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Medical Cannabis Use in Palliative Care: Review of Clinical Effectiveness and Guidelines – An Update

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Abbreviations

HIV	human immunodeficiency virus
RCT	randomized controlled trial
THC	tetrahydrocannabinol

Context and Policy Issues

Palliative care is defined by the World Health Organization as "an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness...".[1] The last days and hours of a person's life can be associated with immense physical as well as emotional suffering.[2] Relief of pain and other distressing symptoms, and enhancement of quality of life, are among the essential elements of good palliative care.[1]

Palliative care could benefit an estimated 69% to 82% of dying individuals in Canada.[3] As Canada's population ages, with increasing prevalence of chronic conditions and treatments resulting in prolonged life, it is expected that there will be an increased need for palliative care services.[3]

Approximately 9% of Canadians (or 2.7 million) reported using cannabis for medical purposes in the first half of 2019.[4] Herbal cannabis (cannabis sativa) contains hundreds of pharmacological components, many of which are not well-characterized. Tetrahydrocannabinol (THC) is the most prevalent pharmacologically active compound and is primarily responsible for the psychoactive and physical effects of cannabis. Cannabidiol (also commonly referred to as CBD) is the second most prevalent. It has very little if any psychotropic effects. Quantity and ratio of these and other components can vary considerably between plants and even within the same plant.[5] Two prescription cannabinoids are currently marketed in Canada: Nabiximols (Sativex) which contains THC and cannabidiol, and Nabilone (Cesamet) which is a synthetic cannabinoid. Dronabinol (Marinol), synthetic THC, was withdrawn from the Canadian market however it is available in other jurisdictions.[6] For the purposes of this report, medical cannabis refers to use of the cannabis plant or its extracts or synthetic cannabinoids for medical purposes.

Medical cannabis may be of value for a number of conditions, including but not limited to pain, nausea and vomiting, depression, anxiety and appetite stimulation.[5] Adverse effects of cannabis are very common, developing in 80% to 90% of patients.[7] These include but are not limited to psychiatric disturbances, sedation, speech disorders, impaired memory, dizziness, ataxia, addiction, irritability, and driving impairment. Risk of adverse effects is likely lower with cannabidiol alone as compared to THC.[5,7] The potential for drug interactions is also an important concern.[5,8] These risks must be considered along with the an apparent lack of evidence surrounding effectiveness of medical cannabis in many conditions for which its use is promoted.

This report updates and expands on a previous summary of abstracts report.[9]

The objective of the report is to review evidence and guidelines for use of medical cannabis in the palliative care setting.

Research Questions

1. What is the clinical effectiveness of medical cannabis products for symptom control in adult palliative care patients?

2. What are the evidence-based guidelines regarding medical cannabis products for symptom control in adult palliative care patients?

Key Findings

The clinical effectiveness of medical cannabis for symptom control in adult palliative care patients is unclear, due to a lack of quality and quantity of evidence; this lack of evidence applies to the cannabis plant, its extracts and synthetic cannabinoids. From a systematic review of nine randomized controlled trials, low quality evidence suggests that in patients with HIV, dronabinol (a synthetic cannabinoid) may be more effective than placebo for appetite and weight gain, at the expense of increased risk of psychiatric adverse effects. In patients with cancer, dronabinol may be less effective than megestrol for improvement in appetite, weight gain and health-related quality of life, and may increase risk of withdrawal due to adverse events as compared to megestrol. Similarly, in patients with HIV, dronabinol may be less effective than megestrol for weight gain.

Two evidence-based guidelines address the use of medical cannabis in a palliative care setting. The first evidence-based guideline explicitly recommends against the use of medical cannabis as a first or second line option for palliative cancer pain. The guideline suggests that it could be considered in the case of refractory symptoms and with careful consideration of potential risks. The second evidence-based guideline similarly recommends that medical cannabis only be used in the palliative care setting when other treatments have failed, and after consideration of the potential for adverse events and drug interactions.

Methods

Literature Search Methods

This report updates and expands on a previous CADTH summary of abstracts report.[9] For the current report, a limited literature search was conducted by an information specialist on key resources including PubMed, 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 cannabis and palliative care. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2018 and September 24, 2019. The literature search for the previous summary of abstracts report was limited to English language documents published between January 1, 2013 and August 17, 2018.

