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Medical Cannabis for the Treatment of Chronic Pain: A Review of Clinical Effectiveness and Guidelines

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

CBD	cannabidiol
CFPC	College of Family Physicians of Canada
THC	Delta-9-tetrahydrocannabinol

Context and Policy Issues

Chronic pain is defined as pain that persists for more than three months.[1] It may present as headache, musculoskeletal pain, visceral pain, neuropathic pain, pain arising from rheumatic disease, and cancer pain.[1]

Chronic pain is a global problem.[2] In Canada, approximately 25% adults have a chronic pain condition.[2] The prevalence estimates of chronic pain are likely to vary depending on the sample population surveyed, and the assessment method.[3] Costs associated with chronic pain include both direct and indirect costs. It is estimated that in Canada the annual direct cost to the healthcare system is over six billion dollars and the annual indirect cost due to job loss and sick days is over 37 billion dollars.[2] Chronic pain is a problem for the individual suffering, and also a societal burden.

Therapies for management for chronic pain include several pharmacological agents (such as tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and opioid analgesics).[4,5] However, these medications offer limited pain relief and are associated with adverse effects.[4,5] There is increasing interest in the use of cannabis-based medicines. Cannabis-based medicines contain cannabinoids derived from the cannabis plant, including delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), or a combination of THC and CBD[6]. There is, however, uncertainty and controversy regarding the use of cannabis-based medicines for the management of chronic pain.[7]

The purpose of this report is to review the clinical effectiveness of medical cannabis for the treatment of chronic pain. Additionally, this report aims to review the evidence-based guidelines regarding associated with the use of medical cannabis for the treatment of chronic pain.

Research Questions

1. What is the clinical effectiveness of medical cannabis for the treatment of chronic pain?
2. What are the evidence-based guidelines associated with the use of medical cannabis for the treatment of chronic pain?

Key Findings

Based on four overviews (with overlapping systematic reviews), and one systematic review of guidelines,[8] there is some suggestion of benefit with cannabis-based medicines for neuropathic pain. However, benefits need to be weighed against harms. Findings are inconsistent for effect of cannabis-based medicines in patients with fibromyalgia, musculoskeletal pain, Crohn's disease, and multiple sclerosis.

Six evidence-based guidelines were identified. The majority of the guidelines present recommendations for chronic neuropathic pain. The guidelines report that cannabis-based medicines may be considered as a treatment option for patients with neuropathic pain, with

chronic non-cancer pain, and with chronic non-cancer, non-neuropathic pain, but with some caveats. Recommendations are against the use of cannabis-based medicines for pain associated with fibromyalgia and back pain in two guidelines and for pain associated with headache, rheumatoid arthritis and osteoarthritis in one guideline. For pain management in multiple sclerosis patients, one guideline mentions that cannabis-based medicines may or may not be offered, depending on the type cannabis-based medicine and patient condition.

Findings need to be interpreted considering the limitations (such studies of variable quality [low to moderate], and studies of short duration)

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Medline, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Medical Marijuana and chronic pain. No filters were applied to limit the retrieval by study type. The search was also limited to English language documents published between January 1, 2014 and June 24, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults experiencing any type of chronic pain (e.g., osteoarthritis)
Intervention	Medical cannabis, any form/route/dose
Comparator	Q1: Any treatment (e.g., anti-inflammatory medications, opioids); no treatment; placebo. Q2: Not applicable
Outcomes	Q1: Clinical effectiveness and safety (e.g., patient benefits and harms; drug interactions)
Study Designs	Overviews (systematic review of systematic reviews), and evidence-based guidelines

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2014. Studies on acute pain or cancer pain were excluded. Guidelines with unclear methods were excluded.

Critical Appraisal of Individual Studies

The included overviews (systematic reviews of systematic reviews) were critically appraised by one reviewer using AMSTAR 2,[9] and evidence-based guidelines were critically assessed

using AGREE 2.[10] Summary scores were not calculated for the included studies, rather, the strengths and limitations of each individual study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 644 citations were identified in the literature search. Following screening of titles and abstracts, 594 citations were excluded and 50 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 41 publications were excluded for various reasons, and 11 publications met the inclusion criteria and were included in this report. These comprised four overviews (systematic review of systematic reviews),[11-14] one systematic review of guidelines,[8] and six guidelines.[7,15-19] Appendix 1 presents the PRISMA[20] flowchart of the study selection.

Additional references of potential interest are provided in Appendix 6.

Summary of Study Characteristics

Characteristics of the overviews, systematic review of guidelines, and guidelines are summarized and additional details are provided in Appendix 2,Table 2 and Table 3

Study Design

Four relevant overviews[11-14] identified were published between 2017 and 2018. One overview[11] included 23 relevant systematic reviews published between 2007 and 2017. The second overview included 10 systematic reviews published between 2009 and 2016. The third overview included 11 systematic reviews published between 2003 and2016. The last overview included 11 systematic reviews published between 2013 and 2016. There was overlap in the systematic reviews included in the overviews (Appendix 5).

One systematic review[8] of guidelines and six guidelines[7,15-19] were selected. The systematic review[8] of guidelines was published in 2016 and included three relevant guidelines published between 2007 and 2010. The six guidelines[7,15-19] were published between 2014 and 2018. In three guidelines,[15,17,18] the recommendations were graded and in three guidelines[7,16,19] the recommendations were not graded.

Country of Origin

Countries indicated for the first authors of the overviews were Canada,[11] Australia,[14] and Germany.[12,13]

The country indicated for the systematic review[8] of guidelines was China. Countries indicated for the first author of the guideline document, or the guideline development groups were Canada,[15,16,18] US,[17] Australia,[19] and Germany.[7]

Population

The populations assessed were patients with chronic pain, neuropathic pain, rheumatologic pain, fibromyalgia, and myasthenia gravis (MS) in one overview,[11] patients with chronic pain in the second overview,[12] patients with MS in the third overview,[14] and patients requiring pain management or palliative care in the last overview.[13]

The systematic review[8] of guidelines assessed patients with neuropathic pain. Of the six guidelines,[7,15-19] one guideline,[15] was on patients who were refractory to standard medical therapy; the second guideline,[7] was on patients with chronic pain; the third guideline,[19] was on patients with chronic non-cancer pain; the fourth guideline,[18] was on patients with chronic pain or anxiety; the fifth guideline,[16] was on patients with chronic neuropathic pain; and the last guideline.[17] was on patients with MS. The guidelines were intended for health care providers involved with pain management.

Interventions and Comparators

In the overviews[11-14] the interventions were various types of cannabis-based medicines and comparators were placebo; in two overviews[12,13] an active comparator (amitriptyline) was also mentioned and in one overview[14] other treatments were compared but specifics were not reported.

The systematic review[8] of guidelines reviewed guidelines which reported on cannabinoids and also other pharmacologic agents (such as anticonvulsants, topical treatments, and opioids). Four guidelines[7,15,18,19] considered cannabis-based medicines and one guideline[16] considered complimentary and alternative medicines, which included as well cannabis-based medicine; and one guideline[17] included several pharmacological agents including as well cannabis-based medicines.

Outcome

Outcomes considered in the overviews included pain reduction,[11-14] quality of life,[14] tolerability,[13] withdrawal,[11] adverse events,[11-14] and serious adverse events.[11,13]

The systematic review[8] of guidelines and all six guidelines[7,15-19] presented recommendations on pain management. Details regarding levels and grades of recommendations are presented in Appendix 2, Table 3.

Summary of Critical Appraisal

Critical appraisal of the included overviews, systematic review of guidelines, and guidelines are summarized below, and details for the overviews and systematic review of guidelines are presented in Appendix 3, Table 4; and details for the guidelines are presented in Appendix 3, Table 5 and Table 6.

The four overviews[11-14] were generally well conducted. In all four overviews, the objective was stated; a comprehensive literature was conducted; study selection was described; a list of included systematic reviews was presented, data extraction was done in duplicate, quality assessment was conducted, and the quality of the included systematic reviews were found to be variable. Article selection and quality assessment were done in duplicate in three overviews[11,12,14] and was unclear in one overview,[13] Publication bias was investigated in one overview[11] using a Funnel plot, but as both cancer (which is out of scope of this review) and non-cancer pain studies were included in the same plot it was unclear if there was any publication bias with respect to studies on non-cancer pain. In the remaining three overviews[12-14] publication bias was not investigated. In two overviews[11,13] it was mentioned that there were no conflicts of interest, and in two overviews[12,14] conflicts of interest were declared; some of the authors had association with pharmaceutical companies and it was unclear if there was any associated risk of bias with respect to the conduct of the overviews.

The systematic review[8] of the guidelines was generally well conducted. The objective was stated; a comprehensive literature was conducted; study selection was described; a list of included systematic reviews was presented, article selection was done by two reviewers, quality assessment was conducted, and the quality of the included guidelines were found to be variable. It was unclear if data extraction and quality assessment were done in duplicate; publication bias was not investigated The authors mentioned that there were no conflicts of interest.

In all six guidelines,[7,15-19], the scope and purpose were mentioned or apparent, the guideline development group comprised experts in the area, and the target users were mentioned. Patient preferences were considered in one guideline,[15] and not in the remaining five guidelines.[7,16-19] In four guidelines[15-17,19] systematic methods were used to search for evidence, and in two guidelines[7,18] systematic methods appeared to have been used but details were lacking. The strengths and limitations of the evidence was mentioned in four guidelines,[15,17-19] and were not stated in two guidelines[7,16] The method of formulating the recommendation was mentioned in four guidelines[7,15,16,18] and was not stated in two guidelines.[17,19] Health benefits and harms were considered in five guidelines, [7,15-17,19] and was unclear in one guideline.[18] Four guidelines[7,15-17] were externally reviewed, and in two guidelines it was unclear.[18,19] In three guidelines[15,17,18] it was mentioned that there were no conflicts of interest, in two guidelines[7,16] conflicts of interest were declared but procedure to address the issue was not presented, and for one guideline[19] conflicts of interest were not presented.

