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SUMMARY WITH CRITICAL APPRAISAL

Nabilone for Chronic Pain Management: A Review of Clinical Effectiveness and Guidelines – An Update

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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

AE	adverse events
CBD	cannabidiol
CNCP	chronic non-cancer pain
COI	conflict of interest
FMS	fibromyalgia syndrome
MS	Multiple Sclerosis
MSK	musculoskeletal
NP	neuropathic pain
PGC	Prescribing Guidelines Committee
PGIC	patient global impression of change
RCT	randomized controlled trial
SAE	serious adverse events
SR	systematic review
THC	tetrahydrocannabinol
QoL	quality of life

Context and Policy Issues

Among those who self-report the use of medical marijuana, chronic pain is the most common reason followed by others such as anxiety, sleep disorders, and spasticity in Multiple Sclerosis (MS).[1] According to Health Canada, the use of medical marijuana has increased at a rate of almost three times per year since 2014.[2] Despite the growing interest and use of medical cannabinoids, there is still a lack of agreement about their role and clinical effectiveness for chronic pain.[1,3]

Nabilone (Cesamet®) is a synthetic cannabinoid that is chemically similar to the active ingredient in *Cannabis sativa L.* (marijuana), delta-9-tetrahydrocannabinol (delta-9-THC).[4] It is administered orally and has complex effects on the central nervous system, [4] including interaction with the CB1 and CB2 receptors which are the two cannabinoid receptors of the endocannabinoid system.[3,5] These receptors have been linked to potential pain relieving activity through inhibitory effects on pain responses and thus, are of interest for the treatment of chronic pain.[3] Nabilone has been approved by the US Food and Drug Administration[4] and Health Canada[6] to be used for the treatment of nausea and vomiting induced by chemotherapy, and has also been reported for off-label management of pain.[1]

The purpose of this review is to provide evidence on the clinical benefits and harms, as well as evidence-based guidelines on the use of nabilone for the management of chronic pain. This report is an update of a CADTH rapid response report published in 2017[7] and 2011.[8]

Research Questions

1. What is the clinical effectiveness of nabilone for the treatment of chronic pain due to any disease in adults?
2. What are the evidence-based guidelines regarding the use of nabilone for the treatment of chronic pain due to any disease in adults?

Key Findings

Based on two systematic reviews (SRs) that included an evaluation of nabilone for management of chronic pain, there was limited evidence that nabilone may be better than

placebo or known analgesics (such as amitriptyline) in relieving chronic pain. The two evidence-based guidelines that were identified recommended against the use or did not find sufficient evidence to support the use of nabilone for pain management or chronic non-cancer pain; however one of the two guidelines provided a weak recommendation for the consideration of nabilone as a third-line therapy for persistent problematic neuropathic pain (NP) or palliative (end-of-life) cancer pain. Limited evidence was identified regarding the safety of nabilone specifically, but the evidence that was available suggested that cannabinoids are associated with more adverse events (AEs) than placebo, though the majority of reported AEs were non-serious.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, the Cochrane Library, University of York Centre for Reviews and Dissemination Medline, Embase, Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied to limit retrieval. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2016 and October 4, 2018.

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 with chronic pain due to any disease
Intervention	Nabilone (Cesamet)
Comparator	Q1: Active treatments, placebo, or no treatment Q2: No comparator
Outcomes	Q1: Clinical effectiveness (e.g., reduction in pain, pain relief, patient satisfaction) and safety (e.g., harms, adverse events, abuse and misuse) Q2: Guidelines
Study Designs	HTAs, SRs, MAs, RCTs, non-randomized primary studies, and evidence-based guidelines

HTA = health technology assessment; MA = meta-analysis; RCT = randomized controlled trial; SR = systematic review.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, were published prior to 2017, or if the material was covered in either of the two previous versions of this report.[7,8] Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included SRs were critically appraised by one reviewer using the AMSTAR II checklist,[9] and guidelines were assessed with the AGREE II instrument.[10] Summary scores were not

calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 54 citations were identified in the literature search. Following screening of titles and abstracts, 37 citations were excluded and 17 potentially relevant reports from the electronic search were retrieved for full-text review. Three potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 16 publications were excluded for various reasons, and four publications met the inclusion criteria and were included in this report. These comprised two systematic reviews and two evidence-based guidelines. Appendix 1 presents the PRISMA[11] flowchart of the study selection.

Additional references of potential interest are provided in Appendix 6.

Summary of Study Characteristics

Two relevant SRs[12,13] and two relevant evidence-based guidelines[1,14] were identified. Study characteristics are summarized below and details are available in Appendix 2, Tables 2 and 3.

Study Design

One of the two SRs was an overview of SRs, which included 11 reviews, four of which were relevant to the current review based on the inclusion criteria in Table 1.[12] The other SR was also an overview, but included both SRs and prospective cohort studies that were at least 6 months long.[13] Five of the SRs included in the second overview were relevant to this review.[13] The two SRs were published in 2018[12] and 2017,[13] respectively. The total number of individual SRs and prospective cohort studies covered by the two overviews was 45, with publication dates ranging from 2003 to 2016. Overlap of studies included in the SRs is detailed in Appendix 5, Table 8.