Selection Criteria and Methods

One reviewer screened citations and selected studies for eligibility for this report. In the first level of screening, titles and abstracts of articles identified in the electronic database search were reviewed and potentially relevant articles were retrieved and assessed for inclusion.

Full-texts of articles included in the previous CADTH summary of abstracts[9] were also retrieved and assessed for eligibility. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults in palliative care settings
Intervention	Medical cannabis products (e.g., cannabinoids, cannabis)
Comparator	Q1: No treatment; Pharmacological treatments (e.g., medications for experienced symptoms) Q2: Not applicable
Outcomes	Q1: Clinical effectiveness (e.g., safety, change in symptoms such as nausea, headaches, chronic pain) Q2: Guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2018 (with the exception of articles identified in the previous report,[9] with literature search dating back to 2013). Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included systematic review was critically appraised by one reviewer using the AMSTAR 2 tool,[10] and the quality of included guidelines was assessed using the AGREE II instrument.[11] Summary scores were not calculated; rather, a review of the strengths and limitations were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 144 citations were identified in the electronic database search. Following screening of titles and abstracts, 142 citations were excluded and two potentially relevant reports from the electronic search were retrieved for full-text review. Six potentially relevant publications were retrieved from the grey literature search for full text review. Additionally, five full-text publications included in the previous summary of abstracts report were retrieved. Of these potentially relevant articles, 10 publications were excluded for various reasons, and three publications met the inclusion criteria and were included in this report. These comprised one systematic review and two evidence-based guidelines. Appendix 1 presents the PRISMA[12] flowchart of the study selection.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

Systematic reviews

A single systematic review met inclusion criteria. Mucke et al.[13] conducted a systematic review and meta-analysis of nine RCTs, with a search date up to March 15, 2017. Randomized controlled trials with a duration of at least two weeks and enrolling at least 10 patients per treatment group were eligible for inclusion in the systematic review.[13]

Guidelines

Two evidence-based guidelines are included in this report.

Guidelines for prescribing medical cannabinoids in primary care endorsed by the College of Family Physicians of Canada were published in 2018 by Allan et al.[14] Their evidence review consisted of a systematic review of systematic reviews.[15] Guideline recommendations were developed by a working group comprised of family physicians, specialists, a nurse practitioner, pharmacist, and patient representative using an iterative process. The guideline working group used GRADE methodology to rate strength of evidence and recommendations, and worded recommendations accordingly: weak recommendations were presented as "could consider", and strong recommendations as "we recommend", or "we strongly recommend" in some cases where extra emphasis was desired. The guidelines are also published in a different format as a "Toward Optimized Practice (TOP) PEER Simplified Guideline".[16]

Australian Guidelines for the use of medicinal cannabis in treatment of palliative care patients were published in 2017.[17] This guideline was developed as one of five guidelines addressing use of medicinal cannabis in different settings.[17] Their evidence review consisted of a review of reviews. An updated systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted by the Australian National Drug and Alcohol Council (NDARC) in collaboration with Mucke et al.[13] (published separately, also included in this report), and an additional systematic search for observational studies was performed. Strength of evidence was assessed using GRADE methodology. They key to evidence grades was as follows: A= Strong scientific evidence for this use; B=Good scientific evidence for this use; C= Unclear scientific evidence for this use; D=Fair scientific evidence against this use (it may not work); F=Strong scientific evidence against this use (it likely does not work). Method of development of recommendations was not described, apart from a broad description of the formation and composition of a working group.

Country of Origin

Systematic review

The systematic review by Mucke et al. was conducted in Germany.[13] Seven of the RCTs included within the systematic review were conducted in North America, one was conducted in Great Britain, and another in Europe.

Evidence-based Guidelines

The included guidelines were endorsed by the College of Family Physicians of Canada[14] and developed by the Australian Government.[17]

Patient Population

Mucke et al. included RCTs enrolling patients of any age diagnosed with an advanced or end-stage illness. Nine RCTs were included with a total of 1561 participants. There were three broad categories of illness: five studies in patients with terminal cancer (n=758), age range 58 to 66 years; three studies in patients with advanced HIV (n=251), age range 39 to 43 years; and one study in patients with Alzheimer's disease (n=15), age range 65 to 82 years. The overall population was 90.8% male.[13]

A specific population of interest is not defined in the Canadian guidelines.[14] In the systematic review of systematic reviews, published separately,[15] investigators excluded studies where >50% of the population was pediatric. Recommendations for prescribing medical cannabinoids were developed for four broad clinical areas: pain, nausea and vomiting, spasticity and adverse events. Within the category of pain, recommendations specifically addressing the use of cannabinoids for palliative pain were developed and are relevant to this report. The guideline is intended for use in primary care, and is meant to facilitate shared decision-making with patients.[14]

A specific population of interest is also not defined in the Australian guidelines,[17] apart from a focus on palliative care patients. Target users are doctors and patients.