Summary of Findings

Relevant study findings are summarized and a table of the main study findings and authors' conclusions are presented in Appendix 4, Table 7 and Table 8.

Clinical Effectiveness of cannabis-based medicines

Four overviews, [11-14] were identified regarding the use of cannabis-based medicines for patients with non-cancer pain. Relevant findings are summarized, and a table of the main study findings and authors' conclusions are presented in Appendix 4, Table 7.

In the overviews, cannabis-based medicines were mostly compared with placebo. The findings reported below for cannabis-based medicines are with respect to placebo.

One overview[11] reported that there was uncertainty with regard use of cannabinoids for pain management. It reported that there appeared to be some benefit with cannabinoids for neuropathic pain, but adverse effects were common, and benefits need to be weighed against harms.

The second overview[12] reported that findings were inconsistent for the use of cannabis-based medicines for the management of chronic pain; there appeared to be some benefit with respect to chronic neuropathic pain, and the evidence was insufficient with respect to pain associated with rheumatic diseases and fibromyalgia, precluding any definitive conclusions.

The third overview[13] reported that for chronic neuropathic pain there was some reduction in pain with cannabinoids, however there was limited evidence available. The authors reported that there was inadequate evidence to support treatment with cannabinoids in patients with fibromyalgia, Crohn's disease, musculoskeletal pain, and rheumatoid arthritis.

Cannabinoid use in pain management may cause adverse effects related to the central nervous system and psychiatric adverse events.

The fourth overview,[14] based on mostly low-quality evidence, reported that cannabis-based medicines had a positive effect or mixed effect with respect to pain management in MS patients, and the effect sizes were generally small. Effects of cannabis-based medicines on quality of life were mixed. Adverse effects with cannabis-based medicines were generally mild to moderate.

In summary, there is some suggestion of benefit with cannabis-based medicines for neuropathic pain. However, benefits need to be weighed against harms. Findings are inconsistent for the effect of cannabis-based medicines in patients with rheumatic disease, fibromyalgia, musculoskeletal pain, Crohn's disease, and MS.

Guidelines

One systematic review[8] of guidelines and six guidelines[7,15-19] were selected. Relevant recommendations are summarized and related details are presented in Appendix 4, Table 8.

Chronic non-cancer pain

The guideline[19] of the Australian government mentions that cannabinoids should not replace current approved first-line treatments for chronic non-cancer pain.

Chronic non-neuropathic non-cancer pain

The guideline by Hauser et al.[7] mentions that in exceptional cases after careful assessment, cannabis-based medicines can be considered if all established treatments have failed,

Neuropathic pain

One systematic review[8] of guidelines and four guidelines[7,15,16,18] presented recommendations on neuropathic pain. The systematic review of guidelines by Deng et al.[8] recommends the use of cannabinoids as fourth-line treatment of neuropathic pain. The guideline by Hauser et al.[7] mentions that cannabis-based medicines can be considered as third-line therapy for chronic neuropathic pain. The guideline by Allan et al. [15] recommends against the use of medical cannabinoids for first- and second-line therapy for neuropathic pain (strong recommendation). It also mentions that under certain circumstances, medical cannabis could be considered for patients with refractory neuropathic pain (weak recommendation). The College of Family Physicians of Canada (CFPC) guideline[18] mentions that, before authorizing dried cannabis for treating neuropathic pain the physician should first adequately try other pharmacologic and non-pharmacologic therapies, followed by pharmaceutical cannabinoids. The guideline by Moulin et al.[16] recommends cannabinoids for the management of neuropathic pain but cautions that judicious prescribing practices are required.

Pain associated with other conditions:

The guideline by Allan et al.[15] recommends against the use of medical cannabinoids for headache and pain due to rheumatologic conditions (including fibromyalgia, osteoarthritis, rheumatoid arthritis, and back pain) (strong recommendation). The guideline by CFPC[18] does not support the authorization of dried cannabis for treatment of pain conditions commonly seen in primary care, such as fibromyalgia or low back pain (Level III). The

guideline by Yadav et al.[17] mentions that for reduction of patient-reported symptoms of spasticity and pain (excluding central neuropathic pain) in patients with MS, the clinicians may offer oral cannabis extract (Level A),and THC (Level B), It also mentions that for reduction of patient-reported symptoms of spasticity, pain or urinary frequency in patients with MS, the clinicians may offer Savitex, oromucosal cannabinoid spray (Level B) . There is insufficient evidence to support or refute the use of smoked cannabis for the management of spasticity, pain, balance/posture, and cognition in MS patients (Level U).

In summary, majority of the guidelines present recommendations for chronic neuropathic pain.[7,15,16,18] It is reported that cannabis-based medicines may be considered as a treatment option for patients with neuropathic pain, but with some caveats. It is also mentioned that cannabis-based medicines may be considered for patients with chronic non-cancer pain,[19] and for patients with chronic non-cancer, non-neuropathic pain,[7] but with some caveats. Three guidelines[15,17,18] mention pain associated with other conditions (such as fibromyalgia, rheumatologic disease, headache, and MS); recommendations were inconsistent. Recommendations are against the use of cannabis-based medicines for pain associated with fibromyalgia and back pain in two guidelines[15,18] and for pain associated with headache, rheumatoid arthritis, and osteoarthritis in one guideline.[15] For pain management in MS patients, one guideline[17] mentions that cannabis-based medicines may or may not be offered, depending on the type cannabis-based medicine and patient condition.

Limitations

This report has several imitations. This report is intended as an overall summary of the efficacy and safety of cannabis treatment for chronic pain associated with a variety of disease conditions. Considering the many types of cannabis-based medicines studied, and many conditions associated with chronic pain, an exhaustive evaluation of specific cannabis-based medicines for specific pain conditions were beyond the scope of this report.

Though there were several systematic reviews included in the selected overviews, it should be noted that there was some overlap in the included systematic reviews (Appendix 5,**Table 9**). The overviews were well conducted but the evidence on which the findings were based were of variable quality (low to moderate quality) or insufficient, hence definitive conclusions are not possible. Sometimes results include both cancer and non-cancer pain. Though there were fewer studies on cancer pain compared to non-cancer pain, their impact on the results was uncertain. There was limited amount of evidence regarding the comparison of cannabis-based medicines with an active comparator. The studies were generally of short term varying between 4 days to 14 weeks (when reported) and long-term effects are not known. Findings should be interpreted with caution considering the limitations mentioned.

Conclusions and Implications for Decision or Policy Making

Four overviews (systematic review of systematic reviews),[11-14] one systematic review of guidelines,[8] and six evidence-based guidelines.[7,15-19] were identified

Based on four overviews[11-14](with overlapping systematic reviews), one systematic review of guidelines,[8] there is some suggestion of benefit with cannabis-based medicines for neuropathic pain. However, benefits need to be weighed against harms. Findings are inconsistent for effect of cannabis-based medicines in patients with fibromyalgia, musculoskeletal pain, Crohn's disease, and MS.

The majority of the guidelines present recommendations for chronic neuropathic pain.[7,15,16,18] The guidelines report that cannabis-based medicines may be considered as a treatment option for patients with neuropathic pain,[7,15,16,18] with chronic non-cancer pain,[19] and with chronic non-cancer, non-neuropathic pain,[7] but with some caveats. Recommendations are against the use of cannabis-based medicines for pain associated with fibromyalgia and back pain in two guidelines[15,18] and for pain associated with headache, rheumatoid arthritis and osteoarthritis in one guideline[15] For pain management in MS patients, one guideline[17] mentions that cannabis-based medicines may or may not be offered, depending on the type cannabis-based medicine and patient condition. Findings need to be interpreted considering the limitations mentioned.

Potential of adverse events associated with cannabis-based medicines need to be considered. Specific populations of patients may be more vulnerable to adverse effects of cannabis-based medications. High quality studies of longer duration are needed to determine definitively the clinical effectiveness and safety of cannabis-based medicines.

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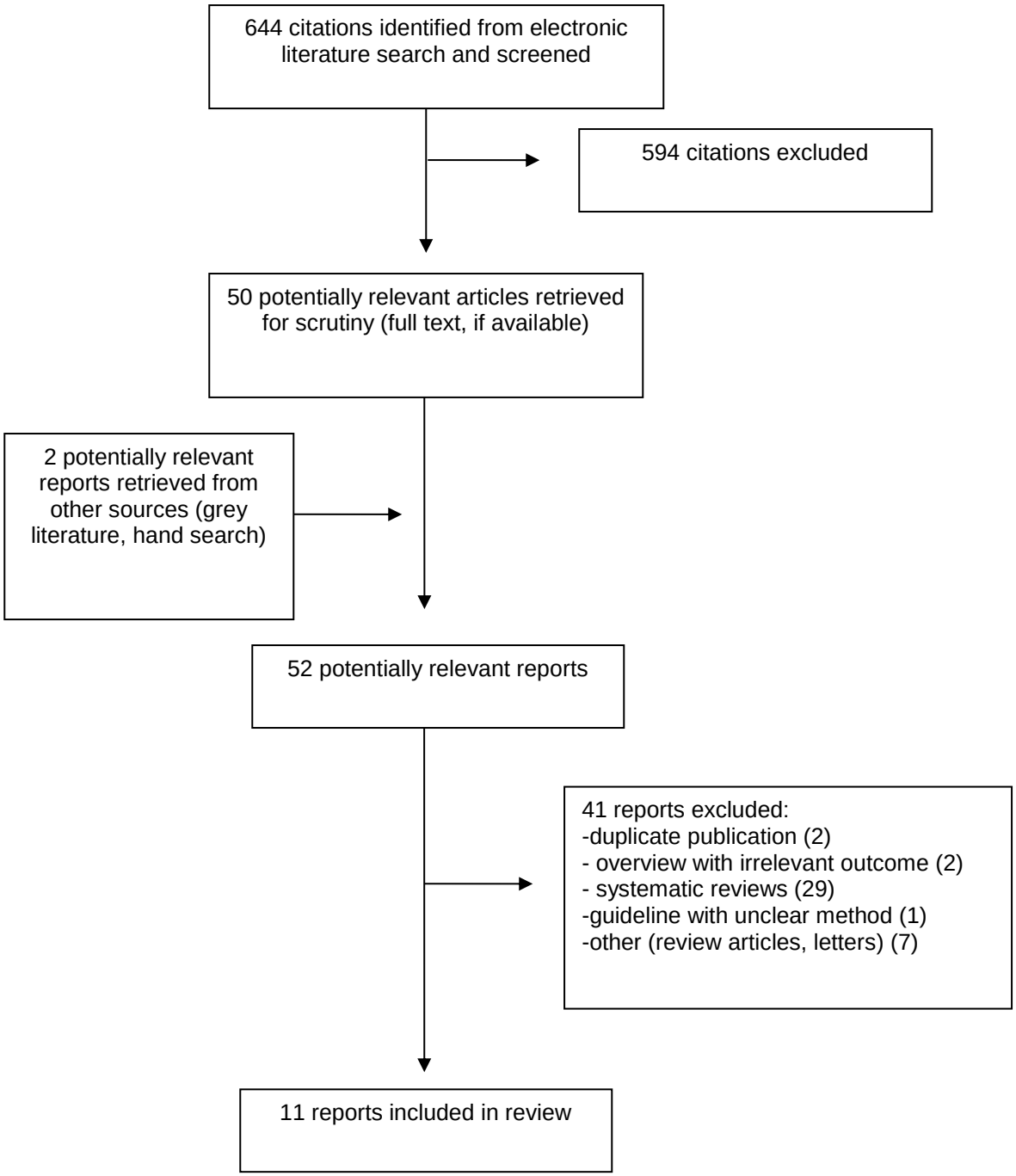
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Overviews (systematic review of systematic reviews)