The two sets of guidelines included in this review were developed by a team of academics forming a Chronic Pain Working Group[14] and a Prescribing Guideline Committee (PGC) formed from an Evidence Review Group.[1] Both of the guidelines were based on a systematic review,[1,14] one of which was previously published.[1,14] The quality of evidence was evaluated using GRADE methodology in both guidelines, which was used to support the strength of recommendations in one of the two.[1] The strength of the recommendations in one guideline was inconsistently graded.[14] Both of the guidelines developed their recommendations through a working group[14] or meeting.[1]

Country of Origin

Authors of the two SRs were based in Australia[12] and Germany[13] and the guidelines were intended for and published by groups from Australia[14] and Canada.[1]

Patient Population

One overview included participants with MS,[12] and the other overview included patients with chronic cancer and non-cancer pain and symptomatic treatment of further somatic symptoms of advanced diseases.[13].The SRs included in the latter overview that also

included primary studies on nabilone involved the following conditions: fibromyalgia syndrome (FMS) and musculoskeletal (MSK) pain.[13] Neither was limited to, but presumably included adults due to the nature of the intervention.[12,13] The age of participants and overall sample size were not reported.[12,13]

One set of guidelines was developed for adults (≥ 18 years of age) considering the management of chronic pain, nausea/vomiting, and spasticity with medical cannabinoids.[1] The other guidelines did not specify a particular patient population; however, stated it was developed to provide doctors and patients with information to help make a decision about the prescription of medicinal cannabis in Australia.[14]

Interventions and Comparators

Both of the overviews included studies that evaluated the effects of plant-based and pharmaceutical-based cannabinoids, which was not limited to but included nabilone.[12,13] One overview indicated doses of nabilone ranged between 0.5 mg and 2 mg/day,[12] and details about the dose were not reported in the other.[13] One also specified that nabilone was administered orally.[13]

Details regarding the comparators were poorly described in both of the overviews. One listed the following interventions were included: nabilone, placebo and other cannabinoids, such as tetrahydrocannabinol (THC), cannabidiol (CBD), combination THC/CBD, *Cannabis sativa*, tetrahydrocannabinolic acid, cannabidiolic acid, canabidivarin, and another delta-9-tetrahydrocannabinol formulation (dronabinol).[12] The other overview listed the following cannabinoids used in the included studies, in addition to nabilone: medical marijuana (joint, vaporizer), THC/CBD spray, fatty acid amide, hydrolase inhibitor, dronabinol, and THC-containing cigarettes.[13] Only data for studies that assessed the use of nabilone were included in this report. As for the comparators, an explicit list was not included in either overview; however based on the results, nabilone was compared to placebo in the studies of both overviews,[12,13] and also compared to amitriptyline in studies included in one of the two overviews.[13]

Both sets of guidelines considered medical cannabinoids, broadly. One set of guidelines stated that this included pharmaceutically derived cannabinoids (e.g. nabilone and nabiximols) as well as medical marijuana.[1] The other set of guidelines provided a list of cannabinoid products in studies of medicinal cannabis for chronic non-cancer pain (CNCP): nabiximols, THC:CBD extracts, dronabinol, THC extract, nabilone, CBD extract, cannabis sativa, and ajulemic acid.[14]

Outcomes

Both of the overviews evaluated pain and adverse events (AEs) as outcomes. One overview reported pain in terms of “reduction of pain” and an “objective rating of improvement in pain”,[12] while the other included SRs that evaluated pain in terms of: mean or change in pain intensity at end of treatment, and 30% pain relief at treatment compared to baseline.[13] In terms of safety, serious adverse events (SAEs), deaths, and discontinuation rate due to AEs were also outcomes of interest specified in that review.[13] Additionally, one of the overviews also included measures of quality of life (QoL) as an outcome.[12] More specifically, the QoL was evaluated in patients based on the patient global impression of change (PGIC) scale, as well as an objective rating of general health status.[12]

The overviews reported other outcomes as well, but they were outside the scope of the current review. Lastly, the length of follow-up ranged from two to 14 weeks in one overview[13] and was not reported in the other.[12]

One set of guidelines provided recommendations on the use of medical cannabinoids, including nabilone, for the management of pain along with nausea and vomiting, and spasticity.[1] The other set of guidelines provided recommendations as well, but they were not specific to nabilone, although a summary of the effects of medicinal cannabis on the following outcomes was provided and summarized in this report: pain intensity, physical functioning, emotional functioning, PGIC scale, withdrawal from studies, and AEs.[14]

Summary of Critical Appraisal

Critical appraisal of the studies and guidelines is summarized below and details are available in Appendix 3, Tables 4 and 5.