Interventions and Comparators

Mucke et al. included RCTs assessing any form of cannabis versus placebo or active control. Six RCTs assessed synthetic THC (dronabinol), three assessed a combination of THC and CBD, and one herbal cannabis (smoked). Seven studies compared medical cannabis to placebo and two to megestrol (a prescription synthetic progestin approved for use as an appetite stimulant).

Canadian guidelines make recommendations surrounding the use of medical cannabis, which includes both medical marijuana and pharmaceutical cannabinoids.[14]

The Australian guideline recommendations similarly apply to the use of medical cannabis, including both plant-based products and synthetic cannabinoids.[17]

Outcomes

In the systematic review conducted by Mucke et al., eligible RCTs reported at least one of the following outcomes: pain reduction ≥30%, body weight, appetite, caloric intake, nausea/vomiting. Findings for many other efficacy, tolerability and safety outcomes were also reported in the systematic review.[13]

The Canadian Guidelines[14] report the proportion of patients experiencing ≥30% reduction in palliative pain.

Australian guidelines[17] were developed using evidence from the systematic review published by Mucke et al,.[13] with primary outcomes of pain reduction ≥30%, body weight, appetite, caloric intake, and nausea/vomiting.

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Systematic review

Quality assessment of the included systematic review was done using the AMSTAR 2 tool.[10]. The systematic review by Mucke et al[13] was of moderate quality overall. A comprehensive search strategy was described, and quality of evidence was assessed using GRADE methodology. Although several reviewers independently screened studies for inclusion and completed data extraction and risk of bias assessments, authors did not clearly state that it was done in duplicate. Detailed population characteristics were not provided (including prior cannabis use). Investigators acknowledged the presence of statistical heterogeneity, but did not discuss or explore this heterogeneity in their interpretation of the results. Additionally, results were not consistently reported with 95% confidence intervals, and there were discrepancies between results presented in text as compared to figures.

Quality of both of the included guidelines was assessed using the AGREE II instrument. The overall objective, clinical questions, and population of interest are broadly stated in both the Canadian[14] and Australian[17,18] guidelines. The Canadian guidelines describe more clearly the involvement of individuals from relevant professional groups, however neither guideline adequately describes patient involvement. The Canadian guidelines clearly describe methods for evidence gathering, development of recommendations, and consideration of strengths and limitations of evidence. The Australian guidelines clearly describe the gathering of evidence, however there is no description of methods for formulation of the recommendations apart from the development of the working groups. Only the Canadian guidelines describe external review by a peer review committee, and only the Australian guidelines describe a procedure for updating the guideline. Recommendations and strength of the recommendations are clearly stated in the Canadian guidelines, however they are lacking detail such as dose and specific agent, likely due to a lack of evidence. The Australian guidelines provide broader statements as recommendations that are not graded. Only the Canadian guidelines include a patient-handout to support guideline implementation, but neither of the guidelines provide adequate discussion of facilitators and barriers to their use, potential resource implications, or auditing/monitoring criteria. The Canadian guidelines include clear statements surrounding funding and competing interests of committee members; the Australian guidelines do not address this.

Summary of Findings

Appendix 4 presents a table of the main study findings and authors' conclusions.

Clinical effectiveness of medical cannabis in palliative care

The single systematic review by Mucke et al. included nine RCTs, of three broad disease categories: terminal cancer (five RCTs), HIV (three RCTs), and Alzheimer's' disease (one cross-over RCT). Evidence for all comparisons and outcomes was rated as low or very low quality according to GRADE assessment for indirectness, imprecision, and reporting bias.

In patients with cancer, there was no statistically significant difference in appetite, caloric intake, nausea/vomiting, or ≥30% reduction in pain, sleep problems, or adverse effects (dizziness, mental health problems, withdrawal due to adverse events or serious adverse events) with any formulation of medical cannabis vs. placebo. In a single RCT of 469 patients, megestrol 800mg per day was superior to dronabinol 5mg/day for appetite, weight gain, health-related quality of life, and with less withdrawal due to adverse events.