First Author, Publication Year, Country	Study Designs and Numbers of Systematic Reviews Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Overviews (Systematic reviews of systematic reviews)				
Allan,[11] 2018, Canada	Overview (systematic review of systematic reviews) on the use of medical cannabinoids. The overview included 23 relevant systematic reviews, published between 2007 and 2017. Numbers of RCTs included in the SRs varied between 2 and 28, and the numbers of patients in the SRs varied between 44 and 2454 Exclusion criteria: SRs not focused on medical cannabinoids, SRs focused on conditions besides pain, spasticity, or nausea and vomiting, SRs of observational studies, SRs in which >50% of the RCTs involved pediatric patients, SRs including <2 RCTs were excluded. This overview had a broad focus and included SRs on acute pain, and cancer related pain. 31 SRs (published between 2001 and 2017) of which 23 reporting on pain and/or adverse events are discussed here. Objective: To assess the effects of medical cannabinoids on pain, spasticity, and nausea and vomiting; and adverse events.	Patients with chronic pain, neuropathic pain, rheumatologic pain, fibromyalgia, and MS Age: NR	Intervention: Cannabinoids Comparator: placebo	Pain, adverse events Study duration: NR
Hauser,[12] 2018, Germany	Overview on the use of cannabis-based medicines. This overview was a qualitative SR of RCTs. This overview included 10 SRs,	Patients with chronic pain (non-cancer and cancer pain). Age: Any age (specific	Interventions: medical cannabis; plant-derived cannabinoids (THC, THC/CBD); synthetic cannabinoid analogues	Change in pain status, tolerability (withdrawals due to adverse events), and safety (frequency of serious adverse events)

Table 2: Characteristics of Included Overviews (systematic review of systematic reviews)

First Author, Publication Year, Country	Study Designs and Numbers of Systematic Reviews Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	published between 2009 and 2016. Country of origin of the systematic reviews were not reported. Exclusion criteria: Qualitative systematic reviews which did not explicitly mention the reasons for not performing meta-analysis were excluded. Objective: To summarize the efficacy, tolerability, and safety of the use of cannabis medicine-based for treating chronic pain (non-cancer and cancer pain)	ages of patients in the SRs were not reported)	(nabilone); or synthetic drugs which manipulate the endocannabinoid system Comparator: placebo (mostly) or active comparator (amitriptyline)	Study duration for RCTs included in the SRs: 4 hours to 14 weeks
Nielsen,[14] 2018, Australia	Overview on the use of cannabis-based medicines. This overview included 11 SRs, published between 2003 and 2016. Country of origin of the systematic reviews were not reported. Exclusion criteria: SRs that did not meet the minimum criteria (i.e. GRADE criteria: comprehensive literature search was conducted and characteristics of the included studies were presented) were excluded Objective: To evaluate the therapeutic potential of cannabinoids for treating MS symptoms	Patients with MS Age: not reported	Interventions: Cannabis Savita, Dronabinol, THC extract, Nabiximols, THC:CBD extracts, Nabilone, CBD extract. Comparator: Placebo (mostly) or active comparator (not specified)	Pain, quality of life, adverse events Other outcomes not relevant for this current report: spasticity; bladder function; ataxis and tremor; and sleep. Study duration of included studies in the included SRs: 3 to 14 weeks
Hauser,[13] 2017, Germany	Overview on the use of cannabis-based medicines. This overview included 11 SRs, published between 2013 and 2016. It also included 3 long-term, prospective observational studies (> 6 months	Patients requiring pain management or palliative care. Age: not reported	Interventions: medical marijuana, Nabilone, THC/CBD, and Dronabinol. Comparator: Placebo or active comparator (amitriptyline)	Pain, adverse events (Other outcomes not relevant for this report included: dyspnea, loss of appetite.) Study duration: ranged

Table 2: Characteristics of Included Overviews (systematic review of systematic reviews)

First Author, Publication Year, Country	Study Designs and Numbers of Systematic Reviews Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	duration) published in 2015, or 2016. Country of origin of the systematic reviews were not reported. Exclusion criteria: Systematic reviews which did not include quantitative analysis and which did not explicitly mention the reasons for not performing meta-analysis were excluded. Objective: To assess the efficacy and risks associated with use of cannabinoids for pain management and palliative care, based on systematic reviews of RCTs and to review prospective observational studies to assess long-term risks			between for the included systematic reviews 5 hours to 14 weeksranged between 6 weeks and 52 weeks in the 3 observational studies
Systematic review of Guidelines				
Deng,[8] 2016, China	Included 3 CPGs relevant for the current report. The CPGs were published between 2007 and 2010. One CPG was from NICE (UK), the second CPG was from IASP (international), and the third CPG was from Latin America. Intended users of the CPGs: physicians involved in the management of neuropathic pain. Exclusion criteria: consensus statements based on expert opinion, and documents focused entirely on a single unique condition were excluded (This systematic review had a broad objective	Patients with neuropathic pain Age: NR	Interventions: Cannabinoids and other pharmacologic agents (such as anticonvulsants, topical treatments, SNRIs, opioids, sodium channel blockers)	Outcomes: Recommendations Follow-up: Not applicable

Table 2: Characteristics of Included Overviews (systematic review of systematic reviews)

First Author, Publication Year, Country	Study Designs and Numbers of Systematic Reviews Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	[management of neuropathic pain] and included 16 CPGs published between 2004 and 2014. Of these 16 CPGs, 3 CPGs reported on cannabinoids and are relevant for this current report. The remaining 13 CPGs did not report on cannabinoids, hence are not discussed here)			

CBD = cannabidiol; CPG = Clinical Practice Guideline; IASP = International Association for the Study of Pain; NICE = National Institute of Health and Care Excellence; NR = not reported; SNRIs = selective serotonin/noradrenaline reuptake inhibitors; SRs = systematic reviews; THC = delota-9-tetrahydrocannabinol

Table 3: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major outcomes considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Systematic review of Guidelines						
Deng,[8] 2016, China						
As this is a systematic review of guidelines, characteristics are presented in Table 2						
Guidelines						
Allan, [15] 2018, Canada						
Intended users: primary care providers. Target population: not specified, appears to be for patients whose conditions are refractory to	Cannabis	Pain, nausea and vomiting, spasticity, and adverse events	The method used for the development of the guideline was based on the Institute of Medicine's outline for Clinical Practice Guidelines We Can Trust[21] and the GRADE methodology.[22] A systematic review of systematic reviews	Recommendations were classified as strong or weak according to the GRADE methodology.[22]	Recommendations were based on consensus. GDG comprised 2 generalist family physicians, 2 pain-management focused family physicians, 1 inner-city family physician, 1 neurologist, 1 oncologist, 1 nurse practitioner, 1 pharmacist, and 1 patient representative	Externally reviewed (by clinicians and patients)

Table 3: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major outcomes considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
standard medical therapy			of RCTs was conducted		Recommendations were graded	
Hauser,[7] 2018, Germany						
Intended user: specialist and non-specialist prescribers Target population: Patients with chronic pain	Cannabis-based medicines	Pain, adverse events	The method used for the development of the position paper was based on the recommendations of a clinical consensus statement development manual by Rosenfeld et al.[23] A selective literature search was conducted. In addition, systematic reviews and guidelines not identified in the search was provided by members of the task force.	Evidence was not graded	Recommendations were based on consensus and finally approved by all members of the task force after two Delphi procedures Members of the task were comprised individuals with clinical and scientific experience. Recommendations were not graded	Externally reviewed
Australian Government,[19] 2017, Australia						
Intended user: Doctors who prescribe medicinal cannabis and their patients	Medicinal cannabis use for CNCP (in palliative care, epilepsy, CINV, MS and chronic pain	Pain intensity, physical functioning, emotional functioning, patient global impression of change, withdrawals from the study, and adverse events	The method used for the development of the guideline was based on the GRADE system.[24] A systematic review of previously published systematic reviews was conducted based on PRISMA	The GRADE system[24] was used.	Recommendations were made by the Chronic Pain Working Group. Also a workshop was held to review the available evidence and included representatives from consumer groups, medical colleges, special societies, and states and territories	Not reported

