REVIEW ON USE OF CANNABIS FOR MEDICAL PURPOSES

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Abbreviations

ADHD	Attention deficit hyperactivity disorder
ALS	Amyotrophic lateral sclerosis
ASD	Autism spectrum disorder
CBD	Cannabidiol
CE	Cannabis extract
CINV	Chemotherapy induced nausea and vomiting
Core SR	Systematic reviews of original studies included in this current review
CNCP	Chronic non-cancer pain
DIN	Drug identification number
MC	Medical cannabis
MS	Multiple sclerosis
NPC	Non-pharmaceutical cannabinoids
NPN	Natural product number
NRSI	Non-randomized study of intervention
OCE	Oral cannabis extract
PCB	Pharmaceutical cannabinoids
PTSD	Post-traumatic stress disorder
ROB	Risk of bias
RCT	Randomized controlled trial
RSR	Reviews of systematic reviews included in this current review
SAD	Social anxiety disorders
SCET	Standardized cannabis extract with THC
SCT	Standardized cannabis with THC
SR	Systematic review
THC	Delta 9-tetrahydrocannabinol

Executive Summary

Cannabis has long been used internationally as a recreational compound and as a therapeutic option for the symptomatic management of many conditions (1). Also known as marijuana, hashish, bhang, cannador, charas or ganja, cannabis comprises two main species (Cannabis sativa and Cannabis indica), which gave rise to hundreds of strains, with numerous chemical compositions and pharmacologic profiles (2, 3).

Cannabis-based medicines are chemical compounds that are either extracted directly from different parts of the cannabis plant or are synthetically prepared (2-4). These compounds exhibit a stimulatory effect on the internal endocannabinoid system, which regulates many neurocognitive functions such as pain, memory, reward processing, mood, and appetite (2, 4).

The two most heavily used medical cannabinoids are cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC) (1, 4). A medical cannabis medication may contain any one of them separately, combined in variable concentrations, or combined with other types of cannabinoids or medications (1, 4). Should they exist together, a delicate balance must be maintained between the non-psychoactive CBD and psychoactive THC to avoid the adverse effects caused by the latter (1).

With the dawn of legalization of cannabis use, many research studies were launched internationally, fueled in part by the motivations of medical cannabis manufacturers, and also due in part to an increasing public demand for new modalities to treat symptoms that are refractory to standard and traditional treatments, with the goal of subsequently improving quality of life.

Original research projects have been predominantly observational in nature with very few clinical trials and randomized controlled trials (RCTs). RCTs would provide high quality evidence on the benefits of cannabis-based medicines for treatment of different conditions, particularly with palliation and with pain and movement disorders.

While pharmaceutical cannabinoids have a reasonable history of evidence for treatment of certain conditions, the current level of evidence for medical cannabis and non-pharmaceutical cannabinoids is largely limited, inconsistent, and predominantly of low quality.

Nevertheless, the current review highlights evidence regarding the benefits of some non-pharmaceutical cannabis-based medicines for treatment of symptoms in particular conditions, such as neuropathic pain; chronic pain conditions (cancer, non-cancer, arthritis-related, MS-related); in palliative care (cancer and HIV/AIDS) for pain, anorexia, nausea, and vomiting; and for spasticity (MS and spinal cord injuries).

The current review includes some limitations, particularly due to the synthesis of information collected via the different systematic reviews rather than collecting the required information directly from original studies. This led to issues stemming from the wide range of study designs included in most of the reviews. The included reviews often lacked valuable information such as details of chemical composition of the cannabis preparations, doses, routes of administration, and treatment duration, which collectively have many pharmacokinetic and pharmacodynamic implications.

Methods

Research question

This review aims at determining whether there is any updated evidence since the last WSIB review regarding the indications for use of medical cannabis for treatment of patients with neuropathic pain, spasticity resulting from a spinal cord injury, chemotherapy-associated nausea and vomiting, HIV/AIDS-associated anorexia, and palliative care, as well as evidence for other indications.

Inclusion/exclusion criteria

The current approach entailed a systematic review of reviews. Two types of reviews were included in the current evidence synthesis: a) Systematic reviews of original studies (Core SR) and, b) Reviews of systematic reviews (RSR). Eligible studies examined the human use of any type of medical cannabis formulation (with the exception of pharmaceutical formulations, which are used for treatment of different conditions). Exclusion criteria were non-systematic reviews; reviews conducted on non-humans; reviews that only examined pharmaceutical cannabis formulations; reviews that focused on cannabis addiction, withdrawal or adverse reactions; reviews that discussed non-health indications of medical cannabis, such as political, legal or economic; and reviews published prior to 2016.

Inclusion in the current review was based on evidence reported on the use of any cannabis formulation that can be accessed legally in Canada except for currently registered cannabis medications commonly referred to as pharmaceutical cannabinoids. Only published evidence was examined for reporting on non-pharmaceutical cannabinoids, which includes any cannabis-based medications as long as they do not currently possess a drug identification number (DIN) or a natural product number (NPN)

Cannabis formulations

The review refers to cannabis/cannabinoid formulations using the same terminology reported in the original WSIB review, except for pharmaceutical preparations. These

preparations include cannabinoids with a DIN or NPN such as Sativex®, Nabiximol®, Dronabinol®, Epidiolex, Marinol and Ajulemic acid, as per regulations of Health Canada and WSIB. In such a case, there was a deliberate categorization of the formulation as pharmaceutical even though it is reported in the original review as, for instance, a medical cannabis/cannabinoid or plant-based cannabinoid.

Search strategy

In this review, publications published from 2016 to the present date were examined. In doing so, a comprehensive, multi-step search strategy to identify published, peer-reviewed, systematic reviews was implemented. No filters were applied to limit the search output. The search was conducted in accordance with the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (5) and following the specific guidance provided by the Cochrane Collaboration (6).

The search strategy for human studies was designed and implemented between March 23-25, 2020. Three major bibliographic databases were searched (Medline Ovid, EMBASE and PubMed) using specific keywords. See Appendix 1 for details on the searched sources, used terms, and search output. Additionally, bibliographies were inspected of examined reviews for additional relevant studies not already identified via the original search.

Identified references from all sources were collated using the EndNote (7) reference management application. EndNote was used to identify potential duplicates, with manual resolution employed to remove additional actual duplicates. Screening of titles and abstracts (level 1) and full-text examination (level 2) were performed independently by two reviewers to identify systematic reviews eligible for inclusion in the review. The review was completed through a multi-level assessment process, using the Distiller SR application (8). Conflicts identified in each step were resolved via consensus prior to moving to the next level.

Data abstraction spreadsheets were developed using Microsoft Office Excel and used to abstract the following information: study design, study population characteristics, exposure assessment, and authors' reported conclusion. Reviewers' comments, if any, were also included. Key characteristics of the included studies are summarized in Table 2 in this report

and provided in full detail in the Supplementary Materials.

Assessing quality of evidence and risk of bias

For assessing the quality of evidence from included systematic reviews of original studies, the AMSTAR2 tool was used (9). This tool, designed only for reviews of clinical trials and non-randomized studies of interventions, includes 16 questions, 7 critical and 9 non-critical. Based on the assessment results, a review would be granted one of four levels of confidence: high, moderate, low, or critically low.

For assessing the quality of evidence in RSR, we used a Health Evidence tool developed by McMaster University (10-12). Whereas this tool is also designed for assessing systematic reviews of original studies, similar to AMSTAR2, it was still applicable to RSR while providing clear guidance on question interpretation without any manipulation to the questions or the scoring system. Based on responses to its ten questions, each review would be assigned an overall rating of “strong”, “moderate”, or “weak”.

Questions used by the two tools as well as results of the assessment of all included reviews are detailed in Appendix 3.

Results

The search strategy resulted in retrieval of 13,229 records from three bibliographic databases. Restricting these records to reviews reduced the available records to 5,101. Electronic and manual de-duplication resulted in removal of 1,677 records, and identification of 3,424 eligible reviews. The cohort of eligible reviews was restricted to those published between 2016 and 2020 (n=468). Title and abstract screening of these reviews led to the exclusion of 336 records, leaving 132 studies for full-text examination.

Upon exclusion of 81 additional studies, 51 systematic reviews were retained for qualitative analysis. However, the current review examines only 49 systematic reviews, including 42 ‘core’ systematic reviews of original studies (13-54) and 7 reviews of systematic reviews (RSR) (55-61). Secondary reviews refer to reviews included in the RSRs.

Two reviews (62, 63) were excluded: Elliot et al. (2019) was excluded as it was superseded by Elliot et al. 2020 (62), and Aviram et al. (2017) was excluded due to repeating information in Table 1 that was suspected to be reported in error. As descriptive tables are the most crucial parts of systematic reviews, Aviram et al. could not be included in confidence (63).

A detailed PRISMA flow diagram (5) summarizing the flow of studies during the selection process is shown in Figure 1. A summary of studies excluded at levels 1 and 2, grouped by reason of exclusion is shown in Table 1, and listed in detail in Appendix 2.

Table 1: Studies excluded at levels 1 and 2 by exclusion reason/group

Level	Exclusion group	Reason for exclusion	# of References
Title & abstract screening	Duplicate reference	Duplicate reference	37
	Irrelevant population	Irrelevant population	3
	Irrelevant exposure	Irrelevant exposure	6
		Only pharmaceutical cannabinoids	3
	Irrelevant indication	Addiction/Withdrawal	199
		No therapeutic indication	44
		Irrelevant study focus	23
	Irrelevant publication type	Irrelevant study design	17
		Non-English reference	4
Full-text examination	Irrelevant exposure	Irrelevant exposure	1
		Mixed cannabinoids	1
		Only pharmaceutical cannabinoids	4
	Irrelevant outcome	No outcome data	1
		Addiction/Withdrawal	6
	Irrelevant population	Irrelevant population	1
	Unavailable full-text	Unavailable full-text	23
	Irrelevant publication type	Irrelevant study design	44

Forty-nine eligible systematic reviews were retained for qualitative assessment, including 7 reviews of systematic reviews. These reviews reported on a wide range of experimental (clinical trials) and observational studies (cohort, case-control, cross-sectional, case reports, case series, chart reviews). A summary of the major characteristics of these systematic reviews is provided in Table 2.

These reviews reported on original studies or reviews that examined the association of many cannabis-based formulations and cannabinoids (plant-based, synthetic, unspecified), for treating patients with a wide range of indications. These indications included pain conditions, palliative care (cancer, HIV/AIDS), movement disorders, psychiatric and neurocognitive diseases/disorders, and other conditions. A detailed listing of the different cannabis formulations with the corresponding indications is provided in Appendix 4

Multiple sclerosis represented the indication most frequently examined with different cannabis formulations, followed by pain conditions (neuropathic and non-neuropathic), post-traumatic stress disorder (PTSD) and epilepsy (including for children). Figure 2 illustrates all the cannabis-indication associations examined by the included reviews.

Individual non-pharmaceutical cannabinoids (mainly CBD, THC, CBD:THC) were reported more frequently compared to medical cannabis preparations (whole plant, extract, resin, cigarettes).

Regarding the risk of bias assessment, 9 systematic reviews reflected a high level of confidence (low risk of bias) in their reporting of evidence compared to 1, 3, and 36 for moderate, low and critically low levels of confidence (low confidence implies high risk of bias), respectively.

Authors concluded there was a positive level of evidence for use of medical cannabis and/or cannabinoids for different indications in 16 reviews, whereas the conclusion in 12 reviews was that the level of evidence was ‘possible’ and in 4 reviews the level of evidence was ‘negative’. Conclusions could not be identified in the authors’ discussions or summaries in 17 of the included reviews.

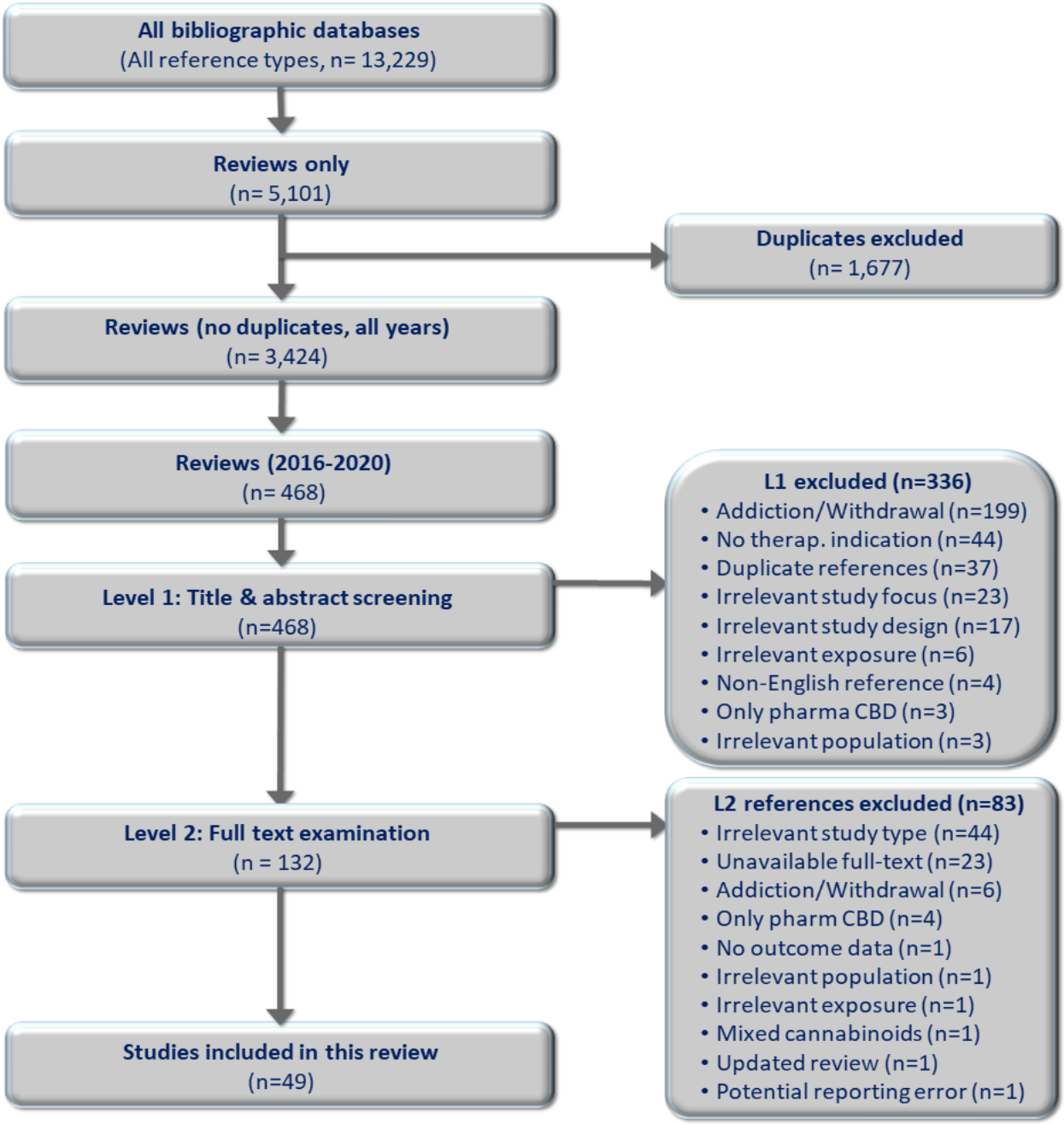

Figure 1: PRISMA flow diagram for eligible studies on medical cannabis

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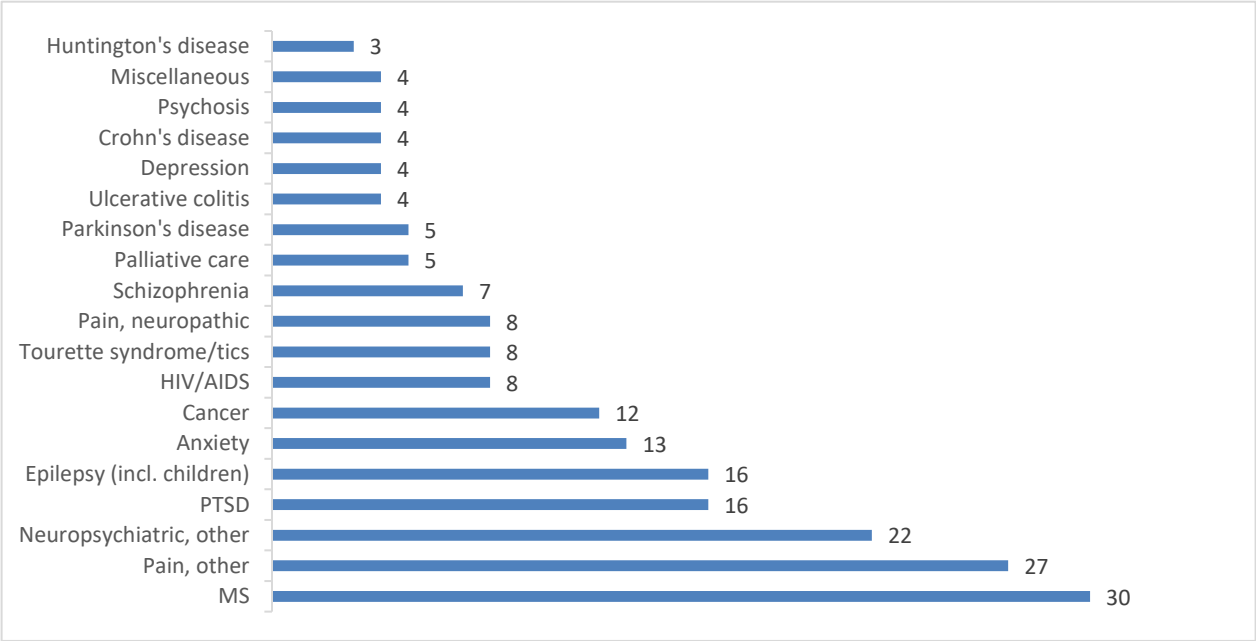

Figure 2: Frequency of indications examined in the included reviews

Table 2: Characteristics of included reviews

Systematic Review	Number Relevant Original studies (Number secondary SRs)	Types of studies	Examined formulations	Indications	Authors' conclusion	Level of confidence
Boland 2020 (13)	1	CT	THC, THC:CBD	Cancer (pain), dementia	U	H
Charernboon 2020 (14)	2	CT	THC	Dementia	U	CL
de Carvalho 2020 (15)	16	CT	Cannabis, CBD	Epilepsy	P	CL
Elliott 2020 (16)	13	CT, cohort, CRS, case series	CBD, CBD:THC	Epilepsy (pediatric)	P	CL
Hindocha 2020 (17)	7	CT, CRV, case reports, case series	Herbal cannabis, cannabis resin, THC, CBD, CBD oil	PTSD	Ps	CL
Johal 2020 (18)	5	CT	Cannabis (inhaled), THC	HIV (sensory neuropathy), MS (spasticity), chronic	P	CL

Systematic Review	Number Relevant Original studies (Number secondary SRs)	Types of studies	Examined formulations	Indications	Authors' conclusion	Level of confidence
				non-cancer pain, neuropathic pain		
Khan 2020 (19)	15	CT, CRV, case reports, case series	CBD	ADHD, SAD, cancer (pain), dementia, epilepsy (pediatric), HIV (sensory neuropathy), MS (spasticity), chronic non-cancer pain	P	CL
Mun 2020 (20)	21	CT	Cannabis, cannabinoids	Chronic non-cancer pain, neuropathic pain	Ps	CL
Rabgay 2020 (21)	10	CT	Cannabis (standardized dried)	Neuropathic pain, PTSD, ADHD	P	CL

Systematic Review	Number Relevant Original studies (Number secondary SRs)	Types of studies	Examined formulations	Indications	Authors' conclusion	Level of confidence
Sarris 2020 (22)	7	CT, CRV, case series	Cannabis, CBD	SAD, cancer (pain), dementia, epilepsy (pediatric)	Ps	CL
Amaniti 2019 (23)	2	CT	Cannabis cigarettes	HIV (sensory neuropathy)	P	CL
Black 2019 (24)	31	CT, cohort, CC, CRS, Quasi experimental	Cannabis sativa, cannabis resin, CBD extract, Marijuana	ADHD, ALS, Alzheimer's disease (agitation), anorexia nervosa, SAD, cancer (cachexia), CINV, cognition	Ps	L
Bonaccorso 2019 (25)	13	CT	CBD, THC	Huntington's disease, MS (bladder dysfunction, gait disorders, spasticity) pain	Ps	CL

Systematic Review	Number Relevant Original studies (Number secondary SRs)	Types of studies	Examined formulations	Indications	Authors' conclusion	Level of confidence
Calapai 2019 (26)	4	CT	CBD	SAD	P	CL
Hoch 2019 (55)		CT	CBD, THC	Alzheimer's disease (dementia), SAD, schizophrenia, Tourette syndrome	P	H
Khoury 2019 (27)	7	CT, case reports	CBD	SAD, cancer (cachexia)	Ps	CL
Millar 2019 (28)	35	CT, case reports, case series	CBD	SAD, cancer (cachexia, pain), CINV, cognition, Crohn's disease (pain), depression, epilepsy	P	CL
Orsolini 2019 (29)	4	CT	THC, CBD	PTSD, Tourette syndrome/tics	Ps	CL

Systematic Review	Number Relevant Original studies (Number secondary SRs)	Types of studies	Examined formulations	Indications	Authors' conclusion	Level of confidence
Wang 2019 (30)	3	CT	CE, THC, THC:CBD	Cancer (cachexia, pain), CINV	P	CL
Yanes 2019 (31)	16	CT	MC/CE	Pain	Ps	CL
Advani 2018 (32)	1	CT	CE, THC	Cancer (cachexia)	U	CL
Allan 2018 (61)	0 (28)	CT	Cannabinoids	Neuropathic pain, CINV, spasticity (mainly MS)	P	H
Behm 2018 (33)	2	CT	CE, THC cannabis cigarettes	MS (gait disorders)	U	CL
De Vita 2018 (34)	12	CT	Plant-based cannabis cigarettes with THC-specific dosages, THS standardized CE, THC	Experimental pain, neuropathic pain (adults), neuropathic pain (HIV/AIDS)	P	CL
Ishak 2018 (35)	1	CRS	Cannabis	Depression, epilepsy, health-related quality of life, HIV/AIDS	P	CL

Systematic Review	Number Relevant Original studies (Number secondary SRs)	Types of studies	Examined formulations	Indications	Authors' conclusion	Level of confidence
				(sensory neuropathy), Huntington's disease		
Kafil 2018 (36)	2	CT	Cannabis, CBD	Ulcerative colitis	U	L
Mucke 2018 (37)	2	CT	Herbal Cannabis Marijuana cigarettes	Palliative care (cancer), PTSD	N	CL
Mucke 2018a (38)	2	CT	Herbal cannabis	Neuropathic pain (adults)	U	H
Nielsen 2018 (56)	0 (11)	CT, CC, CRS	MC, cannabinoids, whole plant extract	MS (spasticity and pain)	P	H
Stockings 2018 (39)	31	CT, cohort, CC, CRS, case report	MC, CE, CBD, THC:CBD, THCA	Epilepsy, health-related quality of life, HIV/AIDS (sensory neuropathy), Huntington's disease, MS (bladder	P	H

