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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Nabilone for the Treatment of Nausea and Vomiting or Anorexia: 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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Context and Policy Issues

Nausea, vomiting, and loss of appetite (anorexia) are common symptoms in many pathological conditions affecting the normal function of the upper gastrointestinal tract.[1] Nausea and vomiting are particularly common side effects of chemotherapy (chemotherapy-induced nausea and vomiting – CINV),[2] radiotherapy (radiotherapy-induced nausea and vomiting – RINV),[3] or anesthesia during surgery (post-operative nausea and vomiting – PONV).[4,5] Pharmacological treatment of nausea and vomiting usually ranges from conventional antiemetics such as antihistamines, benzodiazepines, and dopamine antagonists, to more recently approved antiemetics such as 5HT3 antagonists or NK1-receptor antagonists.[6] Cannabis and its chemical compound cannabinoids, by acting on cell membrane receptors and altering neurotransmitter release, can relieve nausea, vomiting, and improve appetite.[7] Nabilone, a synthetic cannabinoid, has been used to treat nausea and vomiting, loss of appetite, has side effects such as hallucination, drowsiness, depression, dysphoria, vertigo, dry mouth and lack of muscle coordination.[8,9]

This Rapid Response report aims to review the clinical effectiveness of nabilone for the treatment of nausea, vomiting, or anorexia. Guidelines associated with the use of nabilone for the treatment of nausea, vomiting, or anorexia will also be examined. This is an update and upgrade of two previous CADTH reports examining the clinical effectiveness and guidelines pertaining to the use of nabilone for the treatment of nausea and vomiting, or anorexia in adults and adolescents.[10,11]

Research Question

1. What is the clinical effectiveness of nabilone for the treatment of nausea and vomiting, or anorexia in adults and adolescents?

2. What are the evidence-based guidelines associated with the use of nabilone for the treatment of nausea and vomiting, or anorexia in adults and adolescents?

Key Findings

Based on data from one systematic review of systematic reviews and three randomized controlled trials, nabilone was not found to be more effective than conventional antiemetics or placebo for the reduction of nausea or vomiting was not proven in patients with chemotherapy-induced nausea and vomiting, radiotherapy-induced nausea and vomiting or post-operative nausea and vomiting. Nabilone was also found to be associated with more safety concerns such as hallucination, drowsiness, dysphoria, and lack of muscle coordination. In patients with cancer diagnosed with anorexia, nabilone increased daily caloric and carbohydrate intake with similar daily proteins, fat and iron intake compared to placebo. The identified Canadian guideline recommends against the use of medical cannabinoids for general nausea and vomiting in primary care and in pregnancy, owing to the lack of evidence and known harms; medical cannabinoids, in particular nabilone, can be considered as third-line therapy for the treatment of refractory chemotherapy-induced nausea and vomiting.

Methods

This report makes use of a literature search developed for a previous CADTH report. The original literature search was conducted in June 2017 on key resources including PubMed, Embase, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The initial search was also limited to English-language documents published between January 1, 2012 and June 9, 2017. For the current report, database searches were rerun on January 29, 2019 to capture any articles published since the initial search date. The search of major health technology agencies was also updated to include documents published since June 2017.

Selection Criteria and Methods

One reviewer screened citations and selected studies. Citations from the previous report were also screened. 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 and Adolescents (≥ 13 years old) with nausea and vomiting, or anorexia
Intervention	Nabilone (Cesamet)
Comparator	Q1: Active comparators, placebo, no treatment Q2: No comparator
Outcomes	Q1: Clinical effectiveness (e.g., reduction in nausea and vomiting, control/change of weight), and safety (e.g., adverse events, abuse and misuse) Q2: Guidelines
Study Designs	Heath technology assessments, systematic reviews and meta-analyses, RCTs, non-randomized studies, evidence-based guidelines

RCT = randomized controlled trial.

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 2012. Guidelines with unclear methodology were excluded.