Table 3: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major outcomes considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
					Method used to formulate the recommendations were not specified. Recommendations were not grade	
CFPC,[18] 2014, Canada						
Intended users: Not specifically stated but appears to be for prescribers of dried cannabis Target population: Appears to be for patients with chronic pain or anxiety	Chronic pain or anxiety	Cannabis effectiveness, safety, and adverse effects	Literature search was conducted and evidence was reviewed. No details were presented.	Recommendations were classified as Level I (if based on well-conducted controlled trials or meta-analyses), Level II (if based on well- conducted observational studies), Level III (if based on expert opinion)	Recommendations were formulated based on consensus. GDG comprised members of the Addiction Medicine and Chronic Pain Program Committees of the SIFP of the CFPC as well as other SIFP program committee members Recommendations were graded.	Not reported
Moulin,[16] 2014, Canada						
Intended users: physiciuans, nurse practitioner, , and other allied health care individuals involved in the management of neuropathic pain. Target	Pharmacologic management of chronic neuropathic pain (includes cannabis and other agents)	Efficacy and safety (details not presented)	A systematic literature search was conducted (to identify systematic reviews, meta-analyses, and treatment recommendations, guidelines and/or consensus statements) and evidence was reviewed	First line: “if there was high-quality evidence of efficacy (at least one class I study or two consistent class II studies - level of recommendation grade B or better) […]; positive results in at least two NeP models [….], and if they were considered to be straight-forward and of sufficient	Recommendations were formulated based on consensus. GDG comprised individuals with research and clinical expertise relevant to the pathophysiology and management of neuropathic pain. Recommendations were not graded. However, they were classified as first-line, second-line, third-line	Externally reviewed – published in peer-reviewed journal

Table 3: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major outcomes considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
population: not explicitly specified but appears to be individuals with chronic neuropathic pain				tolerability to prescribe and monitor" (*p329*) Second or third line: "if there was high-quality evidence, but the medication required more specialized follow-up and monitoring" (*p329*) Fourth line: if there was at least one positive RCT, but further study was required	or fourth-line.	
Yadav,[17] 2014, US						
Intended users: Appears to be for health care professional involved in the care of MS patients Target population: Patients with MS	Cannabinoids and other complimentary, and alternative medicines (such as ginkgo biloba, Chinese medicine, glucosamine sulphate, massage therapy, mindfulness training, yoga)	Pain and other outcomes (such as spasticity, bladder symptoms, depression, anxiety, sleep, fatigue, cognitive function, tremor, paresthesia, and QoL)	The method used for the development of the guideline was not presented in detail however according to the ANN CPG process manual rigorous methods are followed. A systematic review was conducted	Details were not presented however according to the AAN CPG process manual[25] rigorous methods are followed. According to the manual: levels of recommendation were A, B, C and U. "Level A rating requires at least two consistent Class I studies" (p.49)[a] Level B rating requires at least one Class I study or two consistent Class II studies" (p.49)[a] "Level C rating	Details were not presented however according to the AAN CPG process manual[25] rigorous methods are followed. GDG comprised experts in the area. Recommendations were graded	Externally reviewed - published in a peer-reviewed journal

Table 3: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major outcomes considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
				requires at least one Class II study or two consistent Class III studies" (p.49)[a] Level U is based on insufficient evidence or Class IV studies (i.e., not meeting criteria for Class I to Class III) (p.49)[a]		

CINV = chemotherapy induced nausea and vomiting; CFPC = College of Family Physicians of Canada; CNCP = chronic non-cancer pain; GDG = Guideline Development Group; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; MS = multiple sclerosis; NeP = neuropathic pain;PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses; RCT = randomized controlled trial; SIFP = Section of Family Physicians with Special Interests or Focused Practices

[a]Study class: "**Class I:** Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required: a) primary outcome(s) clearly defined b) exclusion/inclusion criteria clearly defined c) adequate accounting for drop-outs and cross-overs with numbers sufficiently low to have minimal potential for bias d) relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.
Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a-d above OR a RCT in a representative population that lacks one criteria a-d.
Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement
Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion." (p49 of ANN CPG process manual[25])

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[9]

Strengths	Limitations
Allan,[11] 2018, Canada	
• The objective was clearly stated • MEDLINE was searched from 1946 to April 2017, and the Cochrane Library was searched in 2017 were searched until April 2015, starting 1946 for MEDLINE and 1974 for EMBASE. Also, reference list of the included studies and the authors' personal collections were searched. • Study selection was described, and a flow chart was presented • A list of included studies was provided • A list of excluded studies was provided • Article selection was done independently by two reviewers • Data extraction was done independently by two reviewers • Quality assessment was conducted independently by two reviewers using the modified version of AMSTAR (6 criteria were considered instead of 11, scores ranged between 0 and 6, with higher scores indicating better quality; scores ranged between 4 and 6 for >50% of the SRs) • Characteristics of the included systematic reviews were presented • Publication bias was explored using Funnel plots. However, presence of bias could not be ascertained definitely as systematic reviews for both cancer and non-cancer pain were considered. • Mata-analyses were conducted • It was mentioned that there were on conflicts of interest and the project received no external funding	• No major issues were found
Hauser,[12] 2018, Germany	
• The objective was clearly stated • The Cochrane database of SRs, database of abstracts and of reviews and effects (DARE), and PubMed were searched. Also, reference lists of the included systematic reviews were searched and pain medicine experts were contacted. • Study selection was described, and a flow chart was presented • A list of included studies was provided • Article selection was done independently by two reviewers • Data extraction was done independently by two reviewers • Quality assessment was conducted independently by two reviewers using AMSTAR, and it was reported that 4 SRs were of high quality and the remaining 6 SRs were of moderate quality • Characteristics of the included systematic reviews were presented • Mata-analyses were not conducted as the objective was to conduct a qualitative systematic review	• A list of excluded studies was not provided • Publication bias does not appear to have been examined • Conflicts of interest were Two of the three authors were associated with pharmaceutical companies. No funding was received for the current SR

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[9]

Strengths	Limitations
Nielsen,[14] 2018, Australia	
• The objective was clearly stated • Eight databases were searched (Medline, Medline In-Process & Other Non-indexed citations/Ovi, Embase/Ovid, PsycINFO/Ovid, EBM reviews- Cochrane Central Register of Controlled Trials/Ovid from 1980 to 2016 end. • Study selection was described, and a flow chart was presented • A list of included studies was provided • A list of excluded studies was provided • Article selection was done independently by two reviewers • Data extraction was done independently by two reviewers • Quality assessment was conducted independently by two reviewers using AMSTAR. AMSTAR score (0 to 11, higher scores indicating better quality) for the included SRs ranged from 2 to 10. • Characteristics of the included systematic reviews were presented	• Publication bias does not appear to have been examined • Meta-analyses were not conducted • Conflicts of interest were declared. Three authors had association with pharmaceutical companies and the remaining four authors had no conflicts of interest
Hauser,[13] 2017, Germany	
• The objective was clearly stated • The Cochrane database of SRs, database of abstracts and of reviews and effects (DARE), and Medline were searched January 2009 to January 2017 . Also, reference lists of the included systematic reviews were searched, and experts in pain medicine or palliative care were contacted to identify further SRs and long-term studies. • Study selection was described, and a flow chart was presented • A list of included studies was provided • Data extraction was done independently by two reviewers • Quality assessment was conducted using AMSTAR AMSTAR score (0 to 11, higher scores indicating better quality) for the included SRs ranged from 7 to 10 (3 SRs had scores of 9 or 10, and the remaining 8 SRs had scores 7 or 8). • Characteristics of the included systematic reviews were presented • It was mentioned that the authors had no conflicts of interest.	• Unclear if article selection was done in duplicate • Unclear if quality assessment was done in duplicate • List of excluded studies was not provided • Publication bias does not appear to have been examined • Meta-analyses were not conducted
Systematic review of Guidelines	
Deng,[8] 2016, China	
• The objective was clearly stated • Multiple databases (MEDLINE, EMBASE, the National Guideline Clearing House, the Guideline International Network. And Canadian Medical Association Infobase) were searched (search period not specified). In addition, websites	• A list of excluded studies was not provided • Unclear if data extraction was done in duplicate • Publication bias does not appear to have been examined

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[9]

Strengths	Limitations
of related associations, institutes, societies, and communities were searched. Also, reference list of relevant articles were searched. • Study selection was described, and a flow chart was presented • A list of included studies was provided • Article selection was done by two experienced reviewers; unclear if done independently • Quality assessment of the included guidelines was done using AGREEII; unclear if done in duplicate. For the 6 domains: "Scope and Purpose", Stakeholder Involvement" "Rigor of Development", "Clarity of Presentation", "Applicability" and "Editorial Independence" the respective scores were 85%, 91%, 88%, 91%, 35%, and 60% for the CPG from NICE (UK); 78%, 33%, 48%, 91%, 0% and 93% for the CPG from IASP (international); and 76%, 35%, 38%, 52%, 33%, and 0% for the CPG from Latin America . • Characteristics of the included studies were presented, but details were lacking. • Meta-analysis not feasible, as guideline recommendations • The authors mentioned that there were no conflicts of interest.	

