicable • **If RCTs with moderate or high ROB or non-randomised studies of interventions were included in the review, discussion of likely impact of ROB on results and quality of evidence or limitations included in conclusions or summary:** No direct comment on effect of risk of bias on analysis and quality of evidence. "Clinical trial evidence on the use of cannabis products in fibromyalgia was limited to two small studies with short-term duration. No convincing, unbiased evidence suggests that nabilone is of value in treating people with fibromyalgia." p12
Method of analysis	• **Description of method of analysis as per authors:** "We planned to analyse data in three tiers, according to outcome and freedom from known sources of bias (Moore 2010a)... The third tier of evidence related to data from fewer than 200 participants, or where there were significant problems because, for example, of very short duration studies of fewer than four weeks, where there was major heterogeneity between studies, or where there were shortcomings in allocation concealment, attrition or incomplete outcome data. For this third tier of evidence, no data synthesis was reasonable and may be misleading, but an indication of beneficial effects might be possible. There was only third-tier evidence available.

Parameter	Extraction items
	For this third-tier evidence, no data synthesis was reasonable and may have been misleading. Therefore, we did not conduct the planned meta-analysis...The planned subgroup analyses were not possible due to the lack of a sufficient number of studies. Sensitivity analysis We did not perform sensitivity analysis because we did not identify individual peculiarities of the studies under investigation during the review process that were suitable for sensitivity analyses." p8-9 • **Justification for narrative synthesis or meta-analysis:** Not reported • **Justification for combining data in meta-analysis:** Not applicable
Outcome assessed	**List of outcomes assessed and intended timeframes** • Primary outcomes: participant-reported pain relief of 50% or greater, patient Global Impression of Change improvement, withdrawal due to adverse events, serious adverse events • Secondary outcomes: Participant-reported pain relief of 30% or greater, sleep problems, fatigue, depression. Anxiety, health-related quality of life, disability, withdrawals due to lack of efficacy, Participants experiencing any adverse event, other specific adverse events, particularly somnolence, dizziness and drug prescription abuse (addiction). • Intended timeframe: Not specified • Actual timeframe: 6 weeks (including 2-week washout period) and 4 weeks (treatment duration and follow-up for 1 parallel trial)
Results/findings	• **Findings by outcome:** PRIMARY OUTCOMES ○ The authors note that they found no data on two of their primary efficacy outcomes: participant-reported pain relief of 50% or greater, patient global impression of change improvement.

Parameter	Extraction items
	○ Serious adverse events: Both studies (n=72) reported no serious adverse events in participant groups. ○ Withdrawal due to adverse events: In the cross-over trial (n=32), drop-out due to adverse events was 3/20 participants in the nabilone group and 1/20 in the placebo group; drop-out due to adverse events was 1/32 participants in the nabilone group and no participants in the amitriptyline group. Most frequent adverse events were drowsiness, dry mouth, vertigo, and nausea. Neither study reported on abuse of prescribed nabilone. SECONDARY OUTCOMES ○ Pain: One parallel trial (n=40) reported statistically significant improvements in pain associated with nabilone; however, no significant difference was found between nabilone (mean 4.8, SD 2.2), and placebo (mean 5.7, SD 1.8) (data extracted by review authors from figures) (p=0.02)). One cross-over trial (n=32) found no significant differences between nabilone and amitriptyline for pain (statistical analysis not available). ○ Fatigue: No significant differences reported between nabilone and placebo in one parallel trial (n=40) (no summary statistics reported). ○ Sleep: One crossover trial (n=32) reported significant improvements in nabilone (mean 9, SD 10.8) compared with amitriptyline (mean 13, SD 10.8) (data extracted by review authors from figures). ○ Depression: No significant differences reported between nabilone and placebo in one parallel trial (n=40) (no summary statistics reported). ○ Anxiety: One parallel trial (n=40) reported statistically significant improvements in pain associated with nabilone; however, no significant difference was found between nabilone (mean 4.3, SD 1.8) and placebo (mean 4.9, SD 2.2) (p<0.01) (data extracted from figures). ○ Disability: No data reported in either study. ○ Health-related quality of life: One parallel trial (n=40) reported statistically significant improvements in pain associated with nabilone; however, no significant difference was found between nabilone (mean 54, SD 22.3) and

Parameter	Extraction items

placebo (mean 64, SD 13.4); ($p < 0.01$) (data extracted from figures). One cross-over trial (n=32) found no significant differences between nabilone and amitriptyline (no summary statistics reported).

- Adverse events: Neither study reported number of participants who experienced any adverse events. Two studies (n=72) reported no serious adverse events in participant groups. One cross-over study (n=32) reported 91 adverse events possibly or probably related to nabilone therapy. One study (n=40) reported frequency of adverse events in nabilone compared with placebo as follows: drowsiness (7 vs. 1), dry mouth (5 vs. 1), and vertigo (4 vs. 1). One study (n=32) reported frequency of adverse events in nabilone compared with amitriptyline as follows: dizziness (10 vs. 4), nausea (9 vs. 1), dry mouth (7 vs. 1), and drowsiness (6 vs. 1).
- Withdrawal due to adverse events: In the cross-over trial (n=32), drop-out due to adverse events was 3/20 participants in the nabilone group and 1/20 in the placebo group; drop-out due to adverse events was 1/32 participants in the nabilone group and no participants in the amitriptyline group. Most frequent adverse events were drowsiness, dry mouth, vertigo, and nausea. Neither study reported on abuse of prescribed nabilone.

- **GRADE by outcome:** All outcomes rated as very low quality due to indirectness, imprecision and potential reporting bias. No summary of findings table produced by authors.

Outcome	No. studies	GRADE
Pain	2	Very low
Fatigue	2	Very low
Sleep	1	Very low
Depression	2	Very low
Anxiety	2	Very low
Disability	2	Very low
Health-related quality of life	2	Very low
Adverse events	2	Very low

Parameter	Extraction items
	• **Meta-analysis results if available (relative risk, odds ratio, standardised mean difference, 95% confidence intervals, I^2, number of trials or studies, number of participants, random or fixed effects):** No meta-analysis conducted • **Relative risk, odds ratio, standardised mean difference, 95% confidence intervals and p-value for individual studies where meta-analysis is not available:** As above • **Appropriate weighted technique used, adjusted for heterogeneity where necessary:** Not applicable • **Separate summaries reported for RCTs and prospective cohort studies when included in the same review:** Not applicable
Significance/direction	**See above if results listed by outcome:** Very low quality evidence indicates greater reduction of pain and limitations of health-related quality of life associated with nabilone compared to placebo in one study and better effects of nabilone on sleep than amitriptyline in one study. No significant differences between the two drugs noted for pain, mood and health-related quality of life. More frequent drop-out due to adverse events associated with nabilone than control conditions.
Heterogeneity	• **See above if I^2 available:** Not applicable • **Authors' comment on potential impact of heterogeneity on results and quality of evidence:** Not • **Causes of heterogeneity investigated:** Not applicable
Comments	

Appendix G Included reviews

1 Abdallah FW, Hussain N, Weaver T, et al. Analgesic efficacy of cannabinoids for acute pain management after surgery: A systematic review and meta-analysis. Reg Anesth Pain Med 2020;45:509–19.https://doi.org/10.1136/rapm-2020-101340

2 AminiLari M, Wang L, Neumark S, et al. Medical cannabis and cannabinoids for impaired sleep: a systematic review and meta-analysis of randomized clinical trials. Sleep 2022;45:zsab234.https://doi.org/10.1093/sleep/zsab234

3 Andreae MH, Carter GM, Shaparin N, et al. Inhaled cannabis for chronic neuropathic dain: A meta-analysis of individual patient data. J Pain 2015;16:1221–32.https://doi.org/10.1016/j.jpain.2015.07.009

4 Bahji A, Meyyappan AC, Hawken ER. Efficacy and acceptability of cannabinoids for anxiety disorders in adults: A systematic review & meta-analysis. J Psychiatr Res 2020;129:257–64.https://doi.org/10.1016/j.jpsychires.2020.07.030

5 Bajtel Á, Kiss T, Tóth B, et al. The safety of dronabinol and nabilone: A systematic review and meta-analysis of clinical trials. Pharmaceuticals (Basel) 2022;15:100.https://doi.org/10.3390/ph15010100

6 Belgers V, Röttgering JG, Douw L, et al. Cannabinoids to improve health-related quality of life in patients with neurological or oncological disease: A meta-analysis. Cannabis Cannabinoid Res 2023;8:41–55.https://doi.org/10.1089/can.2021.0187

7 Bialas P, Fitzcharles M-A, Klose P, et al. Long-term observational studies with cannabis-based medicines for chronic non-cancer pain: A systematic review and meta-analysis of effectiveness and safety. Eur J Pain 2022;26:1221–33.https://doi.org/10.1002/ejp.1957

8 Black N, Stockings E, Campbell G, et al. Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis. Lancet Psychiatry 2019;6:995–1010.https://doi.org/10.1016/S2215-0366(19)30401-8

9 Boland EG, Bennett MI, Allgar V, et al. Cannabinoids for adult cancer-related pain: systematic review and meta-analysis. BMJ Support Palliat Care 2020;10:14–24.https://doi.org/10.1136/bmjspcare-2019-002032

10 Bosnjak Kuharic D, Markovic D, Brkovic T, et al. Cannabinoids for the treatment of dementia. Cochrane Database Syst Rev 2021;:CD012820.https://doi.org/10.1002/14651858.CD012820.pub2

11 Butler M, Krebs E, Sunderlin B, et al. Medical cannabis for non-cancer pain: A systematic review. Minneapolis, Minnesota: Minnesota Evidence-based Practice Center 2015. https://www.health.state.mn.us/people/cannabis/docs/intractable/medicalcannabisreport.pdf

12 da Rovare VP, Magalhães GPA, Jardini GDA, et al. Cannabinoids for spasticity due to multiple sclerosis or paraplegia: A systematic review and meta-analysis of randomized clinical trials. Complement Ther Med 2017;34:170–85.https://doi.org/10.1016/j.ctim.2017.08.010

13 De Aquino JP, Bahji A, Gómez O, et al. Alleviation of opioid withdrawal by cannabis and delta-9-tetrahydrocannabinol: A systematic review of observational and experimental human studies. Drug Alcohol Depend 2022;241:109702.https://doi.org/10.1016/j.drugalcdep.2022.109702

14 Filippini G, Minozzi S, Borrelli F, et al. Cannabis and cannabinoids for symptomatic treatment for people with multiple sclerosis. Cochrane Database Syst Rev 2022;:CD013444.http://dx.doi.org/10.1002/14651858.CD013444.pub2

15 Fisher E, Moore RA, Fogarty AE, et al. Cannabinoids, cannabis, and cannabis-based medicine for pain management: a systematic review of randomised controlled trials. Pain 2021;162:S45–66.https://doi.org/10.1097/j.pain.0000000000001929

16 Fitzcharles M-A, Baerwald C, Ablin J, et al. 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. Schmerz 2016B;30:47–61.https://doi.org/10.1007/s00482-015-0084-3

17 Fitzcharles M-A, Ste-Marie PA, Häuser W, et al. Efficacy, tolerability, and safety of cannabinoid treatments in the rheumatic diseases: A systematic review of randomized controlled trials. Arthritis Care Res (Hoboken) 2016A;68:681–8.https://doi.org/10.1002/acr.22727

18 Giossi R, Carrara F, Padroni M, et al. Systematic review and meta-analysis seem to indicate that cannabinoids for chronic primary pain treatment have limited benefit. Pain Ther 2022;11:1341–58.https://doi.org/10.1007/s40122-022-00434-5

19 Hammond S, Erridge S, Mangal N, et al. The effect of cannabis-based medicine in the treatment of cachexia: A systematic review and meta-analysis. Cannabis Cannabinoid Res 2021;6:474–87.https://doi.org/10.1089/can.2021.0048

20 Häuser W, Welsch P, Klose P, et al. Efficacy, tolerability and safety of cannabis-based medicines for cancer pain : A systematic review with meta-analysis of randomised controlled trials. Schmerz 2019;33:424–36.https://doi.org/10.1007/s00482-019-0373-3

21 Kafil TS, Nguyen TM, MacDonald JK, et al. Cannabis for the treatment of Crohn's disease. Cochrane Database Syst Rev 2018A;11:CD012853.https://doi.org/10.1002/14651858.CD012853.pub2

22 Kafil TS, Nguyen TM, MacDonald JK, et al. Cannabis for the treatment of ulcerative colitis. Cochrane Database Syst Rev 2018B;11:CD012954.https://doi.org/10.1002/14651858.CD012954.pub2

23 Kopelli E, Samara M, Siargkas A, et al. The role of cannabidiol oil in schizophrenia treatment. a systematic review and meta-analysis. Psychiatry Res 2020;291:113246.https://doi.org/10.1016/j.psychres.2020.113246

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25 Lutge EE, Gray A, Siegfried N. The medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS. Cochrane Database Syst Rev 2013;:CD005175.https://doi.org/10.1002/14651858.CD005175.pub3

26 McDonagh MS, Morasco BJ, Wagner J, et al. Cannabis-based products for chronic pain : A systematic review. Ann Intern Med 2022;175:1143–53.https://doi.org/10.7326/M21-4520

27 McKee KA, Hmidan A, Crocker CE, et al. Potential therapeutic benefits of cannabinoid products in adult psychiatric disorders: A systematic review and meta-analysis of randomised controlled trials. J Psychiatr Res 2021;140:267–81.https://doi.org/10.1016/j.jpsychires.2021.05.044

28 McParland AL, Bhatia A, Matelski J, et al. Evaluating the impact of cannabinoids on sleep health and pain in patients with chronic neuropathic pain: a systematic review and meta-analysis of randomized controlled trials. Reg Anesth Pain Med 2023;48:180–90.https://doi.org/10.1136/rapm-2021-103431

29 Meng H, Johnston B, Englesakis M, et al. Selective cannabinoids for chronic neuropathic pain: A systematic review and meta-analysis. Anesth Analg 2017;125:1638–52.https://doi.org/10.1213/ANE.0000000000002110

30 Mücke M, Phillips T, Radbruch L, et al. Cannabis-based medicines for chronic neuropathic pain in adults. Cochrane Database Syst Rev 2018B;3:CD012182.https://doi.org/10.1002/14651858.CD012182.pub2

31 Mücke M, Weier M, Carter C, et al. Systematic review and meta-analysis of cannabinoids in palliative medicine. J Cachexia Sarcopenia Muscle 2018A;9:220–34.https://doi.org/10.1002/jcsm.12273

32 Noori A, Miroshnychenko A, Shergill Y, et al. Opioid-sparing effects of medical cannabis or cannabinoids for chronic pain: a systematic review and meta-analysis of randomised and observational studies. BMJ Open 2021;11:e047717.https://doi.org/10.1136/bmjopen-2020-047717

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35 Price RL, Charlot KV, Frieler S, et al. The efficacy of cannabis in reducing back pain: A systematic review. Global Spine J 2022;12:343–52.https://doi.org/10.1177/21925682211065411

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Appendix H High-level summaries of included reviews

Specific health conditions (efficacy)

Author (year)	Research question	Intervention categorisation	Evidence summary
CANCER			
PAIN-RELATED OUTCOMES			
Pain intensity			
Boland *et al.* (2020)	To determine the beneficial and adverse effects of cannabinoids compared with placebo or other active agents for the treatment of cancer-related pain in adults from RCTs	THC:CBD products vs placebo	Moderate-certainty evidence indicating no significant difference in pain intensity between THC:CBD formulations and placebo (5 RCTs) in a meta-analysis of adults with cancer. Treatment duration ranged 2-9 weeks, no follow-up periods reported.
Pain relief 50% or greater			
Häuser *et al.* (2019)	How effective and safe are medical cannabis and cannabis-based medicines compared to controls in managing cancer pain in patients of any age?	THC:CBD products vs placebo	Low-certainty evidence indicating no significant difference in likelihood of pain relief of 50% or greater between nabiximols and placebo (4 RCTs) in a meta-analysis of adults with moderate to severe cancer-related pain. Treatment duration ranged 2-5 weeks, no follow-up periods reported.
Combined response (pain relief of 30% or greater and reduced opioid use)			
Häuser *et al.* (2019)	How effective and safe are medical cannabis and cannabis-based medicines compared to controls in managing cancer pain in patients of any age?	THC:CBD products vs placebo	Very low-certainty evidence indicating no significant difference in likelihood of combined response (pain relief of 30% or greater and reduced opioid use) between nabiximols and placebo (1 RCT) in adults with cancer-related pain. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 5 weeks, no follow-up period reported.
Opioid dose reduction			
Noori *et al.* (2021)	To explore the impact of adding medical cannabis on opioid dose, other patient-important outcomes and related harms in patients with chronic pain using prescribed opioid therapy	THC:CBD products vs placebo	Low-certainty evidence indicating no significant difference in opioid dose reduction between treatment with THC:CBD/opioids and opioids (4 RCTs) in a meta-analysis of people living with chronic cancer pain. Treatment duration ranged 2-5 weeks, no follow-up periods reported.
Patient-perceived global improvement of pain			

Author (year)	Research question	Intervention categorisation	Evidence summary
Häuser *et al.* (2019)	How effective and safe are medical cannabis and cannabis-based medicines compared to controls in managing cancer pain in patients of any age?	THC:CBD products vs placebo	Low-certainty evidence indicating significantly improved likelihood of much or very much improved global impression with treatment with nabiximols compared with placebo (2 RCTs) in a meta-analysis of adults with moderate to severe cancer-related pain. One additional RCT with an enriched enrolment randomised withdrawal design, reported separately to the meta-analysis, reported the same findings. Treatment duration was 5 weeks in each study, no follow-up periods reported.
NAUSEA/VOMITING			
Absence of nausea			
Smith *et al.* (2015)	To evaluate the effectiveness and tolerability of cannabis-based medications for chemotherapy-induced nausea and vomiting in adults with cancer	THC products vs placebo	Low-certainty evidence indicating no significant difference in complete absence of nausea between THC and placebo (2 RCTs) in a meta-analysis of adults with cancer. Treatment duration was up to 15 hours, no follow-up periods reported.
Smith *et al.* (2015)	To evaluate the effectiveness and tolerability of cannabis-based medications for chemotherapy-induced nausea and vomiting in adults with cancer	THC products vs active comparator	Moderate-certainty evidence indicating no significant difference in complete absence of nausea between THC and anti-emetic (5 RCTs) in a meta-analysis of adults with cancer. Treatment duration ranged 1-4 days (reported for 4 RCTs), no follow-up periods reported.
Smith *et al.* (2015)	To evaluate the effectiveness and tolerability of cannabis-based medications for chemotherapy-induced nausea and vomiting in adults with cancer	THC products vs placebo in combination with another treatment	Very low-certainty evidence indicating no significant difference in complete absence of nausea between THC/anti-emetic and anti-emetic (1 RCT) in adults with cancer. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was every 6 hours for an unspecified duration, no follow-up periods reported.
Absence of vomiting			
Smith *et al.* (2015)	To evaluate the effectiveness and tolerability of cannabis-based medications for chemotherapy-induced nausea and vomiting in adults with cancer	THC products vs placebo	Moderate-certainty evidence indicating a greater likelihood of reporting complete absence of vomiting with treatment with THC compared to placebo (3 RCTs) in a meta-analysis of adults with cancer. Treatment duration was up to 15 hours (reported for 2 RCTs), no follow-up periods reported.
Smith *et al.* (2015)	To evaluate the effectiveness and tolerability of cannabis-based medications for chemotherapy-induced nausea and vomiting in adults with cancer	THC products vs active comparator	Moderate-certainty evidence indicating no significant difference in complete absence of vomiting between THC and anti-emetic agents (4 RCTs) in a meta-analysis of adults with cancer. Treatment duration ranged 3-4 days (reported for 3 RCTs), no follow-up periods reported.

Author (year)	Research question	Intervention categorisation	Evidence summary
Smith *et al.* (2015)	To evaluate the effectiveness and tolerability of cannabis-based medications for chemotherapy-induced nausea and vomiting in adults with cancer	THC products vs placebo in combination with another treatment	Low-certainty evidence indicating no significant difference in complete absence of vomiting between THC/anti-emetic agents and anti-emetic agents (2 RCTs) in a meta-analysis of adults with cancer. Treatment duration was up to 24 hours (reported for 1 RCT), no follow-up periods reported.
Absence of nausea and vomiting			
Smith *et al.* (2015)	To evaluate the effectiveness and tolerability of cannabis-based medications for chemotherapy-induced nausea and vomiting in adults with cancer	THC products vs placebo	Moderate-certainty evidence indicating a greater likelihood of reporting complete absence of nausea and vomiting with treatment with THC compared to placebo (3 RCTs) in a meta-analysis of adults with cancer. Treatment duration was clearly reported for only 1 RCT (3 days), no follow-up periods reported.
Smith *et al.* (2015)	To evaluate the effectiveness and tolerability of cannabis-based medications for chemotherapy-induced nausea and vomiting in adults with cancer	THC products vs active comparator	Moderate-certainty evidence indicating no significant difference in complete absence of nausea and vomiting between THC and anti-emetic (4 RCTs) in a meta-analysis of adults with cancer. Treatment duration ranged 1-3 days (reported for 2 RCTs), no follow-up periods reported.
Smith *et al.* (2015)	To evaluate the effectiveness and tolerability of cannabis-based medications for chemotherapy-induced nausea and vomiting in adults with cancer	THC products vs placebo in combination with another treatment	Very low-certainty evidence indicating no significant difference in complete absence of nausea and vomiting between THC/anti-emetic and anti-emetic (1 RCT) in adults with cancer. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was every 6 hours for an unspecified duration, no follow-up periods reported.
NUTRITION-RELATED OUTCOMES			
Appetite			
Razmovski-Naumovski *et al.* (2022)	To systematically review the evidence on the efficacy of medicinal cannabis for improving appetite-related symptoms in people with cancer	THC products vs placebo	Low-certainty evidence indicating no significant difference in appetite between THC treatments (nabilone, dronabinol, THC) and placebo (4 RCTs, narrative synthesis) in adults with cancer. Two RCTs found that appetite improved from baseline with treatment with nabilone and dronabnol respectively, but not significantly differently to placebo groups. One RCT found that pre-meal appetite was improved with treatment with dronabinol compared with placebo. Treatment duration/evaluation ranged from 3-8 weeks, with follow-up reported at 4 weeks for one RCT.
Razmovski-Naumovski *et al.* (2022)	To systematically review the evidence on the efficacy of medicinal cannabis for improving appetite-related symptoms in people with cancer	THC products vs placebo in combination with another treatment	Very low-certainty evidence indicating improved appetite with treatment with megestrol acetate compared with dronabinol (1 RCT) in adults with cancer. The same RCT found no significant

Author (year)	Research question	Intervention categorisation	Evidence summary
			difference between a combination treatment (megestrol acetate and dronabinol) and megestrol acetate alone. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was not reported, no follow-up period was reported.
Razmovski-Naumovski *et al.* (2022)	To systematically review the evidence on the efficacy of medicinal cannabis for improving appetite-related symptoms in people with cancer	Mixed cannabinoids vs placebo	Very low-certainty evidence indicating no significant difference in appetite between cannabis extract and placebo (1 RCT) in adults with cancer. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was not reported but evaluation took place up to 6 weeks.
Simon *et al.* (2022)	This review aimed to consider [non-randomised studies of interventions] alongside RCTs for a comprehensive approach to the available evidence on cannabinoid interventions in [cancer-associated cachexia or severe loss of weight and muscle mass], in order to inform clinical decisions and future investigations	Mixed cannabinoids vs placebo	Low-certainty evidence indicating no significant difference in appetite between mixed cannabinoid and placebo (3 RCTs) in a meta-analysis of adults with cancer. Treatment duration ranged 18 days to 8 weeks, with follow-up ranging 30 days to 8 weeks.
Simon *et al.* (2022)	This review aimed to consider [non-randomised studies of interventions] alongside RCTs for a comprehensive approach to the available evidence on cannabinoid interventions in [cancer-associated cachexia or severe loss of weight and muscle mass], in order to inform clinical decisions and future investigations	THC products vs active comparator	Very low-certainty evidence indicating significant improvements in appetite with treatment with megestrol acetate compared with dronabinol (1 RCT) in adults with cancer. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was not reported, no follow-up period was reported.
Weight			
Razmovski-Naumovski *et al.* (2022)	To systematically review the evidence on the efficacy of medicinal cannabis for improving appetite-related symptoms in people with cancer	THC products vs placebo	Low-certainty evidence indicating no significant difference in weight between THC (dronabinol, nabilone, THC) and placebo (3 RCTs, narrative synthesis) in adults with cancer. Treatment duration was not reported but evaluations ranged 4-8 weeks. No follow-up period was reported.
Razmovski-Naumovski *et al.* (2022)	To systematically review the evidence on the efficacy of medicinal cannabis for improving appetite-related symptoms in people with cancer	Mixed cannabinoids vs placebo	Very low-certainty evidence indicating no significant difference in weight between cannabinoid (cannabis extract) placebo (1 RCT) in adults with cancer. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was not reported but evaluation took place up to 6 weeks. No follow-up period was reported.

Author (year)	Research question	Intervention categorisation	Evidence summary
Razmovski-Naumovski *et al.* (2022)	To systematically review the evidence on the efficacy of medicinal cannabis for improving appetite-related symptoms in people with cancer	THC products vs active comparator	Very low-certainty evidence indicating no significant difference in weight between a combination treatment (megestrol acetate and dronabinol) and megestrol acetate alone (1 RCT) in adults with cancer. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was not reported and no follow-up period was reported.
Simon *et al.* (2022)	This review aimed to consider [non-randomised studies of interventions] alongside RCTs for a comprehensive approach to the available evidence on cannabinoid interventions in [cancer-associated cachexia or severe loss of weight and muscle mass], in order to inform clinical decisions and future investigations	THC products vs placebo	Very low-certainty evidence indicating no significant difference in weight change between nabilone and placebo (1 RCT) in adults with cancer. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 8 weeks, no follow-up period was reported.
Simon *et al.* (2022)	This review aimed to consider [non-randomised studies of interventions] alongside RCTs for a comprehensive approach to the available evidence on cannabinoid interventions in [cancer-associated cachexia or severe loss of weight and muscle mass], in order to inform clinical decisions and future investigations	THC products vs active comparator	Very low-certainty evidence indicating significant improvements in self-reported and physician-reported weight gain with treatment with megestrol acetate compared with dronabinol (1 RCT) in adults with cancer. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was not reported, no follow-up period was reported.
Body mass index			
Razmovski-Naumovski *et al.* (2022)	To systematically review the evidence on the efficacy of medicinal cannabis for improving appetite-related symptoms in people with cancer	THC products vs placebo	Very low-certainty evidence indicating no significant difference in body mass index between nabilone and placebo (1 RCT) in adults with cancer. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was not reported but evaluation took place up to 8 weeks. No follow-up period was reported.
Caloric intake per day			
Razmovski-Naumovski *et al.* (2022)	To systematically review the evidence on the efficacy of medicinal cannabis for improving appetite-related symptoms in people with cancer	THC products vs placebo	Very low-certainty evidence indicating no significant difference in calories per day between cannabinoids and placebo (2 RCTs, narrative synthesis) in adults with cancer. Treatment duration was not reported but evaluation ranged 3-8 weeks. No follow-up period was reported.
Protein intake per day			
Razmovski-Naumovski *et al.* (2022)	To systematically review the evidence on the efficacy of medicinal cannabis for improving appetite-related symptoms in people with cancer	THC products vs placebo	Very low certainty mixed evidence for a significant difference in protein per day between cannabinoids and placebo (2 RCTs, narrative synthesis) in adults with cancer, with one RCT reporting no difference and a second reporting a significant increase in

Author (year)	Research question	Intervention categorisation	Evidence summary
			proportion of calories consumed as protein with treatment with dronabinol compared to placebo, although overall increase in protein intake was not significant. Treatment duration was not reported but evaluation ranged 3-8 weeks. No follow-up period was reported.
Carbohydrate intake per day			
Razmovski-Naumovski *et al.* (2022)	To systematically review the evidence on the efficacy of medicinal cannabis for improving appetite-related symptoms in people with cancer	THC products vs placebo	Very low certainty mixed evidence for a significant difference in carbohydrates per day between cannabinoids and placebo (2 RCTs, narrative synthesis) in adults with cancer, with one RCT reporting no difference and a second reporting a significant increase in carbohydrate intake with treatment with cannabinoids compared to placebo. Treatment duration was not reported but evaluation ranged 3-8 weeks. No follow-up period was reported.
Fats intake per day			
Razmovski-Naumovski *et al.* (2022)	To systematically review the evidence on the efficacy of medicinal cannabis for improving appetite-related symptoms in people with cancer	THC products vs placebo	Very low-certainty evidence indicating no significant difference in fats per day between cannabinoids and placebo (2 RCTs, narrative synthesis) in adults with cancer. Treatment duration was not reported but evaluation ranged 3-8 weeks. No follow-up period was reported.
Iron intake per day			
Razmovski-Naumovski *et al.* (2022)	To systematically review the evidence on the efficacy of medicinal cannabis for improving appetite-related symptoms in people with cancer	THC products vs placebo	Very low-certainty evidence indicating no significant difference in iron per day between nabilone and placebo (1 RCT) in adults with cancer. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was not reported but evaluation took place up to 8 weeks. No follow-up period was reported.
Chemosensory perception			
Razmovski-Naumovski *et al.* (2022)	To systematically review the evidence on the efficacy of medicinal cannabis for improving appetite-related symptoms in people with cancer	THC products vs placebo	Very low-certainty evidence indicating significant improvements in chemosensory perception (taste and smell) with treatment with dronabinol compared with placebo (1 RCT) in adults with cancer. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was not reported but evaluation took place up to 3 weeks. No follow-up period was reported.
Satiety			

Author (year)	Research question	Intervention categorisation	Evidence summary
Razmovski-Naumovski *et al.* (2022)	To systematically review the evidence on the efficacy of medicinal cannabis for improving appetite-related symptoms in people with cancer	THC products vs placebo	Very low-certainty evidence indicating significant improvements in satiety with treatment with dronabinol compared with baseline and with placebo (1 RCT) in adults with cancer. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was not reported but evaluation took place up to 3 weeks. No follow-up period was reported.
HIV/AIDS			
MORBIDITY AND MORTALITY			
Morbidity			
Lutge *et al.* (2013)	This review aims to objectively assess the studies that have examined the medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS.	NA	No evidence found for this outcome
Mortality			
Lutge *et al.* (2013)	This review aims to objectively assess the studies that have examined the medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS.	NA	No evidence found for this outcome
CONDITIONS IN OLDER ADULTS			
AGITATION			
Agitation in Alzheimer's disease (Cohen Mansfield Agitation Inventory)			
Van den Elsen *et al.* (2014)	This systematic review aims to integrate the evidence on indications, efficacy, safety and pharmacokinetics of medical cannabinoids in older subjects	THC products vs placebo	Very low-certainty evidence indicating significant improvements in disturbed behaviour with treatment with dronabinol compared with placebo (1 RCT) in adults with Alzheimer's Disease. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 42 days, no follow-up period was reported.
Agitation in Alzheimer's disease (nocturnal motor activity)			
Van den Elsen *et al.* (2014)	This systematic review aims to integrate the evidence on indications, efficacy, safety and pharmacokinetics of medical cannabinoids in older subjects	THC products vs placebo	No evidence was presented for this outcome; one RCT of nocturnal motor activity in adults with Alzheimer's Disease presented no statistical analysis due to very small sample size (n=2).
COGNITIVE FUNCTION			

Author (year)	Research question	Intervention categorisation	Evidence summary
Cognitive function in dementia			
Bosnjak Kuharic *et al.* (2021)	The purpose of this systematic review was to investigate whether cannabinoids could help people with dementia, and whether they have any potential harmful effects	THC products vs placebo	Very low-certainty evidence indicating a small significant improvement in global and specific cognitive function with treatment with nabilone compared with placebo (1 RCT) in adults with dementia. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 14 weeks (6 weeks for nabilone period), no follow-up period was reported.
BREATHLESSNESS IN COPD			
Minute ventilation			
Van den Elsen *et al.* (2014)	This systematic review aims to integrate the evidence on indications, efficacy, safety and pharmacokinetics of medical cannabinoids in older subjects	THC:CBD products vs placebo	Very low-certainty evidence indicating no significant difference in any measure of minute ventilation (breathlessness) between THC:CBD and placebo (1 RCTs) in older adults with COPD. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was one day, no follow-up period was reported.
PetCO2			
Van den Elsen *et al.* (2014)	This systematic review aims to integrate the evidence on indications, efficacy, safety and pharmacokinetics of medical cannabinoids in older subjects	THC:CBD products vs placebo	Very low-certainty evidence indicating no significant difference in PetCO2 (breathlessness) between THC:CBD and placebo (1 RCTs) in olderr adults with COPD. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was one day, no follow-up period was reported.
Breathlessness visual analogue scale			
Van den Elsen *et al.* (2014)	This systematic review aims to integrate the evidence on indications, efficacy, safety and pharmacokinetics of medical cannabinoids in older subjects	THC:CBD products vs placebo	Very low-certainty evidence indicating no significant difference in any measure of visual analog scale for breathlessness between THC:CBD and placebo (1 RCTs) in older adults with COPD. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was one day, no follow-up period was reported.
GENERAL BEHVAIOURAL/PSYCHOLOGICAL SYMPTOMS			
Behavioural and psychological symptoms of dementia			
Paunescu 2020	Which is the level of evidence, from quantitative and qualitative point of view, concerning the efficacy and safety of the treatment with	THC products vs placebo	Very low certainty mixed evidence for a significant difference in neuropsychiatric symptoms (aggression in dementia) between cannabinoids and placebo (6 RCTs, narrative synthesis) in adults

Author (year)	Research question	Intervention categorisation	Evidence summary
	psychotropic cannabinoids of neuropsychiatric symptoms in [Alzheimer's Disease]?		with Alzheimer's Disease or other types of dementia. Four RCTs reported significant improvement in aggression with treatment with THC (dronabinol, nabilone) compared with placebo. Two other RCTs reported no significant difference between dronabinol and placebo. Treatment duration ranged 2-14 weeks, no follow-up periods were reported.
Bosnjak Kuharic *et al.* (2021)	The purpose of this systematic review was to investigate whether cannabinoids could help people with dementia, and whether they have any potential harmful effects	THC products vs placebo	Moderate-certainty evidence indicating no significant difference in behavioural and psychological symptoms of dementia between THC (nabilone, THC, delta-THC namisol) and placebo (3 RCTs) in a meta-analysis of adults with dementia. Treatment duration ranged 3-14 weeks, no follow-up period was reported.
Observed affect in Alzheimer's disease (Lawton Observed Affect Scale-Past)			
Van den Elsen *et al.* (2014)	This systematic review aims to integrate the evidence on indications, efficacy, safety and pharmacokinetics of medical cannabinoids in older subjects	THC products vs placebo	Very low-certainty evidence indicating significant improvements in observed affect with treatment with dronabinol compared with placebo (1 RCT) in adults with Alzheimer's Disease. Positive affect was similar during treatment with placebo and dronabinol, but negative affect descreased over both periods and more during treatment with dronabinol. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 42 days, no follow-up period was reported.
General symptoms of Parkinson's disease (Unified Parkinson's Disease Rating Scale (UPDRS))			
Urbi *et al.* (2022)	The aim of this review was to interrogate the published and unpublished literature for evidence of treatment effects of cannabis in [Parkinson's disease]. We have focused on the potential effects on [Parkinson's disease] severity and progression, as well as effects on motor and non-motor symptoms.	Mixed cannabinoids vs placebo	Very low-certainty evidence indicating a marginal worsening of Total Unified Parkinson's Disease Rating Scale with treatment with cannabinoids (THC, THC:CBD) compared with placebo (2 RCTs) in a meta-analysis of adults with Parkinson's Disease. Treatment duration ranged 4-6 weeks, no follow-up period was reported.
General symptoms of Parkinson's disease (Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS))			
Urbi *et al.* (2022)	The aim of this review was to interrogate the published and unpublished literature for evidence of treatment effects of cannabis in [Parkinson's disease]. We have focused on the potential effects on [Parkinson's disease] severity and progression, as well as effects on motor and non-motor symptoms.	Mixed cannabinoids vs placebo	Very low-certainty evidence indicating significantly less deterioration in non-motor symptoms with treatment with nabilone compared with placebo (1 RCT) in adults with Parkinson's Disease; however, no significant differences were found on other subscales examining motor experiences of daily living, motor examination, and motor complications. The certainty of evidence was downgraded to very low because the

Author (year)	Research question	Intervention categorisation	Evidence summary
			outcome was informed by a single RCT. Treatment duration was 4 weeks, no follow-up period was reported.
MOVEMENT DISORDER			
Levodopa-induced dyskinesia in Parkinson's disease			
Van den Elsen *et al.* (2014)	This systematic review aims to integrate the evidence on indications, efficacy, safety and pharmacokinetics of medical cannabinoids in older subjects	THC:CBD products vs placebo	Very low-certainty evidence for no significant difference in Levodopa-induced dyskinesia between THC:CBD and placebo (1 RCT) in adults with Parkinson's Disease. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 28 days, no follow-up period was reported.
Urbi *et al.* (2022)	The aim of this review was to interrogate the published and unpublished literature for evidence of treatment effects of cannabis in [Parkinson's disease]. We have focused on the potential effects on [Parkinson's disease] severity and progression, as well as effects on motor and non-motor symptoms.	Mixed cannabinoids vs placebo	Very low certainty mixed evidence for a significant difference in Levodopa-induced dyskinesia between cannabinoids (THC (nabilone), THC:CBD) and placebo (2 RCTs, narrative synthesis) in adults with Parkinson's Disease, with one RCT reporting no difference (THC:CBD, 4 weeks treatment duration, no follow-up period specified) and a second reporting a significant improvement with nabilone treatment compared with placebo (one-time treatment, no follow-up period reported).
Tremor in Parkinson's disease			
Urbi *et al.* (2022)	The aim of this review was to interrogate the published and unpublished literature for evidence of treatment effects of cannabis in [Parkinson's disease]. We have focused on the potential effects on [Parkinson's disease] severity and progression, as well as effects on motor and non-motor symptoms.	CBD products vs placebo	Very low-certainty evidence indicating a decrease of tremor amplitude following a single treatment with CBD compared with placebo (1 RCT) in adults with Parkinson's Disease. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. No follow-up period was reported.
NAUSEA/VOMITING			
Nausea and vomiting score			
Van den Elsen *et al.* (2014)	This systematic review aims to integrate the evidence on indications, efficacy, safety and pharmacokinetics of medical cannabinoids in older subjects	THC products vs active comparator	Very low-certainty evidence for no significant difference in chemotherapy-induced nausea and vomiting between THC and prochlorperazine (1 RCTs) in older adults with a wide variety of neoplasms. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was one day, no follow-up period was reported.
NUTRITION-RELATED OUTCOMES			

Author (year)	Research question	Intervention categorisation	Evidence summary
Global impression of change of appetite and food intake			
Van den Elsen *et al.* (2014)	This systematic review aims to integrate the evidence on indications, efficacy, safety and pharmacokinetics of medical cannabinoids in older subjects	NA	One included study reportedly investigated global impression of change of appetite and food intake; however, the review presented no data from this study for this outcome.
Weight in Alzheimer's disease			
Van den Elsen *et al.* (2014)	This systematic review aims to integrate the evidence on indications, efficacy, safety and pharmacokinetics of medical cannabinoids in older subjects	THC products vs placebo	Very low-certainty evidence indicating significantly greater weight gain with treatment with dronabinol compared with placebo (1 RCT) in adults with Alzheimer's Disease. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 42 days, no follow-up period was reported.
Skin fold thickness in Alzheimer's disease			
Van den Elsen *et al.* (2014)	This systematic review aims to integrate the evidence on indications, efficacy, safety and pharmacokinetics of medical cannabinoids in older subjects	THC products vs placebo	Very low-certainty evidence indicating that skin fold thickness increased in adults with Alzheimer's Disease with treatment with dronabinol, but did not increase significantly compared to placebo (1 RCT). The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 42 days, no follow-up period was reported.
Caloric intake in Alzheimer's disease			
Van den Elsen *et al.* (2014)	This systematic review aims to integrate the evidence on indications, efficacy, safety and pharmacokinetics of medical cannabinoids in older subjects	THC products vs placebo	Very low-certainty evidence indicating no significant difference in caloric intake with dronabinol compared with placebo (1 RCT) in adults with Alzheimer's Disease. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 42 days, no follow-up period was reported.
PAIN-RELATED OUTCOMES			
Pain intensity in Parkinson's disease			
Urbi *et al.* (2022)	The aim of this review was to interrogate the published and unpublished literature for evidence of treatment effects of cannabis in [Parkinson's disease]. We have focused on the potential effects on [Parkinson's disease] severity and progression,	Mixed cannabinoids vs placebo	Very low-certainty evidence for no significant difference in pain intensity between cannabinoids (THC, THC:CBD) and placebo (2 RCTs, narrative synthesis) in adults with Parkinson's Disease. Treatment duration was 4 weeks in each case, no follow-up period was reported.