Cannabinoids were superior to placebo in HIV patients for weight gain and appetite but more frequently caused mental health symptoms; these differences were statistically significant. There was no difference in nausea/vomiting or withdrawal due to adverse events. Serious adverse events and psychiatric adverse events were increased with cannabinoids; these differences were statistically significant. For the comparison of megestrol vs dronabinol in patients with HIV, a study of 48 patients found a statistically significant increase in weight gain with megestrol vs dronabinol with no difference in other outcomes or adverse events.

In patients with Alzheimer's disease, statistically significant improvements in weight gain and negative affect were found, with no difference in caloric intake, with dronabinol vs. placebo for 6 weeks in a single 15-patient cross-over study.

The investigators of the systematic review concluded that they were unable to make recommendations surrounding use of cannabis in palliative care due to lack of quality and quantity of evidence.

Guidelines

Canadian guidelines[14] strongly recommend against the use of medical cannabis as a first or second-line option for treatment of cancer-related pain at end-of-life, due to a high risk of harms and limited benefit. They make a weak recommendation to consider cannabinoids for refractory cancer-related pain if two or more other prescribed analgesics have failed to provide adequate pain relief, clinicians discuss risks and benefits with patients, and cannabinoids are prescribed as an adjunct to other analgesics.

Australian guidelines[17] recommend using medical cannabis only after other treatments have failed, due to the lack of evidence. The guidelines also recommend that patients and clinicians be aware of adverse effects and the potential negative impact on quality of life.[17]. Level of evidence is rated as "C" (unclear scientific evidence for this use) for dronabinol in patients with Alzheimer's' disease. In patients with cancer, evidence was rated as "C" for the majority of interventions and outcomes: dronabinol, THC, and THC:CBD for pain; cannabis sativa for symptoms related to cancer and cancer-treatments; dronabinol for appetite and nausea; and nabilone for pain, morphine use, nausea, anxiety, appetite, and overall distress. Evidence was graded as "D" (fair scientific evidence against this use) for dronabinol, THC:CBD, or THC for caloric intake, appetite, weight gain, nausea and vomiting, sleep, depressed mood or quality of life in patients with cancer.

Limitations

The single systematic review included in this report included nine RCTs, with quality of evidence rated as low or very low for all comparisons and outcomes. These RCTs assessed effectiveness of medical cannabis in three broad categories of illness: terminal cancer, HIV, and Alzheimer's disease. There were no studies identified assessing effectiveness of medical cannabis in other palliative care populations.

Dronabinol was the medical cannabis product used in six of the nine RCTs, and it is no longer marketed in Canada. This limits applicability to the Canadian context.

Guideline recommendations did not provide specific guidance surrounding dosing or choice of product, likely owing to the low quality and quantity of evidence surrounding the use medical cannabis in the palliative care setting.

Conclusions and Implications for Decision or Policy Making

A single systematic review of nine RCTs was included in this report.[13] Authors were unable to draw conclusions due to the low quality and quantity of evidence surrounding the use of medical cannabis in the palliative care setting. Medical cannabis was found to be superior to placebo for appetite and weight gain in palliative patients with HIV, however mental health adverse effects were increased. Quality of evidence was rated as very low. Megestrol was found to be superior to dronabinol in palliative patients with cancer for improvement in appetite, weight gain, and health-related quality of life, and with less withdrawal due to adverse events. Megestrol was also found to be superior to dronabinol in patients with HIV for weight gain. Quality of evidence was again rated as very low. The evidence is further limited by applicability to the Canadian context, as dronabinol is not marketed in Canada. In addition to concerns regarding the risk of bias of included RCTs, statistical heterogeneity and lack of detailed baseline characteristics further limits ability to draw conclusions.

Two evidence-based guidelines were included in this report. Their recommendations reflect the known high risk of adverse events of medical cannabis, coupled with uncertain benefit for palliative care patients and the availability of other treatment options. Canadian guidelines provide a strong recommendation against use of medical cannabis as first or second-line option for pain in palliative care.[14] Both guidelines suggest that cannabis could be considered after other options and failed and with careful consideration of risks versus benefits.[14,17] Both guidelines clearly described methods for evidence gathering, however the Australian guidelines did not adequately describe methods of development of recommendations. Neither provided an adequate description of patient involvement.

Further research assessing effectiveness medical cannabis products available in Canada for improvement of symptoms and quality of life in the palliative care setting are needed to reduce uncertainty.