Systematic Review	Number Relevant Original studies (Number secondary SRs)	Types of studies	Examined formulations	Indications	Authors' conclusion	Level of confidence
				dysfunction, gait disorders, spasticity)		
Stockings 2018a (40)	39	CT cohort, CC, CRS	Cannabis sativa, THC, CBD, THC-HS, CT-3	Chronic non-cancer pain, experimental pain, neuropathic pain (adults)	N	L
Torres-Moreno 2018 (41)	5	CT	Cannabis sativa plant extract	MS (bladder dysfunction, gait disorders, spasticity)	Ps	CL
Zhang 2018 (42)	1	CT	THC	Tourette syndrome/tics	N	CL
da Rovare 2017 (43)	6	CT	Cannabis cigarettes, whole-plant CE (THC:CBD)	MS (spasticity), acute pain, chronic pain, chronic non-cancer pain	Ps	CL

Systematic Review	Number Relevant Original studies (Number secondary SRs)	Types of studies	Examined formulations	Indications	Authors' conclusion	Level of confidence
Goldenberg 2017 (44)	6	CT, cohort, CRS	MC	Health-related quality of life	U	CL
Hauser 2017 (57)	0 (11)	CT, cohort	Medical marijuana, FAAH inhibitor, THC	Cancer (pain), neuropathic pain, CINV, cognition, Crohn's disease (pain), depression, epilepsy	U	H
Houze 2017 (58)	0 (2)	CT	Cannabis	Chronic pain	P	H
Lim 2017 (45)	11	CT	THC, CBD, THC-CBD cannador	Anorexia nervosa, SAD, cancer (cachexia, pain), CINV	U	CL
Norton 2017 (46)	3	CRS, pilot studies	Cannabis	Crohn's disease (pain), depression, epilepsy	U	CL

Systematic Review	Number Relevant Original studies (Number secondary SRs)	Types of studies	Examined formulations	Indications	Authors' conclusion	Level of confidence
Nugent 2017 (47)	11	CT, cohort	THC	Chronic pain, experimental pain	N	CL
O'Neil 2017 (59)	3 (2)	CT, cohort, CC	Plant-based cannabis, synthetic cannabis	PTSD, Tourette syndrome/tics, traumatic brain injury	U	M
Osborne 2017 (48)	8	C, cohort	CE, THC, CBD, THC-CBD	Cognition, Crohn's disease (pain), depression	Ps	CL
Stevens 2017 (49)	1	CT	THC	Acute pain	U	CL
Wong 2017 (50)	13	CT, CRS, CRV, case series, case report	OCE, OCE (CBD enriched), THC, CBD	CINV, cognition, Crohn's disease (pain), depression, epilepsy	P	CL
Fitzcharles 2016 (51)	1	CT	PF-04457845		U	CL

Systematic Review	Number Relevant Original studies (Number secondary SRs)	Types of studies	Examined formulations	Indications	Authors' conclusion	Level of confidence
Gruenbaum 2016 (52)	1	CR	Marijuana	Traumatic brain injury	P	CL
Merlin 2016 (53)	1	CT	Cannabis cigarettes	Neuropathic pain (HIV/AIDS)	U	CL
Tafelski 2016 (60)	1	CT	THC	CINV	U	H
Wilkinson 2016 (54)	9	CT, cohort, CRV, case reports	Cannabis (smoked), THC	Alzheimer's disease (agitation), anorexia nervosa, GAD	U	CL

Type of studies: ***CC:*** *case-control;* ***CRS:*** *cross-sectional;* ***CRV:*** *chart review;* ***CT:*** *clinical trial*

Examined formulations: ***Cannabinoids:*** *unspecified cannabinoids****; CBD:*** *cannabidiol****; CE:*** *cannabis extract,* ***FAAH:*** *fatty acid amide hydrolase;* ***MC:*** *medical cannabis;* ***OCE:*** *oral cannabis extract;* ***SCET:*** *standardized cannabis extract with THC****; SCT:*** *standardized cannabis with THC,* ***THC:*** *Delta-9-tetrahydrocannabinol (THC)*

Indications: ***ADHD:*** *attention deficit hyperactivity disorder;* ***ALS:*** *amyotrophic lateral sclerosis;* ***ASD:*** *autism spectrum disorder****;*** ***CINV:*** *chemotherapy induced nausea and vomiting;* ***IBD:*** *inflammatory bowel disease;* ***MS:*** *multiple sclerosis;* ***PTSD:*** *post-traumatic stress disorder;* ***SAD:*** *social anxiety disorder;*

Systematic Review	Number Relevant Original studies (Number secondary SRs)	Types of studies	Examined formulations	Indications	Authors' conclusion	Level of confidence

Authors' conclusions: ***P:*** *positive;* ***Ps:*** *possible;* ***N:*** *negative;* ***U:*** *unclear*

Level of confidence**:** ***CL:*** *critically low;* ***H:*** *high;* ***L:*** *low;* ***M:*** *moderate*

WSIB-approved indications

Neuropathic pain

Neuropathic pain is a clinical state that results from an identifiable lesion or a disease of the somatosensory nervous system (64), which may be caused by certain abnormalities, trauma, or other underlying causes such as stroke or diabetes mellitus.

As per WSIB policy, cannabis can be prescribed for cases of neuropathic pain that are refractory to standard pharmaceutical and non-pharmacological treatments. An acceptable pharmaceutical treatment must involve a minimum of three first-line and/or second-line medications and a pharmaceutical cannabinoid (65).

Since 2016, ten systematic reviews reported on the effectiveness of medical cannabis preparations (cannabis sativa, medical marijuana, herbal cannabis, SCT and THC) for treatment of neuropathic pain in general (18, 21, 31, 37, 40, 47, 57, 61), and in HIV/AIDS patients in particular (53). Additionally, one of these reviews reported on effective use of THC and FAAH hydrolase inhibitor for neuropathic pain and in cancer chemotherapy, respectively (57).

One review (53) reported that median pain was reduced twice as much (34% vs. 17%) in the cannabis group compared to the placebo group. A recent major RSR (61) reported a reduction in neuropathic pain (Odds ratio of 1.37, p-value <0.05) with cannabinoids (pharmaceutical and non-pharmaceutical formulations combined) that corresponded to attaining at least a 30% reduction in symptoms. Three other reviews reported no high-quality evidence to support use of any medical cannabis preparation for treatment of neuropathic pain.

Three recent clinical guidelines reported strong (66), reasonable (67), and consistent (68) evidence for use of medical cannabis and cannabinoids for treating patients with neuropathic pain.

Spasticity due to spinal cord injury

Spinal cord injury is a serious condition with many disabling consequences, such

as neuropathic pain and spasticity, negatively impacting a person's entire lifestyle, activity, and employment. Spasticity involves an increase in muscle tone or stiffness of different body muscles due to factors including injury to the spinal cord. The spread and depth of spinal cord-associated spasticity depends on factors such as the degree, duration, and position of cord injury.

One systematic review reported moderate quality of evidence regarding the effectiveness of using cannabinoids in spasticity following spinal cord injuries (43). Current guidelines set by the College of Physicians and Surgeons of Alberta reported the evidence as reasonable for this indication should standard therapies fail (67); strength of evidence was reported as limited by Health Canada guidelines (68).

Chemotherapy-induced nausea and vomiting

Nausea and vomiting are common, serious, and onerous adverse reactions occurring in patients undergoing cancer therapy. Chemotherapy-induced nausea and vomiting (CINV) is categorized into acute, delayed, anticipatory, and breakthrough types (69). Despite the efficiency of the current modalities for treating most CINV cases, cannabinoids were investigated for treating refractory and breakthrough cases based on the potential for stimulating brain cannabinoid receptors with the resulting inhibition of emesis (60).

Three systematic reviews reported on the use of cannabinoids as THC for management of CINV. Whereas one (60) reported no effect of non-pharmaceutical cannabinoids, two other reviews (50, 61) reported success in preventing vomiting (open label trial) as well as reducing the episodes of nausea and vomiting (two double-blinded RCTs).

Whereas the published evidence, including Canadian (68) and German guidelines (60), does not sufficiently support using cannabis for treatment for CINV, the evidence was reported as being reasonable (67) by the College of Physicians and Surgeons of Alberta.

HIV/AIDS-associated anorexia

HIV/AIDS-associated anorexia is a state of loss of appetite leading to reduced energy intake that is exacerbated with increased resting energy loss. This state may be caused by many factors including HIV infection, a superimposed infection, or treatment of either one of them. Two systematic reviews examined the use of medical cannabis for treating this condition (37, 57). Both reviews reported lack of sufficient evidence to support the use of cannabis. Similarly, guidelines by Health Canada (68) reported limited evidence for use of medical cannabis to treat HIV/AIDS-associated anorexia.

Palliative care

Palliative care refers to the collective strategy aiming at improving the quality of life for patients with life-threatening illnesses, including terminal cases of cancer and HIV/AIDS. Quality of life measures include reducing pain, improving appetite, and improving physical and emotional functioning.

Three systematic reviews reported the lack of adequate evidence for a benefit of using of medical cannabis/marijuana or cannabinoids in palliative care, particularly with cancer pain, anorexia, nausea, and vomiting (13, 31, 37, 57). A 2019 review (30) reported that cannabinoids were effective in improving appetite in cancer patients while reducing their quality of life, which may reflect an adverse reaction to the prescribed cannabinoids. Alternatively, one review reported no significant differences in body weight, appetite, or physical, social, cognitive, and functioning with medical cannabis extract or cannabinoids (THC) (32).

Two clinical guidelines characterized the evidence as reasonable (70) and with potential (1), respectively, for prescribing medical cannabis or cannabinoids for palliative treatment of cancer-related symptoms.

Other indications

Non-cancer pain

This section identifies reviews and guidelines that discussed non-cancer types of pain; however, the non-cancer pain types included in these reviews may reflect various groupings, including chronic (nociceptive), neuropathic, acute, and post-operative pain. This group of pain conditions includes non-cancer types of pain such as chronic (nociceptive), neuropathic, acute, and post-operative pain. Eight reviews reported consistent (21, 31, 34, 35, 58), moderate (18, 43), or insufficient (47) quality of evidence for using medical cannabis and cannabinoids in treating chronic non-cancer pain (CNCP) when in comparison to placebo.

Three additional reviews (20, 40, 57) reported a limited level of evidence for effectiveness of cannabinoids in treating some types of CNCP such as musculoskeletal pain (fibromyalgia) and rheumatoid arthritis (57), with low quality evidence of improved sleep and patient global impression of change. Two reviews reported no effectiveness of cannabinoids: cannabidiol (CBD) for treating CNCP (28), or THC or AZD1940 for acute pain (49).

Recent clinical guidelines characterized the evidence as consistent/reasonable (68, 71) for treating chronic pain of various etiologies, especially in cases where conventional treatments have failed. Evidence was reported as limited to moderate (66, 68) though for using cannabis with headache, migraine and muscloskeletal pain types

Anxiety

Anxiety is an emotional state that is characterized by fear and tension, which may be caused by a number of factors and situations, and may be accompanied with physical symptoms such as sweating, hypertension, palpitations, and dizziness. Prolonged or disproportionate anxiety may be disabling and can lead to a range of disorders including social anxiety disorder (SAD) (72, 73). In SAD, anxiety in certain social situations may be significant enough to disturb a person's daily interactions with others (74). Enduring,

extreme, and uncontrollable stresses may lead to a more generalized form of anxiety (GAD), which would seriously interfere with a person's daily life and may be mistakenly confused with other types of anxiety, panic disorders, and obsessive-compulsive disorders (75)

Seven reviews reported on the use of medical cannabis/cannabinoids for treatment of patients with anxiety. Six reviews (19, 22, 26-28, 45) reported positive results with CBD for treating patients with SAD, based on increasing positive responses and reduced anxiety, cognitive impairment, and discomfort. However, the results of these studies were inconclusive. Only one review reported no effect of medical cannabis (Cannabis sativa, CBD, THC and THC-CBD) for treatment of patients with anxiety disorders (24). Whereas the College of Physicians and Surgeons of Alberta (70) reported reasonable evidence for using medical cannabis/cannabinoids for treating anxiety, an earlier report by Health Canada (68) referred to this evidence as limited.

Post-traumatic stress disorder

Post-traumatic stress disorder (PTSD) is an anxiety disorder that impacts individuals upon being involved or having witnessed an extremely traumatic event, such as war, crime, or a natural disaster (72).

Eight systematic reviews reported on use of different formulations of medical cannabis (herbal cannabis, plant-based cannabis and cannabis resin), and cannabinoids (CBD, THC, CBD:THC). Despite the presence of positive results in some sporadic small-sized studies and case reports, the evidence was consistently reported by all of these reviews as being insufficient and of poor-quality for treating PTSD patients (17, 19, 22, 24, 29, 50, 54, 59). Similarly, the latest guidelines by Health Canada and the Alberta Medical Association report the evidence for using medical cannabis and cannabinoids with PTSD patients as being limited (68) to mixed (76), respectively.

Epilepsy

Epilepsy is a neurological disease that results from disproportionate discharge of electrical impulses from the brain. This state is characterized by recurrent brief attacks of involuntary movement (seizures), which may be localized (partial) or involve the entire body (generalized). With wide variations in their frequency of occurrence, these seizures range from brief lapse of attention to prolonged and violent generalized convulsions, with the potential for associated loss of consciousness and control of bowel or bladder functions (77).

Five recent reviews reported positive and increasing evidence for effectiveness of CBD in reducing seizure frequency or severity in epileptic patients (15, 28, 39, 50), and in treatment-resistant children and adolescents in particular (16, 39). Health Canada's guidelines reported weak, yet emerging, evidence for anti-epileptiform and anti-convulsive properties with CBD, while having mixed pro- and anti-epileptiform and pro- and anti-convulsive effects with THC (68)

Schizophrenia

Schizophrenia is a serious mental illness starting in early adulthood and is characterized by incoherent or illogical thoughts, bizarre behavior and speech, and delusions or hallucinations (72).

Five reviews (19, 22, 26, 27, 55) reported promising evidence, though insufficient, with the use of CBD for patients with schizophrenia, except in treatment-resistant cases. Alternatively, one review reported no improvements in cognition or selective attention in schizophrenia patients (28). No Canadian guidelines were found in relation to use of cannabis-based formulations for treating patients with schizophrenia.

Other Psychotic disorders

This group comprised many disorders, such as bipolar disorder, schizoaffective disorders, postpartum psychosis that is characterized by false beliefs (delusions) and

false perceptions (hallucinations) that reflected loss of grasp on reality. These disorders may be caused by diseases such as HIV, tumors, epilepsy, stroke, Parkinson's disease, dementia, alcohol abuse, and as adverse medication reactions (78).

Six reviews reported a growing, though still limited, evidence of use of cannabis-based medicines for treatment of psychoses (25, 27, 28, 45, 55), or psychotic symptoms in other diseases such as Parkinson's disease (19). However, one review reported no evidence for effectiveness of any cannabinoid type for treatment of any psychotic symptoms (24). Guidelines by Health Canada (68) rated the evidence of using CBD for treating THC-induced psychosis as emerging.

Tourette Syndrome

Tourette syndrome (TS) is a neurological disorder characterized by uncontrollable, involuntary, and repetitive movements and sounds called tics. Tics often start in childhood, reaching their worst level in early teenage years and often improving in late teenage years and early adulthood (79).

Seven recent reviews reported positive, yet insufficient, evidence of low quality for using medical cannabis (54), THC (24, 45, 50, 54, 55), and CBD (19) for treating patients with TS, whereas one review (42) reported no evidence for use of THC with TS. Guidelines by Health Canada (68) rated the evidence of using THC for treating TS as limited.

Multiple Sclerosis

Multiple Sclerosis (MS) is an autoimmune disease of the nervous system involving a degradation of the myelin covering of the nerves. Such degradation leads to a wide range of symptoms resulting from impaired or failed transmission of the nerve impulses: for instance, impairment of cognitive and visual functions, bladder problems, lost skin sensation, muscle weakness, and emotional instability (80)

Six systematic reviews reported on the use of medical cannabis/cannabinoids in

treating different symptoms of MS. Four reviews reported sufficient, high-quality evidence for using medical cannabis (18) and cannabinoids (31, 41, 56, 61) for treating MS pain and spasticity. However, a fifth review (43) reported the evidence as moderate with cannabinoids. Two reviews reported limited and inconsistent evidence for the effectiveness of using cannabinoids for treating gait symptoms (33) and bladder dysfunction (41) in MS patients.

Reasonable evidence was reported by the College of Physicians and Surgeons of Alberta, for using cannabinoids in relieving spasticity due to MS or spinal cord injury, particularly for cases that were refractory to standard therapies (67). However, this evidence was reported as limited by Health Canada for prescribing medical cannabis and cannabinoids with MS-related spasticity, pain, bladder dysfunction, depression, anxiety, and sleep disturbance (68).

Parkinson's disease

Parkinson's disease (PD) is a movement disorder characterized by inadvertent and uncontrollable movements resulting from the progressive loss of certain neurons in charge of producing dopamine; a chemical substance needed for formulating smooth, purposeful movements (81).

Three reviews reported mixed evidence for using CBD (25, 28, 45) and THC (45) to treat patients with Parkinson's disease. Health Canada guidelines (68) reported the evidence as mixed for using medical cannabis, cannabis extract (THC/CBD), and cannabinoids for treating PD patients.

Alzheimer's disease

Alzheimer's disease is an irreversible type of dementia disorder involving gradual memory loss and confusion, which may commonly be mistaken for a normal aging process. These initial symptoms later develop into many behavioral and personality changes, followed by progressive deterioration in other cognitive abilities due to a

progressive atrophy of brain tissue (82).

Three reviews reported mixed evidence for the use of cannabinoids (THC) for treating symptoms of Alzheimer's disease, including agitation, mood, and sleeplessness (45, 54, 55). Health Canada guidelines (68) reported limited evidence for using medical cannabinoids (oral, THC) for treating Alzheimer's disease patients.

Current Canadian guidelines

Many Canadian regulatory and professional entities reported on the level of evidence for using medical cannabis or non-pharmaceutical cannabinoids for treatment of a variety of conditions. Evidence was 'strong' or 'reasonable' with neuropathic pain, and 'possible' or 'potential' with non-neuropathic pain and palliative care (cancer, HIV/AIDS). Evidence of use with other indications ranged between 'mixed', 'limited', 'inadequate', and 'none'. Table 3 provides a summary of the Canadian regulatory and professional guidelines, whereas additional scientific reviews with guideline suggestions are provided in Appendix 5.

Table 3: Canadian guidelines for prescribing medical cannabis and non-pharmaceutical cannabinoids

Source	Agent	Indications	Level of evidence [1]
College of physicians and surgeons of Alberta 2019 (67)	Medicinal cannabinoids (unspecified)	Pain (neuropathic, palliative conditions), CINV, spasticity (MS, spinal cord injury) *Prerequisite: cases unresponsive to standard therapy*	Reasonable
College of physicians and surgeons of Alberta 2019a (70)	Cannabis Medicinal cannabinoids (unspecified)	Cancer symptoms (pain, anorexia, insomnia, anxiety, nausea and vomiting)	Reasonable
Canadian Pain Task Force 2019 (66)	Cannabis	Pain (neuropathic)	Strong
	Cannabis	Pain (musculoskeletal, fibromyalgia, headaches,	Moderate

[1] As reported by the Canadian guidelines

Source	Agent	Indications	Level of evidence [1]
		cancer, MS, arthritis)	
Health Canada 2018 (68)	cannabis and prescription cannabinoids	Quality of life for a variety of different disorders.	Mixed
	Cannabis and certain cannabinoids	CINV	Limited
	Cannabis	HIV/AIDS (wasting syndrome, anorexia), cancer, anorexia nervosa	Limited
	Cannabis	MS and spinal cord injury and disease (including spasticity, spasms, pain, sleep and symptoms of bladder dysfunction)	Limited
	Cannabinoids (THC/CBD)	MS and spinal cord injury and disease (including spasticity, spasms, pain, sleep and symptoms of bladder dysfunction)	Unreported
	Certain cannabinoids	ALS	Mixed
	Cannabis (THC- and CBD-predominant strains)	Epilepsy	Weak
	CBD (in herbal and oil	Epilepsy (seizure frequency, quality of life) among	Unreported

Source	Agent	Indications	Level of evidence [1]
	preparations)	adolescents with rare and serious forms of drug-resistant epilepsy	
	Cannabis (smoked) Cannabis (extract), Cannabinoids (oral THC)	Pain (acute, experimentally-induced)	Limited/ mixed
	Cannabis and Cannabinoids (smoked, vaporized)	Pain (neuropathic, chronic non-cancer), especially in cases unresponsive to standard treatments	Consistent
	Cannabinoids (THC)	“Opioid-sparing” effects and cannabinoid-opioid synergy	Mixed
	Cannabis/ cannabinoids (unspecified)	Pain (headache, migraine)	Limited/ mixed
	Cannabis (inhaled) CBD (oral)	Dystonia	Positive
	THC (oral)	Dystonia	Mixed
	Cannabis (smoked)	Huntington’s disease	Limited
	Cannabis (smoked)	Parkinson's disease	Mixed

Source	Agent	Indications	Level of evidence [1]
	Cannabis extract (THC/CBD)		
	Cannabinoids (unspecified)	Parkinson's disease	Mixed
	THC (oral)	Tourette's syndrome (tics).	Limited
	Cannabis (THC, aerosolized)	Asthma *<u>Warning:</u> inhaling cannabis smoke/vape may irritate the lung and worsen asthmatic symptoms*	Mixed
	Cannabis (THC, CBD/THC) Cannabinoids (unspecified)	Anxiety and depression (e.g. patients with HIV/AIDS, MS, and chronic neuropathic pain).	Limited
	Cannabis THC	Sleep disorders (low doses)	Limited
	Cannabinoids (THC, oral)	PTSD	Limited
	CBD	THC-induced psychosis	Emerging
	Cannabinoids (THC, oral)	Alzheimer’s disease and dementia	Limited
	Cannabinoids (THC, CBD,	Inflammatory skin diseases (dermatitis, psoriasis,	Mixed

Source	Agent	Indications	Level of evidence [1]
	HU210)	pruritus)	
	Cannabis (smoked)	Inflammatory bowel diseases (Crohn's disease, ulcerative colitis)	Limited
	THC	Metabolic syndrome, obesity, diabetes	Limited
	Cannabis	Cancer-associated (chemosensory alterations, weight loss, depression, pain)	Limited
Alberta Medical Association 2018 (76)	Medical marijuana	PTSD	Mixed
BC Cancer, British Columbia 2018 (1)	Cannabis	Cancer-related symptoms (including nausea, anorexia, pain and peripheral neuropathy)	Potential
Canadian Rheumatology Association 2018 (83)	Medical cannabis	Rheumatic diseases (pain relief, sleep promotion) *Prerequisite: cases unresponsive to standard treatment strategies*	Limited
Arthritis Society 2018 (71)	Cannabis	Pain (chronic), other arthritis symptoms	Potential alternative

Summary of evidence for effectiveness of medical cannabis

A summary of the published evidence on the effectiveness of different cannabis-based formulations for treatment of different indications, is provided in Table 4, including additional indications with scarce published evidence that were not detailed in this current review.

