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A Quality Initiative of the Program in Evidence-Based Care (PEBC), Ontario Health (Cancer Care Ontario)

Cancer and the Health Effects of Cannabis and Cannabinoids: An update of the systematic review by the National Academies of Sciences, Engineering, and Medicine (2017) Consensus Study Report

W.K. Evans, L.D. Durocher-Allen, P. Daeninck, D. Hammond, A. Lofters, P. Selby, M. Slaven

Report Date: June 29, 2020

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Executive Summary

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EXECUTIVE SUMMARY

Ontario Health (Cancer Care Ontario) (OH [CCO])'s Prevention and Cancer Control portfolio with the Program in Evidence-Based Care developed this report to evaluate the evidence on the health effects of cannabis and cannabinoids related to cancer to support a position from OH (CCO) to respond to requests from the public and clinical community and to help with the development of knowledge products for healthcare providers and patients.

In 2017, the U.S. National Academies of Sciences, Engineering, and Medicine (NASEM) conducted a comprehensive review titled "The Health Effects of Cannabis and Cannabinoids: The current state of evidence and recommendations for research" [3]. This consensus guideline covered 11 health topics: therapeutic effects, cancer, cardiometabolic risk, respiratory disease, immunity, injury and death, prenatal, perinatal, and postnatal exposure to cannabis, psychosocial, mental health, problem cannabis use, and cannabis use and abuse of other substances. For each health endpoint, the NASEM group identified systematic reviews and primary research literature up to August 1, 2016 and based their conclusions on all relevant fair- and good-quality systematic reviews and primary research up to that date.

The objective of this evidence summary is to build on the NASEM consensus document and to evaluate and add to it updated evidence on the health effects of cannabis and cannabinoids specific to cancer.

SUMMARY OF FINDINGS

The Working Group developed the following conclusions. Outcomes vary for each question. Please see Section 2 of the evidence summary for more details.

1. Are cannabis or cannabinoids an effective treatment for the reduction of chronic pain in cancer patients?

The NASEM concluded that there is substantial evidence supporting cannabis as an effective treatment for chronic pain. It included a variety of medical conditions, most often related to neuropathy, but also other cancer pain, multiple sclerosis, rheumatoid arthritis, and musculoskeletal issues. This evidence review focused on the reduction of chronic pain in adults with cancer; therefore, some important clarifications must be stated.

It should be noted that there are many different causes of pain in patients with cancer (e.g. pain induced by metastases to the liver or bone, pain due to chemotherapy-induced neuropathy, etc.). The systematic reviews found in the updated literature search do not clearly demonstrate whether cannabis is effective for any one type of cancer pain over another. Several of the studies included in the systematic reviews focused on neuropathy but

it was unclear whether the neuropathy was caused by the cancer, the chemotherapy drugs used to treat the cancer, or an unrelated condition (e.g. diabetes, multiple sclerosis, or HIV). Second, while the use of cannabis for the treatment of chronic pain is supported by well-designed clinical trials, the majority of the trials from the NASEM report and the updated search compared cannabis use with a placebo rather than standard-use analgesia. Further, the NASEM report does not clearly state that the use of cannabis-based medicine is not recommended as a first-line agent for treatment of cancer pain. It may be considered an adjunct to other proven analgesics in patients with cancer especially in patients with painful neuropathies. While cannabis-based medicine may reduce chronic pain in cancer patients, the benefits must also be weighed against potential harms from adverse events. Patients with pre-existing mental illness may have more adverse effects from cannabis-based medications. More research is needed comparing cannabis-based medicine with current standard analgesics used to manage cancer pain and studies need to make clear the type(s) of cancer pain being evaluated and the adverse events experienced by cancer patients.

Conclusion: There is limited evidence that cannabis-based medicines may be an effective treatment for chronic pain in some patients with cancer. However, it is important to note that much of this evidence compared cannabis-based medicine against placebo rather than commonly used analgesics for cancer pain. There is also little evidence on the effectiveness of cannabis-based medicines in different types of cancer pain; much of the literature has focused on neuropathy. Furthermore it is important to weigh the benefits of cannabis-based medicine and the potential harms of adverse events (particularly among cancer patients who frequently have multiple comorbidities). Cannabis-based medicine is not supported by evidence as a first or second line agent, but may be considered as a third- or fourth-line agent, where it could be used as an adjuvant therapy to other analgesics.

2. Are cannabis or cannabinoids an effective treatment for cancer?

As no new evidence was found in the updated search, there continues to be insufficient clinical evidence to make any statement about the efficacy of cannabinoids or cannabis as a treatment for cancer. With such limited evidence, it is clear that a research gap exists in relation to cannabis or cannabinoids as potential treatments for any cancer.

Conclusion: There continues to be insufficient evidence to support the use of cannabinoids or cannabis as a treatment for cancer.

3. Are cannabis or cannabinoids an effective treatment for the reduction of chemotherapy-induced nausea and vomiting (CINV)?

The trials found in the NASEM report and in the updated literature predominantly compare cannabinoids with placebo rather than with standard antiemetics. Based on the available evidence, the NASEM report concluded that oral cannabinoids may be as effective as standard antiemetics in the treatment of CINV [3]. The updated literature generally supports this conclusion. Nabilone and dronabinol, which are oral THC preparations, have been available for more than 30 years for the treatment of CINV, although only nabilone is available in Canada. There are a few trials of cannabis in comparison to placebo or standard antiemetics. Mild to moderate adverse events were common in patients taking cannabis or cannabinoids. Although rare, heavy cannabis use is paradoxically associated with the cannabinoid hyperemesis syndrome and cyclic nausea and vomiting with abdominal pain.

Conclusion: There is conclusive evidence that oral cannabinoids are effective antiemetics in the treatment of CINV but insufficient evidence exists comparing oral cannabinoids with the currently available, most effective anti-emetics used in cancer care.

4. Are cannabis or cannabinoids an effective treatment for anorexia and weight loss associated with cancer-associated anorexia-cachexia syndrome?

Weight loss and anorexia are common side effects in patients with cancer. The NASEM report concluded that there was insufficient evidence to support or refute cannabis or cannabinoids as an effective treatment for cancer-associated anorexia-cachexia syndrome and anorexia nervosa. The updated search found one systematic review/meta-analysis suggesting cannabinoids increased appetite, but did not increase overall quality of life. A small pilot RCT from the primary literature showed no difference in appetite, but found that patients in the nabilone group had increased carbohydrate consumption. The combined evidence from NASEM and the updated search is insufficient to establish cannabinoids as an effective treatment for cancer-associated anorexia-cachexia syndrome and anorexia nervosa.

Conclusion: There is insufficient evidence on the use of cannabinoids as an effective treatment for cancer-associated anorexia-cachexia syndrome and anorexia nervosa.

5a. Is there an association between cannabis use and the incidence of lung cancer?

There is limited literature evaluating cannabis smoking and the incidence of lung cancer and an updated search failed to identify any new literature on the topic. However, it is difficult to study the relationship between smoking cannabis and lung cancer for several reasons. First, many cannabis smokers are also tobacco smokers. Secondly, it is difficult to quantify the amount of cannabis smoked. The number of cigarettes smoked and the duration of smoking tobacco expressed as pack-years is well established as a useful measure to quantify the risk of developing lung cancer. An appropriate similar measure for cannabis has not been determined because joint size and the purity of product vary. Also, how a joint is smoked differs from how a tobacco cigarette is smoked. The chemical exposure profile of cannabis smoke is similar to that of tobacco smoke. Although the quantity of cannabis smoked tends to be less than that of tobacco, cannabis is usually smoked without a filter and in smoking dynamics studies, it has been shown that the overall burden of particulates delivered to the respiratory tract of habitual cannabis users is four times greater when smoking cannabis than smoking the same amount of tobacco [23].

Conclusion: There is moderate evidence of no statistically significant association between cannabis smoking and the incidence of lung cancer.

5b. Is there an association between cannabis use and the incidence of head and neck cancer?

No new evidence was found in the updated search and one systematic review was identified in the NASEM report [23]. In this meta-analysis of nine case-control studies, the authors found no association between lifetime cannabis use and the development of head and neck cancer, after controlling for tobacco use, age, sex, and race [23].

Conclusion: There is moderate evidence of no statistically significant association between cannabis use and the incidence of head and neck cancer.

5c. Is there an association between cannabis use and the incidence of testicular cancer?

The updated search found one retrospective cohort. In this 42-year follow-up study, an association was observed of "heavy" cannabis use and cryptorchidism with the development of testicular cancer. The combined evidence from the NASEM report and from the updated evidence review suggests a possible association between frequent cannabis use and testicular cancer, particularly in those with heavier and long-term use. However, further research is needed to develop a more fulsome understanding of which testicular tumours may be associated with cannabis use, and the role of frequency and chronicity of cannabis use, current cannabis use, and age of cannabis exposure.

Conclusion: There is limited evidence of a statistical association between current, frequent, or chronic cannabis smoking and non-seminoma-type testicular germ cell tumours.

5d. Is there an association between cannabis use and the incidence of esophageal cancer?

No new evidence was found in the updated search and one population-based case-control study was identified in the NASEM report [27]. After adjustments for demographic factors, alcohol and tobacco use, and relevant medical, environmental and socioeconomic information, no statistically significant increase in the risk of developing esophageal cancer was observed in participants with a cumulative cannabis exposure of one to 10 years of joint use or 30 or more years of joint use [27]. Among participants who never smoked cigarettes, there was no statistical difference in the risk of developing esophageal cancer between those who had never smoked cannabis and those who smoked cannabis [27]. As no new evidence was found, there continues to be insufficient evidence of an association between cannabis use and the incidence of esophageal cancer.

Conclusion: There is insufficient evidence to demonstrate an association between cannabis smoking and the incidence of esophageal cancer**.**

5e. Is there an association between cannabis use and the incidence of other cancers in adults?

No new evidence was found in the updated search. The NASEM report included one epidemiologic review of eight studies on cannabis use and the risk of prostate, cervical, anal, bladder, and penile cancers, as well as malignant glioma, non-Hodgkin lymphoma, and Kaposi's sarcoma [24]. The authors found that there was insufficient data to draw any conclusions and that further well-designed studies on cannabis use and cancer were warranted. As no new evidence was found, there continues to be insufficient evidence of an association between cannabis smoking and the incidence of other malignancies in adults.

Conclusion: There is insufficient evidence to demonstrate an association between cannabis use and the incidence of other malignancies in adults.

6. Is there an association between cannabis use and the incidence of cancer in offspring?

The updated literature search found no new evidence. The NASEM report found an epidemiology report, which included six studies [24]. Four of the studies found that maternal cannabis use during pregnancy was associated with childhood leukemia, astrocytoma, and rhabomyosarcoma. While these studies had large sample sizes and reported on recreational drug use during pregnancy and birth, there were limitations including a small number of exposed cases, potential recall bias leading to possible exposure misclassification, and no dose-response assessment. A case-control study of childhood acute myelogenous leukemia

conducted by Trivers and colleagues found no association with parental marijuana use, and maternal marijuana use frequency was not associated with leukemia risk. Another case-control study of childhood neuroblastoma did not observe an increased risk after adjusting for household income, age at diagnosis and other drugs used. An increased risk of neuroblastoma with maternal marijuana use in the first trimester, but not for the second or third trimester was observed. As no new evidence was found in the updated search, there continues to be insufficient evidence to demonstrate an association between cannabis smoking and the incidence of cancer in offspring.

Conclusion: There is insufficient evidence to demonstrate an association between parental cannabis use and subsequent risk of developing any malignancies in offspring.

7.**Are cannabis or cannabinoids an effective treatment for spasticity associated with spinal cord injury?**

There was no new evidence found in the updated evidence search. The NASEM report found one systematic review [15], which included 14 randomized placebo-controlled trials. Three of the trials included patients with paraplegia caused by spinal cord injury. Unfortunately, none of the three studies were included in the pooled estimates because they were either not full publications or had insufficient data to allow summary estimates to be generated. As no new evidence was found in the updated search, there continues to be insufficient evidence to make any statement on whether cannabinoids are an effective treatment for spasticity in patients with paralysis due to spinal cord injury.

