FINAL REPORT

Rapid Review of Evidence on Therapeutic Benefits of Cannabis During Cancer Treatment

Prepared for:
Canadian Partnership Against Cancer

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Executive Summary

OBJECTIVE: The objective of this rapid review is to assess the current evidence based on cannabis use and cancer treatment for the Canadian Partnership Against Cancer. This report addresses the following research question:

- What are the therapeutic benefits (if any) of cannabis use during active cancer treatment?

METHODS: A comprehensive search of literature from 2013 to the present was developed and conducted using five bibliographic databases, consisting of Medline, Embase, CINAHL, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials. References captured by the search and identified through supplementary sources underwent two levels of screening for eligibility: level 1 title and abstract screening, and level 2 full-text evaluation. The selection of studies for inclusion was performed independently by two reviewers using the eligibility criteria developed prior to the conduct of this review. Any discrepancies were resolved by consensus.

RESULTS: A total of three primary studies and nine reviews (including systematic reviews, overviews of systematic reviews, and quasi-systematic reviews) were captured by the search strategy and included in the findings described in this report. RSI's observations are based on a review of the articles identified as eligible, and these are summarized in Table 1 below.

Table 1. Summary of findings from eligible reviews and primary studies, outlined by outcome.

Reviews	Primary Studies

Chemotherapy-induced Nausea and Vomiting
• Cannabis may be more effective than placebo in reducing chemotherapy-induced nausea and vomiting (based on two reviews)
• Cannabis in combination with other antiemetics may be more effective than placebo in combination with antiemetics (based on one review)
• Cannabis may be just as effective as, if not more than, other antiemetics (similar efficacy based on one review; greater efficacy based on two reviews)
• Strength of evidence
  ◦ *Among reviews reporting on weight or certainty of evidence, results varied from very low to strong.*
  ◦ *Although some reviews reported results that suggest a therapeutic benefit from cannabis use (reflected in observations above), the review authors concluded unclear effectiveness due to the low quality of evidence (more details are provided in the results section).*
 	
Appetite Stimulation in Anorexic or Cachectic Cancer Patients
	Pain, Nausea, and Appetite
	• There was no clear evidence of reduction in pain and nausea or improvement in appetite, as results were inconsistent between studies (nausea and appetite based on two studies; pain based on three studies)
	
	Anxiety
	• Anxiety was significantly worse among cannabis users than nonusers (based on one study)
	
	Tiredness, Sleep, Drowsiness, Antalgic Medication Use, Time Needed for a 20% Pain Increase, Anti-Emetic Medication Use, Weight Fluctuations, Feeding Tube Requirement, Mood, Depression, Overall Well-Being, Quality of Life Improvement, Physical Quality of Life, Mental Quality of Life, Allodynia, and Hyperalgesia
	• No significant difference in outcome between cannabis users and nonusers (each outcome based on one study)

Reviews	Primary Studies
• No clear evidence as results were inconsistent between studies of small and large sample sizes (based on one review)	

Background

The federal government in Canada has approved the use of medical cannabis when prescribed by a physician since 2013, initially under the *Marihuana for Medical Purposes Regulations,* and since 2016 under the new *Access to Cannabis for Medical Purposes Regulations.* These Regulations allow Canadians who have been prescribed cannabis for medical purposes to access legal sources of medical cannabis (in fresh, dried or oil form) via licensed producers; alternatively, they may produce, or designate someone to produce, a limited amount of cannabis for their own medical purposes. In October 2018, cannabis was legalized for recreational (non-medical) use in Canada under the *Cannabis Act*.

The Canadian Partnership Against Cancer (the Partnership) is assessing the current evidence base on cannabis use and cancer risk and benefits during cancer treatment. Risk Sciences International (RSI) was contracted to provide support to the Partnership through conducting a rapid review of evidence on the potential therapeutic benefits of cannabis use during active cancer treatment.

Objective

The research question of interest to the Partnership for the current rapid review is the following:

- What are the therapeutic benefits (if any) of cannabis use during active cancer treatment?

Approach

Literature Search Strategy

The search strategy was established prior to the conduct of this review, and was based on two concepts, "cannabis" and "cancer", as outlined in Figure 1. Five electronic literature databases were consulted during the conduct of this work: Medline, Embase, CINAHL, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials. Since there is a significant (98%)[1] overlap between PubMed and Medline, and PubMed allows only limited control over search terms, a literature search in PubMed was not performed.

All searches were conducted on January 15, 2019 and restricted to references published from 2013 up to that date. References captured by the search were imported into an EndNote database, and duplicates removed. Additionally, the reference lists of systematic reviews were scanned to supplement the primary search.

[1] See, for example: https://kemh.libguides.com/library/search_tips/faqs/difference_between_pubmed_medline_embase

The search consisting of keywords and MeSH terms developed for the use in Medline is presented in Figure 1. These search terms were then adapted for the use in other electronic databases. The detailed search strategies are provided in Appendix 1.

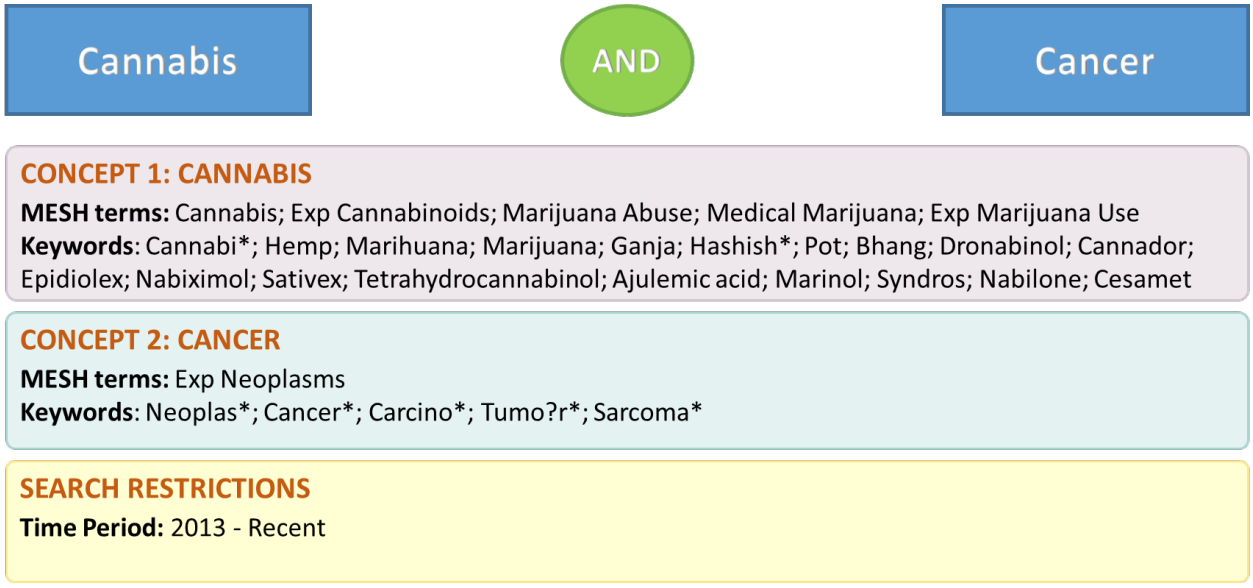

Figure 1. Concepts and search terms used in developing the literature search strategy.

Eligibility Criteria and Study Selection

Articles captured by the current search strategy and identified through other sources were subject to level 1 (title and abstract) and level 2 (full text) screening using the eligibility criteria that were developed in collaboration with the Partnership prior to the conduct of this review (Table 2). In cases where the study location was not reported, eligibility was determined based on the study authors' country of affiliation. This restriction by study location (region/country) was not applied when screening for reviews, as they may consist of studies conducted across several countries, some of which may be listed as part of the current inclusion criteria. The selection of studies was independently performed by two reviewers; any discrepancies were resolved by consensus.

Table 2. Eligibility criteria for the selection of studies on the therapeutic benefits of cannabis during active cancer treatment.

