

Appendix 1: Methodological details

We use a standard protocol for preparing rapid evidence profiles (REP) to ensure that our approach to identifying research evidence is as systematic and transparent as possible in the time we were given to prepare the profile.

Reviewing the effectiveness of cannabis on symptoms of select conditions

11 January 2024

[MHF product code: REP 63]

Identifying research evidence

For this REP, we searched Health Systems Evidence, PubMed and PsychInfo for:

- 1) evidence syntheses
- 2) single studies conducted with Canadian Veterans.

We searched [Health Systems Evidence](#), [PubMed](#) and [PsychInfo](#) using open search terms for (cannabis OR cannabinoid OR marijuana OR CBD OR THC) AND (anxiety OR chronic pain OR depression OR post*traumatic stress disorder OR sleep) and applied filters for systematic reviews and a date restriction of the past five years. In addition, we searched [PubMed](#) and [PsychInfo](#) for single studies using open search terms for (cannabis OR cannabinoid OR marijuana OR CBD OR THC) AND (anxiety OR chronic pain OR depression OR post*traumatic stress disorder OR sleep) AND (veteran OR armed forces OR military) AND (Canada) combined with a date restriction of the past five years. Links provide access to the full search strategy.

Each source for these documents is assigned to one team member who conducts hand searches (when a source contains a smaller number of documents) or keyword searches to identify potentially relevant documents. A final inclusion assessment is performed both by the person who did the initial screening and the lead author of the rapid evidence profile, with disagreements resolved by consensus or with the input of a third reviewer on the team. The team uses a dedicated virtual channel to discuss and iteratively refine inclusion/exclusion criteria throughout the process, which provides a running list of considerations that all members can consult during the first stages of assessment.

During this process we include published, pre-print and grey literature. We do not exclude documents based on the language of a document. However, we are not able to extract key findings from documents that are written in languages other than Chinese, English, French or Spanish. We provide any documents that do not have content available in these languages in an appendix containing documents excluded at the final stages of reviewing. We excluded documents that did not directly address the research questions and the relevant organizing framework.

Assessing relevance and quality of evidence

We assess the relevance of each included evidence document as being of high, moderate or low relevance to the question.

Two reviewers independently appraised the quality of the guidelines we identified as being highly relevant using AGREE II. We used three domains in the tool (stakeholder involvement, rigour of development and editorial independence) and classified guidelines as high quality if they were scored as 60% or higher across each of these domains.

Two reviewers independently appraise the methodological quality of evidence syntheses that are deemed to be highly relevant. Disagreements are resolved by consensus with a third reviewer if needed. AMSTAR rates overall methodological quality on a scale of 0 to 11, where 11/11 represents an evidence synthesis of the highest quality. High-quality evidence syntheses are those with scores of eight or higher out of a possible 11, medium-quality evidence syntheses are those with scores between four and seven, and low-quality evidence syntheses are those with scores less than four. It is important to note that the AMSTAR tool was developed to assess evidence syntheses focused on clinical interventions, so not all criteria apply to those pertaining to health-system arrangements or to economic and social responses. Where the denominator is not 11, an aspect of the tool was considered not relevant by the raters. In comparing ratings, it is therefore important to keep both parts of the score (i.e., the numerator and denominator) in mind. For example, an evidence synthesis that scores 8/8 is generally of comparable quality to another scoring 11/11; both ratings are considered 'high scores.' A high score signals that readers of the evidence synthesis can have a high level of confidence in its findings. A low score, on the other hand, does not mean that the evidence synthesis should be discarded, merely that less confidence can be placed in its findings and that the evidence synthesis needs to be examined closely to identify its limitations. (Lewin S, Oxman AD, Lavis JN, Fretheim A. SUPPORT Tools for evidence-informed health Policymaking (STP): 8. Deciding how much confidence to place in a systematic review. *Health Research Policy and Systems* 2009; 7 (Suppl1):S8.)

Identifying experiences from other countries and from Canadian provinces and territories

For each REP, we work with the requestors to collectively decide on what countries (and/or states or provinces) to examine based on the question posed. For other countries, we search relevant government and stakeholder websites including those of Departments or Offices of Veteran's Affairs in each of the 'Five Eyes' countries and their relevant health insurance providers. In Canada, a similar approach was used, searching the website of Veterans Affairs Canada. While we do not exclude content based on language. Where information is not available in English, Chinese, French or Spanish, we attempt to use site-specific translation functions or Google translate. A full list of websites and organizations searched is available upon request.

Preparing the profile

Each included document is cited in the reference list at the end of the REP. For all included guidelines, evidence syntheses and single studies (when included), we prepare a small number of bullet points that provide a summary of the key findings, which are used to summarize key messages in the text. Protocols and titles/questions have their titles hyperlinked, given that findings are not yet available.

We then draft a summary that highlights the key findings from all highly relevant documents (alongside their date of last search and methodological quality) as well as key findings from the jurisdictional scan.

Appendix 2: Summary of key findings from included evidence syntheses and single studies about the effectiveness of cannabis on symptoms of select conditions

Select conditions and cannabis composition	Anxiety	Chronic pain	Depression	Post-traumatic stress disorder	Sleep conditions (primary or secondary as a symptom of other conditions)
CBD	<p><i>Health outcomes</i></p> <ul style="list-style-type: none"> Two recent medium-quality evidence syntheses found CBD reduced anxiety levels among those with anxiety disorders including generalized anxiety and social anxiety (1; 2) <ul style="list-style-type: none"> However, sub-group analysis in one recent medium-quality evidence synthesis showed no significant improvement in levels of anxiety (1) Three recent medium-quality evidence syntheses found a reduction in anxiety levels following orally administered (capsule or sublingual spray) CBD, particularly for social anxiety disorder (3-5) <ul style="list-style-type: none"> One of the recent medium-quality evidence syntheses identified single doses ranging from 300 to 600 mg as being effective, with the timelines for effects ranging from single daily doses to trials of up to 10 weeks (4) 	<p><i>Health outcomes</i></p> <ul style="list-style-type: none"> One recent high-quality review found medicinal CBD dosages ranging from 39 mg to 1.5 g per day resulted in reduced chronic non-cancer pain over the long-term (i.e., over six months) <ul style="list-style-type: none"> However, the evidence for this finding is graded as being very low (6) One recent medium-quality evidence synthesis found CBD alone or in combination with THC may provide pain relief for individuals with chronic non-cancer pain (7) 	<p><i>Health outcomes</i></p> <ul style="list-style-type: none"> One recent medium-quality evidence synthesis found CBD had no effect on depressive symptoms (1) 		<p><i>Health outcomes</i></p> <ul style="list-style-type: none"> One recent medium-quality evidence synthesis found CBD may be beneficial in the management of comorbid insomnia in patients with chronic pain and PTSD (8)
THC (incl. nabilone and dronabinol)		<p><i>Health outcomes</i></p> <ul style="list-style-type: none"> One recent medium-quality evidence synthesis found that dronabinol reduced symptoms of chronic pain as compared to a placebo but not against active comparator (1) 		<p><i>Health outcomes</i></p> <ul style="list-style-type: none"> Three recent medium-quality reviews found significant improvements in PTSD symptoms 	<p><i>Health outcomes</i></p> <ul style="list-style-type: none"> Two recent high-quality reviews and one recent medium-quality evidence synthesis found nabilone improved sleep scores