Critical Appraisal of Individual Studies

The included systematic reviews (SR), randomized controlled studies (RCTs), and guidelines were critically appraised by one reviewer using the AMSTAR II,[12] Downs and Black,[13] and AGREE II[14] checklists, respectively. Summary scores were not calculated. Instead, the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 117 citations were identified in the literature search. Following screening of titles and abstracts, 113 citations were excluded and potentially four relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, one publication was excluded for various reasons, while five publications met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA flowchart of the study selection.

Summary of Study Characteristics

A detailed summary of the included studies is provided in Appendix 2.

Study design

One SR of SRs,[15] three RCTs,[16-18] and one guideline[19] were included. The SR performed review on six SRs of RCTs, published between 2001 and 2015.

The RCTs were double-blind placebo controlled single-centre trials, and the guideline was evidence-based, from the Canadian Cannabinoids Prescribing Guideline Committee. The guideline identified evidence from a systematic review of relevant studies, and recommendations were made based on the consensus of clinical expert opinion.

Population

The SR examined studies regarding patients at risk of nausea and vomiting from chemotherapy for any type of cancer.[15]

One RCT included 33 patients (mean age 61.1 years) with advanced non-small cell lung cancer diagnosed with anorexia,[16] one RCT included 340 patients (mean age 49.8 years) with general anesthesia for elective surgery with risk for post-operative nausea and vomiting,[17] and one RCT included 56 patients (mean age 63.5 years) undergoing radiotherapy for head and neck cancer.[18]

The guideline makes recommendations regarding the use of medical cannabinoids for patients with pain, nausea and vomiting, and spasticity.[19]

Interventions and comparators

The SR compared cannabinoids at any dose to active treatments such as antipsychotics, dopamine antagonists and steroids, or placebo.[15] The RCTs compared nabilone 0.5mg/day or 1.0mg/day with placebo.[16-18]

The guideline made recommendations regarding the medical use of cannabinoids.[19]

Outcomes

The SR narratively reported risk of nausea and vomiting from chemotherapy.[15]

The RCTs reported appetite and incidence of chemotherapy-induced nausea and vomiting (CINV),[16] PONV,[17] and appetite and nausea,[18] using the PONV Impact scale or European Organization Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). EORTC QLQ-C30 scores range from 0 to 100, where 100 is the best score. A difference of 15 points is considered significant enough to change clinical practice.

The guideline reported recommendations on the medical use of cannabinoids.[19]

Summary of Critical Appraisal

The included SR[15] provided an a priori design and performed a systematic literature search. Procedures for the independent duplicate selection and data extraction of studies were in place, making it less likely that errors in study selection or data extraction occurred. A list of included studies and characteristics were provided, and quality assessment was used in formulating conclusions. The review did not assess publication bias, which is an important factor in understanding the extent to which findings from included, published studies could over-represent any observed effect, did not include a list of excluded studies and did not perform meta-analysis.

The included clinical trials[16-18] are RCTs, patients and assessors were blinded to treatment assignment, the hypotheses were clearly described, the method of selection from the source population and representation were described, losses to follow-up were reported, main outcomes, interventions, patient characteristics, and main findings were clearly described, and estimates of random variability and actual probability values were provided. One study did not perform power calculation to detect a clinically important effect which may obscure the effect of the intervention,[16] one study only included female patients which may have limited the generalizability of the findings,[17] and one study had large number of patients lost to follow-up which may have interfered with the power to detect clinically important effect.[18]

The included guideline[19] had specific and unambiguous recommendations, with a systematic and clearly described method of searching for and selecting the evidence, and clearly described methods to formulate the recommendations. Health benefits and risks were stated, and procedures to update the guideline were provided. It is unclear whether the guideline was piloted among target users, or whether patients' views and preferences were sought. Potential cost implications of applying the recommendations were not included in the guideline.

Details of the strengths and limitations of the included studies are summarized in Appendix 3.

Summary of Findings

Clinical effectiveness of nabilone for the treatment of nausea and vomiting or anorexia

The SR of SRs pertaining to patients undergoing chemotherapy[15] did not perform meta-analysis and therefore did not provide pooled estimate with statistical significance. Findings were inconsistent from the SRs on the efficacy of cannabinoids compared to conventional antiemetics or placebo on the incidence of nausea and vomiting. Cannabinoids resulted in higher incidence of side effects such as hallucination, drowsiness, and dysphoria. There was no RCT identified in the systematic reviews that compared cannabinoids to more recently approved antiemetics such as 5HT3 antagonists or NK1-receptor antagonists. The

authors concluded that cannabinoids could not be recommended as first or second line treatment for CINV.