Inclusion Criteria	Exclusion Criteria
Study/Document Type	
• Peer-reviewed literature • Primary human studies (intervention or observational studies) • Systematic reviews and meta-analyses • Overviews of systematic reviews • Quasi-systematic reviews	• Grey literature • Animal or cell studies • News articles, narrative reviews, editorials, conference abstracts, case reports, risk projections, research protocols

Inclusion Criteria	Exclusion Criteria
Publication Date	
• 2013 - Current	• Prior to 2013
Publication Language	
• English	• All other languages
Region/Country	
• Canada • Australia • New Zealand • Northwest Europe • Other G7 countries: USA, France, Germany, Italy, Japan, United Kingdom	• All other countries
Population	
• Patients with cancer	• Patients without cancer
Exposure/Intervention	
• All forms and routes of cannabis use during active cancer treatment	• Cannabis use post cancer treatment
Outcomes	
• All therapeutic benefits	• None

Data Abstraction

In preparation for populating tabular summaries of key findings, data abstraction forms were developed for relevant reviews (systematic reviews, overviews of systematic reviews, and quasi-systematic reviews) and original research articles identified for inclusion.

Data abstracted from eligible reviews included the article type, research objectives, health endpoints, search methods, number of studies included, whether a meta-analysis was performed, main results, conclusions and limitations reported by the review authors, as well as any RSI comments.

Similarly, information abstracted from relevant original research articles included characteristics of the study (location, design, and sample size) and participants (age, sex, and active treatment received), exposure data (form, route, and intensity), outcome and its method of ascertainment, main quantitative results and adjusted covariates, conclusions and limitations reported by study authors, as well as any RSI comments.

Results

Search Results and Study Selection

The search of five electronic databases retrieved a total of 2,174 references. Following the removal of duplicates and supplementation with articles identified from reference lists of systematic reviews, 1,841 references were retained and screened by title and abstract for relevance. Of the 61 references identified as potentially eligible, 49 were excluded following full-text evaluation for reasons including study type, country of study, and active cancer treatment status. In total, 12 relevant articles reporting on the

therapeutic benefits of cannabis use during active cancer treatment, published in English from 2013 onwards, were selected for inclusion. Articles included in this rapid review comprise primary studies, systematic reviews, overviews of systematic reviews, and quasi-systematic reviews. The search strategy and screening process is illustrated in Figure 2. Appendix 2 contains a complete list of the studies that were excluded, with rationale, following full-text evaluation. As well, a list of included studies can be found in Appendix 3.

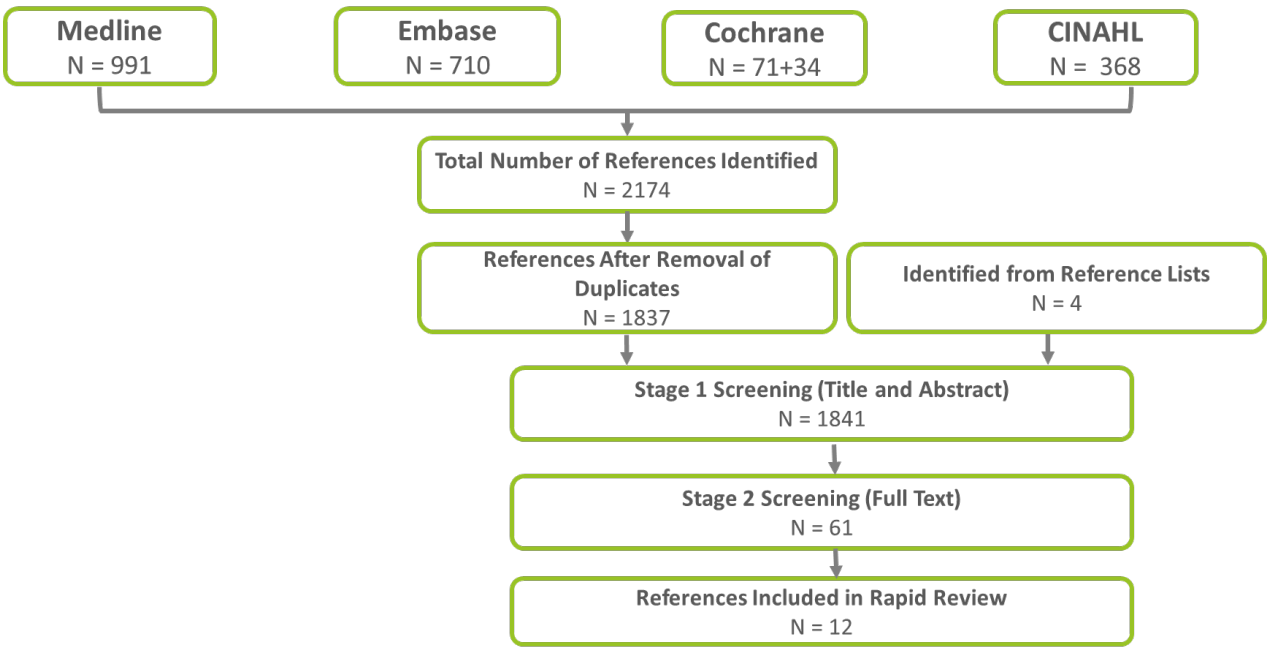

Figure 2. Flow diagram illustrating the results from the search strategy and screening process.

Systematic Reviews, Overviews of Systematic Reviews, and Quasi-systematic Reviews

The current search strategy identified a total of **nine relevant systematic reviews, overviews of systematic reviews, and quasi-systematic reviews.** The publication dates of these included reviews were quite recent, ranging from 2015 to 2018. All reviews identified as eligible reported on either chemotherapy-induced nausea and vomiting (CINV) or appetite in anorexic or cachectic cancer patients. Research findings of these reviews are described below by outcome, as well, more information can be found in data abstraction tables found in Appendix 4.

Chemotherapy-Induced Nausea and Vomiting

Most reviews identified in the literature that were eligible for inclusion investigated the effectiveness of cannabis on nausea and vomiting from chemotherapy treatments. Specifically, eight of the nine included reviews reported on this outcome. In this section, systematic reviews that were captured by the current search strategy but included in an overview of systematic reviews were not described or individually interpreted; however, data specific to these individual articles have been extracted and are provided in the data abstraction tables found in Appendix 4.

The reviews included in this synthesis suggest that cannabinoids may be more effective than placebos for the management of nausea and vomiting induced by chemotherapy. As well, there is some evidence that cannabinoids may be just as effective as other antiemetics, if not more. However, these findings should be interpreted and used with caution, as the weight or certainty of evidence varied between reviews in the current literature. For instance, while a committee of experts from the NASEM reported strong evidence from RCTs that supports the therapeutic benefits of oral cannabinoids for CINV (NASEM, 2017), other reviews evaluating the certainty of evidence using GRADE have reported scores ranging from very low to moderate (Allan et al., 2018; Morales et al., 2017). As well, while a greater effect of cannabinoids was suggested by results from Schussel et al. (2018) relative to placebo, Morales et al. (2017) also found a greater effect of cannabinoids in combination with other antiemetics, relative to placebo in combination with antiemetics. However, these study authors concluded that the benefits of cannabinoids are unclear as the quality of evidence is insufficient. Finally, many of the included reviews reported a potential for adverse effects associated with the use of cannabis; although this was not an objective of the current rapid review, it may be of interest to investigate further to determine if the potential therapeutic benefits outweigh the potential risks of treatment.

The overview of systematic reviews conducted by **Schussel et al. (2018)** included five systematic reviews of randomized controlled trials published from 2001 to 2015; among these articles, one was identified for inclusion in the present rapid review (Smith et al., 2015), and the remaining four were published prior to 2013 and thus were not captured by the current search strategy. Based on the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) score, the methodological quality of included reviews varied from low (N = 2), moderate (N = 2), and high (N = 1). Findings from this overview suggest that "**cannabinoids were superior than placebo and, in general, similar to standard antiemetics alone or in combination**." (p. 571) However, the study authors also conclude that "**there is no good quality evidence to recommend or not the use of cannabinoids for CINV**." (p. 567) Furthermore, **more adverse events were observed with the use of cannabinoids than with standard antiemetics**.