Select conditions and cannabis composition	Anxiety	Chronic pain	Depression	Post-traumatic stress disorder	Sleep conditions (primary or secondary as a symptom of other conditions)
		<ul style="list-style-type: none"> Two recent medium-quality evidence syntheses found synthetic cannabis products with high THC-to-CBD ratios was associated with moderate improvements in pain severity compared to placebo trials, but was also associated with an increase in adverse events, namely sedation, dizziness and nausea (9; 10) One recent medium-quality review found THC, as compared to other types of cannabis, may have a modest analgesic effect for chronic neuropathic pain conditions (11) 		(including nightmares) from nabilone and dronabinol when compared to a placebo (1; 12; 13) <ul style="list-style-type: none"> However, one of the medium-quality evidence syntheses found many health risks from THC products including THC-related cognition dysfunction and risk of psychosis (12) 	when compared to a placebo (1; 14; 15) <ul style="list-style-type: none"> One recent low-quality evidence synthesis found THC showed more promise at improving sleep than other forms of cannabis, but conclusions are limited due to heterogeneity in timing and dosages (16)
THC:CBD in equivalent amounts (incl. nabiximols)	<i>Health outcomes</i> <ul style="list-style-type: none"> One recent high-quality evidence synthesis found THC:CBD led to reductions in anxiety among those with a diagnosed anxiety disorder compared to placebos but did not result in a significant improvement against active comparators (17) One recent medium-quality evidence synthesis found nabiximols administered through oro-mucosal spray, orally or sublingually, were effective in reducing symptoms of social anxiety disorder (5) 		<i>Health outcomes</i> <ul style="list-style-type: none"> One recent medium-quality evidence synthesis found minor improvements in depressive symptoms from nabiximols compared to a placebo (1) One recent medium-quality evidence synthesis found no effect of nabiximols on symptoms of depression, and suggested that higher doses may worsen depressive symptoms (18) 	<i>Health outcomes</i> <ul style="list-style-type: none"> A single small study included in a recent high-quality evidence synthesis found a benefit of pharmaceutical THC:CBD compared to placebo in improving global functioning and nightmare frequency for those with PTSD but had no significant effect on sleep quality (17) 	
Not specified		<i>Health outcomes</i> <ul style="list-style-type: none"> One recent high-quality and two recent medium-quality evidence syntheses found 	<i>Health outcomes</i> <ul style="list-style-type: none"> One recent medium-quality and one low-quality evidence synthesis 	<i>Health outcomes</i> <ul style="list-style-type: none"> One recent medium-quality evidence synthesis 	<i>Health outcomes</i> <ul style="list-style-type: none"> One recent medium-quality evidence synthesis found limited evidence to

Select conditions and cannabis composition	Anxiety	Chronic pain	Depression	Post-traumatic stress disorder	Sleep conditions (primary or secondary as a symptom of other conditions)
		<p>medicinal cannabis when consumed orally (as opposed to when inhaled) may result in very small reductions in chronic-cancer and non-cancer pain as well as very small improvement in physical functioning and sleep quality (19-21)</p> <ul style="list-style-type: none"> Two recent medium-quality evidence syntheses found cannabinoid treatment in patients with chronic primary pain had limited benefit on pain relief, despite clear patient-perceived benefit (11; 22) <p><i>Care experiences</i></p> <ul style="list-style-type: none"> One recent medium-quality evidence synthesis and one single study found mixed patient willingness to try medicinal cannabis, with the majority reporting that they chose to use it for symptom reduction and that it generally improved their pain (23; 24) 	<p>found cannabis (both medicinal and recreational) to be associated with worsened courses and functioning of major depressive disorder (18; 25)</p> <ul style="list-style-type: none"> However, another recent medium-quality review found uncertain results for the effects of cannabis on the clinical course of depression (26) 	<p>found cannabis use may be linked to the onset of PTSD in individuals that have experienced trauma</p> <ul style="list-style-type: none"> However the same review found nabilone may help to combat nightmares related to PTSD (26) Two recent medium-quality evidence syntheses found the evidence related to cannabinoids and PTSD to be inconclusive and often reliant on small samples, though there is some indication that it may help to reduce sleep disturbances (20; 27) 	<p>support the clinical use of cannabinoid therapies for sleep disorders given the high risk-of-bias in the research completed to date (28)</p> <ul style="list-style-type: none"> One recent high-quality evidence synthesis found medicinal cannabis may improve impaired sleep among people living with chronic pain, but that the effect is likely small and should be weighed against adverse events (15)

Appendix 3: Key findings from evidence syntheses, sorted by relevance

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations
<ul style="list-style-type: none"> Conditions <ul style="list-style-type: none"> Anxiety Chronic pain Depression PTSD Sleep disorders Composition <ul style="list-style-type: none"> Natural Synthetic Health outcomes <ul style="list-style-type: none"> Symptom reduction 	<p>Cannabinoids demonstrate a beneficial effect for some conditions including chronic pain, nausea and vomiting, PTSD and sleep disorders but little to no effect for other mental health conditions such as anxiety, depression or psychosis (1)</p> <ul style="list-style-type: none"> The meta-analysis found beneficial effect of cannabinoids on chronic pain, nausea and vomiting, seizure frequencies for those with epilepsy, PTSD (from dronabinol and nabilone) and sleep disorders (with nabiximols demonstrating the highest efficacy) The meta-analysis found that while cannabinoids may help to reduce anxiety levels, no sub-group analysis showed significant improvements in anxiety Similarly, the meta-analysis found no attenuations of depressive symptoms or improvement in schizophrenia and psychosis 	High	No	7/11	2022	No	Not reported
<ul style="list-style-type: none"> Conditions <ul style="list-style-type: none"> Anxiety Chronic pain Depression Composition <ul style="list-style-type: none"> Synthetic Routes of administration <ul style="list-style-type: none"> Oral Health outcomes <ul style="list-style-type: none"> Symptom reduction 	<p>There is some evidence that synthetic cannabis products with high THC-to-CBD ratios may be associated with moderate improvement in short-term pain severity when compared to placebo trials and improved sleep when compared to other cannabis products (9)</p> <ul style="list-style-type: none"> The review found synthetic products, including sublingual extracted cannabis, with high THC-to-CBD ratios (e.g., higher than 98% THC) may be associated with moderate improvement in short-term pain severity when compared to placebo-based trials Compared to other cannabis products, quality of life was not different, but statistically significantly better sleep outcomes were reported among the high THC-to-CBD ratio group Low THC-to-CBD ratio products have insufficient evidence to draw conclusions Synthetic products with high THC-to-CBD ratios were associated with moderate increase in risk for sedation and dizziness 	High	No	6/11	2022	No	Not reported
<ul style="list-style-type: none"> Conditions <ul style="list-style-type: none"> Chronic pain Composition <ul style="list-style-type: none"> Natural Synthetic Routes of administration <ul style="list-style-type: none"> Oral 	<p>Orally consumed medical cannabis may result in a very small reduction in pain among those with chronic cancer and non-cancer pain as well as small improvements in physical functioning and sleep as compared to a placebo (19)</p> <ul style="list-style-type: none"> Medical cannabis when consumed orally (as opposed to when inhaled) compared to a placebo results in small increases in the proportion of patient experiencing pain relief 	High	No	6/11	2021	Yes	None reported

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations
<ul style="list-style-type: none"> Health outcomes <ul style="list-style-type: none"> Symptom reduction Adverse events 	<ul style="list-style-type: none"> Medical cannabis taken orally when compared to a placebo resulted in very small improvements in physical function and small improvements in sleep quality Medical cannabis taken orally resulted in no changes in emotional, role or social functionality and was found to result in small increases in risk of transient cognitive impairment, vomiting, drowsiness, impaired attention and nausea Among the included studies the majority used fixed doses of cannabis, with two included studies comparing dose response relationships and did not identify any, but cannabis with a higher amount of THC was associated with higher risk of adverse events Reported results are for relatively short follow-up periods from between one and five months 						
<ul style="list-style-type: none"> Conditions <ul style="list-style-type: none"> Sleep disorders Composition <ul style="list-style-type: none"> Natural Synthetic Routes of administration <ul style="list-style-type: none"> Oral Health outcomes <ul style="list-style-type: none"> Symptom reduction 	<p>THC showed more promise at improving sleep than other forms of cannabis, but drawing any strong conclusions is not possible given the heterogeneity in the measuring instruments, drug timing, cannabinoid types of dosages used (16)</p> <ul style="list-style-type: none"> Included studies used a range of cannabis types, including CBD, THC, dronabinol, nabilone and THC-CBD combinations and the most common form of administration was capsules, followed by oral solution and oro-mucosal spray Among included RCTs, a little less than half (seven of 19) demonstrated positive results, while the majority (seven of 12) of non-randomized trials reported positive results THC demonstrated the most positive results among randomized control trials 	High	No	3/9	2021	No	Not reported
<ul style="list-style-type: none"> Conditions <ul style="list-style-type: none"> Anxiety Composition Routes of administration <ul style="list-style-type: none"> Oral Health outcomes <ul style="list-style-type: none"> Symptom reduction Adverse events 	<p>A small number of studies found the role of CBD in the management of anxiety disorders promising, but no conclusions could be determined with respect to dosing (3)</p> <ul style="list-style-type: none"> Included studies examined the use of CBD in generalized anxiety disorders, social anxiety disorders and in the anxiety component of PTSD and examined its administration orally as a capsule or sublingually as a spray Doses included in studies varied significantly, between 6 and 400 mg per dose 	High	No	5/9	2019	No	Not reported
<ul style="list-style-type: none"> Conditions <ul style="list-style-type: none"> PTSD Composition 	<p>Additional research is needed to determine the effect of CBD on PTSD (12)</p>	High	No	4/9	2019	No	None reported