Systematic Reviews

The scope and purpose for both overviews was clearly described, and they were based on a comprehensive literature search that included multiple databases and at least one trial registry.[12,13] The two overviews included a risk of bias assessment and an assessment of quality for included reviews and studies using validated tools, and also provided justification for excluded studies.[12,13] An assessment of risk of bias was performed in both overviews,[12,13] but details regarding the methodology and assessment of results was not provided for one of the overviews.[13]

Adequate detail for the SRs and other studies that were included was provided for the two overviews; however, as a SR of SRs, detail regarding the primary studies was lacking.[12,13] Further, neither of the overviews stated whether the review methods were established *a priori*, and it was not clear whether study selection was performed in duplicate in one review.[13] The other overview used a data extraction tool which was piloted and reviewed, though additional detail about the use of this tool, including validation of the data that was extracted was unclear.[12] Lastly, potential sources of a conflict of interest (COI) was provided for both of the overviews, which both suggested there were no apparent issues regarding COIs,[12,13] but only one of the two SRs provided information about related funding.[12]

Guidelines

The scope, purpose, and evidence associated with recommendations or guidance was described for both of the included guidelines, as well as the population that the guideline is meant to apply to[1,14]; however, one set of guidelines only provided a vague description of the target audience.[14] One of the two guidelines included stakeholder involvement, developed by a committee consisting of a variety of relevant health care professionals from across the country, and a patient representative.[1] They also sought feedback from clinicians and patients outside the committee prior to finalization.[1] In contrast, the other guideline did not provide a list of members included and did not report seeking outside feedback from relevant stakeholders.[14] Both of the guidelines,[1,14] were developed based on a systematic literature review, with one[1] based on a SR previously conducted by the group.

The recommendations were graded in one guideline,[1] and not in the other, although the evidence supporting recommendations was graded.[14] The method for formulating the recommendations was not clearly described, but it was suggested that both were

developed by a working group[14] or committee.[1] It was mentioned in one guideline that there were no COIs,[1] and details regarding COIs were not clear in the other guideline.[14]

Summary of Findings

Clinical Effectiveness of Nabilone for Chronic Pain

The overviews included in this report described studies that evaluated the clinical effectiveness of nabilone for chronic pain in terms of pain relief and QoL. Measures of safety were also described. Appendix 4 presents a table of the main study findings and authors' conclusions.

Pain relief

Pain relief as a result of the use of nabilone was assessed in patients with three types of conditions: MS,[12] FMS,[13] and MSK pain.[13] The two studies that reported on patients with MS concluded that the evidence presented mixed findings regarding the effect of nabilone on pain relief when compared to placebo.[12] The overview that was focused on pain associated with rheumatic diseases (FMS and MSK pain) also concluded that the information available provided mixed results.[13] This was based on one RCT that showed no difference and four RCTs that showed no statistically significant difference in pain relief due to nabilone in comparison to placebo or amitriptyline, as well as two RCTs that reported greater pain relief by nabilone compared to placebo where statistical significance was not reported.[13]

Quality of life

One of the overviews included two reviews reporting on two RCTs that evaluated QoL as an outcome for treatment with nabilone.[12] Information regarding the methodology of these two RCTs was limited. One of the two studies reported an improvement in an objective rating of general health status, but detail regarding an effect size or statistical testing was not reported.[12] The other study of 15 participants also reported an improvement in QoL in 100% of patients receiving nabilone, based on the PGIC scale, compared to 43% of patients receiving placebo; however this was not statistically significant.[12] This difference was not statistically significant and based on a small sample size.[12] The GRADE rating of this study was moderate.[12]

Safety

Both of the overviews included in this report included reviews that reported on safety measures associated with the use of nabilone for chronic pain.[12,13] In general, more AEs were reported for patients receiving nabilone and other cannabinoids than those receiving placebo; however, rates of AEs were low and only one SAE was reported among six of the studies describing SAEs that were included in the overviews.[12,13] Withdrawals due to AEs were also more common amongst those using nabilone in comparison to placebo or amitriptyline.[12,13]

Guidelines

Two sets of guidelines regarding the use of cannabinoids for treatment of chronic pain were included in this report and summarized in Appendix 4, Table 7. In general, the guidelines did not support the use of cannabinoids, including nabilone, for the treatment of chronic pain due to a lack of sufficient evidence on the topic.[1,14]

"There was insufficient evidence for most subtypes of pain. … For pain associated with rheumatologic conditions, 3 systematic reviews reported insufficient evidence for benefit in fibromyalgia, osteoarthritis, rheumatoid arthritis, and back pain. Given these findings, and the high risk of harms, the PGC recommends against cannabinoids for these conditions." (p. 115)[1]

Although one set of guidelines did provide a "weak recommendation" that clinicians may consider medical cannabinoids as an adjunct to other prescribed analgesics as a third-line therapy for NP or palliative (end-of-life) cancer pain, when current therapies for pain relief have been "persistently problematic".[1] It should be noted that this follows a strong recommendation *"against the use of medical cannabinoids as first- or second-line therapy in NP and palliative cancer pain owing to limited benefits and high risk of harms"*. (p. 112)[1]