Conclusion: There is insufficient evidence to suggest that cannabinoids are an effective treatment for spasticity in patients with paralysis due to spinal cord injury.

Cancer and the Health Effects of Cannabis and Cannabinoids: An update of the systematic review by the National Academies of Sciences, Engineering, and Medicine (2017) Consensus Study Report

Systematic Review

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, OH (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC is a provincial initiative of OH (CCO) supported by the Ontario Ministry of Health (OMH). All work produced by the PEBC and CCO Prevention & Cancer Control (P&CC) Division is editorially independent from the OMH.

INTRODUCTION

In 2001, medical cannabis was legalized in Canada, followed by legalization of non-medical or 'recreational' cannabis under the *Cannabis Act,* which was passed in October 2018 [1]. Increasing access to legal cannabis has occurred in parallel with increasing diversity in the types of cannabis products available to consumers, including cannabis edibles, orally ingested oils and capsules, high-potency cannabis oils for vaping and solid concentrates. In October 2019, the *Cannabis Act* was amended to allow cannabis edibles and extracts to be produced and sold. Medical cannabis is a broad term that refers to several different practices. The term can be used to refer to pharmaceutical cannabinoids, including synthetic cannabinoids (e.g. nabilone) and cannabis extracts (nabiximols or 'sativex'). The term "medical cannabis" is more commonly used to refer to the system under which Canadians can receive authorization from their health care provider to access cannabis from licensed producers for medical purposes [2]. Until legalization of non-medical cannabis in October 2018, authorization to use medical cannabis was the only way Canadians could legally access cannabis. Finally, medical cannabis is often used to refer to the practice of using cannabis for therapeutic purposes, regardless of whether authorization has been received. Although the term medical cannabis is widely used to describe specific products, medical cannabis products do not differ from non-medical products in Canada, regardless of whether individuals have authorization for medical cannabis or not

To date, there is limited robust evidence regarding the short- and long- term health effects (i.e., harms and benefits) of cannabis, particularly with respect to new modes of administration, which may have distinct physiological effects. There is a particular need for greater understanding of the potential harms and benefits of cannabis use among vulnerable populations, including cancer patients, who use a diverse range of cannabis products for both therapeutic and recreational reasons.

Within this context, the U.S. National Academies of Sciences, Engineering, and Medicine (NASEM) conducted a comprehensive review published in 2017 titled "The Health Effects of Cannabis and Cannabinoids: The current state of evidence and recommendations for research" [3]. This consensus guideline covered 11 health topics: therapeutic effects, cancer, cardiometabolic risk, respiratory disease, immunity, injury and death, prenatal, perinatal, and postnatal exposure to cannabis, psychosocial, mental health, problem cannabis use, and cannabis use and abuse of other substances. For each health endpoint, the NASEM

group identified systematic reviews and primary research literature up to August 1, 2016 and based their conclusions on all relevant fair- and good-quality systematic reviews and primary research up to that date.

The objective of this evidence summary is to build on the NASEM consensus document and to evaluate and add to it updated evidence on the health effects of cannabis and cannabinoids specific to cancer. This evidence will be used to support a position from OH (CCO) to respond to requests from the public and clinical community and to help in the development of knowledge products for healthcare providers and patients.

RESEARCH QUESTIONS

The research questions are from the NASEM document [3].

- **Question 1:** Are cannabis or cannabinoids effective treatments for the reduction of chronic pain from cancer?
- **Question 2:** Are cannabis or cannabinoids effective treatments for cancer?
- **Question 3:** Are cannabis or cannabinoids effective treatments for the reduction of chemotherapy-induced nausea and vomiting?
- **Question 4:** Are cannabis or cannabinoids effective treatments for anorexia and weight loss associated with cancer-associated anorexia-cachexia syndrome
- **Question 5**: Is there an association between cannabis use and the incidence of:
    a. lung cancer?
    b. head and neck cancer?
    c. testicular cancer?
    d. esophageal cancers?
    e. other cancers in adults?
- **Question 6:** Is there an association between cannabis use and the incidence of cancer in offspring?
- **Question 7:** Are cannabis or cannabinoids effective treatments for spasticity associated with spinal cord injury in people with cancer?

TARGET POPULATION

1. People with cancer using cannabis or cannabinoids as a treatment for cancer or for symptom management while undergoing treatment and/or palliative care.
2. People who use cannabis and/or cannabinoids (with respect to the risk of developing cancer).

INTENDED PURPOSE

This evidence summary is intended to support a position statement from OH (CCO) in response to requests from the public and the clinical community.

INTENDED USERS

Policy makers who wish to provide guidance to the public and the clinical community regarding the use and potential risks of cannabis related to cancer.

METHODS

This evidence summary was developed by a Working Group consisting of representatives from medical oncology, primary care, palliative care, health care research, and health research methodology at the request of the OH CCO P&CC Division. The Working Group was responsible for reviewing the identified evidence and drafting the summary.

Conflict of interest declarations for all authors are summarized in Appendix 1, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

A 2017 consensus guideline from NASEM, with a comprehensive and extensive literature review, formed the foundation of this evidence summary [3]. The PEBC health research methodologist updated the NASEM search from the original end search date of August 1, 2016 following the NASEM protocol exactly and replicating the literature search and quality assessments to the best of our ability for the sections on the therapeutic effects of cannabis in relation to chronic cancer pain, chemotherapy-induced nausea and vomiting (CINV), cancer-associated anorexia and weight loss, spasticity, and other cancer health effects.

Search for Systematic Reviews

The NASEM search was run in MEDLINE, Embase, and the Cochrane Database of Systematic Reviews databases to identify literature published between January 1999 and August 2016. Due to the large number of articles of potential interest, systematic reviews were reviewed first. Inclusion criteria were as follows:

1. Deemed a true systematic review based on the presence of the key elements of a systematic review (using 6 preset questions):
    1. Does the article describe a search involving at least two databases?
    2. Does the article describe a search involving appropriate search terms?
    3. Does the article describe a search involving pre-specified eligibility criteria?
    4. Does the article include a risk-of-bias discussion and/or quality assessment?
    5. Does the article include a meta-analysis or qualitative synthesis of findings?
    6. Does the article report on one or more health effects of cannabis on humans?
2. Deemed fair to good quality based on quality assessment questions compromising five attributes: study eligibility criteria, how studies were identified and considered for inclusion, how data were collected and appraised by the authors, the methods by which study findings were selected and synthesized, and whether any conflict of interests were addressed.

For this evidence summary, the search strategy for systematic reviews, used in the NASEM report was extended to January 2020. See Appendix 2 for the search strategy. Where more than one good-or fair- quality systematic review was found, priority was given to the most recently published systematic review.

Search for Primary Literature

In the NASEM report, for every research question with an associated good- or fair-quality systematic review, relevant primary literature published after the cut-off date of the literature search used in that particular systematic review was also reviewed. Where a good- or fair-quality systematic review was not found, good or fair-quality primary literature published between January 1, 1999, and August 1, 2016 was reviewed. Articles were excluded if they were editorials, abstracts, opinion pieces, grey literature, or non-peer-reviewed studies.

For this evidence summary, the search for primary literature was identical to that of the NASEM report and was extended to January 2020. Using the NASEM approach, identified articles that addressed at least one of the research questions, were in English, and were published after August 1, 2016 and not included in the NASEM consensus guideline were evaluated for inclusion. A review of the titles and abstracts was conducted by LDDA. For studies that warranted full-text review, LDDA reviewed each study independently and if uncertainty existed, WKE was consulted as second reviewer

Data Extraction and Quality Assessment

Data from the included studies from the updated search were independently extracted by LDDA. If there was more than one publication for the same study, only the most updated or recent versions of the data were reported in the results. All extracted data and information were audited by an independent auditor.

Following the NASEM protocol, any article that was deemed a true systematic review was assessed for quality based on the questions outlined in Appendix 4. To ensure accuracy, the systematic reviews were rated independently by at least two people and disagreements were resolved by a third reviewer. Based on the responses to these questions, systematic reviews were rated as good, fair, or poor. Only good- or fair-quality systematic reviews were included in literature search results.

The randomized controlled trials (RCTs) were assessed using the Cochrane Risk of Bias tool, where six domains of bias are assessed: random sequence generation, allocation concealment, blinding participants, personal and outcome assessment, incomplete outcome data, selective reporting, and other concerns. Each domain was judged as being at low, high, or unclear risk of bias (ROB) [4]. The qualities of cohort and case-control studies were assessed using the Newcastle-Ottawa Scale, which assessed studies using three dimensions: selection of study groups, comparability of study groups, and determination of endpoints and exposures [5]. Only good-or fair-quality primary studies were included in literature search results.

Synthesizing the Evidence

Meta-analysis was not planned due to the nature of the data.

RESULTS AND DISCUSSION

NASEM results

The NASEM literature search covered a broad topic area of various health endpoint groups and found more than 10,700 relevant abstracts between January 1999 and August 2016 [3]. Specifically, for the cancer endpoint, there were a total of 1,418 articles found (313 systematic reviews and 1,111 primary literature articles). After identification and quality assessment, 29 relevant articles were included (3 systematic reviews and 26 studies). The evidence from NASEM is presented in the evidence tables and summarized in the discussion (Tables 1-8).

Updated Literature Results

A PRISMA flow diagram of the complete search is available in Appendix 3. Following the NASEM approach, each review was evaluated for key elements to determine if it was a true systematic review. Five systematic reviews [6-11] were found to be good or fair quality and are described in Appendix 4.

The updated search for primary literature retrieved 4211 articles and of these, 35 were retained for full-text review. Three met the inclusion criteria [12-14]. Studies were assessed for quality and those results can be found in Appendix 5 and 6.

For each research question, the text below describes the evidence from the updated search. A “discussion of findings” section (modeled on the NASEM document structure) summarizes the evidence from both the NASEM report and the updated search. Accompanying evidence tables summarize the studies from the NASEM report and updated search in more detail.

1. Are cannabis or cannabinoids an effective treatment for the reduction of chronic pain in cancer patients?

Results from Updated Search: Systematic Reviews

The updated evidence for the reduction of chronic pain in cancer patients comes from four systematic reviews (Table 1) [6-8,10]. Two systematic reviews specifically looked at pain due to cancer that is uncontrolled by opioids [7,8] (Table 1). Boland et al conducted a search to find RCTs which assessed the effects of cannabinoids compared with either placebo or other active agents for the treatment of cancer-related pain uncontrolled by opioids (pain being the primary outcome) [7]. Five RCTs comparing nabiximols oral mucosal spray (Sativex) and tetrahydrocannabinol:cannabidiol (THC:CBD) extract or THC extract to placebo were found (Table 1). A meta-analysis found no difference between cannabinoids and placebo in the average pain intensity score. A second meta-analysis with only phase III studies was also conducted and the results also showed no benefits from cannabinoid use. In regards to adverse events, cannabinoids had a significantly higher rate of somnolence and dizziness when compared with placebo, but these scores were low (e.g. 8.9% vs. 5.9% for dizziness) and non-serious. There was also a trend towards higher odds of nausea and vomiting in the cannabinoid groups. Similarly, in the systematic review by Häuser et al [8] four RCTs were found that were covered in Boland et al [7]; however, different outcomes were analyzed. In their meta-analysis, cannabis users showed higher pain relief of 50% or greater than the placebo group; however, these results were statistically insignificant (Table 1). Cannabis users also showed more serious adverse events compared with placebo; however these results were also insignificant.

In 2018, Allan et al. conducted a systematic review of reviews for medical cannabinoids and found seven systematic reviews with meta-analyses examining pain [6]. Two of these, Whiting et al. (2015) and Andreae et al (2015) were described in the NASEM report (Table 1) and two were published before 2010. The remaining three systematic reviews with meta-analyses (Petzke et al. 2016; Lobos Urbina and Pena Duran, 2016; Mucke et al. 2016) reported a 30% or more pain reduction for cannabinoids versus placebo. All demonstrated similar positive effects; however, only one had statistically significant results. Allan et al. conducted a meta-analysis and found that approximately 39% of patients taking medical cannabinoids had significantly better pain reduction (30% or better) compared with 30% of placebo patients (Table 1). Allan et al also conducted sensitivity analyses within pain management (for ≥30% pain reduction) based on medical cannabinoid types and found that inhaled cannabinoids had an relative risk (RR) of 1.52 (95% confidence interval [CI] 1.17-1.99; numbers needed to treat [NNT] 6) and buccal-spray had an RR of 1.28 (95% CI 1.02-1.61; NNT 16). No RCTs were identified examining the effect of oral medications on pain reduction of 30% or more.