AGREE II = Appraisal of Guidelines Research and Evaluation II; CPG = Clinical Practice Guideline; IASP = International Association for the Study of Pain; NICE = National Institute of Health and Care Excellence; SR = systematic review; SRs = systematic reviews

Table 5: Strengths and Limitations of Guidelines using AGREE II[10]

Item	Guideline			
	Allan, [15] 2018, Canada	Hauser,[7], 2018, Germany	Australian Government, [19] 2017, Australia	CFPC,[18] 2014, Canada
Domain 1: Scope and Purpose				
1. The overall objective(s) of the guideline is (are) specifically described.	y	y	y	y
2. The health question(s) covered by the guideline is (are) specifically described.	Apparent but not specifically presented as questions	Apparent but not specifically presented as questions	Apparent but not specifically presented as questions	Apparent but not specifically presented as questions
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Apparent but not specifically mentioned	Apparent but not specifically mentioned	Apparent but not specifically mentioned	Apparent but not specifically mentioned
Domain 2: Stakeholder Involvement				
4. The guideline development group includes	y	y	y	y

Table 5: Strengths and Limitations of Guidelines using AGREE II[10]

Item	Guideline			
	Allan, [15] 2018, Canada	Hauser,[7], 2018, Germany	Australian Government, [19] 2017, Australia	CFPC,[18] 2014, Canada
individuals from all relevant professional groups.				
5. The views and preferences of the target population (patients, public, etc.) have been sought.	y	unclear	unclear	unclear
6. The target users of the guideline are clearly defined.	y	y	y	y
Domain 3: Rigour of Development				
7. Systematic methods were used to search for evidence.	y	Appears to be so, details lacking	y	Appears to be so, details lacking
8. The criteria for selecting the evidence are clearly described.	y	Not stated	Not stated	Not stated
9. The strengths and limitations of the body of evidence are clearly described.	y	Not sated	y	To some extent
10. The methods for formulating the recommendations are clearly described.	y	y	Not stated	y
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	y	y	y	unclear
12. There is an explicit link between the recommendations and the supporting evidence.	y	y	Sometimes unclear	Unclear -details lacking
13. The guideline has been externally reviewed by experts prior to its publication.	y	y	Not stated	Not stated
14. A procedure for updating the guideline is provided.	Not stated	Not stated	Will be updated as new evidence emerges but updating procedure not specified	Not stated
Domain 4: Clarity of Presentation				
15. The recommendations are specific and unambiguous.	y	y	y	y
16. The different options for management of the condition or health issue are clearly presented.	Not stated	y	Not stated	Not stated
17. Key recommendations are easily identifiable.	y	y	y	y
Domain 5: Applicability				
18. The guideline describes facilitators and	Not stated	Not stated	Not stated	Not stated

Table 5: Strengths and Limitations of Guidelines using AGREE II[10]

Item	Guideline			
	Allan, [15] 2018, Canada	Hauser,[7], 2018, Germany	Australian Government, [19] 2017, Australia	CFPC,[18] 2014, Canada
barriers to its application.				
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Not stated	Not stated	Not stated	Not stated
20. The potential resource implications of applying the recommendations have been considered.	Not stated	Not stated	Not stated	Not stated
21. The guideline presents monitoring and/or auditing criteria.	Not stated	Not stated	y	Not stated
Domain 6: Editorial Independence				
22. The views of the funding body have not influenced the content of the guideline.	y	y	Not stated	Not stated
23. Competing interests of guideline development group members have been recorded and addressed.	y	Declared but procedure for addressing any conflicts of interest were not presented	Not stated	y

y = yes (i.e. criteria were met);

Table 6 : Strengths and Limitations of Guidelines using AGREE II[10]

Item	Guideline	
	Moulin,[16] 2014, Canada	Yadav (AAN)[a],[17] 2014, US
Domain 1: Scope and Purpose		
1. The overall objective(s) of the guideline is (are) specifically described.	y	y
2. The health question(s) covered by the guideline is (are) specifically described.	Apparent but not specifically presented as questions	y
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Apparent but not specifically mentioned	y
Domain 2: Stakeholder Involvement		
4. The guideline development group includes individuals from all relevant professional groups.	y	y
5. The views and preferences of the target population (patients, public, etc.) have been sought.	unclear	unclear
6. The target users of the guideline are clearly	y	y

Table 6 : Strengths and Limitations of Guidelines using AGREE II[10]

Item	Guideline	
	Moulin,[16] 2014, Canada	Yadav (AAN)[a],[17] 2014, US
defined.		
Domain 3: Rigour of Development		
7. Systematic methods were used to search for evidence.	y	y
8. The criteria for selecting the evidence are clearly described.	y	Not stated
9. The strengths and limitations of the body of evidence are clearly described.	Not stated	To some extent
10. The methods for formulating the recommendations are clearly described.	y	Not stated
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	y	y
12. There is an explicit link between the recommendations and the supporting evidence.	y	y
13. The guideline has been externally reviewed by experts prior to its publication.	y	y
14. A procedure for updating the guideline is provided.	To be updated but procedure for updating not presented	Not stated
Domain 4: Clarity of Presentation		
15. The recommendations are specific and unambiguous.	y	y
16. The different options for management of the condition or health issue are clearly presented.	y	y
17. Key recommendations are easily identifiable.	y	y
Domain 5: Applicability		
18. The guideline describes facilitators and barriers to its application.	Not stated	Not stated
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	A treatment algorithm presented	Not stated
20. The potential resource implications of applying the recommendations have been considered.	Not stated	Not stated
21. The guideline presents monitoring and/or auditing criteria.	Not stated	Not stated
Domain 6: Editorial Independence		
22. The views of the funding body have not influenced the content of the guideline.	Not stated	Not stated

Table 6 : Strengths and Limitations of Guidelines using AGREE II[10]

Item	Guideline	
	Moulin,[16] 2014, Canada	Yadav (AAN)[a],[17] 2014, US
23. Competing interests of guideline development group members have been recorded and addressed.	Several authors had association with pharmaceutical industries	y

ANN – American Academy of Neurology;

[a]Of note the AAN guideline by Yadav et al. is a summary guideline and details of the guideline development process are available in the AAN CPG process manual[25] which indicates that rigorous methods are followed

Appendix 4: Main Study Findings and Authors' Conclusions

Table 7: Summary of Findings Included Systematic Reviews and Meta-Analyses

<table>
<tr><th>Main Study Findings</th><th>Authors' Conclusion</th></tr>
<tr><td colspan="2">Overviews (Systematic review of Systematic Reviews)</td></tr>
<tr><td colspan="2">Allan,[11] 2018, Canada</td></tr>
<tr><td>
Pain
<table>
<tr><th rowspan="2">Outcome</th><th rowspan="2">No. of SRs</th><th rowspan="2">No. of RCTs (no. of patients) in each SR</th><th colspan="2">Cannabinoids versus placebo</th></tr>
<tr><th>Effect measure</th><th>Effect size</th></tr>
<tr><td>≥ 30% reduction in pain (neuropathic)</td><td>2</td><td>8(1370), and 2 (537)</td><td>RR</td><td>1.62, and 1.34; significant for both</td></tr>
<tr><td>≥ 30% reduction in pain (chronic or palliative)</td><td>2</td><td>5 (405), and 9 (1346)</td><td>RR</td><td>1.23, and 1.34; non-significant for both</td></tr>
<tr><td>Pain (chronic)</td><td>1</td><td>7 (278)</td><td>SMD</td><td>0.61, significant</td></tr>
<tr><td>Change in pain on VAS from 0 to 10 (MS)</td><td>1</td><td>7 (298)</td><td>Using VAS from 0 to 10</td><td>0.8 more pain reduction, significant</td></tr>
</table>
Two SRs reported insufficient evidence for benefit in rheumatologic pain and fibromyalgia

Adverse events
<table>
<tr><th rowspan="2">Outcome</th><th rowspan="2">No. of SRs</th><th rowspan="2">No. of RCTs (no. of patients) in each SR</th><th colspan="2">Cannabinoids versus placebo</th></tr>
<tr><th>Effect measure</th><th>Effect size (range)</th></tr>
<tr><td>Overall adverse events</td><td>4</td><td>4 (1025), 3 (666), 23 (2068), and 29 (3714)[a]</td><td>RR</td><td>1.18 to 1.86, significant in 4 SRs</td></tr>
<tr><td rowspan="3">Serious adverse events</td><td>2</td><td>6(1031), 23 (2068)</td><td>RR</td><td>1.15, and 1.04; not significant for both</td></tr>
<tr><td>1</td><td>11 (1568)</td><td>RD</td><td>1%, not significant</td></tr>
<tr><td>1</td><td>34 (3248)[a]</td><td>OR</td><td>1.41, significant</td></tr>
<tr><td rowspan="3">Withdrawals</td><td>3</td><td>6 (1031), 11 (1574), and 3 (666)</td><td>RR</td><td>1.20 to 3.04, significant in 2 SRs and non-significant in 1 SR</td></tr>
<tr><td>1</td><td>23 (2755)[a]</td><td>OR</td><td>2.94, significant</td></tr>
<tr><td>2</td><td>7 (508), and 24 (2737)</td><td>Event rate</td><td>4.3% versus 3.6%, and 7% versus 2%</td></tr>
</table>
[a]This SR also included studies on cancer patients, and it is likely that outcomes for cancer patients were also included
</td><td>"There is some uncertainty about whether cannabinoids improve pain, but if they do, it is neuropathic pain and the benefit is likely small. Adverse effects are very common, meaning benefits would need to be considerable to warrant trials of therapy." (p. e78)</td></tr>
<tr><td colspan="2">Hauser,[12] 2018, Germany</td></tr>
<tr><td>
Conclusions of each systematic review are presented below.