Table 4: Summary of evidence for use of cannabis-based medicines

Indication	Formulation	Evidence	Study(s)
Neuropathic pain	Cannabis sativa, medical marijuana, herbal cannabis, standardized dried cannabis, SCT, THC	Consistent	(18, 21, 37, 40, 47, 53, 57, 61, 65-68)
Spasticity (Spinal cord injury)	Cannabinoids	Insufficient	(43, 67)
CINV	Cannabinoids	Inconsistent	(50, 60, 61, 67, 68)
Anorexia (HIV/AIDS)	Medical cannabis	Limited	(37, 57, 68)
Palliative care	Medical cannabis, cannabinoids	Reasonable	(1, 70)
Chronic non-cancer pain (CNCP)[2]	Medical cannabis, cannabinoids	Consistent	(18, 21, 31, 34, 35, 43, 58, 68, 71)
Anxiety	Medical cannabis, cannabinoids	Inconclusive	(19, 22, 26-28, 45, 68)
PTSD	Medical cannabis (herbal cannabis, plant-based	Insufficient	(17, 19, 22, 24, 29, 50, 54, 59, 68, 76)

[2] CNCP: may also include neuropathic pain

Indication	Formulation	Evidence	Study(s)
	cannabis and cannabis resin), and cannabinoids (CBD, THC, CBD:THC).		
Epilepsy	CBD	Insufficient (emerging)	(15, 16, 28, 39, 50, 68)
Schizophrenia	CBD	Insufficient (promising)	(19, 22, 26-28, 55)
Other psychotic disorders	Cannabis-based medicines	Insufficient (emerging)	(19, 24, 25, 27, 28, 45, 55, 68)
Tourette syndrome	THC	Insufficient	(19, 24, 42, 45, 50, 54, 55, 68)
MS	Medical cannabis, cannabinoids	Inconsistent	(18, 33, 41, 43, 56, 61, 67, 68)
Parkinson's disease	Medical cannabis, cannabis extract (THC/CBD), cannabinoids (CBD, THC)	Inconsistent	(25, 28, 45, 68)
Alzheimer's disease	Medical cannabinoids (oral, THC)	Inconsistent	(45, 54, 55, 68)
Other indications[3]			
Neurocognitive diseases/disorders			
ALS	cannabinoids	No evidence	(45)
ASD	CBD	Emerging	(19, 25, 26)
	THC	Moderate	(19)

[3] Indications with scarce evidence that are not discussed in detailes in this report

Indication	Formulation	Evidence	Study(s)
ADHD	CBD	Potential	(22)
	Cannabinoids	Scarce	(24)
Depression	CBD	Promising	(26)
	Cannabinoids	Scarce	(24)
Dementia	Cannabinoids	No benefit	(57)
	THC	Insufficient (agitation)	(45)
Insomnia	CBD	Reduce insomnia	(19, 22)
Movement disorders			
Dystonia	cannabinoids	No evidence	(45)
Huntington's disease	CBD	Positive	(28)
	THC	Inadequate	(45)
Other diseases			
Diabetes Mellitus	CBD	No significant change	(28)
Crohn's disease	CBD	Inadequate	(28, 57)
Ulcerative colitis	Medical marijuana	No evidence	(57)
Fatty liver disease	CBD	No significant change	(28)
Anorexia	Cannabinoids	No benefit	(57)

Indication	Formulation	Evidence	Study(s)
Graft vs host disease	CBD	Effective	(28)

Safety

Reporting on adverse events associated with the different cannabis formulations was not consistently performed by the included reviews. Approximately half (47%) of reviews did not report clearly on adverse events associated with medical cannabis or non-pharmaceutical cannabinoids, whereas some reported on such information for the entire range of formulations without specifics.

Of the adverse events reported by the included reviews (see Figure 3), dizziness, cognitive disturbances, euphoria/dysphoria, fatigue, and somnolence were the most commonly reported. All individual cases of adverse events were grouped under the miscellaneous category. More details on these adverse events are provided in Appendix 6.

There is not enough evidence to conclude any difference in safety between the different cannabis or cannabinoid formulations, either in general or in relation to specific diseases and/or specific populations.

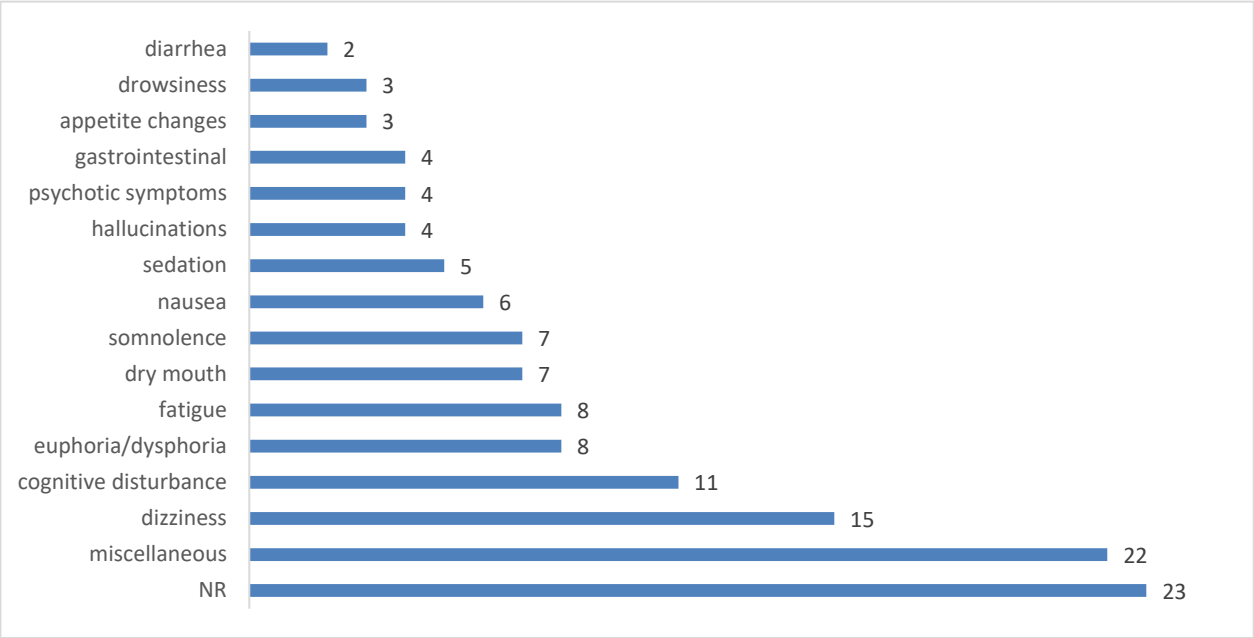

Figure 3: Frequency of adverse events examined in the included reviews

Discussion

Cannabis has been a well-known illicit drug popularly used on a global scale for many years due to its psychoactive properties. In the past few decades, a sharp rise in public and professional interest has placed a focus on new uses of cannabis and its different components and formulations for treatment of medical diseases and conditions, particularly those that are refractory to standard or traditional therapies. These interests were further heightened by the legalization of cannabis use in many countries, including Canada, which passed the Cannabis Act in the fall of 2018.

A few cannabis-based medications, collectively referred to as pharmaceutical cannabinoids, have already been prescribed by doctors in many countries, including Canada, for years. The success of these medications and increase in public pressure on physicians fueled more interest in investigating the effectiveness and safety of other cannabis-based medications, currently referred to as non-pharmaceutical cannabinoids, for treatment of other diseases and conditions.

This systematic review summarizes the published, peer-reviewed evidence, as well as regulatory and professional positions, on the use of non-pharmaceutical cannabis-based medicines to inform decision-making on their use for treatment of conditions.

As the current review focused on synthesizing the evidence generated by recently published systematic reviews, the evidence synthesis was subsequently limited by the type, breadth, and depth of information provided in these systematic reviews. Reporting in these reviews was inconsistent regarding the types, composition, doses, routes of administration, and frequency and duration of treatment with cannabis-based formulations, as well as on the methods of assessment of effectiveness in treating the different indications.

Systematic reviews included in this current review reflected a wide range of objectives that did not necessarily match those of the current review, leading to omission of valuable information. For example, the objective of the ‘core’ review by Ishak et al 2018 (35) was to report on the impact of current treatments, including medical cannabis, on HIV-associated pain and depression (HIV-associated). The authors reported on effectiveness of cannabis only in relation to these two comorbidities, whereas the individual studies included in the

Ishak et al. review (such as Woolridge et al. 2005 (84)) reported on additional HIV-associated indications such as anorexia, nausea, anxiety, neuropathy, tingling, numbness, weight loss, headache, tremor, diarrhea, constipation, tiredness, memory loss, slurred speech, and visual defects.

One of the major limitations of this review involved lack of consensus among included systematic reviews on the definition and composition of the examined cannabis-based formulations. Whereas original studies may have been more explicit in profiling the examined formulations, the systematic reviews used different definitions or categorizations for describing the examined formulations. One possible explanation in any given review is that lack of detail resulted from an attempt to pool results and generate meaningful conclusions. Moreover, one formulation examined in one study might be reported differently across two or more systematic reviews that report on this original study. A few reviews generated additional confusion through using the term pharmaceutical grade cannabinoids to describe non-pharmaceutical cannabinoids, with no details on their chemical composition.

Many of the systematic reviews reported on cannabis and cannabinoid formulations without any specification, resulting in limited extrapolation of those results to formulations. The majority of the studies described used pure presentations of CBD or formulations with known concentrations of CBD and THC and, hence, their results cannot be extended to non-purified forms, extracts, or smoked cannabis.

Most of the systematic reviews reflected a high level of heterogeneity in the designs of included studies, patient populations, interventions, comparisons, and outcome assessment, which made the pooling and usability of their information difficult. This also manifested itself in the absence of valuable information on the examined cannabis formulations such as, for instance, the chemical composition, doses, frequency and routes of administration, and treatment duration, all of which collectively have many pharmacokinetic and pharmacodynamic implications on the assessment of suitability of a specific formulation and for a specific indication. For example, pooling different cannabis formulations (such as plant-based with synthetic or with pharmaceutical or with non-pharmaceutical cannabinoids) may undermine, mask, or amplify the effects of one of them in favour of the other. For a proper assessment of safety of a specific formulation, evidence must be synthesized based on

specific chemical composition (e.g., CBD-THC: 1-1 is different from 1-9), route of administration (inhaled route may not be suitable for those with respiratory conditions like asthma), and dosing protocol (frequency of administration, duration of treatment) which may require some adjustments for people with certain comorbidities.

Another commonly encountered issue involved the inconsistent use of and reporting on outcome measures such as change in symptom severity, frequency, remission, hospitalization, and patient or care person's subjective versus objective perception of improvement – consistently defined outcome measures would be informative in any assessment of the efficacy of uses of medical cannabis.

Reporting on the risk of bias by many of the included 'core' reviews was insufficient, inconsistent, inappropriate, or not reported, with the resulting reduction in the level of confidence in their reported evidence (80% of 'core' reviews ranked as low or critically low). Whereas the current review used the most robust tool for assessing the risk of bias and overall quality of evidence with 'core' reviews (AMSTAR2 (9)), this tool was not flexible for use with RSR. A decision was made to apply a different review tool that could be applied for use with RSRs. (Health Evidence (10-12)). These two tools have similar domains but are not calibrated to each, as they involve different scoring and different items for scoring. Using two tools within one review may have introduced inconsistencies on the quality assessment in any synthesis of evidence across studies, especially when judging a pool of reviews (Core and RSR together) for the overall strength of evidence.

This review helped to identify formulations with promising evidence, as well as disease indications in high demand for new treatment modalities, such as multiple sclerosis and different chronic pain conditions.

Appendices

Appendix 1. Search methodology, terms and output

Strategy

Search Question	**Efficacy and safety of use of medical cannabis and non-pharmaceutical cannabinoids?**	
Major Concepts	1. Medical cannabis 2. Indications	
Search Terms	**Concept 1**	**Concept 2**
	Cannabis, medical marijuana, cannabinoids	Pain, neuropsychiatric disorders, movement disorders, chemotherapy-associated side effects, palliative care

Output

Searched databases	Results	Level of selection
Medline	2,324	Cannabis + all outcomes
EMBASE	8,020	
PubMed	2,883	
Total - all reference types	13,229	
Total - all reference types - no duplicates	9,444	
Total - reviews only - no duplicates	3,424	All years
Final - reviews only (2016-2020)	**468**	**2016 – 2020**

Medline Ovid [4]

Concept	#	Medline query	Results
	1	exp Cannabis/	8,936
	2	cannabis.tw.	16,256
	3	(medic* adj3 cannabis).tw.	1,328
	4	exp Medical Marijuana/	1,118
	5	(med* adj3 marijuana).tw.	1,219
	6	or/1-5	22,111
	7	exp Pain/	389,613
	8	(neuropath* adj3 pain*).tw.	22,592
	9	exp Pain Management/	32,928
	10	(pain* adj3 manag*).tw.	35,125
	11	exp Chronic Pain/	13,735
	12	(chronic* adj3 pain*).tw.	63,051
	13	exp Cancer Pain/	1,160
	14	(cancer* adj3 pain*).tw.	11,321
	15	exp Pain, Intractable/	6,166
	16	(intractable adj3 pain*).tw.	3,955
	17	exp Pain, Postoperative/	40,244
	18	(postoperative adj3 pain*).tw.	28,712
	19	exp Pain, Referred/	340
	20	(referr* adj3 pain*).tw.	3,612

[4] *MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present*

Concept	#	Medline query	Results
	21	exp Breakthrough Pain/	302
	22	breakthrough pain*.tw.	941
	23	exp Neuralgia/	20,045
	24	neuralgi*.tw.	13,290
	25	exp Causalgia/	675
	26	causalgi*.tw.	588
	27	exp neuralgia, postherpetic/	1,052
	28	(postherpetic adj3 neuralgi*).tw.	1,990
	29	exp Piriformis Muscle Syndrome/	129
	30	piriformis muscle syndrome.tw.	49
	31	bilateral neuralgia*.tw.	7
	32	exp Nociceptive Pain/	1,316
	33	(nocicep adj3 pain*).tw.	1
	34	exp Headache Disorders/	33,890
	35	headache disorder*.tw.	2,652
	36	exp Headache/	27,417
	37	exp Tension-Type Headache/	1,965
	38	tension-type headache*.tw.	2,946
	39	exp Cluster Headache/	2,590
	40	cluster headache*.tw.	3,045
	41	Paroxysmal Hemicrania/	108
	42	(paroxysmal adj3 hemicrania*).tw.	420

Concept	#	Medline query	Results
	43	SUNCT Syndrome/	148
	44	SUNCT syndrome.tw.	175
	45	Trigeminal Autonomic Cephalalgias/	195
	46	cephalalgia*.tw.	681
	47	cephalodynia*.tw.	1
	48	hemicrania.tw.	868
	49	headache*.tw.	81,962
	50	Migraine Disorders/	24,888
	51	Ophthalmoplegic Migraine/	54
	52	migraine*.tw.	33,961
	53	exp Earache/	764
	54	earache*.tw.	440
	55	(ear* adj3 pain*).tw.	5,309
	56	exp Eye Pain/	641
	57	(eye adj3 pain*).tw.	1,890
	58	exp Facial Neuralgia/	10,005
	59	(fac* adj3 neuralgi*).tw.	652
	60	exp Facial Pain/	8,974
	61	(fac* adj3 pain*).tw.	14,418
	62	exp Trigeminal Neuralgia/	6,705
	63	(trigeminal adj3 neuralgi*).tw.	6,092
	64	exp Trigeminal Nerve Injuries/	1,692

Concept	#	Medline query	Results
	65	(trigeminal adj3 injur*).tw.	296
	66	(trigeminal adj3 pain*).tw.	1,348
	67	exp Glossalgia/	286
	68	exp Neck Pain/	6,864
	69	(neck adj3 pain*).tw.	12,150
	70	exp Shoulder Pain/	4,724
	71	(shoulder* adj3 pain*).tw.	9,393
	72	exp Back Pain/	38,363
	73	(back adj3 pain*).tw.	48,487
	74	exp Low Back Pain/	21,419
	75	low back pain*.tw.	26,324
	76	exp Failed Back Surgery Syndrome/	314
	77	failed back surgery syndrome.tw.	730
	78	exp Flank Pain/	613
	79	(flank* adj3 pain).tw.	3,634
	80	exp Mastodynia/	165
	81	mastodynia*.tw.	203
	82	(breast* adj3 pain*).tw.	2,148
	83	exp Pelvic Girdle Pain/	133
	84	exp Pudendal Neuralgia/	91
	85	(pudendal adj3 neuralgi*).tw.	128
	86	exp Sciatica/	4,968

Concept	#	Medline query	Results
	87	(sciatic* adj3 neuralgia*).tw.	86
	88	(sciatic* adj3 pain*).tw.	1,908
	89	exp Morton Neuroma/	50
	90	morton neuroma*.tw.	70
	91	exp Metatarsalgia/	312
	92	metatarsalgia*.tw.	711
	93	exp Musculoskeletal Pain/	4,843
	94	(musculoskeletal adj3 pain*).tw.	6,951
	95	exp Myalgia/	1,627
	96	myalgi*.tw.	9,417
	97	exp Myofascial Pain Syndromes/	6,454
	98	(myofascial adj3 pain*).tw.	2,248
	99	exp Arthralgia/	12,849
	100	arthralgi*.tw.	8,192
	101	exp Mastodynia/	165
	102	mastodynia*.tw.	203
	103	Palliative Medicine/	335
	104	Palliative Care/	53,082
	105	"Hospice and Palliative Care Nursing"/	800
	106	Terminal Care/	27,663
	107	(terminal* adj3 car*).tw.	31,426
	108	palliative.tw.	60,617

Concept	#	Medline query	Results
	109	hospice.tw.	11,385
	110	exp Dystonia/	9,574
	111	Dystonic Disorders/	2,599
	112	(general* adj3 dystonia*).tw.	1,012
	113	(focal adj3 dystonia*).tw.	1,646
	114	(multi* adj3 dystonia*).tw.	136
	115	(adult* adj3 dystonia*).tw.	319
	116	(segment* adj3 dystonia*).tw.	336
	117	hemidystonia*.tw.	195
	118	(secondary adj3 dystonia*).tw.	454
	119	writer* cramp*.tw.	569
	120	exp Meige Syndrome/	293
	121	meige syndrome.tw.	144
	122	Torticollis/	3,539
	123	torticollis.tw.	3,187
	124	cervical dystonia*.tw.	1,516
	125	intermittent torticollis.tw.	5
	126	spasmodic torticollis.tw.	799
	127	wryneck.tw.	27
	128	exp Spasm/	9,695
	129	exp Hemifacial Spasm/	1,134
	130	spasm*.tw.	26,963

Concept	#	Medline query	Results
	131	(Fac* adj3 spasm*).tw.	636
	132	hemifacial spasm*.tw.	2,004
	133	hemifacial myokymia*.tw.	3
	134	exp Blepharospasm/	1,301
	135	blepharospasm*.tw.	1,825
	136	exp Trismus/	1,620
	137	trismus.tw.	2,212
	138	exp Muscle Spasticity/	9,014
	139	(muscle* adj3 spas*).tw.	3,761
	140	clasp knife spasticity.tw.	-
	141	clasp-knife spasticity.tw.	-
	142	muscle spasticity.tw.	421
	143	(limb* adj3 spasticit*).tw.	939
	144	spastic*.tw.	25,133
	145	vomiting/	23,201
	146	nausea/	15,787
	147	emesis.tw.	6,565
	148	emetic.tw.	3,644
	149	Antiemetics/	8,959
	150	Anorexia/	4,919
	151	anorexia.tw.	28,956
	152	(loss adj3 appetite).tw.	4,430

Concept	#	Medline query	Results
	153	(chemotherapy adj3 nausea).tw.	2,129
	154	(chemotherapy adj3 vomiting).tw.	570
	155	(chemotherapy adj3 emesis).tw.	529
	156	Acquired Immunodeficiency Syndrome/	76,090
	157	HIV/	19,560
	158	Acquired Immunodeficiency Syndrome/	76,090
	159	exp Multiple Sclerosis/	57,692
	160	multiple sclerosis.tw.	72,718
	161	exp Amyotrophic Lateral Sclerosis/	18,418
	162	amyotrophic lateral sclerosis.tw.	22,400
	163	Parkinson Disease/	65,020
	164	parkinson* disease.tw.	89,211
	165	Tourette Syndrome/	4,262
	166	tourette* syndrome.tw.	4,555
	167	Spinal Cord Injuries/	37,032
	168	spinal cord injury*.tw.	33,460
	169	spinal cord laceration*.tw.	3
	170	spinal cord transection*.tw.	1,449
	171	spinal cord contusion*.tw.	658
	172	spinal cord trauma*.tw.	915
	173	traumatic mylopath*.tw.	-
	174	post-traumatic mylopath*.tw.	-

Concept	#	Medline query	Results
	175	post traumatic mylopath*.tw.	-
	176	Traumatic Brain Injury/	5,659
	177	traumatic brain injur*.tw.	35,096
	178	exp Dementia/	162,149
	179	dementia*.tw.	105,986
	180	exp Epilepsy/	109,698
	181	epilep*.tw.	133,571
	182	Irritable Bowel Syndrome/	7,102
	183	irritable bowel.tw.	12,923
	184	Neurogenic Bowel/	130
	185	(neurogenic adj3 bowel).tw.	346
	186	exp Stress Disorders, Post-Traumatic/	31,776
	187	posttraumatic stress disorder*.tw.	18,025
	188	post traumatic stress disorder*.tw.	10,888
	189	post-traumatic stress disorder*.tw.	10,888
	190	posttraumatic neuros*.tw.	11
	191	post traumatic neuros*.tw.	39
	192	post-traumatic neuros*.tw.	39
	193	Combat Disorders/	3,092
	194	(combat* adj3 disorder*).tw.	407
	195	(moral adj3 injur*).tw.	163
	196	Anxiety/	78,840

Concept	#	Medline query	Results
	197	Anxiety Disorders/	33,093
	198	anxiet*.tw.	185,021
	199	(anxiet* adj3 order*).tw.	285
	200	hypervigilance.tw.	692
	201	nervousness.tw.	1,599
	202	Anti-Anxiety Agents/	18,503
	203	(anxiety adj3 agent*).tw.	252
	204	(anxiety adj3 drug*).tw.	1,266
	205	(anxiety adj3 medica*).tw.	1,330
	206	exp Depression/	115,709
	207	(depress* adj3 agent*).tw.	866
	208	(depress* adj3 drug*).tw.	4,582
	209	(depress* adj3 medica*).tw.	4,696
	210	exp Sleep Wake Disorders/	87,501
	211	sleep wake disorder*.tw.	287
	212	(sleep adj3 disorder*).tw.	24,148
	213	(sleep adj3 syndrome*).tw.	11,759
	214	Dyssomnias/	390
	215	dyssomnia*.tw.	103
	216	Parasomnias/	492
	217	parasomnia*.tw.	1,190
	218	"Sleep Initiation and Maintenance Disorders"/	12,759