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations
<ul style="list-style-type: none"> ○ Natural ○ Synthetic • Routes of administration <ul style="list-style-type: none"> ○ Oral • Outcomes <ul style="list-style-type: none"> ○ Health outcomes <ul style="list-style-type: none"> ▪ Symptom reduction ▪ Adverse events 	<ul style="list-style-type: none"> • The included studies identified a significant overlap between PTSD and substance use disorders, with many individuals self-medicating to mitigate distressing PTSD symptoms, particularly expectations for anxiety and reduced tension • Limited evidence has shown positive findings for CBD and its ability to reduce fear and consolidate emotional memories • Despite having some potential positive effects, many health risks including dependence and THC-related cognition dysfunction and risk of psychosis remain 						
<ul style="list-style-type: none"> • Conditions <ul style="list-style-type: none"> ○ Chronic pain • Routes of administration <ul style="list-style-type: none"> ○ Oral ○ Smoked ○ Vapourized • Outcomes <ul style="list-style-type: none"> ○ Consumer experiences ○ Provider experiences 	<p>Clinical practice guidelines suggest that cannabis may be used for medical purposes to reduce symptoms experienced as result of cancer and non-cancer related chronic pain</p> <ul style="list-style-type: none"> • New evidence-based clinical practice guidelines on cannabis use for medical purposes and chronic pain based on a high-quality recent evidence synthesis describe the following recommendations <ul style="list-style-type: none"> ○ if existing standard of care is not sufficient, providers should offer a trial of cannabis for medical purposes, conditional on shared decision-making ○ non-inhaled forms should be offered first to people living with chronic cancer or non-cancer pain with whom the decision has been made to offer a trial of cannabis for medical purposes ○ cannabis may be offered to those living with chronic cancer or non-cancer pain currently using prescription opioids, and interested in reducing their use of opioids ○ when the standard of care is not sufficient among people living with chronic cancer or non-cancer pain, individuals should be offered a trial of cannabis for medical purposes before a trial of opioids 	High	No	Not yet published	2022	Yes	None reported
<ul style="list-style-type: none"> • Conditions <ul style="list-style-type: none"> ○ Anxiety ○ Depression ○ PTSD • Composition <ul style="list-style-type: none"> ○ Synthetic • Outcomes <ul style="list-style-type: none"> ○ Health outcomes 	<p>Medicinal THC:CBD may be effective for reducing symptoms among those with anxiety when compared to placebos and active comparators, while single studies found that THC:CBD improved global functioning in PTSD and CBD improved global functioning for psychosis (17)</p> <ul style="list-style-type: none"> • The review examined the effects of medicinal cannabinoids on a range of mental health conditions • The majority of included RCTs were quite small, had short follow-up periods and tended to examine pharmaceutical THC (with or without CBD, largely nabiximols and nabilone) 	High	No	10/11	2018	Yes	Not reported

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations
<ul style="list-style-type: none"> Adverse events 	<ul style="list-style-type: none"> For depression, THC:CBD did not significantly improve symptoms of depression compared to either placebos or active comparators (very low evidence GRADE) For anxiety, THC:CBD led to significant greater reduction in anxiety symptoms than did placebos but no difference was identified in one RCT against active comparators <ul style="list-style-type: none"> CBD was not found to have a significant improvement in anxiety symptoms compared to a placebo For PTSD, a single small RCT found a benefit of pharmaceutical THC:CBD compared to placebo in improving global functioning and nightmare frequency but had no significant effect on sleep quality For psychosis, a single small RCT reported on the use of pharmaceutical THC:CBD amongst participants with psychosis and found no significant change in positive symptoms but a worsening of negative symptoms compared to a placebo <ul style="list-style-type: none"> CBD was not found to significantly improve total symptoms, positive symptoms or negative symptoms compared to a placebo or active comparators Pharmaceutical THC:CBD led to significantly more adverse events and withdrawals due to adverse events, with an estimate that one additional participant would experience an adverse event for every seven participants treated with pharmaceutical THC:CBD 						
<ul style="list-style-type: none"> Conditions <ul style="list-style-type: none"> Anxiety Depression PTSD Composition <ul style="list-style-type: none"> Synthetic Dosage Outcomes <ul style="list-style-type: none"> Health outcomes <ul style="list-style-type: none"> Adverse events 	<p>The review found that there is insufficient evidence to adequately determine the efficacy of THC alone, CBD alone, defined CBD-THC combinations or plant marijuana to treat individuals with anxiety disorders, affective disorders or PTSD (13)</p> <ul style="list-style-type: none"> The review aimed to examine whether THC and CBD influence clinical symptoms of anxiety and depression among individuals with psychiatric disorders For anxiety conditions, two small studies reported mixed findings on the impact of synthetic THC, while two studies (one examining a single-dose of CBD and one of daily-dosed CBD for four weeks) found beneficial effects among individuals with social anxiety disorder <ul style="list-style-type: none"> Single doses of nabilone did not result in changes in symptoms of anxiety, though a one-month trial of daily low-dose (1 mg three times per day) nabilone improved symptoms Single dose of 400–600 mg of CBD prior to an anxiety inducing effect may reduce symptoms 	High	No	4/9	2020	No	None reported

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations
	<ul style="list-style-type: none"> Daily nabilone treatment (0.5 mg) for seven weeks reduced the frequency of nightmares among a small number of military Veterans as compared to placebos 						
<ul style="list-style-type: none"> Conditions <ul style="list-style-type: none"> Depression Frequency of use Outcomes <ul style="list-style-type: none"> Health outcomes <ul style="list-style-type: none"> Adverse events 	<p>Cannabis use is associated with worsened course and functioning of bipolar disorder and major depressive disorder, but additional research is needed to examine how this varies by type, amount and frequency of cannabis use (18)</p> <ul style="list-style-type: none"> The review found cannabis use among those with bipolar disorder and mood disorders to be significantly higher than the general population, and was generally higher among men than women Similarly, the daily use of tobacco was more prevalent in individuals with bipolar and mood disorder who used cannabis in the past six months compared to those who did not; alcohol use was also more common in individuals with bipolar disorder who use cannabis Cannabis use was associated with differences in the severity, type and frequencies of episodes in bipolar disorder, including an increased likelihood of mixed episodes as well as increased severity of manic symptoms and global illness severity Increased severity of both depressive and psychotic symptoms was seen in individuals with bipolar disorder and cannabis use and nicotine was correlated with adverse outcomes in bipolar disease, often signalling the presence of other comorbidities For mood disorders, cannabis use was associated with illness severity and increased anhedonia, weight changes, insomnia and hypersomnia Cannabis use was associated with an increased incidence of the first episode of bipolar disorder and was earlier in those who use higher quantities of cannabis (e.g., more than 10 times a month) 	High	No	6/10	2020	Yes	Personal characteristics associated with discrimination (mental health condition)
<ul style="list-style-type: none"> Composition <ul style="list-style-type: none"> Semi-synthetic Synthetic Routes of administration <ul style="list-style-type: none"> Oral Dosage <ul style="list-style-type: none"> High (greater than 10.0 mg) Outcomes <ul style="list-style-type: none"> Health outcomes 	<p>CBD had mild and moderate adverse effects in most studies, with the most common being drowsiness, sedation, fatigue, dizziness, headache, diarrhoea, nausea, decreased appetite and abdominal discomfort (29)</p> <ul style="list-style-type: none"> The review examined adverse effects from randomized clinical trials that reported data on adverse effects from oral administrations with formulations containing purified CBD (greater than 98% CBD) Doses included in the studies included fixed doses of between 300 and 800 mg/day and doses adjusted by weight from 20 mg/kg/day to 50 mg/kg/day CBD showed mild and moderate adverse events in most studies with the most common was increased gastrointestinal symptoms, somnolence, loss of appetite, and increased fatigue 	High	No	5/9	2022	No	None reported