The other set of guidelines did not provide support for the use of nabilone and other cannabinoids for chronic pain as well.[14] Further, the GRADE quality of evidence used to support the guidelines were "very low" to "low". In general, this guideline reported that there was no significant evidence of effect on pain intensity, although it may be more effective than placebo.[14] A lack of evidence to support a change in QoL in terms of emotional functioning or improvement in depressive or anxiety symptoms was also reported.[14]

Overall, the two sets of guidelines had limited evidence regarding the safety of nabilone; however, one did suggest that when considering the use of cannabinoids, nabilone is safer than smoked or vaporized cannabinoids; however, the quality of evidence supporting this comment was not stated.[14]

"In terms of mode of delivery there are concerns about the safety of smoked or vapourised cannabinoids. Delivery of pharmaceutical grade products such as nabiximols, dronabinol or THC extracts is safer." (p.12)

Further, there was very low quality of evidence supporting that there was no difference in the rate of AEs between groups for studies about nabilone.[14]

Limitations

There was heterogeneity across the studies included in the SRs in the populations included, dosages used, comparators, outcomes, and reporting. Also, the use of concomitant analgesics and other medications was either permitted or unclear, which may have under or over exaggerated the effects of nabilone on pain. Moreover, as noted in the discussion for the overviews, the history of use of cannabinoids was not addressed in any of the SRs, which if considered may have altered the results of the studies. Further, the sample sizes were small and the majority of the primary studies concerning nabilone that were included in the SRs included in the overviews were of "low" to "very low" quality according to the GRADE quality of evidence assessment. None of the included references (SRs and guidelines) were specific to nabilone, but rather they provided a review of various medical cannabinoids for the treatment of chronic pain. As such, the relevant evidence pertaining to nabilone was limited, which negatively affects the generalizability of the conclusions. Moreover, as the unit of analysis in the included studies was SRs, detail regarding the primary studies was limited as well.

Conclusions and Implications for Decision or Policy Making

In total, two overviews and two evidence-based guidelines were identified for this review. The conditions that were addressed included MS, FMS, and MSK pain. This report was an update of the 2017 report,[7] which was an update of the original 2011 report[8] on nabilone for chronic pain. The results of this report are in-line with the reviews that were previously conducted.

All of the sources identified for this review included information about medical cannabinoids beyond nabilone and the evidence had various limitations, thus caution should be used when considering the results. In general, authors' concluded that evidence regarding the clinical effectiveness of nabilone was insufficient to confirm or deny it's use, although there was weak support for the use of nabilone as a third-line, add-on therapy if used with other prescribed analgesics, specifically for NP or palliative (end-of-life) cancer pain that is persistently problematic. Regarding safety of the use of nabilone, it seems to be a well-tolerated intervention with few minor AEs reported such as sedation and dizziness, but this is also based on limited evidence. Larger studies regarding nabilone specifically, with a longer duration are required to properly evaluate the clinical effectiveness and safety of nabilone for management of chronic pain.