One RCT examined the efficacy and safety of 8 weeks of treatment with nabilone for patients with advanced non-small cell lung cancer diagnosed with anorexia.[16] Patients who received nabilone increased their caloric intake (mean 342 kcal) compared to placebo and those who received nabilone significantly increased daily intake of carbohydrates compared to placebo. There was no statistical significant difference in increase in daily intake of proteins, fat, or iron between those who received nabilone versus patients receiving placebo and there was no statistically significant difference in nausea or vomiting in patients receiving nabilone compared to baseline. The authors concluded that nabilone was an adequate and safe therapeutic option to aid in the treatment of patients diagnosed with anorexia due to non-small cell lung cancer.

One RCT examined the efficacy and safety of single dose nabilone versus placebo for patients undergoing general anesthesia for elective surgery with risk for PONV.[17] There was no statistically significant difference in the PONV between the 2 groups. Those who received nabilone had more lack of muscle coordination than those in the control group but there was a similar incidence of other symptoms such as drowsiness, depression, hallucination, dry mouth, and vertigo. The authors concluded that nabilone given before a surgical procedure was ineffective in reducing PONV.

One RCT examined the efficacy of 8 weeks of treatment with nabilone for patients with head and neck cancer undergoing radiotherapy.[18] There was no statistically significant difference found on the incidence of nausea or loss of appetite between the nabilone and placebo groups. The authors concluded that nabilone did not improve patients' quality of life over placebo.

Guidelines

One guideline provides recommendations on the use medical cannabinoids for pain, nausea and vomiting, and spasticity in primary care.[19]

Regarding the management of nausea and vomiting, the guideline recommends against the use of medical cannabinoids for general nausea and vomiting in general care or in pregnancy, owing to the lack of evidence and known harms (strong recommendation). For CINV, the guideline recommends against the use of medical cannabinoids as first- or second-line treatment of CINV owing to limited comparison with first-line agents and known harms (strong recommendation).

With respect to the types of cannabinoids, the guideline recommends the use of nabilone (strong recommendation) but not nabiximols or medical cannabis (either smoked, the use of oil, or edibles) as they have not been adequately studied (strong recommendation). The guideline further states that while there is evidence regarding dronabinol, it is no longer available in Canada.

Details of findings are presented in Appendix 4.

Limitations

Findings reported in this review came from SR that did not provide pooled estimate with statistical significance, and from RCTs with relative small sample size that may not have detected clinically important effects. There was no studies identified either in the included systematic review or in this review, that compared cannabinoids to more recently approved

antiemetics such as 5HT3 antagonists or NK1-receptor antagonists; this may limit the generalizability of the comparative efficacy of nabilone and antiemetics.

Conclusions and Implications for Decision or Policy Making

Findings from a systematic review of systematic reviews published up to 2015 found inconsistent data on efficacy, and worse findings on safety, of cannabinoids compared to conventional antiemetics or placebo for the treatment of CINV. The systematic review did not find RCTs that compared cannabinoids to more recently approved antiemetics such as 5HT3 antagonists or NK1-receptor antagonists.

More recent placebo-controlled RCTs found that single dose nabilone was also ineffective in reducing the risk of PONV in patients undergoing general anesthesia for elective surgery, as well as in improving nausea and vomiting or appetite in patients with RINV. Nabilone significantly increased daily caloric and carbohydrate intake, but results were similar regarding daily protein, fat, and iron intake compared to placebo in patients with advanced non-small cell lung cancer diagnosed with anorexia.