Concept	#	Medline query	Results
	219	insomnia*.tw.	20,388
	220	sleep disorder*.tw.	18,621
	221	exp Schizophrenia/	103,385
	222	schizophreni*.tw.	120,701
	223	exp Psychotic Disorders/	51,428
	224	(Psycho* adj3 disorder*).tw.	26,400
	225	psychos*.tw.	155,460
	226	psychotic.tw.	32,716
	227	(schizoaffective adj3 disorder*).tw.	4,762
	228	(schizophreniform adj3 disorder*).tw.	637
	229	(reactive adj3 psychos*).tw.	288
	230	or/7-229	2,165,706
cannabis + ALL	231	6 and 230	6,293
	232	limit 231 to yr="2016 - 2020"	2,342
reviews only (all outcomes)	233	limit 232 to (meta analysis or "systematic review" or systematic reviews as topic)	557
cannabis + pain	234	or/7-109	722,771
	235	6 and 234	1,255
	236	limit 235 to yr="2016 - 2020"	603
cannabis + movement dis.	237	or/110-144	71,503
	238	6 and 237	316
	239	limit 238 to yr="2016 - 2020"	115

Concept	#	Medline query	Results
cannabis + nausea / vomiting	240	or/145-155	72,910
	241	6 and 240	527
	242	limit 241 to yr="2016 - 2020"	194
cannabis + neuropsychiatric / immunology	243	or/156-229	1,398,686
	244	6 and 243	5,190
	245	limit 244 to yr="2016 - 2020"	1,853

EMBASE [5]

Concept	#	Embase query	Results
	1	exp Cannabis/	36,262
	2	cannabis.tw.	23,223
	3	bhang.tw.	58
	4	cannador.tw.	44
	5	charas.tw.	42
	6	ganja.tw.	93
	7	ganjah.tw.	-
	8	hashish.tw.	904
	9	marihuana.tw.	1,637
	10	marijuana.tw.	16,656
	11	(hemp adj3 extract*).tw.	57
	12	exp medical cannabis/	2,102
	13	(medic* adj3 cannab*).tw.	2,267
	14	(medic* adj3 marihuana).tw.	53
	15	(medic* adj3 marijuana).tw.	1,546
	16	or/1-15	51,456
	17	exp pain/	1,360,076
	18	exp chronic pain/	59,895
	19	(intractable adj3 pain*).tw.	6,267
	20	exp neuropathic pain/	31,950

[5] Embase: Excerpta Medica Database Guide

Concept	#	Embase query	Results
	21	(neuropathic adj3 pain*).tw.	30,566
	22	exp pain clinic/	3,519
	23	(pain* adj3 clinic*).tw.	25,107
	24	(pain* adj3 managment*).tw.	38
	25	exp cancer pain/	20,430
	26	(cancer* adj3 pain*).tw.	19,173
	27	(malignan* adj3 pain*).tw.	2,124
	28	exp postoperative pain/	66,823
	29	postoperative pain*.tw.	34,689
	30	post operative pain*.tw.	6,353
	31	exp referred pain/	1,170
	32	(referr* adj3 pain*).tw.	6,048
	33	exp breakthrough pain/	1,515
	34	(breakthrough adj3 pain*).tw.	2,118
	35	exp neuralgia/	112,071
	36	neuralgi*.tw.	19,685
	37	postherpetic neuralgia/	5,642
	38	exp trigeminus neuralgia/	11,987
	39	(trigem* adj3 neuralgi*).tw.	8,569
	40	(trigem* adj3 pain*).tw.	2,112
	41	hypoglossal neuralgia/	2
	42	glossopharyngeal neuralgia/	666

Concept	#	Embase query	Results
	43	cervicobrachial neuralgia/	3,767
	44	pudendal neuralgia/	232
	45	burning feet syndrome/	103
	46	(burning adj3 feet).tw.	235
	47	carpal tunnel syndrome/	15,519
	48	carpal tunnel syndrome.tw.	10,796
	49	cauda equina syndrome/	2,612
	50	cauda equina syndrome.tw.	1,995
	51	complex regional pain syndrome/	4,340
	52	(regional adj3 pain*).tw.	6,816
	53	cubital tunnel syndrome/	2,599
	54	cubital tunnel syndrome.tw.	792
	55	metatarsalgia/	1,334
	56	metatarsalgi*.tw.	1,059
	57	morton neuroma*.tw.	92
	58	radicular pain/	4,204
	59	(radicular adj3 pain*).tw.	4,629
	60	sciatica/	2,076
	61	(sciatic* adj3 pain*).tw.	2,902
	62	(sciatic* adj3 neuralgi*).tw.	180
	63	sunct syndrome/	516
	64	tarsal tunnel syndrome/	1,138

Concept	#	Embase query	Results
	65	bilateral neuralgia.tw.	17
	66	nociceptive pain/	1,568
	67	exp complex regional pain syndrome type II/	383
	68	causalg*.tw.	996
	69	exp headache/	220,866
	70	exp "headache and facial pain"/	313,038
	71	(headache* adj3 disorder*).tw.	6,241
	72	cephalgi*.tw.	655
	73	cephalodynia*.tw.	2
	74	hemicrania*.tw.	1,513
	75	headache*.tw.	139,266
	76	exp migraine/	65,704
	77	migraine*.tw.	54,448
	78	exp otalgia/	5,275
	79	(ear* adj3 ache*).tw.	237
	80	(ear* adj3 pain*).tw.	8,445
	81	(ear* adj3 neuralgi*).tw.	58
	82	(otic adj3 neuralgia*).tw.	1
	83	exp eye pain/	9,047
	84	(eye* adj3 pain*).tw.	3,827
	85	occular pain*.tw.	1
	86	exp face pain/	10,946

Concept	#	Embase query	Results
	87	(fac* adj3 pain*).tw.	20,747
	88	exp glossodynia/	566
	89	glossodyni*.tw.	231
	90	glossalgi*.tw.	78
	91	exp neck pain/	23,239
	92	(neck adj3 pain*).tw.	17,529
	93	musculoskeletal pain/	10,752
	94	(musculoskeletal adj3 pain*).tw.	10,258
	95	exp shoulder pain/	16,172
	96	(shoulder* adj3 pain*).tw.	13,203
	97	exp backache/	110,583
	98	backache*.tw.	3,545
	99	(back adj3 ache*).tw.	323
	100	backpain*.tw.	257
	101	(back adj3 pain*).tw.	70,897
	102	dorsalgi*.tw.	172
	103	discogenic pain/	642
	104	(discogenic adj3 pain*).tw.	1,318
	105	failed back surgery syndrome/	1,682
	106	failed back surgery syndrome.tw.	1,299
	107	exp low back pain/	58,308
	108	low* back pain*.tw.	39,291

Concept	#	Embase query	Results
	109	low* backpain*.tw.	50
	110	lowback pain*.tw.	145
	111	low* backache*.tw.	364
	112	chronic low* back pain*.tw.	8,831
	113	(loin* adj3 pain*).tw.	1,039
	114	(lumba* adj3 pain*).tw.	6,979
	115	lumba* syndrome.tw.	134
	116	lumbalgesia*.tw.	1
	117	lumbalgia*.tw.	389
	118	lumba* spine syndrome.tw.	15
	119	lumbodynia*.tw.	47
	120	lumbago*.tw.	2,132
	121	(lumbosacral adj3 pain*).tw.	896
	122	lumbosacral root syndrome.tw.	3
	123	(lumbosacroiliac adj3 strain*).tw.	-
	124	myalgi*.tw.	15,799
	125	exp arthralgia/	60,689
	126	arthralgi*.tw.	15,758
	127	(joint* adj3 pain*).tw.	22,188
	128	arthrodynia*.tw.	17
	129	exp myofascial pain/	7,937
	130	(myofascial adj3 pain*).tw.	3,101

Concept	#	Embase query	Results
	131	exp palliative therapy/	112,409
	132	palliative.tw.	100,947
	133	exp hospice care/	10,119
	134	hospice.tw.	18,376
	135	exp terminal care/	68,487
	136	(terminal adj3 car*).tw.	32,527
	137	(symptomatic adj3 treatment*).tw.	28,048
	138	exp dystonia/	23,959
	139	dystonia*.tw.	22,869
	140	exp generalized dystonia/	1,029
	141	exp dystonic disorder/	11,380
	142	(dystoni* adj3 disorder*).tw.	1,217
	143	exp focal dystonia/	8,175
	144	(focal adj3 dystonia*).tw.	2,620
	145	exp cervical dystonia/	3,119
	146	(cerviacal adj3 dystonia*).tw.	-
	147	anterocollis.tw.	125
	148	laterocollis.tw.	144
	149	retrocollis.tw.	213
	150	(spasmodic adj3 torticollis).tw.	1,234
	151	exp oromandibular dystonia/	461
	152	exp blepharospasm/	3,712

Concept	#	Embase query	Results
	153	blepharospasm*.tw.	2,692
	154	exp focal hand dystonia/	915
	155	exp Meige syndrome/	251
	156	meige* syndrome.tw.	374
	157	exp oromandibular dystonia/	461
	158	exp spasmodic dysphonia/	674
	159	exp multifocal dystonia/	75
	160	exp musician's dystonia/	207
	161	(musician* adj3 cramp*).tw.	74
	162	writer's cramp/	498
	163	(writer* adj3 cramp*).tw.	892
	164	exp myoclonus dystonia/	435
	165	exp paroxysmal dystonia/	178
	166	exp segmental dystonia/	401
	167	exp torsion dystonia/	1,236
	168	(torsion* adj3 spasm*).tw.	99
	169	exp torticollis/	5,249
	170	torticollis.tw.	4,640
	171	contracted neck.tw.	9
	172	(neck adj3 torsion).tw.	182
	173	wryneck.tw.	38
	174	exp muscle spasm/	89,048

Concept	#	Embase query	Results
	175	(muscle adj3 spas*).tw.	5,796
	176	(muscular adj3 spas*).tw.	903
	177	involuntary muscle* contraction*.tw.	279
	178	myospas*.tw.	64
	179	exp hemifacial spasm/	2,959
	180	(hemifacial adj3 spasm*).tw.	2,631
	181	(unilateral adj3 spasm*).tw.	113
	182	exp trismus/	4,351
	183	(jaw* adj3 lock*).tw.	142
	184	lockjaw*.tw.	93
	185	exp spasticity/	27,476
	186	(spas* adj3 disease*).tw.	1,049
	187	exp muscle hypertonia/	48,388
	188	(muscle* adj3 hypertoni*).tw.	599
	189	(muscular adj3 hypertoni*).tw.	279
	190	spasticism.tw.	1
	191	exp "chemotherapy induced nausea and vomiting"/	9,030
	192	"chemotherapy-associated nausea and vomiting".tw.	22
	193	"chemotherapy-related nausea and vomiting".tw.	77
	194	"chemotherapy-associated nausea/vomiting".tw.	3
	195	"chemotherapy-induced nausea and emesis".tw.	56

Concept	#	Embase query	Results
	196	"chemotherapy-induced nausea/emesis".tw.	2
	197	"chemotherapy-induced nausea/vomiting".tw.	89
	198	"chemotherapy-related nausea and emesis".tw.	6
	199	exp nausea/	216,838
	200	exp "nausea and vomiting"/	365,766
	201	exp chemotherapy induced nausea/	75
	202	exp vomiting/	214,725
	203	vomiting.tw.	116,474
	204	emesis.tw.	10,851
	205	exp anorexia/	62,362
	206	exp appetite disorder/	117,632
	207	(appetite adj3 disorder*).tw.	304
	208	(loss adj3 appetite).tw.	8,348
	209	exp feeding disorder/	85,033
	210	(feeding adj3 disorder*).tw.	1,172
	211	exp anorexia nervosa/	21,008
	212	anorexia nervosa.tw.	16,627
	213	exp eating disorder/	52,081
	214	(eating adj3 disorder*).tw.	27,252
	215	exp anorexigenic agent/	78,738
	216	anorexi*.tw.	48,494
	217	anorectic*.tw.	4,316

Concept	#	Embase query	Results
	218	anorexant*.tw.	7
	219	antiappetite*.tw.	6
	220	(appetite adj3 depress*).tw.	635
	221	(appetite adj3 inhibit*).tw.	436
	222	(appetite adj3 reduc*).tw.	2,067
	223	(appetite adj3 restrain*).tw.	17
	224	(appetite adj3 suppress*).tw.	2,370
	225	exp Human immunodeficiency virus/	193,169
	226	(immunodeficiency adj3 virus).tw.	98,499
	227	HIV.tw.	389,293
	228	exp acquired immune deficiency syndrome/	140,130
	229	acquired immunodeficiency syndrome.tw.	16,504
	230	exp demyelinating disease/	179,179
	231	(demyelinat* adj3 disease*).tw.	11,859
	232	exp multiple sclerosis/	131,824
	233	multiple sclerosis.tw.	115,503
	234	(disseminated adj3 sclerosis).tw.	1,153
	235	insular sclerosis.tw.	5
	236	exp amyotrophic lateral sclerosis/	38,232
	237	amyotrophic lateral sclerosis.tw.	31,069
	238	(als adj3 dementia).tw.	1,470
	239	Lou Gehrig* disease.tw.	187

Concept	#	Embase query	Results
	240	exp Parkinson disease/	153,480
	241	parkinson* disease.tw.	130,618
	242	paralysis agitans.tw.	299
	243	parkinson dementia complex.tw.	70
	244	exp Gilles de la Tourette syndrome/	8,133
	245	Tourette* disease.tw.	142
	246	Tourette* syndrome.tw.	5,880
	247	tic/	9,655
	248	(fac* adj3 twitch*).tw.	482
	249	(nervous adj3 tic*).tw.	65
	250	(nervous adj3 twitch*).tw.	17
	251	tic* disorder*.tw.	1,864
	252	exp dementia/	361,053
	253	dementia*.tw.	157,661
	254	exp Alzheimer disease/	196,945
	255	alzheimer disease.tw.	21,658
	256	(Alzheimer adj3 dementia).tw.	5,703
	257	exp Huntington chorea/	27,010
	258	huntington* chorea*.tw.	1,921
	259	huntington* disease.tw.	20,040
	260	exp spinal cord injury/	78,164
	261	exp cervical spinal cord injury/	3,658

Concept	#	Embase query	Results
	262	spinal cord injur*.tw.	49,118
	263	spinal cord lacerati*.tw.	3
	264	exp spinal cord transsection/	3,377
	265	spinal cord transection*.tw.	1,834
	266	exp spinal cord transverse lesion/	739
	267	spinal cord transverse lesion*.tw.	-
	268	spinal cord contusion*.tw.	824
	269	exp spinal cord compression/	16,757
	270	spinal cord compression*.tw.	8,114
	271	exp brown sequard syndrome/	863
	272	brown sequard syndrome.tw.	641
	273	exp traumatic brain injury/	49,121
	274	traumatic brain injur*.tw.	51,303
	275	traumatic brain lesion*.tw.	170
	276	(brain adj3 trauma*).tw.	56,724
	277	(cerebr* adj3 trauma*).tw.	4,501
	278	(trauma adj3 encephalopathy).tw.	90
	279	posttraumatic encephalopathy.tw.	54
	280	exp epilepsy/	253,685
	281	epilep*.tw.	206,516
	282	"seizure, epilepsy and convulsion"/	102
	283	seizure*.tw.	185,688

Concept	#	Embase query	Results
	284	convulsi*.tw.	43,154
	285	exp irritable colon/	26,108
	286	irritable colon syndrome*.tw.	276
	287	irritable bowel syndrome*.tw.	20,317
	288	exp neurogenic bowel/	654
	289	(neurogen* adj3 bowel).tw.	602
	290	exp bladder irritation/	897
	291	(irritabl* adj3 bladder).tw.	225
	292	nervous bladder.tw.	10
	293	exp overactive bladder/	15,958
	294	(bladder adj3 overactiv*).tw.	11,962
	295	(detrusor adj3 overactiv*).tw.	5,167
	296	exp anxiety disorder/	241,092
	297	exp anxiety disorder/	241,092
	298	(anxiety adj3 disorder*).tw.	52,006
	299	nervousness.tw.	2,786
	300	hypervigilance.tw.	971
	301	exp anxiolytic agent/	200,652
	302	(anxi* adj3 agent*).tw.	1,592
	303	(anxi* adj3 drug*).tw.	4,515
	304	(anxi* adj3 medic*).tw.	3,170
	305	anti anxiety agent*.tw.	148

Concept	#	Embase query	Results
	306	anti anxiety drug*.tw.	263
	307	anti anxiety medic*.tw.	119
	308	exp posttraumatic stress disorder/	58,848
	309	posttraumatic stress disorder*.tw.	20,976
	310	post-traumatic stress disorder*.tw.	14,398
	311	(posttraumatic adj3 neuros*).tw.	50
	312	(post-traumatic adj3 neuros*).tw.	83
	313	(posttraumatic adj3 psych*).tw.	1,096
	314	post-traumatic psych*.tw.	156
	315	PTSD.tw.	30,472
	316	(traumatic adj3 stress*).tw.	20,550
	317	(combat* adj3 disorder*).tw.	536
	318	(war* adj3 neuros*).tw.	740
	319	(war* adj3 psych*).tw.	6,905
	320	exp depression/	474,606
	321	depressi*.tw.	537,757
	322	exp mood disorder/	517,836
	323	(mood adj3 disorder*).tw.	30,626
	324	exp dysphoria/	6,000
	325	dysphoria*.tw.	4,522
	326	exp dysthymia/	8,882
	327	dysthymia*.tw.	2,902

Concept	#	Embase query	Results
	328	"mixed anxiety and depression"/	777
	329	"mixed anxiety and depression".tw.	299
	330	"mixed depression and dementia"/	137
	331	"mixed depression and dementia".tw.	5
	332	mourning syndrome/	122
	333	(mourning adj3 syndrome).tw.	3
	334	perry syndrome/	95
	335	perry syndrome.tw.	92
	336	exp antidepressant agent/	441,069
	337	(antidepress* adj3 agent*).tw.	3,546
	338	(antidepress* adj3 drug*).tw.	13,805
	339	(antidepress* adj3 medic*).tw.	8,218
	340	(depressi* adj3 agent*).tw.	701
	341	(depressi* adj3 drug*).tw.	4,659
	342	(depressi* adj3 medic*).tw.	6,425
	343	exp sleep disorder/	237,192
	344	(sleep* adj3 disorder*).tw.	42,690
	345	(disturbanc* adj3 sleep*).tw.	27,904
	346	sleep wake disorder*.tw.	468
	347	dyssomni*.tw.	175
	348	exp insomnia/	68,232
	349	insomnia*.tw.	36,598

Concept	#	Embase query	Results
	350	hyposomnia*.tw.	44
	351	sleepless*.tw.	1,440
	352	"sleep initiation and maintenance disorder*".tw.	16
	353	(sleep adj3 initiation).tw.	691
	354	exp schizophrenia/	194,052
	355	schizophren*.tw.	171,056
	356	exp schizophrenia spectrum disorder/	198,219
	357	"schizophrenia spectrum disorder*".tw.	3,526
	358	exp schizoaffective psychosis/	10,136
	359	(schizoaffective adj3 psychos*).tw.	580
	360	schizo affective psychos*.tw.	80
	361	(schizoaffective adj3 disorder*).tw.	7,252
	362	schizo affective disorder*.tw.	320
	363	exp schizophreniform disorder/	1,583
	364	(schizophreniform adj3 disorder*).tw.	918
	365	(schizophreniform adj3 psychos*).tw.	338
	366	exp psychosis/	307,156
	367	psychos*.tw.	225,587
	368	psychot*.tw.	148,691
	369	psychotic disorder*.tw.	13,973
	370	or/17-369	5,059,534
cannabis + ALL	371	16 and 370	27,296

Concept	#	Embase query	Results
Reviews only (all outcomes)	372	limit 371 to yr="2016 - 2020"	8,068
	373	limit 372 to (meta analysis or "systematic review")	3,916
cannabis + pain	374	or/17-137	1,685,112
	375	16 and 374	4,759
	376	limit 375 to yr="2016 - 2020"	1,988
cannabis + movement dis.	377	or/138-190	169,899
	378	16 and 377	1,058
	379	limit 378 to yr="2016 - 2020"	348
cannabis + nausea / vomiting	380	or/191-224	587,795
	381	16 and 380	3,290
	382	limit 381 to yr="2016 - 2020"	1,184
cannabis + neuropsychiatric / immunology	383	or/225-369	3,344,764
	384	16 and 383	25,160
	385	limit 384 to yr="2016 - 2020"	7,122

PubMed

Concept	#	PubMed query	Results
Cannabis/ cannabinoids	1	((((((((cannabis[MeSH Terms]) OR cannabis sativa[MeSH Terms]) OR cannabis indica[MeSH Terms]) OR marijuana[MeSH Terms]) OR hashish[MeSH Terms]) OR cannabis[Text Word]) OR marihuana[Text Word]) OR marijuana[Text Word]) OR hashish[Text Word]	32,789
Pain	2	((((((((chronic pain[MeSH Terms]) OR (intractable pain[MeSH Terms])) OR (neuropathic pain[MeSH Terms])) OR (pain	524,816

Concept	#	PubMed query	Results
		clinic[MeSH Terms])) OR ("cancer pain"[MeSH Terms])) OR (postoperative pain[MeSH Terms])) OR (referred pain[MeSH Terms])) OR (breakthrough pain[MeSH Terms])) OR ("neuralgia"[MeSH Terms])) OR ("burning mouth syndrome"[MeSH Terms])) OR ("carpal tunnel syndrome"[MeSH Terms])) OR ("cauda equina syndrome"[MeSH Terms]))) OR ("complex regional pain syndromes"[MeSH Terms])) OR ("cubital tunnel syndrome"[MeSH Terms])) OR (metatarsalgia[MeSH Terms])) OR ("morton neuroma"[MeSH Terms])) OR ("radiculopathy"[MeSH Terms])) OR (sciatica[MeSH Terms])) OR (sunct syndrome[MeSH Terms])) OR (tarsal tunnel syndrome[MeSH Terms])) OR (tarsal tunnel entrapment neuropathy[MeSH Terms])) OR (nociceptive pain[MeSH Terms])) OR ("complex regional pain syndromes"[MeSH Terms])) OR ("causalgia"[MeSH Terms])) OR ("headache"[MeSH Terms])) OR ("headache disorders"[MeSH Terms])) OR ("migraine disorders"[MeSH Terms])) OR ("facial pain"[MeSH Terms]))) OR ("eye pain"[MeSH Terms])) OR ("glossalgia"[MeSH Terms])) OR ("neck pain"[MeSH Terms])) OR ("shoulder pain"[MeSH Terms])) OR ("back pain"[MeSH Terms])) OR ("failed back surgery syndrome"[MeSH Terms])) OR ("low back pain"[MeSH Terms])) OR ("myalgia"[MeSH Terms])) OR ("myofascial pain syndromes"[MeSH Terms])) OR ("arthralgia"[MeSH Terms])) OR ("palliative care"[MeSH Terms])) OR ("hospice care"[MeSH Terms])) OR ("terminal care"[MeSH Terms])) OR (chronic adj3 pain*[Text Word])) OR (chronic pain*[Text Word])) OR (intractable pain*[Text	