Allan et al. (2018) conducted a systematic review of systematic reviews which identified five articles related to the effects of medical cannabinoids on CINV, where two were already identified for inclusion in this rapid review (Whiting et al., 2015; Smith et al., 2015), and the remaining three were published between 2001 and 2009, earlier than the date of interest for this review. The risk of bias was determined using a modified AMSTAR score which ranged from 0 to 6, where lower risk was indicated by higher values; of the systematic reviews assessed, scores varied from 2 (N = 1), 3 (N = 1), 5 (N = 1), and 6 (N = 2). As well, the certainty of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Two responder meta-analyses on the control of CINV were conducted. In the comparison between **medical cannabinoids and placebo** which was based on seven randomized controlled trials (RCTs), more patients receiving the **former exhibited control over CINV** (RR: 3.60; 95% CI: 2.55, 5.09), and the **certainty of evidence was considered moderate**. Similarly, **more patients receiving cannabinoids demonstrated control over CINV than those taking other antiemetics, specifically neuroleptics** (RR: 1.85; 95% CI: 1.18, 2.91); these results were based on 14 RCTs and the **certainty of evidence was considered low**. The study authors conclude that "[t]here is **reasonable**

evidence that cannabinoids improve nausea and vomiting after chemotherapy… Adverse effects are very common, meaning benefits would need to be considerable to warrant trials of therapy." (p. e78)

A comprehensive review with characteristics of a systematic review was conducted by the **National Academies of Sciences, Engineering, and Medicine [NASEM] (2017)**, and covered multiple therapeutic benefits of cannabinoids, including its use as an antiemetic for CINV. In particular, several databases were searched, relevant systematic reviews of fair/good quality were included, and additional primary research of similar quality following the most recent review publication date was acquired. In total, three systematic reviews, all of which were captured by the current search strategy of this rapid review (Whiting et al., 2015; Smith et al., 2015; Philips et al., 2016), and one primary study published in 2007 were identified as eligible. From the articles included in this weight-of-evidence evaluation, the following conclusion was reached: "**There is conclusive evidence that oral cannabinoids are effective antiemetics in the treatment of chemotherapy-induced nausea and vomiting**" (p. 94).

Morales et al. (2017) conducted a structured summary where primary studies were identified from systematic reviews, a meta-analysis was performed, and the certainty of evidence was evaluated using the GRADE approach. A total of four randomized trials investigating the use of cannabinoids with standard antiemetic therapy for CINV were identified. Although **an increase in the control of CINV was observed with the addition of cannabinoids compared to placebo among oncological patients receiving standard antiemetic therapy (RR: 1.92; 95% CI: 1.26, 2.91),** the **certainty of evidence was found to be very low**. As a result of the very low certainty of evidence, the study authors conclude that **evidence on the effectiveness of cannabinoids with standard antiemetics for the control of CINV is unclear**. As well, based on three of the four studies with reported data, findings with **moderate certainty of evidence** indicate that **use of cannabinoids will likely result in an increase in adverse effects**.

The systematic review by **Wong et al. (2017)** focused on the use of medical cannabinoids in study samples consisting of **children and adolescents**. Of the 22 studies included, six reported on CINV and were published from 1979 to 2015. A significant decrease in measures of CINV was reported with cannabinoids compared to antiemetics among four double-blind RCTs. The statistical significance of study findings could not be assessed with the other two studies, which were a retrospective chart review and an open-label trial; however, improvements to CINV with cannabinoids were also suggested. Overall, the results from this review "**demonstrate that THC [tetrahydrocannabinol] is more efficacious than antiemetics such as prochloperazine, metoclopramide, and domperidone, although side effects of drowsiness and dizziness were common**" (p. 11).

Appetite in Anorexic or Cachectic Cancer Patients

Of the nine reviews identified with the current search strategy, only one reported on cannabis use and the stimulation of appetite among anorexic or cachectic cancer patients. This scoping review conducted by **Peng et al. (2016)** was included as characteristics of a systematic review were demonstrated: specifically, the study authors searched multiple electronic databases, provided a list of the search terms used, and presented a flow diagram illustrating the study selection process. In total, eight studies published from 1990 to 2015 were included in the qualitative synthesis. The study findings demonstrate that, "[s]mall studies (n = 6) suggest [a] positive correlation between tetrohydrocannabinol (THC) and

appetite whereas large clinical trials (n = 2) suggest otherwise" (p.435). Based on this review, results are inconsistent between studies of small and large sample sizes; therefore**, the effect of cannabis on appetite stimulation is unclear**. However, it is important to note that the treatment status of studies included in this review varied from active treatment, unclear treatment status, and a possible mix of both.

Original Studies

Following the evaluation of full-text articles, **three primary studies** were identified as relevant and included in the current review. Research findings from these studies are described below, and data abstraction tables for the corresponding studies can be found in Appendix 4.

Overall Findings from Original Studies

Based on the primary studies included in this review, there is insufficient evidence to support a finding of therapeutic benefits of cannabis use during active cancer treatment. Outcomes assessed in the three studies were either nonsignificant between groups or worse for marijuana users than for nonusers. Furthermore, there were inconsistent observations for several outcomes addressed in different studies; in particular, pain, nausea, and a lack of appetite were significantly worse among marijuana users in one study, but nonsignificant differences were also observed for similar outcomes in the other studies. Overall, as recent primary studies investigating the therapeutic benefits of cannabis are scarce, more research is critical before any definitive conclusions are made on the study outcomes discussed.

Saadeh et al. (2018)

Saadeh et al. (2018) conducted a study consisting of 175 cancer patients, aged 20 to 86 years, who were undergoing **intravenous and/or oral chemotherapy**. Users of marijuana within the last 30 days were identified using a questionnaire, and included various possible administration routes, such as joints, electronic devices, edibles, water pipes, and more. The outcomes of interest were evaluated using the Edmonton Symptom Assessment Scale and compared between users and nonusers of marijuana. **No significant differences between groups at p<0.05 were reported for tiredness, drowsiness, depression, and overall wellbeing**; **however, pain, nausea, lack of appetite, and anxiety were found to be worse among marijuana users than nonusers**.

Côté et al. (2016)

Côté et al. (2016) reported on a randomized double-blind placebo-controlled trial conducted in Canada, which consisted of patients with **head and neck cancer**, aged 18 to 80 years, who were undergoing **radiotherapy, postoperative radiotherapy, radiochemotherapy, or postoperative radiochemotherapy**. Of the 56 patients randomized to either the Nabilone (treatment) group or the placebo group, only 32 study participants remained by the seventh week. The study outcomes were assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, the EORTC QLQ-H&N35, a visual analog scale, and several questionnaires. **No significant differences between groups** at p<0.05 were reported for the outcomes investigated, including **quality of life improvement, pain, antalgic medication use, time needed for a 20% pain increase, appetite, weight fluctuation, feeding tube requirement, nausea, anti-emetic medication use, sleep, and mood**.

Lynch et al. (2014)

Lynch et al. (2014) conducted a double-blind, placebo-controlled, crossover pilot trial consisting of patients suffering from **neuropathic pain** for three months **following chemotherapy**. A total of 18 study participants were first randomized to receive either Nabiximols, an oral mucosal spray, or the placebo, and a two-week washout phase was allocated between study medications to prevent a carry over of effects; by the end of the study, only 16 patients remained. Outcomes were assessed using a numeric rating scale for pain intensity (NRS-PI), the Short Form-36 Health Survey (SF-36), and quantitative sensory testing (QST). **No significant difference in pain intensity was observed between the Nabiximols and placebo groups**. However, results from the responder analysis where five patients exhibited a minimum decline of 2-points in pain intensity with treatment "trended towards statistical significance". Additionally, **no significant differences were observed for all secondary outcomes assessed, including physical quality of life, mental quality of life, allodynia, and hyperalgesia**.

Overall Summary of Findings

A total of 12 articles investigating the therapeutic benefits of cannabis use during active cancer treatment were captured by the current search strategy and included in this synthesis. A need for more research reporting on the use of cannabis for CINV was identified. In general, the study findings suggest that cannabis may be more effective than placebo, and just as effective as, if not more than, other antiemetics. As well, greater effectiveness of cannabis in combination with other antiemetics has been suggested relative to placebo with antiemetics. However, among reviews evaluating the weight or certainty of evidence, reports varied from very low to strong. In addition, although some reviews reported results that suggest a possible therapeutic benefit for CINV (reflected in the general observations above), the review authors concluded unclear effectiveness of cannabis due to the low quality of evidence. As only one scoping review reporting on appetite stimulation in anorexia and cachectic cancer patients was identified, results were inconsistent between small and large studies (small, but not large, studies suggested a positive association between THC and appetite); therefore, no clear evidence was provided on the effectiveness of cannabis.

Research from primary studies reported on a variety of outcomes related to pain, mood, quality of life, and more; these study endpoints were either worse among marijuana users or not significantly different between groups. Although the included studies provide no evidence of any therapeutic benefits from cannabis use during active cancer treatment for the outcomes assessed, recent literature in this area of research was scarce; therefore, further investigations are needed before more firm conclusions can be made. The main research findings for each outcome, summarized by study type, are shown in Table 1.