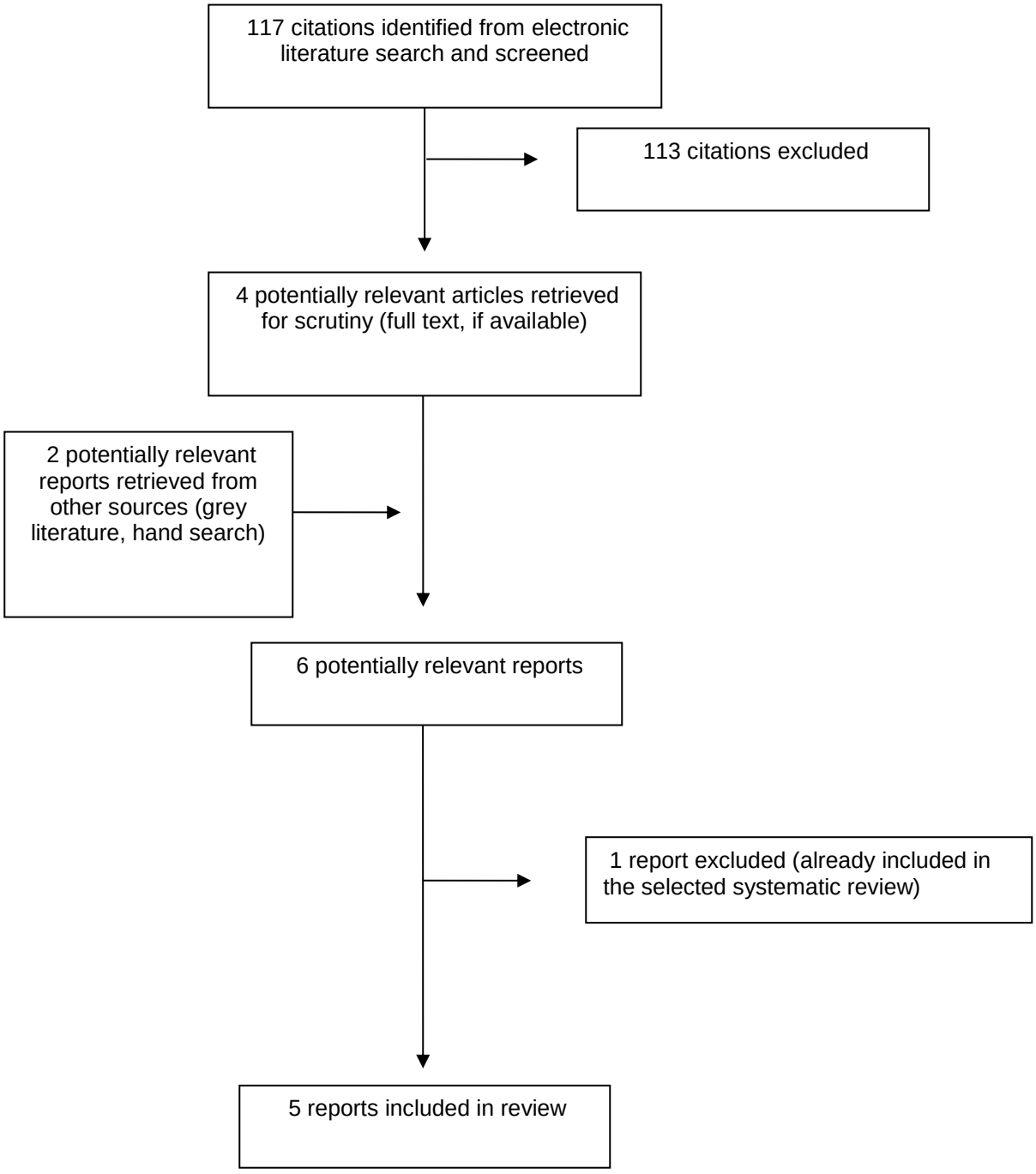
The included Canadian guideline recommends against the use of medical cannabinoids for general nausea and vomiting in general care or in pregnancy, owing to the lack of evidence and known harms. The guideline also recommends against the use of medical cannabinoids as first- or second-line treatment of CINV; medical cannabinoids, in particular nabilone, can be considered in the treatment of refractory CINV.

Findings from larger RCTs comparing nabilone to conventional antiemetics and newly approved antiemetics may reduce uncertainty regarding the use of cannabinoids in the treatment of nausea, vomiting, and anorexia.