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations
<ul style="list-style-type: none"> Adverse events 	<ul style="list-style-type: none"> Serious adverse effects were reported in only three studies, all related to epilepsy taking place at doses between 20 mg/kg/day to 50 mg/kg/day 						
<ul style="list-style-type: none"> Condition <ul style="list-style-type: none"> Chronic pain Composition <ul style="list-style-type: none"> Natural Synthetic Routes of administration <ul style="list-style-type: none"> Oral Dosage Composition <ul style="list-style-type: none"> Natural Semi-synthetic Synthetic Outcomes <ul style="list-style-type: none"> Health outcomes <ul style="list-style-type: none"> Symptom reduction Adverse events 	<p>Long-term (six months and over) reported pain reduction from medical CBD, but the general use of cannabinoids cannot be endorsed for treatment of pain due to lack of evidence from high-quality research (6)</p> <ul style="list-style-type: none"> The review examined the effectiveness, tolerability and safety of cannabis-based medicines for chronic non-cancer pain in observational studies with a duration of longer than 26 weeks All studies used medical cannabis, either inhaled (smoking or vaporizer) and/or oral drops with dosages that ranged from 140 mg THC and 39 mg CBD to 1.5 g/day Approximately 21% of patients reported pain relief of 50% or greater and 38% reported pain relief of 30% or greater, but this is based on very low-quality evidence In addition, CBD was found to have a positive effect on symptoms such as anxiety, depression, sleep problems and health-related quality of life with a range of effect sizes The review also noted a lack of inclusion of participants from different ethnicities in the included studies, limiting the generalization of any findings 	High	No	9/10	2021	Yes	Ethnicity
<ul style="list-style-type: none"> Condition <ul style="list-style-type: none"> Chronic pain Outcomes <ul style="list-style-type: none"> Health outcomes <ul style="list-style-type: none"> Symptom reduction 	<p>Low-quality evidence indicates that CBD, either alone or in combination with equal amounts of THC may be beneficial in the management of comorbid insomnia in patients with cancer, multiple sclerosis, psychiatric disorders, chronic pain and PTSD (8)</p> <ul style="list-style-type: none"> The review examined the effects of CBD in the management of insomnia All included studies reported some level of improvement in the insomnia symptoms of at least a portion of their participants following the administration of CBD-containing products In studies that investigated the effects of products with nearly equal ratios of CBD to THC, about half reported statistically significant improvements in insomnia symptoms 	High	No	6/9	2021	No	Not reported
<ul style="list-style-type: none"> Condition <ul style="list-style-type: none"> Sleep disorders Composition <ul style="list-style-type: none"> Natural Synthetic 	<p>There is limited evidence to support the clinical use of cannabinoid therapies for the treatment of sleep disorders given the lack of published research and the high risk-of-bias in the research that has been completed (28)</p>	High	No	7/9	2019	No	Not reported

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations
<ul style="list-style-type: none"> Outcomes <ul style="list-style-type: none"> Health outcomes <ul style="list-style-type: none"> Symptom reduction 	<ul style="list-style-type: none"> The review synthesized findings on cannabinoids as therapeutics for sleep There is some preliminary evidence that cannabinoid therapies may be beneficial for individuals with sleep apnoea, insomnia, PTSD-related nightmares, restless leg syndrome, rapid eye movement sleep disorder and narcolepsy 						
<ul style="list-style-type: none"> Condition <ul style="list-style-type: none"> Chronic pain Composition <ul style="list-style-type: none"> Natural Synthetic Routes of administration Outcomes <ul style="list-style-type: none"> Health outcomes <ul style="list-style-type: none"> Symptom reduction 	<p>Cannabinoid treatment in patients with chronic primary pain had limited benefit on pain relief and generally low-quality evidence; the exception may be for the long-term treatment of pain associated with fibromyalgia (22)</p> <ul style="list-style-type: none"> Randomized controlled trials included seven studies that focused on different cannabinoid compounds and preparations including sublingual cannabis THC-rich oil, dronabinol oral capsules, oral nabilone, CBD gums, and inhaled vaporized pharmaceutical-grade medicinal cannabis, each of which are compared to matching placebo Studies focused on the new IASP ICD-11 chronic primary pain definition Cannabinoid treatment yielded a statistically non-significant reduction in pain for the chronic primary pain population (most of which were patients with fibromyalgia) Long-term administration (more than four months) showed limited evidence of efficacy of cannabinoids in pain reduction, and the pain reduction that was present was only identified in fibromyalgia patients 	High	No	7/11	2021	No	Not reported
<ul style="list-style-type: none"> Condition <ul style="list-style-type: none"> Chronic pain Composition <ul style="list-style-type: none"> Synthetic Routes of administration Outcomes <ul style="list-style-type: none"> Health outcomes <ul style="list-style-type: none"> Symptom reduction 	<p>Evidence regarding the efficacy of cannabinoids for chronic pain treatment shows clear patient-perceived benefit but is inconsistent on other treatment effects, though THC may have a modest analgesic effect for chronic neuropathic pain conditions and inhaled smoked or vaporized cannabis may be an effective route of administration (11)</p> <ul style="list-style-type: none"> The review summarized the efficacy and secondary effects of cannabinoids for chronic pain management for any type of chronic pain Studies included a range of formulations and routes of administration including nabilone, dronabinol, oral mucosal spray (with 2.7 mg of THC and 2.5 mg of CBD), oral mucosal spray containing only THC, THC tablets, inhaled pharmaceutical grade cannabis, and sublingual oil Eight of 12 studies concluded that there were no significant impacts on pain intensity in cannabis-treatment group compared to control groups Five studies found that cannabis treatment used an analgesic effect that was better than the control agent 	High	No	4/9	2019	No	Not reported

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations
	<ul style="list-style-type: none"> ○ The use of nabilone, smoked THC and THC oil for the treatment of chronic neuropathic pain was associated with pain reduction in three of five RCTs • THC may be effective for managing chronic neuropathic pain conditions and fibromyalgia • Patient-perceived benefit was significant in favour of cannabis 						
<ul style="list-style-type: none"> • Condition <ul style="list-style-type: none"> ○ Chronic pain • Composition • Routes of administration <ul style="list-style-type: none"> ○ Oral ○ Topical • Outcomes <ul style="list-style-type: none"> ○ Consumer experiences 	<p>Values and preferences of those using cannabis for symptom management for chronic pain are highly variable and improvement in symptoms and reduction of prescription medications are important factors influencing patient decisions to use medical cannabis (23)</p> <ul style="list-style-type: none"> • The review examined patients' values and preferences towards the use of medical cannabis among people living with chronic pain • The review included 15 studies, most of which were conducted in the U.S. but one from Canada was included • Two key themes were identified: the first was values and preferences towards medical cannabis for chronic pain, while the second was factors that influenced patient's decisions regarding use of medical cannabis • Low certainty evidence found that patients had mixed levels of willingness to use medical cannabis and most patients who used medical cannabis reported positive attitudes towards its use; generally non-white individuals were less willing to try medical cannabis for chronic pain • People living with chronic pain who chose to use medical cannabis generally believe it was effective for reducing their pain and allowed them to reduce the use of other prescribed medication • Patients with histories of substance use preferred medical cannabis over prescription opioids and some believed it to be safer than other analgesics • Moderate certainty evidence showed that most people living with chronic pain preferred using a blend of indica and sativa and preferred balanced ratios of THC:CBD or high CBD formulations, with only a minority of patients preferring high THC products • Women preferred to use topical preparations as opposed to vaporizing or smoking, and patients who used cannabis recreationally preferred smoking • High to moderate evidence showed that most people with chronic pain chose to use medical cannabis for symptom relief, specifically for managing pain, sleep, appetite and nausea and reported that it generally improved their symptoms 	High	No	7/9	2020	Yes	Race/ethnicity