Lastly, Nugent et al conducted a systematic review to investigate the benefits of plant-based cannabis preparations for the treatment of chronic pain in adult patients with cancer [10]. Pharmaceutically prepared cannabinoids were excluded (e.g. dronabinol and nabilone). In total, there were three trials (n = 547) that investigated moderate to severe intractable pain related to cancer. Two of the trials had unclear risk of bias (ROB) and the other had high ROB. The authors found that these trials provide insufficient evidence due to the small number of studies and their methodological limitations.

Results from Updated Search: Primary Literature

The Working Group did not identify any good-quality primary literature that reported on cannabis or cannabinoids for the treatment of chronic pain in cancer patients that were published subsequent to the data collection period of the most recently published good- or fair-quality systematic review addressing the research question.

Results from the NASEM report

The relevant evidence from the NASEM report is summarized in Table 1.

Discussion of Findings

The research question investigated whether cannabis or cannabinoids are an effective treatment for the reduction in chronic pain in patients with cancer. The NASEM concluded that there is substantial evidence supporting cannabis as an effective treatment for chronic pain. It included a variety of medical conditions, most often related to neuropathy, but also other cancer pain, multiple sclerosis, rheumatoid arthritis, and musculoskeletal issues. This evidence review focused on the reduction of chronic pain in adults with cancer; therefore, some important clarifications must be stated.

It should first be noted, there are many different causes of pain in patients with cancer (e.g. pain induced by metastases to the liver or bone, pain due to chemotherapy-induced neuropathy, etc.). The systematic reviews found in the updated literature search do not clearly demonstrate whether cannabis is effective for any one type of cancer pain over another. Several of the studies included in the systematic reviews focused on neuropathy but it was unclear whether the neuropathy was caused by the cancer, the chemotherapy drugs used to treat the cancer, or an unrelated condition (e.g. diabetes, multiple sclerosis, or HIV). The specific role of cannabis in treating neuropathic pain in cancer has been explored in pre-clinical animal models, but its effects in human patients are as yet unknown.

Second, while the use of cannabis for the treatment of chronic pain is supported by well-designed clinical trials, the majority of the trials from the NASEM report and the updated search compared cannabis use with a placebo rather than standard-use analgesia. There is a need for further trials to compare cannabis-based medicine with analgesia typically used to control cancer pain to better inform the current management of chronic pain in patients with cancer.

The NASEM report does not clearly state that the use of cannabis-based medicine is not recommended as a first-line agent for treatment of cancer pain. It may be considered an adjunct to other proven analgesics in patients with cancer, especially in patients with painful neuropathies. An accompanying guideline to the systematic review by Allan et al recommended against the use of medical cannabinoids for first- and second-line therapy for neuropathic pain, but indicated it could be considered for refractory neuropathic pain together with other analgesics [6].

While cannabis-based medicine may reduce chronic pain in cancer patients, the benefits must also be weighed against potential harms from adverse events. Patients with pre-existing mental illness may have more adverse effects from cannabis-based medications. More research is needed comparing cannabis-based medicine with current standard analgesics used to manage cancer pain and studies need to make clear the type(s) of cancer pain being evaluated and the adverse events experienced by cancer patients.

Conclusion: There is limited evidence that cannabis-based medicines may be an effective treatment for chronic pain in some patients with cancer. However, it is important to note that much of this evidence compared cannabis-based medicine against placebo rather than commonly used analgesics for cancer pain. There is also little evidence on the effectiveness of cannabis-based medicines in different types of cancer pain; much of the literature has focused on neuropathy. Furthermore it is important to weigh the benefits of cannabis-based medicine and the potential harms of adverse events (particularly among cancer patients who frequently have multiple comorbidities). Cannabis-based medicine is not supported by evidence as a first or second line agent, but may be considered as a third- or fourth-line agent, where it could be used as an adjuvant therapy to other analgesics.

Table 1. Systematic Reviews and Primary Literature on Chronic Pain

Author, Search Date	Inclusion criteria	Intervention/ comparison	Condition	Findings	Included studies
Updated literature search- Systematic Reviews					
Boland et al., 2020 [7] *1974 to Aug 1 2019*	RCTs that assessed the effects of cannabinoids compared with placebo or other active agents for the treatment of cancer related pain uncontrolled by opioids in adults (pain being primary outcome)	Nabiximols oral mucosal spray (N=3); Sativex (N=2); THC:CBD extract or THC extract (N=1) vs. placebo	Cancer, chemo induced neuropathic pain	*Pain intensity:* *Meta-analysis results (N=5 RCTs)*:* No difference between cannabinoids and placebo in the difference in change of average NRS pain scores: mean difference -0.21 (95% CI -0.48 to 0.07, p=0.14) If only phase III studies in meta-analysis, there was no benefit from cannabinoid use : mean difference -0.02 (95% CI -0.21 to 0.16. p=0.80) *Adverse events:* In general, cannabinoids were found to have a higher risk of adverse events compared to placebo Meta-analysis showed higher odds of somnolence (OR 2.69, 95% CI 1.54-4.71, p<0.001) and dizziness (OR 1.58 95% CI 0.99 to 2.51, p=0.05) in the cannabinoid group. Higher odds of nausea (OR 1.41 95% CI 0.97 to 2.05, p=0.08) and vomiting (OR 1.34 95% CI 0.85 to 2.11, p=0.21) in cannabinoid group but were not significant.	Lichtman et al. 2018; Fallon et al. 2017 Study 1 and 2;Lynch et al. 2014; Portenoy et al. 2012; Johnson et al. 2010
Häuser et al., 2019 [8] *Inception to December 2018*	RCT with at least two weeks' double blind duration, studies with parallel, cross-over, and enriched enrolment randomized withdrawal design with at least 20 participants. Full journal publications	Oromucosal nabiximol or THC(N=5) vs. placebo	Pain due to cancer uncontrolled by opioids. Pain due to cancer treatment (e.g. chemo induced neuropathic pain) were excluded.	*Meta analysis (N=4)* Parallel design involving 1333 pts; quality of evidence was very low for all comparisons Two studies reported on previous cannabis use (ranged between 6-13%) a) *Pain relief of 50% or greater* CBM (11.8%) vs. placebo (9.7%), RD 0.00, 95% CI -0.03 to 0.04, p =0.82, I^2=0%) *b) Serious adverse events* CBM (23.9%) vs. placebo (21.2%), RD 1.06; 95% CI 0.86 to 1.32, p= 0.56, I^2= 0%	Fallon et al. 2017(study a & b); Johnson et al. 2010; Lichtman et al. 2018; Portenoy et al. 2012

*Pain intensity was a secondary outcome in Portenoy et al., data were not available for the mean pain differences of all three doses combined, only low dose (1-4 sprays) was included in the meta-analysis.

Allan et al. 2018 [6] *1946-April 2017*	Systematic reviews (with or without meta-analysis) of RCTs examining medical cannabinoids for the management of pain.	Medical cannabinoids vs. placebo	Neuropathic pain, chronic pain, cancer pain	*Pain:* Meta-analysis results of 15 RCTs from Andreae 2015, Whiting 2015 and Petzke (15 studies [13 neuropathic; 2 cancer]) showed that 39% of pts taking medical cannabinoids attained 30% or better pain reduction compared to 30% of placebo pts (RR 1.37, 95% CI 1.14 to 1.64), NNT= 11 *a) Sensitivity analysis based on cannabinoid types:* Inhaled cannabinoids (5 RCTs): RR = 1.52 (95% CI 1.17 to 1.99), NNT =6 Buccal-spray cannabinoids (10 RCTs): RR=1.28, 95% CI 1.02 to 1.61, NNT = 16 Oral medications- No RCT founds Two cancer pain systematic reviews (SRs), not included in meta-analysis: Lubos, Urbina and Pena Duran 2016: RR 1.35 (95% CI 0.63 to 2.09), I^2= NR Tateo 2017: inconsistently reported outcomes. Data NR.	Systematic reviews (RCTs in SR) Andreae 2015 (Abrams 2007, Ellis 2009, Ware 2010, Wilsey 2008, 2013) Whiting 2015 (GW Pharmaceuticals 2005; Johnson 2010; Portenoy 2012); Petzke 2016 (Berman 2004, Langford 2013, Lynch 2014, Nurmikko 2007, Rog 2005, Selvarajah 2010, Serpell 2014) Tateo, 2017 Lobos Urbina and Pena Duran, 2016
Nugent et al. 2017 [10] *Inception to March 2017*	English-language studies (controlled clinical trials and cohort studies) assessing the effects on non-pregnant adults of plant-based cannabis preparations or whole-plant extracts (e.g. nabiximols). Dronabinol or nabilone were not included. Plant-based cannabis preparations can include any preparation of the cannabis plant itself or cannabis plant extracts	Plant-based cannabis preparations vs. placebo	Neuropathic Pain; Cancer	*Neuropathic Pain (N=13 trials)* Central or peripheral neuropathic pain related to various health conditions (HIV associated, chemo-induced, diabetic, spinal cord injury). Eleven had low ROB, 1 unclear and 1 high Low strength evidence that cannabis may alleviate neuropathic pain in some patients Nine studies, intervention pts more likely to report at least 30% improvement in pain (RR1.43, 95%CI 1.16 to 1.88, I^2= 38.6%, p =0.111) Most of these studies were small, with few reported outcomes past 2-3 weeks, no long term outcomes *Cancer (N=3 trials):* Moderate to severe intractable pain, exact cause of pain unspecified Two had unclear ROB, 1 high ROB Authors concluded that overall these trials provide insufficient evidence due to small number of studies, methodological limitations (e.g. high attrition, exclusion of pts with variable pain scores)	*Cancer:* Noyes, 1975; Johnson et al. 2010; Portenoy et al., 2012 *Neuropathic pain:* Lynch et al. 2014, Serpell et al.,2013, Wilsey et al.2007, Berman et al. 2004; Ellis et al., 2009; Abrams et al., 2007; Wallace et al., 2015; Ware et al., 2010; Wilsey et al., 2012; Notcutt et al., 2004; Wilsey et al., 2016; Selvarajah et al., 2010; Nurmikko et al., 2007

NASEM Evidence: Systematic Reviews					
Whiting et al. 2015 [15] *Inception to April 2015*	RCTs that compared cannabinoids with usual care, placebo or no treatment among multiple indications, including nausea and vomiting due to chemo, chronic pain and spasticity due to paraplegia	Cannabinoids vs. placebo	Neuropathic pain (central, peripheral or not specified), cancer pain, or chemo induced pain.	Total of 28 studies on 10 different conditions. Of interest to this research question was neuropathic pain (central, peripheral, or not specified; 12 studies), cancer pain (3 studies), and chemo-induced pain (1 study). *Meta-analysis:* 8 trials- 1 smoked THC and 7 nabiximols Reduction in pain of at least 30% was greater with cannabinoids vs. placebo (OR 1.41 [95% CI 1.03 to 11.48]; 8 trials) Pain conditions evaluated in trials were neuropathic (OR 1.38 [CI 0.93 to 2.03]; 6 trials) and cancer pain (OR 1.41 [CI 0.99 to 2.00] 2 trials) Nabiximol was also associated with a greater average reduction in the NRS assessment of pain (WMD, −0.46 [95% CI −0.80 to −0.110] 6 trials), brief pain inventory-short form, severity composite index (WMD, −0.17 [95% CI −0.50 to 0.16] 3 trials), neuropathic pain scale (WMD, −3.89 [95% CI, −7.32 to −0.47] 5 trials), and the proportion of patients reporting improvement on a global impression of change score (OR, 2.08 [95% CI, 1.21 to 3.59] 6 trials) compared with placebo.	Abrams et al. 2007; GW Pharmaceuticals 2005; Johnson et al. 2010; Langford et al., 2013; Nurmikko et al. 2007, Portenoy et al. 2012, Selvarajah et al. 2010, Serpell et al., 2014
Andreae et al. 2015 [16] *Inception to April 2014*	All RCTs investigating chronic painful neuropathy	Inhaled cannabis vs. placebo	Chronic neuropathic pain	Pooled treatment effects using hierarchical random effects Bayesian responder model Individual pts data (N=178 participants with 405 observed responses from 5 RCTs following pts for days to weeks Evidence that inhaled cannabis results in short-term reduction in chronic neuropathic pain for 1 in every 5-6 pts (NNT=5.6; Bayesian 95% credible interval 3.4-14)	Abrams et al. 2007; Ellis et al. 2009; Ware et al. 2010; Wilsey et al. 2008; Wilsey et al. 2013;

CBM= cannabis-based medicine; Chemo= chemotherapy; CI = confidence interval; NASEM= U.S. National Academies of Sciences, Engineering, and Medicine;NNT= numbers needed to treat; NR= not reported; NRS = numeric rating scale; OR = odds ratio; Pts= patients; RCT = randomized controlled trial; RD= Risk difference; ROB = risk of bias; RR= Relative Risk; SR= systematic reviews; THC = tetrahydrocannabinol; WMD = weighted mean difference

2. Are cannabis or cannabinoids an effective treatment for cancer?

Results from Updated Search: Systematic Reviews and Primary Literature

The Working Group did not identify any good- to fair-quality systematic reviews or any good-quality primary literature that reported on cannabis or cannabinoids for the treatment of cancer that were published during the data collection period.