Author (year)	Research question	Intervention categorisation	Evidence summary
	as well as effects on motor and non-motor symptoms.		
MENTAL HEALTH/WELLBEING			
Anxiety in Parkinson's disease			
Urbi *et al.* (2022)	The aim of this review was to interrogate the published and unpublished literature for evidence of treatment effects of cannabis in [Parkinson's disease]. We have focused on the potential effects on [Parkinson's disease] severity and progression, as well as effects on motor and non-motor symptoms.	Mixed cannabinoids vs placebo	Very low-certainty evidence indicating a decrease in anxiety with treatment with CBD (single treatment) and with THC (treatment duration 4 weeks) compared with placebo (2 RCTs, narrative synthesis) in adults with Parkinson's Disease. No follow-up periods were reported.
Quality of life in Parkinson's disease			
Urbi *et al.* (2022)	The aim of this review was to interrogate the published and unpublished literature for evidence of treatment effects of cannabis in [Parkinson's disease]. We have focused on the potential effects on [Parkinson's disease] severity and progression, as well as effects on motor and non-motor symptoms.	Mixed cannabinoids vs placebo	Very low certainty mixed evidence for a significant difference in quality of life between cannabinoids (THC, THC:CBD) and placebo (2 RCTs, narrative synthesis) in adults with Parkinson's Disease, with one RCT reporting no difference (THC:CBD, 4 weeks treatment duration, no follow-up period specified) and a second reporting a significant improvements with CBD treatment compared with placebo (6 weeks treatment duration, no follow-up period reported).
SLEEP-RELATED OUTCOMES			
Sleep quality in Parkinson's disease			
Urbi *et al.* (2022)	The aim of this review was to interrogate the published and unpublished literature for evidence of treatment effects of cannabis in [Parkinson's disease]. We have focused on the potential effects on [Parkinson's disease] severity and progression, as well as effects on motor and non-motor symptoms.	THC products vs placebo	Very low-certainty evidence for significantly improved sleep quality with treatment with nabilone compared with placebo (1 RCT) in adults with Parkinson's Disease. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 4 weeks, no follow-up period was reported.
INFLAMMATORY BOWEL DISEASE			
CLINICAL REMISSION			
Clinical remission rates in Crohn's disease			

Author (year)	Research question	Intervention categorisation	Evidence summary
Kafil *et al.* (2018a)	To assess the efficacy and safety of cannabis for induction and maintenance of remission in people with Crohn's disease	Cannabis products vs placebo	Very low-certainty evidence indicating no significant difference in clinical remission between THC (cannabis cigarette) and placebo (1 RCT) in adults with Crohn's disease. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 16 weeks (8 weeks intervention, 8 weeks placebo) with an additional follow-up after 2 weeks.
Kafil *et al.* (2018a)	To assess the efficacy and safety of cannabis for induction and maintenance of remission in people with Crohn's disease	CBD products vs placebo	Very low-certainty evidence indicating no significant difference in clinical remission between 5% CBD cannabis oil and placebo (1 RCT) in adults with Crohn's disease. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 16 weeks (8 weeks intervention, 8 weeks placebo), no follow-up period was reported.
Clinical remission rates in ulcerative colitis			
Kafil *et al.* (2018b)	To assess the efficacy and safety of cannabis and cannabinoids for the treatment of patients with [ulcerative colitis]	CBD products vs placebo	Very low-certainty evidence indicating no significant difference in clinical remission between CBD and placebo (1 RCT) in adults with ulcerative colitis. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 10 weeks, no follow-up period was reported.
MENTAL HEALTH AND NEUROPSYCHOLOGICAL CONDITIONS			
PSYCHOTIC DISORDERS			
Remission from psychotic disorders			
Black *et al.* (2019)	To examine the available evidence for all types of medicinal cannabinoids and all study designs (controlled and observational) to ascertain the impact of medicinal cannabinoids on remission from and symptoms of depression, anxiety, post-traumatic stress disorder, and psychosis, as well as symptoms of attention deficit hyperactivity disorder (ADHD) and Tourette syndrome, either as the primary disorder or secondary to other disorders; and the impact of medicinal cannabinoids on	NA	No evidence found for this outcome

Author (year)	Research question	Intervention categorisation	Evidence summary
	outcomes including global functioning, quality of life, and patient or caregiver impression of change. We also examined the safety of medicinal cannabinoids for mental health symptoms and disorders, including all-cause, serious, and treatment-related adverse events and study withdrawals.		
Positive symptoms of psychosis			
Black *et al.* (2019)	To examine the available evidence for all types of medicinal cannabinoids and all study designs (controlled and observational) to ascertain the impact of medicinal cannabinoids on remission from and symptoms of depression, anxiety, post-traumatic stress disorder, and psychosis, as well as symptoms of attention deficit hyperactivity disorder (ADHD) and Tourette syndrome, either as the primary disorder or secondary to other disorders; and the impact of medicinal cannabinoids on outcomes including global functioning, quality of life, and patient or caregiver impression of change. We also examined the safety of medicinal cannabinoids for mental health symptoms and disorders, including all-cause, serious, and treatment-related adverse events and study withdrawals.	THC products vs placebo	Very low-certainty evidence indicating no significant difference in positive symptoms of psychosis between intravenous THC and placebo (1 RCT) in adults. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was three weeks, no follow-up period was reported.
Black *et al.* (2019)	To examine the available evidence for all types of medicinal cannabinoids and all study designs (controlled and observational) to ascertain the impact of medicinal cannabinoids on remission from and symptoms of depression, anxiety, post-traumatic stress disorder, and psychosis, as well as symptoms of attention deficit hyperactivity disorder (ADHD) and Tourette syndrome, either as the primary disorder or secondary to other disorders; and the impact of medicinal cannabinoids on outcomes including global functioning, quality of life, and patient or caregiver impression of change. We also examined the safety of medicinal cannabinoids for mental health symptoms and	CBD products vs placebo	Low-certainty evidence indicating no significant difference in positive symptoms of psychosis between CBD and placebo (2 RCTs) in a meta-analysis of adults. Treatment duration was 6 weeks in both studies; no follow-up period was reported.

Author (year)	Research question	Intervention categorisation	Evidence summary
	disorders, including all-cause, serious, and treatment-related adverse events and study withdrawals.		
Black *et al.* (2019)	To examine the available evidence for all types of medicinal cannabinoids and all study designs (controlled and observational) to ascertain the impact of medicinal cannabinoids on remission from and symptoms of depression, anxiety, post-traumatic stress disorder, and psychosis, as well as symptoms of attention deficit hyperactivity disorder (ADHD) and Tourette syndrome, either as the primary disorder or secondary to other disorders; and the impact of medicinal cannabinoids on outcomes including global functioning, quality of life, and patient or caregiver impression of change. We also examined the safety of medicinal cannabinoids for mental health symptoms and disorders, including all-cause, serious, and treatment-related adverse events and study withdrawals.	CBD products vs active comparator	Very low-certainty evidence indicating no significant difference in positive symptoms of psychosis between CBD and active comparator (amisulpride) (1 RCT) in adults. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 4 weeks, no follow-up period was reported.
Negative symptoms of psychosis			
Black *et al.* (2019)	To examine the available evidence for all types of medicinal cannabinoids and all study designs (controlled and observational) to ascertain the impact of medicinal cannabinoids on remission from and symptoms of depression, anxiety, post-traumatic stress disorder, and psychosis, as well as symptoms of attention deficit hyperactivity disorder (ADHD) and Tourette syndrome, either as the primary disorder or secondary to other disorders; and the impact of medicinal cannabinoids on outcomes including global functioning, quality of life, and patient or caregiver impression of change. We also examined the safety of medicinal cannabinoids for mental health symptoms and disorders, including all-cause, serious, and treatment-related adverse events and study withdrawals.	THC products vs placebo	Very low-certainty evidence indicating significant worsening of negative symptoms of psychosis with treatment with intravenous THC compared with placebo (1 RCT) in adults. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was three weeks, no follow-up period was reported.

Author (year)	Research question	Intervention categorisation	Evidence summary
Black *et al.* (2019)	To examine the available evidence for all types of medicinal cannabinoids and all study designs (controlled and observational) to ascertain the impact of medicinal cannabinoids on remission from and symptoms of depression, anxiety, post-traumatic stress disorder, and psychosis, as well as symptoms of attention deficit hyperactivity disorder (ADHD) and Tourette syndrome, either as the primary disorder or secondary to other disorders; and the impact of medicinal cannabinoids on outcomes including global functioning, quality of life, and patient or caregiver impression of change. We also examined the safety of medicinal cannabinoids for mental health symptoms and disorders, including all-cause, serious, and treatment-related adverse events and study withdrawals.	CBD products vs placebo	Low-certainty evidence indicating no significant difference in negative symptoms of psychosis between CBD and placebo (2 RCTs) in a meta-analysis of adults. Treatment duration was 6 weeks in both studies; no follow-up period was reported.
Black *et al.* (2019)	To examine the available evidence for all types of medicinal cannabinoids and all study designs (controlled and observational) to ascertain the impact of medicinal cannabinoids on remission from and symptoms of depression, anxiety, post-traumatic stress disorder, and psychosis, as well as symptoms of attention deficit hyperactivity disorder (ADHD) and Tourette syndrome, either as the primary disorder or secondary to other disorders; and the impact of medicinal cannabinoids on outcomes including global functioning, quality of life, and patient or caregiver impression of change. We also examined the safety of medicinal cannabinoids for mental health symptoms and disorders, including all-cause, serious, and treatment-related adverse events and study withdrawals.	CBD products vs active comparator	Very low-certainty evidence indicating no significant difference in negative symptoms of psychosis between CBD and active comparator (amisulpride) (1 RCT) in adults. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 4 weeks, no follow-up period was reported.
Total symptoms of psychosis/schizophrenia			
Black *et al.* (2019)	To examine the available evidence for all types of medicinal cannabinoids and all study designs (controlled and observational) to ascertain the	CBD products vs placebo	Low-certainty evidence indicating no significant difference in total symptoms of psychosis between CBD and placebo (2 RCTs)

Author (year)	Research question	Intervention categorisation	Evidence summary
	impact of medicinal cannabinoids on remission from and symptoms of depression, anxiety, post-traumatic stress disorder, and psychosis, as well as symptoms of attention deficit hyperactivity disorder (ADHD) and Tourette syndrome, either as the primary disorder or secondary to other disorders; and the impact of medicinal cannabinoids on outcomes including global functioning, quality of life, and patient or caregiver impression of change. We also examined the safety of medicinal cannabinoids for mental health symptoms and disorders, including all-cause, serious, and treatment-related adverse events and study withdrawals.		in a meta-analysis of adults. Treatment duration was 6 weeks in both studies; no follow-up period was reported.
Black *et al.* (2019)	To examine the available evidence for all types of medicinal cannabinoids and all study designs (controlled and observational) to ascertain the impact of medicinal cannabinoids on remission from and symptoms of depression, anxiety, post-traumatic stress disorder, and psychosis, as well as symptoms of attention deficit hyperactivity disorder (ADHD) and Tourette syndrome, either as the primary disorder or secondary to other disorders; and the impact of medicinal cannabinoids on outcomes including global functioning, quality of life, and patient or caregiver impression of change. We also examined the safety of medicinal cannabinoids for mental health symptoms and disorders, including all-cause, serious, and treatment-related adverse events and study withdrawals.	CBD products vs active comparator	Very low-certainty evidence indicating no significant difference in total symptoms of psychosis between CBD and active comparator (amisulpride) (1 RCT) in adults. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 4 weeks, no follow-up period was reported.
Kopelli *et al.* (2020)	To conduct a systematic review and meta-analysis focusing only on RCTs in patients with schizophrenia or other types of schizophrenia-like psychoses that assessed the efficacy of CBD oil compared to placebo or any antipsychotic drug either as monotherapy or add-on therapy	CBD products vs active comparator	Very low-certainty evidence indicating no significant difference in total symptoms of schizophrenia between CBD and amisulpride (1 RCT) in adults with schizophrenia. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 4 weeks, no follow-up period was reported.
Kopelli *et al.* (2020)	To conduct a systematic review and meta-analysis focusing only on RCTs in patients with schizophrenia	CBD products vs placebo	Low-certainty evidence indicating no significant difference in total symptoms of schizophrenia between CBD (add-on therapy

Author (year)	Research question	Intervention categorisation	Evidence summary
	or other types of schizophrenia-like psychoses that assessed the efficacy of CBD oil compared to placebo or any antipsychotic drug either as monotherapy or add-on therapy		to stable antipsychotic treatment) and placebo (2 RCTs) in a meta-analysis of adults with schizophrenia or related psychotic disorders. Treatment duration was 6 weeks in both studies, no follow-up periods were reported.
McKee *et al.* (2021)	The aim of this systematic review and meta-analyses is to not only offer the most recent examination of the literature in this area, but as well approach the clinical indications for [cannabinoid-based products] in mental health from the lens of a health regulatory board; to review high-level evidence in a systematic review/meta-analyses process	CBD products vs placebo	Very low certainty mixed evidence for a significant improvement in total positive/negative symptoms of schizophrenia between CBD and placebo (2 RCTs, narrative synthesis) in adults with schizophrenia, with one RCT reporting no significant change and a second reporting a statistically but not clinically significant improvement with treatment with CBD compared to placebo. Trial length ranged 6-8 weeks.
McKee *et al.* (2021)	The aim of this systematic review and meta-analyses is to not only offer the most recent examination of the literature in this area, but as well approach the clinical indications for [cannabinoid-based products] in mental health from the lens of a health regulatory board; to review high-level evidence in a systematic review/meta-analyses process	CBD products vs active comparator	Very low-certainty evidence indicating no significant difference in improvement in positive/negative psychotic symptomatology between CBD and amisulpride (1 RCT) in adults with schizophrenia. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Trial length was 4 weeks.
McKee *et al.* (2021)	The aim of this systematic review and meta-analyses is to not only offer the most recent examination of the literature in this area, but as well approach the clinical indications for [cannabinoid-based products] in mental health from the lens of a health regulatory board; to review high-level evidence in a systematic review/meta-analyses process	THC products vs placebo	Very low-certainty evidence indicating short-term worsening of positive and negative symptoms of schizophrenia with treatment with THC compared with placebo (1 RCT) in adults with schizophrenia. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment was administered on three test days, each separated by at least 7 days.
Cognitive function in schizophrenia			
Kopelli *et al.* (2020)	To conduct a systematic review and meta-analysis focusing only on RCTs in patients with schizophrenia or other types of schizophrenia-like psychoses that assessed the efficacy of CBD oil compared to placebo or any antipsychotic drug either as monotherapy or add-on therapy	CBD products vs placebo	Very low-certainty evidence indicating no significant difference in cognitive functioning between CBD (add-on therapy to stable antipsychotic treatment) and placebo (2 RCTs) in a meta-analysis of adults with schizophrenia or related psychotic disorders. Treatment duration was 6 weeks in both studies, no follow-up periods were reported.
McKee *et al.* (2021)	The aim of this systematic review and meta-analyses is to not only offer the most recent examination of the literature in this area, but as	CBD products vs placebo	Very low-certainty evidence indicating no significant difference cognition between CBD and placeo (1 RCT) in adults with schizophrenia. The certainty of evidence was downgraded to very

Author (year)	Research question	Intervention categorisation	Evidence summary
	well approach the clinical indications for [cannabinoid-based products] in mental health from the lens of a health regulatory board; to review high-level evidence in a systematic review/meta-analyses process		low because the outcome was informed by a single RCT. Trial length was 6 weeks.
McKee *et al.* (2021)	The aim of this systematic review and meta-analyses is to not only offer the most recent examination of the literature in this area, but as well approach the clinical indications for [cannabinoid-based products] in mental health from the lens of a health regulatory board; to review high-level evidence in a systematic review/meta-analyses process	THC products vs placebo	Very low-certainty evidence indicating short-term worsening of cognitive functioning with treatment with THC compared with placebo (1 RCT) in adults with schizophrenia. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment was administered on three test days, each separated by at least 7 days.
ANXIETY DISORDERS			
Remission from anxiety disorder			
Black *et al.* (2019)	To examine the available evidence for all types of medicinal cannabinoids and all study designs (controlled and observational) to ascertain the impact of medicinal cannabinoids on remission from and symptoms of depression, anxiety, post-traumatic stress disorder, and psychosis, as well as symptoms of attention deficit hyperactivity disorder (ADHD) and Tourette syndrome, either as the primary disorder or secondary to other disorders; and the impact of medicinal cannabinoids on outcomes including global functioning, quality of life, and patient or caregiver impression of change. We also examined the safety of medicinal cannabinoids for mental health symptoms and disorders, including all-cause, serious, and treatment-related adverse events and study withdrawals.	NA	No evidence found for this outcome
Generalised anxiety disorder symptoms			
Bahji *et al.* (2020)	To comprehensively appraise the evidence for the efficacy and acceptability of a range of cannabinoid and cannabis-preparations—including THC, CBD,	Mixed cannabinoids and cannabis products vs placebo	Low-certainty evidence indicating significant improvements in anxiety symptoms with treatment with cannabinoids (nabilone, CBD) compared with placebo groups (3 RCTs) in a meta-analysis

Author (year)	Research question	Intervention categorisation	Evidence summary
	and their synthetic analogues—in reducing symptoms associated with anxiety disorders		of adults with generalised anxiety disorder. Treatment duration ranged 1-4 weeks, no follow-up period was reported.
Bahji *et al.* (2020)	To comprehensively appraise the evidence for the efficacy and acceptability of a range of cannabinoid and cannabis-preparations—including THC, CBD, and their synthetic analogues—in reducing symptoms associated with anxiety disorders	Cannabis products vs cannabis products	Very low-certainty evidence indicating significant reduction in anxiety symptoms with medical cannabis (1 open-label RCT) in adults with generalised anxiety disorder. The certainty of evidence was downgraded to very low because the outcome was informed by a single open-label RCT. Treatment duration was 10 months.
Remission from post-traumatic stress disorder (PTSD)			
Black *et al.* (2019)	To examine the available evidence for all types of medicinal cannabinoids and all study designs (controlled and observational) to ascertain the impact of medicinal cannabinoids on remission from and symptoms of depression, anxiety, post-traumatic stress disorder, and psychosis, as well as symptoms of attention deficit hyperactivity disorder (ADHD) and Tourette syndrome, either as the primary disorder or secondary to other disorders; and the impact of medicinal cannabinoids on outcomes including global functioning, quality of life, and patient or caregiver impression of change. We also examined the safety of medicinal cannabinoids for mental health symptoms and disorders, including all-cause, serious, and treatment-related adverse events and study withdrawals.	NA	No evidence found for this outcome
PTSD symptoms			
McKee *et al.* (2021)	The aim of this systematic review and meta-analyses is to not only offer the most recent examination of the literature in this area, but as well approach the clinical indications for [cannabinoid-based products] in mental health from the lens of a health regulatory board; to review high-level evidence in a systematic review/meta-analyses process	THC products vs placebo	Very low-certainty evidence indicating significant improvement in PTSD symptoms (recurring and distressing dreams) with treatment with nabilone compared with placebo (1 RCT) in adults with PTSD. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 16 weeks, no follow-up period was reported.
Social anxiety disorder symptoms			

Author (year)	Research question	Intervention categorisation	Evidence summary
Bahji *et al.* (2020)	To comprehensively appraise the evidence for the efficacy and acceptability of a range of cannabinoid and cannabis-preparations—including THC, CBD, and their synthetic analogues—in reducing symptoms associated with anxiety disorders	CBD products vs placebo	Low-certainty evidence indicating significant improvements in anxiety symptoms with treatment with CBD compared with placebo groups (2 RCTs, narrative synthesis) in adults with social anxiety disorder. Treatment duration was 1 day or 2 treatment days separated by 7 days, no follow-up period was reported..
McKee *et al.* (2021)	The aim of this systematic review and meta-analyses is to not only offer the most recent examination of the literature in this area, but as well approach the clinical indications for [cannabinoid-based products] in mental health from the lens of a health regulatory board; to review high-level evidence in a systematic review/meta-analyses process	CBD products vs placebo	Very low-certainty evidence indicating significant improvement in anxiety symptoms with CBD compared with placebo (2 RCTs, narrative synthesis) in adults with social anxiety disorder. Treatment duration was 1 day or 2 treatment days separated by 7 days, no follow-up period was reported.
Anxiety symptoms			
Black *et al.* (2019)	To examine the available evidence for all types of medicinal cannabinoids and all study designs (controlled and observational) to ascertain the impact of medicinal cannabinoids on remission from and symptoms of depression, anxiety, post-traumatic stress disorder, and psychosis, as well as symptoms of attention deficit hyperactivity disorder (ADHD) and Tourette syndrome, either as the primary disorder or secondary to other disorders; and the impact of medicinal cannabinoids on outcomes including global functioning, quality of life, and patient or caregiver impression of change. We also examined the safety of medicinal cannabinoids for mental health symptoms and disorders, including all-cause, serious, and treatment-related adverse events and study withdrawals.	Mixed cannabinoids vs placebo	Low-certainty evidence indicating significant improvements in anxiety symptoms with treatment with THC (with or without CBD) compared with placebo groups (7 RCTs) in a meta-analysis of adults. Treatment duration ranged 1 day to 12 weeks, no follow-up period was reported.
Black *et al.* (2019)	To examine the available evidence for all types of medicinal cannabinoids and all study designs (controlled and observational) to ascertain the impact of medicinal cannabinoids on remission from and symptoms of depression, anxiety, post-traumatic stress disorder, and psychosis, as well as symptoms of attention deficit hyperactivity disorder (ADHD) and Tourette syndrome, either as the	THC products vs active comparator	Very low-certainty evidence indicating no significant difference in anxiety symptoms between THC (nabilone) and active comparator (ibuprofen) (1 RCT) in adults. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 8 weeks, no follow-up period was reported.

Author (year)	Research question	Intervention categorisation	Evidence summary
	primary disorder or secondary to other disorders; and the impact of medicinal cannabinoids on outcomes including global functioning, quality of life, and patient or caregiver impression of change. We also examined the safety of medicinal cannabinoids for mental health symptoms and disorders, including all-cause, serious, and treatment-related adverse events and study withdrawals.		
Black *et al.* (2019)	To examine the available evidence for all types of medicinal cannabinoids and all study designs (controlled and observational) to ascertain the impact of medicinal cannabinoids on remission from and symptoms of depression, anxiety, post-traumatic stress disorder, and psychosis, as well as symptoms of attention deficit hyperactivity disorder (ADHD) and Tourette syndrome, either as the primary disorder or secondary to other disorders; and the impact of medicinal cannabinoids on outcomes including global functioning, quality of life, and patient or caregiver impression of change. We also examined the safety of medicinal cannabinoids for mental health symptoms and disorders, including all-cause, serious, and treatment-related adverse events and study withdrawals.	CBD products vs placebo	Very low-certainty evidence indicating no significant difference in anxiety symptoms between CBD and placebo (2 RCTs) in a meta-analysis of adults. Treatment duration was one day in both studies, no follow-up period was reported.
McKee *et al.* (2021)	The aim of this systematic review and meta-analyses is to not only offer the most recent examination of the literature in this area, but as well approach the clinical indications for [cannabinoid-based products] in mental health from the lens of a health regulatory board; to review high-level evidence in a systematic review/meta-analyses process	THC products vs placebo	Very low-certainty evidence indicating significant improvement in anxiety symptoms with treatment with nabilone compared with placebo (1 RCT) in adults with an anxiety disorder. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 28 days, no follow-up period was reported.
Obsessive compulsive disorder symptoms			
McKee *et al.* (2021)	The aim of this systematic review and meta-analyses is to not only offer the most recent examination of the literature in this area, but as	Cannabis products vs placebo	Very low-certainty evidence indicating no significant difference in OCD symptomatology between high-THC cannabis and placebo (1 RCT) in adults with OCD. Patients administered placebo had lower

Author (year)	Research question	Intervention categorisation	Evidence summary
	well approach the clinical indications for [cannabinoid-based products] in mental health from the lens of a health regulatory board; to review high-level evidence in a systematic review/meta-analyses process		anxiety scores than in the cannabis condition. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment was administered on three test days, no follow-up period was reported.
McKee *et al.* (2021)	The aim of this systematic review and meta-analyses is to not only offer the most recent examination of the literature in this area, but as well approach the clinical indications for [cannabinoid-based products] in mental health from the lens of a health regulatory board; to review high-level evidence in a systematic review/meta-analyses process	Cannabis products vs placebo	Very low-certainty evidence indicating no significant difference in OCD symptomatology between low-THC cannabis and placebo (1 RCT) in adults with OCD. Patients administered placebo had lower anxiety scores than in the cannabis condition. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment was administered on three test days, no follow-up period was reported.
MOOD DISORDERS			
Remission from depression			
Black *et al.* (2019)	To examine the available evidence for all types of medicinal cannabinoids and all study designs (controlled and observational) to ascertain the impact of medicinal cannabinoids on remission from and symptoms of depression, anxiety, post-traumatic stress disorder, and psychosis, as well as symptoms of attention deficit hyperactivity disorder (ADHD) and Tourette syndrome, either as the primary disorder or secondary to other disorders; and the impact of medicinal cannabinoids on outcomes including global functioning, quality of life, and patient or caregiver impression of change. We also examined the safety of medicinal cannabinoids for mental health symptoms and disorders, including all-cause, serious, and treatment-related adverse events and study withdrawals.	NA	No evidence found for this outcome
Depression symptoms			
Black *et al.* (2019)	To examine the available evidence for all types of medicinal cannabinoids and all study designs (controlled and observational) to ascertain the impact of medicinal cannabinoids on remission from and symptoms of depression, anxiety, post-	Mixed cannabinoids vs placebo	Low-certainty evidence indicating no significant difference in depression symptoms between THC (with or without CBD) and placebo (12 RCTs) in a meta-analysis of adults. Treatment duration ranged 1 day to 156 weeks, no follow-up periods reported.

Author (year)	Research question	Intervention categorisation	Evidence summary
	traumatic stress disorder, and psychosis, as well as symptoms of attention deficit hyperactivity disorder (ADHD) and Tourette syndrome, either as the primary disorder or secondary to other disorders; and the impact of medicinal cannabinoids on outcomes including global functioning, quality of life, and patient or caregiver impression of change. We also examined the safety of medicinal cannabinoids for mental health symptoms and disorders, including all-cause, serious, and treatment-related adverse events and study withdrawals.		
Black *et al.* (2019)	To examine the available evidence for all types of medicinal cannabinoids and all study designs (controlled and observational) to ascertain the impact of medicinal cannabinoids on remission from and symptoms of depression, anxiety, post-traumatic stress disorder, and psychosis, as well as symptoms of attention deficit hyperactivity disorder (ADHD) and Tourette syndrome, either as the primary disorder or secondary to other disorders; and the impact of medicinal cannabinoids on outcomes including global functioning, quality of life, and patient or caregiver impression of change. We also examined the safety of medicinal cannabinoids for mental health symptoms and disorders, including all-cause, serious, and treatment-related adverse events and study withdrawals.	THC products vs placebo	Very low-certainty evidence indicating no significant difference in depression symptoms between THC (nabilone) and active comparator (ibuprofen) (1 RCT) in adults. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was eight weeks, no follow-up periods reported.
Black *et al.* (2019)	To examine the available evidence for all types of medicinal cannabinoids and all study designs (controlled and observational) to ascertain the impact of medicinal cannabinoids on remission from and symptoms of depression, anxiety, post-traumatic stress disorder, and psychosis, as well as symptoms of attention deficit hyperactivity disorder (ADHD) and Tourette syndrome, either as the primary disorder or secondary to other disorders; and the impact of medicinal cannabinoids on	Cannabis products vs placebo	Very low-certainty evidence indicating no significant difference in depression symptoms between plant cannabis and placebo (1 RCT) in adults. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was five days, no follow-up periods reported.

Author (year)	Research question	Intervention categorisation	Evidence summary
	outcomes including global functioning, quality of life, and patient or caregiver impression of change. We also examined the safety of medicinal cannabinoids for mental health symptoms and disorders, including all-cause, serious, and treatment-related adverse events and study withdrawals.		
EATING DISORDERS			
Weight in anorexia nervosa			
McKee *et al.* (2021)	The aim of this systematic review and meta-analyses is to not only offer the most recent examination of the literature in this area, but as well approach the clinical indications for [cannabinoid-based products] in mental health from the lens of a health regulatory board; to review high-level evidence in a systematic review/meta-analyses process	THC products vs placebo	Very low-certainty evidence indicating significant increase in body weight with treatment with dronabinol compared with placebo (1 RCT) in adults with anorexia nervosa. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Trial length was 12 weeks with 4 weeks of treatment with dronabinol.
Rosager *et al.* (2021)	To identify all randomized controlled clinical trials that have exposed patients with anorexia nervosa to cannabinoids and assessed the effects on (1) weight and (2) other outcomes	THC products vs placebo	Very low-certainty evidence indicating significantly higher weight gain with treatment with dronabinol compared with placebo (1 RCT) in adults with anorexia nervosa. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 4 weeks; no follow-up period was reported.
Rosager *et al.* (2021)	To identify all randomized controlled clinical trials that have exposed patients with anorexia nervosa to cannabinoids and assessed the effects on (1) weight and (2) other outcomes	Cannabis products vs active comparator	Very low-certainty evidence indicating no significant difference in weight change between cannabis and diazepam (1 RCT) in adults with anorexia nervosa. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 5 weeks, no follow-up period was reported.
SUBSTANCE DEPENDENCE			
Withdrawal symptoms/discomfort in cannabis use disorder			
McKee *et al.* (2021)	The aim of this systematic review and meta-analyses is to not only offer the most recent examination of the literature in this area, but as well approach the clinical indications for [cannabinoid-based products] in mental health from	THC products vs placebo	Very low-certainty evidence indicating significantly improved withdrawal symptoms with treatment with dronabinol compared with placebo, in combination with motivational enhancement and relapse prevention therapy (1 RCT) in adults with cannabis use disorder. The certainty of evidence was downgraded to very

Author (year)	Research question	Intervention categorisation	Evidence summary
	the lens of a health regulatory board; to review high-level evidence in a systematic review/meta-analyses process		low because the outcome was informed by a single RCT. Trial length was 12 weeks.
McKee *et al.* (2021)	The aim of this systematic review and meta-analyses is to not only offer the most recent examination of the literature in this area, but as well approach the clinical indications for [cannabinoid-based products] in mental health from the lens of a health	THC products vs placebo	Very low-certainty evidence indicating no significant difference in withdrawal discomfort between dronabinol and placebo (2 RCTs) in a meta-analysis of adults with cannabis use disorder. Trial length ranged 40-51 days.
McKee *et al.* (2021)	The aim of this systematic review and meta-analyses is to not only offer the most recent examination of the literature in this area, but as well approach the clinical indications for [cannabinoid-based products] in mental health from the lens of a health regulatory board; to review high-level evidence in a systematic review/meta-analyses process	THC:CBD products vs placebo	Moderate-certainty evidence indicating no significant difference in withdrawal discomfort between nabiximols and placebo (4 RCTs) in a meta-analysis of adults with cannabis use disorder. Trial length ranged 8-12 weeks for three studies, with one study reporting a 6-day treatment regimen and 28-day follow-up period.
Cravings in cannabis use disorder			
McKee *et al.* (2021)	The aim of this systematic review and meta-analyses is to not only offer the most recent examination of the literature in this area, but as well approach the clinical indications for [cannabinoid-based products] in mental health from the lens of a health regulatory board; to review high-level evidence in a systematic review/meta-analyses process	THC:CBD products vs placebo	Very low-certainty evidence indicating no significant difference in cravings between nabiximols and placebo (2 RCTs, narrative synthesis) in adults with cannabis use disorder. Trial length ranged 8-12 weeks.
Treatment retention/abstinence in cannabis use disorder			
McKee *et al.* (2021)	The aim of this systematic review and meta-analyses is to not only offer the most recent examination of the literature in this area, but as well approach the clinical indications for [cannabinoid-based products] in mental health from the lens of a health regulatory board; to review high-level evidence in a systematic review/meta-analyses process	THC products vs placebo	Very low-certainty evidence indicating significantly improved treatment retention after 8 weeks with treatment with dronabinol compared with placebo, in combination with motivational enhancement and relapse prevention therapy (1 RCT) in adults with cannabis use disorder. However, this study observed no difference between the groups in abstinence after 2 weeks. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Trial length was 12 weeks.

Author (year)	Research question	Intervention categorisation	Evidence summary
McKee *et al.* (2021)	The aim of this systematic review and meta-analyses is to not only offer the most recent examination of the literature in this area, but as well approach the clinical indications for [cannabinoid-based products] in mental health from the lens of a health regulatory board; to review high-level evidence in a systematic review/meta-analyses process	THC:CBD products vs placebo	Low certainty mixed evidence for a significant difference in treatment retention/abstinence between nabiximols and placebo (3 RCTs, narrative synthesis) in adults with cannabis use disorder. Two RCTs reported no difference between groups. A third study reported significantly improved treatment retention with treatemnt with nabiximols compared with placebo; however, the effects were not observed beyond three days after cessation of treatment. Trial length was 12 weeks for the two studies reporting null findings, and the study with positive findings reported a 6-day treatment regimen and 28-day follow-up period.
Cannabis consumption (amounts) in cannabis use disorder			
McKee *et al.* (2021)	The aim of this systematic review and meta-analyses is to not only offer the most recent examination of the literature in this area, but as well approach the clinical indications for [cannabinoid-based products] in mental health from the lens of a health regulatory board; to review high-level evidence in a systematic review/meta-analyses process	THC products vs placebo	Very low-certainty evidence indicating no significant difference in amount of cannabis consumed between dronabinol and placebo, in combination with motivational enhancement and relapse prevention therapy (1 RCT) in adults with cannabis use disorder. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Trial length was 12 weeks.
McKee *et al.* (2021)	The aim of this systematic review and meta-analyses is to not only offer the most recent examination of the literature in this area, but as well approach the clinical indications for [cannabinoid-based products] in mental health from the lens of a health regulatory board; to review high-level evidence in a systematic review/meta-analyses process	THC products vs placebo	Very low-certainty evidence indicating no significant difference in amount of cannabis consumed between nabilone and placebo (1 RCT) in adults with cannabis use disorder. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Trial length was 10 weeks.
McKee *et al.* (2021)	The aim of this systematic review and meta-analyses is to not only offer the most recent examination of the literature in this area, but as well approach the clinical indications for [cannabinoid-based products] in mental health from the lens of a health regulatory board; to review high-level evidence in a systematic review/meta-analyses process	THC:CBD products vs placebo	Very low-certainty evidence indicating significant reduction in amount of cannabis consumed with treatment with nabiximols compared with placebo (in combination with cognitive behavioural therapy) (1 RCT) in adults with cannabis use disorder. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Trial length was 12 weeks.