Appendix 1: Search Strategy

Medline

#	Searches	Results
1	Marijuana Abuse/ or CANNABIS/ or Cannabi*.mp. or exp Cannabinoids/	40529
2	exp "Marijuana Use"/	4531
3	Medical Marijuana/	748
4	Hemp.mp.	813
5	Marihuana.mp.	1118
6	Marijuana.mp.	17850
7	Ganja.mp.	52
8	Hashish*.mp.	574
9	Bhang.mp.	30
10	Dronabinol.mp.	6717
11	Cannador.mp.	3
12	Epidiolex.mp.	19
13	Nabiximol.mp.	3
14	Sativex.mp.	173
15	Tetrahydrocannabinol.mp.	6411
16	Ajulemic acid.mp.	44
17	Marinol.mp.	85
18	Syndros.mp.	4
19	Nabilone.mp.	301
20	Cesamet.mp.	18
21	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	47680
22	exp Neoplasms/	3121661
23	neoplas*.mp.	2715423
24	cancer*.mp.	1618688
25	carcino*.mp.	962773
26	tumo?r*.mp.	1948933
27	sarcoma*.mp.	117553
28	22 or 23 or 24 or 25 or 26 or 27	4138188
29	21 and 28	2634
30	limit 29 to yr="2013 -Current"	**991**

Embase

#	Searches	Results
1	Cannabi*.mp. or cannabis addiction/ or exp "cannabis use"/ or cannabis/	70029
2	exp cannabinoid/	61950
3	exp "Cannabis (genus)"/	243
4	Hemp.mp.	1064
5	Marihuana.mp.	1705
6	Marijuana.mp.	16086
7	Ganja.mp.	79
8	Hashish*.mp.	890
9	Pot.mp.	32374
10	Bhang.mp.	54
11	Dronabinol.mp.	7359
12	Cannador.mp.	44
13	Epidiolex.mp.	82
14	Nabiximol.mp.	15
15	Sativex.mp.	642
16	Tetrahydrocannabinol.mp.	12062
17	Ajulemic acid.mp.	1013
18	Marinol.mp.	573
19	Syndros.mp.	11
20	Nabilone.mp.	1304
21	Cesamet.mp.	256
22	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21	114018
23	exp neoplasm/ or Neoplas*.mp.	4576824
24	exp neoplasm/ or Neoplas*.mp.	4576824
25	Cancer*.mp.	3313786
26	Carcino*.mp.	1508533
27	Tumo?r*.mp.	3092550
28	Sarcoma*.mp.	169162
29	23 or 24 or 25 or 26 or 27 or 28	5752577
30	22 and 29	9057
31	limit 30 to yr="2013 -Current"	4246
32	limit 31 to exclude medline journals	**710**

Cochrane Database of Systematic Reviews

#	Searches	Results
1	Cannabi*.mp.	121
2	Hemp.mp.	6
3	Marihuana.mp.	20
4	Marijuana.mp.	67
5	Ganja.mp.	3
6	Hashish*.mp.	17
7	Pot.mp.	17
8	Bhang.mp.	3
9	Dronabinol.mp.	17
10	Cannador.mp.	2
11	Epidiolex.mp.	1
12	Nabiximol.mp.	0
13	Sativex.mp.	9
14	Tetrahydrocannabinol.mp.	25
15	Ajulemic acid.mp.	0
16	Marinol.mp.	9
17	Syndros.mp.	1
18	Nabilone.mp.	15
19	Cesamet.mp.	5
20	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19	173
21	Neoplas*.mp.	1152
22	Cancer*.mp.	2518
23	Carcino*.mp.	996
24	Tumo?r*.mp.	1496
25	Sarcoma*.mp.	155
26	21 or 22 or 23 or 24 or 25	3210
27	20 and 26	57
28	limit 27 to last 7 years	43
29	limit 28 to protocols	9
30	28 not 29	**34**

Cochrane Central Register of Controlled Trials

#	Searches	Results
1	cannabi*.mp. or cannabis/ or exp cannabinoids/	2588
2	Hemp.mp.	30
3	Marihuana.mp.	112
4	Marijuana.mp. or marijuana smoking/	1510
5	Ganja.mp.	3
6	Hashish*.mp.	10
7	Pot.mp.	115
8	Bhang.mp.	1
9	Dronabinol.mp.	791
10	Cannador.mp.	1
11	Epidiolex.mp.	8
12	Nabiximol.mp.	0
13	Sativex.mp.	100
14	Tetrahydrocannabinol.mp.	725
15	Ajulemic acid.mp.	47
16	Marinol.mp.	24
17	Syndros.mp.	0
18	Nabilone.mp.	124
19	Cesamet.mp.	5
20	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19	3509
21	Neoplas*.mp. or exp Neoplasms/	77050
22	Cancer*.mp.	113419
23	Carcino*.mp.	33003
24	Tumo?r*.mp.	54022
25	Sarcoma*.mp.	1956
26	21 or 22 or 23 or 24 or 25	162544
27	20 and 26	214
28	limit 27 to yr="2013 -Current"	100
29	limit 28 to medline records	29
30	28 not 29	**71**

CINAHL

#	Searches	Results
S1	((MH "Medical Marijuana") OR (MH "Cannabis") OR "Cannabi*") OR Hemp OR Marihuana OR Marijuana OR Ganja OR Hashish* OR Pot OR Bhang OR Dronabinol OR Cannador OR Epidiolex OR Nabiximol	15,950
S2	Sativex OR Tetrahydrocannabinol OR Ajulemic acid OR Marinol OR Syndros OR Nabilone OR Cesamet	455
S3	S1 or S2	16,028
S4	(MH "Neoplasms+") OR Neoplas* OR Cancer* OR Carcino* OR Tumo#r* OR Sarcoma*	601,776
S5	S3 and S4	689
S6	S3 and S4 Limiters - Published Date: 20130101-20191231	**368**

Appendix 2. Reasons for Exclusion at Stage 2 Full Text Screening.

Table A1. Cannabis and benefits: Reasons for exclusion at stage 2 full text screening.

Reference	Reason for Exclusion
1. Abuhasira R, Schleider LB, Mechoulam R, Novack V. Epidemiological characteristics, safety and efficacy of medical cannabis in the elderly. European Journal of Internal Medicine. 2018;49:44-50.	• Study conducted in Israel
2. Bao Y, Kong X, Yang L, Liu R, Shi Z, Li W, et al. Complementary and alternative medicine for cancer pain: an overview of systematic reviews. Evidence-Based Complementary & Alternative Medicine: eCAM. 2014;2014:170396.	• Overview of systematic review and meta-analysis included a study on cannabis and chronic pain from cancer and other health conditions but not necessarily from treatment
3. Bar-Lev Schleider L, Mechoulam R, Lederman V, Hilou M, Lencovsky O, Betzalel O, et al. Prospective analysis of safety and efficacy of medical cannabis in large unselected population of patients with cancer. European Journal of Internal Medicine. 2018;49:37-43.	• Study conducted in Israel
4. Bar-Sela G, Tauber D, Mitnik I, Sheinman-Yuffe H, Bishara-Frolova T, Aharon-Peretz J. Cannabis-related cognitive impairment: a prospective evaluation of possible influences on patients with cancer during chemotherapy treatment as a pilot study. Anti-Cancer Drugs. 2019;30(1):91-7.	• Study conducted in Israel
5. Bar-Sela G, Vorobeichik M, Drawsheh S, Omer A, Goldberg V, Muller E. The medical necessity for medicinal cannabis: prospective, observational study evaluating the treatment in cancer patients on supportive or palliative care. Evidence-Based Complementary & Alternative Medicine: eCAM. 2013;2013:510392.	• Study conducted in Israel
6. Behrend SW. Cannabinoids may be therapeutic in breast cancer. Oncology Nursing Forum. 2013;40(2):191-2.	• Narrative review
7. Beuken - van Everdingen MHJ, Graeff A, Jongen JLM, Dijkstra D, Mostovaya I, Vissers KC. Pharmacological Treatment of Pain in Cancer Patients: The Role of Adjuvant Analgesics, a Systematic Review. Pain Practice. 2017;17(3):409-19.	• Systematic review included 2 studies which did not mention active cancer treatment