References

1. Mayo Clinic. Symptoms: nausea and vomiting. Causes. 2018; https://www.mayoclinic.org/symptoms/nausea/basics/causes/sym-20050736. Accessed 2019 Feb 27.
2. Canadian Cancer Society. Side effects of chemotherapy. *Chemotherapy and other drug therapies: chemotherapy.* http://www.cancer.ca/en/cancer-information/diagnosis-and-treatment/chemotherapy-and-other-drug-therapies/chemotherapy/side-effects-of-chemotherapy/?region=on. Accessed 2019 Feb 27.
3. Canadian Cancer Society. Side effects of radiation therapy. *Radiation therapy.* http://www.cancer.ca/en/cancer-information/diagnosis-and-treatment/radiation-therapy/side-effects-of-radiation-therapy/?region=on. Accessed 2019 Feb 27.
4. Feinleib J, Kwan LH, Yamani A. Postoperative nausea and vomiting. In: Post TW, ed. *UpToDate*. Waltham (MA): UpToDate; 2018: www.uptodate.com. Accessed 2019 Feb 27.
5. Shaikh SI, Nagarekha D, Hegade G, Marutheesh M. Postoperative nausea and vomiting: a simple yet complex problem. *Anesth Essays Res.* 2016;10(3):388-396.
6. Longstreth GF. Approach to the adult with nausea and vomiting. In: Post TW, ed. *UpToDate*. Waltham (MA): UpToDate; 2018: www.uptodate.com. Accessed 2019 Feb 27.
7. Smith LA, Azariah F, Lavender VTC, Stoner NS, Bettiol S. Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. *Cohrane Database of Sysyematic Reviews.* 2015(11):CD009464.
8. Cesamet (nabilone) capsules, for oral administration [label]. Costa Mesa (CA): Valent Pharmaceuticals International; 2006 May: https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/018677s011lbl.pdf. Accessed 2019 Feb 26.
9. Canadian Cancer Society. Cannabis and cannabinoids for medical purposes. *Complementary therapies: medial cannabis and cannabinoids*. http://www.cancer.ca/en/cancer-information/diagnosis-and-treatment/complementary-therapies/medical-cannabis-and-cannabinoids/?region=on. Accessed 2019 Feb 27.
10. Nabilone for the treatment of nausea and vomiting, or anorexia: clinical effectiveness and guidelines. *(CADTH Rapid response report: reference list)*. Ottawa (ON): CADTH; 2017: https://cadth.ca/sites/default/files/pdf/htis/2017/RA0912%20Nabilone%20for%20Nausea%2C%20Vomiting%2C%20and%20Anorexia%20Final.pdf. Accessed 2019 Feb 26.
11. Nabilone for the treatment of nausea and vomiting, or anorexia: clinical effectiveness and guidelines – an update. *(CADTH Rapid response report: reference list)*. Ottawa (ON): CADTH; 2018: https://cadth.ca/sites/default/files/pdf/htis/2018/RA0973%20Nabilone%20for%20Nausea%2C%20Vomiting%2C%20and%20Anorexia%20Final.pdf. Accessed 2019 Feb 26.
12. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017;358:j4008. http://www.bmj.com/content/bmj/358/bmj.j4008.full.pdf. Accessed 2019 Feb 27.
13. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health.* 1998;52(6):377-384. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf. Accessed 2019 Feb 27.
14. Agree Next Steps Consortium. The AGREE II Instrument. Hamilton (ON): AGREE Enterprise; 2017: https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf. Accessed 2019 Feb 27.
15. Tafelski S, Hauser W, Schafer M. Efficacy, tolerability, and safety of cannabinoids for chemotherapy-induced nausea and vomiting--a systematic review of systematic reviews. *Schmerz.* 2016;30(1):14-24.
16. Turcott JG, Del Rocio Guillen Nunez M, Flores-Estrada D, et al. The effect of nabilone on appetite, nutritional status, and quality of life in lung cancer patients: a randomized, double-blind clinical trial. *Supportive Care Cancer.* 2018;26(9):3029-3038.
17. Levin DN, Dulberg Z, Chan AW, Hare GM, Mazer CD, Hong A. A randomized-controlled trial of nabilone for the prevention of acute postoperative nausea and vomiting in elective surgery. *Can J Anaesth.* 2017;64(4):385-395.
18. Cote M, Trudel M, Wang C, Fortin A. Improving quality of life with nabilone during radiotherapy treatments for head and neck cancers: a randomized double-blind placebo-controlled trial. *Ann Otol Rhinol Laryngol.* 2016;125(4):317-324.
19. Allan GM, Ramji J, Perry D, et al. Simplified guideline for prescribing medical cannabinoids in primary care. *Can Fam Physician.* 2018;64(2):111-120.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