Author (year)	Research question	Intervention categorisation	Evidence summary
Maintenance (reduction in use and reduction in cravings) in cannabis use disorder			
McKee *et al.* (2021)	The aim of this systematic review and meta-analyses is to not only offer the most recent examination of the literature in this area, but as well approach the clinical indications for [cannabinoid-based products] in mental health from the lens of a health regulatory board; to review high-level evidence in a systematic review/meta-analyses process	THC products vs placebo	Very low-certainty evidence indicating significant improvement in maintenance (reduction in use and reduction in cravings) with treatment with dronabinol compared with placebo (3 RCTs, narrative synthesis) in adults with cannabis use disorder. Trial length ranged 40-51 days for two studies, with one study reporting 3 treatment sessions separated by at least 7 days.
Cravings in opioid use disorder			
McKee *et al.* (2021)	The aim of this systematic review and meta-analyses is to not only offer the most recent examination of the literature in this area, but as well approach the clinical indications for [cannabinoid-based products] in mental health from the lens of a health regulatory board; to review high-level evidence in a systematic review/meta-analyses process	CBD products vs placebo	Very low-certainty evidence indicating significantly less craving and anxiety reponses with treatment with Epidiolex (CBD) compared with placebo (1 RCT) in adults with opioid use disorder. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Trial length was 6 weeks.
Withdrawal symptoms in opioid use disorder/opioid dependence			
McKee *et al.* (2021)	The aim of this systematic review and meta-analyses is to not only offer the most recent examination of the literature in this area, but as well approach the clinical indications for [cannabinoid-based products] in mental health from the lens of a health regulatory board; to review high-level evidence in a systematic review/meta-analyses process	THC products vs placebo	Low-certainty evidence indicating some degree of improved withdrawal symptoms with treatment with dronabinol compared with placebo (2 RCTs, narrative synthesis) in adults with opioid use disorder, with one RCT reporting improvement and the other reporting weak but short-lived effects. Trial length ranged 5-8 weeks.
de Aquino *et al.* (2022)	Investigating opioid withdrawal-alleviating effects of both cannabis and THC among opioid-dependent persons, regardless of [opioid use disorder] treatment status	THC products vs placebo	Very low-certainty evidence indicating significant reduction in opioid withdrawal symptoms with treatment with dronabinol compared with placebo (1 RCT) in adults with opioid dependence. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 8 days with follow-up of 5 weeks.
de Aquino *et al.* (2022)	Investigating opioid withdrawal-alleviating effects of both cannabis and THC among opioid-dependent	THC products vs active comparator	Very low-certainty evidence indicating significant reduction in opioid withdrawal symptoms with treatment with oxycodone

Author (year)	Research question	Intervention categorisation	Evidence summary
	persons, regardless of [opioid use disorder] treatment status		compared with dronabinol (2 RCTs using the same dataset; narrative synthesis) in adults with opioid dependence. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 5 weeks, no follow-up period was reported.
Tobacco use/cravings in tobacco use disorder			
McKee *et al.* (2021)	The aim of this systematic review and meta-analyses is to not only offer the most recent examination of the literature in this area, but as well approach the clinical indications for [cannabinoid-based products] in mental health from the lens of a health regulatory board; to review high-level evidence in a systematic review/meta-analyses process	CBD products vs placebo	Very low-certainty evidence indicating significant reduction in cigarettes smoked with treatment with CBD compared with placebo (1 RCT) in adults with tobacco use disorder. Nicotine craving fell significantly during the treatment phase but was not maintained at follow-up. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment was administered on two days, separated by one week, with a 21-day follow-up.
NEURODEVELOPMENTAL DISORDERS			
Attention deficit hyperactivity disorder (ADHD) symptoms			
Black *et al.* (2019)	To examine the available evidence for all types of medicinal cannabinoids and all study designs (controlled and observational) to ascertain the impact of medicinal cannabinoids on remission from and symptoms of depression, anxiety, post-traumatic stress disorder, and psychosis, as well as symptoms of attention deficit hyperactivity disorder (ADHD) and Tourette syndrome, either as the primary disorder or secondary to other disorders; and the impact of medicinal cannabinoids on outcomes including global functioning, quality of life, and patient or caregiver impression of change. We also examined the safety of medicinal cannabinoids for mental health symptoms and disorders, including all-cause, serious, and treatment-related adverse events and study withdrawals.	THC:CBD products vs placebo	Very low-certainty evidence indicating no significant difference in symptoms of ADHD between nabiximols and placebo (1 RCT) in adults with ADHD. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 6 weeks, no follow-up period was reported.
McKee *et al.* (2021)	The aim of this systematic review and meta-analyses is to not only offer the most recent examination of the literature in this area, but as	THC:CBD products vs placebo	Very low-certainty evidence indicating no significant difference in cognitive performance and activity levels between nabiximols and placebo (1 RCT) in adults with ADHD. The certainty of

Author (year)	Research question	Intervention categorisation	Evidence summary
	well approach the clinical indications for [cannabinoid-based products] in mental health from the lens of a health regulatory board; to review high-level evidence in a systematic review/meta-analyses process		evidence was downgraded to very low because the outcome was informed by a single RCT. Trial length was 6 weeks.
Tic severity in Tourette's syndrome			
Black *et al.* (2019)	To examine the available evidence for all types of medicinal cannabinoids and all study designs (controlled and observational) to ascertain the impact of medicinal cannabinoids on remission from and symptoms of depression, anxiety, post-traumatic stress disorder, and psychosis, as well as symptoms of attention deficit hyperactivity disorder (ADHD) and Tourette syndrome, either as the primary disorder or secondary to other disorders; and the impact of medicinal cannabinoids on outcomes including global functioning, quality of life, and patient or caregiver impression of change. We also examined the safety of medicinal cannabinoids for mental health symptoms and disorders, including all-cause, serious, and treatment-related adverse events and study withdrawals.	THC products vs placebo	Very low-certainty evidence indicating no significant difference in tic severity between THC and placebo (2 RCTs) in a meta-analysis of adults with Tourette syndrome. Treatment duration ranged from 1 day to 6 weeks, no follow-up period was reported.
McKee *et al.* (2021)	The aim of this systematic review and meta-analyses is to not only offer the most recent examination of the literature in this area, but as well approach the clinical indications for [cannabinoid-based products] in mental health from the lens of a health regulatory board; to review high-level evidence in a systematic review/meta-analyses process	THC products vs placebo	Very low-certainty evidence indicating significant improvement in global tic scores and tic frequency and severity with treatment with dronabinol compared with placebo (2 RCTs, narrative synthesis) in adults with Tourette syndrome. Trial length ranged 4 to 6 weeks.
PALLIATIVE CARE			
PAIN-RELATED OUTCOMES			
Pain reduction of 30% or greater in cancer			
Mucke *et al.* (2018a)	To evaluate the efficacy, tolerability, and safety of cannabinoids as an adjunct or complementary therapy in palliative medicine	Mixed cannabinoids vs placebo	Low-certainty evidence indicating significantly greater likelihood of pain reduction of ≥ 30% with treatment with cannabinoids (THC:CBD spray, THC extract) compared with placebo (1 RCT) in

Author (year)	Research question	Intervention categorisation	Evidence summary
			adults with cancer. Treatment duration ranged from 16 days to 9 weeks, no follow-up period was reported.
NUTRITION-RELATED OUTCOMES			
Body weight change in cancer			
Mucke *et al.* (2018a)	To evaluate the efficacy, tolerability, and safety of cannabinoids as an adjunct or complementary therapy in palliative medicine	Mixed cannabinoids vs placebo	Very low-certainty evidence indicating no significant difference in weight gain between cannabinoids and placebo (1 RCT) in adults with cancer. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 6 weeks, no follow-up period was reported.
Mucke *et al.* (2018a)	To evaluate the efficacy, tolerability, and safety of cannabinoids as an adjunct or complementary therapy in palliative medicine	THC products vs active comparator	Very low-certainty evidence indicating significantly greater weight gain with treatment with megestrol acetate compared with dronabinol (1 RCT) in adults with cancer. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration ranged 57-80 days, no follow-up period was reported.
Caloric intake in cancer			
Mucke *et al.* (2018a)	To evaluate the efficacy, tolerability, and safety of cannabinoids as an adjunct or complementary therapy in palliative medicine	THC products vs placebo	Very low-certainty evidence indicating no significant difference in caloric intake between dronabinol and placebo (1 RCT) in adults with cancer. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 22 days, no follow-up period was reported.
Appetite in cancer			
Mucke *et al.* (2018a)	To evaluate the efficacy, tolerability, and safety of cannabinoids as an adjunct or complementary therapy in palliative medicine	Mixed cannabinoids and cannabis products vs placebo	Very low-certainty evidence indicating no significant difference in appetite between cannabis/cannabinoids and placebo (3 RCTs) in a meta-analysis of adults with cancer. Treatment duration ranged 16 days to 6 weeks, no follow-up period was reported.
Mucke *et al.* (2018a)	To evaluate the efficacy, tolerability, and safety of cannabinoids as an adjunct or complementary therapy in palliative medicine	THC products vs active comparator	Very low-certainty evidence indicating significantly improved appetite with treatment with megestrol acetate compared with dronabinol (1 RCT) in adults with cancer. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration ranged 57-80 days, no follow-up period was reported.
Nausea and vomiting in cancer			

Author (year)	Research question	Intervention categorisation	Evidence summary
Mucke *et al.* (2018a)	To evaluate the efficacy, tolerability, and safety of cannabinoids as an adjunct or complementary therapy in palliative medicine	Mixed cannabinoids vs placebo	Low-certainty evidence indicating no significant difference in weight gain between cannabinoids (THC:CBD, THC extract) and placebo (2 RCTs) in a meta-analysis of adults with cancer. Treatment duration was 16 weeks, no follow-up period was reported.
Body weight change in HIV			
Mucke *et al.* (2018a)	To evaluate the efficacy, tolerability, and safety of cannabinoids as an adjunct or complementary therapy in palliative medicine	Mixed cannabinoids and cannabis products vs placebo	Low-certainty evidence indicating no significant difference in weight gain between cannabinoids (dronabinol, cannabis) and placebo (2 RCTs) in a meta-analysis of adults with HIV. Treatment duration ranged 3-6 weeks, no follow-up period was reported.
Mucke *et al.* (2018a)	To evaluate the efficacy, tolerability, and safety of cannabinoids as an adjunct or complementary therapy in palliative medicine	THC products vs active comparator	Very low-certainty evidence indicating significantly greater weight gain with treatment with megestrol acetate compared with dronabinol (1 RCT) in adults with HIV. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 12 weeks, no follow-up period was reported.
Mucke *et al.* (2018a)	To evaluate the efficacy, tolerability, and safety of cannabinoids as an adjunct or complementary therapy in palliative medicine	Cannabis vs THC	Very low-certainty evidence indicating significantly greater weight gain with treatment with herbal cannabis compared with dronabinol (1 RCT) in adults with HIV. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 3 weeks, no follow-up period was reported.
Appetite in HIV			
Mucke *et al.* (2018a)	To evaluate the efficacy, tolerability, and safety of cannabinoids as an adjunct or complementary therapy in palliative medicine	THC products vs placebo	Very low-certainty evidence indicating significantly increased appetite with treatment with dronabinol compared with placebo (1 RCT) in adults with HIV. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 6 weeks, no follow-up period was reported.
Nausea and vomiting in HIV			
Mucke *et al.* (2018a)	To evaluate the efficacy, tolerability, and safety of cannabinoids as an adjunct or complementary therapy in palliative medicine	THC products vs placebo	Very low-certainty evidence indicating no significant difference in nausea and vomiting between dronabinol and placebo (1 RCT) in adults with HIV. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 6 weeks, no follow-up period was reported.

Author (year)	Research question	Intervention categorisation	Evidence summary
Mucke *et al.* (2018a)	To evaluate the efficacy, tolerability, and safety of cannabinoids as an adjunct or complementary therapy in palliative medicine	THC products vs active comparator	Very low-certainty evidence indicating no significant difference in nausea and vomiting between dronabinol and megestrol acetate (1 RCT) in adults with HIV. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 12 weeks, no follow-up period was reported.
Body weight change in Alzheimer's Disease			
Mucke *et al.* (2018a)	To evaluate the efficacy, tolerability, and safety of cannabinoids as an adjunct or complementary therapy in palliative medicine	THC products vs placebo	Very low-certainty evidence indicating significantly greater weight gain with treatment with dronabinol compared with placebo (1 RCT) in adults with Alzheimer's Disease. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 6 weeks per treatment period, no follow-up period was reported.
Caloric intake in Alzheimer's Disease			
Mucke *et al.* (2018a)	To evaluate the efficacy, tolerability, and safety of cannabinoids as an adjunct or complementary therapy in palliative medicine	THC products vs placebo	Very low-certainty evidence indicating no significant difference in caloric intake between dronabinol and placebo (1 RCT) in adults with Alzheimer's Disease. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 6 weeks per treatment period, no follow-up period was reported.
SLEEP-RELATED OUTCOMES			
Sleeping dysfunction in cancer			
Mucke *et al.* (2018a)	To evaluate the efficacy, tolerability, and safety of cannabinoids as an adjunct or complementary therapy in palliative medicine	Mixed cannabinoids vs placebo	Very low-certainty evidence indicating no significant difference in sleeping disorder between cannabinoids (dronabinol, THC:CBD spray) and placebo (2 RCTs) in a meta-analysis of adults with cancer. Treatment duration ranged from 16-22 days, no follow-up period was reported.
Fatigue			
Mucke *et al.* (2018a)	To evaluate the efficacy, tolerability, and safety of cannabinoids as an adjunct or complementary therapy in palliative medicine	NA	No evidence found for this outcome
MENTAL HEALTH / WELLBEING			
Depressive mood in HIV			
Mucke *et al.* (2018a)	To evaluate the efficacy, tolerability, and safety of cannabinoids as an adjunct or complementary therapy in palliative medicine	THC products vs active comparator	Very low-certainty evidence indicating no significant difference in depressive mood between dronabinol and megestrol acetate (1 RCT) in adults with HIV. The certainty of evidence was

Author (year)	Research question	Intervention categorisation	Evidence summary
			downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 12 weeks, no follow-up period was reported.
Health-related quality of life in cancer			
Mucke *et al.* (2018a)	To evaluate the efficacy, tolerability, and safety of cannabinoids as an adjunct or complementary therapy in palliative medicine	THC products vs active comparator	Very low-certainty evidence indicating significantly improved health-related quality of life with treatment with megestrol acetate compared with dronabinol (1 RCT) in adults with cancer. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration ranged 57-80 days, no follow-up period was reported.
Health-related quality of life in HIV			
Mucke *et al.* (2018a)	To evaluate the efficacy, tolerability, and safety of cannabinoids as an adjunct or complementary therapy in palliative medicine	THC products vs active comparator	Very low-certainty evidence indicating no significant difference in health-related quality of life between dronabinol and megestrol acetate (1 RCT) in adults with HIV. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 12 weeks, no follow-up period was reported.
Negative affect in Alzheimer's Disease			
Mucke *et al.* (2018a)	To evaluate the efficacy, tolerability, and safety of cannabinoids as an adjunct or complementary therapy in palliative medicine	THC products vs placebo	Very low-certainty evidence indicating significant reduction in negative affect with treatment with dronabinol compared with placebo (1 RCT) in adults with Alzheimer's Disease. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 6 weeks per treatment period, no follow-up period was reported.
RHEUMATIC DISEASES			
PAIN-RELATED OUTCOMES			
Pain intensity			
Fitzcharles *et al.* (2016a)	To assess the efficacy, tolerability, and safety of cannabinoids (phyto- and syntheto-) in the management of rheumatic diseases	THC:CBD products vs placebo	Very low-certainty evidence indicating no significant difference in pain intensity between nabiximols and placebo (1 RCT) in adults with rheumatic disease. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 5 weeks, no follow-up period was reported.

Author (year)	Research question	Intervention categorisation	Evidence summary
Fitzcharles *et al.* (2016a)	To assess the efficacy, tolerability, and safety of cannabinoids (phyto- and syntheto-) in the management of rheumatic diseases	THC products vs placebo	Very low-certainty evidence indicating significant improvement in pain intensity with treatment with nabilone compared with placebo (1 RCT) in adults with rheumatic disease. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 8 weeks, no follow-up period was reported.
Fitzcharles *et al.* (2016a)	To assess the efficacy, tolerability, and safety of cannabinoids (phyto- and syntheto-) in the management of rheumatic diseases	THC products vs active comparator	Very low-certainty evidence indicating no significant difference in pain intensity between nabilone and amitriptyline (1 RCT) in adults with rheumatic disease. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 2 weeks per treatment period, no follow-up period was reported.
Fitzcharles *et al.* (2016b)	[To examine] the literature for evidence of the efficacy, tolerability, and safety of cannabinoids in chronic spinal pain, [fibromyalgia syndrome], [osteoarthritis], and [rheumatoid arthritis] pain	THC products vs placebo	Very low certainty mixed evidence for a significant difference in pain intensity between nabilone and placebo (2 RCTs, narrative synthesis) in adults with rheumatic disease, with one RCT reporting no difference and a second reporting a significant improvement in pain intensity with treatment with nabilone compared to placebo. Treatment duration was 4 weeks per treatment period, and one study had a 16-week follow-up period.
Fitzcharles *et al.* (2016b)	[To examine] the literature for evidence of the efficacy, tolerability, and safety of cannabinoids in chronic spinal pain, [fibromyalgia syndrome], [osteoarthritis], and [rheumatoid arthritis] pain	THC products vs active comparator	Very low-certainty evidence indicating no significant difference in pain intensity between nabilone and amitriptyline (1 RCT) in adults with rheumatic disease. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 2 weeks per treatment period, no follow-up period was reported.
Morning pain on movement			
Fitzcharles *et al.* (2016a)	To assess the efficacy, tolerability, and safety of cannabinoids (phyto- and syntheto-) in the management of rheumatic diseases	THC:CBD products vs placebo	Very low-certainty evidence indicating significant improvements in morning pain on movement with treatment with nabiximols compared with placebo (1 RCT) in adults with rheumatic disease. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 5 weeks, no follow-up period was reported.
Morning pain at rest			
Fitzcharles *et al.* (2016a)	To assess the efficacy, tolerability, and safety of cannabinoids (phyto- and syntheto-) in the management of rheumatic diseases	THC:CBD products vs placebo	Very low-certainty evidence indicating significant improvements in morning pain at rest with treatment with nabiximols compared with placebo (1 RCT) in adults with rheumatic disease. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 5 weeks, no follow-up period was reported.

Author (year)	Research question	Intervention categorisation	Evidence summary
Fitzcharles *et al.* (2016b)	[To examine] the literature for evidence of the efficacy, tolerability, and safety of cannabinoids in chronic spinal pain, [fibromyalgia syndrome], [osteoarthritis], and [rheumatoid arthritis] pain	THC:CBD products vs placebo	Very low-certainty evidence indicating significant improvements in morning pain at rest with treatment with nabiximols compared with placebo (1 RCT) in adults with rheumatic disease. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 5 weeks, no follow-up period was reported.
Pain reduction of 50% or greater			
Fitzcharles *et al.* (2016b)	[To examine] the literature for evidence of the efficacy, tolerability, and safety of cannabinoids in chronic spinal pain, [fibromyalgia syndrome], [osteoarthritis], and [rheumatoid arthritis] pain	NA	No evidence found for this outcome
Pain reduction of 50% or greater in fibromyalgia			
Walitt *et al.* (2016)	To assess the efficacy, tolerability and safety of cannabinoids for fibromyalgia symptoms in adults	NA	No evidence found for this outcome
GLOBAL IMPRESSION OF CHANGE			
Patient global impression of change			
Fitzcharles *et al.* (2016b)	[To examine] the literature for evidence of the efficacy, tolerability, and safety of cannabinoids in chronic spinal pain, [fibromyalgia syndrome], [osteoarthritis], and [rheumatoid arthritis] pain	NA	No evidence found for this outcome
Walitt *et al.* (2016)	To assess the efficacy, tolerability and safety of cannabinoids for fibromyalgia symptoms in adults	NA	No evidence found for this outcome
SLEEP-RELATED OUTCOMES			
Sleep quality			
Fitzcharles *et al.* (2016a)	To assess the efficacy, tolerability, and safety of cannabinoids (phyto- and syntheto-) in the management of rheumatic diseases	THC:CBD products vs placebo	Very low-certainty evidence indicating significant improvements in sleep quality with treatment with nabiximols compared with placebo (1 RCT) in adults with rheumatic disease. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 5 weeks, no follow-up period was reported.
Fitzcharles *et al.* (2016a)	To assess the efficacy, tolerability, and safety of cannabinoids (phyto- and syntheto-) in the management of rheumatic diseases	THC products vs active comparator	Very low-certainty evidence indicating no significant difference in sleep quality between nabilone and amitriptyline (1 RCT) in adults with rheumatic disease; both groups reported significant improvements in sleep quality, but onlny a marginal advantage was reported for the nabilone group on one of two metrics. The

Author (year)	Research question	Intervention categorisation	Evidence summary
			certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 2 weeks per treatment period, no follow-up period was reported.
QUALITY OF LIFE			
Quality of life			
Fitzcharles *et al.* (2016a)	To assess the efficacy, tolerability, and safety of cannabinoids (phyto- and syntheto-) in the management of rheumatic diseases	THC products vs placebo	Very low-certainty evidence indicating significant improvement in quality of life with treatment with nabilone compared with placebo (1 RCT) in adults with rheumatic disease. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 8 weeks, no follow-up period was reported.
Fitzcharles *et al.* (2016a)	To assess the efficacy, tolerability, and safety of cannabinoids (phyto- and syntheto-) in the management of rheumatic diseases	THC products vs active comparator	Very low-certainty evidence indicating no significant difference in quality of life between nabilone and amitriptyline (1 RCT) in adults with rheumatic disease. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 2 weeks per treatment period, no follow-up period was reported.
SPINAL CORD INJURY			
PAIN-RELATED OUTCOMES			
Pain intensity			
Thomas *et al.* (2022)	What is the current level of evidence on the effect of cannabis/cannabinoids upon pain intensity in [spinal cord injury]?	THC products vs active comparator	Very low-certainty evidence indicating significant improvement in pain intensity with treatment with low THC and high THC compared with placebo (1 RCT) in adults with spinal cord injury. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment was administered on single treatment days with minimum 3-day washout periods between testing days, no follow-up period was reported.
Thomas *et al.* (2022)	What is the current level of evidence on the effect of cannabis/cannabinoids upon pain intensity in [spinal cord injury]?	THC:CBD products vs placebo	Very low-certainty evidence indicating no significant difference in pain intensity between nabiximols and placebo (1 RCT) in adults with spinal cord injury. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 21-30 days, no follow-up period was reported.
Thomas *et al.* (2022)	What is the current level of evidence on the effect of cannabis/cannabinoids upon pain intensity in [spinal cord injury]?	THC products vs active comparator	Very low-certainty evidence indicating no significant difference in pain intensity between dronabinol and diphenhydramine (1 RCT) in adults with spinal cord injury. The certainty of evidence was downgraded to very low because the outcome was informed by a

Author (year)	Research question	Intervention categorisation	Evidence summary
			single RCT. Treatment duration was 56 days per treatment period, no follow-up period was reported.
MULTIPLE SCLEROSIS			
SPASTICITY-RELATED OUTCOMES			
Observer-rated spasticity (Ashworth scale)			
Torres-Moreno *et al.* (2018)	To evaluate the therapeutic efficacy and tolerability of medicinal cannabinoids to treat the symptoms of spasticity, pain, and bladder dysfunction in patients with [multiple sclerosis]	Mixed cannabinoids vs placebo	Moderate-certainty evidence indicating no significant difference in observer-rated spasticity between cannabis extract and placebo (4 RCTs) in a meta-analysis of adults with multiple sclerosis. Treatment duration ranged 4-20 weeks, no follow-up period was reported.
Torres-Moreno *et al.* (2018)	To evaluate the therapeutic efficacy and tolerability of medicinal cannabinoids to treat the symptoms of spasticity, pain, and bladder dysfunction in patients with [multiple sclerosis]	THC:CBD products vs placebo	Low-certainty evidence indicating no significant difference in observer-rated spasticity between nabiximols and placebo (8 RCTs) in a meta-analysis of adults with multiple sclerosis. Treatment duration ranged 6-50 weeks, no follow-up period was reported.
Torres-Moreno *et al.* (2018)	To evaluate the therapeutic efficacy and tolerability of medicinal cannabinoids to treat the symptoms of spasticity, pain, and bladder dysfunction in patients with [multiple sclerosis]	THC products vs active comparator	Moderate-certainty evidence indicating no significant difference in observer-rated spasticity between dronabinol and placebo (3 RCTs) in a meta-analysis of adults with multiple sclerosis. Treatment duration ranged 15-20 weeks, no follow-up period was reported.
Subjective spasticity			
Torres-Moreno *et al.* (2018)	To evaluate the therapeutic efficacy and tolerability of medicinal cannabinoids to treat the symptoms of spasticity, pain, and bladder dysfunction in patients with [multiple sclerosis]	Mixed cannabinoids vs placebo	Low-certainty evidence indicating significant improvement in subjective spasticity with treatment with cannabis extract compared with placebo (3 RCTs) in a meta-analysis of adults with multiple sclerosis. Treatment duration ranged 14-15 weeks, no follow-up period was reported.
Torres-Moreno *et al.* (2018)	To evaluate the therapeutic efficacy and tolerability of medicinal cannabinoids to treat the symptoms of spasticity, pain, and bladder dysfunction in patients with [multiple sclerosis]	THC:CBD products vs placebo	Low-certainty evidence indicating significant improvement in subjective spasticity with treatment with nabiximols compared with placebo (9 RCTs) in a meta-analysis of adults with multiple sclerosis. Treatment duration ranged 6-50 weeks, no follow-up period was reported.
Torres-Moreno *et al.* (2018)	To evaluate the therapeutic efficacy and tolerability of medicinal cannabinoids to treat the symptoms of spasticity, pain, and bladder dysfunction in patients with [multiple sclerosis]	THC products vs active comparator	Low-certainty evidence indicating no significant difference in subjective spasticity between dronabinol and placebo (3 RCTs) in a meta-analysis of adults with multiple sclerosis. Treatment duration ranged 15 weeks to 3 years, no follow-up period was reported.

Author (year)	Research question	Intervention categorisation	Evidence summary
Filippini *et al.* (2022)	To assess benefit and harms of cannabinoids including synthetic, or herbal and plant-derived cannabinoids, for symptomatic treatment in [multiple sclerosis]	Mixed cannabinoids vs placebo	Low-certainty evidence indicating significantly greater reduction in spasticity with treatment with cannabinoids compared with placebo groups (7 RCTs) in a meta-analysis of adults with multiple sclerosis. Treatment duration ranged 4-14 weeks, no follow-up period was reported.
Spasticity reduction of 30% or greater			
Filippini *et al.* (2022)	To assess benefit and harms of cannabinoids including synthetic, or herbal and plant-derived cannabinoids, for symptomatic treatment in [multiple sclerosis]	THC:CBD products vs placebo	Low-certainty evidence indicating significantly greater likelihood of spasticity reduction of 30% or greater with treatment with cannabinoids compared with placebo groups (5 RCTs) in a meta-analysis of adults with multiple sclerosis. Treatment duration ranged 6-14 weeks, no follow-up period was reported.
PAIN-RELATED OUTCOMES			
Pain			
Torres-Moreno *et al.* (2018)	To evaluate the therapeutic efficacy and tolerability of medicinal cannabinoids to treat the symptoms of spasticity, pain, and bladder dysfunction in patients with [multiple sclerosis]	Mixed cannabinoids vs placebo	Low-certainty evidence indicating significant improvement in pain with treatment with cannabis extract compared with placebo (3 RCTs) in a meta-analysis of adults with multiple sclerosis. Treatment duration ranged 14-15 weeks, no follow-up period was reported.
Torres-Moreno *et al.* (2018)	To evaluate the therapeutic efficacy and tolerability of medicinal cannabinoids to treat the symptoms of spasticity, pain, and bladder dysfunction in patients with [multiple sclerosis]	THC:CBD products vs placebo	Low-certainty evidence indicating no significant difference in pain between nabiximols and placebo (6 RCTs) in a meta-analysis of adults with multiple sclerosis. Treatment duration ranged 5-15 weeks, no follow-up period was reported.
Torres-Moreno *et al.* (2018)	To evaluate the therapeutic efficacy and tolerability of medicinal cannabinoids to treat the symptoms of spasticity, pain, and bladder dysfunction in patients with [multiple sclerosis]	THC products vs placebo	Very low-certainty evidence indicating significant improvement in pain (borderline statistical significance) with treatment with nabilone compared with placebo (1 RCT) in adults with multiple sclerosis. Treatment duration was 9 weeks, no follow-up period was reported.
Torres-Moreno *et al.* (2018)	To evaluate the therapeutic efficacy and tolerability of medicinal cannabinoids to treat the symptoms of spasticity, pain, and bladder dysfunction in patients with [multiple sclerosis]	THC products vs placebo	Low-certainty evidence indicating no significant difference in pain between dronabinol and placebo (4 RCTs) in a meta-analysis of adults with multiple sclerosis. Treatment duration ranged 9 weeks to 3 years, no follow-up period was reported.
Filippini *et al.* (2022)	To assess benefit and harms of cannabinoids including synthetic, or herbal and plant-derived cannabinoids, for symptomatic treatment in [multiple sclerosis]	Mixed cannabinoids vs placebo	Low-certainty evidence indicating significant improvements in neuropathic pain with treatment with cannabinoids compared with placebo groups (8 RCTs) in a meta-analysis of adults with multiple sclerosis. Treatment duration ranged 3-16 weeks, no follow-up period was reported.
Pain relief of 50% or greater			

Author (year)	Research question	Intervention categorisation	Evidence summary
Filippini *et al.* (2022)	To assess benefit and harms of cannabinoids including synthetic, or herbal and plant-derived cannabinoids, for symptomatic treatment in [multiple sclerosis]	THC products vs placebo	Very low-certainty evidence indicating significantly greater likelihood of pain relief of 50% or greater with treatment with dronabinol compared with placebo (1 RCT) in adults with multiple sclerosis. The certainty of evidence was downgraded to very low because the outcome was informed by a single RCT. Treatment duration was 3 weeks, no follow-up period was reported.
BLADDER-RELATED OUTCOMES			
Bladder dysfunction			
Torres-Moreno *et al.* (2018)	To evaluate the therapeutic efficacy and tolerability of medicinal cannabinoids to treat the symptoms of spasticity, pain, and bladder dysfunction in patients with [multiple sclerosis]	Mixed cannabinoids vs placebo	Moderate-certainty evidence indicating significant improvement in bladder dysfunction with treatment with cannabis extract compared with placebo (3 RCTs) in a meta-analysis of adults with multiple sclerosis. Treatment duration ranged 4-15 weeks, no follow-up period was reported.
Torres-Moreno *et al.* (2018)	To evaluate the therapeutic efficacy and tolerability of medicinal cannabinoids to treat the symptoms of spasticity, pain, and bladder dysfunction in patients with [multiple sclerosis]	THC:CBD products vs placebo	Low-certainty evidence indicating no significant difference in bladder dysfunction between nabiximols and placebo (4 RCTs) in a meta-analysis of adults with multiple sclerosis. Treatment duration ranged 6-15 weeks, no follow-up period was reported.
Torres-Moreno *et al.* (2018)	To evaluate the therapeutic efficacy and tolerability of medicinal cannabinoids to treat the symptoms of spasticity, pain, and bladder dysfunction in patients with [multiple sclerosis]	THC products vs placebo	Low-certainty evidence indicating no significant difference in bladder dysfunction between dronabinol and placebo (3 RCTs) in a meta-analysis of adults with multiple sclerosis. treatment duration ranged 15 weeks to 3 years, no follow-up period was reported.
QUALITY OF LIFE			
Health-related quality of life			
Filippini *et al.* (2022)	To assess benefit and harms of cannabinoids including synthetic, or herbal and plant-derived cannabinoids, for symptomatic treatment in [multiple sclerosis]	Mixed cannabinoids vs placebo	Low-certainty evidence indicating no significant difference in health-related quality of life between cannabinoids and placebo (8 RCTs) in a meta-analysis of adults with multiple sclerosis. Treatment duration ranged 3 weeks to 36 months, no follow-up period was reported.
GLOBAL IMPRESSION OF CHANGE			
Patient-rated global impression of change			
Filippini *et al.* (2022)	To assess benefit and harms of cannabinoids including synthetic, or herbal and plant-derived cannabinoids, for symptomatic treatment in [multiple sclerosis]	Mixed cannabinoids vs placebo	Low-certainty evidence indicating significant improvement in patient global impression of change with treatment with cannabinoids compared with placebo (8 RCTs) in a meta-analysis of adults with multiple sclerosis. Treatment duration was 4-50 weeks, no follow-up period was reported.

Mixed health conditions (efficacy)

Author (year)	Research question	Intervention categorisation	Evidence summary
MIXED HEALTH CONDITIONS (EFFICACY)			
PAIN			
Pain intensity			
Bialas *et al.* (2022)	To assess the long-term effectiveness, tolerability and safety of cannabis-based medicines in the management of chronic noncancer pain in patients of any age in long-term observational studies	Mixed cannabinoids and cannabis products vs. placebo	Very low-certainty evidence indicated significant improvement in pain intensity in the medicinal cannabis compared with placebo groups comprising adult populations with various health conditions (six prospective cohort studies). Trial durations ranged from 6 to 12 months; no follow-up was reported.
Longo *et al.* (2021)	In adults with chronic pain, what is the effect of cannabis on pain intensity?	Mixed cannabinoids and cannabis products vs. placebo	Very low-certainty evidence indicated mixed findings in pain intensity between the mixed cannabinoids and placebo groups comprising adult populations with various health conditions (10 RCTs, narrative synthesis). Five studies reported no significant improvement in the mixed cannabinoids compared with placebo groups, and five RCTs reported no significant difference between the mixed cannabinoids and cannabis compared with placebo groups. Trial durations ranged from 1 to 18 weeks, and no follow-up was reported.
Sainsbury *et al.* (2021)	To evaluate the effectiveness of cannabis-based medications as therapeutic agents compared to placebo intervention in patients with chronic neuropathic pain	Mixed cannabinoid and cannabis products vs. placebo	Low-certainty evidence indicated a significant improvement in pain intensity in the mixed cannabinoids and cannabis groups compared with placebo groups comprising adult populations with chronic neuropathic pain (six RCTs, meta-analysis). Intervention durations ranged from four 4-hour sessions to 14 days, and no follow-up was reported.
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	Mixed cannabinoid products vs. placebo	Low-certainty evidence indicated a significant improvement in pain intensity in extracted products with high ratios of THC to CBD compared with placebo groups comprising adult populations with fibromyalgia and multiple sclerosis (two RCTs, meta-analysis). Intervention durations ranged from 8 to 12 weeks; no follow-up was reported.