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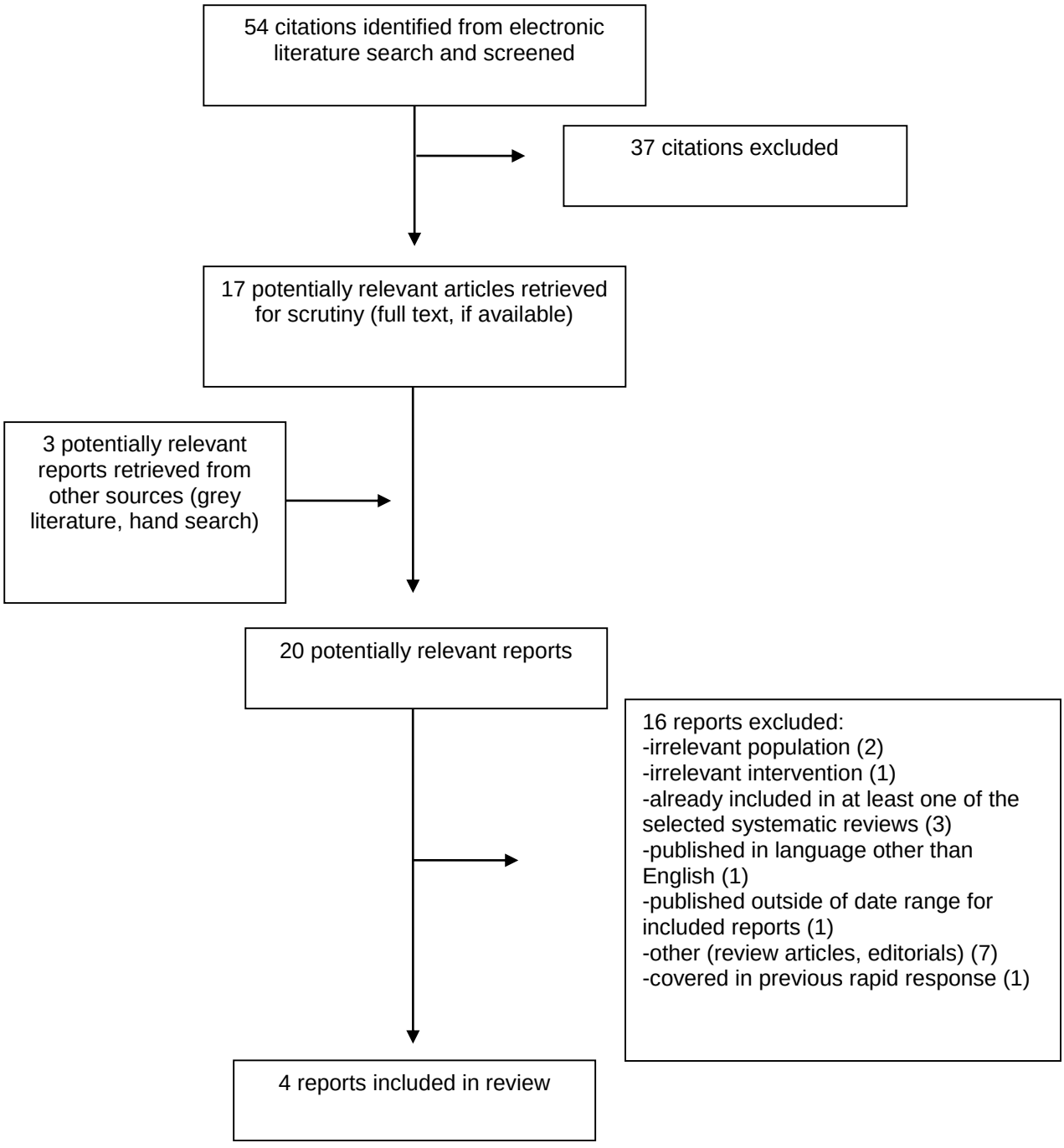
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Nielsen[12] 2018 Australia	*Overview of SRs: 11 SRs containing 32 studies* Of the 11SRs on cannabis and cannabinoids, four included relevant studies (3 crossover RCTs, 1 parallel RCT) about nabilone	*Participants with MS* 48 participants* in relevant studies *Sex/gender=NR; age=NR	Nabilone* or placebo *0.5 to 2 mg/day *Route of administration=NR	*Pain*, QoL**, AE* *Reduction of pain, objective rating of improvement in pain **Objective rating of general health status, PGIC Follow-up: NR
Hauser[13] 2017 Germany	*Overview of SRs and prospective cohort studies ≥ 6 months: 11 SRs and 3 prospective observation studies included* 5 SRs (10 studies) were on nabilone	*Patients with chronic cancer and non-cancer pain and symptomatic treatment of further somatic symptoms of advanced diseases. No age or country restrictions applied.* Included patients with: fibromyalgia, rheumatoid arthritis, musculoskeletal pain, osteoarthritis, dementia, and chronic NP	Oral nabilone* or placebo, amitriptyline* *Dose=NR	*Efficacy (mean pain intensity or change in pain intensity or ≥ 30% pain relief), tolerability, safety (SAEs, deaths)* Outcomes: pain relief, sleep quality, discontinuation due to AEs, SAEs Follow-up: 2 to 14 weeks

AE = adverse event; mg = milligram; HRQoL = health-related quality of life; MS = multiple sclerosis; NP = neuropathic pain; NR = not reported; PGIC = patient global impression of change; RCT = randomized controlled trial; SAE = serious AE; SF-36 = short-form 36 QoL instrument; WDAE = withdrawal due to AE

Note: Italicized text refers to the characteristics of the SR, and the non-italicized text is specific to the studies included in the SR that evaluated nabilone as an intervention.

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
Simplified guideline for prescribing medical cannabinoids in primary care, 2018[1]						
These guidelines are intended for use in primary care.	Broadly, the use of medical cannabinoids for the management of pain, nausea	Outcomes were not explicitly outlined a priori, but were reported as part of the	The evidence used for the development of this guideline was	GRADE methodology was followed to assess the quality of	A multi-disciplinary 10-member PGC developed the guideline following the Institute of Medicine's	A Peer Review Committee distributed the guideline