Systematic reviews of cannabis-based medicines for any type of chronic pain

Systematic Review by Whiting et al. (2015)
"There was moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain" (p.462)

Systematic Review by Martin-Sanchez (2009)
</td><td>"We provide an overview of systematic reviews on the efficacy, tolerability and safety of cannabis-based medicines for chronic pain management. There are inconsistent findings of the efficacy of cannabinoids in neuropathic pain and painful spasms in multiple sclerosis.</td></tr>
</table>

Table 7: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
"Currently available evidence suggests that cannabis treatment is moderately efficacious for treatment of chronic pain, but beneficial effects may be partially (or completely) offset by potentially serious harms" (p.462) **Systematic reviews of cannabis-based medicines for chronic neuropathic pain** Systematic Review by Petzke et al. (2016) "Short-term and intermediate-term therapy with cannabinoids can be considered in selected patients with chronic neuropathic pain after failure of first-line and second-line therapies" (p.463) Systematic Review by Andreae et al. (2015): "Inhaled cannabis appears to provide short-term relief from chronic neuropathic pain for one in five to six patients treated" (p.463) Systematic Review by Finnerup et al. (2015) "Cannabinoids have weak recommendations against their use in neuropathic pain" (p.463) Systematic Review by Jawahar et al. (2013) "The relatively small number of trials in multiple sclerosis patients with chronic pain precludes specific recommendations for treatment strategies"(p.463) **Systematic reviews of cannabis-based medicines for rheumatic disease** Systematic Review by Fitzcharles et al. (2016a) "There is insufficient evidence for recommendation for any cannabinoid preparations for symptom management in patients with chronic pain associated with rheumatic diseases." (p.464) Systematic review by Fitzcharles et al. (2016b) "Pain relief and effect on sleep may have some potential therapeutic benefit, but with considerable mild to moderate adverse events. There is currently insufficient evidence to recommend cannabinoid treatments for management of rheumatic diseases pending further study." (p.464) Systematic Review by Walitt et al. (2016) "We found no convincing, unbiased, high-quality evidence suggesting that nabilone is of value in treating people with fibromyalgia" (p.464) **Systematic reviews of cannabis-based medicines for cancer pain** Systematic review by Mucke et al. (2016) "due to the sparse amount of data, it is not possible to recommend a favoured use of cannabis products for cancer pain." (p.466)	There are inconsistent results on tolerability and safety of cannabis-based medicines for any chronic pain." (p455) "The available evidence comparing patient outcomes following cannabis-based medicines treatment versus placebo appears insufficient to make well-founded conclusions about the clinical advantage and use of cannabis-based medicines for the management of cancer and non-cancer pain." (p468)
Neilsen,[14],Australia	
Systematic reviews of cannabis-based medicines for treatment of pain in MS **Outcome: Pain** Intervention | No. of | Finding | Quality | Conclusion	"In conclusion, reviews identified evidence that would support a trial of cannabinoids for pain […] in a patient with multiple sclerosis. Effect sizes are

Table 7: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings					Authors' Conclusion
	studies (No. of RCTs)		assessment of evidence		generally small suggesting only modest effects may be expected. Adverse events were generally mild to moderate, although caution is warranted in specific populations of patients with multiple sclerosis with greater vulnerability to adverse effects from cannabinoids." (p10 of 12)
Cannabis sativa (smoked)	1 (1)	Positive effect	Low	Insufficient evidence	
Dronabinol	4 (3)	Positive effect	Low to high	Some evidence of positive effect	
THC extract	3 (2)	Positive effect	Very low to low	Some evidence of positive effect	
Nabiximols	8 (5)	Positive effect	Very low to moderate	Inconsistent evidence	
THC:CBD extract	7 (5)	Mixed effect	Very low to moderate	Inconsistent evidence	
Nabilone	1 (1)	Positive effect	Very low	Insufficient evidence	
CBD extract	2 (2)	Mixed effect	Low	Insufficient evidence	

Outcome: Quality of life

Intervention	No. of studies (No. of RCTs)	Finding	QA of evidence	Conclusion
Cannabis sativa (smoked)	2 (2)	Mixed effect	Low	Insufficient evidence
Dronabinol	2 (2)	Mixed effect	Low to high	Insufficient evidence
THC extract	none	NA	NA	NA
Nabiximols	5 (5)	Mixed effect	Moderate	Some evidence of positive effect
THC:CBD extract	3 (3)	Mixed effect	Low to high	Inconsistent evidence
Nabilone	2 (2)	Mixed effect	Very low to moderate	Insufficient evidence
CBD extract	none	NA	NA	NA

Outcome: Adverse events

Intervention	No. of studies (No. of RCTs)	Finding	QA of evidence	Conclusion
Cannabis sativa (smoked)	2 (2)	AEs > comparator	Low	Insufficient evidence
Dronabinol	8 (6)	AEs > comparator	Very low to high	Mild AEs likely
THC extract	1 (1)	AEs > comparator	Low	Mild AEs likely
Nabiximols	10 (7)	AEs > comparator	Very low to moderate	Mild AEs likely
THC:CBD extract	8 (6)	AEs > comparator	Low to high	Mild AEs likely
Nabilone	3 (3)	AEs > comparator	Very low to low	Mild AEs likely
CBD extract	1 (1)	AEs > comparator	Low	Insufficient evidence

Table 7: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
(Note: Quality of evidence was based on the GRADE approach in Cochrane Handbook V5.1 High: RCTs or double-upgraded observational studies; Moderate: downgraded RCTs, or upgraded observational studies Low: double downgraded RCTs, or observational studies; Very low: triple-downgraded RCTs, or downgraded observational studies, or case series/case reports)	
Hauser,[13] 2017, Germany	
Conclusions of each systematic review are presented below. **Systematic reviews of cannabinoids for chronic neuropathic pain** Systematic review by Petzke et al. (2016) Studies: 15 studies (1619 patients with chronic neuropathic disease) Efficacy: For >30% pain relief with cannabinoids compared with placebo, RD (95% CI): 0.01 (0.03 to 0.16) Safety: For cannabinoids compared with placebo: discontinuation due to adverse event, RD 0.04 (0.01 to 0.07); central nervous system adverse events: RD (95% CI), 0.38 (0.18 to 0.58); psychiatric disorders: RD (95% CI), 0.11 (0.06 to 0.16). No statistically significant group difference for SAEs. Conclusion: "Short-term and mid-term treatment may be considered in selected patients with chronic neuropathic pain after failure of first- and second-line therapy." (p.631) Systematic review by Andreae et al. (2015) Studies: 5 studies (178 patients with chronic neuropathic pain) Efficacy: For medical marijuana compared with placebo, for >30% pain relief: OR (95% CI), 3.2 (1.59 to 7.24) Safety: No quantitative data synthesis Conclusion: "Inhaled cannabis appears to result in short-term relief of neuropathic pain in 1 of 5–6 patients treated." (p631) Systematic review by Jawar et al. (2013) Studies: 3 studies (400 patients neuropathic pain) Efficacy: For cannabinoids compared with placebo: SMD (95% CI), 0.08 (0.74 to 0.89) Safety: No quantitative data synthesis Conclusion: "Due to the comparatively small number of studies evaluating multiple-sclerosis patients with chronic pain, no specific treatment recommendations can be made." (p.631) **Systematic reviews of cannabinoids for pain associated with rheumatic diseases** Systematic Review by Fitzcharles et al. (2016a) Studies: 4 RCTs (204 patients with fibromyalgia, rheumatoid arthritis, or osteoarthritis) Efficacy: For fibromyalgia patients THC/CBD reduced pain, and nabilone reduced pain in some patients but not in some patients. Study on osteoarthritis patients was terminated early as the FAAHI inhibitor showed no effect. Safety: Dizziness, cognitive problems, vertigo and nausea were reported by 50% of the patients Conclusion: "The current evidence is inadequate to recommend cannabinoids for the treatment of pain associated with rheumatic diseases" (Supplement: eTable 2) Systematic review by Fitzcharles et al. (2016b) Studies: 4 RCTs (160 patients with fibromyalgia, rheumatoid arthritis or musculoskeletal pain) Efficacy: No statistically significant difference between nabilone and placebo with respect to	"•Limited evidence is available to support the use of tetrahydrocannabinol/cannabidiol spray for the treatment of chronic neuropathic pain. •According to the quality criteria of evidence-based medicine, the available evidence for cannabinoids is inadequate for the indications of loss of appetite in patients with cancer or HIV/AIDS, fibromyalgia syndrome, Crohn's disease, musculoskeletal pain, rheumatoid arthritis, chronic pancreatitis, and cancer pain. •The use of cannabinoids in pain management and palliative medicine should be regarded as individual therapeutic trials, except for chronic neuropathic pain. •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)." (p.633)

Table 7: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
pain relief in fibromyalgia patients and in patients with musculoskeletal pain.. THC/CBD spray showed significant improvement in morning resting pain relief and pain on motion, but not in reducing overall and current pain intensity in patients with rheumatoid arthritis. No statistically significant difference between nabilone and amitriptyline with respect to pain relief in fibromyalgia patients. Safety: In fibromyalgia patients, discontinuation was numerically higher with nabilone compared to either placebo or amitriptyline. No SAE were reported in fibromyalgia or rheumatoid arthritis patients. One SAE was reported with nabilone in one patient with musculoskeletal pain. Conclusion: "The current evidence is inadequate to recommend cannabinoids for the treatment of pain associated with rheumatic diseases." (Supplement: eTable 2) Systematic Review by Walitt et al. (2016) Studies: 2 RCTs (72 patients with fibromyalgia) Efficacy: Compared with placebo, there was greater pain relief with nabilone in patients with fibromyalgia. There was no statistically significant difference in pain relief with nabilone compared with amitriptyline. Safety: Conclusion: "There is no unbiased and high quality evidence available to show benefits of nabilone in FMS patients." (Supplement: eTable 2) **Systematic reviews of cannabinoids for visceral pain** Systematic Review by Voltz et al. (2016) 1 RCT (21 patients with Crohn's disease) Efficacy: No significant difference in in remission rate; significant relief of abdominal pain ($P < 0.05$) Safety: No difference in tolerability with medical marijuana compared with placebo. No withdrawals or serious adverse events were reported Conclusion: "Currently, considering an individual therapeutic trial of tetrahydrocannabinol in gastroenterology is limited to symptomatic relief of pain and loss of appetite in patients with Crohn's disease, but only after failure of all established pharmacotherapy options and careful risk–benefit assessment" (Supplement: eTable 3)	
Systematic Review of Guidelines	
Deng,[8] 2016, China	
See recommendations in **Table** 8	

AE = adverse events: CBD = cannabinoid; CI = confidence interval; CNCP = chronic non-cancer pain; FAAH1 = fatty-acid amide hydrolase; FMS = fibromyalgia syndrome; GRADE = Grading of Assessment, Development and Evaluation; MS = multiple sclerosis; NA = not applicable; OR = odds ratio; QA = quality assessment; RCT = randomized controlled trial; RD = risk difference; RR = relative risk; SAE = serious adverse events; SMD = standardized mean difference; SR = systematic reviews; SRs = systematic reviews; THC = delta-9-tetrahydrocannabinol; VAS = visual analog scale.