Results from the NASEM Report:

The relevant evidence from the NASEM report is summarized in Table 2.

Discussion of Findings

As no new evidence was found in the updated search, there continues to be insufficient clinical evidence to make any statement about the efficacy of cannabinoids or cannabis as a treatment for cancer. With such limited evidence, it is clear that a research gap exists in relation to cancer with cannabis or cannabinoids as treatments for cancer.

Conclusion: There continues to be insufficient evidence to support the use of cannabinoids or cannabis as a treatment for cancer.

3. Are cannabis or cannabinoids an effective treatment for the reduction of chemotherapy-induced nausea and vomiting (CINV)?

Results from Updated Search: Systematic Reviews

In total, two systematic reviews [11,17] were found (Table 3). First, Allan et al summarized five systematic reviews with meta-analyses examining medical cannabinoids versus placebo or other antiemetics for CINV [17]. While five systematic reviews were found, only one provided additional information beyond that of the NASEM report. Mucke et al. looked at improvement in nausea and vomiting symptoms versus placebo in palliative patients based on two RCTs and did not observe statistical significance (Table 2). Allan et al conducted a responder meta-analysis (7 RCTs) and found that patients had greater control of nausea and vomiting when taking medical cannabinoids compared with a placebo. Results from another responder meta-analysis (14 RCTs) demonstrated that approximately 31% of patients taking medical cannabinoids had better control of nausea and vomiting compared with 16% taking neuroleptics. The authors noted that there were larger effect estimates for patient preferences than for improvement in symptoms.

Second, Schussel et al conducted an overview of systematic reviews and found five systematic reviews (Smith 2015, Cotter 2009, Davis 2008, Mochado Rocha et al., 2008, Tramèr 2001) focusing on the effects of cannabinoids as a treatment for CINV in patients with cancer [11]. The systematic review by Smith et al is described in the NASEM report and will not be discussed further. In comparing cannabinoids versus placebo, four of five systematic reviews agreed that cannabinoids seemed to be superior to placebo in the management of CINV. The exception, Machado Rocha et al (2008) concluded that placebo and cannabinoids were similar. In comparing cannabinoids versus other antiemetics, one systematic review found that cannabinoids seemed to be superior to antiemetics (Tramèr et al., 2001). While other systematic reviews found differences, Mochado Rocha et al. (2008), concluded that prochlorperazine, alizapride, and domperidone were similar to nabilone; prochlorperazine and chlorpromazine were similar to levonantradol but prochlorperazine was inferior to dronabinol. Davis (2008) found that metoclopramide, chlorpromazine, and ondansetron were as effective as nabilone and nabilone was superior to prochlorperazine, alizapride, and domperidone in some instances. The systematic review by Cotter (2009) concluded that prochlorperazine, thiethylperazine, and ondansetron were comparable to THC. Many patients reported that they preferred cannabinoids over placebo and other antiemetics, despite the higher rate of adverse events. Commonly reported adverse events were “feeling high”, feeling sedated, dizziness, and postural hypotension. Schussel et al concluded that cannabinoids may be considered a therapeutic option for CINV; however, it is not entirely clear whether they are superior to traditional antiemetics regarding effectiveness and safety.

Table 2. Systematic review on cannabis and cannabinoids as a treatment for cancer

Author, Search Date	Inclusion criteria	Intervention/ comparison	Condition	Findings	Included studies
NASEM Evidence:- Systematic Reviews					
Rocha et al. [18]	All studies involving antitumoral effects (cellular and molecular mechanisms) of cannabinoids were considered.	Antitumoral effects		A total of 35 studies were found, which included patients with gliomas, laboratory animals with gliomas, tumour cells (gliomas) in vitro experiments The majority of these studies were preclinical studies. All 16 in vivo studies found an anti-tumour effect for cannabinoids.	Please see Rocha et al. [17] for a list of included studies

NASEM= U.S. National Academies of Sciences, Engineering, and Medicine

Results from Updated Search: Primary Literature

An additional search of the primary literature since the end search dates of the reviews by Allan et al [16] and Schussel et al [10] identified one additional primary study (Table 3). Polito et al [13] conducted a multicentre, retrospective review of pediatric patients receiving nabilone for acute CINV prophylaxis (n =110). Most of the patients (75.4%) received highly emetogenic chemotherapy (HEC); including 19.1% that received hematopoietic stem cell transplant conditioning. Among all patients, 52.3% of patients receiving nabilone had complete chemotherapy-induced vomiting control. One-third of patients experienced adverse events due to the nabilone, but these were considered grade 2 or less. The most commonly adverse events were sedation, dizziness, euphoria, and headaches. Ten patients discontinued nabilone use due to adverse events.

Results from the NASEM Report:

The relevant evidence from the NASEM report is summarized in Table 3.

Discussion of Findings

The research question investigated whether cannabis or cannabinoids are an effective treatment for the reduction of CINV. The trials found in the NASEM report and in the updated literature predominantly compare cannabinoids with placebo rather than with standard antiemetics. Based on the available evidence, the NASEM report concluded that oral cannabinoids may be as effective as standard antiemetics in the treatment of CINV [3]. The updated literature generally supports this conclusion. Nabilone and dronabinol, which are oral THC preparations, have been available for more than 30 years for the treatment of CINV, although only nabilone is available in Canada. There are a few trials of cannabis in comparison to placebo or standard antiemetics. Mild to moderate adverse events were common in patients taking cannabis or cannabinoids. Although rare, heavy cannabis use is paradoxically associated with the cannabinoid hyperemesis syndrome, and cyclic nausea and vomiting with abdominal pain. There is a need for future trials to compare cannabis-based medicine against the current best antiemetics (such as serotonin 5 HT3 receptor antagonists [ondansetron, granisetron]).

Conclusion: There is conclusive evidence that oral cannabinoids are effective antiemetics in the treatment of CINV but insufficient evidence exists comparing oral cannabinoids with the currently available, most effective anti-emetics used in cancer care.

Table 3. Systematic reviews and primary literature on nausea and vomiting from chemotherapy

Author, Search Date	Inclusion criteria	Intervention/ comparison	Condition	Findings	Included studies
Updated literature search: Systematic Reviews					
Allan et al. 2018 [17] *1946-April 2017*	SRs (with or without meta-analysis) of RCTs examining medical cannabinoids for the nausea and vomiting	Medical cannabinoids vs. placebo or antiemetics	Nausea and vomiting from chemotherapy, nausea and vomiting in palliative patients	Five SRs were found that performed meta-analyses (one newer than 2016) Results from the responder meta-analysis (N=7 RCTs) found patients had greater control of nausea and vomiting when taking medical cannabinoids compared to placebo (47% vs. 13%, RR = 3.60 (95% CI 2.55 to 5.09), NNT of 3, Z=7.24 (p<0.0001) Results from another responder meta-analysis (N =14 RCTs) indicated that approximately 31% of patients taking medical cannabinoids had control of nausea and vomiting compared to 16% taking neuroleptics (RR = 1.85, 95% CI 1.18 to 2.91; NNT of 7, Z=2.67 (p=0.008).	Whiting et al. 2015; Smith et al. 2015; Mücke et al. 2016; Mochado Rocha et al. 2008; Tramèr et al. 2001
Schussel et al. 2017 [11] Search Dates not provided.	SR on cannabinoids for the treatment of CINV	Medical cannabinoids vs. placebo or aniemetics	Nausea and/or vomiting attributed to any type of scheme of chemotherapy for cancer	Summarized 5 SRs published between 2001 and 2015 that only included RCTs *Cannabinoids vs. placebo* Four out of 5 SRs agreed that cannabinoids seem to be superior to placebo, one concluded that cannabinoids seemed to be similar *Cannabinoids vs. other antiemetics* All compared different types of cannabinoid-based drugs to different antiemetics and combinations of results were not possible. Tramer et al.- cannabinoids seem superior to antiemetics Smith et al.- prochlorperazine similar to cannabinoids Machado Rocha et al.- prochlorperazine, alizapride, and domperidone similar to nabilone; prochlorperazine and chlorpromazine also similar to levonantradol, but prochlorperazine inferior to dranabinol. Davis metoclopramide, chlorpromazine, and ondansetron as effective as nabilone, nabilone showing some superiority to prochloperazine, alizapride, and domperidone. Cotter- prochlorperazine, thiethylperazine, and ondansetron comparable to THC *Adverse Events:* Higher in patients using cannabinoids when compared with standard antiemetics Authors concluded that while adverse events more frequent, cannabinoids were effective and superior to placebo to treat CINV but not superior to standard antiemetics.	Cotter 2009; Davis 2008; Machado Rocha et al. 2008; Smith et al. 2015; Tramèr et al. 2001

NASEM Evidence: Systematic Reviews					
Philips et al. 2016 [19]	SR on cannabinoid therapies for children receiving chemotherapy	prochlorperazine (vs. nabilone), domperidone (vs. nabilone) & prochlorperazine &metoclopramide (separate randomizations in THC trial)	Nausea and vomiting from chemotherapy	Summarized 28 trials but only 3 involved cannabinoids therapies for children receiving chemo Trial 1 (unclear risk of bias) THC 10 mg/m^2 5x/day of chemo was superior to prochlorperazine in complete control of acute nausea and vomiting. Trial 2 reported better nausea severity scores with nabilone vs. domperidone. Trial 3 (largest and most recent) THC vs. prochlorperazine found no benefit over the control.	Chan 1987 Dalzell 1986 Ekert 1979
Whiting et al. 2015 [15] *Inception to April 2015*	RCTs that compared cannabinoids with usual care, placebo or no treatment among multiple indications, including CINV, chronic pain and spasticity due to paraplegia	Cannabinoids vs. placebo or active comparators (proclorperazine chlorpromazine, dromperidone, alizapride, hydroxyzine, metoclopramide and ondansetron)	Nausea and vomiting due to chemotherapy	Summarized 28 trials, most before 1984. 23 had high ROB and 5 had unclear ROB All suggested a greater benefit of cannabinoids compared with both active comparators and placebo, although not all reached statistical significance in the studies Patients showing a complete nausea and vomiting response were more common with cannabinoids than placebo (OR, 3.82, 95% CI 1.55 to 9.42) in 3 low quality evidence trials of dronabinol and nabiximol.	Broader 1982 Long 1982 Duran 2010, Meiri 2007 Lane 1991 1989 McCabe 1988; Chan 1987 1984 Pomeroy 1986 Dalzell 1986 Niederie 1986 Heim 1984 Hutcheon 1983 George 1983 Jones 1982 Wada 1982 Johansson 1982 Orr 1980 1981 Einhorn 1981 Steele 1980 Sallan 1980 Frytak 1979 Ahmedzai 1983 Ungerleider 1982 Sheidler 1984 Harden-Harrison 2012 Grunberg 2012 Levitt 1982 Solvay Pharmaceuticals 2014 Frytak 1979 Jhangiani 2005 McCabe 1981 Herman 1979 Melhem-Bertrandt 2014