Author (year)	Research question	Intervention categorisation	Evidence summary
Giossi *et al.* (2022)	To conduct a systematic review with a meta-analysis to investigate the role of cannabinoids in the treatment of chronic primary pain	Mixed cannabinoid products vs. placebo	Low-certainty evidence indicated no significant difference in pain intensity between mixed cannabinoids and placebo groups of adults experiencing chronic pain (six RCTs, meta-analysis). Trial durations ranged from 2 days to 8 weeks; no follow-up was reported.
Meng *et al.* (2017)	To determine the analgesic efficacy of selective cannabinoids compared with conventional management or placebo for chronic [neuropathic pain] after at least 2 weeks after commencement of treatment	Mixed cannabinoid products vs. mixed control	High-certainty evidence indicated a significant improvement in pain intensity in the mixed cannabinoids compared with mixed control groups comprising adult populations with various health conditions experiencing chronic neuropathic pain (10 RCTs, meta-analysis). Trial durations ranged from 2 to 14 weeks, and no follow-up period was specified.
Meng *et al.* (2017) (subgroup analysis central pain)	To determine the analgesic efficacy of selective cannabinoids compared with conventional management or placebo for chronic [neuropathic pain] after at least 2 weeks after commencement of treatment	Mixed cannabinoid products vs. placebo	High-certainty evidence indicated a significant improvement in mixed cannabinoids compared with placebo groups in a meta-analysis (five RCTs, subgroup analysis) of adults with chronic neuropathic pain. Trial durations ranged from 2 to 14 weeks, and no follow-up period was specified.
Meng *et al.* (2017) (subgroup analysis peripheral pain)	To determine the analgesic efficacy of selective cannabinoids compared with conventional management or placebo for chronic [neuropathic pain] after at least 2 weeks after commencement of treatment	Mixed cannabinoid products vs. placebo	Moderate-certainty evidence indicated no significant difference between mixed cannabinoids compared with placebo groups in a meta-analysis (four RCTs, subgroup analysis) of adults with chronic neuropathic pain. Trial durations was 5 to 15 weeks, no follow-up period was reported.
Sainsbury *et al.* (2021)	To evaluate the effectiveness of cannabis-based medications as therapeutic agents compared to placebo intervention in patients with chronic neuropathic pain	Cannabis products vs. placebo	Low-certainty evidence indicated significant improvement in pain intensity in the THC compared with placebo groups comprising adult populations with chronic neuropathic pain (two RCTs, meta-analysis). Intervention durations ranged from three 150-minute sessions to 14 weeks; no follow-up was reported.
Price *et al.* (2022)	To evaluate the efficacy of medical cannabis in reducing pain in patients following spine surgery, for patients suffering from chronic low back or neck pain, and patients affected by previous spinal cord injury pain	Cannabis products vs. placebo	Very low-certainty evidence indicated significant improvement in pain intensity in cannabis compared with placebo groups comprising adult populations with spinal cord injury and multiple sclerosis (one RCT, Narrative synthesis). Intervention duration was three eight-hour sessions; follow-up was one, two and three-hour post-intervention.
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	Cannabis vs. usual care	Low-certainty evidence indicated mixed finding in cannabis and usual care in a population of adults with various health conditions (chronic non-cancer pain, neuropathic pain, musculoskeletal pain) (three prospective cohort studies, narrative review). Two studies reported no significant difference, one study reported significant improvement in cannabis compared with usual care (one prospective cohort study, narrative review). Treatment

Author (year)	Research question	Intervention categorisation	Evidence summary
			duration ranged from 12 weeks to 4 years, no follow-up was reported.
Meng *et al.* (2017)	To determine the analgesic efficacy of selective cannabinoids compared with conventional management or placebo for chronic [neuropathic pain] after at least 2 weeks after commencement of treatment	THC/CBD products vs. placebo	High-certainty evidence indicated significantly improved pain intensity in the THC:CBD (nabiximols) compared with placebo groups comprising adult populations with various health conditions experiencing chronic neuropathic pain (six RCTs, meta-analysis). Trial durations ranged from 2 to 14 weeks, and no follow-up period was specified.
Butler *et al.* (2015)	The review addresses the following key questions: 1) What are the benefits (short-term and long-term) of cannabis use for the treatment of non-cancer pain? 2) What are the harms (short-term and long-term) of cannabis use for the treatment of non-cancer pain?	THC/CBD products vs. placebo	Low-certainty evidence found a significant improvement in pain intensity in nabiximols compared with placebo groups comprising adult populations with neuropathic pain (four RCTs, meta-analysis). Trial durations ranged from 4 to 14 weeks; no follow-up was reported.
Butler *et al.* (2015)	The review addresses the following key questions: 1) What are the benefits (short-term and long-term) of cannabis use for the treatment of non-cancer pain? 2) What are the harms (short-term and long-term) of cannabis use for the treatment of non-cancer pain?	THC/CBD products vs. placebo	Very low-certainty evidence indicated no significant improvement in pain intensity in THC:CBD compared with placebo groups comprising adult populations with various health conditions (multiple sclerosis, allodynia) (three RCTs, meta-analysis). Trial durations ranged from 4 to 14 weeks; no follow-up was reported.
Oordt *et al.* (2021)	To investigate the efficacy, effectiveness, safety, cost-effectiveness, and budget impact of medical cannabis use in chronic pain and spasticity	THC/CBD products vs. placebo	Very low-certainty evidence indicated mixed findings on the efficacy of THC:CBD spray compared with placebo in pain intensity in a narrative review (seven RCTs) of adults with various health conditions. In six RCTs, no significant difference was reported between the THC:CBD and placebo groups (cancer, neuropathic pain). One RCT reported a significant improvement in the THC:CBD group for musculoskeletal pain in a population of adults with rheumatoid arthritis. Trial durations ranged from 3 to 14 weeks, and follow-up was conducted at the end of the intervention.
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	THC/CBD products vs. placebo	Low-certainty evidence indicated a significant improvement in pain intensity in extracted products with comparable compared with placebo groups comprising adults with various health conditions experiencing chronic pain (seven RCTs, meta-analysis). Intervention durations ranged from 4 to 15 weeks, and no follow-up was reported.
Sainsbury *et al.* (2021)	To evaluate the effectiveness of cannabis-based medications as therapeutic agents compared to	THC/CBD products vs. placebo	Moderate-certainty evidence indicated a significant improvement in pain intensity in the THC:CBD compared with placebo groups comprising adult populations with chronic neuropathic pain (five

Author (year)	Research question	Intervention categorisation	Evidence summary
	placebo intervention in patients with chronic neuropathic pain		RCTs, meta-analysis). Intervention durations ranged from 2 to 14 weeks, and no follow-up was reported.
Oordt *et al.* (2021)	To investigate the efficacy, effectiveness, safety, cost-effectiveness, and budget impact of medical cannabis use in chronic pain and spasticity	THC products vs. placebo	Very low-certainty evidence indicated a significant improvement in pain intensity in the THC (dronabinol) compared with placebo groups comprising an adult population with multiple sclerosis (one RCT, narrative synthesis). Trial duration was 16 weeks, and follow-up was conducted at the end of treatment.
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	THC products vs. placebo	Low-certainty evidence of a significant improvement in pain intensity in synthetic products with high ratios of THC to CBD compared with placebo groups comprising adult populations experiencing chronic pain in various health conditions (six RCTs, meta-analysis). Intervention durations ranged from 4 to 16 weeks.
Meng *et al.* (2017)	To determine the analgesic efficacy of selective cannabinoids compared with conventional management or placebo for chronic [neuropathic pain] after at least 2 weeks after commencement of treatment	THC products vs. placebo	Very low-certainty evidence indicated a significant improvement in pain intensity in the dronabinol compared with placebo groups comprising an adult population experiencing central neuropathic pain (one RCT, narrative synthesis). Trial duration was 3 weeks, with follow-up at the end of the intervention.
Vortubec (2022)	To explore the published evidence regarding effectiveness of cannabinoids in orofacial pain management in a dental setting	THC products vs. placebo	Very low-certainty evidence indicated no significant improvement in pain intensity in the THC (nabilone and intravenous THC) compared with placebo groups comprising adult populations experiencing orofacial pain (two RCTs, narrative synthesis). Trial duration was not reported clearly; however, the review authors reported follow-up every 7 days during the intervention and 28 days after the intervention in one RCT; and at the intervention midpoint, 30 minutes, 24 hours, and 1 month post-intervention in the other RCT.
Abdallah *et al.* (2020)	To evaluate analgesic outcomes in patients receiving cannabis compounds for acute pain management in the surgical setting.	THC products vs. placebo	Very low-certainty evidence indicated mixed findings in THC products compared with placebo. In a narrative review (two RCTs), one RCT reported no significant difference between the THC and placebo groups, whereas the other RCT reported significantly higher pain in the nabilone compared with placebo groups. Intervention durations ranged from 24 to 48 hours post-operation; no follow-up was reported.
Sainsbury *et al.* (2021)	To evaluate the effectiveness of cannabis-based medications as therapeutic agents compared to placebo intervention in patients with chronic neuropathic pain	THC products vs. placebo	Very low-certainty evidence indicated a significant improvement in the dronabinol compared with placebo groups comprising an adult population experiencing chronic neuropathic pain (one RCT, narrative synthesis). Trial duration was 21 days, and no follow-up was reported.

Author (year)	Research question	Intervention categorisation	Evidence summary
Meng *et al.* (2017)	To determine the analgesic efficacy of selective cannabinoids compared with conventional management or placebo for chronic [neuropathic pain] after at least 2 weeks after commencement of treatment	THC products vs. mixed control	Moderate-certainty evidence indicated no significant difference in pain intensity between the THC (nabilone) compared with mixed control (placebo and dihydrocodeine) groups comprising adult populations with various health conditions experiencing chronic neuropathic pain (three RCTs, meta-analysis). Trial durations ranged from 5 to 9 weeks, and no follow-up period was specified.
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	THC vs. active control	Very low-certainty evidence indicated a significant improvement in the THC (nabilone) compared with gabapentin groups comprising an adult population with neuropathic pain (one prospective cohort study, narrative synthesis). No significant difference was reported between the cannabinoid-only group and the combined cannabinoid and gabapentin group. Trial duration was 6 months, and no follow-up was reported.
Longo *et al.* (2021)	In adults with chronic pain, what is the effect of cannabis on pain intensity?	THC products vs. active control	Very low-certainty evidence indicated no significant difference in pain intensity between mixed cannabinoid and active control groups (amitriptyline, diazepam, diphenhydramine) in a narrative review (three RCTs) of adults with various health conditions. Treatment duration was 16 days to 18 weeks, no follow-up was reported.
Giossi *et al.* (2022)	To conduct a systematic review with a meta-analysis to investigate the role of cannabinoids in the treatment of chronic primary pain	THC products vs. active control	Very-low-certainty evidence indicated no significant improvement in pain intensity in the THC compared with amitriptyline groups comprising an adult population experiencing orofacial pain (one RCT, narrative synthesis). Trial duration was 10 weeks, and no follow-up period was reported.
Price *et al.* (2022)	To evaluate the efficacy of medical cannabis in reducing pain in patients following spine surgery, for patients suffering from chronic low back or neck pain, and patients affected by previous spinal cord injury pain	THC products vs. active control	Very low-certainty evidence indicated no significant difference in pain intensity in the THC compared with active control groups (diphenhydramine and mannitol) comprising an adult population with spinal cord injury (two RCTs, narrative synthesis). Trial duration was 4 weeks, and follow-up was at the end of the intervention in one RCT. Trial duration was not clearly reported in the other RCT, however authors reported follow-up 14 days after the intervention.
Vortubec (2022)	To explore the published evidence regarding effectiveness of cannabinoids in orofacial pain management in a dental setting	CBD products vs. placebo	Very low-certainty evidence significant improvement in pain intensity in the CBD compared with placebo groups comprising an adult population experiencing orofacial pain (one RCT, narrative synthesis). Trial duration was not reported clearly; however, the review authors reported a follow-up 14 days after the intervention.

Author (year)	Research question	Intervention categorisation	Evidence summary
Quintero *et al.* (2022)	To evaluate the safety and effectiveness of cannabinoids used by routes other than oral or inhalation for neuropathic pain compared to placebo or other medications in terms of pain relief, quality of life and adverse events	CBD products vs. placebo	Very low-certainty evidence indicated mixed evidence in pain intensity between CBD oil and placebo groups in a narrative review (1 RCTs) of adults with neuropathic pain. This study reported significant ($p<0.05$) decrease in intense (-1.24 vs. -0.59) and cold (-1.63 vs. -0.43) sensations in favour of CBD oil compared with placebo. This study also reported a significant decrease in sharp and itchy sensations in favour of placebo compared with CBD oil. Treatment duration was 4 weeks, no follow-up was reported.
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	CBD products vs. placebo	Authors reported insufficient evidence to draw conclusion on the efficacy of CBD compared with placebo groups.
Sainsbury *et al.* (2021)	To evaluate the effectiveness of cannabis-based medications as therapeutic agents compared to placebo intervention in patients with chronic neuropathic pain	CBD products vs. placebo	Very low-certainty evidence indicated no significant difference between the CBD and placebo groups comprising an adult population with chronic neuropathic pain (one RCT, narrative synthesis). Trial duration was 2 weeks, and no follow-up was reported.
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	CBDV products vs. placebo	Authors reported insufficient evidence to draw conclusion on the efficacy of CBDV compared with placebo groups.
Sainsbury *et al.* (2021)	To evaluate the effectiveness of cannabis-based medications as therapeutic agents compared to placebo intervention in patients with chronic neuropathic pain	CBDV products vs. placebo	Very low-certainty evidence indicated no significant difference between the CBDV and placebo groups comprising an adult population with chronic neuropathic pain (one RCT, narrative synthesis). Trial duration was 4 weeks, and no follow-up was reported.
Sainsbury *et al.* (2021)	To evaluate the effectiveness of cannabis-based medications as therapeutic agents compared to placebo intervention in patients with chronic neuropathic pain	CT-3 vs. placebo	Very low-certainty evidence indicated no significant difference between the CT-3 and placebo groups comprising an adult population with chronic neuropathic pain (one RCT, narrative synthesis). Trial duration was 1 week, and no follow-up was reported.
Pain reduction equal to or greater than 30%			
Bialas *et al.* (2022)	To assess the long-term effectiveness, tolerability and safety of cannabis-based medicines in the management of chronic noncancer pain in patients of any age in long-term observational studies	Mixed cannabinoid and cannabis products vs. placebo	Very low-certainty evidence indicated a significant improvement in the mixed cannabinoids and cannabis groups compared with placebo groups comprising adult populations with various health conditions (six prospective cohort studies, meta-analysis). Trial durations ranged from 6 to 12 months, and no follow-up was reported.
Andreae *et al.* (2015)	To perform a Bayesian responder meta-analysis of individual patient data to study whether inhaled	Cannabis products vs. placebo	Moderate-evidence indicating significant improvement in the THC (inhaled *Cannabis sativa*) compared with placebo groups comprising adult populations with neuropathic pain (five RCTs,

Author (year)	Research question	Intervention categorisation	Evidence summary
	cannabis provides relief for chronic neuropathic pain.		meta-analysis). Intervention durations ranged from 2 hours to 5 weeks; additional details on follow-up were unclear.
Fisher *et al.* (2021) (<7 days duration)	To provide a comprehensive summary of the evidence from primary randomised controlled trials (RCTs) of cannabinoids, cannabis, and [cannabis-based medicine] in clinical acute and chronic pain management, across the lifespan	Cannabis products vs. placebo	Moderate-certainty evidence indicating significant improvement in pain in the cannabis compared with placebo groups comprising adult populations with chronic pain (neuropathic pain, neuropathic pain after injury) (two RCTs, meta-analysis). Trial durations ranged from 18 to 24 hours, and no follow-up was reported.
Fisher *et al.* (2021) (>7 days duration)	To provide a comprehensive summary of the evidence from primary randomised controlled trials (RCTs) of cannabinoids, cannabis, and [cannabis-based medicine] in clinical acute and chronic pain management, across the lifespan	Cannabis products vs. placebo	Very low-certainty evidence indicated a significant improvement in pain in the cannabis compared with placebo groups comprising an adult population with multiple sclerosis (one RCT, narrative synthesis). Trial duration was 12 weeks, and no follow-up was reported.
Butler (2015)	The review addresses the following key questions: 1) What are the benefits (short-term and long-term) of cannabis use for the treatment of non-cancer pain? 2) What are the harms (short-term and long-term) of cannabis use for the treatment of non-cancer pain?	THC/CBD products vs. placebo	Low-certainty evidence indicated no significant improvement in pain in nabiximols compared with placebo groups comprising adult populations with various health conditions (multiple sclerosis, diabetic neuropathy, allodynia) (three RCTs, meta-analysis). Trial durations ranged from 5 to 14 weeks; no follow-up was reported.
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	THC/CBD products vs. placebo	Low-certainty evidence indicated no significant difference between comparable THC:CBD products and placebo groups comprising adult populations with chronic, non-cancer pain (four RCTs, meta-analysis). Intervention durations ranged from 5 to 15 weeks, and no follow-up was reported.
Fisher *et al.* (2021) (>7 days duration)	To provide a comprehensive summary of the evidence from primary randomised controlled trials (RCTs) of cannabinoids, cannabis, and [cannabis-based medicine] in clinical acute and chronic pain management, across the lifespan	THC/CBD products vs. placebo	Low-certainty evidence indicated a significant improvement in pain in nabiximols compared with placebo groups comprising adult populations with chronic pain (cancer, multiple sclerosis, neuropathic pain, allodynia) (six RCTs, meta-analysis). Trial durations ranged from 2 to 15 weeks, and no follow-up was reported.
Oordt *et al.* (2021)	To investigate the efficacy, effectiveness, safety, cost-effectiveness, and budget impact of medical cannabis use in chronic pain and spasticity	THC/CBD products vs. placebo	Very low-certainty evidence indicated no significant difference in reducing pain by ≥30% between THC:CBD spray and placebo groups comprising adult populations with various health conditions (four RCTs, meta-analysis). Trial durations ranged from 4 to 14 weeks, and follow-up was conducted at the end of treatment.
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	THC products vs. placebo	Very low-certainty evidence indicated significant improvement in whole products with a high ratio of THC to CBD compared with placebo groups comprising an adult population with diabetic

Author (year)	Research question	Intervention categorisation	Evidence summary
			neuropathy pain (one RCT, narrative synthesis). Trial duration was 5 weeks; no follow-up was reported.
Fisher *et al.* (2021) (>7 days duration)	To provide a comprehensive summary of the evidence from primary randomised controlled trials (RCTs) of cannabinoids, cannabis, and [cannabis-based medicine] in clinical acute and chronic pain management, across the lifespan	THC products vs. placebo	Low-certainty evidence indicated no significant difference between THC and placebo groups comprising adult populations with chronic pain (multiple sclerosis, cancer) (two RCTs, meta-analysis). Intervention durations ranged from 2 weeks to 3 years, and no follow-up was reported.
Fisher *et al.* (2021) (<7 days duration)	To provide a comprehensive summary of the evidence from primary randomised controlled trials (RCTs) of cannabinoids, cannabis, and [cannabis-based medicine] in clinical acute and chronic pain management, across the lifespan	THC products vs. placebo/codeine	Very low-certainty evidence indicated a significant improvement in pain in the THC congener compared with placebo/codeine groups comprising an adult population with cancer (one RCT, narrative synthesis). Trial duration was 5 days; no follow-up was reported.
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	CBD products vs. placebo	Authors reported insufficient evidence to draw conclusion on the efficacy of CBD compared with placebo groups.
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	CBDV products vs. placebo	Authors reported insufficient evidence to draw conclusion on the efficacy of CBDV compared with placebo groups.
Pain reduction equal to or greater than 50%			
Bialas *et al.* (2022)	To assess the long-term effectiveness, tolerability and safety of cannabis-based medicines in the management of chronic noncancer pain in patients of any age in long-term observational studies	Mixed cannabinoids and cannabis products vs. placebo	Very low-certainty evidence indicated a significant improvement in the mixed cannabinoids and cannabis compared with placebo groups comprising adult populations with various health conditions (six prospective cohort studies, meta-analysis). Trial durations ranged from 6 to 12 months; no follow-up was reported.
Mücke *et al.* (2018b)	To assess the efficacy, tolerability, and safety of cannabis-based medicines (herbal, plant-based, synthetic) compared to placebo or conventional drugs for conditions with chronic neuropathic pain in adults	Mixed cannabinoid products vs. placebo	Low-certainty evidence indicated a significant improvement in mixed cannabinoids compared with placebo groups (eight RCTs, meta-analysis) comprising adults with chronic neuropathic pain. The review authors note that this difference was not clinically significant. Trial durations ranged from 2 to 14 weeks, and no follow-up was reported.
Oordt *et al.* (2021)	To investigate the efficacy, effectiveness, safety, cost-effectiveness, and budget impact of medical cannabis use in chronic pain and spasticity	THC/CBD products vs. placebo	Very low-certainty evidence indicated no significant difference in pain reduction equal to or greater than 50% between THC:CBD spray and placebo groups comprising adult populations with various health conditions (four RCTs, meta-analysis). Trial durations ranged from 4 to 14 weeks, and follow-up was carried out at the end of treatment.
Mücke *et al.* (2018b)	To assess the efficacy, tolerability, and safety of cannabis-based medicines (herbal, plant-based, synthetic) compared to placebo or conventional	THC/CBD products vs. placebo	Very low-certainty evidence indicated significant improvement in the THC:CBD compared with placebo groups comprising an adult

Author (year)	Research question	Intervention categorisation	Evidence summary
	drugs for conditions with chronic neuropathic pain in adults		population with multiple sclerosis (one RCT, narrative synthesis). Trial duration was 4 weeks; no follow-up was reported.
Fisher *et al.* (2021) (>7 days duration)	To provide a comprehensive summary of the evidence from primary randomised controlled trials (RCTs) of cannabinoids, cannabis, and [cannabis-based medicine] in clinical acute and chronic pain management, across the lifespan	THC/CBD products vs. placebo	Low-certainty evidence indicated no significant difference between the THC:CBD and placebo groups comprising adult populations with chronic pain (two RCTs, meta-analysis). Trial durations ranged from 4 to 14 weeks, and no follow-up was reported.
Mücke *et al.* (2018b)	To assess the efficacy, tolerability, and safety of cannabis-based medicines (herbal, plant-based, synthetic) compared to placebo or conventional drugs for conditions with chronic neuropathic pain in adults	THC products vs. placebo	Very low-certainty evidence indicated no significant difference in nabilone compared with placebo groups comprising an adult population with diabetic neuropathy (one RCT, narrative synthesis). Trial duration was 4 weeks, and no follow-up was reported.
Fisher *et al.* (2021) (<7 days duration)	To provide a comprehensive summary of the evidence from primary randomised controlled trials (RCTs) of cannabinoids, cannabis, and [cannabis-based medicine] in clinical acute and chronic pain management, across the lifespan	THC product vs. mixed control	Very low-certainty evidence indicated no significant differences between the THC and codeine/placebo groups comprising adult populations with cancer (two RCTs, meta-analysis). Trial duration was 5 days; no follow-up was reported.
Patient global impression of change of pain			
Butler *et al.* (2015)	The review addresses the following key questions: 1) What are the benefits (short-term and long-term) of cannabis use for the treatment of non-cancer pain? 2) What are the harms (short-term and long-term) of cannabis use for the treatment of non-cancer pain?	Mixed cannabinoids products vs. placebo	Very low-certainty evidence indicated a significant improvement in the mixed cannabinoid (nabiximols, nabilone) compared with placebo groups (two RCTs, meta-analysis) comprising adult populations with multiple sclerosis. Trial durations ranged from 4 to 9 weeks, and no follow-up was reported.
Mücke *et al.* (2018b)	To assess the efficacy, tolerability, and safety of cannabis-based medicines (herbal, plant-based, synthetic) compared to placebo or conventional drugs for conditions with chronic neuropathic pain in adults	THC/CBD products vs. placebo	Low-certainty evidence indicated a statistically significant improvement in the THC:CBD compared with placebo groups comprising adult populations experiencing chronic neuropathic pain (six RCTs, meta-analysis). The review authors note that this difference was not clinically significant. Trial durations ranged from 3 to 15 weeks, and no follow-up was reported.
Mücke *et al.* (2018b)	To assess the efficacy, tolerability, and safety of cannabis-based medicines (herbal, plant-based, synthetic) compared to placebo or conventional drugs for conditions with chronic neuropathic pain in adults	THC products vs. placebo	Very low-certainty evidence indicated a significant improvement in the THC (nabilone) compared with placebo groups comprising an adult population with diabetic neuropathy (one RCT, narrative synthesis). Trial duration was 4 weeks, and no follow-up was reported.
Morphine consumption			

Author (year)	Research question	Intervention categorisation	Evidence summary
Abdallah *et al.* (2020)	To evaluate analgesic outcomes in patients receiving cannabis compounds for acute pain management in the surgical setting.	THC products vs. placebo	Very low-certainty evidence indicated no significant difference in cumulative oral morphine equivalent consumption at 24 hours postoperatively between the THC and control groups (two RCTs, narrative synthesis). Trial durations ranged from 24 to 48 hours post-operation, and no follow-up was reported.
QUALITY OF LIFE			
Health-related quality of life			
Belgers *et al.* (2023)	To assess the effects of cannabinoids on [health-related quality of life] in oncological patients and patients with [central nervous system] disease	Mixed cannabinoid products vs. mixed control	Low-certainty evidence indicated no significant difference in health-related quality of life between mixed cannabinoid and mixed control groups (megestrol acetate, placebo) comprising adult populations with cancer and central nervous system disorders (13 RCTs, meta-analysis). Intervention durations ranged from 2 to 14 weeks, and no follow-up period was specified.
Belgers *et al.* (2023)	To assess the effects of cannabinoids on [health-related quality of life] in oncological patients and patients with [central nervous system] disease	THC/CBD products vs. placebo	Moderate-certainty evidence indicating no significant difference in health-related quality of life in the THC:CBD compared with placebo groups comprising adult populations with cancer and central nervous system disorders (five RCTs, meta-analysis). Intervention durations ranged from 6 to 12 weeks; no follow-up period was specified.
Belgers *et al.* (2023) (subgroup analysis)	To assess the effects of cannabinoids on [health-related quality of life] in oncological patients and patients with [central nervous system] disease	THC products vs. mixed control	Low-certainty evidence indicating no significant difference in health-related quality of life between the THC and mixed control groups comprising adult populations with cancer and central nervous system disorders (six RCTs, meta-analysis). Intervention durations ranged from 2 weeks to 80 days, and no follow-up period was specified.
Oordt *et al.* (2021) (subgroup analysis)	To investigate the efficacy, effectiveness, safety, cost-effectiveness, and budget impact of medical cannabis use in chronic pain and spasticity	THC/CBD products vs. placebo	Very low-certainty evidence reporting no significant difference in quality of life in THC/CBD compared with placebo groups in a narrative review (four RCTs) of adults with multiple sclerosis and allodynia. Trial durations ranged from 4 to 14 weeks with follow-up at the end of treatment.
Oordt *et al.* (2021)	To investigate the efficacy, effectiveness, safety, cost-effectiveness, and budget impact of medical cannabis use in chronic pain and spasticity	THC products vs. placebo	Very low-certainty evidence reporting no significant difference in quality of life in the THC (dronabinol) compared with placebo groups comprising an adult population with allodynia experiencing neuropathic pain (one RCT, narrative synthesis). Trial duration was 4 weeks with follow-up at the end of treatment.
Quality of life (cancer and cachexia)			

Author (year)	Research question	Intervention categorisation	Evidence summary
Hammond *et al.* (2021)	To compare the effects of cannabis-based medicinal products against both placebo and active treatment in anorexia–cachexia syndrome for appetite stimulation, change in body mass, and [quality of life].	Mixed cannabinoid products vs. mixed control	Low-certainty evidence indicated no significant difference in quality of life between mixed cannabinoid and mixed control groups (three RCTs, meta-analysis) comprising adult populations with cancer and HIV. Intervention durations ranged from 4 to 8 weeks, and no follow-up period was specified.
SPASTICITY			
Spasticity intensity			
da Rovare *et al.* (2017)	To summarize the effects of cannabinoids compared with usual care, placebo for spasticity due to multiple sclerosis (MS) or paraplegia	Mixed cannabinoid and cannabis products vs. placebo	Low-certainty evidence indicated no significant difference between mixed cannabinoids and cannabis groups compared with placebo groups comprising adult populations with spasticity (seven RCTs, meta-analysis). Trial durations ranged from 2 to 10 weeks, and no follow-up was reported.
Oordt *et al.* (2021)	To investigate the efficacy, effectiveness, safety, cost-effectiveness, and budget impact of medical cannabis use in chronic pain and spasticity	THC/CBD products vs. placebo	Very low-certainty evidence indicated mixed findings for adult populations with multiple sclerosis (two RCTs, narrative synthesis). One RCT reported no significant difference between THC:CBD and placebo groups, while the other RCT reported a significant improvement in the THC:CBD compared with placebo groups. Trial durations ranged from 6 to 14 weeks, and follow-up was conducted at the end of treatment.
Reduction in spasticity equal to or greater than 30%			
Oordt *et al.* (2021)	To investigate the efficacy, effectiveness, safety, cost-effectiveness, and budget impact of medical cannabis use in chronic pain and spasticity	THC/CBD products vs. placebo	Very low-certainty evidence indicated no significant difference between the THC:CBD spray and placebo groups comprising adult populations with multiple sclerosis (two RCTs, meta-analysis). Trial durations ranged from 6 to 14 weeks, and follow-up was conducted at the end of treatment.
Spasm frequency			
da Rovare *et al.* (2017)	To summarize the effects of cannabinoids compared with usual care, placebo for spasticity due to multiple sclerosis (MS) or paraplegia	Mixed cannabinoid and cannabis products vs. placebo	Very low-certainty evidence indicated no significant difference between mixed cannabinoids and cannabis compared with placebo groups comprising adult populations with spasticity (six RCTs, meta-analysis). Trial durations ranged from 3 to 10 weeks, and no follow-up was reported.
Spasm severity			
da Rovare *et al.* (2017)	To summarize the effects of cannabinoids compared with usual care, placebo for spasticity due to multiple sclerosis (MS) or paraplegia	Mixed cannabinoid and cannabis products vs. placebo	Very low-certainty evidence indicated no significant difference between mixed cannabinoids and cannabis groups compared with placebo groups comprising adult populations with spasticity (three RCTs, meta-analysis). Intervention durations ranged from 7 to 10 weeks, and no follow-up was reported.

Author (year)	Research question	Intervention categorisation	Evidence summary
Observer-rated spasticity			
Oordt *et al.* (2021)	To investigate the efficacy, effectiveness, safety, cost-effectiveness, and budget impact of medical cannabis use in chronic pain and spasticity	THC/CBD products vs. placebo	Low-certainty evidence indicated a significant improvement in observer-rated spasticity for the THC:CBD groups comprising adult populations with various health conditions (amyotrophic lateral sclerosis, multiple sclerosis) (two RCTs, narrative synthesis). Trial durations ranged from 2 to 4 weeks, and follow-up was conducted at the end of treatment.
Oordt *et al.* (2021)	To investigate the efficacy, effectiveness, safety, cost-effectiveness, and budget impact of medical cannabis use in chronic pain and spasticity	THC products vs. placebo	Very low-certainty evidence indicated a significant improvement in observer-rated spasticity in THC (dronabinol) compared with placebo groups comprising an adult population with multiple sclerosis (one RCT, narrative synthesis). Trial duration was 8 weeks, and follow-up was conducted at the end of treatment and again at 12 months.
CACHEXIA			
Appetite			
Hammond *et al.* (2021)	To compare the effects of cannabis-based medicinal products against both placebo and active treatment in anorexia–cachexia syndrome for appetite stimulation, change in body mass, and [quality of life].	Mixed cannabinoid products vs. placebo	Low-certainty evidence indicated no significant difference in appetite between mixed cannabinoid and placebo groups comprising adult populations with cancer associated cachexia (two RCTs, meta-analysis). Intervention durations ranged from 4 to 6 weeks, and no follow-up period was specified.
Weight loss/gain			
Hammond *et al.* (2021)	To compare the effects of cannabis-based medicinal products against both placebo and active treatment in anorexia–cachexia syndrome for appetite stimulation, change in body mass, and [quality of life].	THC products vs. mixed control	Very low-certainty evidence indicated no significant difference in weight changes between THC (dronabinol, nabilone) and mixed control groups (megestrol acetate and placebo) comprising adult populations with cancer and HIV (two RCTs, meta-analysis). Intervention durations ranged from 8 to 12 weeks, and no follow-up period was specified.
SLEEP			
Sleep quality			
Aminilari (2022)	To explore the effectiveness of medical cannabis for impaired sleep	Mixed cannabinoid and cannabis products vs. placebo	Moderate-certainty evidence indicated a significant improvement in sleep quality in the mixed cannabinoids and cannabis compared with placebo groups comprising adult populations with various health conditions (16 RCTs, meta-analysis). Trial durations were reported as follow-ups ranging from 14 to 98 days.
McParland (2023)	To evaluate the impact of therapeutic cannabinoids on sleep quality, analgesic efficacy, and adverse effects in patients with neuropathic pain syndromes	Mixed cannabinoid and cannabis products vs. placebo	High-certainty evidence indicated significantly improved sleep quality in the cannabinoid and cannabis compared with placebo groups comprising adult populations with various health conditions experiencing chronic neuropathic pain (six RCTs, meta-

Author (year)	Research question	Intervention categorisation	Evidence summary
			analysis). Trial durations ranged from 2 to 15 weeks, and no follow-up period was specified.
Aminilari (2022)	To explore the effectiveness of medical cannabis for impaired sleep	THC products vs. placebo	Very low-certainty evidence indicated no significant difference in sleep quality between the THC (nabilone) and placebo groups comprising an adult population undergoing radiotherapy for head and neck carcinomas (one RCT, narrative synthesis). Intervention duration/follow-up was 70 days.
Sleep disturbance			
Aminilari (2022)	To explore the effectiveness of medical cannabis for impaired sleep	Mixed cannabinoid products vs. placebo	Low-certainty evidence indicated a significant improvement in sleep disturbance in the mixed cannabinoid compared with placebo groups of adult populations with cancer and non-cancer-related health conditions (16 RCTs, meta-analysis). Trial durations were reported as follow-ups ranging from 14 to 84 days.
Aminilari (2022) (subgroup cancer)	To explore the effectiveness of medical cannabis for impaired sleep	Mixed cannabinoid products vs. placebo	Moderate-certainty evidence indicated significant improvement in sleep quality in cannabinoid compared with placebo groups (5 RCTs) in a meta-analysis of a adults with cancer. Treatment duration was reported as follow-up ranging from 14 to 84 days.
Aminilari (2022) (subgroup non-cancer)	To explore the effectiveness of medical cannabis for impaired sleep	Mixed cannabinoids products vs. placebo	Moderate-certainty evidence indicated significant improvement in sleep quality in cannabinoid compared with placebo groups (11 RCTs) in a meta-analysis of adults with non-cancer health conditions. Treatment duration was reported as follow-up ranging from 35 to 56 days.
Aminilari (2022)	To explore the effectiveness of medical cannabis for impaired sleep	THC products vs. active control	Very low-certainty evidence found significant improvements in sleep disturbance in THC products compared with diazepam groups comprising an adult population with anorexia nervosa (one RCT, narrative synthesis). Intervention duration/follow-up was 28 days.
PTSD nightmares			
Aminilari (2022)	To explore the effectiveness of medical cannabis for impaired sleep	THC products vs. placebo	Very low-certainty evidence indicated no significant difference in PTSD nightmares between the THC (nabilone) and placebo groups among an adult population undergoing radiotherapy for head and neck carcinomas (one RCT, narrative synthesis). Intervention duration/follow-up was 14 days.
Sleepiness			
Aminilari (2022)	To explore the effectiveness of medical cannabis for impaired sleep	THC products vs. placebo	Very low-certainty evidence indicated significantly reduced sleepiness in the THC (dronabinol) compared with placebo groups comprising an adult population with moderate obstructive sleep apnoea (one RCT, narrative synthesis). Intervention duration/follow-up was 42 days.

Author (year)	Research question	Intervention categorisation	Evidence summary
Insomnia			
Aminilari (2022)	To explore the effectiveness of medical cannabis for impaired sleep	THC products vs. active control	Very low-certainty evidence indicated significantly improved insomnia in the THC (nabilone) compared with active control (amitriptyline) groups comprising an adult population with fibromyalgia (one RCT, narrative synthesis). Intervention duration/follow-up was 14 days.
Sleep interruptions			
Aminilari (2022)	To explore the effectiveness of medical cannabis for impaired sleep	THC products vs. active control	Very low-certainty evidence found no significant difference between the THC (nabilone) and active control (dihydrocodeine) groups comprising an adult population with chronic neuropathic pain (one RCT, narrative synthesis). Intervention duration/follow-up was 42 days.
Daytime somnolence			
McParland (2023)	To evaluate the impact of therapeutic cannabinoids on sleep quality, analgesic efficacy, and adverse effects in patients with neuropathic pain syndromes	Mixed cannabinoid products vs. placebo	High-certainty evidence found a significantly higher likelihood of daytime somnolence in the mixed cannabinoids compared with placebo groups comprising adult populations with various health conditions experiencing chronic neuropathic pain (six RCTs, meta-analysis). Trial durations ranged from 2 to 15 weeks, and no follow-up period was specified.
MENTAL HEALTH/WELL-BEING			
Mental health/well-being			
Belgers *et al.* (2023)	To assess the effects of cannabinoids on [health-related quality of life] in oncological patients and patients with [central nervous system] disease	Mixed cannabinoid products vs. mixed control	Low-certainty evidence indicated no significant difference in mental health/well-being between mixed cannabinoids and mixed controls (placebo and megestrol acetate) comprising adult populations with cancer and central nervous system disorders (13 RCTs, meta-analysis). Intervention durations ranged from 2 weeks to 36 months, and no follow-up period was specified.
Belgers *et al.* (2023)	To assess the effects of cannabinoids on [health-related quality of life] in oncological patients and patients with [central nervous system] disease	THC/CBD products vs. placebo	Low-certainty evidence indicating no significant difference in mental health/well-being between the THC:CBD and placebo groups comprising adult populations with cancer and central nervous system disorders (five RCTs, meta-analysis). Intervention durations ranged from 5 to 12 weeks; no follow-up period was specified.
Belgers *et al.* (2023)	To assess the effects of cannabinoids on [health-related quality of life] in oncological patients and patients with [central nervous system] disease	THC products vs. placebo	Low-certainty evidence indicated no significant difference in mental health/well-being between THC and placebo groups comprising adult populations with cancer and central nervous system disorders (six RCTs, meta-analysis). Intervention durations ranged from 2 months; no follow-up period was specified.

Author (year)	Research question	Intervention categorisation	Evidence summary
OVERALL FUNCTION OR DISABILITY			
Overall function or disability			
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	Cannabis vs. usual care	Very low-certainty evidence indicated no significant difference in overall function or disability in the cannabis compared with usual care groups comprising adults with neuropathic pain (one prospective cohort study, narrative synthesis). Trial duration was 6 months, and no follow-up was reported.
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	THC/CBD products vs. placebo	Low-certainty evidence indicated a significant improvement in overall function or disability in products with comparable ratios of THC to CBD compared with placebo groups comprising adult populations with chronic, non-cancer pain (six RCTs, meta-analysis). Intervention durations ranged from 5 to 15 weeks; no follow-up was reported.
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	THC/CBD products vs. placebo	Very low-certainty evidence of a significant improvement in overall function or disability for extracted products with high ratios of THC to CBD compared with placebo groups comprising an adult population with fibromyalgia (one RCT, narrative synthesis). Trial duration was 8 weeks, and no follow-up was reported.
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	THC products vs. placebo	Low-certainty evidence found no significant difference in overall function or disability between products with a high THC:CBD ratio and placebo groups comprising adult populations with chronic, non-cancer pain (multiple sclerosis, diabetic neuropathy) (two RCTs, meta-analysis). Intervention durations ranged from 5 to 9 weeks; no follow-up was reported.
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	THC vs. active control	Very low-certainty evidence indicated no significant difference in THC compared with gabapentin groups or THC compared with combined THC and gabapentin groups (one prospective cohort study, narrative synthesis). Trial duration was 6 months, and no follow-up was reported.