First author, Year, Country	Literature Search Strategy	Inclusion Criteria	Exclusion Criteria	Number of Studies Outcomes
Tafelski,[15] 2016, Germany	Systematic review of systematic reviews *"The following electronic databases were searched from their inception through to November 30, 2015: Pubmed/MEDLINE, the Cochrane Library, and the Database of Abstracts of Reviews of Effects (DARE). The literature search was constructed around search terms for "chemotherapy induced nausea and vomiting," systematic reviews, and meta-analyses and adapted for each database"* (p 15)	Studies: "*Systematic reviews should meet the preferred reporting items for systematic reviews and meta-analyses (PRISMA) criteria and include randomized controlled trials (RCTs) with crossover or parallel-group design with active or placebo control groups or both"* (p 14) Participants: *"Patients presenting with any type of cancer and receiving chemotherapeutic treatment (low, moderate, or high emetic potential), independent of gender, age, country, and clinical setting"* (p 14) Interventions: "*CBs, either phytocannabinoids such as herbal cannabis (hashish, marihuana), plant-based CBs (nabiximole), or pharmacological synthetic CBs (e.g., cannabidiol, dronabinol, levonantradol, nabilone) at any dose, by any route, compared with other conventional agents or placebo, or both for CINV*" (p 14)	Reviews not fulfilling the inclusion criteria	Review of 6 systematic reviews of RCTs Narrative reviews on efficacy and safety of pharmaceutical cannabinoids (dronabinol, levonantradol, and nabilone or whole plant extract nabiximol) compared with placebo or conventional antiemetics.

CB = cannabinoids; CINV = chemotherapy-induced nausea and vomiting; RCT = randomized controlled trial

Table 3: Characteristics of Included Randomized Controlled trials

First Author, Year, Country	Study Design Objectives	Intervention Comparators	Patients	Main Study Outcomes
Turcott,[16] 2018, Mexico	Randomized, double-blind, placebo-controlled clinical trial "*to assess the effect of Nabilone vs. placebo on the appetite, nutritional status, and quality of life in patients diagnosed with advanced Non-small cell lung cancer (NSCLC)*" (p 3029)	Nabilone (0.5 mg/2 weeks followed by 1.0 mg/6 weeks) Placebo	Patients with advanced non-small cell lung cancer diagnosed with anorexia (21% male; 79% female) Nabilone: 14 patients at week 1 (5 lost to follow-up) Placebo: 19 patients at week 1 (6 lost to follow-up)	Appetite, nausea or vomiting using EORTC QLQ-C30 (Score ranges from 0 to best score 100, and a difference of 15 points considered significant enough to change clinical practice)
Levin,[17] 2017, Canada	Randomized, double-blind, placebo-controlled clinical trial *The purpose of this study was to evaluate the effectiveness of a single dose of nabilone for the prevention of PONV* (p 385)	Nabilone (0.5mg single dose) Placebo	Patients undergoing general anesthesia for elective surgery with risk for PONV (100% female) Nabilone: 172 patients (0 lost to follow-up) Placebo: 168 patients (6 lost to follow-up)	Incidence of PONV using PONV Impact Scale Side effects such as drowsiness, depression, vertigo, lack of muscle coordination
Cote,[18] 2016, Canada	Randomized, double-blind, placebo-controlled clinical trial To examine the effects of nabilone versus placebo on quality of life and side effects during radiotherapy for head and neck carcinomas	Nabilone (0.5 mg/1 week followed by 1.0 mg/7 weeks) Placebo	Patients undergoing radiotherapy (82% male, 18% female) Nabilone: 28 patients (9 lost to follow-up) Placebo: 28 patients (16 lost to follow-up)	Appetite, nausea or vomiting using EORTC QLQ-C30 (Score ranges from 0 to best score 100, and a difference of 15 points is considered significant enough to change clinical practice)