Updated evidence: Primary literature					
Polito et al. 2018 [13] Multi-centre retrospective review	Pediatric patients receiving nabilone (N= 110) for acute CINV prophylaxis between Dec 1 2010-Aug 1 2015	Nabilone plus a 5-HT3 antagonist for CINV prophylaxis	Acute chemo-induced vomiting prophylaxis	Only patients receiving a dose of nabilone before the administration of the first chemo dose of a chemo block were eligible. Approximately half (52.3%) experienced complete CINV control regardless of chemotherapy emetogenicity. No differences between patients who did and did not receive dexamethasone (p=0.3419), even when chemo emetogenicity was considered (HEC: p = 0.3216; MEC p = 0.8654). Adverse events attributable to nabilone were experienced by 34% of patients; the most common were sedation, dizziness, euphoria, and headache. Nabilone was discontinued by 10 patients due to adverse events.	N/A
NASEM Evidence: Primary literature					
Meiri et al. 2007 [20] Double blind placebo-controlled study		Dronabinol or ondansetron or combination therapy vs. placebo	Delayed CINV	N= 64 randomized, 61 analyzed for efficacy TR = nausea intensity <5mm on VAS, no vomiting/retching, no rescue antiemetic) TR similar with dronabinol (54%), ondansetron (58% and combination therapy (47%) vs. placebo (20%) Nausea absence significantly greater in dronabinol 71%, ondansetron 64%, combination therapy 53% vs. placebo 15%, p<0.05 for all).	N/A

Chemo= chemotherapy; CIV= chemotherapy induced vomiting; CINV = chemotherapy induced nausea and vomiting; CI = confidence interval; HEC = highly emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy; N/A = not applicable; NASEM = U.S. National Academies of Sciences, Engineering, and Medicine; NNT = numbers needed to treat; RCT = randomized controlled trial; ROB RR = relative risk; SR= systematic review; THC = tetrahydrocanabinol; TR = total response; VAS = visual analogue scale

4. Are cannabis or cannabinoids an effective treatment for anorexia and weight loss associated with cancer-associated anorexia-cachexia syndrome?

Results from Updated Search: Systematic Reviews

The Working Group identified one systematic review that included three placebo controlled RCTs of the benefits and harms of cannabinoids in patients with cancer cachexia [8] (Table 4). Compared with placebo, cannabinoids increased appetite, but did not improve the overall quality of life of patients. The authors indicated that the decline of quality of life could be due to the side effects of cannabinoids.

Results from Updated Search: Primary Literature

In a placebo-controlled pilot RCT, Turcott et al investigated the effect of nabilone on appetite, nutritional status, and quality of life in 47 patients with stage III/IV non-small cell lung cancer patients with anorexia [14]. Baseline differences included lower performance status, older age, and greater weight loss in the past six months. At eight weeks, both groups had increased appetite, but patients in the nabilone group consumed more carbohydrates than patients in the placebo group (Table 4).

Results from the NASEM Report:

The relevant evidence from the NASEM report is summarized in Table 4.

Discussion of Findings

The research question investigated whether cannabis or cannabinoids are effective treatments for cancer-associated anorexia-cachexia syndrome and anorexia nervosa. Weight loss and anorexia are common side effects in patients with cancer. The NASEM report concluded that there was insufficient evidence to support or refute cannabis or cannabinoids as an effective treatment for cancer-associated anorexia-cachexia syndrome and anorexia nervosa. The updated search found one systematic review/meta-analysis suggesting cannabinoids increased appetite, but did not increase overall quality of life. A small pilot RCT from the primary literature showed no difference in appetite, but found that patients in the nabilone group had increased carbohydrate consumption. The combined evidence from NASEM and the updated search is insufficient to establish cannabinoids as an effective treatment for cancer-associated anorexia-cachexia syndrome and anorexia nervosa. Further randomized trials are needed on plant-derived cannabis and its effect on appetite and weight in which weight gain is the primary end point.

Conclusion: There is insufficient evidence on the use of cannabinoids as an effective treatment for cancer-associated anorexia-cachexia syndrome and anorexia nervosa.

Table 4. Systematic reviews and primary literature on anorexia and weight loss associated with cancer-associated anorexia-cachexia syndrome.

Author, Search Date	Inclusion criteria	Intervention/comparison	Condition	Findings	Included studies
Updated literature search: Systematic Reviews					
Wang et al. 2019 [9] *Inception to Dec 2019*	Double blind RCTs looking at appetite, overall QoL, body weight and therapy-related adverse events	THC (2.5mg) vs. placebo THC:CBD (2.7mg THC/2.5 CBD) or THC (2.7mg) vs. placebo or CE (2.5 THC/1 mg CBD) or THC (2.5mg) vs. placebo	Cancer Cachexia	N= 3 RCTs (n=466, 337 cannabinoids group vs 129 placebo) Meta-analysis: *Appetite:* Cannabinoids increased appetite (MD 0.27 [95% CI (-0.51 to 1.04]. p=0.50). Subgroup analysis, appetite in THC (MD 0.09 [95% CI -0.77 to 0.95] and CE (MD 0.24 [95% CI -0.74 to 1.23] similarly increased with cannabinoid treatment *Quality of Life (n= 2 studies)* Found a decline in QOL of pts in cannabinoids compared to placebo (MD -12.39 [95% CI -24 to 0-.57], p =0.04)	Brisbois 2011 Johnson 2010 Strasser 2006
Updated evidence: Primary literature					
Turcott et al. 2018 [14] Randomized double blind placebo controlled pilot study	Pts with advanced (Stage III or IV) NSCLC) with a good performance status (ECOG 0-2), diagnosed with anorexia	Nabilone (0.5mg daily/2 weeks, subsequently 1 mg daily/6 weeks) vs. placebo	Anorexia/cachexia	N = 47 pts randomized Baseline difference between the groups; the experimental group had worse performance status, older age, and greater weight loss in the previous 6 months. At the 4-week and 8-week evaluations, there were no statistical differences for appetite or for anthropometric and biochemical variables The appetite increase for each group was similar; however, there was a statistically significant improvement in VAS for the experimental group (p =0.006). Experimental group consumed significantly more carbohydrates in the 8-week evaluation period	N/A
NASEM evidence: Primary literature					
Strasser et al. 2006 [21] Phase III multicenter randomized double blind controlled trial	Patients with advanced cancer and weight loss (>5% over 6 months)	Randomized 2:2:1 to receive cannabis extract (standardized to THC 2.5 mg and cannabidiol 1.0mg), THC 2.5mg or placebo, 2x day for 6 weeks	Weight loss	Only 164 of 243 patients completed the trial. Intent to treat analysis yielded no differences between the groups in appetite, QoL, or toxicity. Increased appetite by 73% of cannabis-extract group, 58% of THC group and 69% placebo group. Recruitment was terminated early as it was unlikely to find differences between treatment arms.	N/A

Jatoi et al. 2002 [22]	Patients (≥ 18 years of age) with incurable malignancy other than brain, breast, ovarian, or endometrial cancer were eligible. Self-reported weight loss of at least 5 pounds during past 2 months and physician estimated caloric intake of less than 20 calories/kg of body weight per day	(1) oral megestrol acetate 800mg/day liquid suspension plus placebo, (2) oral dronabinol 2.5 mg twice daily plus placebo, or (3) both agents	Cancer associated anorexia	N = 469 Megestrol acetate was superior to dronabinol for appetite improvement (75% vs. 49%, p<0.001) and for ≥ 10% baseline weight gain (11% vs. 3%, p=0.02). Combination treatment resulted in no difference in appetite or weight compared with megestrol acetate alone Authors concluded megestrol acetate provided superior anorexia palliation compared to dronabinol alone. Combination therapy did not appear to provide any additional benefit.	N/A

CBD = cannabidiol; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; MD = mean difference; N/A not applicable; NASEM = U.S. National Academies of Sciences, Engineering, and Medicine; NSCLC = non-small cell lung cancer; QoL quality of life; RCT = randomized controlled trials; THC = tetrahydrocannabinol; VAS = Visual analogue scale

5a. Is there an association between cannabis use and the incidence of lung cancer?

Results from Updated Search: Systematic Reviews and Primary Literature

The Working Group did not identify any good- to fair-quality systematic reviews or primary literature on the association between cannabis use and lung cancer incidence.

Results from the NASEM Report:

The relevant evidence from the NASEM report is summarized in Table 5.

Discussion of Findings

Limited evidence evaluating cannabis smoking and the incidence of lung cancer and an updated search failed to identify any new literature on the topic. However, it is difficult to study the relationship between smoking cannabis and lung cancer for several reasons. First, many cannabis smokers are also tobacco smokers. Secondly, it is difficult to quantify the amount of cannabis smoked. The number of cigarettes smoked and the duration of smoking tobacco expressed as pack-years is well established as a useful measure to quantify the risk of developing lung cancer. An appropriate similar measure for cannabis has not been determined because joint size and the purity of product vary. Also, how a joint is smoked differs from how a tobacco cigarette is smoked. The chemical exposure profile of cannabis smoke is similar to that of tobacco smoke. Although the quantity of cannabis smoked tends to be less than that of tobacco, cannabis is usually smoked without a filter and in smoking dynamics studies; it has been shown that the overall burden of particulates delivered to the respiratory tract of habitual cannabis users is four times greater when smoking cannabis than smoking the same amount of tobacco [23].

Conclusion: There is moderate evidence of no statistically significant association between cannabis smoking and the incidence of lung cancer.

5b. is there an association between cannabis use and the incidence of head and neck cancer?

Results from Updated Search: Systematic Reviews

The Working Group did not identify any good- to fair-quality systematic reviews or primary studies on the association between cannabis use and head and neck cancer incidence.

Results from the NASEM report:

The relevant evidence from the NASEM report is summarized in Table 5.

Discussion of Findings

The research question investigated whether an association exists between cannabis use and the incidence of head and neck cancer. No new evidence was found in the updated search and one systematic review was identified in the NASEM report [23]. In this meta-analysis of nine case-control studies, the authors found no association between lifetime cannabis use and the development of head and neck cancer, after controlling for tobacco use, age, sex, and race [23]. The NASEM report concluded that there is moderate evidence of no statistically significant association between cannabis use and the incidence of head and neck cancer.

Conclusion: There is moderate evidence of no statistically significant association between cannabis use and the incidence of head and neck cancer.