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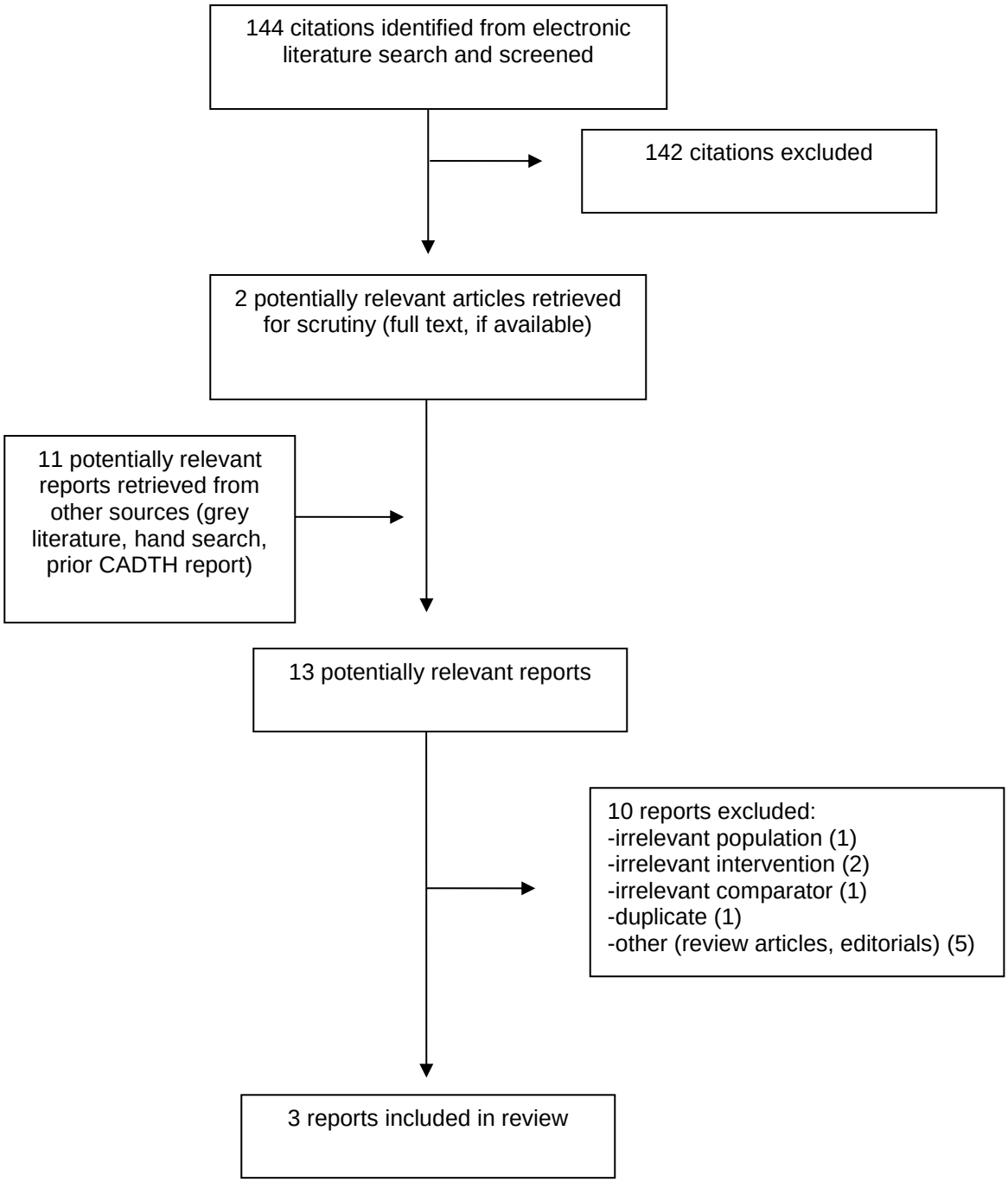
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Review and Meta-Analysis