Reference	Reason for Exclusion
8. Blake A, Wan BA, Malek L, DeAngelis C, Diaz P, Lao N, et al. A selective review of medical cannabis in cancer pain management. Annals of Palliative Medicine. 2017;6(Suppl 2):S215-S22.	• Narrative review
9. Cabeza C, Corsi O, Perez-Cruz P. Are cannabinoids an alternative for cachexia-anorexia syndrome in patients with advanced cancer? Medwave. 2017;17(9):e7130.	• Overview of systematic review with no mention of active cancer treatment
10. CADTH. Canadian Agency for Drugs and Technologies in Health CADTH Rapid Response Reports. 2014;09:12.	• PDF unavailable
11. Darkovska-Serafimovska M, Serafimovska T, Arsova-Sarafinovska Z, Stefanoski S, Keskovski Z, Balkanov T. Pharmacotherapeutic considerations for use of cannabinoids to relieve pain in patients with malignant diseases. Journal of pain research. 2018;11:837-42.	• Systematic review included 3 studies on chronic pain from malignant diseases in terminal stages (cancer, HIV, and MS) • No mention of active cancer treatment
12. Elder JJ, Knoderer HM. Characterization of Dronabinol Usage in a Pediatric Oncology Population. The Journal of Pediatric Pharmacology & Therapeutics. 2015;20(6):462-7.	• Does not have an exposure comparison group
13. Fallon MT, Albert Lux E, McQuade R, Rossetti S, Sanchez R, Sun W, et al. Sativex oromucosal spray as adjunctive therapy in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy: two double-blind, randomized, placebo-controlled phase 3 studies. British Journal of Pain. 2017;11(3):119-33.	• No mention of active cancer treatment
14. Farzaei MH, Bahramsoltani R, Rahimi R. Phytochemicals as Adjunctive with Conventional Anticancer Therapies. Current Pharmaceutical Design. 2016;22(27):4201-18.	• PDF unavailable
15. Golan H, Fisher T, Toren A. The Role of Cannabinoids in the Treatment of Cancer in Pediatric Patients. Israel Medical Association Journal: Imaj. 2017;19(2):89-94.	• Narrative review
16. Guzman M. Cannabis for the Management of Cancer Symptoms: THC Version 2.0? Cannabis and Cannabinoid Research. 2018;3(1):117-9.	• Narrative review

Reference	Reason for Exclusion
17. Harrison AM, Heritier F, Childs BG, Bostwick JM, Dziadzko MA. Systematic Review of the Use of Phytochemicals for Management of Pain in Cancer Therapy. BioMed Research International. 2015;2015:506327.	• None of the 7 studies included in this systematic review addressed cannabis
18. Hauser W, Fitzcharles MA, Radbruch L, Petzke F. Cannabinoids in Pain Management and Palliative Medicine. Deutsches Arzteblatt International. 2017;114(38):627-34.	• Review of systematic reviews included 2 references reporting on cannabinoids for cancer pain which were either ineligible or already captured by the current search strategy
19. Häuser W, Petzke F, Fitzcharles MA, Häuser W. Efficacy, tolerability and safety of cannabis-based medicines for chronic pain management - An overview of systematic reviews. European Journal of Pain. 2018;22(3):455-70.	• Overview of systematic reviews included 3 references which were either ineligible or already captured by the current search strategy • Conclusion of overview addressed chronic pain in general, rather than cancer pain specifically
20. Huebner J, Muenstedt K, Muecke R, Micke O. The integration of methods from complementary and alternative medicine in reviews on supportive therapy in oncology and the resulting evidence. Trace Elements and Electrolytes. 2013;30(1):24-8.	• Narrative review
21. Imam A. Evidence level of integrative medicine in supportive care. Asia Pacific journal of clinical oncology. 2014;10(154).	• PDF unavailable
22. Jemos C, Villa J, Zuniga Guerrero AM, Guardamagna VA, Omodeo Sale E. The use of cannabis oil in oncological pain: Analysis of the outcomes in real practice at a cancer centre. European Journal of Hospital Pharmacy. 2018;25 (Supplement 1):A149.	• Conference abstract
23. Johnson JR, Lossignol D, Burnell-Nugent M, Fallon MT. An open-label extension study to investigate the long-term safety and tolerability of THC/CBD oromucosal spray and oromucosal THC spray in patients with terminal cancer-related pain refractory to strong opioid analgesics. Journal of Pain & Symptom Management. 2013;46(2):207-18.	• No mention of active cancer treatment
24. Kasvis P, Vigano M, Vigano A. Health-related quality of life across cancer cachexia stages. See PDF. Annals of Palliative Medicine. 2018;05:05.	• No mention of active cancer treatment

Reference	Reason for Exclusion
25. Kenyon J, Liu W, Dalgleish A. Report of Objective Clinical Responses of Cancer Patients to Pharmaceutical-grade Synthetic Cannabidiol. Anticancer Research. 2018;38(10):5831-5.	• Case report
26. Lichtman AH, Lux EA, McQuade R, Rossetti S, Sanchez R, Sun W, et al. Results of a Double-Blind, Randomized, Placebo-Controlled Study of Nabiximols Oromucosal Spray as an Adjunctive Therapy in Advanced Cancer Patients with Chronic Uncontrolled Pain. Journal of Pain & Symptom Management. 2018;55(2):179-88.e1.	• No mention of active cancer treatment
27. Lobos Urbina D, Pena Duran J. Are cannabinoids effective for treatment of pain in patients with active cancer? Medwave. 2016;16 Suppl 3:e6539.	• Review of systematic reviews with no mention of active cancer treatment
28. Marks DH, Friedman A. The Therapeutic Potential of Cannabinoids in Dermatology. Skin Therapy Letter. 2018;23(6):1-5.	• Narrative review
29. Mousa A, Petrovic M, Laszlo S, Fleshner N. Is there a therapeutic role for cannabis in advanced prostate cancer? Exploring the patterns and predictors of use among men receiving androgen-deprivation therapy. Canadian Urological Association Journal. 2018;12 (6 Supplement 2):S126.	• Conference abstract
30. Mucke M, Phillips T, Radbruch L, Petzke F, Hauser W. Cannabis-based medicines for chronic neuropathic pain in adults. Cochrane Database of Systematic Reviews. 2018(3).	• Systematic review included a study on chemotherapy-induced neuropathic pain which was already captured by the current search strategy
31. Mucke M, Weier M, Carter C, Copeland J, Degenhardt L, Cuhls H, et al. Systematic review and meta-analysis of cannabinoids in palliative medicine. Journal of Cachexia, Sarcopenia and Muscle. 2018;9(2):220-34.	• Systematic review does not distinguish between active and non-active cancer treatment
32. Murff HJ. Review: Weak evidence of benefits of cannabis for chronic neuropathic pain; moderate to weak evidence of adverse effects. ACP Journal Club. 2017;167(12):1-.	• Overview of one systematic review which focused on chronic neuropathic pain from several diseases including cancer • No mention of active cancer treatment
33. Nalley C. Management of Chemotherapy-induced Nausea & Vomiting. Oncology Times. 2017;39(23):33-43.	• Conference summary

Reference	Reason for Exclusion
34. Parmar JR, Forrest BD, Freeman RA. Medical marijuana patient counseling points for health care professionals based on trends in the medical uses, efficacy, and adverse effects of cannabis-based pharmaceutical drugs. Research In Social & Administrative Pharmacy. 2016;12(4):638-54.	• Narrative review
35. Polito S, Dupuis LL, Sung L, Patel P, Ning W, Khanna M. Nabilone for prevention of acute chemotherapy-induced nausea and vomiting in children: A single centre retrospective review. Canadian Journal of Hospital Pharmacy. 2017;70 (1):67.	• Conference abstract
36. Rocha FC, Dos Santos Junior JG, Stefano SC, da Silveira DX. Systematic review of the literature on clinical and experimental trials on the antitumor effects of cannabinoids in gliomas. Journal of Neuro-Oncology. 2014;116(1):11-24.	• Systematic review included one human study which was ineligible as it was published in 2006; all other studies were experimental
37. Santana TA, Trufelli DC, Matos LL, Cruz FM, Del Giglio A. Meta-analysis of adjunctive non-NK1 receptor antagonist medications for the control of acute and delayed chemotherapy-induced nausea and vomiting. Supportive Care in Cancer. 2015;23(1):213-22.	• Systematic review included a study on cannabinoids but was ineligible as it was published in 2007
38. Schroder S, Beckmann K, Franconi G, Meyer-Hamme G, Friedemann T, Greten HJ, et al. Can medical herbs stimulate regeneration or neuroprotection and treat neuropathic pain in chemotherapy-induced peripheral neuropathy? Evidence-Based Complementary & Alternative Medicine: eCAM. 2013;2013:423713.	• Systematic review included one study on cannabis in a rat model
39. Shin S, Mitchell C, Mannion K, Smolyn J, Meghani SH. An Integrated Review of Cannabis and Cannabinoids in Adult Oncologic Pain Management. Pain Management Nursing. 2018;06:06.	• Systematic review reported on cancer pain not necessarily associated with active cancer treatment. • Included a study on chemotherapy-induced neuropathic pain which was already captured by the current search strategy
40. Tateo S. State of the evidence: Cannabinoids and cancer pain-A systematic review. Journal of the American Association of Nurse Practitioners. 2017;29(2):94-103.	• Review included one study on chemotherapy associated pain which was already captured by the current search strategy