Table 5. Systematic reviews and primary literature on the association between cannabis use and the incidence of lung cancer, and head and neck cancer

Author, Search Date	Inclusion criteria	Intervention/ comparison	Condition	Findings	Included studies
NASEM Evidence: Systematic Reviews					
Zhang et al. 2015 [24] No search. International Lung Cancer Consortium 2 published and 4 unpublished	Studies on cannabis smoking and lung cancer risk (primary incident and histologically confirmed lung cancer cases	Habitual vs. non habitual vs. never users	Lung Cancer	Pooled data from 6 case-controls studies of 2159 lung cancer patients and 2985 controls from US, Canada, UK and New Zealand controlled for socio-demographic status, tobacco smoking status, and pack years Habitual versus nonhabitual or never users= overall OR = 0.96 (95% CI 0.66 to 1.38), p =0.17 Nonhabitual or never user vs. smoked 1 or more joint equivalents = summary OR = 0.88 (95%CI 0.63–1.24), p 0.86 Nonhabitual or never user vs. consumed at least 10 joint-years = summary OR = 0.94 (95%CI 0.67–1.32), p =0.40 Adenocarcinoma cases: Nonhabitual or never user vs. smoked 1 or more joint equivalent = summary OR = 1.73 (95%CI 0.75– 4.00), p =0.05 Nonhabitual or never user vs. consumed at least 10 joint-years = summary OR = 1.74 (95%CI 0.85–3.55), p =0.09 No association was found for the squamous cell carcinoma based on small numbers	Aldington et al., 2008; Hashibe et al. 2006, 4 unpublished studies with unpublished data
de Carvalho et al. 2015 [23] *Inception to July 2015*	Case control studies, cohort or systematic reviews, allocation criteria defined for cases and controls, cases with definitive diagnosis of head and neck cancer, matched controls at least by gender and age. No restrictions on the geographical location, age, or gender.	Cannabis use and the development of head and neck cancer	Head and Neck Cancer	6 articles, total 9 case control studies 12.6% of cases and 14.3% of controls were cannabis users All were considered for data analysis Analysis was adjusted for age, gender, race and tobacco Meta-analysis results indicated no associated between exposure and disease (OR =1.02, 95%CI 0.912-1.143, z =0.362, p=0.72)	Berthiller et al., 2009, Feng et al., 2009; Hashibe et al., 2006; Liang et al., 2009; Marks et al., 2014; Zhang et al. 1999

NASEM evidence: Primary literature					
Huang et al. 2015 [25] *Inception to August 2014*	Epidemiologic studies that assessed marijuana use and provided risk estimates for marijuana exposure	Marijuana use and lung cancer risk	Lung Cancer	Evaluated 6 studies, including Zhang et al. 2015 and 2 studies included in that review. Of the 3 remaining, 2 were described in Zhang et al. as having several limitations. The third study: Callaghan et al. 2013- looked at lung cancer risk among 49,321 Swedish male military conscripts over 40 years. Adjusted for tobacco smoking, alcohol consumption, respiratory conditions and socioeconomic status at time of conscription Compared with participants who never used cannabis, those who did more than 50 times at baseline had a significant risk of developing lung cancer (HR= 2.12, 95%CI 1.08-4.14, p nr)	Hsairi et al. 1993 Hashibe et al., 2006; Berthiller et al.,2008; Aldington et al., 2008 Callaghan et al.,2013 Zhang et al. 2014

CI= confidence intervals; HR= hazard ratio; NASEM = U.S. National Academies of Sciences, Engineering, and Medicine; nr = not reported; OR = odds ratio

5c. Is there an association between cannabis use and the incidence of testicular cancer?

Results from Updated Search: Systematic Reviews

The Working Group did not identify any good- to fair-quality systematic reviews that reported an association between cannabis use and the incidence of testicular cancer.

Results from Updated Search: Primary Literature

From the updated literature search, one primary study was found. Callaghan et al. [12] conducted a 42-year follow-up study of 49,343 men, 18 to 21 years old who underwent conscription assessment for the Swedish military (1969 to1970). Registry databases were used to evaluate whether cannabis use was related to the incidence of testicular cancer. In a fully adjusted model of all covariates, no association was observed between lifetime ever use of cannabis and the development of testicular cancer (adjusted hazard ratio [aHR] 1.42; 95% CI 0.83 to 2.45); cryptorchidism was the only significant variable (aHR 6.26; 95% CI, 2.30 to 17.01). In a fully adjusted model of all covariates, both "heavy" cannabis use (i.e., more than 50 times in lifetime at time of assessment; aHR, 2.57; 95% CI, 1.02 to 6.50) and cryptorchidism (aHR, 6.24; 95% CI 2.30-16.97) were associated with the development of testicular cancer. Tobacco use and alcohol consumption were not associated with testicular cancer.

Results from the NASEM Report:

The relevant evidence from the NASEM report is summarized in Table 6

Discussion of Findings

The current research question investigated whether an association exists between the use of cannabis or cannabinoids and the incidence of testicular cancer. The NASEM report concluded that there was limited evidence of a statistically significant association between any one of current, frequent, or chronic cannabis smoking and non-seminoma-type testicular germ cell tumours. The evidence base consisted of a systematic review and meta-analysis conducted by Gurney et al., showed an association between current cannabis use and the risk of developing testicular germ cell tumour. Current users included those who reported smoking at least once a week and chronic users who smoked for 10 years or longer [26]. This group was also at higher risk of developing non-seminoma tumours than seminoma tumours. The NASEM report also found an epidemiology review of the same three case-control studies as found in Gurney et al., which found no association between participants who had ever smoked cannabis and the risk of developing testicular cancer [25]. A risk was found in those who smoked one or more times per day or week and chronic users who had smoked for 10 years or longer. Gurney et al., however, noted that the epidemiology review did not distinguish between seminoma and non-seminoma-type tumours, failed to assess the quality of included studies, and provided limited information on meta-analysis methods [25].

The updated search found one retrospective cohort, a 42 year follow-up study observed an association of "heavy" cannabis use and cryptorchidism with the development of testicular cancer. The combined evidence from the NASEM report and from the updated evidence review suggests a possible association between frequent cannabis use and testicular cancer, particularly in those with heavier and long-term use. However, further research is needed to develop a more fulsome understanding of which testicular tumours may be associated with cannabis use, and the role of frequency and chronicity of cannabis use, current cannabis use, and age of cannabis exposure.

Conclusion: There is limited evidence of a statistical association between current, frequent, or chronic cannabis smoking and non-seminoma-type testicular germ cell tumours.

Table 6. Systematic reviews and primary literature on the association between cannabis use and the incidence of testicular cancer

Author, Search Date	Inclusion criteria	Intervention/comparison	Condition	Findings	Included studies
Updated literature search: Primary literature					
Callaghan et al. 2017 [12] *Retrospective cohort study (42 year follow up)* *N = 49, 343*	Swedish males born between 1949 and 1951 who underwent medical and psychological assessment for Swedish military service (1969-1970). Age at conscription was between 18-21 years.	"Lifetime, ever cannabis use" (if participant ever used cannabis) "Lifetime level of cannabis use" and incidence of testicular cancer	Testicular cancer	In a fully adjusted model of all covariates (age,family history of testicular cancer, cryptorchidism, tobacco and alcohol use: No significant relationship between lifetime ever use of cannabis and development of testicular cancer (aHR 1.42, 95% CI 0.83 to 2.45); cryptorchidism was the only significant variable (aHR 6.26; 95% CI 2.30 to 17.01). "Heavy" cannabis use, i.e. ≥50 times in a lifetime, as measured at conscription (aHR, 2.57; 95% CI, 1.02 to 6.50) and cryptorchidism (aHR, 6.24; 95% CI 2.30 to 16.97) were significantly related to testicular cancer, whereas tobacco use and alcohol consumption were non-significant to the outcome.	N/A
NASEM evidence: Systematic Review					
Gurney et al. 2015 [26] *January 1 1980 - May 13 2015*	Had to report associations between cannabis and testicular cancer. Were only included if data provided	Cannabis use and the risk of developing TGCT	TGCT	Systematic review and meta-analysis of 3 case-control studies (N = 2,138; 719 cases and 1,419 controls). Ever-use cannabis and developing TGCT (OR 1.19, 95 % CI 0.72 to 1.95), and association of former use with TGCT (OR: 1.54, CI 0.84 to 2.85) was insignificant Current use of cannabis increased the odds of developing by 62 % (OR: 1.62, 95% CI 1.13 to 2.31). Frequency of cannabis was associated with developing TGCT, weekly (or greater) nearly doubling the odds of TGCT development (OR 1.92, 95% CI 1.35 to 2.72). Association between the duration of cannabis use (≥10 years vs. never use) and TGCT development (OR 1.50, 95% CI 1.08 to 2.09). Current smokers were at a higher risk of developing non-seminoma tumors compared to seminoma tumors.	Daling et al. 2009; Trabert et al. 2011 Lacson et al. 2012
NASEM evidence : Primary literature					
Huang et al. 2015 [25] *Inception to August 2014*	Epidemiologic studies for which assessed marijuana use and provided risk estimates for marijuana exposure	Marijuana use and testicular cancer risk	Testicular cancer	No association between participants who had ever smoked cannabis and the risk of developing testicular cancer Significant risk found between those who smoked one or more times per day or week (OR, 1.56, 95% CI = 1.09 to 2.23) and chronic users who had smoked for 10 years or longer (OR, 1.50, 95% CI 1.08 to 2.09).	Daling et al. 2009; Trabert et al. 2011 Lacson et al. 2012

aHR= adjusted hazard ratio; CI= confidence interval; NASEM = U.S. National Academies of Sciences, Engineering, and Medicine; OR= odds ratio; TGCT= testicular germ cell tumours

5d. Is there an association between cannabis use and the incidence of esophageal cancer?

Results from Updated Search: Systematic Reviews and Primary Literature'

The Working Group members did not identify any good- to fair-quality systematic reviews or primary literature that reported on an association between cannabis use and the incidence of esophageal cancers.

Results from the NASEM Report:

A summary of evidence from the NASEM search is outlined in Table 7

Discussion of Findings

The research question investigated whether an association exists between cannabis use and the incidence of esophageal cancer. The NASEM report included one population-based case-control study [27]. After adjustments for demographic factors, alcohol and tobacco use, and relevant medical, environmental and socioeconomic information, no statistically significant increase in the risk of developing esophageal cancer was observed in participants with a cumulative cannabis exposure of one to 10 years of joint use or 30 or more years of joint use. Among participants who never smoked cigarettes, there was no statistical difference in the risk of developing esophageal cancer between those who had never smoked cannabis and those who smoked cannabis.

Conclusion: There is insufficient evidence to demonstrate an association between cannabis smoking and the incidence of esophageal cancer**.**

5e. Is there an association between cannabis use and the incidence of other cancers in adults?

Results from Updated Search: Systematic Reviews and Primary Literature

The Working Group members did not identify any good- to fair-quality systematic reviews or primary literature that reported an association between cannabis use and the incidence of other cancers in adults.

Results from the NASEM report:

The relevant evidence from the NASEM report is summarized in Table 7.

Discussion of Findings

The research question investigated whether there is an association between cannabis use and the incidence of other cancers in adults. The NASEM report included one epidemiologic review of eight studies on cannabis use and the risk of prostate, cervical, anal, bladder, and penile cancers, as well as malignant glioma, non-Hodgkin lymphoma, and Kaposi's sarcoma [25]. The authors found that there was insufficient data to draw any conclusions and that further well-designed studies on cannabis use and cancer were warranted. As no new evidence was found, there continues to be insufficient evidence of an association between cannabis smoking and the incidence of other malignancies in adults.

Conclusion: There is insufficient evidence to demonstrate an association between cannabis use and the incidence of other malignancies in adults.