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations
	<ul style="list-style-type: none"> Unwillingness to use medical cannabis related to major side effects, additional or negative social consequences 						
<ul style="list-style-type: none"> Conditions <ul style="list-style-type: none"> Anxiety Depression PTSD Composition <ul style="list-style-type: none"> Natural Synthetic Outcomes <ul style="list-style-type: none"> Health outcomes <ul style="list-style-type: none"> Symptom reduction Adverse events 	<p>Cannabis use is linked to onset and poorer clinical course in bipolar disorder and PTSD but this finding is not as clear in depression and anxiety disorders and additional long-term research is needed (26)</p> <ul style="list-style-type: none"> The review examined the contributions of cannabis to mood and anxiety disorders and its potential therapeutic effects The review included 47 studies, nine of which contained data for more than one diagnostic category Cannabis use does not appear to be a clear independent risk factor for the onset of most mood and anxiety disorders or symptoms, with the potential exception of PTSD for which there is preliminary evidence that continued cannabis use may increase the odds of developing PTSD in those that have been exposure to trauma, but this finding has not been replicated Cannabis use may negatively affect the course of bipolar disorder, in particular the severity, persistence and frequency of manic episodes, and is also associated with symptom severity for PTSD and depression but it has not been shown to affect the relapse and remission rates, quality of life or suicidality in these disorders There is some potential benefit from CBD for social anxiety disorder as well as the use of nabilone to combat nightmares related to PTSD, which may have to do with the pure THC analogue 	High	No	4/9	2018	No	Not reported
<ul style="list-style-type: none"> Conditions <ul style="list-style-type: none"> Chronic pain Composition Outcomes <ul style="list-style-type: none"> Health outcomes <ul style="list-style-type: none"> Symptom reduction Adverse events 	<p>The majority of included studies indicated a reduction in symptoms of chronic pain with CBD alone and with CBD:THC in equal ratio, though evidence included significant heterogeneity with respect to dosing (7)</p> <ul style="list-style-type: none"> The review aimed to examine the effectiveness of CBD in managing chronic pain The review included 15 articles, with the majority of literature coming from the U.S. Patients included in the studies had a range of chronic pain conditions including fibromyalgia, symptomatic peripheral neuropathy, osteoarthritis, and neurofibromatosis Of the included studies, nine showed a reduction in pain when CBD was administered, while three studies stated no significant improvement in pain relief when CBD was administered CBD may reduce the adverse effects of THC, which could enhance the safety profile for medication in chronic pain 	High	No	6/10	Published 2022	Yes	Not reported

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations
	<ul style="list-style-type: none"> Common side effects included fatigue, diarrhoea, alterations in appetite/weight, drowsiness, nausea, vomiting and dry mouth 						
<ul style="list-style-type: none"> Conditions <ul style="list-style-type: none"> PTSD Composition <ul style="list-style-type: none"> Natural Synthetic Outcomes <ul style="list-style-type: none"> Health outcomes <ul style="list-style-type: none"> Symptom reduction Adverse events 	<p>Studies on cannabinoids and PTSD are small and of relatively low quality, leading to inconclusive findings, but there is some evidence that cannabinoids may help reduce sleep disturbances and nightmares caused by PTSD, though this should be weighed against some of the long-term harms of cannabis use among those with PTSD or who have witnessed trauma (27)</p> <ul style="list-style-type: none"> The review examined the effects of synthetic cannabinoids, pharmaceutically derived whole plant extracts and whole plant products on CBD The review included 10 studies, of which three examined the effects of nabilone, one oral THC, two CBD oil and four smoked herbal preparations Insufficient evidence was found to support the use of cannabinoids as psychopharmacological treatment for PTSD The review did find concurrence with other systematic reviews that cannabinoids may help with sleep disturbances and may be more effective and with less risk of addiction in comparison to alternatives such as benzodiazepines 	High	No	7/9	2018	No	Not reported
<ul style="list-style-type: none"> Conditions <ul style="list-style-type: none"> Sleep disorders Routes of administration Composition <ul style="list-style-type: none"> Natural Synthetic Outcomes <ul style="list-style-type: none"> Health outcomes <ul style="list-style-type: none"> Symptom reduction Adverse events 	<p>Cannabis may improve sleep among patients with primary and secondary insomnia, but additional studies are needed to determine the most appropriate dosage and composition (14)</p> <ul style="list-style-type: none"> The review included five trials examining the effects of cannabis on individuals with primary and second insomnia All included studies used different orally administered cannabis-based products, either with or without concomitant medication; these included: <ul style="list-style-type: none"> single doses of 10, 20 and 30 mg or placebo over a single night two weeks intervention of nabilone (0.5 mg daily) or amitriptyline (10 mg daily) with the opportunity to double dose after seven days, followed by a two-week washout period 2.5 mg of THC in olive oil twice daily, increased to 5 mg if well tolerated as adjunctive therapy, most patients were administered 25 mg daily rich soft gels containing 15.7 mg CBD and 0.5 mg THC Non-randomized studies found a favourable effect of cannabinoids compared with baseline at less than four weeks follow-up and a favourable effect at eight weeks 	High	No	8/11	2019	No	Not reported

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations
	<ul style="list-style-type: none"> Two RCTs reported that nabilone improved the severity of insomnia more than amitriptyline after two weeks of treatment, though no difference was identified in overall sleep quality Commonly reported side effects were dry mouth, insomnia, fatigue or drowsiness, dizziness, headache/migraine and constipation 						
<ul style="list-style-type: none"> Conditions <ul style="list-style-type: none"> Chronic pain PTSD Composition <ul style="list-style-type: none"> Natural Synthetic Outcomes <ul style="list-style-type: none"> Health outcomes <ul style="list-style-type: none"> Symptom reduction 	<p>Literature on cannabis use for treatment of symptoms related to chronic non-cancer pain is promising, while literature for PTSD remains largely inconclusive (20)</p> <ul style="list-style-type: none"> Overview examined the literature from 2016 to 2019 on the effects of cannabis for symptoms of 11 different conditions including chronic non-cancer pain and PTSD, including 13 reviews graded moderate to high quality for chronic non-cancer pain (seven of which indicated cannabis improved outcomes, while six were inconclusive) Of the studies that investigated pain reduction or quality of life, 10 indicated an improvement, one indicated mixed findings, three indicated no change and three were inconclusive Of the nine studies examining safety outcomes of medical cannabis in patients with chronic non-cancer pain, six studies indicated a worsening, one mixed findings and two were inconclusive For PTSD, among eight studies investigating symptoms reduction, two indicated mixed findings while six were inconclusive 	High	No	4/9	2018	No	Not reported
<ul style="list-style-type: none"> Conditions <ul style="list-style-type: none"> Chronic pain PTSD Outcomes <ul style="list-style-type: none"> Health outcomes <ul style="list-style-type: none"> Symptom reduction 	<p>Much of the evidence of cannabis use among Veterans shows negative health outcomes, with concerns about worsening of mood disorders and associations with an increase in substance use (25)</p> <ul style="list-style-type: none"> The review aimed to examine the consequences and correlates of cannabis use in Veterans as well as the implications of the evidence for treatment and policy The review included 86 studies contributing to a range of themes including level of cannabis use, overlapping alcohol and cannabis use and cannabis use in the transition from military to civilian life Some Veterans who use cannabis report greater substance use, typically heavy alcohol consumption, though this often subsides if cannabis is prescribed medically Veterans who use cannabis tend to report either worse or the same levels of mental health problems as Veterans who do not use cannabis and a single retrospective analysis has suggested improvement in PTSD symptoms in Veterans 	High	No	3/9	2019	No	Not reported