Table 8: Summary of Recommendations in Included Guidelines

Evidence and Recommendations	Strength of Evidence and Recommendations
Systematic Review of Guidelines	
Deng,[8] 2016, China	
Evidence: It was reported that evidence-based approach was used, but details were not presented **Recommendation:** Three guidelines recommended the use of cannabinoids as fourth line analgesics for the management of neuropathic pain.	**Strength of Evidence:** Not reported **Strength of Recommendation:** Not reported
Guidelines	
Allan, [15] 2018, Canada	
<u>Headache</u> **Evidence:** **I**nsufficient evidence (1 flawed cross-over RCT) on benefit, and known harms **Recommendation:** "We recommend against use of medical cannabinoids for headache owing to lack of evidence and known harms (strong recommendation)" (*p.112*) **<u>Pain due to rheumatologic conditions</u>** (including fibromyalgia, osteoarthritis, rheumatoid arthritis, and back pain) **Evidence:** Insufficient evidence for benefit (reported in 3 systematic reviews) and high risk of harms **Recommendation**: "We recommend against use of medical cannabinoids for pain associated with rheumatologic conditions (including osteoarthritis and back pain) owing to lack of evidence and known harms (strong recommendation)" (*p.112*) **<u>Neuropathic pain:</u>** **Evidence:** One meta-analysis showed a greater number of patients achieved >30% pain reduction with cannabinoids. However sensitivity analysis using RCTs of large size or longer duration found no effect. Harms resulting from cannabinoids were consistent and common among the various conditions evaluated. One overview reported that the risk of adverse events and withdrawals were numerically higher with cannabinoids compared with placebo (adverse events: 80% versus 60%; withdrawals: 11% versus 3%). **Recommendations:** "We recommend against medical cannabinoids as first- or second-line therapy in neuropathic pain owing to limited benefits and high risk of harms (strong recommendation) -Clinicians could consider medical cannabinoids for refractory neuropathic pain, with the following considerations (weak recommendation): - a discussion has taken place with patients regarding the benefits and risks of medical cannabinoids for pain - patients have had a reasonable therapeutic trial* of ≥ 3 prescribed analgesics† and have persistent problematic pain despite optimized analgesic therapy	**<u>Headache</u>** **Strength of Evidence:** Not reported **Strength of Recommendation:** Strongly against **<u>Pain due to rheumatologic conditions</u>** **Strength of Evidence:** Not reported **Strength of Recommendation:** Strongly against **<u>Neuropathic pain:</u>** **Strength of Evidence:** Not reported **Strength of Recommendation:** Strongly against (with respect to cannabinoid use as first- or second line therapy); Weak (with respect to use of cannabinoids for refractory neuropathic pain)

Table 8: Summary of Recommendations in Included Guidelines

Evidence and Recommendations	Strength of Evidence and Recommendations
- medical cannabinoids are adjuncts to other prescribed analgesics" (*p112*) *Note:* "*Reasonable therapeutic trial is defined as 6 weeks of therapy with an appropriate dose, dose titration, and monitoring (eg, function, quality of life). †Other prescribed therapies for neuropathic pain management include, but are not limited to (in no particular order), tricyclic antidepressants (e.g.,, amitriptyline, nortriptyline), gabapentinoids (gabapentin, pregabalin), or selective norepinephrine reuptake inhibitor antidepressants (duloxetine, venlafaxine). The committee believed that ≥ 3 medications should be trialed before considering cannabinoids or opioids." (*p.112*)	
Hauser,[7] 2018, Germany	
Chronic neuropathic pain **Evidence:** One overview found that findings on efficacy of cannabinoids compared to placebo were inconsistent. One systematic review reported that inhaled cannabis appeared to provide short-term relief. No data on intermediate term were available A second systematic review reported that the between group risk difference with respect to >30% pain relief was not statistically significant. A third systematic review concluded that for short-term or intermediate term cannabis-based medicines may be considered in selective patients with chronic neuropathic pain, after first- and second line treatments have failed. A fourth systematic review concluded that there was no high-quality evidence suggesting the use cannabis-based medicines was of value. In addition, potential benefits might be outweighed by the potential harms associated with cannabis-based medicines **Recommendations:** "Cannabis-based medicines can be considered as third-line therapy for chronic neuropathic pain." (p.1553) **Chronic non-neuropathic non-cancer pain** **Evidence:** One systematic review concluded that there was insufficient evidence to support cannabis-based treatment for patients with chronic non-neuropathic non-cancer pain **Recommendation:** "In exceptional cases, cannabis-based medicines can be considered as an individual therapeutic trial, if all established treatments have failed and after careful analyses and multidisciplinary assessment." (p.1554)	**Strength of Evidence: Not reported** **Strength of Recommendation:** Not reported **Strength of Evidence: Not reported** **Strength of Recommendation:** Not reported
Australian Government,[19] 2017, Australia	
<u>Overall management of CNCP</u> **Evidence:** Not reported **Recommendations:** "A comprehensive sociopsychobiomedical assessment of the patient with CNCP is appropriate; The use of medications, including medicinal cannabis, is not the core component of therapy for CNCP; Patient education is a critical component of therapy for CNCP, particularly with respect to	**<u>Overall management of CNCP</u>** **Strength of Evidence:** Not reported **Strength of Recommendation:** Not reported

Table 8: Summary of Recommendations in Included Guidelines

Evidence and Recommendations	Strength of Evidence and Recommendations
expectations of drug therapy; and There is a need for larger trials of sufficient quality, size and duration to examine the safety and efficacy of medicinal cannabis use in CNCP." (*p3*) **Cannabinoids as second-line therapy for CNCP** **Evidence:** Evidence was derived using 102 studies (4 studies reported on cannabis as first-line therapy; 81 studies reported on cannabis as second-line therapy in addition to existing medication regimens; and 17 studies did not report the place of cannabis in the therapeutic hierarchy) **Recommendation:** "Most evidence on medicinal cannabis use in CNCP is derived from studies where cannabinoids were adjuvant interventions. Cannabinoids should not replace current approved first-line treatments for pain and there is significant potential for drug interactions which needs further study." (p14) **Tolerability of cannabinoids** **Evidence:** Evidence for the various types of cannabinoids was derived from several studies (number of studies varied between 1 and 10 depending on the type of cannabinoid) **Recommendation:** "Adverse effects of long-term medicinal cannabis use is poorly understood. Long term studies are required to explore this issue." (*p.19*) **Patient's response to cannabis treatment** **Evidence:** Duration of treatment in most RCTs and observational studies was less than 12 weeks. In three observational studies the duration of treatment was 12 months or longer. **Recommendation:** "In the absence of strong evidence for dosing and specific preparations of cannabis or cannabinoids in the treatment of CNCP, it is recommended that any treating physician who elects to initiate cannabinoid therapy should assess response to treatment, effectiveness and adverse effects after 1 month. This is best achieved as part of a research project or clinical audit." (*p.20*)	**Cannabinoids as second-line therapy for CNCP** **Strength of Evidence:** Not reported **Strength of Recommendation:** Not reported **Tolerability of cannabinoids** **Strength of Evidence:** Very low to moderate **Strength of Recommendation:** Not reported **Patient's response to cannabis treatment** **Strength of Evidence:** Not reported **Strength of Recommendation:** Not reported
CFPC,[18] 2014, Canada	
Evidence: For chronic neuropathic pain, the evidence was obtained from five controlled trials of small size and short duration (1 to 15 days). No information was available on functional status, quality of life and other important outcomes The safety and effectiveness of dried cannabis has not been studied for conditions such as fibromyalgia and back pain. **Recommendation 1:** "There is no research evidence to support the authorization of dried cannabis as a treatment for pain conditions commonly seen in primary care, such as fibromyalgia or low back pain (Level III). Authorizations for dried cannabis should only be considered for patients with neuropathic pain that has failed to respond to standard treatments (Level I)." (*p.3*)	**Strength of Evidence: Not reported** **Strength of Recommendation:** Level III or Leve I as indicated in the adjacent column.

Table 8: Summary of Recommendations in Included Guidelines

Evidence and Recommendations	Strength of Evidence and Recommendations
Evidence: Before considering treatment with cannabinoids, established effective pharmacological and non-pharmacological treatments need to be tried. **Recommendation 2:** "If considering authorizing dried cannabis for treatment of neuropathic pain, the physician should first consider a) adequate trials of other pharmacologic and nonpharmacologic therapies and b) an adequate trial of pharmaceutical cannabinoids (Level I). (*p.3*) **Other recommendations** not specifically for chronic pain are listed below but not discussed further. **Recommendation:** "Dried cannabis is not appropriate for patients who: a) Are under the age of 25 (Level II) b) Have a personal history or strong family history of psychosis (Level II) c) Have a current or past cannabis use disorder (Level III) d) Have an active substance use disorder (Level III) e) Have cardiovascular disease (angina, peripheral vascular disease, cerebrovascular disease, arrhythmias) (Level III) f) Have respiratory disease (Level III) or g) Are pregnant, planning to become pregnant, or breastfeeding (Level II)" (*p.3*) **Recommendation:** "Dried cannabis should be authorized *with caution* in those patients who: a) Have a concurrent active mood or anxiety disorder (Level II) b) Smoke tobacco (Level II) c) Have risk factors for cardiovascular disease (Level III) or d) Are heavy users of alcohol or taking high doses of opioids or benzodiazepines or other sedating medications prescribed or available over the counter (Level III)" (*p.3*) **Recommendation:** "Physicians should follow the regulations of their provincial medical regulators when authorizing dried cannabis (Level III). (*p4*) Recommendation: "Physicians should assess and monitor all patients on cannabis therapy for potential misuse or abuse (Level III)." (*p4*) Recommendation: "Before signing a medical document authorizing dried cannabis for pain, the physician should do all of the following: a) Conduct a pain assessment (Level II) b) Assess the patient for anxiety and mood disorders (Level II) c) Screen and assess the patient for substance use disorders (Level II)" (*p4*) **Recommendation:** The physician should regularly monitor the patient's response to treatment with dried cannabis, considering the patient's function and quality of life in addition to pain relief (Level III). The physician should discontinue authorization if the therapy is not clearly effective or is causing the patient harm. (Level III)." (*p.4*)	