Table 7. Systematic reviews and primary literature on the association between cannabis use and the incidence of esophageal cancer, and "other" cancer

Author, Search Date	Inclusion criteria	Intervention/ comparison	Condition	Findings	Included studies
NASEM Evidence:- Primary Literature					
Hashibe et al. 2006 [27]	Residents of Los Angeles County at time of diagnoses of esophageal cancer or at the time of recruitment for controls, between 18-65 yrs, spoke English or Spanish,	Cannabis use and the incidence of esophageal cancer	Esophageal cancer	Population-based case-control study, N= 108 for esophageal cancer Adjusted for demographic factors, alcohol and tobacco use Risk of developing Cumulative cannabis exposure (1-10 years) vs. never used cannabis : OR 0.77, 95% CI 0.36 to 1.6, p=ns Cumulative cannabis exposure (30 or more joint years) vs. never used cannabis: OR 0.53, 95% CI 0.22 to 1.3. p=ns Among participants who never smoked cigarettes, those who ever smoked cannabis vs. those who never smoked cannabis OR 0.79, 95% CI –0.30 to2.1	N/A
Huang et al. 2015 [25] *Inception to August 2014*	Epidemiologic studies that assessed marijuana use and provided risk estimates for marijuana exposure	Marijuana use and various 'other' cancers	Prostate and cervical	Cohort study 27,920 men and 36,935 woman aged 15-49 years Adjusted for race, age, education, and alcohol use Compared to individuals who did not smoke cannabis, current/former cannabis users (>6 occasions) had higher incidence of prostate cancer in compared with men who never smoked cigarettes (RR 3.1, 95% CI 1.0 to 9.5) and cervical cancer in woman who never smoked cigarettes (RR 1.6 95% CI 1.2 to 2.2) Compared to those who did not smoke cannabis or smoked on only 1-6 occasions vs. current/former cannabis smokers, no significant risk of developing prostate or cervical cancer.	Sidney et al. 1997
			Brain tumours	Cohort study 133, 881 aged 25 and older Controlled for demographic and socioeconomic factors and alcohol and tobacco use Non users of cannabis vs. at least once per month use was associated with significant risk of malignant adult-onset glioma (RR 2.8 95%CI 1.3 to 6.2) Compared to non-users, users had significant risk of developing brain tumour with weekly cannabis use (RR 3.2 95%CI 1.1 to 9.2) or monthly cannabis use (RR, 3.6, 95%CI 1.3 to 10.2).	Efrid et al., 2004

			Non-Hodgkin lymphoma	Population-based case-control trial (3,376 women and heterosexual men) Never users compared to cannabis (less than 40 times), statistical decrease risk of developing non-Hodgkin lymphoma (adjusted for sex, age, education). (OR 0.68, 95% CI 0.55–0.84). Those who used cannabis >40 occasions, risk was further depressed (OR 0.57 95% CI 0.44 to 0.74).	Holly et al. 1999
				Population-based case-control study (378 HIV-negative men and women diagnosed with non-Hodgkin lymphoma vs. controls) matched for age, biological sex, race, language of interview, neighbourhood of residences at time of diagnosis No significant difference in risk between users (cannabis at anytime) vs. never users (OR, 0.86, 95% CI 0.50 to 1.48). This held true even when using cannabis only 1-5 times (OR, 0.68, 95% CI = 0.34 to 1.38) or on more than 900 occasions (OR, 1.09, 95% CI = 0.48 to 2.48).	Nelson et al. 1997
			Penile Cancer	Case-control study (110 cases and 255 age matched controls) Adjusted for alcohol and cigarette use, age, number of sexual partners No difference in risk of developing penile cancer between ever used vs. never used cannabis (OR, 1.5, 95 % CI = 0.7–3.2)	Madden et al. 1993
			Anal cancer	Case-control study (148 men and women diagnosed with anal cancer were matched by age, biological sex, year of diagnosis, and area of residence to 166 male and female controls diagnosed with colon cancer No statistical risk difference in anal cancer in ever used cannabis vs. never used cannabis, after adjusting for age, residence, cigarette use (RR, 0.8, 95% CI 0.2 to 4.0).	Daling et al. 1987
			Kaposi's sarcoma	Cohort study (1,335 participants, homosexual men coinfected with HIV and human herpes virus 8) Cannabis use in the 6 months preceding data collection not significantly more likely to develop Kaposi's sarcoma compared to non users during that period (HR, 1.00, 95% CI 0.79 to 1.28), controlled for alcohol use, tobacco smoking and sexual activity characteristics	Chao et al. 2009

			Bladder Cancer	Data from California Men's Health study (84, 170 men ages 45-69 yrs) Adjusted for age, race, and body mass index Compared to those who neither used cannabis or tobacco vs. those that used cannabis but not tobacco, had a significantly reduced risk of developing bladder cancer (HR 0.55 95%CI 0.31 to 1.00). After stratifying cannabis use by levels of cumulative cannabis exposure, decreased risk was only significant for users smoking on 3-10 occasions (HR 0.57 95% CI 0.34 to 0.96). After stratifying by age, participants who smoked cannabis but not tobacco, risk of bladder cancer was significantly decreased only for users between age 45-54 (HR 0.26 95% CI 0.07 to 0.92).	Thomas et al. 2015
			Transitional cell carcinoma	Case control study of 52 Veterans Affairs pts younger than 61 yrs were age matched with 104 controls More cases compared to controls reported ever using cannabis (88.5% vs. 69.2%, p = 0.008). More cases compared to controls had higher mean number of joint years of smoked cannabis (48.0 joint-years vs. 28.5 joint-years, p = 0.022). Adjusted for potential confounders of tobacco use, there was a significant association between increasing joint years of cannabis and risk of transitional cell carcinoma (p trend = 0.01).	Chacko et al. 2006

CI= confidence intervals; HR = hazard ratios; N/A = not applicable; NASEM = U.S. National Academies of Sciences, Engineering, and Medicine; ns not significant; OR= odds ratio; pts = patients; RR = relative risks; yrs = years

6. Is there an association between cannabis use and the incidence of cancer in offspring?

Results from Updated Search: Systematic Reviews and Primary Literature

The Working Group members did not identify any good- to fair-quality systematic reviews or primary literature that reported an association between cannabis use and the incidence of cancer in offspring.

Results from the NASEM Report:

A summary of evidence from the NASEM search is outlined in Table 8.

Discussion of Findings

The research question investigated whether there was an association between cannabis use and the incidence of cancer in offspring. The updated literature search found no new evidence. The NASEM report found an epidemiology report, which included six studies. Four of the studies found that maternal cannabis use during pregnancy was associated with childhood leukemia, astrocytoma, and rhabomyosarcoma. While these studies had large sample sizes and reported on recreational drug use during pregnancy and birth, there were limitations including a small number of exposed cases, potential recall bias leading to possible exposure misclassification, and no dose-response assessment. A case-control study of childhood acute myelogenous leukemia conducted by Trivers and colleagues found no association with parental marijuana use, and maternal marijuana use frequency was not associated with leukemia risk. Another case-control study of childhood neuroblastoma did not observe an increased risk after adjusting for household income, age at diagnosis and other drugs used. An increased risk of neuroblastoma with maternal marijuana use in the first trimester, but not for the second or third trimester was observed. As no new evidence was found in the updated search, there continues to be insufficient evidence to make any statement to support or refute an association between cannabis smoking and the incidence of cancer in offspring.

Conclusion: There is insufficient evidence to demonstrate an association between parental cannabis use and subsequent risk of developing any malignancies in offspring.

Table 8. Systematic reviews and primary literature on the association between cannabis use and the incidence of cancer in offspring

Author, Search Date	Inclusion criteria	Intervention/ comparison	Condition	Findings	Included studies
NASEM Evidence:- Primary Literature					
Huang et al. 2015 [25] *Inception to August 2014*	Epidemiologic studies that assessed marijuana use and provided risk estimates for marijuana exposure	Marijuana use and incidence of cancer in offspring	Acute non-lymphoblastic leukemia (ANLL)	Case-control study (N=204) Cases diagnosed by age 17 matched to controls by age, race, and residential location. Maternal use of cannabis during, and in the year preceding pregnancy was associated with a significant risk of ANLL (RR 10, p = 0.005). Parental use of cannabis during the same period was not a significant risk of ANLL Children whose mother used cannabis during or in the year preceding pregnancy were younger at age of diagnosis vs. children whose mother did not use cannabis during that time (37.7 months [mean] vs. 96.1 months [mean], p = 0.007)	Robinson et al. 1989
			Acute myeloid leukemia (AML)	Case-control study (N=517) cases with AML by 17 years and match with 610 controls by age, race, and residential location Maternal use of cannabis during or 3 months preceding pregnancy, lower risk of AML in children vs. non maternal use during same time (OR 0.43, 95% CI 0.23 to 0.80). Mothers who use cannabis 3 months before pregnancy at least once weekly had children with lower risk of developing AML vs. mothers who used less than once weekly (OR 0.19, 95% CI 0.06 to 0.59 vs. OR 0.57, 95% CI 0.26 to 1.29) Overall paternal cannabis use significantly associated with risk of AML (OR 1.37, 95% CI 1.02 to1.83); however, no significant association paternal use of cannabis during pregnancy and 3 months preceding and risk of AML (OR 1.02 95% CI 0.67 to1.53).	Trivers et al. 2006
			AML or acute lymphoblastic leukemia (ALL)	Case-control study, 2343 cases of AML or ALL matched by age, race, biological sex, and residential location Cases whose fathers who ever used cannabis had a significant risk of developing ALL or AML compared to those whose fathers never used (OR 1.5, CI nr p <0.01).	Wen et al. 2000

			Rhabdomyosarcoma, neuroblastoma, astrocytoma	Case-control study, 322 children younger than 21 years diagnosed with rhabdomyosarcoma matched by age, race, sex of 322 controls Children whose mothers used cannabis in 12 months before birth significantly more likely to develop disease than children whose mothers didn't (OR 3.0, 95%CI 1.4 to 6.5), adjusted for complications during pregnancy and other potential confounders Children whose fathers used cannabis in the year prior to birth were at significantly greater risk of developing rhabdomyosarcoma than children whose father did not (OR 2.0 95% CI 1.3 to3.3). Use of cannabis and cocaine were highly correlated, as were maternal and paternal use of cannabis	Grufferman et al. 1993
			Astrocytoma	Case-control study N=163 cases diagnosed by 14 years with astrocytoma or related tumours and match to controls by age, race, and residential location Borderline significant association between maternal use of cannabis in the 10 months preceding their child's birth and the risk of astrocytoma (OR 2.8, 95% CI 0.9 to 9.9 ,p = 0.07)	Kuijten et al. 1990
			neuroblastoma	538 cases diagnosed by 19 years, age matched to 504 controls Maternal use of cannabis during pregnancy vs. non users during any measure time, significantly associated with greater risk of offspring neuroblastoma, adjusted for use of other recreational drugs (OR 2.51 95% CI 1.18 to5.83). Significant association between incidence of neuroblastoma and maternal use of cannabis during first trimester (OR 4.75, 95% CI 1.55 to 16.48), but not second or third trimester, in the month preceding conception, or period between birth and diagnosis	Bluhm et al. 2006

ANLL = Acute non-lymphoblastic leukemia; AML = Acute myeloid leukemia; ALL = acute lymphoblastic leukemia; CI = confidence intervals; HR = hazard ratios; NASEM = U.S. National Academies of Sciences, Engineering, and Medicine; nr = not reported; OR = odds ratio; RR = relative risks; yrs = years

7.Are cannabis or cannabinoids an effective treatment for spasticity associated with spinal cord injury?

Results from Updated Search: Systematic Reviews and Primary Literature

The Working Group members did not identify any good- to fair-quality systematic reviews or primary literature that reported on whether cannabis or cannabinoids was effective treatment for spasticity associated with spinal cord injury.

Results from the NASEM Report:

The NASEM report found one systematic review [15], which included 14 randomized placebo-controlled trials. Three of the trials included patients with paraplegia caused by spinal cord injury. Unfortunately, none of the three studies were included in the pooled estimates because they were either not full publications or had insufficient data to allow summary estimates to be generated.

Discussion of Findings

The research question investigated whether cannabis or cannabinoids are an effective treatment for spasticity associated with spinal cord injury. There was no new evidence found in the updated evidence search. As no new evidence was found in the updated search, there continues to be insufficient evidence to make any statement on whether cannabinoids are an effective treatment for spasticity in patients with paralysis due to spinal cord injury.

Conclusion: There is insufficient evidence to suggest that cannabinoids are an effective treatment for spasticity in patients with paralysis due to spinal cord injury.

EVIDENCE SUMMARY CONCLUSIONS

This evidence summary used the NASEM consensus document as a foundation and conducted an updated evidence summary to find evidence on the health effects of cannabis and cannabinoids in relations to cancer. OH (CCO) will use this evidence to support a position statement from OH (CCO) in response to requests from the public and the clinical community and to help in the development of knowledge products for healthcare providers and patients.

INTERNAL REVIEW

The evidence summary was reviewed by Jonathan Sussman, Sheila McNair, Cindy Walker-Dilks, Glenn Fletcher, and Emily Vella. The Working Group was responsible for ensuring any necessary changes were made.

Acceptance by OH (CCO) Prevention and Cancer Control

After internal review, the report was presented to the OH (CCO) Prevention and Cancer Control and the document was fully accepted.