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention, total daily dose/ Comparator(s)	Clinical Outcomes, Length of Follow-Up
Mucke, 2018[13] Germany	9 RCTs (total n=1561)	**Cancer:** 5 studies, age range 58-66 (n=758) **HIV:** 3 studies, age range 39-43 (n=251) **Alzheimer's:** 1 study, age range 65-82 (n=15) 90.8% male overall	**Cancer:** dronabinol 5-20mg/placebo (n=46) dronabinol 5mg /megestrol 800mg/dronabinol + megestrol/placebo (n=469) THC+CBD oromucosal spray 2.7mg:2.5mg max 48 pump actions/THC oromucosal spray 2.7mg max 48 pump actions/placebo (n=157) THC+CBD oromucosal spray 2.7mg:2.5mg low (1-4pump actions)/medium (6-10 pump actions)/high (11-16 pump actions)/placebo (n=360) THC+CBD oral 5mg+2mg/THC oral 5mg/placebo (n=243) **HIV:** Herbal Cannabis (3.95% THC, 0.9g) up to 3 cigarettes/dronabinol 7.5mg/placebo dronabinol 5mg/placebo Megestrol 750mg / Megestrol 750mg+ dronabinol 5mg/ Megestrol 250mg + dronabinol 5mg / placebo **Alzheimer's:** dronabinol 5mg/placebo	Primary outcomes: pain reduction ≥30%, body weight, appetite, caloric intake, nausea/vomiting Length of follow up: Cancer: 16 days to 11 weeks (median 8 weeks) HIV: 3 to 12 weeks (median 6 weeks) Alzheimer's disease: 6 weeks

CBD = cannabidiol; HIV = Human immunodeficiency virus; RCT = randomized controlled trial; THC = 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
Allan, 2018[14]					
Patients with pain receiving	Use of medical cannabis	≥ 30% reduction in pain	Systematic review of	AMSTAR, GRADE	Iterative process. 10-member guideline committee reviewed

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
palliative care, Primary care clinicians	(medical marijuana and pharmaceutical cannabinoids) for pain, nausea and vomiting, spasticity as well as adverse events		systematic reviews (published separately)[15]		evidence; discussed at meetings, and composed key recommendations. Recommendations were drafted and discussed further. Distributed to outside clinicians for feedback and edited. Final approval by guideline committee.
Australia, 2017[17]					
Doctors and patients, palliative care setting	Medical cannabis (plant-based or synthetic cannabinoids) in palliative care setting	Efficacy: pain reduction ≥ 30%, body weight, appetite, caloric intake, nausea/vomiting (primary endpoints); multiple other endpoints relating to efficacy, tolerability and safety	Review of reviews, Systematic review and meta-analysis of RCTs (published separately,[13] and also included in this report), and systematic search for observational studies	Cochrane Risk of Bias Tool, GRADE	Working group consisted of individuals from state and territory departments of health, healthcare professional organizations, clinicians from hospitals and primary health care networks, and consumer representative groups. -Method of development of recommendations was not specifically described.

RCT = randomized controlled trial

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[10]

Strengths	Limitations
Mucke, 2018[13]	
• Clear research question • Comprehensive search strategy • Conflicts of interest and funding reported • Quality of evidence assessed using GRADE methodology • Indicated that analytical methods and inclusion criteria were established a priori	• Detailed population characteristics not provided • Inadequate justification for pooling data in meta-analysis • Inadequate justification for choice of included study designs • List of excluded studies not provided • Substantial statistical heterogeneity was reported, but not discussed • Several reviewers independently completed data extraction -and risk of bias assessments, but authors did not clearly state that it was done in duplicate • No assessment of publication bias

Table 5: Strengths and Limitations of Guidelines using AGREE II[11]

Item	Guideline	
	Allan, 2018[14]	Australia, 2017[17]
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.	No	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.	Unable to assess	Unable to assess
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	Yes
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.	Yes	No

Table 5: Strengths and Limitations of Guidelines using AGREE II[11]

Item	Guideline	
	Allan, 2018[14]	Australia, 2017[17]
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	Unable to assess
14. A procedure for updating the guideline is provided.	No	Yes
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
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.	No	No
21. The guideline presents monitoring and/or auditing criteria.	No	No
Domain 6: Editorial Independence		
22. The views of the funding body have not influenced the content of the guideline.	Yes	Unable to assess
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 of Included Systematic Review and Meta-Analysis