Concept	#	PubMed query	Results
		Word])) OR (neuropathic pain*[Text Word])) OR (pain* clinic*[Text Word])) OR (cancer pain*[Text Word])) OR (postoperative pain*[Text Word])) OR (referred pain*[Text Word])) OR (breakthrough pain*[Text Word])) OR (neuralgi*[Text Word])) OR (burning mouth syndrome*[Text Word])) OR (carpal tunnel syndrome[Text Word])) OR (cauda equina syndrome[Text Word])) OR (complex regional pain syndrome*[Text Word])) OR (cubital tunnel syndrome[Text Word])) OR (metatarsalgi*[Text Word])) OR (morton neuroma*[Text Word])) OR (radiculopathy*[Text Word])) OR (sciatic*[Text Word])) OR (sunct syndrome[Text Word])) OR (tarsal tunnel syndrome[Text Word])) OR (tarsal tunnel entrapment neuropath*[Text Word])) OR (nociceptive pain*[Text Word])) OR (causalgia*[Text Word])) OR (headache*[Text Word])) OR (migraine[Text Word])) OR (fac* pain*[Text Word])) OR (eye* pain*[Text Word])) OR (glossalgi*[Text Word])) OR (neck pain*[Text Word])) OR (shoulder* pain*[Text Word])) OR (back pain*[Text Word])) OR (failed back surgery syndrome[Text Word])) OR (low back pain*[Text Word])) OR (lowback pain*[Text Word])) OR (myalgi*[Text Word])) OR (myofascial pain syndrome*[Text Word])) OR (arthralgia*[Text Word])) OR (palliative[Text Word])) OR (hospice[Text Word])) OR (terminal care[Text Word])	
Movement disorders	3	((((((((((((((((((((("dystonia"[MeSH Terms]) OR ("dystonic disorders"[MeSH Terms])) OR ("torticollis"[MeSH Terms])) OR ("blepharospasm"[MeSH Terms])) OR ("meige syndrome"[MeSH Terms])) OR (writer's cramp[MeSH Terms])) OR (wryneck[MeSH Terms])) OR ("muscle	41,592

Concept	#	PubMed query	Results
		spasticity"[MeSH Terms])) OR ("hemifacial spasm"[MeSH Terms])) OR ("trismus"[MeSH Terms])) OR (lockjaw[MeSH Terms])) OR ("muscle hypertonia"[MeSH Terms])) OR (dystoni*[Text Word])) OR (torticollis[Text Word])) OR (blepharospasm[Text Word])) OR (meige* syndrome[Text Word])) OR (writer* cramp*[Text Word])) OR (wryneck[Text Word])) OR (muscle* spas*[Text Word])) OR (muscular spas*[Text Word])) OR (hemifacial spasm*[Text Word])) OR (trismus[Text Word])) OR (lockjaw[Text Word])) OR (muscle* hypertoni*[Text Word])) OR (muscular hypertoni*[Text Word])	
Chemotherapy / AIDS - N&V	4	((((((((((((((((((((((((("nausea"[MeSH Terms]) OR ("nausea/chemically induced"[MeSH Terms])) OR ("vomiting"[MeSH Terms])) OR ("vomiting, anticipatory/chemically induced"[MeSH Terms])) OR ("anorexia"[MeSH Terms])) OR ("anorexia nervosa"[MeSH Terms])) OR ("appetite regulation"[MeSH Terms])) OR ("appetite stimulants"[MeSH Terms])) OR (appetite disorder[MeSH Terms])) OR ("anorexia nervosa/drug therapy"[MeSH Terms])) OR ("acquired immunodeficiency syndrome"[MeSH Terms])) OR ("immunocompromised host"[MeSH Terms])) OR (nausea[Text Word])) OR (vomiting[Text Word])) OR (chemotherapy induced nausea[Text Word] AND vomiting[Text Word])) OR (chemotherapy associated nausea[Text Word] AND vomiting[Text Word])) OR (chemotherapy related nausea[Text Word] AND vomiting[Text Word])) OR (anorexi*[Text Word])) OR (appetite disorder*[Text Word])) OR (loss of appetite[Text Word])) OR (appetite	593,286

Concept	#	PubMed query	Results
		regulat*[Text Word])) OR (appetite stimula*[Text Word])) OR (anorexigenic agent*[Text Word])) OR (anorexigenic medic*[Text Word])) OR (anorexigenic drug*[Text Word])) OR (anorexigenic treatment*[Text Word])) OR (human immunodeficiency virus[Text Word])) OR (HIV[Text Word])) OR (acquired immune deficiency syndrome[Text Word])) OR (immunocompromi*[Text Word])	
Neuropsychiatric/ immunotoxicity	5	**((("multiple sclerosis"[MeSH Terms]) OR ("amyotrophic lateral sclerosis"[MeSH Terms])) OR ("parkinson disease"[MeSH Terms])) OR ("tourette syndrome"[MeSH Terms])) OR ("tic disorders"[MeSH Terms])) OR ("dementia"[MeSH Terms])) OR ("alzheimer disease"[MeSH Terms])) OR ("huntington disease"[MeSH Terms])) OR ("spinal cord diseases/injuries"[MeSH Terms])) OR ("spinal cord compression"[MeSH Terms]))) OR ("brown-sequard syndrome"[MeSH Terms])))) OR (traumatic brain injury[MeSH Terms])) OR ("epilepsy"[MeSH Terms])) OR ("epileptic syndromes"[MeSH Terms])) OR ("seizures"[MeSH Terms])) OR ("irritable bowel syndrome"[MeSH Terms])) OR ("anxiety"[MeSH Terms])) OR ("anxiety disorders"[MeSH Terms])) OR ("anxiety disorders/drug therapy"[MeSH Terms])) OR ("stress disorders, post-traumatic"[MeSH Terms])) OR ("combat disorders"[MeSH Terms])) OR ("depression"[MeSH Terms])) OR ("depression/drug therapy"[MeSH Terms])) OR ("depression/drug effects"[MeSH Terms])) OR ("mood disorders"[MeSH**	441,909

Concept	#	PubMed query	Results
		Terms])) OR ("mood disorders/drug therapy"[MeSH Terms])) OR ("antidepressive agents"[MeSH Terms])) OR ("sleep disorders, circadian rhythm"[MeSH Terms])) OR ("sleep disorders, circadian rhythm/drug therapy"[MeSH Terms])) OR ("sleep disorders, intrinsic"[MeSH Terms])) OR ("sleep disorders, intrinsic/drug therapy"[MeSH Terms])) OR ("sleep wake disorders"[MeSH Terms])) OR ("sleep wake disorders/drug therapy"[MeSH Terms])) OR ("sleep wake disorders/drug effects"[MeSH Terms])) OR ("sleep initiation and maintenance disorders"[MeSH Terms])) OR ("schizophrenia"[MeSH Terms])) OR ("schizophrenia spectrum and other psychotic disorders"[MeSH Terms])) OR ("schizophrenia spectrum and other psychotic disorders/drug therapy"[MeSH Terms])) OR ("schizophrenia spectrum and other psychotic disorders/drug effects"[MeSH Terms])) OR (schizoaffective disorder[MeSH Terms])) OR ("schizoid personality disorder"[MeSH Terms])) OR ("schizoid personality disorder/therapy"[MeSH Terms])) OR ("psychotic disorders"[MeSH Terms])) OR ("psychotic disorders/drug therapy"[MeSH Terms])) OR ("psychotic disorders/drug effects"[MeSH Terms])) OR (multiple sclerosis[Text Word] OR disseminated sclerosis[Text Word] OR amyotrophic lateral sclerosis[Text Word] OR dementia*[Text Word] OR Lou Gehrig* disease[Text Word] OR parkinson* disease[Text Word] OR paralysis agitans[Text Word] OR Tourette* disease[Text Word] OR Tourette*	

Concept	#	PubMed query	Results
		syndrome[Text Word] OR Tic disorder*[Text Word] OR Alzheimer*[Text Word] OR huntington* chorea*[Text Word] OR huntington* disease[Text Word] OR spinal cord injur*[Text Word] OR spinal cord lacerati*[Text Word] OR spinal cord transection*[Text Word] OR spinal cord contusion*[Text Word] OR spinal cord compression*[Text Word] OR brown sequard syndrome[Text Word] OR traumatic brain injur*[Text Word] OR brain trauma*[Text Word] OR epilep*[Text Word] OR seizure*[Text Word] OR convulsi*[Text Word] OR irritabl* colon[Text Word] OR irritabl* bowel[Text Word] OR neurogen* bowel[Text Word] OR irritabl* bladder[Text Word] OR nervous bladder[Text Word] OR overactive bladder[Text Word] OR detrusor overactiv*[Text Word] OR anxiety disorder*[Text Word] OR anxi* agent*[Text Word] OR anxi* drug*[Text Word] OR anxi* medic*[Text Word] OR anti anxiety agent*[Text Word] OR anti anxiety drug*[Text Word] OR anti anxiety medic*[Text Word] OR posttraumatic stress disorder*[Text Word] OR post-traumatic stress disorder*[Text Word] OR posttraumatic neuros*[Text Word] OR post-traumatic neuros*[Text Word] OR posttraumatic psych*[Text Word] OR post-traumatic psych*[Text Word] OR PTSD[Text Word] OR combat* disorder*[Text Word] OR war* neuros*[Text Word] OR war* psych*[Text Word] OR depressi*[Text Word] OR mood disorder*[Text Word] OR dysphoria*[Text Word] OR dysthymia*[Text Word] OR mourning syndrome[Text Word] OR perry syndrome[Text Word]	

Concept	#	PubMed query	Results
		OR antidepress* agent*[Text Word] OR antidepress* drug*[Text Word] OR antidepress* medic*[Text Word] OR depressi* agent*[Text Word] OR depressi* drug*[Text Word] OR depressi* medic*[Text Word] OR sleep* disorder*[Text Word] OR sleep disturbance[Text Word] OR sleep wake disorder*[Text Word] OR insomnia*[Text Word] OR hyposomnia*[Text Word] OR sleepless*[Text Word] OR sleep initiation[Text Word] AND maintenance disorder*[Text Word] OR sleep initiation[Text Word] OR schizophren*[Text Word] OR schizophrenia spectrum disorder*[Text Word] OR schizoaffective[Text Word] OR schizophreniform[Text Word] OR psychos*[Text Word] OR psychot*[Text Word]	
ALL indications	6	Or/2-5	2,315,563
Cannabis + ALL ind.	7	1 and 6	9,479
	8	Limit 7 to : ("2016/01/01"[Date - Publication] : "3000"[Date - Publication])	2,887
	9	Limit 8 to: (("meta-analysis"[Publication Type]) OR ("systematic review"[Publication Type]))	596
Cannabis + pain	10	1 and 2	1,037
	11	("2016/01/01"[Date - Publication] : "3000"[Date - Publication])	527

Concept	#	PubMed query	Results
Cannabis + movmt.	12	1 and 3	178
	13	("2016/01/01"[Date - Publication] : "3000"[Date - Publication])	50
Cannabis + n/v	14	1 and 4	2,119
	15	("2016/01/01"[Date - Publication] : "3000"[Date - Publication])	729
Cannabis + ns/ imm	16	1 and 5	8,802
	17	("2016/01/01"[Date - Publication] : "3000"[Date - Publication])	2,520

Appendix 2. Excluded studies (with reasons for exclusion)

Level	Bibliography	Reason for exclusion
1	Ahmed, S.,Bachu, R.,Kotapati, P.,Adnan, M.,Ahmed, R.,Farooq, U.,Saeed, H.,Khan, A. M.,Zubair, A.,Qamar, I.,Begum, G. (2019). Use of Gabapentin in the Treatment of Substance Use and Psychiatric Disorders: A Systematic Review Front Psychiatry, 10(#issue#), 228	Addiction/Withdrawal
1	Aldridge, R. W.,Story, A.,Hwang, S. W.,Nordentoft, M.,Luchenski, S. A.,Hartwell, G.,Tweed, E. J.,Lewer, D.,Vittal Katikireddi, S.,Hayward, A. C. (2018). Morbidity and mortality in homeless individuals, prisoners, sex workers, and individuals with substance use disorders in high-income countries: a systematic review and meta-analysis Lancet, 391(10117), 241-250	Addiction/Withdrawal
1	Alharbi, F. F.,El-Guebaly, N. (2016). Cannabis and amphetamine-type stimulant-induced psychoses: A systematic overview Addictive Disorders and their Treatment, 15(4), 190-200	Addiction/Withdrawal
1	Almli, L.,Tang, Y.,Meyers, J.,Koenen, K.,Marmar, C.,Shin, J.,Maihofer, A.,Nievergelt, C.,Conneely, K.,Ressler, K. (2017). Problematic alcohol use behavior comorbidity in a highly traumatized urban cohort and its GWAS association with an eqtl of the SCLT1 gene European Neuropsychopharmacology, 27 (Supplement 2)(#issue#), S135-S136	Addiction/Withdrawal

Level	Bibliography	Reason for exclusion
1	Anderson, L. J.,Flynn, A.,Pilgrim, J. L. (2017). A global epidemiological perspective on the toxicology of drug-facilitated sexual assault: A systematic review Journal of Forensic and Legal Medicine, 47(#issue#), 46-54	Addiction/Withdrawal
1	Anonymous, (2018). Abstract Book - 2nd World Congress of World Association on Dual Disorder, WADD Heroin Addiction and Related Clinical Problems. Conference: 2nd World Congress of World Association on Dual Disorder, WADD, 20(Supplement 2), #Pages#	Addiction/Withdrawal
1	Anonymous, (2019). Abstracts of the XXVIth World Congress of Psychiatric Genetics (WCPG), 11 - 15 October 2018, Glasgow, Scotland European Neuropsychopharmacology, 29 (Supplement 4)(#issue#), S1021-S1342	Addiction/Withdrawal
1	Arimany, M. S.,Fortea, A.,Ilzarbe, D.,Sugranyes, G.,Baeza, I. (2018). Long-Acting Injectable Atypical Antipsychotic Use in a Child and Adolescent Inpatient Psychiatry Unit: An Observational Study Journal of the American Academy of Child and Adolescent Psychiatry, 57 (10 Supplement)(#issue#), S169	Addiction/Withdrawal
1	Arranz, B.,Garriga, M.,García-Rizo, C.,San, L. (2018). Clozapine use in patients with schizophrenia and a comorbid substance use disorder: A systematic review Eur Neuropsychopharmacol, 28(2), 227-242	Addiction/Withdrawal
1	Asuzu, K.,Matin, A.,Van Noord, M.,Onigu-Otite, E.	Addiction/Withdrawal

Level	Bibliography	Reason for exclusion
	(2018). Electronically-delivered interventions to reduce cannabis use in adolescents: A systematic review Adolescent Psychiatry, 8(3), 195-213	
1	Atkinson, D. L. (2017). Prescription stimulant abuse on college campuses Journal of the American Academy of Child and Adolescent Psychiatry, 56 (10)(#issue#), S79	Addiction/Withdrawal
1	Baandrup, L.,Ostrup Rasmussen, J.,Klokker, L.,Austin, S.,Bjornshave, T.,Fuglsang Bliksted, V.,Fink-Jensen, A.,Hedegaard Fohlmann, A.,Peter Hansen, J.,Kristine Nielsen, M.,Sandsten, K. E.,Schultz, V.,Voss-Knude, S.,Nordentoft, M. (2016). Treatment of adult patients with schizophrenia and complex mental health needs - A national clinical guideline Nordic Journal of Psychiatry, 70(3), 231-240	Addiction/Withdrawal
1	Badowski, S.,Smith, G. (2020). Cannabis use during pregnancy and postpartum Canadian family physician Medecin de famille canadien, 66(2), 98-103	Addiction/Withdrawal
1	Bagot, K. S. (2017). Cannabis use amongst college-aged students Journal of the American Academy of Child and Adolescent Psychiatry, 56 (10)(#issue#), S78	Addiction/Withdrawal
1	Barkin, J. A.,Nemeth, Z.,Saluja, A. K.,Barkin, J. S. (2016). A systematic review of cannabis use and the development of acute pancreatitis American Journal of Gastroenterology, 111 (Supplement 1)(#issue#), S50-	Addiction/Withdrawal

Level	Bibliography	Reason for exclusion
	S51	
1	Barkin, J. A.,Nemeth, Z.,Saluja, A. K.,Barkin, J. S. (2016). Cannabis induced acute pancreatitis: A systematic review Pancreas, 45 (10)(#issue#), 1497	Addiction/Withdrawal
1	Bartoli, F.,Crocamo, C.,Carra, G. (2019). Cannabis use disorder and suicide attempts in bipolar disorder: A meta-analysis Neuroscience and Biobehavioral Reviews, 103(#issue#), 14-20	Addiction/Withdrawal
1	Basu, K.,Sabesan, P.,Palaniyappan, L. (2019). An effect-size meta-analysis of white matter damage related to cannabis use: Relevance to the anatomy of psychosis Schizophrenia Bulletin, 45 (Supplement 2)(#issue#), S224	Addiction/Withdrawal
1	Batet Sanchez, D. (2016). Neuroimaging of first-episode-psychosis in cannabis users: A review Psiquiatria Biologica, 23(3), 103-111	Addiction/Withdrawal
1	Becerra Darriba, H. (2019). P.744 Is N-acetylcysteine a promising pharmacological treatment for cannabis and cocaine cessation? European Neuropsychopharmacology, 29 (Supplement 6)(#issue#), S500-S501	Addiction/Withdrawal
1	Belbasis, L.,Köhler, C. A.,Stefanis, N.,Stubbs, B.,van Os, J.,Vieta, E.,Seeman, M. V.,Arango, C.,Carvalho, A. F.,Evangelou, E. (2018). Risk factors and peripheral biomarkers for schizophrenia spectrum disorders: an umbrella review of meta-analyses Acta Psychiatr	Addiction/Withdrawal

Level	Bibliography	Reason for exclusion
	Scand, 137(2), 88-97	
1	Berry, M. S.,Johnson, M. W. (2018). Does being drunk or high cause HIV sexual risk behavior? A systematic review of drug administration studies Pharmacol Biochem Behav, 164(#issue#), 125-138	Addiction/Withdrawal
1	Bevilacqua, L.,Hale, D.,Barker, E. D.,Viner, R. (2017). Conduct problems trajectories and psychosocial outcomes in early adulthood: A systematic review and meta-analysis Archives of Disease in Childhood, 102 (Supplement 1)(#issue#), A50	Addiction/Withdrawal
1	Bevilacqua, L.,Hale, D.,Barker, E. D.,Viner, R. (2018). Conduct problems trajectories and psychosocial outcomes: a systematic review and meta-analysis Eur Child Adolesc Psychiatry, 27(10), 1239-1260	Addiction/Withdrawal
1	Bleckwenn, M.,Heister, L.,Weckbecker, M.,Weckbecker, K.,Mucke, M. (2016). Misuse of Substitution Drugs in the Substitution-Based Therapy European Addiction Research, 22(6), 322-328	Addiction/Withdrawal
1	Bogaty, S. E. R.,Lee, R. S. C.,Hickie, I. B.,Hermens, D. F. (2018). Meta-analysis of neurocognition in young psychosis patients with current cannabis use J Psychiatr Res, 99(#issue#), 22-32	Addiction/Withdrawal
1	Bouhlal, S.,Temko, J. E.,Farokhnia, M.,Lee, M. R.,Leggio, L. (2016). The role of the gut microbiome in phenotypes associated with alcohol and other addictive disorders: A systematic review Alcoholism: Clinical and	Addiction/Withdrawal

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	Experimental Research, 1)(#issue#), 102A	
1	Bowtell, M.,Ratheesh, A.,McGorry, P.,Killackey, E.,O'Donoghue, B. (2018). Clinical and demographic predictors of continuing remission or relapse following discontinuation of antipsychotic medication after a first episode of psychosis. A systematic review Schizophr Res, 197(#issue#), 9-18	Addiction/Withdrawal
1	Bridges, S.,Kini, R.,Parker, R.,Handley, M.,Das, M. (2019). Psychiatric disorder and its correlates in indigenous Australian prisoners: A systematic review Australian and New Zealand Journal of Psychiatry, 53 (Supplement 1)(#issue#), 108	Addiction/Withdrawal
1	Brown, R. A.,Dakkak, H.,Seabrook, J. A. (2018). Is Breast Best? Examining the effects of alcohol and cannabis use during lactation Journal of Neonatal-Perinatal Medicine, 11(4), 345-356	Addiction/Withdrawal
1	Buccelli, C.,Della Casa, E.,Paternoster, M.,Niola, M.,Pieri, M. (2016). Gender differences in drug abuse in the forensic toxicological approach Forensic Science International, 265(#issue#), 89-95	Addiction/Withdrawal
1	Campeny, E.,Lopez-Pelayo, H.,Nutt, D.,Blithikioti, C.,Oliveras, C.,Nuno, L.,Maldonado, R.,Florez, G.,Arias, F.,Fernandez-Artamendi, S.,Villalbi, J. R.,Sellares, J.,Ballbe, M.,Rehm, J.,Balcells-Olivero, M. M.,Gual, A. (2020). The blind men and the elephant: Systematic review of systematic reviews of cannabis	Addiction/Withdrawal

Level	Bibliography	Reason for exclusion
	use related health harms European Neuropsychopharmacology., #volume#(#issue#), #Pages#	
1	Cancilliere, M. K.,Yusufov, M.,Weyandt, L. (2018). Effects of Co-occurring marijuana use and anxiety on brain structure and functioning: A systematic review of adolescent studies J Adolesc, 65(#issue#), 177-188	Addiction/Withdrawal
1	Cancino Botello, M. C.,Canseco Navarro, M. D. L. A.,Pena Serrano, A.,Molina Lopez, F.,Hernandez Sanchez, J. M. (2016). Psychosis, cause or consequence of substance use disorder European Psychiatry, 33 (SUPPL.)(#issue#), S376	Addiction/Withdrawal
1	Candido, F. J.,Souza, R.,Stumpf, M. A.,Fernandes, L. G.,Veiga, R.,Santin, M.,Kluthcovsky, A. (2018). The use of drugs and medical students: A literature review Revista da Associacao Medica Brasileira, 64(5), 462-468	Addiction/Withdrawal
1	Carbia, C.,Corral, M.,Cadaveira, F. (2017). Episodic memory in young binge drinkers: A neuropsychological approach Alcohol and Alcoholism, 52 (Supplement 1)(#issue#), i4	Addiction/Withdrawal
1	Carey, C.,Agrawal, A.,Hartz, S.,Bierut, L.,Bogdan, R. (2017). Associations between polygenic risk for psychiatric disorders and substance dependence European Neuropsychopharmacology, 27 (Supplement 2)(#issue#), S204	Addiction/Withdrawal