Reference	Reason for Exclusion
41. Tringale KR, Shi Y, Hattangadi JA. Marijuana Utilization in Cancer Patients: A Comprehensive Analysis of National Health and Nutrition Examination Survey Data from 2005-2014. International Journal of Radiation Oncology, Biology, Physics. 2017;99:S11-S.	• Conference abstract
42. Tsang CC, Giudice MG. Nabilone for the Management of Pain. Pharmacotherapy:The Journal of Human Pharmacology & Drug Therapy. 2016;36(3):273-86.	• Review focused on cancer and non-cancer pain. The section on cancer pain only discussed one study which does not mention active cancer treatment and was published in 2008
43. Turcott JG, Del Rocio Guillen Nunez M, Flores-Estrada D, Onate-Ocana LF, Zatarain-Barron ZL, Barron F, et al. The effect of nabilone on appetite, nutritional status, and quality of life in lung cancer patients: a randomized, double-blind clinical trial. Supportive Care in Cancer. 2018;26(9):3029-38.	• Study conducted in Mexico
44. van den Beuken-van Everdingen MH, de Graeff A, Jongen JL, Dijkstra D, Mostovaya I, Vissers KC, et al. Pharmacological Treatment of Pain in Cancer Patients: The Role of Adjuvant Analgesics, a Systematic Review. Pain Practice. 2017;17(3):409-19.	• Systematic review included only 2 studies related to cannabis and were either ineligible or already captured by the current search strategy
45. van den Elsen GA, Ahmed AI, Lammers M, Kramers C, Verkes RJ, van der Marck MA, et al. Efficacy and safety of medical cannabinoids in older subjects: a systematic review. Ageing research reviews. 2014;14:56-64.	• Systematic review included one study on chemotherapy induced nausea and vomiting but was ineligible as it was published in 1982
46. Welliver M. CANNABINOID AGONISTS FOR NAUSEA AND VOMITING. Gastroenterology Nursing. 2016;39(2):137-8.	• Narrative review
47. Wilkie G, Sakr B, Rizack T. Medical Marijuana Use in Oncology. JAMA Oncology. 2016;2(5):670-5.	• Narrative review
48. Zaki P, Blake A, Wolt A, Chan S, Zhang L, Wan A, et al. The use of medical cannabis in cancer patients. Journal of Pain Management. 2017;10(4):353-62.	• No mention of active cancer treatment
49. Zhang H, Xie M, Archibald SD, Jackson BS, Gupta MK. Association of Marijuana Use With Psychosocial and Quality of Life Outcomes Among Patients With Head and Neck Cancer. JAMA Otolaryngology-- Head & Neck Surgery. 2018;144(11):1017-22.	• Outcome assessed prior to treatment

Appendix 3: List of Included Studies

Semi-Systematic Reviews, Systematic Reviews, and Overviews of Systematic Reviews

1. Allan GM, Finley CR, Ton J, Perry D, Ramji J, Crawford K, et al. Systematic review of systematic reviews for medical cannabinoids: Pain, nausea and vomiting, spasticity, and harms. Canadian family physician Medecin de famille canadien. 2018;64(2):e78-e94.
2. Morales M, Corsi O, Pena J. Are cannabinoids effective for the management of chemotherapy induced nausea and vomiting? Medwave. 2017;17(9):e7119.
3. NASEM. The National Academies of Sciences, Engineering and Medicine. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. 2017.
4. Peng M, Khaiser M, Ahrari S, Pasetka M, DeAngelis C. Medical marijuana as a therapeutic option for cancer anorexia and cachexia: A scoping review of current evidence. Journal of Pain Management. 2016;9(4):435-47.
5. Phillips RS, Friend AJ, Gibson F, Houghton E, Gopaul S, Craig JV, et al. Antiemetic medication for prevention and treatment of chemotherapy-induced nausea and vomiting in childhood. Cochrane Database of Systematic Reviews. 2016;2:CD007786.
6. Schussel V, Kenzo L, Santos A, Bueno J, Yoshimura E, de Oliveira Cruz Latorraca C, et al. Cannabinoids for nausea and vomiting related to chemotherapy: Overview of systematic reviews. Phytotherapy Research. 2018;32(4):567-76.
7. Smith LA, Azariah F, Lavender VT, Stoner NS, Bettiol S. Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. Cochrane Database of Systematic Reviews. 2015(11):CD009464.
8. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, et al. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. JAMA. 2015;313(24):2456-73.
9. Wong SS, Wilens TE. Medical Cannabinoids in Children and Adolescents: A Systematic Review. Pediatrics. 2017;140(5):1-16.

Original Studies

1. Cote M, Trudel M, Wang C, Fortin A. Improving Quality of Life With Nabilone During Radiotherapy Treatments for Head and Neck Cancers: A Randomized Double-Blind Placebo-Controlled Trial. Annals of Otology, Rhinology & Laryngology. 2016;125(4):317-24.
2. Lynch ME, Cesar-Rittenberg P, Hohmann AG. A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. Journal of Pain & Symptom Management. 2014;47(1):166-73.
3. Saadeh CE, Rustem DR. Medical Marijuana Use in a Community Cancer Center. Journal of oncology practice/American Society of Clinical Oncology. 2018;14(9):e566-e78.

Appendix 4: Tabular Summaries of Included Studies

Semi-Systematic Reviews, Systematic Reviews, and Overviews of Systematic Reviews

Table A2. Cannabis and benefits: Data abstraction table for systematic reviews, overviews of systematic reviews, and quasi-systematic reviews.

Reference [Article Type]	Objective and Health Endpoint	Comprehensiveness	Meta-analysis	Results	Authors' Reported Conclusions and Limitations	Comments
Schussel, 2018 [Overview of Systematic Reviews]	**Objective** • "to present the findings and to conduct a critical appraisal of SRs [systematic reviews] focusing on the effects of cannabinoids as a treatment for nausea and vomiting in cancer patients during chemotherapy" (p. 567) **Health Endpoints** • Nausea and vomiting from chemotherapy	**Search Method** • Electronic databases searched include EMBASE, PEDro, CINAHL, Cochrane Database of Systematic Reviews, LILACS, Medline and PsycINFO **Studies Included** • N = 5 systematic reviews from 2001 – 2015	• No	• "The included SRs concluded that cannabinoids were superior than placebo and, in general, similar to standard antiemetics alone or in combination. Patient reported outcomes indicate that patients tend to prefer cannabinoids over placebo and other antiemetics, however, cannabinoids had a higher rate of adverse events when compared with traditional antiemetics." (p. 571)	**Authors' Reported Conclusions** • "cannabinoids were effective and superior to placebo to treat CINV. Although adverse events are more frequent among patients treated with cannabinoids when compared with other antiemetics, more participants preferred cannabinoids over other antiemetics. This overview demonstrates the need for future studies to evaluate the effectiveness and safety of cannabinoids for treating CINV." (p. 575 – 576) **Authors' Reported Limitations** • "this study did not retrieve data directly from published or unpublished clinical trials; instead, it collected data from published SRs. Therefore, we were compelled to rely on the information reported by the authors' review on matters such as the description of interventions and the portrayal of outcomes." (p. 575) • "the five included SRs are not independent given the significant overlap of primary studies included in them. In	• Included systematic reviews were of randomized controlled trials