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
The target population is adults (≥ 18 years of age).	and vomiting, and spasticity, as well as AEs from medical cannabinoid are addressed in this guideline. Medical cannabinoids include: pharmaceutically derived cannabinoids (nabilone and nabiximols), and medical marijuana.	report. Pain outcomes ≥30% reduction in chronic (NP + cancer) pain, ≥30% reduction in NP pain, ≥30% reduction in palliative pain, change in chronic pain Nausea & Vomiting outcomes control of nausea and vomiting Spasticity global impression of change, ≥30%improvement in spasticity, change in spasticity Adverse events were also reported in terms of event rate and NNTH	based on a previously published systematic review.[15]	evidence used in this guideline.	outline for "*Clinical Guidelines We Can Trust*" and GRADE methodology.	to external clinicians and patients for peer review and feedback. Feedback was received from 40 individuals, followed by revision of the guidelines and final approval by the PGC.
Guidance for the use of medicinal cannabis in the treatment of chronic non-cancer pain in Australia, 2017[14]						
This guideline document is intended for doctors and their patients in Australia.	The use of medicinal cannabis therapy in general, as well as the use of medicinal cannabis for the treatment of palliative care, chemotherapy-induced nausea and vomiting, MS, and chronic pain was addressed.	The following outcomes were summarized: pain intensity, physical functioning, emotional functioning, PGIC, Withdrawal from the study, AEs.	The evidence for this guideline was based on previously published reviews from databases including Medline, Embase, PsychINFO and EBM Reviews based on PRISMA145. Searches were limited to	GRADE Quality of Evidence methodology was followed to assess the quality of evidence used in this guideline.	The recommendations were made by the Chronic Pain Working Group. In addition, a workshop that included patients with CNCP, representative consumer groups, medical colleges, special societies, and states and territories was held in Sydney to review the available evidence. The recommendations	NR

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
			publications between 1980 and early 2017. Titles and abstracts were screened in duplicate. A total of 102 studies were examined (26 parallel RCTs, 23 cross-over RCTs, 53 observational studies).		provided were not graded.	

AE = adverse events; CNCP = chronic non-cancer pain; NNTH = number needed to harm; NP = neuropathic pain; PGC = Prescribing Guidelines Committee; PGIC = Patient Global Impression of Change

Appendix 3: Critical Appraisal of Included Publications

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

Strengths	Limitations
Nielsen, 2018[12]	
- Research questions, objectives, inclusion criteria, and exclusion criteria were clearly described - A literature search that included four named databases and one trial registry was conducted; a sample search of Medline was provided - Study selection was performed in duplicate and disagreement was resolved by consensus in all cases - A list of excluded studies was provided including reasons for exclusion - The AMSTAR tool was used to assess risk of bias at the review level and GRADE criteria was used to assess the studies included in reviews - The reviewers investigated whether funding was reported for the included reviews - Potential sources of COI and details of any related funding was provided; no apparent issues regarding COIs	- Did not explicitly state that review methods were established prior to conduct of the review - A standardized data extraction tool was implemented, which was piloted and reviewed before the results of the extraction were finalized; however, details regarding review of the data extraction were not provided - Adequate detail of the SRs included in the overview was provided; however, the detail regarding the primary studies included in those SRs was limited
Hauser, 2017[13]	
- Research questions, objectives, inclusion criteria, and exclusion criteria were clearly described - A literature search strategy including three named databases and one trial registry was provided along with key words; reference sections of SRs were searched further - The review methods were defined a priori and published in PROSPERO - The study designs included (SRs and prospective observational studies) were selected based on the highest level of evidence according to the study authors Data extraction was performed in duplicate - Excluded studies and justification for exclusion was summarized in-text - The risk of bias in individual studies was discussed along with the results of the review	- Did not explicitly state that study selection was performed in duplicate - Risk of bias appears to have been assessed by the Cochrane Collaboration risk-of-bias tool, but details regarding the methodology and assessment results were not provided - Adequate detail of the included studies was provided; however, the detail regarding the primary studies included in those SRs was limited - Inclusion of COI statement in individual studies was included, but no information regarding sources of funding was provided

COI = conflict of interest; EBM = evidence-based medicine; NP = neuropathic pain; SR = systematic review

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

Item	Guideline	
	Allan, 2018 [1]	Australia, 2017 [14]
Domain 1: Scope and Purpose		
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes	Yes
Domain 2: Stakeholder Involvement		
4. The guideline development group includes individuals from all relevant professional groups.	Yes	Yes
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Yes	No
6. The target users of the guideline are clearly defined.	Yes	Yes
Domain 3: Rigour of Development		
7. Systematic methods were used to search for evidence.	Yes	Yes
8. The criteria for selecting the evidence are clearly described.	Yes	No
9. The strengths and limitations of the body of evidence are clearly described.	Yes	Yes
10. The methods for formulating the recommendations are clearly described.	No	No
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Yes	Yes
13. The guideline has been externally reviewed by experts prior to its publication.	Yes	Yes
14. A procedure for updating the guideline is provided.	No	No
Domain 4: Clarity of Presentation		
15. The recommendations are specific and unambiguous.	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes	No
17. Key recommendations are easily identifiable.	Yes	Yes
Domain 5: Applicability		
18. The guideline describes facilitators and barriers to its application.	No	No

Item	Guideline	
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Yes	No
20. The potential resource implications of applying the recommendations have been considered.	Yes	No
21. The guideline presents monitoring and/or auditing criteria.	No	Yes
Domain 6: Editorial Independence		
22. The views of the funding body have not influenced the content of the guideline.	Yes	No
23. Competing interests of guideline development group members have been recorded and addressed.	Yes	No