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1	Carney, T.,Myers, B. J.,Louw, J.,Okwundu, C. I. (2016). Brief school-based interventions and behavioural outcomes for substance-using adolescents Cochrane Database Syst Rev, #volume#(1), Cd008969	Addiction/Withdrawal
1	Carney, R.,Cotter, J.,Firth, J.,Bradshaw, T.,Yung, A. R. (2017). Cannabis use and symptom severity in individuals at ultra high risk for psychosis: a meta-analysis Acta Psychiatr Scand, 136(1), 5-15	Addiction/Withdrawal
1	Carrigan, N.,Barkus, E. (2016). A systematic review of the relationship between psychological disorders or substance use and self-reported cognitive failures Cogn Neuropsychiatry, 21(6), 539-564	Addiction/Withdrawal
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1	Chand, M.,Walfird, M.,Kanwar, S.,Hirsch, A. (2016). Telemission and telepathy in the absence of schizophrenia Journal of Neuropsychiatry and Clinical Neurosciences, 28 (3)(#issue#), e38-e39	Addiction/Withdrawal
1	Charron, C. B.,Leung, J. M. (2019). The Safety and Efficacy of Marijuana in Persons Living with HIV AIDS Rev, 21(2), 84-92	Addiction/Withdrawal
1	Chronopoulou, E.,Seshadri, S. (2016). Preconceptual health and fertility treatment-an evidence based approach Human Reproduction, 31 (Supplement	Addiction/Withdrawal

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1	Coentre, R.,Talina, M. C.,Gois, C.,Figueira, M. L. (2017). Depressive symptoms and suicidal behavior after first-episode psychosis: A comprehensive systematic review Psychiatry Research, 253(#issue#), 240-248	Addiction/Withdrawal
1	Cohen, A.,Perkel, C. (2017). The purple hex: Psychosis associated with abuse of propylhexedrine nasal inhalers by a young adult with history of ADHD seeking replacement for stimulant medication-with literature review and historical context ADHD Attention Deficit and Hyperactivity Disorders, 9 (1 Supplement)(#issue#), S50	Addiction/Withdrawal
1	Coleman, J.,Dela Cruz, A.,Wakhlu, S. (2019). Neurostimulation for treatment of addiction: State of the evidence American Journal on Addictions, 28 (3)(#issue#), 184	Addiction/Withdrawal
1	Coles, A. S.,Kozak, K.,George, T. P. (2018). A review of brain stimulation methods to treat substance use disorders American Journal on Addictions, 27(2), 71-91	Addiction/Withdrawal
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1	Colizzi, M.,Bhattacharyya, S. (2018). Cannabis use and the development of tolerance: a systematic review of human evidence Neurosci Biobehav Rev, 93(#issue#), 1-25	Addiction/Withdrawal
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1	Davis, J. P.,Smith, D. C.,Briley, D. A. (2017). Substance use prevention and treatment outcomes for emerging adults in non-college settings: A meta-Analysis Psychology of Addictive Behaviors, 31(3), 242-254	Addiction/Withdrawal
1	Dehghanmehr, S.,Mir, A.,Sheikhi, M.,Mirshekari, N.,Mirsargazi, Z.,Salarzaei, M. (2017). Main causes of drug compatibility and recurrence (A systematic review) Journal of Pharmaceutical Sciences and Research, 9(11), 2011-2015	Addiction/Withdrawal
1	Dellazizzo, L.,Potvin, S.,Beaudoin, M.,Luigi, M.,Dou, B. Y.,Giguere, C. E.,Dumais, A. (2019). Cannabis use	Addiction/Withdrawal

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	and violence in patients with severe mental illnesses: A meta-analytical investigation Psychiatry Research, 274(#issue#), 42-48	
1	Dini, G.,Bragazzi, N. L.,Montecucco, A.,Rahmani, A.,Durando, P. (2019). Psychoactive drug consumption among truck-drivers: A systematic review of the literature with meta-analysis and meta-regression Journal of Preventive Medicine and Hygiene, 60(2), E124-E139	Addiction/Withdrawal
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1	Dowling, N. A.,Merkouris, S. S.,Greenwood, C. J.,Oldenhof, E.,Toumbourou, J. W.,Youssef, G. J. (2017). Early risk and protective factors for problem gambling: A systematic review and meta-analysis of longitudinal studies Clin Psychol Rev, 51(#issue#), 109-124	Addiction/Withdrawal
1	Drummer, O. H.,Gerostamoulos, D.,Woodford, N. W. (2019). Cannabis as a cause of death: A review Forensic Science International, 298(#issue#), 298-306	Addiction/Withdrawal
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2	Araujo, R.,Sorensen, A. A.,Konkiel, S.,Bloem, B. R. (2017). Top Altmetric Scores in the Parkinson's Disease Literature Journal of Parkinson's Disease, 7(1), 81-87	Irrelevant study type
2	Bakshi, C.,Barrett, A. M. (2019). Impact of recreational and medicinal marijuana on surgical patients: A review American Journal of Surgery, 217(4), 783-786	Irrelevant study type
2	Boongmongkol, T.,Jitkritsadakul, O.,Bhidayasiri, R. (2019). The systematic review on cannabinoids as a treatment of Parkinson's disease Movement Disorders Clinical Practice, 6 (Supplement 1)(#issue#), S55-SS57	Irrelevant study type
2	Busse, J.,Wang, L.,Kamal El Din, M.,Craigie, S.,Montoya, L.,Riva, J.,Mulla, S.,Lopes, L.,Vogel, N.,Chen, E.,Kirmayr, K.,De Oliveira, K.,Olivieri, L.,Kaushal, A.,Chaparro, L.,Oyberman, I.,Agarwal, A.,Couban, R.,Tsoi, L.,Lam, T. (2018). Opioids for chronic non-cancer pain: A systematic review of randomized controlled trials Pain Practice, 18 (Supplement 1)(#issue#), 54-55	Irrelevant study type
2	Chapman, E. J.,Edwards, Z.,Boland, J. W.,Maddocks, M.,Fettes, L.,Malia, C.,Mulvey, M. R.,Bennett, M. I. (2020). Practice review: Evidence-based and effective management of pain in patients with advanced cancer Palliative Medicine.,	Irrelevant study type

Level	Bibliography	Reason for exclusion
	#volume#(#issue#), #Pages#	
2	Chen, J. W.,Borgelt, L. M.,Blackmer, A. B. (2019). Cannabidiol: A New Hope for Patients With Dravet or Lennox-Gastaut Syndromes Annals of Pharmacotherapy, 53(6), 603-611	Irrelevant study type
2	Claflin, S.,Claflin, S. B.,Van Der Mei, I.,Taylor, B. V. (2017). Complementary and alternative treatments of multiple sclerosis: A review of the evidence from 2001-2016 Multiple Sclerosis, 23 (13)(#issue#), NP13	Irrelevant study type
2	Cooper, Z. D.,Abrams, D. I. (2019). Considering abuse liability and neurocognitive effects of cannabis and cannabis-derived products when assessing analgesic efficacy: a comprehensive review of randomized-controlled studies American Journal of Drug and Alcohol Abuse, 45(6), 580-595	Irrelevant study type
2	Darkovska-Serafimovska, M.,Serafimovska, T.,Arsova-Sarafinovska, Z.,Stefanoski, S.,Keskovski, Z.,Balkanov, T. (2018). Pharmacotherapeutic considerations for use of cannabinoids to relieve pain in patients with malignant diseases Journal of Pain Research, 11(#issue#), 837-842	Irrelevant study type
2	Doeve, B.,Van Schaik, F.,Van De Meeberg, M.,Fidder, H. (2019). Cannabis and cannabinoids for the treatment of inflammatory bowel disease: A systematic review and meta-analysis Journal of Crohn's and Colitis, 13 (Supplement 1)(#issue#), S335-S336	Irrelevant study type
2	Doyle, A.,Harvey, J. (2020). Cannabis and Epilepsy Journal of Dual Diagnosis, 16(1), 75-82	Irrelevant study type
2	Ferreira-Junior, N. C.,Campos, A. C.,Guimaraes, F. S.,Del-	Irrelevant study type

Level	Bibliography	Reason for exclusion
	Bel, E.,Zimmermann, P. M. D. R.,Brum Junior, L.,Hallak, J. E.,Crippa, J. A.,Zuardi, A. W. (2019). Biological bases for a possible effect of cannabidiol in Parkinson's disease Revista brasileira de psiquiatria, #volume#(pagination), #Pages#	
2	Hauser, W.,Finn, D. P.,Kalso, E.,Krcevski-Skvarc, N.,Kress, H. G.,Morlion, B.,Perrot, S.,Schafer, M.,Wells, C.,Brill, S. (2018). European Pain Federation (EFIC) position paper on appropriate use of cannabis-based medicines and medical cannabis for chronic pain management European Journal of Pain (United Kingdom), 22(9), 1547-1564	Irrelevant study type
2	Hugos, C.,Rice, J.,Cameron, M. (2019). Cannabis use in people with MS and spasticity: A cross-sectional analysis Multiple Sclerosis Journal, 25 (7)(#issue#), 1031-1032	Irrelevant study type
2	Hwang, J. K.,Clarke, H. (2016). Cannabis and pain: A review Journal of Pain Management, 9(4), 395-413	Irrelevant study type
2	Khanna, R., Khanna, R., Denny, G., & Kwatra, S. (2019). Cannabinoids for the treatment of refractory chronic pruritus Journal of the American Academy of Dermatology, 81 (4 Supplement 1)(#issue#), AB29	Irrelevant study type
2	Kolar, D. (2018). Addictive potential of novel treatments for refractory depression and anxiety Neuropsychiatric Disease and Treatment, 14(#issue#), 1513-1519	Irrelevant study type
2	Kupfer, M.,Formal, C. S. (2020). Non-opioid pharmacologic treatment of chronic spinal cord injury-related pain The journal of spinal cord medicine, #volume#(#issue#), 1-10	Irrelevant study type
2	Lanza, G.,Ferri, R.,Bella, R.,Ferini-Strambi, L. (2017). The impact of drugs for multiple sclerosis on sleep Multiple Sclerosis, 23(1), 5-13	Irrelevant study type

Level	Bibliography	Reason for exclusion
2	Lochte, B. C.,Beletsky, A.,Samuel, N. K.,Grant, I. (2017). The Use of Cannabis for Headache Disorders Cannabis and Cannabinoid Research, 2(1), 61-71	Irrelevant study type
2	Makary, P.,Parmar, J. R.,Mims, N.,Khanfar, N. M.,Freeman, R. A. (2018). Patient Counseling Guidelines for the Use of Cannabis for the Treatment of Chemotherapy-Induced Nausea/Vomiting and Chronic Pain Journal of Pain and Palliative Care Pharmacotherapy, 32(4), 216-225	Irrelevant study type
2	McGaw, C. D. (2017). The cannabinoids as therapeutic agents in the management of pain West Indian Medical Journal, 66(5), 576-580	Irrelevant study type
2	Miller, N. S.,Oberbarnscheidt, T. (2017). Health policy for marijuana Journal of Global Drug Policy and Practice, 11(3), #Pages#	Irrelevant study type
2	Norton, C.,Czuber-Dochan, W.,Artom, M.,Sweeney, L.,Hart, A. (2017). Systematic review of interventions for chronic abdominal pain management in inflammatory bowel disease Journal of Crohn's and Colitis, 11 (Supplement 1)(#issue#), S363	Irrelevant study type
2	Oberbarnscheidt, T.,Miller, N. (2019). Marijuana-is it medicine? American Journal on Addictions, 28 (3)(#issue#), 202-203	Irrelevant study type
2	Pamplona, F. A.,Da Silva, L. R.,Coan, A. C. (2018). Potential clinical benefits of CBD-Rich cannabis extracts over purified CBD in treatment-resistant epilepsy: Observational data meta-analysis Frontiers in Neurology, 9 (SEP) (no pagination)(3389), #Pages#	Irrelevant study type
2	Park, J. Y.,Wu, L. T. (2017). Prevalence, reasons, perceived	Irrelevant study type

Level	Bibliography	Reason for exclusion
	effects, and correlates of medical marijuana use: A review Drug and Alcohol Dependence, 177(#issue#), 1-13	
2	Peng, M.,Khaiser, M.,Ahrari, S.,Pasetka, M.,DeAngelis, C. (2016). Medical marijuana as a therapeutic option for cancer anorexia and cachexia: A scoping review of current evidence Journal of Pain Management, 9(4), 435-447	Irrelevant study type
2	Pergjika, A.,Ballard, R. R.,DeAntonio, M. (2019). Kids and Cannabinoids: What Is the Evidence? Journal of the American Academy of Child and Adolescent Psychiatry, 58 (10 Supplement)(#issue#), S83-S84	Irrelevant study type
2	Pratt, M.,Stevens, A.,Thuku, M.,Butler, C.,Skidmore, B.,Wieland, L. S.,Clemons, M.,Kanji, S.,Hutton, B. (2019). Benefits and harms of medical cannabis: A scoping review of systematic reviews Systematic Reviews, 8 (1) (no pagination)(320), #Pages#	Irrelevant study type
2	Pupillo, E.,Bianchi, E.,Pasina, L.,Beghi, E. (2018). Potentially severe drug-drug interactions in ALS patients Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 19 (Supplement 1)(#issue#), 358	Irrelevant study type
2	Rice, J.,Cameron, M. (2018). Cannabinoids for Treatment of MS Symptoms: State of the Evidence Current Neurology and Neuroscience Reports, 18 (8) (no pagination)(50), #Pages#	Irrelevant study type
2	Rohleder, C.,Muller, J. K.,Lange, B.,Leweke, F. M. (2016). Cannabidiol as a potential new type of an antipsychotic. A critical review of the evidence Frontiers in Pharmacology, 7 (NOV) (no pagination)(422), #Pages#	Irrelevant study type
2	Rong, C.,Lee, Y.,Carmona, N. E.,Cha, D. S.,Ragguett, R. M.,Rosenblat, J. D.,Mansur, R. B.,Ho, R. C.,McIntyre, R. S.	Irrelevant study type

Level	Bibliography	Reason for exclusion
	(2017). Cannabidiol in medical marijuana: Research vistas and potential opportunities Pharmacological Research, 121(#issue#), 213-218	
2	Sarzi-Puttini, P.,Ablin, J.,Trabelsi, A.,Fitzcharles, M. A.,Marotto, D.,Hauser, W. (2019). Cannabinoids in the treatment of rheumatic diseases: Pros and cons Autoimmunity Reviews, 18 (12) (no pagination)(102409), #Pages#	Irrelevant study type
2	Schaefer, M.,Tafelski, S.,Hauser, W. (2019). Efficacy, tolerability, and safety of cannabinoids for chemotherapy-induced nausea and vomiting Medical Cannabis and Cannabinoids, 2 (2)(#issue#), 81	Irrelevant study type
2	Schloss, J.,Brown, D.,Steel, A. (2017). Medicinal cannabis and cancer: A narrative systematic literature review Asia-Pacific Journal of Clinical Oncology, 13 (Supplement 4)(#issue#), 221	Irrelevant study type
2	Sheriff, T.,Lin, M. J.,Dubin, D.,Khorasani, H. (2019). The potential role of cannabinoids in dermatology Journal of Dermatological Treatment., #volume#(#issue#), #Pages#	Irrelevant study type
2	Turna, J.,Patterson, B.,Van Ameringen, M. (2017). Is cannabis treatment for anxiety, mood, and related disorders ready for prime time? Depression and Anxiety, 34(11), 1006-1017	Irrelevant study type
2	Valentino, W. L.,McKinnon, B. J. (2019). What is the evidence for cannabis use in otolaryngology?: A narrative review American Journal of Otolaryngology - Head and Neck Medicine and Surgery, 40(5), 770-775	Irrelevant study type
2	Walsh, Z.,Gonzalez, R.,Crosby, K.,S. Thiessen M,Carroll,	Irrelevant study type

Level	Bibliography	Reason for exclusion
	C.,Bonn-Miller, M. O. (2017). Medical cannabis and mental health: A guided systematic review Clin Psychol Rev, 51(#issue#), 15-29	
2	Wilens, T.,Wong, S. S. (2019). 46.2 Medical Marijuana in Kids: Evidence Sufficient for Legalization? Journal of the American Academy of Child and Adolescent Psychiatry, 58 (10 Supplement)(#issue#), S369	Irrelevant study type
2	Freeman, A. M.,Petrilli, K.,Lees, R.,Hindocha, C.,Mokrysz, C.,Curran, H. V.,Saunders, R.,Freeman, T. P. (2019). How does cannabidiol (CBD) influence the acute effects of delta-9-tetrahydrocannabinol (THC) in humans? A systematic review Neuroscience and Biobehavioral Reviews, 107(#issue#), 696-712	Mixed cannabinoids
2	Kosiba, J. D.,Maisto, S. A.,Ditre, J. W. (2019). Patient-reported use of medical cannabis for pain, anxiety, and depression symptoms: Systematic review and meta-analysis Social Science and Medicine, 233(#issue#), 181-192	No outcome data
2	Akgun, K.,Essner, U.,Seydel, C.,Ziemssen, T. (2019). Daily Practice Managing Resistant Multiple Sclerosis Spasticity With Delta-9-Tetrahydrocannabinol: Cannabidiol Oromucosal Spray: A Systematic Review of Observational Studies Journal of Central Nervous System Disease, 11(no pagination), #Pages#	Only pharmaceutical cannabinoids
2	Hauser, W.,Welsch, P.,Klose, P.,Radbruch, L.,Fitzcharles, M. A. (2019). Efficacy, tolerability and safety of cannabis-based medicines for cancer pain : A systematic review with meta-analysis of randomised controlled trials Der Schmerz, 33(5), 424-436	Only pharmaceutical cannabinoids

Level	Bibliography	Reason for exclusion
2	Lattanzi, S.,Brigo, F.,Trinka, E.,Zaccara, G.,Cagnetti, C.,Del Giovane, C.,Silvestrini, M. (2018). Efficacy and Safety of Cannabidiol in Epilepsy: A Systematic Review and Meta-Analysis Drugs, 78(17), 1791-1804	Only pharmaceutical cannabinoids
2	Walitt, B.,Klose, P.,Fitzcharles, M. A.,Phillips, T.,Hauser, W. (2016). Cannabinoids for fibromyalgia Cochrane Database of Systematic Reviews, 7(#issue#), CD011694	Only pharmaceutical cannabinoids
2	Ali, A. (2016). Cannabis usage in the context of neurological disease: Clinical cases and a review of the literature West Indian Medical Journal, 65 (Supplement 1)(#issue#), 22	Unavailable full-text
2	Amato, L.,Minozzi, S.,Mitrova, Z.,Parmelli, E.,Saulle, R.,Cruciani, F.,Vecchi, S.,Davoli, M. (2017). [Systematic review of safeness and therapeutic efficacy of cannabis in patients with multiple sclerosis, neuropathic pain, and in oncological patients treated with chemotherapy] Epidemiol Prev, 41(5-6), 279-293	Unavailable full-text
2	Carrillo, M. R.,Jennings, G. E.,Le, C.,Dong, A.,Devineni, D.,Sahafi, R.,Goo, H.,Afghani, B. (2016). Use of medical marijuana for treatment of pediatric patients with epilepsy Journal of Investigative Medicine, 64 (1)(#issue#), 200-201	Unavailable full-text
2	De Almeida Pereira, F.,Torres, A. C.,Philadelpho, V. O.,Ornellas, L. I.,Veloso, C. R.,Viana, G. P. M.,Filho, A. D. S. A. (2018). Effects of cannabidiol on the frequency of epileptic seizures: A systematic review. [Portuguese] Revista Brasileira de Neurologia e Psiquiatria, 22(1), 86-100	Unavailable full-text
2	Farzaei, M. H.,Shahpiri, Z.,Bahramsoltani, R.,nia, M. M.,Najafi, F.,Rahimi, R. (2017). Efficacy and Tolerability of Phytomedicines in Multiple Sclerosis Patients: A Review	Unavailable full-text

Level	Bibliography	Reason for exclusion
	CNS Drugs, 31(10), 867-889	
2	Ferber, S. G.,Namdar, D.,Hen-Shoval, D.,Eger, G.,Koltai, H.,Shoval, G.,Shbiro, L.,Weller, A. (2020). The "entourage effect": Terpenes coupled with cannabinoids for the treatment of mood disorders and anxiety disorders Current Neuropharmacology, 18(2), 87-96	Unavailable full-text
2	Fitzcharles, M. A.,Hauser, W. (2019). Cannabis-Based Medicines and Medical Cannabis in Rheumatic Diseases: A Treasure Chest or Pandora's box Current Treatment Options in Rheumatology, 5(4), 258-271	Unavailable full-text
2	Häuser, W.,Petzke, F.,Fitzcharles, M. A. (2018). Efficacy, tolerability and safety of cannabis-based medicines for chronic pain management - An overview of systematic reviews Eur J Pain, 22(3), 455-470	Unavailable full-text
2	Jett, J. (2019). IBS11.03 Cannabis and Lung Cancer Journal of Thoracic Oncology, 14 (10 Supplement)(#issue#), S102	Unavailable full-text
2	Jouanjus, E.,Barreiros, P.,Lapeyre-Mestre, M. (2019). The therapeutic benefits of cannabis and cannabinoids evaluated by phase 3 randomized controlled clinical trials: a systematic review of recent literature European Journal of Clinical Pharmacology, 75 (Supplement 1)(#issue#), S66	Unavailable full-text
2	Kayser, R. R.,Snorrason, I.,Haney, M.,Lee, F. S.,Simpson, H. B. (2019). The Endocannabinoid System: A New Treatment Target for Obsessive Compulsive Disorder? Cannabis and Cannabinoid Research, 4(2), 77-87	Unavailable full-text
2	Lattanzi, S.,Brigo, F.,Cagnetti, C.,Trinka, E.,Silvestrini, M. (2018). Efficacy and Safety of Adjunctive Cannabidiol in	Unavailable full-text

Level	Bibliography	Reason for exclusion
	Patients with Lennox-Gastaut Syndrome: A Systematic Review and Meta-Analysis CNS Drugs, 32(10), 905-916	
2	Likar, R.,Kostenberger, M.,Nahler, G. (2020). Cannabidiol in cancer treatment. [German] Schmerz., #volume#(#issue#), #Pages#	Unavailable full-text
2	Mallaret, M.,Micallef, J.,Fouilhe-Sam Lai, N. (2019). Cannabidiol is bad for you! Fundamental and Clinical Pharmacology, 33 (Supplement 1)(#issue#), 77	Unavailable full-text
2	Mamalis, S.,Sidiropoulou, K.,Pliakou, E.,Passos, I. D.,Mironidou-Tzouveleki, M. (2016). The use of cannabis and cannabinoids for medical purposes Hippokratia, 20 (Supplement 1)(#issue#), 18	Unavailable full-text
2	Moller, J.,Kelber, O.,Nieber, K. (2019). Herbal medicinal products are an important option for the treatment of functional GI diseases in children-a systematic review Planta Medica, 85 (18)(#issue#), 1559	Unavailable full-text
2	Oxentine, H.,Musec, M.,Johnson, T. (2017). Medical marijuana: Can't we all just get a bong? American Journal on Addictions, 26 (3)(#issue#), 277	Unavailable full-text
2	Parekh, T.,Mathew, S.,Goudreau, C.,Lonergan, A.,Piran, P.,Malpe, C. (2017). Awareness of epilepsy risk factors and treatment in a south florida community-an observational study Annals of Neurology, 82 (Supplement 21)(#issue#), S159-S160	Unavailable full-text
2	Pinho, C.,Leitao, M.,Oliveira, A. I. (2016). Cannabis sativa L. and inflammatory bowel disease Atencion Primaria, 48 (Supplement C)(#issue#), 147	Unavailable full-text
2	Sanadgol, N.,Zahedani, S. S.,Sharifzadeh, M.,Khalseh,	Unavailable full-text

Level	Bibliography	Reason for exclusion
	R.,Barbari, G. R.,Abdollahi, M. (2017). Recent Updates in Imperative Natural Compounds for Healthy Brain and Nerve Function: A Systematic Review of Implications for Multiple Sclerosis Curr Drug Targets, 18(13), 1499-1517	
2	Santibanez, R. A.,Sepehry, A. A.,Hsiung, G. Y. R. (2017). Cannabis and Alzheimer's disease: A systematic review of the evidence Alzheimer's and Dementia, 13 (7)(#issue#), P614	Unavailable full-text
2	Shatkin, J. P. (2017). Sleep education and hygiene Journal of the American Academy of Child and Adolescent Psychiatry, 56 (10)(#issue#), S146	Unavailable full-text
2	Wong, S. S.,Wilens, T. E. (2017). Medical uses of cannabinoids in children and adolescents: A systematic review Journal of the American Academy of Child and Adolescent Psychiatry, 56 (10)(#issue#), S295	Unavailable full-text
3	Elliott, J.,DeJean, D.,Clifford, T.,Coyle, D.,Potter, B. K.,Skidmore, B.,Alexander, C.,Repetski, A. E.,Shukla, V.,McCoy, B.,Wells, G. A. (2019). Cannabis-based products for pediatric epilepsy: A systematic review Epilepsia, 60(1), 6-19	As the review by Elliot et al. 2020 represented a repetition of its earlier report in 2019 with few relevant updates, we opted in to examine the more updated version of 2020.
3	Aviram, J.,Samuelly-Leichtag, G. (2017). Efficacy of Cannabis-Based Medicines for Pain Management: A Systematic Review and Meta-Analysis of Randomized Controlled Trials Pain Physician, 20(6), E755-e796	Reference contained inconsistent information and was deemed unnecessary.