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Appendix 1: Affiliations and Conflict of Interest Declarations

Name	Affiliation	Declarations of interest
William K. Evans- lead author Medical Oncologist Professor Emeritus	Department of Oncology, McMaster University, Hamilton, Ontario Board of the Hamilton Community Foundation Cancer Assistance Program Board of Directors Ontario Health (Cancer Care Ontario) Juravinski Hospital Cancer Centre at Hamilton Health Sciences Hamilton Niagara Haldimand Brant LHIN	None declared
Paul Daeninck Attending Medical Oncologist Assistant Professor Cross-appointment to the Department of Family Medicine Consultant in Palliative Medicine	St. Boniface Unit Cancer Care Manitoba University of Manitoba Winnipeg, Manitoba Winnipeg Regional Health Authority Palliative Care Program	Has received $500 or more in a single year to as in a consulting capacity for Shoppers Drug Mart, Tetra Pharma and Reformulary. Has published 2 papers with recommendations regarding cannabis use in cancer patients and has been interviewed by media outlets regarding use of medical cannabis.
David Hammond Professor CIHR-PHAC Chair in Applied Public Health	University of Waterloo Waterloo, Ontario Canadian Institutes of Health Research Public Health Agency of Canada	Provided paid expert testimony on behalf of the province of Quebec in a legal challenge to the cannabis control act. These activities have no relation to any business/commercial/for profit entity.
Aisha Lofters Clinical Scientist Family Practitioner Assistant Professor	St. Michael's Hospital Academic Family Health Team Li Ka Shing Knowledge Institute of St. Michael's Hospital University of Toronto Toronto, Ontario	None declared
Peter Selby Chief of Medicine Clinician Scientist Professor	The Centre for Addiction and Mental Health Dalla Lana School of Public Health at the University of Toronto Toronto, Ontario	Has received $500 or more in a single year to act in a consulting capacity for Johnson & Johnson Group of companies (ERNT Advisory Board), Pfizer Canada Inc (Champix National Advisory Board) and consulting for Evidera Inc, Miller Medical Communications , NVision Insight Group, Myeline and Associates and Boehringer Ingelheim
Marissa Slaven Assistant Clinical Professor Department of Family Medicine	Hamilton Health Sciences McMaster University Hamilton, Ontario	Has been awarded $800 000 for research for a study on cannabis in cancer pain. This is at the clinical trial stage.
Lisa Durocher-Allen Health Research Methodologist	Program in Evidence-Based Care McMaster University Hamilton, Ontario	None declared

Appendix 2: Literature Search Strategy

MEDLINE

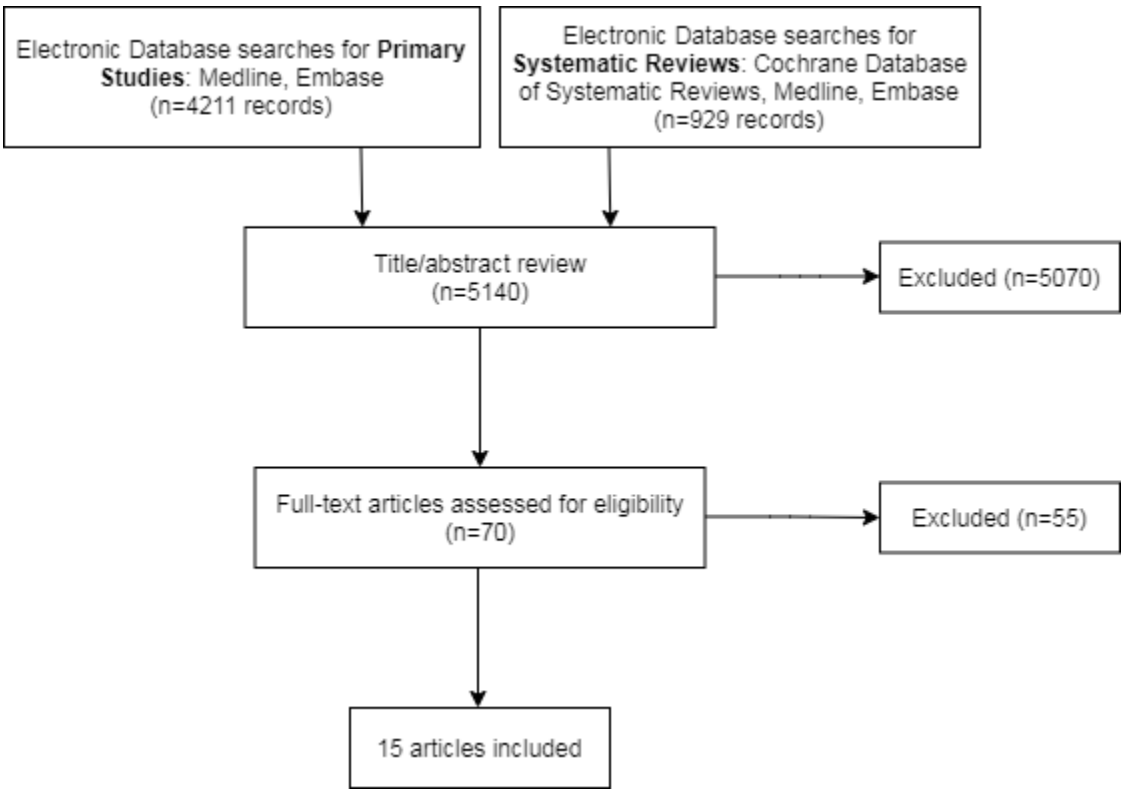
1 Cannabis/
2 Marijuana Smoking/
3 Marijuana Abuse/
4 Medical Marijuana/
5 Cannabinoids/
6 Dronabinol/
7 (cannabis or marijuana or cannabinoid or dronabinol or marinol).ti,ab.
8 nabilone.ti,ab.
9 or/1-8
10 k2.ti,ab.
11 spice.ti,ab.
12 or/10-11
13 9 not 12
14 Mice/ or mice.ti,ab.
15 Rats/ or rats.ti,ab.
16 or/14-15
17 13 not 16
18 17
19 limit 18 to (english language and humans)
20 limit 19 to (classical article or clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or evaluation studies or guideline or journal article or multicenter study or observational study or practice guideline or pragmatic clinical trial or randomized controlled trial or validation studies)
21 limit 19 to (addresses or autobiography or biograprahy or case reports or clinical conference or comment or congresses or consensus development conference or consensus development conference, nih or "corrected and republished article" or dataset or dictionary or directory or duplicate publication or editorial or english abstract or festschrift or government publications or historical article or in vitro or interactive tutorial or interview or introductory journal article or lectures or legal cases or legislation or letter or meta analysis or news or newspaper article or overall or patient education handout or periodical index or personal narratives or portraits or published erratum or research support, non us gov't or retracted publication or "retraction of publication" or "review" or "scientific integrity review" or systematic reviews or technical report or video-audio media or webcasts)
22 20 not 21
23 limit 22 to ed=20160801-20190801
24 limit 19 to (meta-analysis or "review" or systematic reviews)
25 limit 19 to (addresses or autobiography or bibliography or biography or case reports or clinical conference or comment or congresses or consensus development or consensus development conference, nih or "corrected and republished article" or dataset or dictionary or directory or duplicate publication or editorial or english abstract or festschrift or government publications or historical article or in vitro or interactive tutorial or interview or introductory journal article or lectures or legal cases or legislation or letter or news or newspaper article or overall or patient education handout or periodical index or personal narratives or portraits or published erratum or research support, non us gov't or retracted publication or "retraction of publication" or "scientific integrity review" or technical report or video-audio media or webcasts)
26 24 not 25
27 limit 26 to ed=20160801-20200130

EMBASE

1 clinical article/
2 case report/
3 clinical trial/
4 controlled clinical trial/
5 phase 1 clinical trial/
6 phase 2 clinical trial/

7 phase 3 clinical trial/
8 phase 4 clinical trial/
9 randomized controlled trial/
10 double blind procedure/
11 single blind procedure/
12 crossover procedure/
13 multicenter study/
14 controlled study/
15 "clinical trial (topic)"/
16 "controlled clinical trial (topic)"/
17 "phase 1 clinical trial (topic)"/
18 "phase 2 clinical trial (topic)"/
19 "phase 3 clinical trial (topic)"/
20 "phase 4 clinical trial (topic)"/
21 "randomized controlled trial (topic)"/
22 "multicenter study (topic)"/
23 cannabis/
24 cannabis addiction/ or medical cannabis/ or "cannabis use"/ or cannabis smoking/ or cannabis derivative/
25 cannabinoid/
26 dronabinol/
27 nabilone/
28 (Cannabis or marijuana or cannabinoid or dronabinol or nabilone or marinol).ti,ab.
29 or/24-29
30 k2.ti,ab.
31 spice.ti,ab.
32 or/31-32
33 30 not 33
34 Mice/ or mice.ti,ab.
35 Rats/ or rats.ti,ab.
37 or/35-36
38 34 not 37
39 or/1-23
40 38 and 39
41 limit 40 to (journal and article)
42 limit 40 to (book or book series or chapter or conference abstract or conference paper or conference proceeding or "conference review" or editorial or erratum or letter or note or "review" or short survey or trade journal)
43 41 not 42
44 case report/
45 43 not 44
46 45
47 limit 46 to (human and english language)
48 limit 47 to yr="2016-Current"
49 limit 48 to dd=20160801-20190801
50 meta analysis/
51 "meta analysis (topic)"/
52 "systematic review (topic)"/
53 or/50-52
54 38 and 53
55 limit 54 to (journal and (article or review))
56 55
57 limit 56 to (human and english language)
58 limit 57 to yr="2016-Current"
59 limit 58 to dd=20160801-20200130

Appendix 3: PRISMA Flow Diagram



Appendix 4: Quality assessment of systematic reviews and level of concern for study eligibility criteria

	Allan et al. 2018	Boland et al. 2020	Hauser et al. 2019	Nugent 2017	Schussel 2017
Study eligibility criteria					
a. Was an "a priori" design provided?	High	Low	Low	Low	High
b. Were study edibility criteria clearly specified?	Low	Low	Low	Low	Low
c. Were restrictions in eligibility criteria appropriate?	Low	Low	Low	Low	Low
Identification and collection of studies					
e. Was a comprehensive literature search performed?	Low	Low	Low	Low	Low
f. Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	Low	Low	Low	Low	Low
g. Were restrictions based on date, publication format, or language appropriate?	Low	Low	Low	Low	Low
h. Was selection bias avoided?	Low	Low	Low	Low	High
Data collection and study appraisal					
i. Were at least two individuals involved in study selection and data extraction?	Low	Low	Low	Low	Low
j. Were the characteristics of the included studies provided?	Low	Low	Low	Low	Low
k. Was the scientific quality of the included studies assessed and documented?	Low	Low	Low	Low	Low
Synthesis and findings					
l. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Low	Low	Low	Low	Low
m. Was the methods used to combine the finding of studies appropriate?	Low	Low	Low	Low	N/A
n. Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Low	Low	Low	Low	N/A
o. Was the likelihood of publication bias assessed?	Low	Low	Low	High	Low
p. Are the stated conclusions supported by the data presented?	Low	Low	Low	Low	Low
Conflict of interest					
q. Was the conflict of interest for the systematic review stated?	Low	Low	Low	Low	Low
Overall quality					
r. Rate the overall quality of the systematic review (Good, Fair, Poor)	Good	Good	Good	Good	Good

Low= Low level of concern; High = High level of concern

Appendix 5: Risk of Bias of included randomized controlled studies

Study	Random sequence generation	Allocation concealment	Blinding of participants/personal	Blinding of outcome assessments	Incomplete outcome data	Selective reporting
Turcott et al.	Low	Unclear	Low	Unclear	Low	Low

Appendix 6: Newcastle-Ottawa scale for assessment of included cohort study and included case-control study

Quality Assessment criteria for cohort study	Callaghan et al, 2017
Selection	
Representativeness of exposed cohort?	Yes
Selection of the non-exposed cohort?	Yes
Ascertainment of exposure?	Yes
Demonstration that outcome of interest was not present at start of study?	Yes
Comparability	
Study controls for age, tobacco smoking	Yes
Study controls for at least 3 additional risk factors?	Yes
Outcome	
Assessment of outcome?	Yes
Was follow-up long enough for outcome to occur?	Yes
Adequacy of follow up of cohorts?	Yes
Overall Quality Score (Maximum 9)	8