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings Included Systematic Reviews

Main Study Findings	Authors' Conclusion
Nielsen, 2018[12]	
Efficacy ***Pain*** Two reviews reporting on one RCT provided the following results regarding the effect of nabilone on pain: • ***"significant improvement in muscle spasms and pain"*** (n=NR, GRADE rating: VL) • ***"significant reduction of pain"*** (n=13, GRADE rating: VL) Note: Effect sizes and details of statistical testing were not reported.	• Regarding the reviews reporting on cannabinoids for the treatment of pain in patients with MS, the authors' noted the following for the studies on nabilone: *"Some reviews concluded that there was insufficient evidence…"* **(p.4; suppl. Table 6)**
QoL Two reviews reporting on two RCTs provided the following results regarding the effect of nabilone on QoL: • ***"Improvement on PGIC"***, intervention 100% vs. placebo 43%, OR (95% CI) = 21.9 (0.91, 523.4), (n=15, GRADE rating: M) • *"significant improvement in objective rating of general health status"* (GRADE rating: VL; sample size, effect size, statistical testing = NR)	• Authors reported that *"four reviews examined the effect of cannabinoids on overall quality of life* [two of which assessed nabilone]… *Reviews provided evidence of mixed findings on the effect of cannabinoids on quality of life, with reviews reporting data from studies that found both positive and negative effects on quality of life."* **(p.8-9)** ○ The studies relating to the effect of nabilone on QoL reported a "positive effect" and "no change"**(Suppl. Table 11)**
Safety ***AEs*** Three reviews reporting on three RCTs provided the following results regarding AEs of nabilone: • "minor sedation" and "moderate sedation" (n=1, GRADE rating: VL) • Moderate dizziness (n=2) and weakness in legs (n=2), (N=14, GRADE rating: L) • No dropouts and no SAEs (N=15, GRADE rating: L)	• Conclusion related to AEs was not specific to nabilone; however, author concluded that *"AEs were consistently rated as more common in study participants who received cannabinoids than placebo."* **(p.9)**
Hauser, 2017[13]	
Efficacy ***Pain*** **Nabilone-specific data** was **only reported for pain associated with rheumatic diseases (FMS, and MSK pain), based on** three **SRs** that **includ**ed four **relevant RCTs**. The findings by SR that were provided are summarized below: • Mixed results from two RCTS of FMS patients, one reported nabilone led to pain relief (n=40) and the other reported nabilone did not reduce pain (n=32), (AMSTAR score = 7) • Three RCTs reported no statistically significant difference between nabilone and comparators (placebo, amitriptyline) with regard to pain relief in FMS patients and MSK patients (AMSTAR score = 8) • Two RCTs of FMS patients, one reported greater pain relief by nabilone vs. placebo, the other reported no statistically	• The review stated that *"The authors for all 3 SRs concluded that the current evidence base is inadequate to recommend cannabinoids for the treatment of pain associated with rheumatic diseases"* **(p. 629)**

Main Study Findings	Authors' Conclusion
significant difference when compared to amitriptyline (AMSTAR score = 9) *Safety* • One review summarized safety results for multiple cannabinoids, therefore the data regarding nabilone specifically is not clear (AMSTAR score = 7) **WDAE** • One RCT reported 15% nabilone group and 5% placebo group WDAE, patient group was unclear; and one RCT reported 3.1% nabilone group vs. 0 amitriptyline group WDAE among patients with FMS (AMSTAR score = 8) • One RCT reported 7.7% nabilone vs. 5% placebo and 0 amitriptyline WDAE (AMSTAR score = 9) **SAE** • Two RCTS (one of FMS patients, one unclear) reported no SAE, and one RCT of patients with MSK pain reported one SAE which occurred in the nabilone group (AMSTAR score = 8) ○ SAE reported was a dizziness-related fall with fracture • One RCT reported no SAE (AMSTAR score = 9)	

AMSTAR = A MeaSurement Tool to Assess systematic Reviews; CI = confidence interval; FMS = fibromyalgia syndrome; L = low; M = moderate; MS = multiple sclerosis; MSK = musculoskeletal; OR = odds ratio; RCT = randomized controlled trial; SAE = serious adverse events; QoL = quality of life; VL = very low; WDAE = withdrawals due to adverse events

Table 7: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
Allan, 2018 [1]	
"There was insufficient evidence for most subtypes of pain. … For pain associated with rheumatologic conditions, 3 systematic reviews reported insufficient evidence for benefit in fibromyalgia, osteoarthritis, rheumatoid arthritis, and back pain. Given these findings, and the high risk of harms, the PGC recommends against cannabinoids for these conditions." **(p.115)**	Strong recommendation
Neuropathic pain: 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:*
  ○ *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*
  ○ *medical cannabinoids are adjuncts to other prescribed analgesics*
	Weak recommendation
	