Safety and tolerability

Author (year)	Research question	Intervention categorisation	Evidence summary

SAFETY AND TOLERABILITY			
NERVOUS SYSTEM ADVERSE EVENTS			
Dizziness			
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	Cannabis vs. usual care	Very low-certainty evidence indicated no significant difference between cannabis and usual care groups in a narrative review (1 prospective cohort study) of adults with chronic non-cancer pain. Treatment duration was 13 months, no follow-up was reported.
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	THC/CBD products vs. placebo	Very low-certainty evidence indicated significantly increased likelihood in THC/CBD compared with placebo groups in a meta-analysis (6 RCTs) of adults with mixed health conditions (cancer, rheumatoid arthritis, multiple sclerosis, neuropathic pain). Treatment duration was 4 to 15 weeks, no follow-up was reported.
Bajtel *et al.* (2022)	To analyse the [adverse events] of dronabinol and nabilone based on the meta-analysis of placebo-controlled trials	THC products vs. placebo	Very low-certainty evidence indicated significant increased risk in THC (nabilone) compared with placebo groups in a meta-analysis (3 RCTs) of adults with mixed health conditions (dementia, pain) experiencing neuropathic pain. Treatment duration was 3 sessions to 14 weeks, no follow-up was reported.
Bajtel *et al.* (2022)	To analyse the [adverse events] of dronabinol and nabilone based on the meta-analysis of placebo-controlled trials	THC products vs. placebo	Moderate-certainty evidence indicated significant increased risk in THC (dronabinol) compared with placebo groups in a meta-analysis (8 RCTs) of adults with mixed health conditions (multiple sclerosis, gastrointestinal transit and postprandial satiation, older people, dementia, irritable bowel syndrome). Treatment duration was 2 days to 16 weeks, no follow-up was reported.
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	THC products vs. placebo	Moderate-certainty evidence indicated significantly increased likelihood in THC compared with placebo groups in a meta-analysis (3 RCTs) of adults with mixed health conditions (multiple sclerosis, visceral pain). Subgroup analysis was conducted by cannabinoid type (synthetic, extract). There was significantly increased likelihood in THC compared with placebo group in both subgroup analyses. Treatment duration was 7 to 16 weeks, no follow-up was reported.
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	THC vs. mixed control (placebo and gabapentin)	Very low-certainty evidence indicated no significant difference between THC and gabapentin groups a narrative review (1 prospective cohort study) of adults with mixed neuropathic pain. Treatment duration ranged from 6 months, no follow-up was reported.
Sedation			
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	Cannabis vs. usual care	Very low-certainty evidence indicated significantly increased risk in cannabis compared with usual care groups in a narrative review (1

			prospective cohort study) of adults with chronic non-cancer pain. Treatment duration was 13 months, no follow-up was reported.
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	THC/CBD vs. placebo	Low-certainty evidence indicated significantly increased risk in THC/CBD groups in a meta-analysis (6 RCTs) of adults with mixed health condition (cancer, rheumatoid arthritis, multiple sclerosis, neuropathic pain). Treatment duration was 4 to 16 weeks, no follow-up was reported.
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	THC products vs. placebo	Moderate-certainty evidence indicated significantly increased risk in THC groups in a meta-analysis (3 RCTs) of adults with mixed health conditions (visceral pain, fibromyalgia, multiple sclerosis). Treatment duration was 4 to 16 weeks, no follow-up was reported.
Bosnjak-Kuharic *et al.* (2021)	To determine the efficacy and safety of cannabinoids for the treatment of dementia	THC vs. placebo	Very low-certainty evidence indicated significantly increased risk in THC compared with placebo groups consisting of an adult population with dementia (1 RCT, narrative review). Treatment duration was 14 weeks, no follow-up was reported.
Paunescu 2020	Which is the level of evidence, from quantitative and qualitative point of view, concerning the efficacy and safety of the treatment with psychotropic cannabinoids of neuropsychiatric symptoms in Alzheimer's Disease?	THC vs. placebo	Very low-certainty evidence indicated significantly increased risk in THC compared with placebo groups consisting of an adult population with dementia (1 RCT, narrative review). Treatment duration was 14 weeks, no follow-up was reported.
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	THC vs. mixed control (placebo and gabapentin)	Very low-certainty evidence indicated significantly lower risk in THC compared with gabapentin groups a narrative review (1 prospective cohort study) of adults with mixed neuropathic pain. Treatment duration ranged from 6 months, no follow-up was reported.
Drowsiness			
Bajtel *et al.* (2022)	To analyse the [adverse events] of dronabinol and nabilone based on the meta-analysis of placebo-controlled trials	THC products vs. placebo	Very low-certainty evidence indicated significantly increased risk in THC (nabilone) compared with placebo groups in a meta-analysis (3 RCTs) of adults with mixed health conditions (spasticity-related pain, fibromyalgia, spinal cord injury). Treatment duration was 4 to 10 weeks, no follow-up was reported.
Bajtel *et al.* (2022)	To analyse the [adverse events] of dronabinol and nabilone based on the meta-analysis of placebo-controlled trials	THC products vs. placebo	Very low-certainty evidence indicated no significant difference between THC (dronabinol) and placebo groups in a meta-analysis (3 RCTs) of adults with mixed health conditions (multiple sclerosis, gastrointestinal transit and postprandial satiation, older people). Treatment duration was 2 days to 6 weeks, no follow-up was reported.
Dry mouth			
Bajtel *et al.* (2022)	To analyse the [adverse events] of dronabinol and nabilone based on the	THC products vs. placebo	Very low-certainty evidence indicated significantly increased risk in THC (nabilone) compared with placebo groups in a meta-analysis (4 RCTs) of adults with mixed health conditions (spasticity-related pain, fibromyalgia,

	meta-analysis of placebo-controlled trials		spinal cord injury). Treatment duration was 3 sessions to 8 weeks, no follow-up was reported.
Bajtel *et al.* (2022)	To analyse the [adverse events] of dronabinol and nabilone based on the meta-analysis of placebo-controlled trials	THC products vs. placebo	Moderate-certainty evidence indicated significantly increased risk in THC (dronabinol) compared with placebo groups in a meta-analysis (6 RCTs) of adults with mixed health conditions (multiple sclerosis, gastrointestinal transit and postprandial satiation, older people, dementia). Treatment duration was 2 days to 16 weeks, no follow-up was reported.
Headache			
Bajtel *et al.* (2022)	To analyse the [adverse events] of dronabinol and nabilone based on the meta-analysis of placebo-controlled trials	THC products vs. placebo	Very low-certainty evidence indicated significantly increased risk in THC (nabilone) compared with placebo groups in a meta-analysis (4 RCTs) of adults with mixed health conditions (spasticity-related pain, fibromyalgia, spinal cord injury). Treatment duration was 3 sessions to 8 weeks, no follow-up was reported.
Bajtel *et al.* (2022)	To analyse the [adverse events] of dronabinol and nabilone based on the meta-analysis of placebo-controlled trials	THC products vs. placebo	Low-certainty evidence indicated significant increased risk in THC (dronabinol) compared with placebo groups in a meta-analysis (9 RCTs) of adults with mixed health conditions (multiple sclerosis, gastrointestinal transit and postprandial satiation, older people, dementia, irritable bowel syndrome, cancer, pain). Treatment duration was 2 days to 16 weeks, no follow-up was reported.
Fatigue			
Bajtel *et al.* (2022)	To analyse the [adverse events] of dronabinol and nabilone based on the meta-analysis of placebo-controlled trials	THC products vs. placebo	Moderate-certainty evidence indicated no significant difference increased risk in THC (dronabinol) compared with placebo groups in a meta-analysis (4 RCTs) of adults with mixed health conditions (pain, multiple sclerosis, dementia). Treatment duration was 3 to 16 weeks, no follow-up was reported.
Impotence			
Hammond *et al.* (2021)	To compare the effects of cannabis-based medicinal products against both placebo and active treatment in anorexia–cachexia syndrome for appetite stimulation, change in body mass, and quality of life	THC vs. active control (megestrol acetate)	Very low-certainty evidence indicated significantly lower likelihood of impotence in dronabinol compared with active control (megestrol acetate) groups consisting of adults with cancer associated cachexia (1 RCT, narrative review). Treatment duration was 4 weeks, no follow-up was reported.
Any nervous system disorder adverse events			
Bosnjak-Kuharic *et al.* (2021)	To determine the efficacy and safety of cannabinoids for the treatment of dementia	THC vs. placebo	Very low-certainty evidence indicated no significant difference between THC and placebo groups consisting of an adult population with dementia (1 RCT, narrative review). Treatment duration was 3 weeks, no follow-up was reported.
Hammond *et al.* (2021)	To compare the effects of cannabis-based medicinal products against both	THC vs. placebo	Very low-certainty evidence indicated significantly increased likelihood in THC (dronabinol) compared with placebo groups consisting of an adult

	placebo and active treatment in anorexia–cachexia syndrome for appetite stimulation, change in body mass, and quality of life		population with AIDS (1 RCT, narrative review). Treatment duration was 6 weeks, no follow-up was reported.
GASTROINTESTINAL SYSTEM ADVERSE EVENTS			
Nausea			
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	Cannabis vs. usual care	Very low-certainty evidence indicated significantly increased risk in cannabis compared with usual care groups in a narrative review (1 prospective cohort study) of adults with chronic non-cancer pain. Treatment duration was 13 months, no follow-up was reported.
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	THC/CBD vs. placebo	Low-certainty evidence indicated significantly increased risk in THC/CBD groups in a meta-analysis (6 RCTs) of adults with mixed health condition (cancer, rheumatoid arthritis, multiple sclerosis, neuropathic pain). Treatment duration was 4 to 16 weeks, no follow-up was reported.
Bajtel *et al.* (2022)	To analyze the [adverse events] of dronabinol and nabilone based on the meta-analysis of placebo-controlled trials	THC product vs. placebo	Moderate-certainty evidence indicated no significant difference between THC (dronabinol) and placebo groups in a meta-analysis (5 RCTs) of adults with mixed health conditions (pain, multiple sclerosis, gastrointestinal transit and postprandial satiation, older people). Treatment duration was 2 days to 16 weeks, no follow-up was reported.
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	THC product vs. placebo	Moderate-certainty evidence indicated no significant difference between THC and placebo groups in a meta-analysis (2 RCTs) of adults with mixed health condition (visceral pain, multiple sclerosis). Treatment duration was 7 to 16 weeks, no follow-up was reported.
Any gastrointestinal system adverse events			
Bosnjak-Kuharic *et al.* (2021)	To determine the efficacy and safety of cannabinoids for the treatment of dementia	THC vs. placebo	Very low-certainty evidence indicated no significant difference betwenn THC and placebo groups consisting an adult population with dementia (1 RCT, narrative review). Treatment duration was 3 weeks, no follow-up was reported.
PSYCHIATRIC SYSTEM DISORDER ADVERSE EVENTS			
Any psychiatric system disorder adverse events			
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	Cannabis vs. usual care	Very low-certainty evidence indicated no significant difference in cannabis compared with usual care groups consisting of adult population with chronic non-cancer pain (1 prospective cohort, narrative synthesis). Treatment duration was 13 months, no follow-up was reported.

Bosnjak-Kuharic *et al.* (2021)	To determine the efficacy and safety of cannabinoids for the treatment of dementia	THC vs. placebo	Very low-certainty evidence indicated no significant difference between THC and placebo groups consisting an adult population with dementia (1 RCT, narrative review). Treatment duration was 3 weeks, no follow-up was reported.
ANY SPECIFIC ADVERSE EVENTS			
Any specific adverse events			
Urbi *et al.* (2022)	To integrate the evidence on indications, efficacy, safety and pharmacokinetics of medical cannabinoids in older subjects	Mixed cannabinoid vs. mixed control (placebo and prochlorperazine)	Low-certainty evidence indicated 266 adverse events in cannabinoid compared with 133 adverse events in mixed control groups (placebo and prochlorperazine) groups consisting of older adults with various health conditions (cancer, dementia, Parkinson's Disease, COPD) (4 RCTs, narrative synthesis). Treatment duration was 1 day--6 weeks, no follow-up was reported. Authors did not report inferential statistics, therefore we cannot comment on the significance of these findings.
Hammond *et al.* (2021)	The aim of this review was to interrogate the published and unpublished literature for evidence of treatment effects of cannabis in Parkinson's disease. We have focused on the potential effects on Parkinson's disease severity and progression, as well as effects on motor and non-motor symptoms	THC/CBD vs. placebo	Very low-certainty evidence indicated no significant difference between THC/CBD (cannador) and placebo groups consisting adult populations with Parkinson's Disease (1 RCT, narrative synthesis). Treatment duration was 4 weeks, no follow-up was reported.
Paunescu 2020	To compare the effects of cannabis-based medicinal products against both placebo and active treatment in anorexia–cachexia syndrome for appetite stimulation, change in body mass, and quality of life	THC:CBD vs. placebo	Very low-certainty evidence indicated no significant difference between THC:CBD (cannabis extract) and placebo groups consisting of adults with cancer associated cachexia (1 RCT, narrative review) Treatment duration was six weeks, no follow-up was reported.
Bosnjak-Kuharic *et al.* (2021)	Which is the level of evidence, from quantitative and qualitative point of view, concerning the efficacy and safety of the treatment with psychotropic cannabinoids of neuropsychiatric symptoms in Alzheimer's Disease?	THC vs. placebo	Very low-certainty evidence indicated no significant difference between THC and placebo groups consisting adult populations with dementia (2 RCTs, narrative synthesis). Treatment duration was 3 to 12 weeks, no follow-up was reported.
Urbi *et al.* (2022)	To determine the efficacy and safety of cannabinoids for the treatment of dementia	THC vs. placebo	Low-certainty evidence indicated 160 individual adverse events in THC groups (nabilone, namisol, dronabinol) compared with 131 individual adverse events in placebo groups consisting adult populations with dementia (4 RCTs, narrative synthesis). Treatment duration was 3 to 14

			weeks, no follow-up was reported. Authors did not report inferential statistics, therefore we cannot comment on the significance of these findings.
Hammond *et al.* (2021)	The aim of this review was to interrogate the published and unpublished literature for evidence of treatment effects of cannabis in Parkinson's disease. We have focused on the potential effects on Parkinson's disease severity and progression, as well as effects on motor and non-motor symptoms	THC vs. placebo	Very low-certainty evidence indicated no significant difference between THC (nabilone) and placebo groups consisting adult populations with Parkinson's Disease (2 RCTs, narrative synthesis). Treatment duration was 4 weeks, no follow-up was reported.
Hammond *et al.* (2021)	To compare the effects of cannabis-based medicinal products against both placebo and active treatment in anorexia–cachexia syndrome for appetite stimulation, change in body mass, and quality of life	THC vs. placebo	Low-certainty evidence indicated no significant difference between THC and placebo groups comprising adult populations with various health conditions (AIDS, cancer) (3 RCTs, narrative review). Treatment duration was 6--8 weeks, no follow-up was reported.
Urbi *et al.* (2022)	To compare the effects of cannabis-based medicinal products against both placebo and active treatment in anorexia–cachexia syndrome for appetite stimulation, change in body mass, and quality of life	THC vs. active control (megestrol acetate)	Low-certainty evidence indicated no significant difference between THC and active control (megestrol acetate) groups comprising adult populations with various health conditions (HIV, cancer) (2 RCTs, narrative review). Treatment duration was 4--12 weeks, no follow-up was reported.
Quintero *et al.* (2022)l	The aim of this review was to interrogate the published and unpublished literature for evidence of treatment effects of cannabis in Parkinson's disease. We have focused on the potential effects on Parkinson's disease severity and progression, as well as effects on motor and non-motor symptoms	CBD vs. placebo	Very low-certainty evidence indicated no significant difference between CBD (CBD capsule) and placebo groups consisting adult populations with Parkinson's Disease (2 RCTs, narrative synthesis). Treatment duration was 4 weeks, no follow-up was reported.
van den Elsen (2014)	we aimed at evaluating the safety and effectiveness of cannabinoids used by routes other than oral or inhalation for neuropathic pain compared to placebo or other medications in terms of pain relief, quality of life and adverse events	CBD products vs. placebo	Very low-certainty evidence indicated no adverse events in CBD or placebo groups in a narrative review (1 RCT) of adult with back pain. Treatment duration was 4 weeks, no follow-up was reported
SERIOUS ADVERSE EVENTS			

Mortality			
Oordt *et al.* (2021)	To investigate the efficacy, effectiveness, safety, cost-effectiveness, and budget impact of medical cannabis use in chronic pain and spasticity	THC/CBD products vs. placebo	Low-certainty evidence indicated no significant difference between THC/CBD products compared with placebo groups in a meta-analysis (2 RCTs) of adults with cancer. Treatment duration was 3 weeks, no follow-up was reported.
Oordt *et al.* (2021)	To investigate the efficacy, effectiveness, safety, cost-effectiveness, and budget impact of medical cannabis use in chronic pain and spasticity	THC/CBD products vs. placebo	Low-certainty evidence indicated no deaths across THC/CBD spray and placebo groups in a narrative review (2 RCTs) of adults with multiple sclerosis or allodynia. Treatment duration was 3 weeks, follow-up was end of treatment.
Oordt *et al.* (2021)	To investigate the efficacy, effectiveness, safety, cost-effectiveness, and budget impact of medical cannabis use in chronic pain and spasticity	THC/CBD products vs. placebo	Very low-certainty evidence indicated no deaths across THC/CBD spray and placebo groups in a narrative review (1 RCT) of adults with rheumatoid arthritis. Treatment duration was 3 weeks, follow-up was end of treatment.
Bosnjak-Kuharic *et al.* (2021)	To investigate the efficacy, effectiveness, safety, cost-effectiveness, and budget impact of medical cannabis use in chronic pain and spasticity	THC products vs. placebo	Very low-certainty evidence indicated no deaths across THC and placebo groups in a narrative review (1 RCT) of adults with multiple sclerosis. Treatment duration was 16 weeks, no follow-up was reported.
Oordt *et al.* (2021)	To determine the efficacy and safety of cannabinoids for the treatment of dementia	THC vs. placebo	Very low-certainty evidence indicated no significant difference in mortality across THC (nabilone and dronabinol) and placebo groups consisting adult populations with dementia (2 RCTs, meta-analysis). Treatment duration was 12 to 14 weeks, no follow-up was reported.
Any serious adverse events			
Mücke *et al.* (2018b)	To assess the efficacy, tolerability, and safety of cannabis-based medicines (herbal, plant-based, synthetic) compared to placebo or conventional drugs for conditions with chronic neuropathic pain in adults	Mixed cannabinoids and cannabis vs. placebo	Low-certainty evidence indicated no significant difference between mixed cannabinoid and cannabis compared with placebo groups in a meta-analysis (13 RCTs) of adults with mixed health conditions (multiple sclerosis, spinal cord injury, cancer, diabetes, HIV, plexus injury, pain). Treatment duration was 2 to 15 weeks, no follow-up was reported.
van den Elsen *et al.* (2014)	To integrate the evidence on indications, efficacy, safety and pharmacokinetics of medical cannabinoids in older subjects	Mixed cannabinoid vs. placebo	Very low-certainty evidence indicated one serious adverse event (grand mal seizure) in cannabinoid compared with no serious adverse events in placebo groups consisting of older adults with various health conditions (dementia, Parkinson's Disease, COPD) (4 RCTs, narrative synthesis). Treatment duration was 1 day--6 weeks, no follow-up was reported. Authors did not report inferential statistics, therefore we cannot comment on the significance of these findings.

McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	Cannabis vs. usual care	Very low-certainty evidence indicated significantly increased risk in cannabis compared with usual care groups in a narrative review (1 prospective cohort study) of adults with chronic non-cancer pain. Treatment duration was 13 months, no follow-up was reported.
Häuser *et al.* (2019)	How effective and safe are medical cannabis and cannabis-based medicines compared to controls in managing cancer pain in patients of any age?	THC/CBD vs. placebo	Low-certainty evidence indicated no significant difference between THC/CBD and placebo groups consisting adult populations with cancer (4 RCTs, meta-analysis). Treatment duration was 2-5 weeks, no follow-up was reported.
Häuser *et al.* (2019)	How effective and safe are medical cannabis and cannabis-based medicines compared to controls in managing cancer pain in patients of any age?	THC/CBD vs. placebo	Very low-certainty evidence indicated no significant difference between THC/CBD and placebo groups consisting of an adult population with cancer (1 RCT, narrative review). Treatment duration was 5 weeks, no follow-up was reported.
Fitzcharles *et al.* (2018b)	To examine the literature for evidence of the efficacy, tolerability, and safety of cannabinoids in chronic spinal pain, [fibromyalgia syndrome], [osteoarthritis], and [rheumatoid arthritis] pain	THC/CBD vs. placebo	Very low-certainty evidence indicated 0% prevalence in THC/CBD groups compared with 2% in placebo groups consisting of an adult population with rheumatic diseases (1 RCT, narrative synthesis). Treatment duration was 5 weeks, no follow-up was reported. Authors did not report inferential statistics, , therefore we cannot comment on the significance of these findings.
Fitzcharles *et al.* (2018b)	To examine the literature for evidence of the efficacy, tolerability, and safety of cannabinoids in chronic spinal pain, [fibromyalgia syndrome], [osteoarthritis], and [rheumatoid arthritis] pain	THC vs. placebo	Very low-certainty evidence indicated 3.3% prevalence in THC (nabilone) groups compared with 0% in placebo groups consisting of an adult population with rheumatic diseases (1 RCT, narrative synthesis). Treatment duration was 4 weeks, no follow-up was reported. Authors did not report inferential statistics; therefore we cannot comment on the significance of these findings.
Fitzcharles *et al.* (2018b)	To assess the efficacy, tolerability and safety of cannabinoids for fibromyalgia symptoms in adults	THC vs. placebo	Very low-certainty evidence indicated 0% prevalence in THC (nabilone) groups compared with 0% in placebo groups consisting an adult population with rheumatic diseases (1 RCT, narrative synthesis). Treatment duration was 4 weeks, no follow-up was reported. Authors did not report inferential statistics; therefore we cannot comment on the significance of these findings.
Walitt *et al.* (2016)	To assess the efficacy, tolerability and safety of cannabinoids for fibromyalgia symptoms in adults	THC vs. active control (amitriptyline)	Very low-certainty evidence indicated 0% prevalence in THC (nabilone) groups compared with 0% in amitriptyline groups consisting an adult population with rheumatic diseases (1 RCT, narrative synthesis). Treatment duration was 2 weeks, no follow-up was reported. Authors did not report inferential statistics; therefore we cannot comment on the significance of these findings.
Walitt *et al.* (2016)	To examine the literature for evidence of the efficacy, tolerability, and safety of cannabinoids in chronic spinal pain,	THC vs. active control (amitriptyline)	Very low-certainty evidence indicated 0% prevalence in THC (nabilone) groups compared with 0% in amitriptyline groups consisting of an adult population with rheumatic diseases (1 RCT, narrative synthesis).

	[fibromyalgia syndrome], [osteoarthritis], and [rheumatoid arthritis] pain		Treatment duration was 4 weeks, no follow-up was reported. Authors did not report inferential statistics; therefore we cannot comment on the significance of these findings.
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	THC vs. mixed control (placebo and gabapentin)	Very low-certainty evidence indicated no significant difference between THC and gabapentin groups a narrative review (1 prospective cohort study) of adults with mixed neuropathic pain. Treatment duration ranged from 6 months, no follow-up was reported.
TOLERABILITY			
Withdrawal due to adverse events			
McDonagh *et al.* (2022)	To assess the efficacy, tolerability, and safety of cannabis-based medicines (herbal, plant-based, synthetic) compared to placebo or conventional drugs for conditions with chronic neuropathic pain in adults	Mixed cannabinoids and cannabis vs. placebo	Low-certainty evidence indicated increased prevalence in mixed cannabinoid and cannabis compared with placebo groups in a meta-analysis (13 RCTs) of adults with mixed health conditions (multiple sclerosis, spinal cord injury, cancer, diabetes, and peripheral and central pain, HIV, plexus injury). Treatment duration was 2 to 15 weeks, no follow-up was reported.
Mücke *et al.* (2018b)	To evaluate the benefits and harms of cannabinoids for chronic pain	Cannabis vs. usual care	Very low-certainty evidence indicated increased prevalence in cannabis (4.65%) compared with usual care groups in a narrative review (1 prospective cohort study) of adults with chronic non-cancer pain. Treatment duration was 13 months, no follow-up was reported.
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	THC/CBD products vs. placebo	Low-certainty evidence indicated no significant difference between THC/CBD products compared with placebo groups in a meta-analysis (5 RCTs) of adults with mixed health conditions (rheumatoid arthritis, multiple sclerosis, neuropathic pain). Treatment duration was 5 to 15 weeks, no follow-up was reported.
Häuser *et al.* (2019)	How effective and safe are medical cannabis and cannabis-based medicines compared to controls in managing cancer pain in patients of any age?	THC/CBD vs. placebo	Low-certainty evidence indicated significantly increased risk in THC/CBD compared with placebo groups consisting adult populations with cancer (4 RCTs, meta-analysis). Treatment duration was 2-5 weeks, no follow-up was reported.
Häuser *et al.* (2019)	How effective and safe are medical cannabis and cannabis-based medicines compared to controls in managing cancer pain in patients of any age?	THC/CBD vs. placebo	Very low-certainty evidence indicated significantly increased risk in THC/CBD compared with placebo groups consisting of an adult population with cancer (1EERW RCT, narrative review). Treatment duration was 5 weeks, no follow-up was reported.
Fitzcharles *et al.* (2018b)	To examine the literature for evidence of the efficacy, tolerability, and safety of cannabinoids in chronic spinal pain, [fibromyalgia syndrome], [osteoarthritis], and [rheumatoid arthritis] pain	THC/CBD vs. placebo	Very low-certainty evidence indicated 0% withdrawals in THC/CBD groups compared with 11% in placebo groups consisting of an adult population with rheumatic diseases (1 RCT, narrative synthesis). Treatment duration was 5 weeks, no follow-up was reported. Authors did not report inferential statistics; therefore we cannot comment on the significance of these findings.

Oordt *et al.* (2021)	To investigate the efficacy, effectiveness, safety, cost-effectiveness, and budget impact of medical cannabis use in chronic pain and spasticity	THC/CBD vs. placebo	Very low-certainty evidence indicated no significant difference between THC/CBD products compared with placebo groups in a meta-analysis (2 RCTs) of adults with cancer. Treatment duration was 3 weeks, no follow-up was reported.
Oordt *et al.* (2021)	To investigate the efficacy, effectiveness, safety, cost-effectiveness, and budget impact of medical cannabis use in chronic pain and spasticity	THC/CBD vs. placebo	Very low-certainty evidence indicated significant increased risk in THC/CBD compared with placebo groups in a meta-analysis (4 RCTs) of adults with mixed health conditions (multiple sclerosis, allodynia) experiencing neuropathic pain. Treatment duration was 4-14 weeks, no follow-up was reported.
Bahji *et al.* (2020)	To comprehensively appraise the evidence for the efficacy and acceptability of a range of cannabinoid and cannabis-preparations—including THC, CBD, and their synthetic analogues—in reducing symptoms associated with anxiety disorders		No findings on withdrawal due to adverse events were reported despite being a primary outcome of the study.
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	THC products vs. placebo	Moderate-certainty evidence indicated no significant difference between THC and placebo groups in a meta-analysis (5 RCTs) of adults with mixed health conditions (fibromyalgia, multiple sclerosis, visceral pain). Subgroup analysis was conducted by cannabinoid type (synthetic, extract). No significant difference was found in synthetic THC compared with placebo (4 RCTs), however significantly increased risk was reported in THC extract compared with placebo groups (1 RCT). Treatment duration was 4 to 16 weeks, no follow-up was reported.
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	THC products vs. placebo	Moderate-certainty evidence indicated no significant difference in synthetic THC compared with placebo groups in a meta-analysis (4 RCTs, subgroup analysis) of adults with mixed health conditions (fibromyalgia, multiple sclerosis, visceral pain). Treatment duration was 4 to 16 weeks, no follow-up was reported.
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	THC products vs. placebo	Very low-certainty evidence indicated significantly increased risk in THC extract compared with placebo groups (1 RCT, subgroup analysis) consisting of adults with multiple sclerosis. Treatment duration was 12 weeks, no follow-up was reported.
Paunescu *et al.* (2020)	Which is the level of evidence, from quantitative and qualitative point of view, concerning the efficacy and safety of the treatment with psychotropic cannabinoids of	THC vs. placebo	Very low-certainty evidence indicated one drop-out in THC and one drop-out in placebo groups consisting of an adult population with dementia (1 RCT, narrative synthesis). Treatment duration was 12 weeks, no follow-up was reported. Authors did not report inferential statistics; therefore we cannot comment on the significance of these findings.

	neuropsychiatric symptoms in Alzheimer's Disease?		
Oordt *et al.* (2021)	To investigate the efficacy, effectiveness, safety, cost-effectiveness, and budget impact of medical cannabis use in chronic pain and spasticity	THC products vs. placebo	Very low-certainty evidence indicated withdrawal of 9.7% of participants due to adverse events in treatment arm compared to 0.9% in placebo arm in a narrative review (1 RCT) of adults with multiple sclerosis. No summary statistics were reported. Treatment duration was 16 weeks, no follow-up was reported.
Fitzcharles *et al.* (2018b)	To examine the literature for evidence of the efficacy, tolerability, and safety of cannabinoids in chronic spinal pain, [fibromyalgia syndrome], [osteoarthritis], and [rheumatoid arthritis] pain	THC vs. placebo	Very low-certainty evidence indicated 15% withdrawals in THC (nabilone) groups compared with 0% in placebo groups consisting of an adult population with rheumatic diseases (1 RCT, narrative synthesis). Treatment duration was 4 weeks, no follow-up was reported. Authors did not report inferential statistics; therefore we cannot comment on th significance of these findings.
Walitt *et al.* (2016)	To assess the efficacy, tolerability and safety of cannabinoids for fibromyalgia symptoms in adults	THC vs. placebo	Very low-certainty evidence indicated 15% withdrawals in THC (nabilone) groups compared with 0% in placebo groups consisting of an adult population with rheumatic diseases (1 RCT, narrative synthesis). Treatment duration was 4 weeks, no follow-up was reported. Authors did not report inferential statistics; therefore we cannot comment on the significance of these findings.
Walitt *et al.* (2016)	To assess the efficacy, tolerability and safety of cannabinoids for fibromyalgia symptoms in adults	THC vs. active control (amitriptyline)	Very low-certainty evidence indicated 3% withdrawals in THC (nabilone) groups compared with 0% in amitriptyline groups consisting of an adult population with rheumatic diseases (1 RCT, narrative synthesis). Treatment duration was 2 weeks, no follow-up was reported. Authors did not report inferential statistics, therefore we cannot comment on the significance of these findings.
Fitzcharles *et al.* (2018b)	To examine the literature for evidence of the efficacy, tolerability, and safety of cannabinoids in chronic spinal pain, [fibromyalgia syndrome], [osteoarthritis], and [rheumatoid arthritis] pain	THC vs. active control (amitriptyline)	Very low-certainty evidence indicated 3% withdrawals in THC (nabilone) groups compared with 0% in amitriptyline groups consisting of an adult population with rheumatic diseases (1 RCT, narrative synthesis). Treatment duration was 2 weeks, no follow-up was reported. Authors did not report inferential statistics; therefore we cannot comment on the significance of these findings.
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	THC vs. mixed control (placebo and gabapentin)	Very low-certainty evidence indicated no significant difference between THC and gabapentin groups or between the cannabinoid group and the combined cannabinoid/gabapentin group in a narrative review (1 prospective cohort study) of adults with mixed neuropathic pain. Treatment duration was six months, no follow-up was reported.

Appendix I Review characteristics of included reviews

Author (year)	Research question	Study population(s)	Countries	No. of studies / Sample size/ study design	Age/ gender	Study intervention(s)/ comparator(s)	Primary outcome(s)	Secondary outcome(s)	Treatment duration/ follow-up	Primary study years	Industry funding for primary studies
Abdallah *et al.* (2020)	To evaluate analgesic outcomes in patients receiving cannabis compounds for acute pain management in the surgical setting	Acute pain management associated with: Acute fracture or trauma (n=56); renal surgery (n=100); elective abdominal hysterectomy (n=20); various major surgeries (n=41); radial prostatectomy (n=105); various elective surgeries (n=340)	Not reported	6 n=662 RCT	Not reported Not reported	Cannabinoids or cannabinoid containing product (levonantradol, THC, nabilone) Vs. Control (not specified 6 RCTs). Additional active comparator arms include pethidine (1 RCT); ketoprofen (1 RCT)	Analgesic consumption, as measured by cumulative oral morphine equivalent consumption the first 24 hour time interval; Rest pain severity, as measured by Visual Analog Scale (VAS) pain scores, at 24 hours postoperatively	Cumulative postoperative oral morphine equivalent (mg) up to 48 h; postoperative rest pain severity (VAS) (0–2 h), 6, and 12 h. Safety outcomes: opioid-related side effects and cannabinoid-related side effects	0-12 hours post-operative Not reported	1981 - 2017	No
AminiLari *et al.* (2021)	To explore the effectiveness of medical cannabis for impaired sleep	Impaired sleep associated with: Chronic pain (n=2172); Cancer-related pain (n=1674); neuropathic pain (n=984); Parkinson's	Not reported	38 5058 RCT	23.6-67.0 years 53.3% female	Medical cannabis or cannabinoids (Nabilone, Sativex, Dronabinol, Cannabis flowers, Cannador, Cannabis extract, Delta-9	Sleep quality, sleep disturbance, other sleep-related outcomes	Adverse events	2-16 weeks 14-105 days	1983 - 2020	Industry funded (16 RCTs); non-industry funded (7 RCTs);

Author (year)	Research question	Study population(s)	Countries	No. of studies / Sample size/ study design	Age/ gender	Study intervention(s)/ comparator(s)	Primary outcome(s)	Secondary outcome(s)	Treatment duration/follow-up	Primary study years	Industry funding for primary studies
		Disease (n=57); post-traumatic stress disorder (n=10); anorexia nervosa (n=11); HIV-associated neuropathic pain (n=34); multiple sclerosis (n=43); sleep apnea (n=73)				THC, Whole plant extracts) Vs. Placebo or active comparator					not reported (2 RCTs); partially industry funded (13 RCTs)
Andreae *et al.* (2015)	To perform a Bayesian responder meta-analysis of individual patient data to study whether inhaled cannabis provides relief for chronic neuropathic pain	Chronic neuropathic pain associated with: HIV (n=89); trauma or surgery (n=23); spinal cord injury, peripheral neuropathy, or nerve injury (n=38); reflex sympathetic dystrophy, peripheral neuropathy, postherpetic neuralgia, poststroke pain, multiple sclerosis, or spinal cord injury (n=39)	Not reported	5 189 RCT	45.4-50 years 25.9% female	Inhaled cannabis Vs. Placebo	Neuropathic pain	Adverse events	5 hours-2 weeks Hours to days or weeks	2007 - 2013	No

Author (year)	Research question	Study population(s)	Countries	No. of studies / Sample size/ study design	Age/ gender	Study intervention(s)/ comparator(s)	Primary outcome(s)	Secondary outcome(s)	Treatment duration/follow-up	Primary study years	Industry funding for primary studies
Bahji *et al.* (2020)	To comprehensively appraise the evidence for the efficacy and acceptability of a range of cannabinoid and cannabis preparations in reducing symptoms associated with anxiety disorders	Anxiety symptoms associated with: Generalised anxiety disorder (n=323); post-traumatic stress disorder (n=176); social affective disorder (n=34)	Brazil, Israel, North America	11 533 RCT, open-label	23.5-52.3 years 32.8% female	Cannabis based medications (nabilone, THC, CBD) Vs. Placebo; not reported	Generalised anxiety disorder; social anxiety disorder; post traumatic stress disorder; study discontinuation due to adverse events	Adverse events	1 - 104 weeks Not reported	1981 - 2017	Not reported
Bajtel *et al.* (2022)	To analyse the adverse events of dronabinol and nabilone based on the meta-analysis of placebo-controlled trials	Adverse events of cannabinoid medicines used for: Chemosensory perception (n=46); chest pain (n=19); dementia (n=89); fibromyalgia (n=40); gastrointestinal transit (n=66); hyperalgesia and other central nervous	Austria/Germany, Canada, Denmark, Netherlands, UK, USA	16 1046 RCT	22.5-87 years 57.3% female	Dronabinol or nabilone Vs. Placebo	Adverse events	None	2 days-16 weeks Not reported	2002 - 2019	Not reported

Author (year)	Research question	Study population(s)	Countries	No. of studies / Sample size/ study design	Age/ gender	Study intervention(s)/ comparator(s)	Primary outcome(s)	Secondary outcome(s)	Treatment duration/follow-up	Primary study years	Industry funding for primary studies
		system symptoms (n=30); multiple sclerosis (n=699); older people (n=12); spasticity (n=13); spinal cord injury and spasticity (n=12); not reported (n=20)									
Belgers *et al.* (2023)	To assess the effects of cannabinoids on health-related quality of life in oncological patients and patients with central nervous system disease	Amyotrophic lateral sclerosis (n=27); Alzheimer's disease (n=42); cancer (n=747); Huntington's disease (n=26); multiple sclerosis (n=1620); Parkinson's disease (n=91)	Not reported	17 2553 RCT	Not reported	Cannabinoids (dronabinol, nabilone, cannabis extract, CBD) Vs. Placebo or active comparator	Health-related quality of life, mental well-being	None	2 weeks-36 months Not reported	2002 - 2021	Industry funded (11 RCTs); not industry funded (6 RCTs)
Bialas *et al.* (2022)	To assess the long-term effectiveness, tolerability and safety of cannabis-based medicines in	Chronic non-cancer pain associated with: Neuropathic pain, musculoskeletal pain, other pain, visceral pain, headache, combinations (n=1045);	Canada (2); Israel (2); Italy (2)	6 2686 Prospective cohort	36-82 years 50.6% female	Cannabinoids (either phytocannabinoids such as herbal cannabis [hashish, marihuana], plant-based cannabinoids [cannabidiol,	Pain intensity from baseline to follow-up, pain relief of 50%/30% or greater, adverse events (drop-out due	Sleep, depression, anxiety, health-related quality of life, opioid cessation, adverse events (nervous system disorders, psychiatric disorders, gastrointestinal	6-12 months Not reported	2015 - 2021	Not reported (2 studies); cannabis-producing

Author (year)	Research question	Study population(s)	Countries	No. of studies / Sample size/ study design	Age/ gender	Study intervention(s)/ comparator(s)	Primary outcome(s)	Secondary outcome(s)	Treatment duration/follow-up	Primary study years	Industry funding for primary studies
	the management of chronic noncancer pain in patients of any age in long-term observational studies	fibromyalgia (n=102); Musculoskeletal pain, neuropathic pain, lower back pain, other pain conditions, cancer (n=206); back pain, osteoarthritis, chronic headaches (n=751); fibromyalgia, cancer, post-traumatic stress disorder (n=367); nociceptive pain, neuropathic pain, other (n=215)				nabiximole] or pharmacological [synthetic] cannabinoids [e.g. dronabinol, levonantradol, nabilone]) Vs. No comparison	to adverse events and proportion of patients with serious adverse events), patients that completed study, patients that dropped out due to lack of efficacy, disability	disorders, pulmonary disorders), aberrant drug behaviour			enterprise, by public funding (1 study); cannabis-producing enterprise (1 study); no funding (1 study)
Black *et al.* (2019)	To examine the available evidence for all types of medicinal cannabinoids and all study designs to ascertain the impact of medicinal cannabinoids	Remission from and symptoms associated with: Depression (n=2551); anxiety (n=605); Tourette (n=36); attention deficit hyperactivity disorder (n=30); post-traumatic stress disorder (n=10); psychosis (n=281)	Brazil; Canada; Germany; Italy; Netherlands; Spain; Switzerland; UK; UK, Israel, Czech Republic; UK,	36 3088 RCT	23.6-61.2 years 54% female	Any type and formulation of medicinal cannabinoid (Nabiximols, dronabinol, nabilone, cannabis sativa, THC or CBD or THC:CBD extract) Vs.	Depression, anxiety, attention deficit hyperactivity disorder, Tourette syndrome, post-traumatic stress disorder, psychosis	Global functioning, quality of life, and patient or caregiver impression of change, safety of medicinal cannabinoids for mental health symptoms and disorders, including all-cause, serious, and treatment-related	1 days to 156 weeks Not reported	2001 - 2018	Not reported