Table 8: Summary of Recommendations in Included Guidelines

Evidence and Recommendations	Strength of Evidence and Recommendations
Recommendation: "Patients taking dried cannabis should be advised not to drive for at least: a) Four hours after inhalation (Level II) b) Six hours after oral ingestion (Level II) c) Eight hours after inhalation or oral ingestion if the patient experiences euphoria (Level II)" (*p4*) **Recommendation:** "When authorizing dried cannabis therapy for a patient, the physician should advise the patient of harm reduction strategies (Level III)."(*p.4*) **Recommendation:** "The physician should manage disagreements with patients about decisions around authorization, dosing, or other issues with unambiguous, evidence-based statements (Level III). "(*p.4*) **Recommendation:** "The physician who is authorizing cannabis for a particular clinical indication must be primarily responsible for managing the care for that condition and following up with the patient regularly (Level III). Physicians seeking a second opinion on the potential clinical use of cannabis for their patient should only refer to facilities that meet standards for quality of care typically applied to specialized pain clinics (Level III). In both instances, it is essential that the authorizing physician, if not the patient's most responsible health care provider, communicate regularly with the family physician providing ongoing comprehensive care for the patient (Level III)." (*p.4*) **Recommendation:** "Given the weak evidence for benefit and the known risks of using cannabis, the only sensible advice for physicians involved with authorizing dried cannabis is the maxim "Start low, and go slow" (Level III)." (*p.5*) **Recommendation:** Although it is not required by the MMPR, physicians should specify the percentage of THC on the medical document for all authorizations for dried cannabis, just as they would specify dosing when prescribing any other analgesic (Level III). (*p.5*)	
Moulin (Canadian Pain Society),[16] 2014, Canada	
Evidence: Three trials found positive effects with cannabinoids in terms of pain management. In addition, one systematic review including seven trials found positive effects in six trials and negative effect in one trial with cannabinoids in terms of pain management. **Recommendation:** "One class of medication is recommended for third-line treatment in the management of NeP – cannabinoids." (*p.330*) It was also mentioned that use of cannabinoids is recommended but judicious prescribing practices are required.	**Strength of Evidence:** Not reported **Strength of Recommendation:** Not reported
Yadav (American Academy of Neurology),[17] 2014, US	

Table 8: Summary of Recommendations in Included Guidelines

Evidence and Recommendations	Strength of Evidence and Recommendations
Evidence 1 Evidence obtained from studies: two Class I, one Class II, and one Class III. **Recommendation 1:** "Clinicians might offer OCE to patients with MS to reduce patient-reported symptoms of spasticity and pain (excluding central neuropathic pain) (Level A)" (*p.1087*)	**Evidence 1:** Class I, II and III. **Recommendation 1:** Level A
Evidence 2 Evidence obtained from studies: one Class I and one Class II . **Recommendation 2:** "Clinicians might offer THC to patients with MS to reduce patient-reported symptoms of spasticity and pain (excluding central neuropathic pain) (Level B)." (*p.1087*)	**Evidence 2:** Class I and II. **Recommendation 2:** Level B
Evidence 3: Evidence obtained from one Class I study each, for the outcomes mentioned in the associated recommendation below. **Recommendation 3:** "Clinicians might offer Sativex oromucosal cannabinoid spray (nabiximols), where available, to reduce symptoms of spasticity, pain, or urinary frequency, although it is probably ineffective for improving objective spasticity measures or number of urinary incontinence episodes (Level B)." (*p.1087*)	**Evidence 3:** Class I. **Recommendation 3:** Level B
Evidence 4: Insufficient evidence **Recommendation 4:** "Data are inadequate to support or refute use of the following in MS (Level U): […] Smoked cannabis for spasticity, pain, balance/posture, and cognition" (*p.1088*)	**Evidence 4:** Insufficient. **Recommendation 4:** Level U

CNCP = chronic non-cancer pain; MMPR = Marihuana for Medical Purposes Regulations; MS = multiple sclerosis; NeP = neuropathic pain; OCE = oral cannabis extract; RCT = randomized controlled trial; THC = delta-9-tetrahydrocannabinoid.

Appendix 5: Overlap between Included Systematic Reviews

Table 9: Systematic Review Overlap between Included Overviews

Primary Study Citation	Systematic Review Citation			
	Allan, [15] 2018, Canada	Hauser,[12] 2018, Germany	Nielsen,[14] 2018, Australia	Hauser,[13] 2017, Germany
Andreae, 2015	X	X		X
Andrzejewski, 2016			X	
Ben Amar, 2006			X	
Boychuk, 2015	X			
CADTH, 2010a	X			
CADTH, 2010b	X			
CADTH, 2011	X			
Campbell	X			
Deshpande, 2015	X			
Finnerup, 2015		X		
Fitzcharles, 2016a	X	X		X
Fitzcharles, 2016b	X	X		X
Iskedjian, 2007	X			
Jawahar, 2013		X	X	X
Jensen, 2015	X			
Karst, 2010			X	
Koppel, 2014	X		X	
Lakhan, 2009			X	
Lynch, 2011	X			
Lynch, 2015	X			
Ludge, 2013				X
Martin-Sanchez, 2009	X	X		
Meza, 2017	X			
Mills, 2007			X	
Mücke, 2016	X	X		X
Nugent, 2017	x			
Petzke, 2016	X	X		X
Shakespeare, 2003			X	
Tsang, 2016	X			
Voltz, 2016				X

Table 9: Systematic Review Overlap between Included Overviews

Primary Study Citation	Systematic Review Citation			
	Allan, [15] 2018, Canada	Hauser,[12] 2018, Germany	Nielsen,[14] 2018, Australia	Hauser,[13] 2017, Germany
Wade, 2010	X			
Wang, 2008	X		X	
Walitt, 2016	X	X		X
Whiting, 2015	X	X	X	X
Zhormitsky, 2012			X	

Appendix 6: Additional References of Potential Interest

Systematic reviews not included in the selected overviews. These were excluded as the decision was to include only overviews (systematic review of systematic reviews).

Ho C, Martinusen D, Lo C. A Review of Cannabis in Chronic Kidney Disease Symptom Management. *Can J Kidney Health Dis.* 2019;6:2054358119828391.

Millar SA, Stone NL, Bellman ZD, Yates AS, England TJ, O'Sullivan SE. A systematic review of cannabidiol dosing in clinical populations. *Br J Clin Pharmacol.* 2019;20:20.

Yanes JA, McKinnell ZE, Reid MA, et al. Effects of cannabinoid administration for pain: A meta-analysis and meta-regression. *Exp Clin Psychopharmacol.* 2019;23:23.

IsHak WW, Wen RY, Naghdechi L, et al. Pain and Depression: A Systematic Review. *Harv Rev Psychiatry.* 2018;26(6):352-363.

Stockings E, Campbell G, Hall WD, et al. Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. *Pain.* 2018;159(10):1932-1954.

Vuckovic S, Srebro D, Vujovic KS, Vucetic C, Prostran M. Cannabinoids and Pain: New Insights From Old Molecules. *Front Pharmacol.* 2018;9:1259.

Allende-Salazar RF, Rada G. Are cannabinoids an effective treatment for chronic non-cancer pain? *Medwave.* 2017;17(Suppl2):e6972.

Aviram J, Samuelly-Leichtag G. Efficacy of Cannabis-Based Medicines for Pain Management: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Pain physician.* 2017;20(6):E755-E796.

Goldenberg M, Reid MW, IsHak WW, Danovitch I. The impact of cannabis and cannabinoids for medical conditions on health-related quality of life: A systematic review and meta-analysis. *Drug Alcohol Depend.* 2017;174:80-90.

Meng H, Johnston B, Englesakis M, Moulin DE, Bhatia A. Selective Cannabinoids for Chronic Neuropathic Pain: A Systematic Review and Meta-analysis. *Anesth Analg.* 2017;125(5):1638-1652.

Meza R, Pena J, Garcia K, Corsi O, Rada G. Are cannabinoids effective in multiple sclerosis? *Medwave.* 2017;17(Suppl1):e6865.

Noel C. Evidence for the use of "medical marijuana" in psychiatric and neurologic disorders. *Ment Health Clin.* 2017;7(1):29-38.

Norton C, Czuber-Dochan W, Artom M, Sweeney L, Hart A. Systematic review: interventions for abdominal pain management in inflammatory bowel disease. *Aliment Pharmacol Ther.* 2017;46(2):115-125.

Nugent SM, Morasco BJ, O'Neil ME, et al. The Effects of Cannabis Among Adults With Chronic Pain and an Overview of General Harms: A Systematic Review. *Ann Intern Med.* 2017;167(5):319-331.

Mehta S, McIntyre A, Janzen S, Loh E, Teasell R, Spinal Cord Injury Rehabilitation Evidence T. Systematic Review of Pharmacologic Treatments of Pain After Spinal Cord Injury: An Update. *Arch Phys Med Rehabil.* 2016;97(8):1381-1391.e1381.

Merlin JS, Bulls HW, Vucovich LA, Edelman EJ, Starrels JL. Pharmacologic and non-pharmacologic treatments for chronic pain in individuals with HIV: a systematic review. *AIDS Care.* 2016;28(12):1506-1515.

Hill KP. Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems: A Clinical Review. *JAMA.* 2015;313(24):2474-2483.