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations
<ul style="list-style-type: none"> Conditions <ul style="list-style-type: none"> Chronic pain Composition <ul style="list-style-type: none"> Natural Synthetic Routes of administration <ul style="list-style-type: none"> Oral Oro-mucosal and intranasal Smoked Outcomes <ul style="list-style-type: none"> Health outcomes <ul style="list-style-type: none"> Symptom reduction Adverse events Consumer experiences 	<p>The study identified moderate evidence supporting cannabinoids in treating chronic, non-cancer pain at two weeks with little evidence that cannabinoids increase the risk of experiencing serious adverse events (21)</p> <ul style="list-style-type: none"> The thirty-six included trials examined smoked cannabis, oro-mucosal cannabis sprays and oral cannabinoids Oral cannabinoids had a larger reduction in pain as compared to oro-mucosal and smoked formulations, but this difference was not significant Although serious adverse events were rare, and similar across cannabinoid and placebo groups, there was an increased risk of non-serious adverse events with cannabinoids in comparison with placebo 	High	No	9/11	2018	No	Not identified
<ul style="list-style-type: none"> Conditions <ul style="list-style-type: none"> Chronic pain Composition <ul style="list-style-type: none"> Synthetic Routes of administration <ul style="list-style-type: none"> Oral <ul style="list-style-type: none"> Oils and oral solutions Oro-mucosal and intranasal Outcomes <ul style="list-style-type: none"> Health outcomes <ul style="list-style-type: none"> Symptom reduction Adverse events 	<p>Low to moderate strength evidence suggest small improvement in pain (mostly neuropathic) and moderate to large increases in common adverse events with high and comparable THC-to-CBD ratio extracted cannabinoids and synthetic products during short-term treatment (10)</p> <ul style="list-style-type: none"> Compared to a placebo, comparable THC-to-CBD ratio oral spray was associated with a small benefit in change in pain severity and overall function, but there was a large increased risk of dizziness and sedation, and a moderate increased risk of nausea Synthetic products with high THC-to-CBD ratios were associated with a moderate improvement in pain severity, a moderate increase in sedation and a large increase in nausea It was not possible to determine effects from whole-plant cannabis and other comparisons 	High	Yes	8/11	2023	No	Not reported

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations
<ul style="list-style-type: none"> Conditions <ul style="list-style-type: none"> Anxiety Chronic pain Composition Routes of administration <ul style="list-style-type: none"> Oral <ul style="list-style-type: none"> Oils and oral solutions Oro-mucosal and intranasal Smoked Vaporized Dosage <ul style="list-style-type: none"> High (greater than 10.0 mg) Outcomes <ul style="list-style-type: none"> Health outcomes <ul style="list-style-type: none"> Symptom reduction Adverse events 	<p>The evidence supported single dose positive effects on social anxiety disorder, short medium-term effects on schizophrenia symptom improvement, and lack of effect in the short medium-term on cognitive functioning in psychotic disorders (4)</p> <ul style="list-style-type: none"> Most studies reported no adverse events with acute administration and mild to moderate adverse events with chronic administration Most of the included studies demonstrated an improvement in anxiety levels after single doses of oral CBD with doses ranging from 300 to 600 mg 	High	No	7/10	2019	Yes	Not reported
<ul style="list-style-type: none"> Conditions <ul style="list-style-type: none"> Chronic pain Sleep disturbances Composition <ul style="list-style-type: none"> Natural Synthetic Routes of administration <ul style="list-style-type: none"> Oral Outcomes <ul style="list-style-type: none"> Health outcomes <ul style="list-style-type: none"> Symptom reduction 	<p>Medical cannabis and cannabinoids may improve impaired sleep among people living with chronic pain but the effect is likely small (15)</p> <ul style="list-style-type: none"> The review examined randomized controlled trials of the effects of medical cannabis or cannabinoids on sleep The review included 39 studies, 25 of which focused on individuals with chronic non-cancer pain and a single trial of an individual with PTSD Only one included a study focused on inhaled cannabis, while the remaining 38 administered oral formulations Moderate certainty evidence from 16 trials suggests that medical cannabis and cannabinoids may result in small increases in sleep quality Cannabinoids showed a small increase in the proportion of patients reporting reduced sleep disturbance, with a significant effect for non-cancer related pain Low certainty evidence suggests that nabilone when compared to a placebo may reduce the frequency and intensity of nightmares among 	High	No	9/11	2021	Yes	Not reported

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations
<ul style="list-style-type: none"> Adverse events 	<p>PTSD patients but had no benefit for total sleep time or numbers of awakenings each night</p> <ul style="list-style-type: none"> Adverse events included dizziness, somnolence, dry mouth, fatigue and nausea 						
<ul style="list-style-type: none"> Conditions <ul style="list-style-type: none"> Anxiety PTSD Sleep disorders Routes of administration <ul style="list-style-type: none"> Oral Oro-mucosal and intranasal Compositions <ul style="list-style-type: none"> Semi-synthetic Synthetic Outcomes <ul style="list-style-type: none"> Health outcomes <ul style="list-style-type: none"> Symptom reduction 	<p>Cannabidiol (CBD) and nabiximols successfully alleviated psychotic symptoms and cognitive impairments for a variety of psychiatric disorders (5)</p> <ul style="list-style-type: none"> Evidence was found supporting the use of CBD or nabiximols for social anxiety, along with other psychiatric disorders There was weaker evidence supporting the use of CBD or nabiximols for insomnia, anxiety and PTSD Included studies used a range of methods of administration including oro-mucosal nabiximols spray, oral administration and sublingual 	High	No	7/9	2020	No	Not reported
<ul style="list-style-type: none"> Conditions <ul style="list-style-type: none"> Chronic pain Routes of administration <ul style="list-style-type: none"> Oral <ul style="list-style-type: none"> Oils and oral solutions Edible Smoked Vaporized Outcomes <ul style="list-style-type: none"> Health outcomes <ul style="list-style-type: none"> Adverse events 	<p>There is very low certainty evidence that adverse events associated with using medical cannabis for chronic pain are common, and that serious adverse events are rare (31)</p> <ul style="list-style-type: none"> Evidence of very low certainty demonstrated that adverse events (26%), particularly psychiatric events (13.5%), are common among users of medical cannabis for chronic pain Evidence of the same quality found that serious events are less common (13.5%) Methods of administration from included studies included smoking, vaping, ingesting, oils, extracts, hashish and edibles of herbal cannabis, as well as products such as nabiximols, THC products and mixed CBD and THC products It was found that a greater number of adverse events were reported in studies with a longer follow-up period (over 24 weeks) 	High	No	8/11	2022	Yes	Not reported
<ul style="list-style-type: none"> Conditions <ul style="list-style-type: none"> Anxiety 	<p>There is some evidence that cannabinoids have positive impacts on social anxiety and that medical cannabis positively impacts sleep and PTSD symptoms (2)</p>	High	No	5/10	2020	No	Not reported