Author (year)	Research question	Study population(s)	Countries	No. of studies / Sample size/ study design	Age/ gender	Study intervention(s)/ comparator(s)	Primary outcome(s)	Secondary outcome(s)	Treatment duration/follow-up	Primary study years	Industry funding for primary studies
	on remission from and symptoms (and safety) of depression, anxiety, post-traumatic stress disorder, psychosis, attention deficit hyperactivity disorder and Tourette syndrome		Romania, Poland; UK, Spain, Poland, Czech Republic, Italy; USA, USA, Europe, Latin America and South Africa			Active comparator (amisulpride; dihydrocodeine; ibuprofen) or placebo		adverse events and study withdrawals			
Boland *et al.* (2020)	The aim was to determine the beneficial and adverse effects of cannabinoids compared with placebo or other active agents for the treatment of cancer-related	Cancer-related pain: Cancer (advanced cancer, patients with chemotherapy-induced neuropathic pain (n=18) and cancer-related pain) (n=1460)	Not reported	6 1460 RCT	Not reported (Adult population) Not reported	Cannabinoids (THC/CBD, THC extract, nabiximols, Sativex) and medical cannabis Vs. Placebo	Absolute change in mean pain intensity	Adverse events, dropouts	2-9 weeks Not reported	2010 - 2018	Not reported

Author (year)	Research question	Study population(s)	Countries	No. of studies / Sample size/ study design	Age/ gender	Study intervention(s)/ comparator(s)	Primary outcome(s)	Secondary outcome(s)	Treatment duration/follow-up	Primary study years	Industry funding for primary studies
	pain in adults from RCTs										
Bosnjak-Kuharic *et al.* (2021)	To determine the efficacy and safety of cannabinoids for the treatment of dementia	People with dementia	Canada, The Netherlands, USA	4 126 RCT	Mean age 76.9 years 37.9% female (1 RCT not reported)	Cannabinoids (nabilone, THC, dronabinol) Vs. Placebo	Cognitive function; behavioural and psychological symptoms of dementia; adverse events	Nervous system/psychiatric/gastrointestinal disorders; sedation; change in functional outcomes; dementia severity; agitation/aggression; weight; nutrition; body mass index; Caloric intake; quality of life-Alzheimer's Disease scale; carer burden; all-cause discontinuation; all-cause mortality	3-14 weeks 2 weeks (1 RCT); Not reported (3 RCTs)	1997 - 2019	Non-industry (public) (2 RCTs); public and industry (1 RCT); sponsors and collaborators (1 RCT)
Butler *et al.* (2015)	What are the benefits (short-term and long-term) of cannabis use for the treatment of non-cancer pain? [and] What are the harms (short-	Non-cancer pain associated with: multiple sclerosis (n=549), fibromyalgia (n=72); rheumatoid arthritis (n=58); neuropathic pain (n=966); brachial plexus (n=48); overuse of headache medication (n=30);	Austria, Canada, Denmark, Italy, UK, USA, Czech Republic, Spain, France, Romania, Belgium	19 1764 RCT	39-62.8 years (not reported in 1 RCT) 57.4% female (not reporte	Smokable marijuana; marijuana extraction products; dronabinol; nabilone; nabiximols Vs.	Pain measures (visual analog scales, numeric rating scale amoung others)	Sleep, anxiety, depression, quality of life, global patient satisfaction, neuropathic pain assessed across multiple sclerosis; fibromyalgia; rheumatoid arthritis; other painful conditions	2-124 weeks Not reported	2004 - 2015	Industry (17); not reported (1); no funding (1)

Author (year)	Research question	Study population(s)	Countries	No. of studies / Sample size/ study design	Age/ gender	Study intervention(s)/ comparator(s)	Primary outcome(s)	Secondary outcome(s)	Treatment duration/follow-up	Primary study years	Industry funding for primary studies
	term and long-term) of cannabis use for the treatment of non-cancer pain?	motor neuron syndrome (n=13); chronic non-cancer pain (n=28)			d in 2 RCTs)	Placebo (17 RCTs); amitriptyline (1 RCT); dihydrocodeine (1 RCT)					
de Aquino *et al.* (2022)	To investigate opioid withdrawal-alleviating effects of both cannabis and THC among opioid-dependent persons, regardless of [opioid use disorder] treatment status	Opioid dependence (n=12); opioid use disorder (n=60)	Not reported	2 72 RCT	Not reported Not reported	Cannabis and THC (dronabinol) Vs. Placebo	Opioid withdrawal in response to exposure to cannabis or THC	Adverse events	8 days (1 RCT), 5 weeks (1 RCT) 8 weeks (1 RCT), not reported (1 RCT)	2015 - 2016	Not reported
de Rovare *et al.* (2017)	To summarize the effects of cannabinoids compared with usual care, placebo	Spasticity associated with: multiple sclerosis (n=2246); spinal cord injury (n=127) motor neuron syndrome	Europe, USA, Canada, not reported (1 RCT)	16 2597 RCT	42.4-58.6 years	Cannabis plant, with any compounds such as THC and/or CBD, regardless the type of extracts	Spasticity, spasm frequency, spasm severity	Pain, cognitive function, daily activities, motricity, bladder function, dizziness, somnolence,	2-19 weeks Not reported	2002 - 2013	Not reported

Author (year)	Research question	Study population(s)	Countries	No. of studies / Sample size/ study design	Age/ gender	Study intervention(s)/ comparator(s)	Primary outcome(s)	Secondary outcome(s)	Treatment duration/follow-up	Primary study years	Industry funding for primary studies
	for spasticity due to multiple sclerosis or paraplegia	(n=13); neurological diagnosis (n=21); incontinence (n=135); general spasticity (n=55)			Not reported	(e.g. oil, hash, tinctures) Vs. Placebo		headache, nausea, dry mouth			
Filippini *et al.* (2022)	To assess benefit and harms of cannabinoids including synthetic, or herbal and plant-derived cannabinoids, for symptomatic treatment in [multiple sclerosis]	People with multiple sclerosis	Canada, Czech republic, UK, Austria, Denmark, Italy, Germany, The Netherlands, Switzerland, Belgium, Romania, Spain, France, Poland	25 3763 RCT	18-60 years Range 50-80% female	Any cannabinoids including herbal cannabis, cannabis flowers, plant-based cannabinoids (Nabiximols, Cannabidiol), or synthetic cannabinoids (Dronabinol, Nabilone) Vs. Placebo or any active comparator	Spasticity; chronic neuropathic pain; patient global impression of change; health-related quality of life	Serious adverse events; adverse events; severity of spasms; fatigue; sleep problems; mobility; depression; anxiety; carer's global impression of change; reduced use of other treatments	3 days - 156 weeks Not reported	2002 - 2018	Industry (15 RCTs); public funding (8 RCTs); mixed funding (2 RCTs)
Fisher *et al.* (2021)	To provide a comprehensive summary of the evidence from primary	Clinical acute and chronic pain associated with: neuropathic pain (n=544); cancer	Not reported	30 5869 RCT	39-63.5 years 59.3% female	Any type of cannabinoid product, natural or synthetic (Cannabis, THC:CBD, THC,	30% reduction in pain intensity; 50% reduction in pain intensity	Pain intensity change scores; Physical functioning (change scores); Emotional functioning (change	18 hours - 60 days Not reported	1975 - 2019	Industry (14 RCTs); non-industry

Author (year)	Research question	Study population(s)	Countries	No. of studies / Sample size/ study design	Age/ gender	Study intervention(s)/ comparator(s)	Primary outcome(s)	Secondary outcome(s)	Treatment duration/follow-up	Primary study years	Industry funding for primary studies
	RCTs of cannabinoids, cannabis, and [cannabis-based medicine] in clinical acute and chronic pain management, across the lifespan	(n=1406), acute pain after surgery (n=445); multiple sclerosis (n=2673); diabetes (n=595); spinal cord injury (n=158); brachial plexus avulsion (n=48)			(not reported in 2 RCTs)	dronabinol, nabilone, nabiximols) Vs. Placebo or active comparator (piritramide (1 RCT); placebo and codeine (2 RCTs); placebo and ibuprofen (1 RCT); dihydrocodeine (1 RCT))		scores); sleep quality (change scores); participants with any adverse event			(12 RCTs); not reported (3 RCTs)
Fitzcharles *et al.* (2016) A	To assess the efficacy, tolerability, and safety of cannabinoids (phyto- and syntheto-) in the management of rheumatic diseases	Efficacy, tolerability and safety of cannabinoids associated with: Rheumatoid arthritis (n=58); fibromyalgia (n=71)	Not reported	3 129 RCT	Not reported Not reported	Cannabinoids (nabilone, nabiximols) Vs. Placebo (2 RCTs) or active comparator (amitriptyline (1 RCT))	Pain, sleep disturbance, quality of life	Tolerability, adverse effects	2-8 weeks Not reported	2006 - 2010	Not reported

Author (year)	Research question	Study population(s)	Countries	No. of studies / Sample size/ study design	Age/ gender	Study intervention(s)/ comparator(s)	Primary outcome(s)	Secondary outcome(s)	Treatment duration/follow-up	Primary study years	Industry funding for primary studies
Fitzcharles *et al.* (2016) B	To examine the literature for evidence of the efficacy, tolerability, and safety of cannabinoids in chronic spinal pain, [fibromyalgia syndrome], [osteoarthritis], and [rheumatoid arthritis] pain	Pain associated with: Fibromyalgia (n=72); chronic therapy-resistant pain caused by the skeletal and locomotor system (n=30); rheumatoid arthritis (n=58)	Austria, Canada, UK	4 160 RCT	Mean age range 49-55 years 82.9% female	Cannabinoids (either phytocannabinoids such as herbal cannabis, plant-based cannabinoids or syntheto-cannabinoids Vs. Placebo (3 RCTs); amitriptyline (1 RCT)	Patient-reported pain relief of 50% or greater; Patient global impression of change; Withdrawal due to adverse events; Serious adverse events	Health related quality of life; fatigue; depression; quality of sleep; participant-reported pain relief of >30%; anxiety; disability; adverse events	1-16 weeks Not reported	2006 - 2010	Not reported (1 RCT); Non-industry (1 RCT); Industry (2 RCTs)
Giossi *et al.* (2022)	To conducte a systematic review with a meta-analysis to investigate the role of cannabinoids in the treatment of chronic primary pain	Chronic primary pain associated with: Fibromyalgia (n=115), chronic primary chest pain (n=19), irritable bowel syndrome (n=68), chronic regional pain syndrome (n=22), various chronic secondary pain conditions (n=16)	Not reported	8 240 RCT	Mean age range 31-52 years 83.75% female	Any type and preparation of cannabinoid treatment (THC, dronabinol, nabilone, CBD, bedrocan, bediol, bedrolite) Vs.	Pain (chronic primary pain) reduction	Quality of life, appetite, anxiety, depression and sleep, adverse events	2 days to 10 weeks Not reported	2008 - 2021	Not reported

Author (year)	Research question	Study population(s)	Countries	No. of studies / Sample size/ study design	Age/ gender	Study intervention(s)/ comparator(s)	Primary outcome(s)	Secondary outcome(s)	Treatment duration/follow-up	Primary study years	Industry funding for primary studies
						Placebo (7 RCTs) and amitriptyline (1 RCT)					
Hammond *et al.* (2021)	To compare the effects of cannabis-based medicinal products against both placebo and active treatment in anorexia–cachexia syndrome for appetite stimulation, change in body mass, and quality of life	AIDS patients with anorexia-associated weight loss (n=139); cancer-associated cachexia (n=712); HIV wasting syndrome (n=50); non-small cell lung cancer patients with anorexia (n=33)	Not reported	5 934 RCT	Mean age 53 years Not reported	Cannabis-based medicines or their synthetic analog (dronabinol, cannabis extract, THC, nabilone) Vs. Placebo (3 RCTs); megestrol acetate (2 RCTs)	Change in appetite; Change in weight; Quality of life; Acceptability of treatment	None	4-12 weeks Not reported	1995 - 2018	Not reported
Häuser *et al.* (2019)	How effective and safe are medical cannabis and cannabis-based	All studies included only patients with moderate to severe cancer pain which had not adequately responded to	European; European, Asian and Middle East; Europe and	5 1567 RCT	Mean age range 58-61 years	Medical cannabis and cannabis-based medicines (plant-based cannabinoids [dronabinol, nabiximols]), or	Pain relief of 50% or greater; Global impression to be much or very much	Pain relief of 30% or greater; Mean pain intensity; Sleep problems; Daily maintenance opioid dosage; Daily break-	2-5 weeks Not reported	2010 - 2018	Industry funded (5 RCTs)

Author (year)	Research question	Study population(s)	Countries	No. of studies / Sample size/ study design	Age/ gender	Study intervention(s)/ comparator(s)	Primary outcome(s)	Secondary outcome(s)	Treatment duration/follow-up	Primary study years	Industry funding for primary studies
	medicines compared to controls in managing cancer pain in patients of any age?	opioids, with three studies specifically defining criteria for failure of opioid therapy	the USA; and Europe, USA, Latin America and South Africa		Not reported	pharmacological (synthetic) cannabinoids [nabilone] Vs. Placebo	improved; Drop out due to adverse events; Serious adverse events	through opioid dosage; Nervous system/ Psychiatric/ Gastrointestinal disorder adverse events			
Kafil *et al.* (2018) A	The primary objective was to assess the efficacy and safety of cannabis for induction and maintenance of remission in people with Crohn's disease	Crohn's disease (n=93)	Not reported	3 93 RCT	At least 20 years old (2 RCTs); Not reported (1 RCT) Not reported	Any form of cannabis or its cannabinoid derivatives (natural or synthetic): Cannabis cigarettes, CBD oil, CBD and THC oil Vs. Placebo	Clinical remission rates	Clinical response, C-reactive protein, quality of life, adverse events, serious adverse events	8 weeks 2 weeks	2013 - 2017	Not reported
Kafil *et al.* (2018) B	To assess the efficacy and safety of cannabis and cannabinoids for the treatment of	Ulcerative colitis (all)	Czech Republic; Not reported (1 RCT)	2 92 RCT	18-65 years (1 RCT); Not reporte	Any form of cannabis or cannabinoid derivatives (CBD, THC, cannabis plant) Vs.	Clinical remission at study endpoint; clinical relapse at study endpoint	Clinical response; C-reactive protein; Quality of life; Adverse events; serious adverse events; withdrawal due to adverse events	8-10 weeks Not reported	2018	Industry (1 RCT); Not reported (1 RCT)

Author (year)	Research question	Study population(s)	Countries	No. of studies / Sample size/ study design	Age/ gender	Study intervention(s)/ comparator(s)	Primary outcome(s)	Secondary outcome(s)	Treatment duration/follow-up	Primary study years	Industry funding for primary studies
	patients with ulcerative colitis				d (1 RCT) Not reported	Placebo					
Kopelli *et al.* (2020)	To conduct a systematic review and meta-analysis focusing only on RCTs in patients with schizophrenia or other types of schizophrenia-like psychoses that assessed the efficacy of CBD oil compared to placebo or any antipsychotic drug either as monotherapy or add-on therapy	Acute paranoid schizophrenia (1 RCT); stable chronic schizophrenia (1 RCT); schizophrenia or a related psychotic disorder (1 RCT)	Not reported	3 166 RCT	Mean age range 30.1-47.4 years Not reported	Cannabidiol oil Vs. Placebo or any antipsychotic drug either as monotherapy or add-on therapy (active comparator amisulpride (antipsychotic) (1 RCT)	Efficacy; cognitive function	Extrapyramidal symptoms; weight gain; prolactin increase; response to treatment; positive symptoms; negative symptoms; adverse events	4-6 weeks Not reported	2012 - 2018	Not reported

Author (year)	Research question	Study population(s)	Countries	No. of studies / Sample size/ study design	Age/ gender	Study intervention(s)/ comparator(s)	Primary outcome(s)	Secondary outcome(s)	Treatment duration/follow-up	Primary study years	Industry funding for primary studies
Longo *et al.* (2021)	In adults with chronic pain, what is the effect of cannabis on pain intensity?	Pain associated with: Advanced cancer unalleviated by opioids (n=1539); chronic abdominal pain pancreatitis (n=25); neuropathic pain (n=38); neuropathic pain chemo- therapy (n=18); fibromyalgia (n=57); surgery/chronic pancreatitis (n=65); spinal cord injury (n=7); multiple sclerosis (n=15)	Not reported	13 1764 RCT	Not reported Not reported	Cannabis of any formulation (nabilone, dronabinol, THC:CBD, THC, bedrocan, bediol, bedrolite) Vs. Placebo (10 RCTs); amitriptyline (1 RCT); diazepam (1 RCT); diphenhydramine (1 RCT)	Reduction in pain intensity, pain impact, pain quality	Mood, quality of life, opioid use, patient global impression of change, subject global impression of change, sleep, adverse events and sleep	1-18 weeks Not reported	2010 - 2019	Not reported
Lutge *et al.* (2013)	This review aims to objectively assess the studies that have examined the medical use of cannabis for reducing morbidity and	HIV (N=330)	Not reported	7 330 RCT	Not reported (5 RCTs); age range 21-50 (2 RCTs)	Smoked marijuana, ingested marijuana, smoked hashish, ingested hashish, ingested THC (dronabinol, or any other pharmaceutically produced form) Vs.	Mortality, morbidity	Change in weight, body fat, appetite, food and caloric intake, nausea and vomiting, performance and mood; subjective experience of drug effects; effect on peripheral neuropathy; effect on pharmacokinetics of	21-84 days Not reported	1993 - 2009	Not reported

Author (year)	Research question	Study population(s)	Countries	No. of studies / Sample size/ study design	Age/ gender	Study intervention(s)/ comparator(s)	Primary outcome(s)	Secondary outcome(s)	Treatment duration/follow-up	Primary study years	Industry funding for primary studies
	mortality in patients with HIV/AIDS				Not reported	Placebo		protease inhibitors; effect on viral load and CD4 count; physiological measures; adverse events			
McDonagh *et al.* (2022)	To evaluate the benefits and harms of cannabinoids for chronic pain	Chronic pain associated with: Fibromyalgia (n=50); visceral pain, chronic pancreatitis and postsurgical abdominal pain (n=62); neuropathic pain(multiple sclerosis (n=963), diabetes (n=55), chemotherapy (n=16), mixed(n=556); rheumatoid arthritis (n=58); HIV (n=465); chronic non-cancer pain mixed (n=1945); mixed (primarily musculoskeletal) (n=46)	Not reported	23 RCTs N=1636 Cohort N=2580 RCT and Prospective cohort studies	Mean age range 50-65 years (RCTs); Not reported in cohort studies 67.4% female (RCTs); 59% female (cohort)	Cannabis products (THC, CBD, THC:CBD, CBDV, nabilone, marijuana, mixed cannabis products) Vs. Placebo (18 RCTs); gabapentin (1 prospective cohort); no treatment or usual care (4 prospective cohort)	Pain severity, ≥30% pain improvement, overall function or disability, adverse events, withdrawal due to adverse events, serious adverse events	Quality of life, mental health, sleep, and effect on opioid use	4-16 weeks (RCTs); 12-208 weeks (cohort) Not reported (RCT); 52 weeks (1 cohort study)	2005 - 2021	Not reported

Author (year)	Research question	Study population(s)	Countries	No. of studies / Sample size/ study design	Age/ gender	Study intervention(s)/ comparator(s)	Primary outcome(s)	Secondary outcome(s)	Treatment duration/follow-up	Primary study years	Industry funding for primary studies
McKee *et al.* (2021)	The aim of this systematic review and meta-analyses is to not only offer the most recent examination of the literature in this area, but as well approach the clinical indications for [cannabinoid-based products] in mental health from the lens of a health regulatory board	Attention deficit hyperactivity disorder (n=30); anorexia nervosa (n=48); anxiety (n=54); cannabis use disorder (n=483); obsessive compulsive disorder (n=12); opioid use disorder (n=120); schizophrenia (n=176); post-traumatic stress disorder (n=10); tobacco use disorder (n=24); Tourette's syndrome (n=36)	Not reported	28 933 RCT	Not reported Not reported	A single, or repeated administration of a cannabinoid or [cannabinoid-based products] (nabiximols, dronabinol, CBD, nabilone, cannabis, epidiolex, THC) Vs. Placebo (25 RCTs); amisulpride (1 RCT); motivational enhancement/cognitive behavioural therapy (1 RCT); not reported (1 RCT)	Change in symptom frequency or severity for attention deficit hyperactivity disorder; anorexia nervosa; anxiety; cannabis use disorder; obsessive compulsive disorder; opioid use disorder; schizophrenia; post-traumatic stress disorder; tobacco use disorder; Tourette's syndrome	None	3 days to 16 weeks 28 day follow up (1 RCT), follow-up was not reported (27 RCTs)	1981 - 2020	Not reported

Author (year)	Research question	Study population(s)	Countries	No. of studies / Sample size/ study design	Age/ gender	Study intervention(s)/ comparator(s)	Primary outcome(s)	Secondary outcome(s)	Treatment duration/follow-up	Primary study years	Industry funding for primary studies
McParland *et al.* (2023)	To evaluate the impact of therapeutic cannabinoids on sleep quality, analgesic efficacy, and adverse effects in patients with neuropathic pain syndromes	Neuropathic pain associated with: Multiple sclerosis (n=429); brachial plexus chronic neuropathic pain (n=48); any neuropathic pain (n=125); any peripheral neuropathic pain (n=246); diabetic peripheral neuropathy (n=26); post-traumatic or post-operative neuropathic pain (n=22)	Canada; Netherlands; UK; UK, Czech Republic, Romania, Belgium, Canada; UK, Czech Republic, Canada, Spain, France	8 896 RCT	Mean 51.1 years 62.2% female (not reported in 3 RCTs)	Synthetic and natural cannabinoids for a neuropathic pain state through both inhaled and oral routes (THC, CBD, nabilone) Vs. Placebo	Sleep quality; daytime somnolence	Pain scores; EuroQol 5-D quality of life; patient global impression of change; adverse events	2-15 weeks Not reported	2004 - 2017	Industry (7 RCTs); non-industry (1 RCT)
Meng *et al.* (2017)	To determine the analgesic efficacy of selective cannabinoids compared with conventional management or placebo for	Chronic neuropathic pain associated with: Multiple sclerosis (n=444); brachial plexus root aversion (n=48); multiple aetiologies (n=467); diabetes (n=56); chemotherapy induced (n=18)	Not reported	11 1033 RCT	Mean age range 46-60.8 years 60.3% female	Administration of any of the 3 prescription selective cannabinoids (dronabinol, nabilone, and nabiximols) Vs.	Pain scores	Quality of life, physical function, sleep, anxiety, patient satisfaction, quantitative sensory testing profile	2-15 weeks Not reported	2004 - 2015	Not reported

Author (year)	Research question	Study population(s)	Countries	No. of studies / Sample size/ study design	Age/ gender	Study intervention(s)/ comparator(s)	Primary outcome(s)	Secondary outcome(s)	Treatment duration/follow-up	Primary study years	Industry funding for primary studies
	chronic [neuropathic pain] after at least 2 weeks after commencement of treatment					Placebo (10 RCTs); dihydrocodeine (1 RCT)					
Mucke *et al.* (2018a)	To evaluate the efficacy, tolerability, and safety of cannabinoids as an adjunct or complementary therapy in palliative medicine	Palliative medicine associated with: Cancer (n=1275); HIV/AIDS (n=254); Alzheimer's Disease (n=15)	North America; Great Britain; Europe	9 1544 RCT	Cancer (age range 58–66); HIV (age range 39–43); Alzheimer's Disease (age range 65–82); not reported (n=537)	Herbal cannabis, plant based or synthetic cannabinoids in every form of application and dose (dronabinol, THC:CBD, THC) Vs. Placebo	Efficacy (pain reduction >30%), body weight, appetite, caloric intake, and nausea/vomiting; sleeping dysfunction, fatigue, mood disorders, and health-related quality of life (at the end of each medication phase	Tolerability including number of patients who discontinued the study because of adverse events; dizziness, mental health symptoms, and cognitive dysfunction; safety including number of serious adverse; deaths during medication	16 days to 12 weeks Not reported	1995 - 2012	Not reported

Author (year)	Research question	Study population(s)	Countries	No. of studies / Sample size/ study design	Age/ gender	Study intervention(s)/ comparator(s)	Primary outcome(s)	Secondary outcome(s)	Treatment duration/follow-up	Primary study years	Industry funding for primary studies
					9.2% female						
Mucke *et al.* (2018b)	To assess the efficacy, tolerability, and safety of cannabis-based medicines (herbal, plant-based, synthetic) compared to placebo or conventional drugs for conditions with chronic neuropathic pain in adults	Chronic neuropathic pain associated with: Plexus root avulsion (n=48); HIV (n=34); chronic central and peripheral neuropathic pain (n=96); chemo-therapy-induced np (n=18); diabetes (n=353); spinal cord injury (n=116); pain and allodynia (n=125); post-herpetic neuralgia, peripheral neuropathy, focal nerve lesion, radiculopathy or complex regional pain syndrome (n=246); non-HIV neuropathy (n=23); multiple sclerosis and other neurological conditions (n=70);	Canada, Denmark, Germany, UK, Belgium, Spain, France, Czech Republic, Romania, Belgium, USA	16 1798 RCT	Mean age range 34-61 years 47.2% female	Cannabis-based medicines, either herbal cannabis, plant-based cannabinoids (dronabinol: nabiximols), or pharmacological (synthetic) cannabinoids (e.g. levonantradol, nabilone) Vs. Placebo or any active comparator (dihydrocodeine, 1 RCT)	Participant-reported pain relief of 50% or greater; patient global impression of change much or very much improved; withdrawals due to adverse event; and serious adverse events	Participant-reported pain relief of 30% or greater; participant-reported pain relief of 30% greater; mean pain intensity; health - related quality of life; sleep problems; fatigue; psychological distress; withdrawals due to lack of efficacy; any adverse event; specific adverse events	2-26 weeks Not reported	2004 - 2017	Public funding (3 RCTs); no external funding (1 RCT); industry funded (12 RCTs)

Author (year)	Research question	Study population(s)	Countries	No. of studies / Sample size/ study design	Age/ gender	Study intervention(s)/ comparator(s)	Primary outcome(s)	Secondary outcome(s)	Treatment duration/follow-up	Primary study years	Industry funding for primary studies
		multiple sclerosis (n=669)									
Noori *et al.* (2021)	To explore the impact of adding medical cannabis on opioid dose, other patient-important outcomes and related harms in patients with chronic pain using prescribed opioid therapy	Chronic cancer pain (n=1540)	Not reported	5 1540 RCT	Mean age range 58.0-61.5 years 45.6% female	Medical cannabis (THC:CBD extract, nabiximols) Vs. Prescribed opioids	Opioid dose reduction	Pain relief; sleep disturbance; emotional and physical functioning; adverse events	2-5 weeks Not reported	2010 - 2017	Industry (5 RCTS)
Oordt *et al.* (2021)	To investigate the efficacy, effectiveness, safety, cost-effectiveness, and budget impact of medical cannabis use in chronic pain and spasticity	Separate analyses for chronic pain (advanced cancer n=796, multiple sclerosis n=645 (including drop-outs), allodynia n=371 (including drop-outs), rheumatoid arthritis n=58) and spasticity (multiple sclerosis	Australia, Belgium, Bulgaria, Canada, Czech Republic, Estonia, France, Germany, Hungary, India,	13 3041 RCT	Mean range 47.1-62.8 years 60.7% female (8 RCTs); 5 not	Medical cannabis, prescribed as standalone treatment or add-on treatment (THC:CBD, dronabinol) Vs.	Efficacy for chronic pain (patient-rated pain score, worst pain score, percentage treatment responders, quality of life); efficacy for	None	3-16 weeks 12 month follow-up (1 RCT); Remaining not reported	2003 - 2019	10 RCTs funded by industry; Not reported (3 RCTs)

Author (year)	Research question	Study population(s)	Countries	No. of studies / Sample size/ study design	Age/ gender	Study intervention(s)/ comparator(s)	Primary outcome(s)	Secondary outcome(s)	Treatment duration/follow-up	Primary study years	Industry funding for primary studies
		n=1119, motor neuron disease n=59)	Israel, Italy, Latvia, Lithuania, Poland, Romania, Spain, Taiwan, UK, USA		reported	Placebo/No treatment for chronic pain or spasticity/Standard of care according to the treatment guidelines	spasticity; safety (serious adverse events, withdrawal due to adverse events)				
Paunescu *et al.* (2020)	Which is the level of evidence, from quantitative and qualitative point of view, concerning the efficacy and safety of the treatment with psychotropic cannabinoids of neuropsychiatric symptoms in Alzheimer's Disease?	Alzheimer's Disease (n=41); Alzheimer's Disease, vascular dementia, mixed dementia (n=82); vascular and mixed dementia (n=18); major neurocognitive disorder due to Alzheimer's Disease or Alzheimer's Disease and major vascular neurocognitive disorder (n=77)	Not reported	6 238 RCT	Mean age range 22.6-87.0 years 34.1% female (not reported in 1 RCT)	A natural or synthetic cannabinoid (dronabinol, nabilone) Vs. Placebo	Neuropsychiatric symptoms, adverse events, drop-outs	None	3 days - 7 weeks Not reported	1997 - 2019	Not reported

Author (year)	Research question	Study population(s)	Countries	No. of studies / Sample size/ study design	Age/ gender	Study intervention(s)/ comparator(s)	Primary outcome(s)	Secondary outcome(s)	Treatment duration/follow-up	Primary study years	Industry funding for primary studies
Price *et al.* (2022)	To evaluate the efficacy of medical cannabis in reducing pain in patients following spine surgery, for patients suffering from chronic low back or neck pain, and patients affected by previous spinal cord injury pain	Back pain (disc herniation, foraminal stenosis, scoliosis, spondylarthrosis, osteochondrosis) (n=30); spinal cord injury (n=7); spinal cord injury and multiple sclerosis (n=42)	Austria; USA	3 79 RCT	Mean age range 46.4-50.1 years 45.4% female	Medical cannabinoids (nabilone, dronabinol, THC) Vs. Placebo (1 RCT); diphenhydramine (1 RCT); mannitol (1 RCT)	Efficacy in assessing pain following spinal surgery; efficacy in assessing pain in patients with chronic low back or neck pain; efficacy in assessing pain in patients with chronic pain post spinal cord injury; adverse events	Quality of life	4-12 weeks Not reported	2006 - 2016	Not reported
Quintero *et al.* (2022)	To evaluate the safety and effectiveness of cannabinoids used by routes other than oral or inhalation for neuropathic	Pain relief, quality of life and adverse events associated with: Peripheral neuropathy secondary to diabetes mellitus, idiopathic peripheral neuropathy, drug-	Not reported	1 29 RCT	Mean 68 years; range 35-79 years 37.9% female	Cannabinoids used by routes other than oral or inhalation (CBD oil) Vs. Placebo	Pain relief, adverse events	None	4 weeks Not reported	2020	Not reported

Author (year)	Research question	Study population(s)	Countries	No. of studies / Sample size/ study design	Age/ gender	Study intervention(s)/ comparator(s)	Primary outcome(s)	Secondary outcome(s)	Treatment duration/follow-up	Primary study years	Industry funding for primary studies
	pain compared to placebo or other medications in terms of pain relief, quality of life and adverse events	related neuropathy (n=29)									
Razmovs.ki-Naumovski *et al.* (2022)	To systematically review the evidence on the efficacy of medicinal cannabis for improving appetite-related symptoms in people with cancer	Appetite-related symptoms associated with: Advanced palliative cancer (n=791); head and neck cancer (n=56)	Mexico; Canada; Germany, Switzerland and the Netherlands; USA	5 847 RCT	Mean age range 52.6-67.0 years 38.4% female (4 RCTs); not reported (1 RCT)	Cannabis – natural/synthetic cannabinoids, botanical/extract (nabilone, dronabinol, THC, cannabis extract) Vs. Placebo (4 RCTs); megestrol acetate (1 RCT)	Anorexia, cachexia, weight gain/loss/maintenance or body mass index, food intake, appetite, hunger, food-related sensory experience, satiety	Quality of life, adverse events	3-8 weeks Not reported	2002 - 2018	Not reported
Rosager *et al.* (2021)	To identify all randomized controlled clinical trials that have	Anorexia (n=35)	Not reported	2 35 RCT	Not reported (>18 years old)	Cannabinoids or similar products or analogues (dronabinol, THC)	Weight	Adverse events, physical activity, other	4-7 weeks Not reported	1983 - 2015	Not reported

Author (year)	Research question	Study population(s)	Countries	No. of studies / Sample size/ study design	Age/ gender	Study intervention(s)/ comparator(s)	Primary outcome(s)	Secondary outcome(s)	Treatment duration/follow-up	Primary study years	Industry funding for primary studies
	exposed patients with anorexia nervosa to cannabinoids and assessed the effects on (1) weight and (2) other outcomes				100% female	Vs. Placebo (2 RCTs)					
Sainsbury *et al.* (2021)	To evaluate the effectiveness of cannabis-based medications as therapeutic agents compared to placebo intervention in patients with chronic neuropathic pain	Chronic neuropathic pain associated with: HIV (n=121); complex regional pain syndrome (n=27); avulsed brachial plexus injury (n=48); hyperalgesia and allodynia (n=21); unilateral peripheral neuropathic pain and allodynia (n=125); chronic painful diabetic peripheral neuropathy (n=29); allodynia (n=246); multiple sclerosis (n=24); neurological	Europe and UK; Israel; USA	17 861 RCT	Range 21-77 years 41.7% female	Cannabis-based medications, either herbal forms of cannabis, plant-based cannabinoid compounds (THC/CBD, CBDV), or pharmacological (synthetic) cannabinoid formulations (e.g., nabilone, CT-3, dronabinol) Vs. Placebo	Neuropathic pain intensity and spontaneous pain intensity at baseline and post-treatment, or baseline NP pain and reduction from baseline at post-treatment	Adverse events, neuropathic pain intensity (%), responders with a 30% or more reduction in pain intensity; 50% or more reduction in pain intensity, quality of life, general health, patient global impression change, cognitive decline, sleep quality, expanded disability status, profile of mood states, qualitative testing (allodynia, cold/hot threshold)	3x150 minute sessions – 14 weeks Not reported	2002 - 2020	Industry funded (7 RCTs); not reported (10 RCTs)

Author (year)	Research question	Study population(s)	Countries	No. of studies / Sample size/ study design	Age/ gender	Study intervention(s)/ comparator(s)	Primary outcome(s)	Secondary outcome(s)	Treatment duration/follow-up	Primary study years	Industry funding for primary studies
		disorder (n=20); diabetes mellitus (n=16); neuropathic pain (n=62); spinal cord injury (n=122)									
Simon *et al.* (2022)	This review aimed to consider [non-randomised studies of interventions] alongside RCTs for a comprehensive approach to the available evidence on cannabinoid interventions in cancer-associated cachexia or severe loss of weight and muscle mass	Cancer ("advanced cancer" 3 RCTs, non-small cell lung cancer 1 RCT), with cachexia/weight loss/decreased foot intake/anorexia/malnourishment defined in various ways, including performance status scores	Canada; Germany; Mexico; United Kingdom	4 647 RCT	Range 52.6 – 67 years 41.8% female	Cannabinoid-based interventions included any smoked or ingested medical marijuana, plant-based cannabinoids and synthetic cannabinoids Vs. Equivalent placebo capsules (4 RCTs); 800 mg megestrol acetate plus capsule placebos (1 RCT)	Weight, appetite	Performance status, quality of life, adverse events, mortality	18 days to 8 weeks 30 days to 8 weeks	2002 - 2018	Not reported
Smith *et al.* (2015)	To evaluate the effectiveness	The RCTs included people with a variety of cancers	Not reported	23 1326	Range 24-61 years	Licensed pharmacological interventions based	Absence of nausea, Absence of	Adverse events: Depression, Dysphoria, 'Feeling high',	Not clear (7 RCTs); Day of	1975 - 1991	Not reported

Author (year)	Research question	Study population(s)	Countries	No. of studies / Sample size/ study design	Age/ gender	Study intervention(s)/ comparator(s)	Primary outcome(s)	Secondary outcome(s)	Treatment duration/follow-up	Primary study years	Industry funding for primary studies
	and tolerability of cannabis-based medications for chemotherapy-induced nausea and vomiting in adults with cancer	undergoing different chemotherapy regimens ranging from moderate to high anti-emetic potential, except for one of low emetic potential; five were unclassifiable as reporting of chemotherapy regimen was unclear		RCT	(17 RCTs); Not reported (6 RCTs) 43.7% female (8 RCTs not reported)	on cannabinoids derived from cannabis: used either as monotherapy or adjunct to conventional dopamine antagonists Vs. Placebo (9 RCTs), prochlorperazine (11 RCTs), metoclopramide (2 RCTs), domperidone (1 RCT), and chlorpromazine (1 RCT)	vomiting, Absence of nausea and vomiting	Paranoia, Sedation; Withdrawal due to adverse event	chemotherapy (6 RCTs); 24 hours after chemotherapy (5 RCTs); 3 days (2 RCTs); 4 days (1 RCT); 5 days (1 RCT); 2 cycles (1 RCT) Not reported		
Thomas *et al.* (2022)	What is the current level of evidence on the effect of cannabis/cannabinoids upon pain intensity	Chronic neuropathic pain at least three levels below the spinal cord lesion (n=7); central neuropathic pain (n=158)	Not reported	4 (2 RCTs shared a single cohort) 165	Mean range 46.4-50.1 years 24.1% female	Cannabinoid preparation could involve synthetic cannabinoids (dronabinol, nabilone), whole-plant extracts, isolated or	Pain	Adverse events	3x8 hour sessions - 5 months Not reported	2010 - 2016	Not reported