Reference [Article Type]	Objective and Health Endpoint	Comprehensiveness	Meta-analysis	Results	Authors' Reported Conclusions and Limitations	Comments
					total, 37 primary studies… from the five SRs were included for analyses in this overview. Seven studies were analyzed by only one SR, and 30 were "double-counted." (p. 575) • "The main limitation of this study is related to the methodological quality of the included SRs, rather than to the methodological issues in this overview." (p. 575)	
Whiting, 2015 [Systematic Review and Meta-Analysis]	**Objective** • "To conduct a systematic review of the benefits and adverse events (AEs) of cannabinoids." (p. 2456) **Health Endpoints** • Nausea and vomiting from chemotherapy	**Search Methods** • "Twenty-eight databases and gray literature sources were searched from inception to April 2015 without language restriction …The search strategy was peer reviewed by a second information specialist. Reference lists of included studies were screened." (p. 2457) **Studies Included** • N = 28 studies on nausea and vomiting from chemotherapy	• Yes	• "All studies suggested a greater benefit of cannabinoids compared with both active comparators and placebo, but these did not reach statistical significance in all studies." (p. 2459) • "The average number of patients showing a complete nausea and vomiting response was greater with cannabinoids (dronabinol or nabiximols) than placebo (OR, 3.82 [95% CI, 1.55-9.42]; 3 trials). There was no evidence of heterogeneity for this analysis (I2 = 0%) and results were similar for both dronabinol and nabiximols." (p. 2459 – 2460)	**Authors' Reported Conclusions** • "There was low-quality evidence suggesting that cannabinoids were associated with improvements in nausea and vomiting due to chemotherapy… Cannabinoids were associated with an increased risk of short-term AEs." (p. 2468) **Authors' Reported Limitations** • "We used the Cochrane risk of bias tool to assess the included RCTs. This highlighted a number of methodological weaknesses in the included trials including failure to appropriately handle withdrawals, selective outcome reporting, and inadequate description of methods of randomization, allocation concealment, and blinding." (p. 2467) • "The data analysis was complicated by a number of issues. The included studies	• Systematic review reported on chronic pain; however, included studies also focused on conditions other than chemotherapy induced pain, including neuropathic pain, cancer pain, fibromyalgia, and so on.

Reference [Article Type]	Objective and Health Endpoint	Comprehensiveness	Meta-analysis	Results	Authors' Reported Conclusions and Limitations	Comments
					used a large variety of measures to evaluate outcomes, and even very similar outcomes were often assessed using different measures. Furthermore, a wide range of time points were reported in the included trials, which limited the applicability of the findings of these studies." (p. 2467) • "The majority of the studies were 2-group trials with a placebo control group; however, some studies included active comparisons and multiple groups comparing more than 1 form of cannabinoid, different doses of cannabinoids, or active and placebo comparator groups. This necessitated selecting a single result from each trial to contribute to the meta-analysis to avoid double counting of studies." (p. 2467) • "Studies evaluated various forms of cannabis administered via various routes… and active comparators differed across trials. These differences in form, combined with the variety of outcome measures and the broad indication groupings considered by this review, resulted in a very heterogeneous set of included studies, which meant that meta-analysis was not always possible or appropriate." (p. 2467)	

Reference [Article Type]	Objective and Health Endpoint	Comprehensiveness	Meta-analysis	Results	Authors' Reported Conclusions and Limitations	Comments
					• "Many studies reported insufficient information to allow meta-analysis… or no information on the analysis performed." (p. 2467) • "A further difficulty with the continuous data were that even for the same outcomes, some studies reported results as difference between groups at follow-up and others reported results for difference in change from baseline. As advised by the Cochrane Handbook for Systematic Reviews of Interventions, we combined both types of data when estimating summary mean differences." (p. 2467) • "A potential problem with RCTs using crossover designs is the possible unblinding due to strong treatment or AEs. Additionally, studies of this design were rarely analyzed appropriately and none reported the required data accounting for their crossover design to permit appropriate inclusion in meta-analyses. Primary analyses were therefore based on parallel-group studies, with crossover trials included as sensitivity analyses." (p. 2467)	
Wong, 2017 [Systematic Review]	**Objective** • "To systematically review published reports to identify	**Search Methods** • "Medline, PubMed, and the Cumulative Index to Nursing and	• No	• "Of the double-blind RCTs (n = 5), all reported statistically significant postintervention reductions in the primary	**Authors' Reported Conclusions** • "Although several of the RCTs investigating CINV date back to the 1980s, there is quality	• Systematic review also included studies focusing on conditions other

Reference [Article Type]	Objective and Health Endpoint	Comprehensiveness	Meta-analysis	Results	Authors' Reported Conclusions and Limitations	Comments
	the evidence base of cannabinoids as a medical treatment in children and adolescents." (p. 1) **Health Endpoints** • Chemotherapy-induced nausea and vomiting (CINV)	Allied Health Literature were searched for studies published from 1948 to 2017 and indexed by May 2017 …" (p. 3) **Studies Included** • N = 22 studies (21 articles) in total • N = 6 studies on CINV		outcomes of CINV (n = 4)... Although the remaining reports suggested that cannabinoids were associated with improvements in CINV (n = 2)… the publications were not designed to evaluate the statistical significance of outcomes." (p. 11)	evidence that cannabinoids are effective as an antiemetic in children undergoing chemotherapy. Of note, all 6 studies used a THC cannabinoid, including δ-8-THC, δ-9-THC, dronabinol, and nabilone. The studies demonstrate that THC is more efficacious than antiemetics such as prochloperazine, metoclopramide, and domperidone, although side effects of drowsiness and dizziness were common." (p. 11) **Authors' Reported Limitations** • "between-study heterogeneity in the studied cannabinoid form and dosage (ie, CBD and THC content), indication, and ages of the sample." (p. 12) • "The sample sizes in many studies were small…" (p. 12) • "17 of the 22 studies lacked a control group, and 16 of the 22 studies were not designed to test the statistical significance of changes in outcome measures." (p. 12) • "most studies lacked long-term follow-up to test for potential adverse neurocognitive and psychiatric side effects that have been demonstrated in recreational cannabis studies" (p. 12)	than CINV, including epilepsy, neuropathic pain, posttraumatic stress disorder, spasticity, and Tourette syndrome

Reference [Article Type]	Objective and Health Endpoint	Comprehensiveness	Meta-analysis	Results	Authors' Reported Conclusions and Limitations	Comments
Morales, 2017 [Structured Summary]	**Objective** • To assess "the effect of cannabinoids against placebo in patients under an antiemetic regime, reporting the control of nausea and vomiting during the intervention period" **Health Endpoints** • Nausea and vomiting from chemotherapy	**Search Methods** • "we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies." (Methods) **Studies Included** • N = 4 trials (or 8 references)	• Yes	**Nausea and vomiting control among cannabinoids with standard antiemetic therapy vs. Placebo with standard antiemetic therapy** • Risk Ratio (95% CI) = 1.92 (1.26, 2.91)	**Authors' Reported Conclusions** • "At present, given that the certainty of the evidence is very low, it is unclear whether the addition of cannabinoids to standard antiemetic regimes benefits patients with chemotherapy induced nausea and vomiting. Cannabinoids probably increase adverse effects substantively." (Results and Conclusions) **Authors' Reported Limitations** • "Partial response outcomes were not included due to the high variability of the scales used across different studies in order to quantify the severity of nausea and vomiting." • "Unfortunately, many trials do not report the outcome of interest or only report partial control of symptoms, which limits the number of patients that can be included in our analysis and consequently lowers the certainty of the existing evidence in this matter." • "The identified systematic reviews had important limitations regarding the presented data on the emetogenic potential and administration regime of cannabinoids."	• Structured summary has characteristics of a systematic review

Reference [Article Type]	Objective and Health Endpoint	Comprehensiveness	Meta-analysis	Results	Authors' Reported Conclusions and Limitations	Comments
Phillips, 2016 [Systematic Review]	**Objective** • "To assess the effectiveness and adverse events of pharmacological interventions in controlling anticipatory, acute, and delayed nausea and vomiting in children and young people (aged less than 18 years) about to receive or receiving chemotherapy." (p. 1) **Health Endpoints** • Nausea and vomiting from chemotherapy	**Search Methods** • Electronic databases searched from inception to December 16th /17th, 2014, and include the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, LILACS, and PsycINFO • Also searched conference proceedings, for ongoing clinical trials, as well as references of systematic reviews and included studies **Studies Included** • N = 34 trials in total • N = 4 studies on cannabinoids	• Yes	• "Four studies compared cannabinoids with alternative antiemetics … [and] demonstrate markedly different results" (p. 12)	**Authors' Reported Conclusions** • "Cannabinoids are probably effective, but produce high levels of side effects, which may be experienced as adverse by some patients, but not by others." (p. 15) **Authors' Reported Limitations** • "The lack of adequate numbers of studies undertaking similar comparisons limits any interpretation of the threats to randomization that were identified." (p. 14) • "The outcomes reported were largely related to emesis, rather than the more patient-relevant and often more distressing experience of nausea. Where nausea was reported, it was done without the use of validated symptom scales. Nausea, assessed through self report, is particularly difficult and complex to assess. Children, certainly the very young, may not have the language skills to describe their experience, or understand what they are being asked to describe, and this may in part explain the focus on vomiting." (p. 14) • "We cannot clearly define a route, schedule, or dose of maximal efficiency of any antiemetic medication from this review." (p. 15)	• Pooled analysis not conducted for cannabinoids