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations
<ul style="list-style-type: none"> ○ Depression ○ PTSD ○ Sleep disorders • Routes of administration <ul style="list-style-type: none"> ○ Oral • Dosage <ul style="list-style-type: none"> ○ High (greater than 10.0 mg) • Composition <ul style="list-style-type: none"> ○ Synthetic • Outcomes <ul style="list-style-type: none"> ○ Health outcomes <ul style="list-style-type: none"> ▪ Symptom reduction 	<ul style="list-style-type: none"> • Limited data suggests cannabinoids have a positive impact on the treatment of social anxiety, PTSD and insomnia • Studies examining depression as a secondary outcome for use of nabiximols found no impact; some evidence showed that depressive symptoms were made worse by higher doses • Dosage in included studies ranged from 50 mg to 600 mg • Methods of administration described include capsule, spray and oral administration • Limited evidence found; more research needed 						
<ul style="list-style-type: none"> • Conditions <ul style="list-style-type: none"> ○ Chronic pain • Composition <ul style="list-style-type: none"> ○ Natural ○ Synthetic • Routes of administration <ul style="list-style-type: none"> ○ Oral <ul style="list-style-type: none"> ▪ Oils and oral solutions • Outcomes <ul style="list-style-type: none"> ○ Health outcomes <ul style="list-style-type: none"> ▪ Symptom reduction ▪ Adverse events 	<p>The study found that current recommendations are consistent as weakly recommending medical cannabis as a third- or fourth-line option for chronic non-cancer pain (30)</p> <ul style="list-style-type: none"> • Medical cannabis could be used for treating chronic non-cancer pain generally and for the specific conditions of neuropathic pain, chronic pain in people living with HIV and chronic abdominal pain • Moderate-quality evidence of positive effects from cannabinoids, limited benefits and high risk of adverse effects, and unclear long-term efficacy and safety contributed to the justifications of weak recommendations 	Medium	No	4/9	2020	Yes	Not reported
<ul style="list-style-type: none"> • Conditions <ul style="list-style-type: none"> ○ Anxiety ○ Sleep disorders • Composition <ul style="list-style-type: none"> ○ Natural 	<p>In healthy populations, CBD has an anxiolytic effect, but not proven impact on sleep (32)</p> <ul style="list-style-type: none"> • Studies were included if they examined CBD-based treatments, with or without THC included 	Medium	No	3/9	2022	No	Not reported

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations
<ul style="list-style-type: none"> Routes of administration <ul style="list-style-type: none"> Oral <ul style="list-style-type: none"> Oils and oral solutions Edible Smoked Vaporized Outcomes <ul style="list-style-type: none"> Health outcomes <ul style="list-style-type: none"> Symptom reduction 	<ul style="list-style-type: none"> CBD dosage ranged from 400µg to 900 mg; THC doses ranged from 3.7 mg to 86.4 mg Methods of administration included oral capsules, oil solutions, sprays, vaping, cigarettes, inhalers and edibles Results showed that CBD-only treatments had greater anxiolytic effects when compared to THC, with an inverted U-shaped beneficial dose relationship THC-only treatments had greater anxiogenic and sleep-inducing effects Efficacy of combined treatment depended on the ratio of CBD:THC In clinical populations the impact of combined treatments was reduced 						
<ul style="list-style-type: none"> Conditions <ul style="list-style-type: none"> Chronic pain Composition <ul style="list-style-type: none"> Natural Synthetic Routes of administration <ul style="list-style-type: none"> Oral <ul style="list-style-type: none"> Oils and oral solutions Outcomes <ul style="list-style-type: none"> Health outcomes <ul style="list-style-type: none"> Symptom reduction Adverse events 	<p>The study found that current recommendations are consistent as weakly recommending medical cannabis as a third- or fourth-line option for chronic non-cancer pain (30)</p> <ul style="list-style-type: none"> Medical cannabis could be used for treating chronic non-cancer pain generally and for the specific conditions of neuropathic pain, chronic pain in people living with HIV, and chronic abdominal pain Moderate-quality evidence of positive effects from cannabinoids, limited benefits and high risk of adverse effects, and unclear long-term efficacy and safety contributed to the justifications of weak recommendations 	Medium	No	4/9	2020	Yes	Not reported
<ul style="list-style-type: none"> Compositions <ul style="list-style-type: none"> Synthetic Outcomes <ul style="list-style-type: none"> Health outcomes <ul style="list-style-type: none"> Symptom reduction 	<p>Cannabis benefits pain management with a <7 day treatment duration, and nabiximols benefit pain management with a >7 day treatment duration (33)</p> <ul style="list-style-type: none"> The effectiveness of cannabinoids, cannabis and cannabis-based medicines in managing pain was examined A greater number of adverse events than the control were reported for treatments of cannabis, nabiximols and THC No studies included examined chronic pain 	Low	No	8/9	2021	Yes	Not reported

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations
<ul style="list-style-type: none"> ▪ Adverse events 							
<ul style="list-style-type: none"> • Conditions <ul style="list-style-type: none"> ○ Anxiety ○ PTSD • Compositions <ul style="list-style-type: none"> ○ Natural ○ Synthetic • Outcomes <ul style="list-style-type: none"> ○ Health outcomes <ul style="list-style-type: none"> ▪ Symptom reduction ▪ Adverse events 	<p>THC- and CBD-based medicines are associated with some improvements in symptoms of mental disorders; however, there were some side effects (34)</p> <ul style="list-style-type: none"> • Included studies examined the impact of THC-and CBD-based medicines on Alzheimer's/dementia, substance use disorders, psychoses/schizophrenia, generalized social phobia, PTSD, anorexia nervosa, Tourette's and ADHD • Interventions included dronabinol, nabiximols, THC, nabilone, rimonabant, drinabant and CBD • Single studies showed treatment with CBD-based medicines showed positive results for social anxiety disorder and PTSD, as well as other included disorders 	Low	No	6/10	2019	No	Not reported

Appendix 4: Detailed data extractions from single studies about medicinal cannabis use

Dimension of the organizing framework	Study characteristics	Sample and intervention description	Declarative title and key findings
<ul style="list-style-type: none"> Conditions <ul style="list-style-type: none"> Chronic pain Routes of administration <ul style="list-style-type: none"> Oral <ul style="list-style-type: none"> Oils and oral solutions Edible Outcomes <ul style="list-style-type: none"> Health outcomes Symptom reduction <ul style="list-style-type: none"> Care experiences 	<p><i>Focus of study:</i> Examining the views of Canadian Veterans living in pain and their perception of whether medicinal cannabis had a positive, negative or equivocal effect on seven domains</p> <p><i>Publication date:</i> 2023</p> <p><i>Jurisdiction studied:</i> Canada</p> <p><i>Methods used:</i> Qualitative description</p>	<p>12 Canadian veterans with self-identified chronic pain who have or are currently using licensed medicinal cannabis participate in focus to describe their experience with medicinal cannabis</p>	<p>Canadian Veterans report initiating cannabis use to manage symptoms of pre-existing conditions and despite some negative side effects report improvements in their overall quality of life, sleep, relationships and mood, but concerns remain around the discrepancies in qualitative reports and findings from randomized controlled trials and other similar studies (24)</p> <ul style="list-style-type: none"> The study identified 17 themes split across seven broad categories of cannabis use behaviours, reasons for cannabis use, outcomes from cannabis use, facilitators of cannabis use, barriers to cannabis use, stigma around cannabis use and questions and concerns about cannabis use Most Veterans reported having used cannabis for the past three to seven years, with the majority using ingestible forms, often pills or edibles Most cited the management of symptoms of pre-existing conditions, namely chronic pain, musculoskeletal injury, sleep disturbances, PTSD, depression and anxiety Many Veterans reported switching to medicinal cannabis in efforts to avoid unintended side effects from other medications, namely prescription opioids Veterans reported improved sleep, improved relationships with friends and family, improved mood and improved symptoms management as well as some negative side effects, including unpleasant taste or smell and feeling intoxicated, anxious, and/or paranoid after using too much Veterans reported ease of access for funding for medicinal cannabis including receiving additional support for obtaining medicinal cannabis from private medical cannabis clinics A majority of the Veterans reported that difficulty in finding a family physician or accessing health care services was a barrier to medicinal cannabis use with some Veterans reporting difficulty obtaining a stable supply of medicinal cannabis Many Veterans also expressed insufficient guidance around how to use cannabis from medical professionals and cannabis suppliers as well as continued stigma from within the public
<ul style="list-style-type: none"> Conditions <ul style="list-style-type: none"> Chronic pain Routes of administration <ul style="list-style-type: none"> Oral <ul style="list-style-type: none"> Oils and oral solutions Edible 	<p>Focus of study: Examining the use of cannabis among Canadian Veterans</p> <p>Publication date: 2023</p> <p>Jurisdiction studied: Canada</p>	<p>158 individuals, 90 of whom were self-identified Veterans and 58 non-Veterans</p>	<p>Significant differences were identified between Veterans and non-Veterans in the use and perception of medicinal cannabis (35)</p> <ul style="list-style-type: none"> Male Veterans were more likely to report problems with depression, anxiety and PTSD as compared to non-Veterans Female Veterans were significantly more likely to report medicinal cannabis use for conditions such as PTSD and arthritis