	Strong recommendation

Recommendations	Strength of Evidence and Recommendations

Palliative (end-of-life) cancer pain: We recommend against use of medical cannabinoids as first- or second-line therapy for palliative cancer pain owing to limited benefits and high risk of harms
• *Clinicians could consider medical cannabinoids for **r**efractory pain in palliative cancer patients, with the following considerations:*
  ○ *a discussion has taken place with patients regarding the risks and benefits of medical cannabinoids for pain*
  ○ *patients have had a reasonable therapeutic trial* of ≥ 2 prescribed analgesics and have persistent problematic pain despite optimized analgesic therapy*
  ○ *medical cannabinoids are adjuncts to other prescribed analgesics*
Types of medical cannabinoids for pain:
• *If considering medical cannabinoids, we recommend a pharmaceutically developed product (**nabilone** or nabiximols) as the initial agent*
  ○ ***Nabilone** is off-label for pain and has limited evidence of benefit. However, it is less expensive than nabiximols and dosing is more consistent than for smoked cannabis*
  ○ *Nabiximols is expensive and, in some provinces, only available through specialist prescribing or special authorization. However, nabiximols has better evidence than **nabilone** does*
(p. 112)
	Weak recommendation
	
	Strong recommendation

Australia, 2017 [14]	
The recommendations provided by this guidance document were not specific to nabilone, although nabilone-specific evidence was reported, which supported the recommendations made. The overall recommendations were: *"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 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."* (p.3) <u>A summary of the evidence related to nabilone is summarized below:</u> *"Nabiximols, **nabilone** and THC extract, when separately examined, were much less consistently superior to placebo in producing a 30% reduction in pain or reducing average pain intensity."* **(p.6)** *"Single studies of lesser quality suggest that **nabilone**, cannabis sativa, THC:CBD extracts and ajulemic acid may be more*	Strength of recommendations: not reported <u>GRADE Quality of Evidence:</u> Very Low

Recommendations	Strength of Evidence and Recommendations
effective than placebo in producing a 30% reduction in pain." **(p.7)** • Based on 4 RCTS	Low
*"Six studies (three testing **nabilone**, and three testing cannabis sativa) examined change in pain intensity, and found no significant evidence of effect."* **(p.7)** • Based on 3 observational studies and "change in pain scores" as an outcome	Not reported
"In terms of mode of delivery there are concerns about the safety of smoked or vapourised cannabinoids. Delivery of pharmaceutical grade products such as nabiximols, dronabinol or THC extracts is safer." **(p.12)** *"There was some evidence that patients receiving **nabilone** had significantly improved physical functioning but confidence in this outcome was very low."* **(p.15)** *"Reductions in sleep problems were identified for nabiximols and **nabilone** but confidence in these effects varied and data were not reported for many specific cannabinoids."* **(p.16)** • Based on 5 RCTs and the following outcomes: overall physical functioning, change in sleep problems, and change in QoL	Very low Low (2) to very low (1)
"Patients receiving any cannabinoid did not report any change in overall emotional functioning or improvement in depressive or anxiety symptoms specifically" **(p. 16)** • Based on 3 RCTs and the following outcomes: overall emotional functioning, depressive symptoms, anxiety symptoms	Low
*"Patients…had slightly increased odds of reporting improvement than patients who received placebo… with some evidence for **nabilone**"* **(p. 18)** • Based on 2 RCTs	Very low
Regarding AEs that CNCP patients may experience, there was no difference in the rate of AEs between groups for studies of nabilone • Based on 2 RCTs	

AE = adverse event; CBD = cannabidiol; CNCP = chronic non-cancer pain; RCT = randomized controlled trial; THC = delta-9-tetrahydrocannabinol

Appendix 5: Overlap between Included Systematic Reviews

Table 8: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation	
	Nielsen, 2018[12]	Hauser, 2017[13]
Andreae 2015		X
Andrzejewski 2016	X	
Ben Amar 2006	X	
Fitzcharles 2016		X
Fitzcharles 2016		X
Jawahar 2013	X	X
Karst 2010	X	
Koppel 2014	X	
Krishnan 2013		X
Lakhan 2009	X	
Lutge 2013		X
Mills 2007	X	
Mücke 2016		X
Petzke 2016		X
Shakespeare 2003	X	
Volz 2016		X
Wallitt 2016		X
Wang 2008	X	
Whiting 2015	X	X
Zhornitsky 2012	X	

Note: **Bolded citations** were considered for this report as they included nabilone as an intervention.

Appendix 6: Additional References of Potential Interest

1. Mucke, M., et al. (2018). "Cannabis-based medicines for chronic neuropathic pain in adults." Cochrane Database of Systematic Reviews 3: CD012182.
2. Moulin DE, *et al.* Pharmacological management of chronic neuropathic pain: Revised consensus statement from the Canadian Pain Society. Pain Res Manag. 2014; 19(6).
3. Meng H, *et al.* Selective Cannabinoids for Chronic Neuropathic Pain: A Systematic Review and Meta-Analysis. Chronic Pain Medicine. 2017; 125(5).