Appendix 3. Assessing quality of evidence and risk of bias

AMSTAR2

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

1. Did the research questions and inclusion criteria for the review include the components of PICO?

For Yes:	Optional (recommended)	
☐ Population	☐ Timeframe for follow-up	☐ Yes
☐ Intervention		☐ No
☐ Comparator group		
☐ Outcome		

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?

For Partial Yes:	For Yes:	
The authors state that they had a written protocol or guide that included ALL the following:	As for partial yes, plus the protocol should be registered and should also have specified:	☐ Yes
☐ review question(s)	☐ a meta-analysis/synthesis plan, if appropriate, *and*	☐ Partial Yes
☐ a search strategy	☐ a plan for investigating causes of heterogeneity	☐ No
☐ inclusion/exclusion criteria	☐ justification for any deviations from the protocol	
☐ a risk of bias assessment		

3. Did the review authors explain their selection of the study designs for inclusion in the review?

For Yes, the review should satisfy ONE of the following:	
☐ *Explanation for* including only RCTs	☐ Yes
☐ OR *Explanation for* including only NRSI	☐ No
☐ OR *Explanation for* including both RCTs and NRSI	

4. Did the review authors use a comprehensive literature search strategy?

For Partial Yes (all the following):	For Yes, should also have (all the following):	
☐ searched at least 2 databases (relevant to research question)	☐ searched the reference lists / bibliographies of included studies	☐ Yes
☐ provided keyword and/or search strategy	☐ searched trial/study registries	☐ Partial Yes
☐ justified publication restrictions (e.g. language)	☐ included/consulted content experts in the field	☐ No
	☐ where relevant, searched for grey literature	
	☐ conducted search within 24 months of completion of the review	

5. Did the review authors perform study selection in duplicate?

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	☐ Yes
☐ OR two reviewers selected a sample of eligible studies and achieved good agreement (at least 80 percent), with the remainder selected by one reviewer.	☐ No

6. Did the review authors perform data extraction in duplicate?

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 percent), with the remainder extracted by one reviewer.

☐ Yes
☐ No

7. Did the review authors provide a list of excluded studies and justify the exclusions?

For Partial Yes:

- ☐ provided a list of all potentially relevant studies that were read in full-text form but excluded from the review

For Yes, must also have:

- ☐ Justified the exclusion from the review of each potentially relevant study

☐ Yes
☐ Partial Yes
☐ No

8. Did the review authors describe the included studies in adequate detail?

For Partial Yes (ALL the following):

- ☐ described populations
- ☐ described interventions
- ☐ described comparators
- ☐ described outcomes
- ☐ described research designs

For Yes, should also have ALL the following:

- ☐ described population in detail
- ☐ described intervention in detail (including doses where relevant)
- ☐ described comparator in detail (including doses where relevant)
- ☐ described study's setting
- ☐ timeframe for follow-up

☐ Yes
☐ Partial Yes
☐ No

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?

RCTs

For Partial Yes, must have assessed RoB from

- ☐ unconcealed allocation, *and*
- ☐ lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)

For Yes, must also have assessed RoB from:

- ☐ allocation sequence that was not truly random, *and*
- ☐ selection of the reported result from among multiple measurements or analyses of a specified outcome

☐ Yes
☐ Partial Yes
☐ No
☐ Includes only NRSI

NRSI

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

☐ Yes
☐ Partial Yes
☐ No
☐ Includes only RCTs

10. Did the review authors report on the sources of funding for the studies included in the review?

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

☐ Yes
☐ No

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?

RCTs

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

☐ Yes
☐ No
☐ No meta-analysis conducted

For NRSI

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 NRSI 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 estimates for RCTs and NRSI separately when both were included in the review

☐ Yes
☐ No
☐ No meta-analysis conducted

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?

For Yes:

- ☐ included only low risk of bias RCTs
- ☐ OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.

☐ Yes
☐ No
☐ No meta-analysis conducted

13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?

For Yes:

- ☐ included only low risk of bias RCTs
- ☐ OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results

☐ Yes
☐ No

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 and discussed the impact of this on the results of the review

☐ 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

☐ Yes
☐ No
☐ No meta-analysis conducted

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

☐ Yes
☐ No

Assessment of risk of bias for systematic reviews of original studies using AMSTAR2

Reference	1	2	3	4	5	6	7	8	9 *RCT*	9 *NRSI*	10	11 *RCT*	11 *NRSI*	12	13	14	15	16	Total Score
Boland 2020	Yes	P	Yes	Yes	Yes	Yes	Yes	P	Yes	Only RCT	Yes	No MA	No	No MA	Yes	Yes	No MA	Yes	H
Charernboon 2020	Yes	No	No	No	Yes	Yes	No	P	Yes	Only RCT	No	No MA	No MA	No MA	Yes	Yes	No MA	Yes	CL
de Carvalho 2020	Yes	No	Yes	P	No	No	No	P	No	Only RCT	Yes	No	No	Yes	Yes	No	No	Yes	CL
Elliott 2020	Yes	Yes	No	P	Yes	Yes	Yes	No	Only NRSI	P	Yes	No MA	No MA	No MA	Yes	No	No MA	Yes	CL
Hindocha 2020	Yes	P	Yes	No	Yes	Yes	No	No	Yes	Yes	Yes	No MA	No MA	No MA	Yes	No	No MA	Yes	CL
Johal 2020	Yes	P	Yes	P	Yes	Yes	No	No	Yes	Only RCT	No	Yes	No	Yes	Yes	Yes	Yes	Yes	CL
Khan 2020	No	No	Yes	P	Yes	Yes	No	No	No	No	No	No MA	No MA	No MA	No	No	No	Yes	CL
Mun 2020	Yes	P	Yes	P	Yes	Yes	No	P	No	Only RCT	No	No MA	No MA	No MA	Yes	Yes	No MA	Yes	CL
Rabgay 2020	Yes	P	Yes	P	Yes	Yes	Yes	P	Yes	Only RCT	Yes	Yes	No	No	No	No	No	Yes	CL
Sarris 2020	Yes	No	Yes	P	No	No	No	No	No	No	Yes	No MA	No MA	No MA	No	Yes	No MA	Yes	CL
Amaniti 2019	Yes	P	Yes	P	Yes	Yes	No	P	Yes	Only RCT	Yes	No MA	No MA	No MA	Yes	Yes	No MA	Yes	CL
Black 2019	Yes	P	Yes	P	Yes	Yes	Yes	Yes	Yes	P	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	L
Bonaccorso 2019	Yes	No	No	No	Yes	Yes	No	P	No	Only RCT	No	No MA	No MA	No MA	Yes	No	No MA	Yes	CL
Calapai 2019	No	No	No	No	No	No	No	P	P	Only RCT	No	No MA	No MA	No MA	No	No	No MA	Yes	CL
Khoury 2019	No	No	No	P	Yes	No	No	P	No	No	Yes	No MA	No MA	No MA	Yes	No	No MA	Yes	CL
Millar 2019	Yes	No	Yes	No	Yes	Yes	No	P	Yes	No	Yes	No	No	No	Yes	Yes	No	Yes	CL

Reference	1	2	3	4	5	6	7	8	9 *RCT*	9 *NRSI*	10	11 *RCT*	11 *NRSI*	12	13	14	15	16	Total Score
												MA	MA	MA			MA		
Orsolini 2019	No	No	No	P	Yes	Yes	No	P	No	No	Yes	No MA	No MA	No MA	No	No	No MA	Yes	CL
Wang 2019	Yes	No	Yes	P	Yes	Yes	No	P	Yes	Only RCT	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	CL
Yanes 2019	Yes	No	Yes	No	Yes	Yes	No	No	No	Only RCT	No	Yes	No	No	No	Yes	No	No	CL
Advani 2018	No	P	Yes	P	Yes	Yes	No	No	Yes	Only RCT	No	No MA	No MA	No MA	No	No	No MA	Yes	CL
Behm 2018	No	No	Yes	P	No	No	No	Yes	P	Only RCT	No	No MA	No MA	No MA	Yes	No	No MA	Yes	CL
De Vita 2018	No	Yes	Yes	No	No	No	No	No	Yes	Only RCT	No	Yes	No MA	No	Yes	Yes	Yes	Yes	CL
Ishak 2018	No	No	No	No	Yes	No	No	No	No	No	Yes	No MA	No MA	No MA	No	No	No MA	Yes	CL
Kafil 2018	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Only RCT	Yes	No MA	No MA	No MA	Yes	No	No MA	Yes	L
Mucke 2018	Yes	P	Yes	No	Yes	Yes	Yes	No	Yes	Only RCT	Yes	Yes	No MA	No	Yes	Yes	No	Yes	CL
Mucke 2018a	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Only RCT	Yes	Yes	No MA	Yes	Yes	Yes	Yes	Yes	H
Stockings 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	H
Stockings 2018a	Yes	Yes	Yes	P	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	L
Torres-Moreno 2018	Yes	P	Yes	P	Yes	Yes	P	Yes	Yes	Only RCT	Yes	Yes	No MA	Yes	Yes	Yes	Yes	Yes	CL
Zhang 2018	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Only RCT	No	No MA	No MA	No MA	Yes	Yes	No MA	Yes	CL
da Rovare 2017	Yes	No	Yes	No	Yes	Yes	No	Yes	Yes	Only RCT	No	No	No MA	Yes	Yes	No	Yes	No	CL
Goldenberg 2017	No	No	No	P	No	Yes	No	P	P	No	No	No	No	No	No	No	No	Yes	CL
Lim 2017	No	No	Yes	P	No	No	No	No	Yes	Only RCT	No	No MA	No MA	No MA	Yes	No	No MA	No	CL

Reference	1	2	3	4	5	6	7	8	9 *RCT*	9 *NRSI*	10	11 *RCT*	11 *NRSI*	12	13	14	15	16	Total Score
Norton 2017	Yes	Yes	Yes	No	No	Yes	Yes	Yes	P	P	No	No MA	No MA	No MA	Yes	Yes	No MA	Yes	CL
Nugent 2017	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No	Yes	CL
Osborne 2017	No	No	No	P	No	No	Yes	P	No	No	No	No MA	No MA	No MA	No	No	No MA	Yes	CL
Stevens 2017	Yes	Yes	Yes	P	Yes	Yes	No	Yes	Yes	Only RCT	No	No MA	No MA	No MA	Yes	Yes	No MA	Yes	CL
Wong 2017	No	No	No	P	No	Yes	No	No	No	No	No	No MA	No MA	No MA	Yes	No	No MA	Yes	CL
Fitzcharles 2016	No	No	Yes	P	No	Yes	No	P	Yes	Only RCT	No	No MA	No MA	No MA	Yes	No	No MA	No	CL
Gruenbaum 2016	No	No	Yes	P	Yes	Yes	No	No	No	No	No	No MA	No MA	No MA	No	No	No MA	No	CL
Merlin 2016	No	No	Yes	P	Yes	Yes	No	P	No	Only RCT	No	No MA	No MA	No MA	Yes	No	No MA	No	CL
Wilkinson 2016	No	No	Yes	No	No	No	No	No	No	P	No	No MA	No MA	No MA	No	No	No MA	Yes	CL

CL: critically low; **H:** high; **L:** low; **MA:** meta-analysis; **P:** partial

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Quality Assessment Tool – Review Articles

Instructions for completion:
Please refer to the attached dictionary for definition of terms and instructions for completing each section. For each criteria, score by placing a check mark in the appropriate box.

First Author: _____
Year: _____
Journal: _____
Reviewer: _____

CRITERION	YES	NO
01. Did the authors have a clearly focused question [population, intervention (strategy), and outcome(s)]?		
02. Were appropriate inclusion criteria used to select primary studies?		
03. Did the authors describe a search strategy that was comprehensive? *Circle all strategies used:* ▪ health databases ▪ psychological databases ▪ social science databases ▪ educational databases ▪ other ▪ handsearching ▪ key informants ▪ reference lists ▪ unpublished		
04. Did search strategy cover an adequate number of years?		

For questions 5, 6, and 8, please choose the column relating to the appropriate methodology. Strike a line through the column that does not apply.

05. Quantitative reviews: Did the authors describe the level of evidence in the primary studies included in the review? ▪ Level I → RCTs only ▪ Level II → non-randomized, cohort, case-control ▪ Level III → uncontrolled studies	05. Qualitative reviews: Do the authors provide a clear description of the range of methods in each of the primary studies included in the review?		
06. Quantitative reviews: Did the review assess the methodological quality of the primary studies, including: *(Minimum requirement: 4/7 of the following)* ▪ Research design ▪ Study sample ▪ Participation rates ▪ Sources of bias (confounders, respondent bias) ▪ Data collection (measurement of independent/dependent variables) ▪ Follow-up/attrition rates ▪ Data analysis	06. Qualitative reviews: Did the review assess the methodological quality of the primary studies, including: *(Minimum requirement: 4/7 of the following)* ▪ Suitability of methodology/paradigm to the research question ▪ Sampling (selection of participants / settings / documentation) ▪ Clear description of context, data collection and data analysis ▪ Rigor: → Audit trail → Some coding by 2 or more coders, if appropriate → Deviant case analysis (negative cases) → Respondent validation (member checking) ▪ Triangulation ▪ Reflexivity (researcher and research process) ▪ Relevance (credibility, consistency, applicability, transferability)		
07. Are the results of the review transparent?			
08. Quantitative reviews: Was it appropriate to combine the findings of results across studies?	08. Qualitative reviews: Is there a description of how reviewers determined results were similar enough across studies to compare or combine them?		
09. Were appropriate methods used for combining or comparing results across studies?			
010. Do the data support the author's interpretation?			
	TOTAL SCORE:		

Quality Assessment Rating: (Circle one)
Strong (total score 8 – 10) Moderate (total score 5 – 7) Weak (total score 4 or less)

Assessment of risk of bias of systematic reviews of systematic reviews using the Health Evidence Tool

	Q1. Did the authors have a clearly focused question [population, intervention (strategy), and outcome(s)]?	Q2. Were appropriate inclusion criteria used to select primary studies?	Q3. Did the authors describe a search strategy that was comprehensive?	Q4. Did search strategy cover an adequate number of years?	Q5. Did the authors describe the level of evidence in the primary studies included in the review?	Q6. Did the review assess the methodological quality of the primary studies, including:	Q7. Are the results of the review transparent?	Q8. Was it appropriate to combine the findings of results across studies?	Q9. Were appropriate methods used for combining or comparing results across studies?	Q10. Do the data support the author's interpretation?	Final Score	Final Appraisal
Hoch 2019	1	1	1	1	1	1	1	1	1	1	10	Strong
Allan 2018	0	1	1	1	1	1	1	1	1	1	9	Strong
Nielsen 2018	1	1	0	1	1	1	1	1	1	1	9	Strong
Hauser 2017	1	1	1	1	1	1	1	1	1	1	10	Strong
Houze 2017	1	1	0	1	1	1	1	1	1	1	9	Strong
O'Neil 2017	1	1	1	1	1	0	0	0	1	1	7	Moderate
Tafelski 2017	1	1	0	1	1	1	1	1	1	1	9	Strong

Appendix 4: Reviews sorted by indication and cannabis formulation*, **

* as reported by the original authors

** Cannabis type (MC: medical cannabis, Unspecified: cannabis reported without any specifications, Plant: plant-based cannabinoids, Synthetic: synthetic cannabinoids)

Study	Cannabis type	Cannabis formulation	Indications
Black 2019	MC	Cannabis sativa	ADHD
Khan 2020	Unspecified	CBD	ADHD
Lim 2017	Unspecified	THC	ALS
Wilkinson 2016	Unspecified	THC	Alzheimer's disease (agitation)
Hoch 2019	Unspecified	THC	Alzheimer's disease (dementia)
Lim 2017	Unspecified	THC	Anorexia nervosa
Black 2019	MC	Cannabis sativa	Anxiety
Black 2019	MC	CBD	Anxiety
Lim 2017	Unspecified	CBD	Anxiety
Black 2019	MC	THC	Anxiety
Lim 2017	Unspecified	THC	Anxiety
Lim 2017	Unspecified	THC 0.5 mg/kg : CBD 1 mg/kg	Anxiety
Black 2019	MC	THC-CBD	Anxiety
Calapai 2019	Unspecified	CBD	Anxiety (SAD)
Khan 2020	Unspecified	CBD	Anxiety (SAD)
Khoury 2019	Unspecified	CBD	Anxiety (SAD)
Millar 2019	Synthetic	CBD	Anxiety (SAD)

Study	Cannabis type	Cannabis formulation	Indications
Sarris 2020	Unspecified	CBD	Anxiety (SAD)
Khan 2020	Unspecified	CBD	ASD
Khan 2020	Unspecified	CBD	Bipolar disorders
Khoury 2019	Unspecified	CBD	Bipolar disorders
Sarris 2020	Unspecified	CBD	Bipolar disorders
Hauser 2017	Unspecified	THC	Cancer
Advani 2018	MC	CE	Cancer (cachexia)
Wang 2019	MC	CE	Cancer (cachexia)
Advani 2018	Unspecified	THC	Cancer (cachexia)
Wang 2019	Unspecified	THC	Cancer (cachexia)
Wang 2019	Unspecified	THC:CBD	Cancer (cachexia)
Yanes 2019	THC	Capsule	Cancer (pain)
Boland 2020	Unspecified	THC	Cancer (pain)
Boland 2020	Unspecified	THC : CBD	Cancer (pain)
Hauser 2017	Unspecified	THC	Cancer (pain)
Millar 2019	Synthetic	CBD	Cell transplant
Allan 2018	Unspecified	Medical cannabinoids	CINV
Tafelski 2016	Unspecified	THC	CINV
Wong 2017	Unspecified	THC	CINV
Osborne 2017	Unspecified	CBD	Cognition
Osborne 2017	Unspecified	THC	Cognition

Study	Cannabis type	Cannabis formulation	Indications
Osborne 2017	Unspecified	THC-CBD	Cognition
Millar 2019	Synthetic	CBD	Crohn's disease
Hauser 2017	Unspecified	THC	Crohn's disease
Norton 2017	MC	Cannabis	Crohn's disease (pain)
Norton 2017	MC	Marijuana	Crohn's disease (pain)
Charernboon 2020	Unspecified	THC	Dementia
Ishak 2018	Unspecified	Cannabinoids	Depression
Black 2019	MC	Cannabis sativa	Depression
Black 2019	MC	THC	Depression
Black 2019	MC	THC-CBD	Depression
de Carvalho 2020	MC	Cannabis	Epilepsy
de Carvalho 2020	Unspecified	CBD	Epilepsy
Stockings 2018	Unspecified	CBD	Epilepsy
Wong 2017	Unspecified	CBD	Epilepsy
Wong 2017	MC	CBD enriched OCE	Epilepsy
Stockings 2018	Unspecified	CE	Epilepsy
Stockings 2018	MC	Hemp-based plant extract (Elixinol)	Epilepsy
Stockings 2018	Unspecified	THC : CBD	Epilepsy
Stockings 2018	Unspecified	THCA	Epilepsy

Study	Cannabis type	Cannabis formulation	Indications
Wong 2017	MC	OCE	Epilepsy
Millar 2019	Synthetic	CBD	Epilepsy (adults)
Stockings 2018	MC	MC	Epilepsy (adults)
Elliott 2020	Unspecified	CBD	Epilepsy (pediatric)
Millar 2019	Synthetic	CBD	Epilepsy (pediatric)
Elliott 2020	Unspecified	CBD : THC	Epilepsy (pediatric)
Stockings 2018	MC	MC	Epilepsy (pediatric)
Millar 2019	Synthetic	CBD	Fatty liver disease
Hauser 2017	Unspecified	FAAH hydrolase inhibitor	Fibromyalgia
Goldenberg 2017	MC	MC	Health-related quality of life
Ishak 2018	Unspecified	Cannabinoids	HIV (anxiety)
Ishak 2018	Unspecified	Cannabinoids	HIV (depression)
Ishak 2018	Unspecified	Cannabinoids	HIV (muscle pain)
Ishak 2018	Unspecified	Cannabinoids	HIV (neuropathy)
Johal 2020	MC	Cannabis	HIV (sensory neuropathy)
Amaniti 2019	MC	Cannabis cigarettes	HIV (sensory neuropathy)
Johal 2020	MC	Cannabis	HIV sensory neuropathy
Hauser 2017	Unspecified	THC	HIV/AIDS
Lim 2017	Unspecified	CBD	Huntington's disease
Millar 2019	Synthetic	CBD	Huntington's disease