EORTC QLQ-C30: European Organization Research and Treatment of Cancer Quality of Life Questionnaire; PONV = post-operative nausea and vomiting

Table 4: Characteristics of Included Guidelines

Group, Year	Scope	Population	Evidence	Recommendations Development and Evaluation	Grading System
Allan,[19] 2018, Canada Evidence Review Group (Medical Cannabinoids Prescribing Guideline Committee)	Guidelines for a simplified approach to medical cannabinoid use in primary care	Patients of all age on medical cannabinoid use for pain, nausea and vomiting, and spasticity	A comprehensive review of systematic reviews of RCTs on medical cannabinoid use (databases not reported)	Statements were developed through an iterative online platform then completed through on line communications and telephone meetings by a group of specialists	The evidence and recommendation rating were adopted from the classification developed by the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) workgroup. The GRADE system primarily involves consideration of the following factors: overall study quality (or overall risk of bias or study limitations), consistency of evidence, directness of evidence, and precision of evidence.

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR II[12]

Strengths	Limitations
Tafelski[15]	
• a priori design provided • independent studies selection and data extraction procedure in place • comprehensive literature search performed • list of included studies, studies characteristics provided • quality assessment of included studies provided and used in formulating conclusions • conflict of interest stated	• assessment of publication bias not performed • list of excluded studies not provided • narrative review; no meta-analysis performed

Table 6: Strengths and Limitations of Randomized Controlled Trials using Downs and Black[13]

Strengths	Limitations
Turcott[16]	
• randomized controlled trial • patient and assessor blinded to patient treatment assignment. • hypothesis clearly described • method of selection from source population and representation described • loss to follow-up reported • main outcomes, interventions, patient characteristics, and main findings clearly described • estimates of random variability and actual probability values provided	• study did not perform power calculation to detect a clinically important effect
Levin[17]	
• randomized controlled trial • patient and assessor blinded to patient treatment assignment. • hypothesis clearly described • method of selection from source population and representation described • loss to follow-up reported • main outcomes, interventions, patient characteristics, and main findings clearly described • estimates of random variability and actual probability values provided • power calculation performed to detect a clinically important effect	• all patients were female; this may limit the generalizability of the findings

Table 6: Strengths and Limitations of Randomized Controlled Trials using Downs and Black[13]

Strengths	Limitations
Cote[18]	
• randomized controlled trial • patient and assessor blinded to patient treatment assignment • power calculation performed to detect a clinically important effect • hypothesis clearly described • method of selection from source population and representation described • loss to follow-up reported • main outcomes, interventions, patient characteristics, and main findings clearly described • estimates of random variability and actual probability values provided	• large number of patients lost to follow-up may have interfered with the power to detect clinically important effect

Table 7: Strengths and Limitations of Guidelines using AGREE II[14]

Strengths	Limitations
Allan[19]	
• scope and purpose of the guidelines are clear • the recommendations are specific and unambiguous • the method for searching for and selecting the evidence are clear • methods used for formulating the recommendations are clearly described • health benefits, side effects and risks were stated in the recommendations • procedure for updating the guidelines provided • target users of the guideline are clearly defined	• unclear whether the guideline was piloted among target users • unclear whether patients' views and preferences were sought • potential cost implications of applying the recommendation not included