Author (year)	Research question	Study population(s)	Countries	No. of studies / Sample size/ study design	Age/ gender	Study intervention(s)/ comparator(s)	Primary outcome(s)	Secondary outcome(s)	Treatment duration/follow-up	Primary study years	Industry funding for primary studies
	in spinal cord injury?			RCT		combined cannabinoid preparations (THC only, CBD only, THC-CBD) Vs. Diphenhydramine (1 RCT); placebo (2 RCTs)					
Torres-Moreno *et al.* (2018)	To evaluate the therapeutic efficacy and tolerability of medicinal cannabinoids to treat the symptoms of spasticity, pain, and bladder dysfunction in patients with multiple sclerosis	Patients with multiple sclerosis with a range of symptoms (spasticity, various types of pain, spasms, bladder problems, tremor, and muscle stiffness)	Canada; Czech Republic; Denmark; Italy; Switzerland; UK, Belgium and Romania; UK and Czech Republic; UK, Czech Republic, Canada, Spain and	17 3161 unique participants (2 pairs of RCTs shared cohorts) RCT	Mean age range 45.5-54.9 years (15 RCTs); 2 RCTs not reported 63.2% female (16 RCTs);	Medicinal cannabinoids by oral or oromucosal route (THC/CBD, nabiximols, dronabinol, nabilone) Vs. Placebo	Spasticity (Ashworth Scale and subjective), pain, bladder dysfunction	Tolerability (adverse events)	2 weeks - 3 years Not reported	2002 - 2015	Industry (10 RCTs), non-industry (7 RCTs)

Author (year)	Research question	Study population(s)	Countries	No. of studies / Sample size/ study design	Age/ gender	Study intervention(s)/ comparator(s)	Primary outcome(s)	Secondary outcome(s)	Treatment duration/follow-up	Primary study years	Industry funding for primary studies
			France; UK and Romania; UK, Spain, Poland, Czech Republic and Italy; not reported (1 RCT)		1 RCT not reported						
Urbi *et al.* (2022)	The aim of this review was to interrogate the literature for evidence of treatment effects of cannabis in Parkinson's disease (severity and progression, motor and non-motor symptoms)	Patients with Parkinson's disease (n=82, 3 RCTs), patients with Parkinson's disease and levodopa-induced dyskinesia (n=26, 2 RCT)	Not reported	5 108 RCT	Not reported Not reported	Cannabis or cannabis-based treatment (used alone or combined with other cannabinoids) or other agents, whether synthetic or a direct cannabis extract Vs. Placebo	Total Unified Parkinson's Disease Rating Scale (UPDRS), Motor UPDRS, Parkinson's Disease Questionnaire (PDQ-39), Dyskinesia, tremor, sleep quality, pain, adverse events	None	4-6 weeks Not reported	2001 - 2020	Not reported

Author (year)	Research question	Study population(s)	Countries	No. of studies / Sample size/ study design	Age/ gender	Study intervention(s)/ comparator(s)	Primary outcome(s)	Secondary outcome(s)	Treatment duration/follow-up	Primary study years	Industry funding for primary studies
van den Elsen *et al.* (2014)	This systematic review aims to integrate the evidence on indications, efficacy, safety and pharmacokinetics of medical cannabinoids in older subjects	Efficacy, safety and pharmacokinetics associated with: Chemotherapy-induced nausea and vomiting in a wide variety of neoplasms (n=214, 1 RCT), food refusal and disturbed behaviour (n=15, 1 RCT) and agitation (n=2, 1 RCT) in Alzheimer's disease, levodopa-induced dyskinesia in Parkinson's disease (n=25, 1 RCT), CO2 induced breathlessness in COPD (n=11, 1 RCT)	Not reported	5 267 RCT	Mean age range 47-78 years 49% female (3 RCTs); Not reported (2 RCTs)	Medical cannabinoids administered by any route, at any dose and for any duration (THC, CBD) Vs. Placebo (n=53, 4 RCTs) or Prochlorperazine (n=214, 1 RCT)	Nausea and vomiting, food refusal (body weight, skin fold thickness, caloric intake), disturbed behaviour, levodopa-induced dyskinesia, CO2 induced breathlessness, agitation	None	Treatment cycle duration 1-42 days Not reported	1982 - 2011	Not reported
Votrubec *et al.* (2022)	Are cannabinoid therapeutics effective in (acute and chronic) orofacial pain management,	Orofacial pain associated with: Radiotherapy for head and neck carcinoma (n=56); surgical removal of molar (n=10);	Canada; Poland; USA	3 126 RCT	Range 18-80 years Not reported	Cannabinoids (natural and synthetic) - Nabilone, CBD, THC Vs.	Pain (Visual analog scale, instensity, analgesic)	Adverse events	Single dose (1 RCT); Entire radiotherapy regimen (1 RCT); 2	1977 - 2019	Partial funding by industry (2 RCTs); Public (1 RCT)

Author (year)	Research question	Study population(s)	Countries	No. of studies / Sample size/ study design	Age/ gender	Study intervention(s)/ comparator(s)	Primary outcome(s)	Secondary outcome(s)	Treatment duration/follow-up	Primary study years	Industry funding for primary studies
	when compared to other pharmacological or placebo treatments?	temporomandibular disorder (n=60)				Placebo (2 RCTs); placebo and diazepam (1 RCT)			weeks (1 RCT) Every 7 days during intervention and 28 days after (1 RCT); 14 days after intervention (1 RCT); midpoint/ 30 minutes post intervention/at 24 hours and one month (1 RCT)		
Walitt *et al.* (2016)	To assess the efficacy, tolerability and safety of cannabinoids for fibromyalgia	All participants had fibromyalgia	Canada	2 72 RCT	Range 26-76 years (mean age range	Cannabinoids (either phytocannabinoids(nabiximols) or pharmacological (synthetic) cannabinoids (e.g.	Participant-reported pain relief of 50% or greater, patient Global Impression of	Withdrawal due to adverse events, serious adverse events, fatigue, sleep, depression, anxiety, disability, health-	4-6 weeks Not reported	2008 - 2010	Partial funding by the manufacturer of nabilone (2 RCTs)

Author (year)	Research question	Study population(s)	Countries	No. of studies / Sample size/ study design	Age/ gender	Study intervention(s)/ comparator(s)	Primary outcome(s)	Secondary outcome(s)	Treatment duration/follow-up	Primary study years	Industry funding for primary studies
	symptoms in adults				49-50 years) 87.6% female	dronabinol, levonantradol, nabilone) Vs. Placebo (1 RCT), active comparator amitriptyline (1 RCT)	Change improvement	related quality of life, adverse events			

Appendix J Quality assessment findings of included reviews

Author (year)	PICO	Protocol prior to review and report deviations	Justify primary study design for inclusion	Comprehensive literature search	Duplicate screening	Duplicate data extraction	List of excluded studies	Detailed characteristics of primary studies	Method for assessment of bias	Source of funding for primary studies	Methods for meta-analysis	Meta-analysis and risk of bias in analysis	Risk of bias in discussion of results	Discussed heterogeneity	Publication bias assessed	Conflicts of interest and funding	Overall quality rating of review
Abdallah (2020)	Yes	No	No	Yes	Yes	Yes	No	No	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically low
Aminilari (2022)	Yes	Partial yes	No	Yes	Yes	Yes	No	Partial yes	Partial yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Critically low
Andreae (2015)	Yes	Yes	No	Yes	No	Yes	Yes	Partial yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Bahji (2020)	Yes	No	No	Yes	Yes	Yes	No	No	Yes	No	Yes	No	No	Yes	Yes	No	Critically low
Bajtel (2022)	Yes	Partial yes	No	Partial yes	No	Yes	Yes	No	Yes	No	Yes	No	No	Yes	Yes	No	Critically low
Belgers (2023)	Yes	No	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Critically low
Bialas (2022)	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	No	Yes	Critically low
Black (2019)	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No	No	Yes	No	Yes	Critically low
Boland (2020)	Yes	Partial yes	No	Yes	Yes	Yes	No	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Low

Author (year)	PICO	Protocol prior to review and report deviations	Justify primary study design for inclusion	Comprehensive literature search	Duplicate screening	Duplicate data extraction	List of excluded studies	Detailed characteristics of primary studies	Method for assessment of bias	Source of funding for primary studies	Methods for meta-analysis	Meta-analysis and risk of bias in analysis	Risk of bias in discussion of results	Discussed heterogeneity	Publication bias assessed	Conflicts of interest and funding	Overall quality rating of review
Bosnjak Kuharic (2021)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Low
Butler (2015)	Yes	No	No	Yes	Yes	No	Yes	Partial yes	Yes	Yes	No	No	No	No	No	No	Critically low
da Rovare (2017)	Yes	No	No	Yes	Yes	Yes	No	No	Yes	No	Yes	No	Yes	No	Yes	Yes	Critically low
de Aquino (2022)	No	No	No	Yes	Yes	No	No	No	Yes	No	No meta-analysis	No meta-analysis	No	No	No meta-analysis	Yes	Critically low
Filippini (2022)	Yes	Yes	No	Yes	Yes	Yes	Yes	Partial yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Low
Fisher (2021)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Low
Fitzcharles (2016a)	Yes	No	No	Yes	No	No	Yes	No	Yes	No	No meta-analysis	No meta-analysis	Yes	No	No meta-analysis	Yes	Low

Author (year)	PICO	Protocol prior to review and report deviations	Justify primary study design for inclusion	Comprehensive literature search	Duplicate screening	Duplicate data extraction	List of excluded studies	Detailed characteristics of primary studies	Method for assessment of bias	Source of funding for primary studies	Methods for meta-analysis	Meta-analysis and risk of bias in analysis	Risk of bias in discussion of results	Discussed heterogeneity	Publication bias assessed	Conflicts of interest and funding	Overall quality rating of review
Fitzcharles (2016b)	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No meta-analysis	No meta-analysis	No	Yes	Yes	Yes	Critically low
Giossi (2022)	Yes	Yes	No	Partial yes	Yes	Yes	No	Partial yes	Yes	No	Yes	No	Yes	No	Yes	No	Critically low
Hammond (2021)	Yes	No	No	Yes	Yes	No	No	Partial yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Critically low
Häuser (2019)	Yes	Partial yes	No	Yes	No	Yes	Yes	Partial yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Critically low
Kafil (2018a)	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	No meta-analysis	No meta-analysis	Yes	No	No meta-analysis	Yes	Low
Kafil (2018b)	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No meta-analysis	No meta-analysis	Yes	Yes	Yes	Yes	Moderate
Kopelli (2020)	Yes	Yes	No	Yes	Yes	Yes	No	No	Yes	No	Yes	No	No	Yes	Yes	Yes	Critically low
Longo (2021)	Yes	No	Yes	Partial yes	No	No	No	No	No	No	No meta-	No meta-	Yes	Yes	No meta-	No	Critically low

Author (year)	PICO	Protocol prior to review and report deviations	Justify primary study design for inclusion	Comprehensive literature search	Duplicate screening	Duplicate data extraction	List of excluded studies	Detailed characteristics of primary studies	Method for assessment of bias	Source of funding for primary studies	Methods for meta-analysis	Meta-analysis and risk of bias in analysis	Risk of bias in discussion of results	Discussed heterogeneity	Publication bias assessed	Conflicts of interest and funding	Overall quality rating of review
											analysis	analysis			analysis		
Lutge (2013)	Yes	Partial yes	No	Yes	Yes	Yes	Yes	No	Yes	No	No meta-analysis	No meta-analysis	No	No	No meta-analysis	Yes	Critically low
McDonagh (2022)	Yes	Partial yes	No	Yes	Yes	No	No	No	Partial yes	No	Yes	No	No	Yes	No	Yes	Critically low
McKee (2021)	Yes	No	No	Yes	Yes	No	No	No	Yes	No	No	No	No	No	No	Yes	Critically low
McParland (2023)	Yes	Yes	No	Yes	Yes	Yes	Yes	Partial yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Meng (2017)	Yes	Yes	No	Yes	Yes	No	No	Partial yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Mucke (2018a)	Yes	No	No	Yes	No	No	Yes	Partial yes	Yes	No	No	No	No	No	No	Yes	Critically low
Mucke (2018b)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Low
Noori (2021)	Yes	Partial yes	No	Yes	Yes	Yes	No	Partial yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Low

Author (year)	PICO	Protocol prior to review and report deviations	Justify primary study design for inclusion	Comprehensive literature search	Duplicate screening	Duplicate data extraction	List of excluded studies	Detailed characteristics of primary studies	Method for assessment of bias	Source of funding for primary studies	Methods for meta-analysis	Meta-analysis and risk of bias in analysis	Risk of bias in discussion of results	Discussed heterogeneity	Publication bias assessed	Conflicts of interest and funding	Overall quality rating of review
Oordt (2021)	Yes	No	No	Yes	Yes	No	Yes	Partial yes	Partial yes	Yes	No	No	Yes	No	No	No	Critically low
Paunescu (2020)	No	No	No	Partial yes	No	No	Partial yes	Partial yes	Yes	No	No meta-analysis	No meta-analysis	Yes	No	No meta-analysis	Yes	Critically low
Price (2022)	Yes	No	No	Yes	Yes	Yes	Yes	Partial yes	Yes	No	No meta-analysis	No meta-analysis	No	No	No meta-analysis	Yes	Critically low
Quintero (2022)	Yes	No	No	Partial yes	Yes	Yes	Yes	Partial yes	Yes	No	No meta-analysis	No meta-analysis	No	Yes	No meta-analysis	Yes	Critically low
Razmovski-Naumovski (2022)	Yes	No	No	Yes	Yes	No	No	Yes	Yes	No	No meta-analysis	No meta-analysis	No	No	No meta-analysis	Yes	Critically low
Rosager (2021)	Yes	Partial yes	No	Yes	Yes	No	No	Partial yes	Yes	No	No meta-analysis	No meta-analysis	No	Yes	No meta-analysis	Yes	Critically low

Author (year)	PICO	Protocol prior to review and report deviations	Justify primary study design for inclusion	Comprehensive literature search	Duplicate screening	Duplicate data extraction	List of excluded studies	Detailed characteristics of primary studies	Method for assessment of bias	Source of funding for primary studies	Methods for meta-analysis	Meta-analysis and risk of bias in analysis	Risk of bias in discussion of results	Discussed heterogeneity	Publication bias assessed	Conflicts of interest and funding	Overall quality rating of review
Sainsbury (2021)	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Critically low
Simon (2022)	Yes	No	Yes	Yes	No	No	No	Partial yes	Yes	No	Yes	No	No	Yes	No	Yes	Critically low
Smith (2015)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Moderate
Thomas (2022)	No	No	No	Yes	Yes	No	No	Partial yes	Partial yes	No	No meta-analysis	No meta-analysis	No	No	No meta-analysis	Yes	Critically low
Torres-Moreno (2018)	Yes	Partial yes	No	Yes	Yes	No	Partial yes	Partial yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Critically low
Urbi (2022)	No	No	No	Yes	Yes	No	No	No	Yes	No	No	No	No	No	No	No	Critically low
Van den Elsen (2014)	No	No	No	Partial yes	Yes	No	No	Partial yes	Yes	No	No meta-analysis	No meta-analysis	Yes	No	No meta-analysis	Yes	Critically low
Vortubec (2022)	Yes	Partial yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No meta-	No meta-	Yes	Yes	No meta-	Yes	Low

Author (year)	PICO	Protocol prior to review and report deviations	Justify primary study design for inclusion	Comprehensive literature search	Duplicate screening	Duplicate data extraction	List of excluded studies	Detailed characteristics of primary studies	Method for assessment of bias	Source of funding for primary studies	Methods for meta-analysis	Meta-analysis and risk of bias in analysis	Risk of bias in discussion of results	Discussed heterogeneity	Publication bias assessed	Conflicts of interest and funding	Overall quality rating of review
											analysis	analysis			analysis		
Walitt (2016)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No meta-analysis	No meta-analysis	Yes	Yes	No meta-analysis	Yes	High

Appendix K Grading of Recommendations, Assessment, Development and Evaluation (GRADE) assessments of included reviews

Specific health conditions (efficacy)

Author (year)	Intervention categorisation	No. studies	Study design	Trial quality (ROB randomisation)	Trial quality (ROB blinding outcome assessors)	Inconsistency (heterogeneity)	Imprecision (adequate sample size)	AMSTAR quality rating (critical domains)	Single study review	GRADE score	GRADE rating
CANCER											
PAIN-RELATED OUTCOMES											
Pain intensity											
Boland *et al.* (2020)	THC:CBD products vs. placebo	5	0	0	0	0	0	-1	0	-1	Moderate
Pain relief 50% or greater											
Häuser *et al.* (2019)	THC:CBD products vs. placebo	4	0	-1	-1	0	0	-2	0	-4	Low
Combined response (pain relief of 30% or greater and reduced opioid use)											
Häuser *et al.* (2019)	THC:CBD products vs. placebo	1	0	-1	-1	0	0	-2	Yes	-4	Very low
Opioid dose reduction											
Noori *et al.* (2021)	THC:CBD products vs. placebo	4	0	-1	-1	0	0	-1	0	-3	Low
Patient perceived global improvement of pain											
Häuser *et al.* (2019)	THC:CBD products vs. placebo	3	0	-1	-1	0	0	-2	0	-4	Low
NAUSEA/VOMITING											
Absence of nausea											
Smith *et al.* (2015)	THC products vs. placebo	2	0	-1	0	0	-2	0	-4	-3	Low
Smith *et al.* (2015)	THC products vs. active comparator	5	0	-1	0	0	0	0	-2	-1	Moderate

Author (year)	Intervention categorisation	No. studies	Study design	Trial quality (ROB randomisation)	Trial quality (ROB blinding outcome assessors)	Inconsistency (heterogeneity)	Imprecision (adequate sample size)	AMSTAR quality rating (critical domains)	Single study review	GRADE score	GRADE rating
Smith *et al.* (2015)	THC products vs. placebo in combination with another treatment	1	0	-1	0	0	-2	0	Yes	-3	Very low
Absence of vomiting											
Smith *et al.* (2015)	THC products vs. placebo	3	0	-1	0	0	-1	0	-3	-2	Moderate
Smith *et al.* (2015)	THC products vs. active comparator	4	0	-1	0	0	0	0	-2	-1	Moderate
Smith *et al.* (2015)	THC products vs. placebo in combination with another treatment	2	0	-1	0	-1	-2	0	-5	-4	Low
Absence of nausea and vomiting											
Smith *et al.* (2015)	THC products vs. placebo	3	0	-1	0	0	0	0	-2	-1	Moderate
Smith *et al.* (2015)	THC products vs. active comparator	4	0	-1	0	0	0	0	-2	-1	Moderate
Smith *et al.* (2015)	THC products vs. placebo in combination with another treatment	1	0	-1	0	0	-2	0	Yes	-3	Very low
NUTRITION-RELATED OUTCOMES											
Appetite											
Razmovski-Naumovski *et al.* (2022)	THC products vs. placebo	4	0	-1	-1	-1	0	-1	0	-4	Low
Razmovski-Naumovski *et al.* (2022)	THC products vs. active comparator	1	0	-1	-1	0	0	-1	Yes	-3	Very low
Razmovski-Naumovski *et al.* (2022)	Mixed cannabinoids vs. placebo	1	0	0	-1	0	-1	-1	Yes	-3	Very low
Simon *et al.* (2022)	Mixed cannabinoids vs. placebo	3	0	0	-1	0	0	-2	0	-3	Low
Simon *et al.* (2022)	THC products vs. active comparator	1	0	0	-1	0	0	-2	Yes	-3	Very low
Weight											

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Razmovski-Naumovski *et al.* (2022)	THC products vs. placebo	3	0	-1	0	-1	0	-1	0	-3	Low
Razmovski-Naumovski *et al.* (2022)	Mixed cannabinoids vs. placebo	1	0	0	-1	0	-1	-1	Yes	-3	Very low
Razmovski-Naumovski *et al.* (2022)	THC products vs. active comparator	1	0	-1	-1	0	0	-1	Yes	-3	Very low
Simon *et al.* (2022)	THC products vs. placebo	1	0	-1	-1	0	-2	-2	Yes	-6	Very low
Simon *et al.* (2022)	THC products vs. active comparator	1	0	0	-1	0	0	-2	Yes	-3	Very low
Body mass index											
Razmovski-Naumovski *et al.* (2022)	THC products vs. placebo	1	0	-1	-1	0	-2	-1	Yes	-5	Very low
Caloric intake per day											
Razmovski-Naumovski *et al.* (2022)	THC products vs. placebo	2	0	-1	-1	-1	-2	-1	0	-6	Very low
Protein intake per day											
Razmovski-Naumovski *et al.* (2022)	THC products vs. placebo	2	0	-1	-1	-1	-2	-1	0	-6	Very low
Carbohydrate intake per day											
Razmovski-Naumovski *et al.* (2022)	THC products vs. placebo	2	0	-1	-1	-1	-2	-1	0	-6	Very low
Fats intake per day											
Razmovski-Naumovski *et al.* (2022)	THC products vs. placebo	2	0	-1	-1	-1	-2	-1	0	-6	Very low
Iron intake per day											
Razmovski-Naumovski *et al.* (2022)	THC products vs. placebo	1	0	-1	-1	0	-2	-1	Yes	-5	Very low
Chemosensory perception											
Razmovski-Naumovski *et al.* (2022)	THC products vs. placebo	1	0	0	-1	0	-2	-1	Yes	-4	Very low
Satiety											

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Razmovski-Naumovski *et al.* (2022)	THC products vs. placebo	1	0	0	-1	0	-2	-1	Yes	-4	Very low
HIV/AIDS											
MORBIDITY AND MORTALITY											
Morbidity											
Lutge *et al.* (2013)	NA	0	NA	NA	NA	NA	NA	-1	NA	NA	No evidence found for this outcome
Mortality											
Lutge *et al.* (2013)	NA	0	NA	NA	NA	NA	NA	-1	NA	NA	No evidence found for this outcome
CONDITIONS IN OLDER ADULTS											
AGITATION											
Agitation in Alzheimer's disease (Cohen Mansfield Agitation Inventory)											
Van den Elsen *et al.* (2014)	THC products vs. placebo	1	0	-1	-1	0	-2	-2	Yes	-6	Very low
Agitation in Alzheimer's disease (nocturnal motor activity)											
Van den Elsen *et al.* (2014)	THC products vs. placebo	1	0	0	0	0	-2	-2	Yes	-4	Very low
COGNITIVE FUNCTION											

Author (year)	Intervention categorisation	No. studies	Study design	Trial quality (ROB randomisation)	Trial quality (ROB blinding outcome assessors)	Inconsistency (heterogeneity)	Imprecision (adequate sample size)	AMSTAR quality rating (critical domains)	Single study review	GRADE score	GRADE rating
Cognitive function in dementia											
Bosnjak Kuharic *et al.* (2021)	THC products vs. placebo	1	0	0	0	0	-2	-1	Yes	-3	Very low
BREATHLESSNESS IN COPD											
Minute ventilation											
Van den Elsen *et al.* (2014)	THC:CBD products vs. placebo	1	0	-1	-1	0	-2	-2	Yes	-6	Very low
PetCO2											
Van den Elsen *et al.* (2014)	THC:CBD products vs. placebo	1	0	-1	-1	0	-2	-2	Yes	-6	Very low
Breathlessness visual analogue scale											
Van den Elsen *et al.* (2014)	THC:CBD products vs. placebo	1	0	-1	-1	0	-2	-2	Yes	-6	Very low
GENERAL BEHVAIOURAL/PSYCHOLOGICAL SYMPTOMS											
Behavioural and psychological symptoms of dementia											
Paunescu 2020	THC products vs. placebo	6	0	-1	-1	-1	0	-2	0	-5	Very low
Bosnjak Kuharic *et al.* (2021)	THC products vs. placebo	3	0	0	0	0	-1	-1	0	-2	Moderate
Observed affect in Alzheimer's disease (Lawton Observed Affect Scale-Past)											
Van den Elsen *et al.* (2014)	THC products vs. placebo	1	0	-1	-1	0	-2	-2	Yes	-6	Very low
General symptoms of Parkinson's disease (Unified Parkinson's Disease Rating Scale (UPDRS))											

Author (year)	Intervention categorisation	No. studies	Study design	Trial quality (ROB randomisation)	Trial quality (ROB blinding outcome assessors)	Inconsistency (heterogeneity)	Imprecision (adequate sample size)	AMSTAR quality rating (critical domains)	Single study review	GRADE score	GRADE rating
Urbi *et al.* (2022)	Mixed cannabinoids vs. placebo	2	0	0	-1	-1	-2	-2	0	-6	Very low
General symptoms of Parkinson's disease (Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS))											
Urbi *et al.* (2022)	Mixed cannabinoids vs. placebo	1	0	0	-1	0	-2	-2	Yes	-5	Very low
MOVEMENT DISORDER											
Levodopa-induced dyskinesia in Parkinson's disease											
Van den Elsen *et al.* (2014)	THC:CBD products vs. placebo	1	0	0	0	0	-2	-2	Yes	-4	Very low
Urbi *et al.* (2022)	Mixed cannabinoids vs. placebo	2	0	-1	0	-1	-2	-2	0	-6	Very low
Tremor in Parkinson's disease											
Urbi *et al.* (2022)	CBD products vs. placebo	1	0	0	-1	0	-2	-2	Yes	-5	Very low
NAUSEA/VOMITING											
Nausea and vomiting score											
Van den Elsen *et al.* (2014)	THC products vs. active comparator	1	0	0	-1	0	0	-2	Yes	-3	Very low
NUTRITION-RELATED OUTCOMES											
Global impression of change of appetite and food intake											
Van den Elsen *et al.* (2014)	NA	0	NA	0	-1	NA	NA	-2	NA	NA	No evidence presented for this

Author (year)	Intervention categorisation	No. studies	Study design	Trial quality (ROB randomisation)	Trial quality (ROB blinding outcome assessors)	Inconsistency (heterogeneity)	Imprecision (adequate sample size)	AMSTAR quality rating (critical domains)	Single study review	GRADE score	GRADE rating
											outcome
Weight in Alzheimer's disease											
Van den Elsen *et al.* (2014)	THC products vs. placebo	1	0	-1	-1	0	-2	-2	Yes	-6	Very low
Skin fold thickness in Alzheimer's disease											
Van den Elsen *et al.* (2014)	THC products vs. placebo	1	0	-1	-1	0	-2	-2	Yes	-6	Very low
Caloric intake in Alzheimer's disease											
Van den Elsen *et al.* (2014)	THC products vs. placebo	1	0	-1	-1	0	-2	-2	Yes	-6	Very low
PAIN-RELATED OUTCOMES											
Pain intensity in Parkinson's disease											
Urbi *et al.* (2022)	Mixed cannabinoids vs. placebo	2	0	0	-1	-1	-2	-2	0	-6	Very low
MENTAL HEALTH/WELLBEING											
Anxiety in Parkinson's disease											
Urbi *et al.* (2022)	Mixed cannabinoids vs. placebo	2	0	0	-1	-1	-2	-2	0	-6	Very low
Quality of life in Parkinson's disease											
Urbi *et al.* (2022)	Mixed cannabinoids vs. placebo	2	0	0	-1	-1	-2	-2	0	-6	Very low
SLEEP-RELATED OUTCOMES											
Sleep quality in Parkinson's disease											
Urbi *et al.* (2022)	THC products vs. placebo	1	0	0	0	0	-2	-2	Yes	-4	Very low

Author (year)	Intervention categorisation	No. studies	Study design	Trial quality (ROB randomisation)	Trial quality (ROB blinding outcome assessors)	Inconsistency (heterogeneity)	Imprecision (adequate sample size)	AMSTAR quality rating (critical domains)	Single study review	GRADE score	GRADE rating
INFLAMMATORY BOWEL DISEASE											
CLINICAL REMISSION											
Clinical remission rates in Crohn's disease											
Kafil *et al.* (2018a)	Cannabis products vs. placebo	1	0	-1	0	0	-2	0	Yes	-3	Very low
Kafil *et al.* (2018a)	CBD products vs. placebo	1	0	0	0	0	-2	0	Yes	-2	Very low
Clinical remission rates in ulcerative colitis											
Kafil *et al.* (2018b)	CBD products vs. placebo	1	0	0	0	0	0	0	Yes		Very low
MENTAL HEALTH AND NEUROPSYCHOLOGICAL CONDITIONS											
PSYCHOTIC DISORDERS											
Remission from psychotic disorders											
Black *et al.* (2019)	NA	0	NA	NA	NA	NA	NA	-1	NA	NA	No evidence found for this outcome
Positive symptoms of psychosis											
Black *et al.* (2019)	THC products vs. placebo	1	0	-1	-1	0	-2	-1	Yes	-5	Very low
Black *et al.* (2019)	CBD products vs. placebo	2	0	-1	-1	0	-1	-1	0	-4	Low

Author (year)	Intervention categorisation	No. studies	Study design	Trial quality (ROB randomisation)	Trial quality (ROB blinding outcome assessors)	Inconsistency (heterogeneity)	Imprecision (adequate sample size)	AMSTAR quality rating (critical domains)	Single study review	GRADE score	GRADE rating
Black *et al.* (2019)	CBD products vs. active comparator	1	0	-1	-1	0	-2	-1	Yes	-5	Very low
Negative symptoms of psychosis											
Black *et al.* (2019)	THC products vs. placebo	1	0	-1	-1	0	-2	-1	Yes	-5	Very low
Black *et al.* (2019)	CBD products vs. placebo	2	0	-1	-1	0	-1	-1	0	-4	Low
Black *et al.* (2019)	CBD products vs. active comparator	1	0	-1	-1	0	-2	-1	Yes	-5	Very low
Total symptoms of psychosis/schizophrenia											
Black *et al.* (2019)	CBD products vs. placebo	2	0	-1	-1	0	-1	-1	0	-4	Low
Black *et al.* (2019)	CBD products vs. active comparator	1	0	-1	-1	0	-2	-1	Yes	-5	Very low
Kopelli *et al.* (2020)	CBD products vs. active comparator	1	0	0	-1	0	-2	-1	Yes	-4	Very low
Kopelli *et al.* (2020)	CBD products vs. placebo	2	0	-1	-1	0	-1	-1	0	-4	Low
McKee *et al.* (2021)	CBD products vs. placebo	2	0	0	-1	-1	-1	-2	0	-5	Very low
McKee *et al.* (2021)	CBD products vs. active comparator	1	0	0	0	0	-2	-2	Yes	-4	Very low
McKee *et al.* (2021)	THC products vs. placebo	1	0	-1	-1	0	-2	-2	Yes	-6	Very low
Cognitive function in schizophrenia											
Kopelli *et al.* (2020)	CBD products vs. placebo	2	0	-1	-1	-1	-1	-1	0	-5	Very low
McKee *et al.* (2021)	CBD products vs. placebo	1	0	0	-1	0	-2	-2	Yes	-5	Very low
McKee *et al.* (2021)	THC products vs. placebo	1	0	-1	-1	0	-2	-2	Yes	-6	Very low
ANXIETY DISORDERS											

Author (year)	Intervention categorisation	No. studies	Study design	Trial quality (ROB randomisation)	Trial quality (ROB blinding outcome assessors)	Inconsistency (heterogeneity)	Imprecision (adequate sample size)	AMSTAR quality rating (critical domains)	Single study review	GRADE score	GRADE rating
Remission from anxiety disorder											
Black *et al.* (2019)	NA	0	NA	NA	NA	NA	NA	-1	NA	NA	No evidence found for this outcome
Generalised anxiety disorder symptoms											
Bahji *et al.* (2020)	Mixed cannabinoids and cannabis products vs. placebo	3	0	0	0	0	-2	-2	0	-4	Low
Bahji *et al.* (2020)	Cannabis products vs. cannabis products	1	-1	-1	-1	0	0	-2	Yes	-5	Very low
Remission from post-traumatic stress disorder (PTSD)											
Black *et al.* (2019)	NA	0	NA	NA	NA	NA	NA	-1	NA	NA	No evidence found for this outcome
PTSD symptoms											
McKee *et al.* (2021)	THC products vs. placebo	1	0	-1	-1	0	-2	-2	Yes	-6	Very low
Social anxiety disorder symptoms											
Bahji *et al.* (2020)	CBD products vs. placebo	2	0	0	0	0	-2	-2	0	-4	Low
McKee *et al.* (2021)	CBD products vs. placebo	2	0	-1	-1	-1	-2	-2	0	-7	Very low
Anxiety symptoms											

Author (year)	Intervention categorisation	No. studies	Study design	Trial quality (ROB randomisation)	Trial quality (ROB blinding outcome assessors)	Inconsistency (heterogeneity)	Imprecision (adequate sample size)	AMSTAR quality rating (critical domains)	Single study review	GRADE score	GRADE rating
Black *et al.* (2019)	Mixed cannabinoids vs. placebo	7	0	-1	-1	0	0	-1	0	-3	Low
Black *et al.* (2019)	THC products vs. active comparator	1	0	0	0	0	-2	-1	Yes	-3	Very low
Black *et al.* (2019)	CBD products vs. placebo	2	0	-1	0	-1	-2	-1	0	-5	Very low
McKee *et al.* (2021)	THC products vs. placebo	1	0	-1	-1	0	-2	-2	Yes	-6	Very low
Obsessive compulsive disorder symptoms											
McKee *et al.* (2021)	Cannabis products vs. placebo	1	0	0	0	0	-2	-2	Yes	-4	Very low
McKee *et al.* (2021)	Cannabis products vs. placebo	1	0	0	0	0	-2	-2	Yes	-4	Very low
MOOD DISORDER											
Remission from depression											
Black *et al.* (2019)	NA	0	NA	NA	NA	NA	NA	-1	NA	NA	No evidence found for this outcome
Depression symptoms											
Black *et al.* (2019)	Mixed cannabinoids vs. placebo	12	0	-1	-1	0	0	-1	0	-3	Low
Black *et al.* (2019)	THC products vs. placebo	1	0	0	0	0	-2	-1	Yes	-3	Very low
Black *et al.* (2019)	Cannabis products vs. placebo	1	0	-1	0	0	-2	-1	Yes	-4	Very low
EATING DISORDERS											
Weight in anorexia nervosa											
McKee *et al.* (2021)	THC products vs. placebo	1	0	0	0	0	-2	-2	Yes	-4	Very low

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Rosager *et al.* (2021)	THC products vs. placebo	1	0	0	0	0	-2	-1	Yes	-3	Very low
Rosager *et al.* (2021)	Cannabis products vs. active comparator	1	0	-1	-1	0	-2	-1	Yes	-5	Very low
SUBSTANCE DEPENDENCE											
Withdrawal symptoms/discomfort in cannabis use disorder											
McKee *et al.* (2021)	THC products vs. placebo	1	0	0	0	0	-1	-2	Yes	-3	Very low
McKee *et al.* (2021)	THC products vs. placebo	2	0	-1	-1	0	-2	-2	0	-6	Very low
McKee *et al.* (2021)	THC:CBD products vs. placebo	4	0	0	0	0	0	-2	0	-2	Moderate
Cravings in cannabis use disorder											
McKee *et al.* (2021)	THC:CBD products vs. placebo	2	0	0	-1	-1	-2	-2	0	-6	Very low
Treatment retention/abstinence in cannabis use disorder											
McKee *et al.* (2021)	THC products vs. placebo	1	0	0	0	0	-1	-2	Yes	-3	Very low
McKee *et al.* (2021)	THC:CBD products vs. placebo	3	0	0	0	-1	0	-2	0	-3	Low
Cannabis consumption (amounts) in cannabis use disorder											
McKee *et al.* (2021)	THC products vs. placebo	1	0	0	0	0	-1	-2	Yes	-3	Very low
McKee *et al.* (2021)	THC products vs. placebo	1	0	-1	0	0	-2	-2	Yes	-5	Very low
McKee *et al.* (2021)	THC:CBD products vs. placebo	1	0	0	0	0	-1	-2	Yes	-3	Very low

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Maintenance (reduction in use and reduction in cravings) in cannabis use disorder											
McKee *et al.* (2021)	THC products vs. placebo	3	0	-1	-1	-1	-2	-2	0	-7	Very low
Cravings in opioid use disorder											
McKee *et al.* (2021)	CBD products vs. placebo	1	0	0	0	0	-2	-2	Yes	-4	Very low
Withdrawal symptoms in opioid use disorder/opioid dependence											
McKee *et al.* (2021)	THC products vs. placebo	2	0	0	0	0	-2	-2	0	-4	Low
de Aquino *et al.* (2022)	THC products vs. placebo	1	0	-1	0	0	-2	-2	Yes	-5	Very low
de Aquino *et al.* (2022)	THC products vs. active comparator	2	0	-1	0	-1	-2	-2	0	-6	Very low
Tobacco use/cravings in tobacco use disorder											
McKee *et al.* (2021)	CBD products vs. placebo	1	0	-1	-1	0	-2	-2	Yes	-6	Very low
NEURODEVELOPMENTAL DISORDERS											
Attention deficit hyperactivity disorder (ADHD) symptoms											
Black *et al.* (2019)	THC:CBD products vs. placebo	1	0	0	0	0	-2	-1	Yes	-3	Very low
McKee *et al.* (2021)	THC:CBD products vs. placebo	1	0	0	0	0	-2	-2	Yes	-4	Very low
Tic severity in Tourette's syndrome											
Black *et al.* (2019)	THC products vs. placebo	2	0	-1	-1	0	-2	-1	0	-5	Very low