Study	Cannabis type	Cannabis formulation	Indications
Bonaccorso 2019	Unspecified	CBD	Huntington's disease
Khan 2020	Unspecified	CBD	Insomnia
Sarris 2020	Unspecified	CBD	Insomnia
Nielsen 2018	Unspecified	THC : CBD	MS (ataxia and tremor)
Torres-Moreno 2018	MC	Cannabis sativa	MS (bladder dysfunction)
Nielsen 2018	Unspecified	THC	MS (bladder function) *no cl recom*
Nielsen 2018	Unspecified	THC : CBD	MS (bladder function) *no cl recom*
Nielsen 2018	MC	Cannabis sativa	MS (disability)
Nielsen 2018	Unspecified	THC : CBD	MS (disability)
Behm 2018	MC	Cannabis cigarettes	MS (gait disorders)
Behm 2018	Unspecified	CE-THC	MS (gait disorders)
Yanes 2019	THC	Cigarettes	MS (pain)
Nielsen 2018	MC	Cannabis sativa	MS (pain)
Torres-Moreno 2018	Plant	Cannabis sativa	MS (pain)
Nielsen 2018	Unspecified	CBD	MS (pain)
Nielsen 2018	Unspecified	THC	MS (pain)
Nielsen 2018	Unspecified	THC : CBD	MS (pain)
Nielsen 2018	MC	Cannabis sativa	MS (QOL)
Nielsen 2018	Unspecified	THC : CBD	MS (QOL)
Nielsen 2018	Unspecified	THC	MS (sleep)

Study	Cannabis type	Cannabis formulation	Indications
Nielsen 2018	Unspecified	CBD	MS (sleep) *no cl recom*
Nielsen 2018	Unspecified	CBD: THC	MS (sleep) *no cl recom*
da Rovare 2017	MC	A whole-plant CE (1 THC : 1 CBD)	MS (spasticity)
Johal 2020	MC	Cannabinoids	MS (spasticity)
Johal 2020	MC	Cannabis	MS (spasticity)
Johal 2020	MC	Cannabis	MS (spasticity)
da Rovare 2017	MC	Cannabis cigarettes	MS (spasticity)
Nielsen 2018	MC	Cannabis sativa	MS (spasticity)
Torres-Moreno 2018	Plant	Cannabis sativa	MS (spasticity)
da Rovare 2017	MC	CE (2.5 mg THC: 1.25 mg CBD)	MS (spasticity)
Allan 2018	Unspecified	Medical cannabinoids	MS (spasticity)
Nielsen 2018	Unspecified	THC	MS (spasticity)
Nielsen 2018	Unspecified	THC : CBD	MS (spasticity)
da Rovare 2017	MC	Whole-plant CE (2.5 mg THC : 0.9 mg CBD)	MS (spasticity)
Hauser 2017	Unspecified	FAAH hydrolase	Osteoarthritis

Study	Cannabis type	Cannabis formulation	Indications
		inhibitor	
Ishak 2018	Unspecified	Cannabinoids	Pain
da Rovare 2017	MC	Cannabis cigarettes	Pain
Yanes 2019	MC	MC/CE	Pain
Stevens 2017	Unspecified	THC	Pain, acute
Houze 2017	MC	Cannabis	Pain, chronic
Millar 2019	Synthetic	CBD	Pain, chronic
Nugent 2017	MC	THC	Pain, chronic
Nugent 2017	Unspecified	THC	Pain, chronic
Mun 2020	Unspecified	Cannabinoids	Pain, chronic non-cancer
Mun 2020	MC	Cannabis	Pain, chronic non-cancer
Stockings 2018a	MC	Cannabis sativa	Pain, chronic non-cancer
De Vita 2018	MC	Plant-based cannabis	Pain, chronic
De Vita 2018	Synthetic	AZD1940	Pain, experimental
De Vita 2018	Synthetic	HU210	Pain, experimental
De Vita 2018	Unspecified	THC	Pain, experimental
Stockings 2018a	MC	Cannabis sativa	Pain, fibromyalgia
Stockings 2018a	MC	Cannabis sativa	Pain, IBD
Stockings 2018a	MC	Cannabis sativa	Pain, neuropathic
Allan 2018	Unspecified	Medical cannabinoids	Pain, neuropathic

Study	Cannabis type	Cannabis formulation	Indications
Hauser 2017	MC	Medical marijuana	Pain, neuropathic
Rabgay 2020	MC	SCT	Pain, neuropathic
Yanes 2019	THC	Smoke	Pain, neuropathic
Hauser 2017	Unspecified	THC	Pain, neuropathic
Mucke 2018	MC	Herbal cannabis	Pain, neuropathic (adults)
Hauser 2017	Unspecified	FAAH hydrolase inhibitor	Pain, neuropathic (chemotherapy)
Merlin 2016	MC	Cannabis	Pain, neuropathic (HIV/AIDS)
Johal 2020	MC	Cannabis	Pain, postoperative/ nociceptive
Rabgay 2020	MC	SCET	Pain, postoperative/ nociceptive
Rabgay 2020	Unspecified	THC	Pain, postoperative/ nociceptive
Yanes 2019	THC	Capsule	Pain, postoperative/ nociceptive
Hauser 2017	Unspecified	THC	Pain, visceral
Hauser 2017	Unspecified	THC	Palliative care (cancer)
Mucke 2018	Unspecified	THC (2,5 mg, herbal)	Palliative care (cancer)
Mucke 2018	Unspecified	THC : CB (2,5 mg:1 mg, herbal)	Palliative care (cancer)
Mucke 2018	MC	Herbal Cannabis (0.9 g and 3,95% THC)	Palliative care (HIV/AIDS)

Study	Cannabis type	Cannabis formulation	Indications
Hauser 2017	Unspecified	THC	Palliative care (HIV/AIDS)
Lim 2017	Unspecified	CBD	Parkinson's disease
Millar 2019	Synthetic	CBD	Parkinson's disease
Bonaccorso 2019	Unspecified	CBD	Parkinson's disease
Lim 2017	Unspecified	THC 0.5 mg:CBD 1.25 mg	Parkinson's disease
Bonaccorso 2019	MC	THC	Personality disorders
Bonaccorso 2019	MC	THC-CBD	Personality disorders
Black 2019	MC	Cannabis sativa	Psychosis
Black 2019	MC	CBD	Psychosis
Bonaccorso 2019	Unspecified	CBD	Psychosis
Black 2019	MC	THC	Psychosis
Khan 2020	Unspecified	CBD	Psychosis (Parkinson's disease))
O'Neil 2017	MC	Cannabis	PTSD
Sarris 2020	MC	Cannabis	PTSD
Wilkinson 2016	MC	Cannabis	PTSD
Hindocha 2020	MC	Cannabis resin	PTSD
Hindocha 2020	Unspecified	CBD	PTSD
Khan 2020	Unspecified	CBD	PTSD
Orsolini 2019	Unspecified	CBD	PTSD
Wong 2017	Unspecified	CBD	PTSD

Study	Cannabis type	Cannabis formulation	Indications
Hindocha 2020	MC	Herbal cannabis	PTSD
O'Neil 2017	MC	Plant-based cannabis	PTSD
Hindocha 2020	Unspecified	THC	PTSD
Orsolini 2019	Unspecified	THC	PTSD
Wilkinson 2016	Unspecified	THC	PTSD
Orsolini 2019	MC	THC	PTSD
Orsolini 2019	MC	THC-CBD	PTSD
O'Neil 2017	Synthetic	Cannabis	PTSD
Lim 2017	Unspecified	CBD	Rheumatic diseases
Fitzcharles 2016	Unspecified	PF-04457845	Rheumatic diseases
Hauser 2017	Unspecified	THC	Rheumatic diseases
Hauser 2017	Unspecified	FAAH hydrolase inhibitor	Rheumatoid arthritis
Hoch 2019	Unspecified	CBD	SAD
Calapai 2019	Unspecified	CBD	Schizophrenia
Hoch 2019	Unspecified	CBD	Schizophrenia
Khoury 2019	Unspecified	CBD	Schizophrenia
Millar 2019	Synthetic	CBD	Schizophrenia
Khan 2020	Unspecified	CBD	Schizophrenia
Sarris 2020	Unspecified	CBD	Schizophrenia
Hoch 2019	Unspecified	CBD	Schizophrenia (chronic)

Study	Cannabis type	Cannabis formulation	Indications
Millar 2019	Synthetic	CBD	Sleep disturbance
Black 2019	MC	Cannabis sativa	Tourette syndrome/tics
Khan 2020	Unspecified	CBD	Tourette syndrome/tics
Black 2019	MC	THC	Tourette syndrome/tics
Hoch 2019	Unspecified	THC	Tourette syndrome/tics
Lim 2017	Unspecified	THC	Tourette syndrome/tics
Wilkinson 2016	Unspecified	THC	Tourette syndrome/tics
Wong 2017	Unspecified	THC	Tourette syndrome/tics
Zhang 2018	Unspecified	THC	Tourette syndrome/tics
Gruenbaum 2016	MC	Marijuana	Traumatic brain injury
Millar 2019	Synthetic	CBD	Type II DM
Kafil 2018	MC	Cannabis cigarettes	Ulcerative colitis
Kafil 2018	Unspecified	CBD	Ulcerative colitis
Norton 2017	MC	Cannabis	Ulcerative colitis (pain)
Norton 2017	MC	Marijuana	Ulcerative colitis (pain)

Appendix 5: Major evidence for prescribing cannabis and non-pharmaceutical cannabinoids using evidence from major grey literature

Source	Year	Agent	Indication	Level of evidence
CADTH (85)	2020	Cannabis (oral) CBD	Pediatric epilepsy	Limited
		Cannabis (5% oil formulation containing CBD:THC as 20:1 or 6:1)	Reducing spasticity, sleep difficulties, pain, and improving quality of life relative to baseline in pediatric patients with severe complex motor disorder	Limited
		Medical cannabis	Improving rigidity and cognitive scores, and reducing agitation, disinhibition, irritability, aberrant behavior, and nocturnal behavior disorders as well as aberrant vocalization and resting care in patients with dementia	Low quality
		Cannabis (smoked) THC (oral)	Reducing some PTSD	Low quality
CADTH (86)	2019	Cannabis-based medicines	Chronic neuropathic pain and non-cancer pain	Possible
		Cannabis-based medicines	Fibromyalgia, musculoskeletal pain, headache, rheumatoid arthritis, osteoarthritis, Crohn's disease, and multiple sclerosis.	Inconsistent
CADTH (87)	2019a	Medical cannabis / cannabinoids	Refractory cancer-related/palliative pain (to be considered if two or more other prescribed analgesics have failed, with careful consideration of risks versus benefits, and to be prescribed as an adjunct to other analgesics)	Weak evidence / Alternative option

Appendix 6: Reported adverse events with cannabis and non-pharmaceutical cannabinoids

Review	Formulation	Adverse Events
Boland 2020	THC, THC:CBD, pharmaceutical	Cannabinoids (THC, THC:CBD, and some pharmaceutical) had a higher risk of adverse events when compared with placebo, especially somnolence (OR 2.69 (1.54 to 4.71), p<0.001) and dizziness (OR 1.58 (0.99 to 2.51), p=0.05).
Charernboon 2020	THC	Two studies of THC demonstrated no significant differences for adverse events between THC and placebo (eg. somnolence, dizziness, falls, or europhic mood).
de Carvalho 2020	Cannabis, CBD	Meta-analyses conducted for AEs determining that CBD is safe. Medicinal CNB is as safe as CBD, though only at low THC levels. Adverse events were more prevalent under short-term comparedwith long-term CBD treatment, suggesting lower AE profiles during long-term treatment. Weight loss was the only AE found to be significantly higher for CBDs compared to cannabis.
Elliott 2020	CBD, CBD:THC	Increased risk of gastrointestinal adverse events in children that received a cannabis-based product (CBD) compared to placebo.
Hindocha 2020	Herbal cannabis, cannabis resin, THC, CBD, CBD oil	For THC, no serious adverse events reported in studies. No additional details provided for CBD or whole plant cannabis products in terms of AEs.

Review	Formulation	Adverse Events
Johal 2020	Cannabis (inhaled), cannabinoids	Compared with placebo, cannabinoids were associated with a similar risk of serious AE; however there were a greater number of non-serious treatment related AEs reported for cannabinoids, due largely to events such as dizziness, throat discomfort, asthenia, fatigue, drowsiness, dry mouth, increased appetite, hallucinations, nausea, and refractory spasticity (results described for pharmaceutical and non-pharmaceutical cannabis combined).
Khan 2020	CBD	For schizophrenia and psychosis, no adverse events reported. For cannabis related disorders, no adverse events reported. For other disorders (ADHD, ASD, PTSD) adverse events such as muscular seizures and spasms, somnolence and changes in appetite, fatigue, and sexually inappropriate behavior in a patient with developmental disorder, mild sedation, and mild xerostomia were reported (results not reported by cannabis type).
Mun 2020	Cannabis, cannabinoids	NR
Rabgay 2020	Cannabis (standardized dried)	The analysis results showed statistically significant incidence of euphoria compared with placebo: standardized cannabis with THC (7% of THC; relative risk [RR] 1.74, 95% CI 1.13 to 2.267), THC/CBD (RR 3.14, 95% CI 1.39 to 7.09), and THC (RR 2.98, 95% CI, 1.34 to 6.62)
Sarris 2020	Cannabis, CBD	Occcasional adverse effects revealed in clinical trials include co-ordination problems, dizziness, disorientation, euphoria, drowsiness or fatigue, dry

Review	Formulation	Adverse Events
		mouth, nausea and gastrointestinal upsets (results described for pharmaceutical and non-pharmaceutical cannabis in combination).
Amaniti 2019	Cannabis cigarettes	Amoung the two cannabis studies included, one study reported confusion, dizziness, nausea, significantly more frequent in cannabis group ($p < 0.01$), and the other reported greater frequency of concentration difficulties, fatigue, sleepiness or sedation, increased duration of sleep, reduced salivation, and thirst in cannabis week than placebo week.
Black 2019	Cannabis sativa, cannabis resin, CBD extract, Marijuana	No significant increases in the number of people having adverse events or withdrawing compared with active and placebo comparators for CBD or medical cannabis.
Bonaccorso 2019	CBD, THC	No side effects other than sedation has been reported throughout the studies for CBD. However, further study to assess its impact on suicidal ideation are needed, and the risk of gastrointestinal adverse events; possible alteration in liver function tests; and drug interactions have recently been emphasized.
Calapai 2019	CBD	CBD was well tolerated, and rates of adverse events were similar between the CBD and placebo groups in one of the included studies. No information on adverse events or safety reported for other studies.
Hoch 2019	CBD, THC	Side effects can occur, but severe AEs were mentioned in single cases only.

Review	Formulation	Adverse Events
(55)		No adverse effects have been reported for cannabidiol as treatment for mental disorders. Results for non-pharmaceutical THC not discussed.
Khoury 2019 (27)	CBD	AEs were not always carefully detailed in the studies; when reported, they were insignificant or less intense than the comparative treatment (statement based on mix of pharmaceutical and non-pharmaceutical AEs, including CBD). The most frequently reported AEs are sedation and dizziness.
Millar 2019 (28)	CBD	Mild to moderate adverse events were reported in some studies included in review, while CBD was well tolerated in others. No summary statement explicitly provided by authors.
Orsolini 2019 (29)	THC, CBD	Despite improvements in PTSD symptomatology, there are demonstrable adverse health risks associated with cannabis use, as chronic recreational use is associated with dependence and THC-related cognition dysfunction and risk of psychosis
Wang 2019 (30)	CE, THC, THC:CBD	Treatment related AEs the present meta-analysis included nausea, fatigue, pain, anemia, dizziness, dyspnea, diarrhea, obstipation, somnolence, raised γ-GT, hypercalcemia, hypotension, and so on. A total of 441 patients had 607 AEs (496 in the cannabinoids and 111 in the placebo groups) in the three studies.
Yanes 2019	MC/CE	NR

Review	Formulation	Adverse Events
Advani 2018	CE, THC	NR
Behm 2018	CE, THC cannabis cigarettes	NR
De Vita 2018	Plant-based cannabis cigarettes with THC-specific dosages, THS standardized CE, THC	Authors discuss that psychotropic adverse effects also remain a salient concern among those considering cannabis-based medicines for pain. No other discussion of adverse events or safety.
Ishak 2018	Cannabis	NR
Kafil 2018	Cannabis, CBD	Amoung the two studies included, one study on CBD reported significantly higher risk of adverse events, however the events were mild or moderate in severity. Common adverse events included dizziness, disturbance in attention, headache, nausea and fatigue. The second study, conducted on cannabis as the intervention, reported no adervse events.
Mucke 2018	Herbal Cannabis Marijuana cigarettes	Tolerability (measured by the number of withdrawals because of adverse events) did not differ significantly in cancer (RD: 1.15 [0.80; 1.66]; P = 0.46) and HIV patients (RD: 1.87 [0.60; 5.84]; P = 0.28). Safety did not differ in cancer (RD: 1.12 [0.86; 1.46]; P = 0.39) or HIV patients (4.51 [0.54; 37.45]; P = 0.32) although there was large uncertainty about the latter reflected in the width of the CI

Review	Formulation	Adverse Events
		(statement for both pharmaceutical and non-pharmaceutical cannabis).
Mucke 2018a	Herbal cannabis	There was no difference between all cannabis-based medicines pooled together and placebo in the frequency of serious adverse events (low-quality evidence) (herbal cannabis, THC/CBD oromucosal spray, synthetic or plant-based THC). Herbal cannabis (two studies with 152 participants) was not different to placebo. RD was 0.00 (95% CI -0.08 to 0.08) (P value 0.71).
Nielsen 2018	MC, cannabinoids, whole plant extract	Adverse effects were consistently rated as more common in study participants who received cannabinoids than placebo. However, no specific cannabinoid was identified as having a more serious adverse effect profile than another. Review findings were inconsistent on the effect of the addition of CBD to THC on the adverse effect profile of THC. Some reviews identified evidence of an attenuation of adverse effects related to THC, while other reviews identified greater adverse effects from THC:CBD combinations than THC.
Stockings 2018	MC, CE, CBD, THC:CBD, THCA	There was a greater likelihood of an AE in the intervention group compared to placebo when all studies were pooled together (pharmaceutical and non-pharmaceutical) (RCT pooled RR: 1.24 [95%CI: 1.13-1.36]) overall. For MC, CE, and THC:CBD, there was insufficient evidence to determine AEs. For CBD, mild-to-moderate AEs were likely in the intervention groups.

Review	Formulation	Adverse Events
Stockings 2018a	Cannabis sativa, THC, CBD, THC-HS, CT-3	Compared with placebo groups, patients receiving cannabinoids were more likely to report individual AEs such as dizziness (OR 5.52, 95% CI 4.47-6.83), cognitive attention or disturbance (OR 5.67, 95% CI 2.72-11.79), and confusion and disorientation (OR 5.35, 95% CI 2.31-12.39).
Torres-Moreno 2018	Cannabis sativa plant extract	In the total adverse events analysis, there was a higher risk of withdrawals due to adverse events in the CE (RR, 3.11 patient-years; 95%CI, 1.54-6.28 patient-years) group.
Zhang 2018	THC	Tiredness, dry mouth, dizziness, and muzziness in 41.67% (5/12) of patients in single included studied on THC.
da Rovare 2017	Cannabis cigarettes, whole-plant CE (THC:CBD)	Cannabinoid users experienced an approximately three-fold increased risk of dizziness, somnolence and dry mouth, and an approximately two-fold increased risk of nausea, relative to placebo. These adverse events are significantly more tolerable than those related to the use of the current spasticity therapy, such as respiratory depression, ataxia and hallucinations (result reported as combined for pharmaceutical and non-pharmaceutical).
Goldenberg 2017	MC	Limted data from original studies for AEs, as reported by authors.
Hauser	Medical marijuana, FAAH inhibitor, THC	Two SRs found no statistically significant increase in the incidence of serious adverse events for cannabinoids in comparison with placebo in

Review	Formulation	Adverse Events
	cigarettes	neuropathic or cancer pain (THC cigarettes). The 3 prospective observational studies on medical marijuana and THC/CBD spray detected frequent central nervous and psychiatric adverse events. Overall, authors reported cannabinoid use in pain management and palliative medicine may cause relevant central nervous system (e.g. dizziness) and psychiatric adverse events (e.g. confusion, psychosis).
Houze 2017	Cannabis	Occurrence of adverse effects was particularly frequent with cannabis preparations among first-time cannabinoid users and included symptoms such as euphoria, dysphoria, alterations motor or cognitive function.
Lim 2017	THC, CBD, THC-CBD cannador	Cannabinoids appear to be well-tolerated in these trials. The common short-term effects included dry mouth, dizziness, tiredness, and headache. Indeed, reviews that discussed the adverse effect of cannabis administration have reported that cannabis or cannabinoid administration was associated with a greater risk of non-serious adverse events (when considering both pharmaceutical and non-pharmaceutical cannabis products).
Norton 2017	Cannabis	In one selected study, authors recommended caution in the use of cannabis by CD patients until further studies explore effectiveness and safety. No other discussion of adverse events or safety.

Review	Formulation	Adverse Events
Nugent 2017	THC	Among general populations, limited evidence suggests that cannabis is associated with an increased risk for adverse mental health effects.
O'Neil 2017	Plant-based cannabis, synthetic cannabis	As reported by authors: We found moderate-strength evidence that light to moderate cannabis smoking does not adversely affect lung function over about 20 years. We found low-strength evidence that light to moderate cannabis use is not associated with lung cancer or head and neck cancer diagnoses independent of tobacco use. We found insufficient evidence examining whether cannabis use is associated with cardiovascular events over the long term. We found a consistent association between cannabis use and the development of psychotic symptoms over the short and long term (results discussed for both pharmaceutical and non-pharmaceutical cannabis together).
Osborne 2017	CE, THC, CBD, THC-CBD	NR
Stevens 2017	THC	Significantly more patients in the M-9-THC group reported increased awareness of surroundings compared to those in the placebo group (40% compared to 5%; P = 0.04). No other statistically significant differences existed between groups for adverse effects.
Wong 2017	OCE, OCE (CBD	In controlled trials, THC most commonly led to side effects of drowsiness

Review	Formulation	Adverse Events
	enriched), THC, CBD	and dizziness, with severity associated with higher doses. However, no major side effects were reported with dose reduction. The most common side effects with CBD were somnolence, diarrhea, and decreased appetite. Overall, studies were heterogeneous in the cannabinoid composition and dosage and lacked long-term follow-up to identify potential adverse effects.
Fitzcharles 2016	PF-04457845	Single included study was stopped at interim analysis due to futility. No AEs reported at study termination.
Gruenbaum 2016	Marijuana	NR
Merlin 2016	Cannabis cigarettes	NR
Tafelski 2016	THC	Hallucinations, paranoia, sedation, euphoria, dizziness, dysphoria, depression, hallucinations, focal dystonia
Wilkinson 2016	Cannabis (smoked), THC	AEs reported were generally mild. Patients with pre-existing psychosis or those that are marijuana naïve had greater risk of AEs.

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