Appendix 4: Main Study Findings and Author's Conclusions

Table 8: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
Tafelski[15] (Systematic Review)	
Narrative review without pooled estimate with statistical significance *"There was moderate quality evidence on the efficacy of CBs compared to placebo and conventional antiemetics for CINV. There was moderate quality evidence that pharmaceutical CBs were less tolerated and less safe than placebo and conventional antiemetics in CINV"* (p 14) *Tramer et al. CBs were more effective than active comparators (prochlorperazine, metoclopramide, chlorpromazine, thiethylperazine, haloperidol, domperidone, and alizapride). CBs were less tolerated and less safe than controls.* *Rocha et al. concluded that the antiemetic effect of CBs was superior to controls* (placebo)*. The authors did not assess tolerability and safety.* *Phillips et al. concluded that the data on efficacy of CBs versus conventional drugs were inconsistent. The authors did not assess tolerability and safety compared to controls.* *van den Elsen et al. concluded that cannabinoid therapy in the elderly should be administered carefully including a critical evaluation of the risk–benefit ratio for each individual.* *Whiting et al. described higher therapy response with CBs showing a complete nausea and vomiting response compared with placebo.* *Smith et al. concluded that they are not very confident with their findings regarding effectiveness of CBs for CINV therapy"* (p 19, 20, 21) Cannabinoids resulted in higher incidence of side effects such as hallucination, drowsiness and dysphoria. There was no RCT found that compared cannabinoids to more recently approved antiemetics such as 5HT3 antagonists or NK1-receptor antagonists.	*"With safe and effective antiemetics available, CBs cannot be recommended as first- or second-line therapy for CINV"* (p 14)
Turcott[16] (RCT)	
After 8 weeks of treatment (compared to baseline) No statistically significant increase in daily energy intake, carbohydrate, proteins, fat and iron in patients with nabilone compared to baseline No statistically significant difference in nausea or vomiting in	*"Nabilone is an adequate and safe therapeutic option to aid in the treatment of patients diagnosed with anorexia. Larger trials are necessary in order to draw robust conclusions in regard to its efficacy in lung cancer patients"* (p 3029)

Table 8: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
patients with nabilone compared to baseline. No grade 3 or higher events of nausea reported. *After 8 weeks of treatment (compared to placebo)* Statistically significant increase in daily intake of carbohydrates in patients with nabilone (64 g) compared to patients receiving placebo (*P* = 0.040) No statistical significant difference in increase in daily energy intake, proteins, fat and iron between patients with nabilone and patients receiving placebo Comparison between the 2 groups in nausea and vomiting not reported	
Levin[17] (RCT)	
Incidence of PONV: 20.9% in the nabilone group 21.4% in the placebo group (relative risk, 0.98; 95% confidence interval, 0.89 to 1.11; *P* = 0.99) Side effects: Lack of muscle coordination: 3/172 (1.7%) patients in the nabilone group 0 (0%) patients in the placebo group (*P* < 0.001) No statistically significant difference between the 2 groups in all other symptoms (drowsiness, depression, vertigo)	*"Oral nabilone 0.5 mg given as a single dose prior to surgery is ineffective in reducing PONV"* (p 385)
Cote[18] (RCT)	
No statistically significant difference found on the incidence of nausea or loss of appetite between nabilone group and placebo group	"*At the dosage used, nabilone was not potent enough to improve patient's quality of life over placebo*" (p 317)
Allan[19] (Guidelines)	
"Management of nausea and vomiting *• General: We recommend against use of medical cannabinoids for general nausea and vomiting owing to the lack of evidence and known harms* *-We strongly recommend against medical cannabinoids for nausea and vomiting in pregnancy or hyperemesis gravidarum owing to the lack of evidence, known harms, and unknown harms* *• CINV: We recommend against use of medical cannabinoids as first- or second-line therapy for CINV owing to limited comparisons with first-line agents and known harms* *-Clinicians could consider medical cannabinoids for treatment of refractory CINV, with the following considerations* *— a discussion has taken place with patients regarding the risks and benefits of medical cannabinoids for CINV* *— patients have had a reasonable therapeutic trial of standard therapies‡ and have persistent CINV*	Strength of recommendations Strong recommendation Strong recommendation Strong recommendation Weak recommendation

Table 8: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
— medical cannabinoids are adjuncts to other prescribed Therapies	
•Types of medical cannabinoids for CINV: *-If considering medical cannabinoids, we recommend nabilone*	Strong recommendation
— We recommend against nabiximols and medical marijuana (smoked, oils, or edibles), as it is inadequately studied *— While dronabinol has been studied, it is no longer available in Canada"* (p 112)	Strong recommendation

CBs = cannabinoids; CINV = chemotherapy-induced nausea and vomiting; PONV = post-operative nausea and vomiting