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McKee *et al.* (2021)	THC products vs. placebo	2	0	0	-1	-1	-2	-2	0	-6	Very low
PALLIATIVE CARE											
PAIN-RELATED OUTCOMES											
Pain reduction of 30% or greater in cancer											
Mucke *et al.* (2018a)	Mixed cannabinoids vs. placebo	2	0	-1	-1	0	0	-2	0	-4	Low
NUTRITION-RELATED OUTCOMES											
Body weight change in cancer											
Mucke *et al.* (2018a)	Mixed cannabinoids vs. placebo	1	0	0	0	0	0	-2	Yes	-2	Very low
Mucke *et al.* (2018a)	THC products vs. active comparator	1	0	-1	-1	0	0	-2	Yes	-4	Very low
Caloric intake in cancer											
Mucke *et al.* (2018a)	THC products vs. placebo	1	0	0	-1	0	-2	-2	Yes	-5	Very low
Appetite in cancer											
Mucke *et al.* (2018a)	Mixed cannabinoids and cannabis products vs. placebo	3	0	-1	-1	-1	0	-2	0	-5	Very low
Mucke *et al.* (2018a)	THC products vs. active comparator	1	0	-1	-1	0	0	-2	Yes	-4	Very low
Nausea and vomiting in cancer											
Mucke *et al.* (2018a)	Mixed cannabinoids vs. placebo	2	0	-1	-1	0	0	-2	0	-4	Low
Body weight change in HIV											
Mucke *et al.* (2018a)	Mixed cannabinoids and cannabis products vs. placebo	2	0	-1	-1	0	0	-2	0	-4	Low

Author (year)	Intervention categorisation	No. studies	Study design	Trial quality (ROB randomisation)	Trial quality (ROB blinding outcome assessors)	Inconsistency (heterogeneity)	Imprecision (adequate sample size)	AMSTAR quality rating (critical domains)	Single study review	GRADE score	GRADE rating
Mucke *et al.* (2018a)	THC products vs. active comparator	1	0	-1	-1	0	-2	-2	Yes	-6	Very low
Mucke *et al.* (2018a)	Cannabis vs. THC	1	0	-1	-1	0	-2	-2	Yes	-6	Very low
Appetite in HIV											
Mucke *et al.* (2018a)	THC products vs. placebo	1	0	-1	-1	0	-2	-2	Yes	-6	Very low
Nausea and vomiting in HIV											
Mucke *et al.* (2018a)	THC products vs. placebo	1	0	-1	-1	0	-2	-2	Yes	-6	Very low
Mucke *et al.* (2018a)	THC products vs. active comparator	1	0	-1	-1	0	-2	-2	Yes	-6	Very low
Body weight change in Alzheimer's Disease											
Mucke *et al.* (2018a)	THC products vs. placebo	1	0	-1	-1	0	-2	-2	Yes	-6	Very low
Caloric intake in Alzheimer's Disease											
Mucke *et al.* (2018a)	THC products vs. placebo	1	0	-1	-1	0	-2	-2	Yes	-6	Very low
SLEEP-RELATED OUTCOMES											
Sleeping dysfunction in cancer											
Mucke *et al.* (2018a)	Mixed cannabinoids vs. placebo	2	0	-1	-1	0	-1	-2	0	-5	Very low
Fatigue											
Mucke *et al.* (2018a)	NA	0	NA	NA	NA	NA	NA	-2	NA	-2	No evidence found for this outcome
MENTAL HEALTH / WELLBEING											

Author (year)	Intervention categorisation	No. studies	Study design	Trial quality (ROB randomisation)	Trial quality (ROB blinding outcome assessors)	Inconsistency (heterogeneity)	Imprecision (adequate sample size)	AMSTAR quality rating (critical domains)	Single study review	GRADE score	GRADE rating
Depressive mood in HIV											
Mucke *et al.* (2018a)	THC products vs. active comparator	1	0	-1	-1	0	-2	-2	Yes	-6	Very low
Health-related quality of life in cancer											
Mucke *et al.* (2018a)	THC products vs. active comparator	1	0	-1	-1	0	0	-2	Yes	-4	Very low
Health-related quality of life in HIV											
Mucke *et al.* (2018a)	THC products vs. active comparator	1	0	-1	-1	0	-2	-2	Yes	-6	Very low
Negative affect in Alzheimer's Disease											
Mucke *et al.* (2018a)	THC products vs. placebo	1	0	-1	-1	0	-2	-2	Yes	-6	Very low
RHEUMATIC DISEASES											
PAIN-RELATED OUTCOMES											
Pain intensity											
Fitzcharles *et al.* (2016a)	THC:CBD products vs. placebo	1	0	-1	-1	0	-2	-1	Yes	-5	Very low
Fitzcharles *et al.* (2016a)	THC products vs. placebo	1	0	-1	-1	0	-2	-1	Yes	-5	Very low
Fitzcharles *et al.* (2016a)	THC products vs. active comparator	1	0	0	-1	0	-2	-1	Yes	-4	Very low
Fitzcharles *et al.* (2016b)	THC products vs. placebo	2	0	-1	-1	-1	-2	-1	Yes	-6	Very low
Fitzcharles *et al.* (2016b)	THC products vs. active comparator	1	0	0	-1	0	-2	-1	Yes	-4	Very low
Morning pain on movement											
Fitzcharles *et al.* (2016a)	THC:CBD products vs. placebo	1	0	-1	-1	0	-2	-1	Yes	-5	Very low
Morning pain at rest											

Author (year)	Intervention categorisation	No. studies	Study design	Trial quality (ROB randomisation)	Trial quality (ROB blinding outcome assessors)	Inconsistency (heterogeneity)	Imprecision (adequate sample size)	AMSTAR quality rating (critical domains)	Single study review	GRADE score	GRADE rating
Fitzcharles *et al.* (2016a)	THC:CBD products vs. placebo	1	0	-1	-1	0	-2	-1	Yes	-5	Very low
Fitzcharles *et al.* (2016b)	THC:CBD products vs. placebo	1	0	-1	-1	0	-2	-1	Yes	-5	Very low
Pain reduction of 50% or greater											
Fitzcharles *et al.* (2016b)	NA	0	NA	NA	NA	NA	NA	-1	NA	NA	No evidence found for this outcome
Pain reduction of 50% or greater in fibromyalgia											
Walitt *et al.* (2016)	NA	0	NA	NA	NA	NA	NA	0	NA	NA	No evidence found for this outcome
GLOBAL IMPRESSION OF CHANGE											
Patient global impression of change											
Fitzcharles *et al.* (2016b)	NA	0	NA	NA	NA	NA	NA	-1	NA	NA	No evidence found for this outcome
Walitt *et al.* (2016)	NA	0	NA	NA	NA	NA	NA	0	NA	NA	No evidence found for this outcome

Author (year)	Intervention categorisation	No. studies	Study design	Trial quality (ROB randomisation)	Trial quality (ROB blinding outcome assessors)	Inconsistency (heterogeneity)	Imprecision (adequate sample size)	AMSTAR quality rating (critical domains)	Single study review	GRADE score	GRADE rating
SLEEP-RELATED OUTCOMES											
Sleep quality											
Fitzcharles *et al.* (2016a)	THC:CBD products vs. placebo	1	0	-1	-1	0	-2	-1	Yes	-5	Very low
Fitzcharles *et al.* (2016a)	THC products vs. active comparator	1	0	0	-1	0	-2	-1	Yes	-4	Very low
QUALITY OF LIFE											
Quality of life											
Fitzcharles *et al.* (2016a)	THC products vs. placebo	1	0	-1	-1	0	-2	-1	Yes	-5	Very low
Fitzcharles *et al.* (2016a)	THC products vs. active comparator	1	0	0	-1	0	-2	-1	Yes	-4	Very low
SPINAL CORD INJURY											
PAIN-RELATED OUTCOMES											
Pain intensity											
Thomas *et al.* (2022)	THC products vs. active comparator	1	0	-1	-1	0	-2	-2	Yes	-6	Very low
Thomas *et al.* (2022)	THC:CBD products vs. placebo	1	0	-1	-1	0	-1	-2	Yes	-5	Very low
Thomas *et al.* (2022)	THC products vs. active comparator	1	0	-1	-1	0	-2	-2	Yes	-6	Very low
MULTIPLE SCLEROSIS											
SPASTICITY-RELATED OUTCOMES											
Observer-rated spasticity (Ashworth scale)											
Torres-Moreno *et al.* (2018)	Mixed cannabinoids vs. placebo	4	0	0	0	0	0	-2	0	-2	Moderate
Torres-Moreno *et al.* (2018)	THC:CBD products vs. placebo	8	0	-1	-1	0	0	-2	0	-4	Low
Torres-Moreno *et al.* (2018)	THC products vs. active comparator	3	0	0	0	0	0	-2	0	-2	Moderate

Author (year)	Intervention categorisation	No. studies	Study design	Trial quality (ROB randomisation)	Trial quality (ROB blinding outcome assessors)	Inconsistency (heterogeneity)	Imprecision (adequate sample size)	AMSTAR quality rating (critical domains)	Single study review	GRADE score	GRADE rating
Subjective spasticity											
Torres-Moreno *et al.* (2018)	Mixed cannabinoids vs. placebo	3	0	-1	-1	0	0	-2	0	-4	Low
Torres-Moreno *et al.* (2018)	THC:CBD products vs. placebo	9	0	-1	-1	0	0	-2	0	-4	Low
Torres-Moreno *et al.* (2018)	THC products vs. active comparator	3	0	0	-1	-1	0	-2	0	-4	Low
Filippini *et al.* (2022)	Mixed cannabinoids vs. placebo	7	0	-1	-1	0	0	-1	0	-3	Low
Spasticity reduction of 30% or greater											
Filippini *et al.* (2022)	THC:CBD products vs. placebo	5	0	-1	-1	0	0	-1	0	-3	Low
PAIN-RELATED OUTCOMES											
Pain											
Torres-Moreno *et al.* (2018)	Mixed cannabinoids vs. placebo	3	0	-1	-1	0	0	-2	0	-4	Low
Torres-Moreno *et al.* (2018)	THC:CBD products vs. placebo	6	0	-1	-1	0	0	-2	0	-4	Low
Torres-Moreno *et al.* (2018)	THC products vs. placebo	1	0	0	-1	0	-2	-2	Yes	-5	Very low
Torres-Moreno *et al.* (2018)	THC products vs. placebo	4	0	0	-1	-1	0	-2	0	-4	Low
Filippini *et al.* (2022)	Mixed cannabinoids vs. placebo	8	0	-1	-1	0	0	-1	0	-3	Low
Pain relief of 50% or greater											
Filippini *et al.* (2022)	THC products vs. placebo	1	0	0	0	0	-1	-1	Yes	-2	Very low
BLADDER-RELATED OUTCOMES											
Bladder dysfunction											
Torres-Moreno *et al.* (2018)	Mixed cannabinoids vs. placebo	3	0	0	0	0	0	-2	0	-2	Moderate

Author (year)	Intervention categorisation	No. studies	Study design	Trial quality (ROB randomisation)	Trial quality (ROB blinding outcome assessors)	Inconsistency (heterogeneity)	Imprecision (adequate sample size)	AMSTAR quality rating (critical domains)	Single study review	GRADE score	GRADE rating
Torres-Moreno *et al.* (2018)	THC:CBD products vs. placebo	4	0	-1	-1	0	0	-2	0	-4	Low
Torres-Moreno *et al.* (2018)	THC products vs. placebo	3	0	0	-1	0	0	-2	0	-3	Low
QUALITY OF LIFE											
Health-related quality of life											
Filippini *et al.* (2022)	Mixed cannabinoids vs. placebo	8	0	-1	-1	0	0	-1	0	-3	Low
GLOBAL IMPRESSION OF CHANGE											
Patient-rated global impression of change											
Filippini *et al.* (2022)	Mixed cannabinoids vs. placebo	8	0	-1	-1	0	0	-1	0	-3	Low

Mixed health conditions (efficacy)

Author (year)	Intervention categorisation	No. studies	Study design	Trial quality (ROB randomisation)	Trial quality (ROB blinding outcome assessors)	Inconsistency (heterogeneity)	Imprecision (adequate sample size)	AMSTAR quality rating (critical domains)	Single study review	GRADE score	GRADE rating
MIXED HEALTH CONDITIONS (EFFICACY)											
PAIN											
Pain intensity											
Bialas *et al.* (2022)	Mixed cannabinoid and cannabis products vs. placebo	6	-1	-1	-1	-1	0	-2	0	-6	Very low

Author (year)	Intervention categorisation	No. studies	Study design	Trial quality (ROB randomisation)	Trial quality (ROB blinding outcome assessors)	Inconsistency (heterogeneity)	Imprecision (adequate sample size)	AMSTAR quality rating (critical domains)	Single study review	GRADE score	GRADE rating
Longo *et al.* (2021)	Mixed cannabinoid products vs. placebo	10	0	-1	-1	-1	0	-2	0	-5	Very low
Sainsbury *et al.* (2021)	Mixed cannabinoid and cannabis vs. placebo	6	0	0	-1	0	-1	-1	0	-3	Low
McDonagh *et al.* (2022)	Mixed cannabinoid products vs. placebo	2	0	0	0	-1	0	-2	0	-3	Low
Giossi *et al.* (2022)	Mixed cannabinoid products vs. placebo	6	0	0	0	0	-1	-2	0	-3	Low
Meng *et al.* (2017)	Mixed cannabinoid products vs. mixed control	10	0	0	0	0	0	0	0	0	High
Meng *et al.* (2017) (subgroup analysis central pain)	Mixed cannabinoid vs. placebo	5	0	0	0	0	0	0	0	0	High
Meng *et al.* (2017) (subgroup analysis peripheral pain)	Mixed cannabinoid vs.. mixed control	4	0	0	0	-1	-1	0	0	-2	Moderate
Sainsbury *et al.* (2021)	Cannabis vs. placebo	2	0	0	-1	0	-2	-1	0	-4	Low
Price *et al.* (2022)	Cannabis products vs. placebo	1	0	0	0	0	-2	-1	Yes	-3	Very low
McDonagh *et al.* (2022)	Cannabis vs. usual care	3	-1	0	0	-1	0	-2	0	-4	Low
Meng *et al.* (2017)	THC/CBD products vs. placebo	6	0	0	0	0	0	0	0	0	High
Butler *et al.* (2015)	THC/CBD products vs. placebo	4	0	-1	-1	0	0	-2	0	-4	Low
Butler *et al.* (2015)	THC/CBD products vs. placebo	3	0	-1	-1	-1	0	-2	0	-5	Very low
Oordt *et al.* (2021)	THC/CBD products vs. placebo	7	0	-1	-1	-1	0	-2	0	-5	Very low
McDonagh *et al.* (2022)	THC/CBD products vs. placebo	7	0	-1	-1	0	0	-2	0	-4	Low

Author (year)	Intervention categorisation	No. studies	Study design	Trial quality (ROB randomisation)	Trial quality (ROB blinding outcome assessors)	Inconsistency (heterogeneity)	Imprecision (adequate sample size)	AMSTAR quality rating (critical domains)	Single study review	GRADE score	GRADE rating
Sainsbury *et al.* (2021)	THC/CBD products vs. placebo	5	0	0	-1	0	0	-1	0	-2	Moderate
Oordt *et al.* (2021)	THC vs. placebo	1	0	-1	-1	0	0	-2	Yes	-4	Very low
McDonagh *et al.* (2022)	THC products vs. placebo	6	0	-1	0	0	0	-2	0	-3	Low
Meng *et al.* (2017)	THC products vs. placebo	1	0	0	0	0	-2	0	Yes	-2	Very low
Vortubec (2022)	THC products vs. placebo	2	0	-1	0	-1	-2	-1	0	-5	Very low
Abdallah *et al.* (2020)	THC products vs. placebo	2	0	-1	-1	-1	-1	-2	0	-6	Very low
Sainsbury *et al.* (2021)	THC products vs. placebo	1	0	0	0	0	-2	-1	Yes	-3	Very low
Meng *et al.* (2017)	THC products vs. mixed control	3	0	0	0	-1	-1	0	0	-2	Moderate
McDonagh *et al.* (2022)	THC vs. active control	1	-1	0	0	0	-1	-2	Yes	-4	Very low
Longo *et al.* (2021)	THC vs. active control	3	0	0	0	-1	-2	-2	0	-5	Very low
Giossi *et al.* (2022)	THC products vs. active control	1	0	0	0	0	-2	-2	Yes	-4	Very low
Price *et al.* (2022)	THC products vs. active control	2	0	-1	0	-1	-2	-1	0	-5	Very low
Vortubec (2022)	CBD products vs. placebo	1	0	0	0	0	-2	-1	Yes	-3	Very low
Quintero *et al.* (2022)	CBD products vs. placebo	1	0	-1	-1	0	-2	-2	Yes	-6	Very low
McDonagh *et al.* (2022)	CBD products vs. placebo	1	0	0	-1	0	-1	-2	Yes	-4	Very low
Sainsbury *et al.* (2021)	CBD products vs. placebo	1	0	0	-1	0	-2	-1	Yes	-4	Very low

Author (year)	Intervention categorisation	No. studies	Study design	Trial quality (ROB randomisation)	Trial quality (ROB blinding outcome assessors)	Inconsistency (heterogeneity)	Imprecision (adequate sample size)	AMSTAR quality rating (critical domains)	Single study review	GRADE score	GRADE rating
McDonagh *et al.* (2022)	CBDV products vs. placebo	1	0	0	0	0	-2	-2	Yes	-4	Very low
Sainsbury *et al.* (2021)	CBDV products vs. placebo	1	0	0	-1	0	-2	-1	Yes	-4	Very low
Sainsbury *et al.* (2021)	CT-3 products vs. placebo	1	0	-1	-1	0	-2	-1	Yes	-5	Very low
Pain reduction equal to or greater than 30%											
Bialas *et al.* (2022)	Mixed cannabinoid and cannabis products vs. placebo	6	-1	-1	-1	-1	0	-2	0	-6	Very low
Andreae *et al.* (2015)	Cannabis products vs. placebo	5	0	0	-1	0	-1	0	0	-2	Moderate
Fisher *et al.* (2021) (<7 days duration)	Cannabis products vs. placebo	2	0	0	0	0	0	-1	0	-1	Moderate
Fisher *et al.* (2021) (>7 days duration)	Cannabis products vs. placebo	1	0	0	0	0	-1	-1	Yes	-2	Very low
Butler (2015)	THC/CBD products vs. placebo	3	0	-1	-1	0	0	-2	0	-4	Low
McDonagh *et al.* (2022)	THC/CBD products vs. placebo	4	0	-1	-1	0	0	-2	0	-4	Low
Fisher *et al.* (2021) (>7 days duration)	THC/CBD products vs. placebo	6	0	-1	-1	0	0	-1	0	-3	Low
Oordt *et al.* (2021)	THC/CBD products vs. placebo	4	0	-1	-1	-1	0	-2	0	-5	Very low
McDonagh *et al.* (2022)	THC products vs. placebo	1	0	0	0	0	-2	-2	Yes	-4	Very low
Fisher *et al.* (2021) (>7 days duration)	THC products vs. placebo	2	0	-1	-1	0	0	-1	0	-3	Low

Author (year)	Intervention categorisation	No. studies	Study design	Trial quality (ROB randomisation)	Trial quality (ROB blinding outcome assessors)	Inconsistency (heterogeneity)	Imprecision (adequate sample size)	AMSTAR quality rating (critical domains)	Single study review	GRADE score	GRADE rating
Fisher *et al.* (2021) (<7 days duration)	THC products vs. placebo/codeine	1	0	-1	-1	0	-2	-1	Yes	-5	Very low
McDonagh *et al.* (2022)	CBD products vs. placebo	1	0	0	-1	0	-1	-2	Yes	-4	Very low
McDonagh *et al.* (2022)	CBDV products vs. placebo	1	0	0	0	0	-2	-2	Yes	-4	Very low
Pain reduction equal to or greater than 50%											
Bialas *et al.* (2022)	Mixed cannabinoids and cannabis products	6	-1	-1	-1	-1	0	-2	0	-6	Very low
Mücke *et al.* (2018b)	Mixed cannabinoid products vs. placebo	8	0	-1	-1	0	0	-1	0	-3	Low
Oordt *et al.* (2021)	THC/CBD products vs. placebo	4	0	-1	-1	-1	0	-2	0	-5	Very low
Mücke *et al.* (2018b)	THC/CBD products vs. placebo	1	0	0	-1	0	-2	-1	Yes	-4	Very low
Fisher *et al.* (2021) (>7 days duration)	THC/CBD products vs. placebo	2	0	-1	-1	0	0	-1	0	-3	Low
Mücke *et al.* (2018b)	THC products vs. placebo	1	0	0	-1	0	-2	-1	Yes	-4	Very low
Fisher *et al.* (2021) (<7 days duration)	THC products vs. mixed control	2	0	-1	-1	-1	-2	-1	0	-6	Very low
Patient global impression of change of pain											
Butler *et al.* (2015)	Mixed cannabinoid products vs. placebo	2	0	-1	-1	0	-2	-2	0	-6	Very low
Mücke *et al.* (2018b)	Mixed cannabinoid products vs. placebo	6	0	-1	-1	0	0	-1	0	-3	Low
Mücke *et al.* (2018b)	THC products vs. placebo	1	0	0	-1	0	-2	-1	Yes	-4	Very low

Author (year)	Intervention categorisation	No. studies	Study design	Trial quality (ROB randomisation)	Trial quality (ROB blinding outcome assessors)	Inconsistency (heterogeneity)	Imprecision (adequate sample size)	AMSTAR quality rating (critical domains)	Single study review	GRADE score	GRADE rating
Morphine consumption											
Abdallah *et al.* (2020)	THC products vs. placebo	2	0	-1	-1	-1	-1	-2	0	-6	Very low
QUALITY OF LIFE											
Health-related quality of life											
Belgers *et al.* (2023)	Mixed cannabinoid products vs. placebo	13	0	0	-1	0	0	-2	0	-3	Low
Belgers *et al.* (2023)	THC/CBD products vs. placebo	5	0	0	0	0	0	-2	0	-2	Moderate
Belgers *et al.* (2023) (subgroup analysis)	THC products vs. mixed control	6	0	0	-1	0	0	-2	0	-3	Low
Oordt *et al.* (2021) (subgroup analysis)	THC/CBD products vs. placebo	4	0	-1	-1	-1	0	-2	0	-5	Very low
Oordt *et al.* (2021)	THC products vs. placebo	1	0	-1	-1	0	0	-2	Yes	-4	Very low
Quality of life (cancer and cachexia)											
Hammond *et al.* (2021)	Mixed cannabinoid products vs. mixed control	3	0	-1	0	0	0	-2	0	-3	Low
SPASTICITY											
Spasticity intensity											
da Rovare *et al.* (2017)	Mixed cannabinoid and cannabis products vs. placebo	7	0	-1	0	-1	0	-1	0	-3	Low
Oordt *et al.* (2021)	THC/CBD products vs. placebo	2	0	-1	-1	-1	0	-2	0	-5	Very low
Reduction in spasticity equal to or greater than 30%											

Author (year)	Intervention categorisation	No. studies	Study design	Trial quality (ROB randomisation)	Trial quality (ROB blinding outcome assessors)	Inconsistency (heterogeneity)	Imprecision (adequate sample size)	AMSTAR quality rating (critical domains)	Single study review	GRADE score	GRADE rating
Oordt *et al.* (2021)	THC/CBD products vs. placebo	2	0	-1	-1	-1	0	-2	0	-5	Very low
Spasm frequency											
da Rovare *et al.* (2017)	Mixed cannabinoid and cannabis products vs. placebo	6	0	-1	-1	0	0	-1	0	-3	Low
Spasm severity											
da Rovare *et al.* (2017)	Mixed cannabinoid and cannabis products vs. placebo	3	0	-1	-1	0	-1	-1	0	-4	Low
Observer-rated spasticity											
Oordt *et al.* (2021)	THC/CBD products vs. placebo	2	0	0	-1	-1	0	-2	0	-4	Low
Oordt *et al.* (2021)	THC products vs. placebo	1	0	0	-1	0	0	-2	Yes	-3	Very low
CACHEXIA											
Appetite											
Hammond *et al.* (2021)	Mixed cannabinoid products vs. placebo	2	0	-1	0	0	0	-2	0	-3	Low
Weight loss/gain											
Hammond *et al.* (2021)	Mixed cannabinoid products vs. mixed control	2	0	-1	-1	-1	-2	-2	0	-7	Very low
SLEEP											
Sleep quality											
Aminilari (2022)	Mixed cannabinoid products vs. placebo	16	0	0	-1	0	0	-1	0	-2	Moderate
McParland (2023)	Mixed cannabinoid products vs. placebo	6	0	0	0	0	0	0	0	0	High

Author (year)	Intervention categorisation	No. studies	Study design	Trial quality (ROB randomisation)	Trial quality (ROB blinding outcome assessors)	Inconsistency (heterogeneity)	Imprecision (adequate sample size)	AMSTAR quality rating (critical domains)	Single study review	GRADE score	GRADE rating
Aminilari (2022)	THC products vs. placebo	1	0	0	0	0	-2	-1	Yes	-3	Very low
Sleep disturbance											
Aminilari (2022)	Mixed cannabinoid products vs. placebo	16	0	-1	0	-1	0	-1	0	-3	Low
Aminilari (2022) (subgroup cancer)	Mixed cannabinoid products vs. placebo	5	0	0	0	0	0	-1	0	-1	Moderate
Aminilari (2022) (subgroup non-cancer)	Mixed cannabinoid products vs. placebo	11	0	-1	0	0	0	-1	0	-2	Moderate
Aminilari (2022)	THC products vs. active control	1	0	0	0	0	-2	-1	Yes	-3	Very low
PTSD nightmares											
Aminilari (2022)	THC products vs. placebo	1	0	-1	-1	0	-2	-1	Yes	-5	Very low
Sleepiness											
Aminilari (2022)	THC products vs. placebo	1	0	0	0	0	-2	-1	Yes	-3	Very low
Insomnia											
Aminilari (2022)	THC product vs. active control	1	0	0	0	0	-2	-1	Yes	-3	Very low
Sleep interruptions											
Aminilari (2022)	THC vs. active control	1	0	0	0	0	-2	-1	Yes	-3	Very low
Daytime somnolence											
McParland (2023)	Mixed cannabinoid products vs. placebo	7	0	0	0	0	0	0	0	-1	High
MENTAL HEALTH/WELL-BEING											
Mental health/well-being											

Author (year)	Intervention categorisation	No. studies	Study design	Trial quality (ROB randomisation)	Trial quality (ROB blinding outcome assessors)	Inconsistency (heterogeneity)	Imprecision (adequate sample size)	AMSTAR quality rating (critical domains)	Single study review	GRADE score	GRADE rating
Belgers *et al.* (2023)	Mixed cannabinoid products vs. placebo	13	0	0	-1	0	0	-2	0	-3	Low
Belgers *et al.* (2023)	THC/CBD products vs. placebo	5	0	0	-1	0	0	-2	0	-3	Low
Belgers *et al.* (2023)	THC products vs. placebo	6	0	0	-1	0	0	-2	0	-3	Low
OVERALL FUNCTION OR DISABILITY											
Overall function or disability											
McDonagh *et al.* (2022)	Cannabis vs. usual care	1	-1	-1	0	0	-1	-2	Yes	-5	Very low
McDonagh *et al.* (2022)	THC/CBD products vs. placebo	6	0	-1	-1	0	0	-2	0	-4	Low
McDonagh *et al.* (2022)	THC:CBD products vs. placebo	1	0	0	0	0	-2	-2	Yes	-4	Very low
McDonagh *et al.* (2022)	THC products vs. placebo	2	0	0	0	0	-2	-2	0	-4	Low
McDonagh *et al.* (2022)	THC vs. active control	1	-1	0	0	0	-1	-2	Yes	-4	Very low

Safety and tolerability

Author (year)	Intervention categorisation	No. studies	Study design	Trial quality (ROB randomisation)	Trial quality (ROB blinding outcome assessors)	Inconsistency (heterogeneity)	Imprecision (adequate sample size)	AMSTAR quality rating (critical domains)	Single study review	GRADE score	GRADE rating
SAFETY AND TOLERABILITY											
NERVOUS SYSTEM ADVERSE EVENTS											
Dizziness											

Author (year)	Intervention categorisation	No. studies	Study design	Trial quality (ROB randomisation)	Trial quality (ROB blinding outcome assessors)	Inconsistency (heterogeneity)	Imprecision (adequate sample size)	AMSTAR quality rating (critical domains)	Single study review	GRADE score	GRADE rating
McDonagh *et al.* (2022)	Cannabis vs. usual care	1	-1	-1	-1	0	0	-2	Yes	-5	Very low
McDonagh *et al.* (2022)	THC/CBD products vs. placebo	6	0	-1	-1	-1	0	-3	0	-6	Very low
Bajtel *et al.* (2022)	THC products vs. placebo	3	0	-1	-1	0	-2	-2	0	-6	Very low
Bajtel *et al.* (2022)	THC products vs. placebo	8	0	0	0	0	0	-2	0	-2	Moderate
McDonagh *et al.* (2022)	THC products vs. placebo	3	0	0	0	0	0	-2	0	-2	Moderate
McDonagh *et al.* (2022)	THC vs. mixed control	1	-1	0	-1	0	-1	-2	Yes	-5	Very low
Sedation											
McDonagh *et al.* (2022)	Cannabis vs. usual care	1	-1	-1	-1	0	0	-2	Yes	-5	Very low
McDonagh *et al.* (2022)	THC/CBD vs. placebo	6	0	-1	-1	0	0	-2	0	-4	Low
McDonagh *et al.* (2022)	THC products vs. placebo	3	0	0	0	0	0	-2	0	-2	Moderate
Bosnjak-Kuharic *et al.* (2021)	THC vs. placebo	1	0	0	0	0	-2	-1	Yes	-3	Very low
Paunescu 2020	THC vs. placebo	1	0	-1	-1	0	-2	-2	Yes	-6	Very low
McDonagh *et al.* (2022)	THC vs. mixed control	1	-1	0	-1	0	-1	-2	Yes	-5	Very low
Drowsiness											
Bajtel *et al.* (2022)	THC products vs. placebo	3	0	-1	-1	0	-2	-2	0	-6	Very low
Bajtel *et al.* (2022)	THC products vs. placebo	3	0	0	0	-1	-2	-2	0	-5	Very low
Dry mouth											
Bajtel *et al.* (2022)	THC products vs. placebo	4	0	-1	-1	0	-1	-2	0	-5	Very low
Bajtel *et al.* (2022)	THC products vs. placebo	6	0	0	0	0	0	-2	0	-2	Moderate
Headache											
Bajtel *et al.* (2022)	THC products vs. placebo	4	0	-1	-1	0	-1	-2	0	-5	Very low
Bajtel *et al.* (2022)	THC products vs. placebo	9	0	-1	0	0	0	-2	0	-3	Low
Fatigue											
Bajtel *et al.* (2022)	THC products vs. placebo	4	0	0	0	0	0	-2	0	-2	Moderate
Impotence											
Hammond *et al.* (2021)	THC vs. active control	1	0	0	0	0	0	-2	Yes	-2	Very low
Any nervous system disorder adverse events										0	

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Bosnjak-Kuharic *et al.* (2021)	THC vs. placebo	1	0	0	0	0	-2	-1	Yes	-3	Very low
Hammond *et al.* (2021)	THC vs. placebo	1	0	0	0	0	-1	-2	0	-3	Very low
GASTROINTESTINAL SYSTEM ADVERSE EVENTS											
Nausea											
McDonagh *et al.* (2022)	Cannabis vs. usual care	1	-1	-1	-1	0	0	-2	Yes	-5	Very low
McDonagh *et al.* (2022)	THC/CBD vs. placebo	6	0	-1	-1	0	0	-2	0	-4	Low
Bajtel *et al.* (2022)	THC product vs. placebo	5	0	0	0	0	0	-2	0	-2	Moderate
McDonagh *et al.* (2022)	THC product vs. placebo	2	0	0	0	0	0	-2	0	-2	Moderate
Any gastrointestinal system adverse events											
Bosnjak-Kuharic *et al.* (2021)	THC vs. placebo	1	0	0	0	0	-2	-1	Yes	-3	Very low
PSYCHIATRIC SYSTEM DISORDER ADVERSE EVENTS											
Any psychiatric system disorder adverse events											
McDonagh *et al.* (2022)	Cannabis vs. usual care	1	-1	-1	-1	0	0	-2	Yes	-5	Very low
Bosnjak-Kuharic *et al.* (2021)	THC vs. placebo	1	0	0	0	0	-2	-1	Yes	-3	Very low
ANY SPECIFIC ADVERSE EVENTS											
Any specific adverse events											
Urbi *et al.* (2022)	THC/CBD vs. placebo	1	0	0	0	0	-2	-2	Yes	-4	Very low
Hammond *et al.* (2021)	THC:CBD vs. placebo	1	0	-1	0	0	-1	-2	0	-4	Very low
Paunescu 2020	THC vs. placebo	2	0	-1	0	0	-2	-2	0	-5	Very low
Bosnjak-Kuharic *et al.* (2021)	THC vs. placebo	4	0	0	0	-1	-1	-1	0	-3	Low
Urbi *et al.* (2022)	THC vs. placebo	2	0	0	-1	-1	-2	-2	0	-6	Very low
Hammond *et al.* (2021)	THC vs. placebo	3	0	-1	0	-1	0	-2	0	-4	Low
Hammond *et al.* (2021)	THC vs. active control	2	0	0	0	-1	0	-2	0	-3	Low
Urbi *et al.* (2022)	CBD vs. placebo	2	0	0	-1	-1	-2	-2	0	-6	Very low
Quintero *et al.* (2022)l	CBD products vs. placebo	1	0	-1	-1	0	-2	-2	Yes	-6	Very low

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van den Elsen (2014)	Mixed cannabinoid vs. mixed control	4	0	0	-1	-1	0	-2	0	-4	Low
SERIOUS ADVERSE EVENTS											
Mortality											
Oordt *et al.* (2021)	THC/CBD products vs. placebo	2	0	-1	-1	0	0	-2	0	-4	Low
Oordt *et al.* (2021)	THC/CBD products vs. placebo	2	0	0	-1	0	0	-2	0	-3	Low
Oordt *et al.* (2021)	THC/CBD products vs. placebo	1	0	-1	-1	0	-2	-2	0	-6	Very low
Bosnjak-Kuharic *et al.* (2021)	THC vs. placebo	2	0	-1	-1	-1	-2	-1	0	-6	Very low
Oordt *et al.* (2021)	THC products vs. placebo	1	0	-1	-1	0	0	-2	Yes	-4	Very low
Any serious adverse events											
Mücke *et al.* (2018b)	Mixed cannabinoids vs. placebo	13	0	-1	-1	0	0	-1	0	-3	Low
van den Elsen *et al.* (2014)	Mixed cannabinoid vs. placebo	4	0	-1	-1	-1	-2	-2	0	-7	Very low
McDonagh *et al.* (2022)	Cannabis vs. usual care	1	-1	-1	-1	0	0	-2	Yes	-5	Very low
Häuser *et al.* (2019)	THC/CBD vs. placebo	4	0	-1	-1	0	0	-2	0	-4	Low
Häuser *et al.* (2019)	THC/CBD vs. placebo	1	-1	-1	-1	0	0	-2	0	-5	Very low
Fitzcharles *et al.* (2018b)	THC/CBD vs. placebo	1	0	-1	-1	0	-2	-1	Yes	-5	Very low
Fitzcharles *et al.* (2018b)	THC vs. placebo	1	0	-1	-1	0	-2	-1	Yes	-5	Very low
Fitzcharles *et al.* (2018b)	THC vs. active control	1	0	0	-1	0	-2	-1	Yes	-4	Very low
Walitt *et al.* (2016)	THC vs. placebo	1	0	-1	0	0	-2	0	Yes	-3	Very low
Walitt *et al.* (2016)	THC vs. active control	1	0	0	-1	0	-2	0	Yes	-3	Very low
McDonagh *et al.* (2022)	THC vs. mixed control	1	-1	0	-1	0	-1	-2	Yes	-5	Very low
TOLERABILITY											
Withdrawal due to adverse events											
McDonagh *et al.* (2022)	Cannabis vs. usual care	1	-1	-1	-1	0	0	-2	Yes	-5	Very low
Mücke *et al.* (2018b)	Mixed cannabinoids and cannabis vs. placebo	13	0	-1	-1	0	0	-1	0	-3	Low
McDonagh *et al.* (2022)	THC/CBD products vs. placebo	5	0	-1	-1	0	0	-2	0	-4	Low
Häuser *et al.* (2019)	THC/CBD vs. placebo	4	0	-1	-1	0	0	-2	0	-4	Low

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Häuser *et al.* (2019)	THC/CBD vs. placebo	1	-1	-1	-1	0	0	-2	0	-5	Very low
Fitzcharles *et al.* (2018b)	THC/CBD vs. placebo	1	0	-1	-1	0	-2	-1	Yes	-5	Very low
Oordt *et al.* (2021)	THC/CBD vs. placebo	2	0	-1	-1	-1	0	-2	0	-5	Very low
Oordt *et al.* (2021)	THC/CBD vs. placebo	4	0	-1	-1	-1	0	-2	0	-5	Very low
Bahji *et al.* (2020)	NA	0	NA	NA	NA	NA	NA	-2	NA	NA	No evidence presented for this outcome
McDonagh *et al.* (2022)	THC vs. placebo	5	0	0	0	0	0	-2	0	-2	Moderate
McDonagh *et al.* (2022)	THC vs. placebo	4	0	0	0	0	0	-2	0	-2	Moderate
McDonagh *et al.* (2022)	THC vs. placebo	1	0	0	0	0	0	-2	Yes	-2	Very low
Paunescu *et al.* (2020)	THC vs. placebo	1	0	-1	0	0	-2	-2	Yes	-5	Very low
Oordt *et al.* (2021)	THC vs. placebo	1	0	-1	-1	0	0	-2	Yes	-4	Very low
Fitzcharles *et al.* (2018b)	THC vs. placebo	1	0	-1	-1	0	-2	-1	Yes	-5	Very low
Walitt *et al.* (2016)	THC vs. placebo	1	0	-1	0	0	-2	0	Yes	-3	Very low
Walitt *et al.* (2016)	THC vs. active control	1	0	0	-1	0	-2	0	Yes	-3	Very low
Fitzcharles *et al.* (2018b)	THC vs. active control	1	0	0	-1	0	-2	-1	Yes	-4	Very low
McDonagh *et al.* (2022)	THC vs. mixed control	1	-1	0	-1	0	-1	-2	Yes	-5	Very low