Main Study Findings	Authors' Conclusion
Mucke, 2018[13]	
Cancer (cannabinoids vs. placebo): *No statistically significant difference:* Appetite (n=324/117) SMD 0.81 (95% CI -1.14 to 2.75) Caloric Intake (n=11/10) SMD 0.2 (95% CI -0.66 to 1.06) Dizziness (n=605/218) RR 1.17 (95% CI 0.76 to 1.80) Health-related quality of life (n=324/117) SMD 0.09 (-0.13 to 0.3) Mental health symptoms (n=410/172) RR 0.72 (0.28 to 1.82) Nausea and Vomiting (n=118/59) SMD 0.21 (95% CI -0.1 to 0.52) Pain reduction ≥30% (n=387/150) RR 1.33 (95% CI 0.95 to 1.85) Serious adverse events (n=605/220) RR 1.12 (0.86 to 1.46) Sleeping disorders (n=129/69) SMD -0.09 (95% CI -0.62 to 0.43) Weight loss gain (n=196/48) SMD= 0 (95% CI 0 to 0) Withdrawal due to adverse events (n=605/220) RR 1.15 (0.80 to 1.66) **Cancer (cannabinoids vs. megestrol) (n=469):** *Megestrol superior to cannabinoids:* Appetite 75% vs. 49% (P = 0.0001) Weight gain >10% of baseline 11% vs. 3% (P = 0.02) Health-related quality of life (P = 0.003) Withdrawals due to adverse events (fewer with megestrol) 45% vs. 58% (P = 0.03) *No difference:* Serious adverse events (22% vs. 15%, P = 0.12) **HIV (cannabinoids vs. placebo):** *Cannabinoids superior to placebo:* Appetite (n=139) SMD 0.57 (95% CI 0.11 to 1.03) Weight gain (n=192): SMD 0.57 (95% CI 0.22 to 0.92) *Statistically significant harm with cannabinoids vs placebo:* Mental Health symptoms (n=206) RD 0.05 (95% CI 0.00 to 0.10) Serious adverse events (n=206) RD 0.06 (95% CI: 0.01 to 0.12) *No statistically significant difference:* Health-related quality of life (n=139) SMD -0.24 (95% CI -0.58 to 0.11) Nausea (n=139) SMD 0.20 (95% CI -0.15 to 0.54) Withdrawal due to adverse events (n=206) RD 0.05 (95% CI -0.02 to 0.11) **HIV (cannabinoids vs. megestrol) (n=48)** *Megestrol superior to cannabinoids:* Weight gain (6.5 ± 1.1 kg vs. -2 ± 1.3 kg, P = 0.0001) *No statistically significant difference:* Health-related quality of life, nausea and vomiting, depressive mood, tolerability and safety. **Alzheimer's disease (cannabinoids vs. placebo) (n=15):** *Cannabinoid superior to placebo:* Increased weight gain (P = 0.017) Decrease in negative affect (p= 0.004)	"Following the GRADE methodology, no recommendations can be made for the use of cannabinoids in palliative care treatment for cancer, HIV–AIDS, or dementia. In view of this finding, further research is urgently needed to identify the efficacy and safety of cannabinoids as adjunctive or complementary therapies and to provide evidence-based recommendations on their clinical utility in palliative care."(p.232)

HIV = human immunodeficiency virus; RD = risk difference; RR = relative risk; SMD = standardized mean difference

Table 7: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
Allan, 2018[14]	
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 refractory 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" (p.112)	-Strong recommendation against first-line or second-line use -GRADE quality of evidence for ≥30% reduction in palliative pain: Very low -Weak recommendation to consider in refractory pain
Australia, 2017[17]	
"As there are very few studies on medicinal cannabis treatment in palliative care, it should be used only after standard treatments have failed. It is possible that medicinal cannabis will interact with chemotherapy and other medications used in palliative care. More studies are needed to better understand this."(p.3) "Patients and prescribing clinicians should be aware of possible adverse events such as somnolence, nausea and dizziness. Adverse events such as confusion, pain, diarrhoea or hallucinations may impact the overall aims of the palliative medicine and reduce quality of life, and should be evaluated on a case-by-case basis."(p.11)	Strength of recommendations not provided. **Levels of evidence by disease category:** **Alzheimer's Disease:** Dronabinol for weight gain, mood: C **Cancer:** Dronabinol, THC, THC:CBD for pain: C Cannabis sativa for symptoms related to cancer and cancer-treatments: C Dronabinol for appetite and nausea: C Nabilone for pain, morphine use, nausea, anxiety, appetite, and overall distress: C Dronabinol, THC:CBD or THC for caloric intake, appetite, weight gain, nausea and vomiting, sleep, depressed mood: D

CBD = cannabidiol; THC = tetrahydrocannabinol