Dimension of the organizing framework	Study characteristics	Sample and intervention description	Declarative title and key findings
<ul style="list-style-type: none"> • Dosage • Outcomes <ul style="list-style-type: none"> ○ Health outcomes • Symptom reduction <ul style="list-style-type: none"> ○ Care experiences 	Methods used: Cross-sectional		<ul style="list-style-type: none"> • Perceived effectiveness of medicinal cannabis for both Veterans and non-Veterans was similar for the most common conditions, including insomnia, PTSD, depression, anxiety, acute pain, chronic pain and arthritis • The majority of respondents reported daily use of cannabis for at least one year, with oils identified as the most common mode of administration followed by edibles and vaporized cannabis • Though not significant, male Veterans tended to use higher doses than female Veterans (median THC 11.5 mg/day vs. 4 mg/day, and CBD 20 mg/day vs. 8.5 mg/day) • Compared to non-Veterans, Veterans were more likely to use medicinal cannabis for depression, anxiety, PTSD, sleeping problems and arthritis and were significantly less likely to be concerned about the safety and adverse effects
<ul style="list-style-type: none"> • Conditions <ul style="list-style-type: none"> ○ Chronic pain • Routes of administration <ul style="list-style-type: none"> ○ Oral <ul style="list-style-type: none"> ▪ Oils and oral solutions ▪ Edible • Dosage • Outcomes <ul style="list-style-type: none"> ○ Health outcomes <ul style="list-style-type: none"> ▪ Symptom reduction ○ Care experiences 	<p><i>Focus of study:</i> Examining the prevalence of cannabis use with a consecutive mental health treatment seeking sample of Canadian armed forces members and Veterans</p> <p><i>Publication date:</i> 2023</p> <p><i>Jurisdiction studied:</i> Canada</p> <p><i>Methods used:</i> Cross-sectional</p>	415 Canadian Armed Forces members and Veterans	<p>Many treatment-seeking individuals for PTSD reported current cannabis use for medical or recreational purposes, but no association was identified between cannabis use status and PTSD symptom severity (36)</p> <ul style="list-style-type: none"> • Almost half of the participants reported current cannabis use, with more than half being male and generally falling into a lower income category • The median daily dose for individuals reporting cannabis use for either medical or combined medical/recreational purposes was higher than the median dose reported by individuals using it for recreation alone • Cannabis use was more likely for younger individuals and those reporting bodily pain

Appendix 5: Detailed jurisdictional scan about reimbursement policies for medicinal cannabis

Jurisdictions	Criteria under which cannabis is medically authorized and reimbursed for Veterans
Australia	<ul style="list-style-type: none"> Medicinal cannabis may be covered for Veterans in Australia if prescribed by a treating physician for the following conditions as a second-line treatment after standard therapy has been deemed unsuccessful: <ul style="list-style-type: none"> chronic pain chemotherapy-induced nausea and vomiting palliative care indications anorexia and wasting associated with chronic illness such as cancer spasticity from neurological conditions Other conditions may be eligible so long as there is evidence of effectiveness and safety and if it has been approved by the therapeutic goods association It will not be approved for conditions where its use has not been proven to be effective, harmless and safe such as treatment for a mental health condition Medical cannabis is funded through the Repatriation Pharmaceutical Benefits Scheme, under which there is a 2-tier classification system, whereby tier 1 may be applied for over the phone while tier 2 requires a written assessment from a relevant treating non-GP specialist, confirming that medicinal cannabis would clinically benefit the patient Tier 1 criteria include: <ul style="list-style-type: none"> the client is receiving a maximum of two products at any one time the client is receiving any product or products containing the equivalent, or less, of a total of 40 mg per day of THC or no THC the client has a health condition (see above) where there is an already-established treatment supported under the framework Tier 2 criteria include: <ul style="list-style-type: none"> the client is receiving three or more products at any one time the client is receiving any product or products that contain a total of over 40 mg per day of THC for conditions where there is an already established treatment but where either of the two tier 2 circumstances above exist for conditions not listed above where the application would need to cite evidence (from multiple high-quality studies) to support efficacy of the proposed treatment A concessional co-payment will need to be paid to the pharmacy each time the medical cannabis product is dispensed, unless the patient has reached the concessional safety net limit meaning no further costs for the calendar year
Canada	<ul style="list-style-type: none"> The reimbursement policy from Veterans Affairs Canada has established a maximum three gram per day limit of dried cannabis or its equivalent in fresh marijuana or cannabis oil Veterans Affairs established a fixed rate of up to \$8.50 per gram Cannabis is authorized for a variety of medical conditions
Israel	<ul style="list-style-type: none"> Veterans are eligible for a medical cannabis license provided by a certified doctor in a similar manner to the general population We were unable to identify information on reimbursement policies for Veterans
Netherlands	<ul style="list-style-type: none"> As of 1 January 2020, the use of medicinal cannabis will no longer be reimbursed for Veterans or military personnel
New Zealand	<ul style="list-style-type: none"> We were unable to identify specific programs for Veterans for the reimbursement of medical cannabis in New Zealand The Medicinal Cannabis Scheme came into effect on 1 April 2020 with the commencement of the Misuse of Drugs Regulations, with the purpose of improving access to cannabis for patients who need it Medicinal cannabis is only available on prescription by a physician, which will state the dosage and type of medicinal cannabis product that can be obtained at a pharmacy Medicinal cannabis products must be approved for distribution under the Medicines Act 1981 for any indication within the prescriber's scope of practice Medicinal cannabis products that are not approved but are verified by the Medicinal Cannabis Agency as meeting a minimum quality standard can be prescribed to any patient for any indication within their scope of practice No cannabis products are currently funded by PHARMAC (the New Zealand Pharmaceutical Management Agency) and are not recommended for first-line use for any indication

Jurisdictions	Criteria under which cannabis is medically authorized and reimbursed for Veterans
United Kingdom	<ul style="list-style-type: none"> • We did not identify any specific programs for Veterans • Medicinal cannabis may be prescribed in the U.K. for: <ul style="list-style-type: none"> ○ children and adults with rare, severe forms of epilepsy ○ vomiting or nausea caused by chemotherapy ○ people with muscle stiffness and spasms caused by multiple sclerosis • These may only be prescribed by a specialist hospital doctor within the National Health Service as a second- or third-line treatment option • NICE guidelines currently recommend (and therefore are publicly funded): <ul style="list-style-type: none"> ○ nabilone as an add-on treatment for adults with chemotherapy-induced nausea ○ no cannabis-based products to manage chronic pain in adults (e.g., do not prescribe nabilone, dronabinol, THC or a combination of cannabidiol with THC) ○ for spasticity offer a four-week trial of THC:CBD spray to treat moderate to severe spasticity in adults with multiple sclerosis (and will fund the first 3 10 ml vials if there is agreement for continued funding for people with at least a 20% reduction in spasticity-related symptoms on a 0–10 patient-reported numeric rating scale after 4 weeks) ○ research on the use of cannabis-based medicinal products for severe treatment-resistant epilepsy
United States	<ul style="list-style-type: none"> • The U.S. Department of Veterans Affairs is required to follow all federal laws including those regarding marijuana and as a result does not reimburse any cannabis for medicinal use

Appendix 6: Documents excluded at the final stages of reviewing

Document type	Hyperlinked title
Evidence syntheses	Efficacy, safety and regulation of cannabidiol on chronic pain: A systematic review
Evidence syntheses without systematic and transparent methods	Cannabinoids as an emerging therapy for posttraumatic stress disorder and substance use disorders

Waddell K, Jaspal A, Phelps A, Wilson MG. Rapid evidence profile #63: Reviewing the effectiveness of cannabis on symptoms of select conditions. Hamilton: McMaster Health Forum, 11 January 2024.

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