Reference [Article Type]	Objective and Health Endpoint	Comprehensiveness	Meta-analysis	Results	Authors' Reported Conclusions and Limitations	Comments
					• "This review has very few trials from which to assess the effects of publication bias, or make firm conclusions. As such, it is relatively 'unstable', as a few further trials addressing one specific issue may tip the clinical conclusion in an alternative direction." (p. 15)	
Allan, 2018 [Systematic Review of Systematic Reviews]	**Objective** • "To determine the effects of medical cannabinoids on pain, spasticity, and nausea and vomiting, and to identify adverse events." (p. e78) **Health Endpoints** • Nausea and Vomiting from Chemotherapy	**Search Methods** • Searched MEDLINE (1946 – April 2017), Cochrane (May 2017), and references of included studies • Search restrictions include systematic reviews and English language **Studies Included** • N = 31 systematic reviews in total • N = 5 systematic reviews on nausea and vomiting from chemotherapy	• Yes	**Control of nausea and vomiting from chemotherapy** • <u>Medical cannabinoid vs. placebo - 7 randomized controlled trials (RCTs)</u> RR: 3.60 (95% CI: 2.55, 5.09) • <u>Medical cannabinoid vs. other antiemetic (neuroleptics) – 14 RCTs</u> RR: 1.85 (95% CI: 1.18, 2.91) **Sensitivity Analyses** • Conducted due to high heterogeneity for comparison between cannabinoids and neuroleptics. However, "[a]nalyses of type of cannabinoid and study size subgroups did not resolve the heterogeneity, and there were no differences between subgroups." (p. e85)	**Authors' Reported Conclusions** • "There is reasonable evidence that cannabinoids improve nausea and vomiting after chemotherapy… Adverse effects are very common, meaning that benefits would need to be considerable to warrant trials of therapy." (p. e93) **Authors' Reported Limitations** • "Many of the weaknesses of the included studies… are likely the greatest weaknesses of this study. With our meta-analyses, like others, combining weak studies does not strengthen the quality of the original research, and this needs to be considered when interpreting the results." (p. e93) • "We did not pull all individual RCTs identified in the included systematic reviews and therefore might have missed elements of the RCTs, particularly if the details were not accurately recorded in the included systematic reviews." (p. e93)	• Included systematic reviews with at least 2 RCTs • This systematic review of systematic reviews reported on pain; however, included studies also focused on pain from reasons other than cancer, including multiple sclerosis, palliative care, neuropathic, and so on.

Reference [Article Type]	Objective and Health Endpoint	Comprehensiveness	Meta-analysis	Results	Authors' Reported Conclusions and Limitations	Comments
					• "Because our risk-of-bias evaluation was on systematic reviews, we could not perform a sensitivity analysis based on the quality of included RCTs." (p. e93) • "we report only limited results from descriptive systematic reviews. Given that RCT authors frequently selectively report outcomes and systematic review authors might in turn also selectively report those outcomes, we believed that any reporting of individual RCT outcomes would only compound these potential biases. However, in doing so we might have missed potentially relevant content." (p. e93)	
Smith, 2015 [Systematic Review]	**Objective** • "To evaluate the effectiveness and tolerability of cannabis-based medications for chemotherapy-induced nausea and vomiting in adults with cancer." (p. 1) **Health Endpoints** • Nausea and vomiting from chemotherapy	**Search Methods** • "We identified studies by searching the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, PsycINFO and LILACS from inception to January 2015. We also searched reference lists of reviews and included studies." (p. 1) **Studies Included**	• Yes	**Cannabinoids vs. Placebo** • Complete Absence of Nausea (2 Trials) RR: 2.0 (95% CI: 0.19, 21) • Complete Absence of Vomiting (3 Trials) RR: 5.7 (95% CI: 2.6, 13) • Complete Absence of Nausea and Vomiting (3 Trials) RR: 2.9 (95% CI: 1.8, 4.7) **Cannabinoid vs. Prochlorperazine** • Absence of Nausea (5 Trials) RR: 1.5 (95% CI: 0.67, 3.2) • Absence of Vomiting (4 Trials) RR: 1.1 (95% CI: 0.86, 1.4) • Absence of Nausea and Vomiting (4 Trials) RR: 2.0 (95% CI: 0.74, 5.4)	**Authors' Reported Conclusions** • "The included trials showed that cannabinoids were more effective than placebo and were similar to conventional anti-emetics for treating chemotherapy-induced nausea and vomiting." (p. 22) **Authors' Reported Limitations** • "it is possible that the trials were at risk of observer bias, due to the characteristic adverse effect profile of cannabinoids." (p. 22) • "The majority of the trials were unclear with respect to methods used to generate randomisation sequence and whether randomisation was	• None

Reference [Article Type]	Objective and Health Endpoint	Comprehensiveness	Meta-analysis	Results	Authors' Reported Conclusions and Limitations	Comments
		• **N** = 23 randomized controlled trials (RCTs)		**Cannabinoid with other anti-emetic agent vs. other anti-emetic agent monotherapy** • Absence of Nausea RR: 11 (95% CI: 0.61, 182) • Absence of Vomiting RR: 1.5 (95% CI: 0.69, 3.1) • Absence of Nausea and Vomiting RR: 1.6 (95% CI: 0.68, 3.6)	concealed, so may be at risk of selection bias." (p. 22) • "a large proportion of the trials were of cross-over design, and we were unable to adjust the data to take into account the paired data, which will result in narrower CIs around effect estimates." (p. 22) • "Another weakness was high risk of bias from attrition from the trials. This was largely due to participants being excluded from analyses in the cross-over trials if they did not complete all cross-over periods." (p. 22) • "The quality of the evidence for most outcomes was generally of low quality. The main reasons were due to risk of bias, imprecise results due to few studies or few events (or both) and unexplained heterogeneity." (p. 22) • "Some trials only reported episodes of nausea and vomiting, rather than the proportion of participants with no nausea and vomiting, therefore we did not include these results in meta-analyses." (p. 23) • We also analysed dichotomous outcomes from the cross-over studies without adjusting the analyses, which potentially gives rise to more precise (narrower CIs) estimates of effect." (p. 23)	

Reference [Article Type]	Objective and Health Endpoint	Comprehensiveness	Meta-analysis	Results	Authors' Reported Conclusions and Limitations	Comments
					• "In order to avoid publication bias, we searched for ongoing trials in clinical trial registry databases; however, we identified no further trials." (p. 23)	
NASEM, 2017	**Objective** • "The committee was tasked with conducting a comprehensive review of the current evidence regarding the health effects of using cannabis and cannabis-derived products." (p. xvii) **Health Endpoints** • Nausea and Vomiting from Chemotherapy	**Search Methods** • Databases searched include Medline, Embase, the Cochrane Database of Systematic Reviews, and PsycINFO from January 1, 1999 to August 1, 2016 • Primacy was given to recent systematic reviews (published since 2011) and high-quality primary research that was published after the most recent systematic review. • Only reviews of good or fair quality were considered. • Where no systematic review existed, primary research for the entire period was reviewed **Studies Included** • N = 3 Systematic reviews and 1 primary study	• No	• "There is conclusive evidence that oral cannabinoids are effective antiemetics in the treatment of chemotherapy-induced nausea and vomiting." (p. 94)	**Authors' Reported Conclusions** • See results **Authors' Reported Limitations** • "the committee was not tasked to conduct a systematic review, which would have required a lengthy and robust series of processes." (p. 417) • "…there is a possibility that some literature was missed because of the practical steps taken to narrow a very large literature to one that was manageable within the time frame available to the committee." (p. 6)	• Weight-of-Evidence evaluation • Reported on chronic pain from several conditions, including neuropathy, chemotherapy-induced pain, multiple sclerosis, and so on • Reported on a systematic review on cancer that was captured by the current search but found ineligible
Peng, 2016	**Objective**	**Search Methods**	• No	• "Small studies (n = 6) suggest positive correlation between	**Authors' Reported Conclusions**	• Scoping review with characteristics

Reference [Article Type]	Objective and Health Endpoint	Comprehensiveness	Meta-analysis	Results	Authors' Reported Conclusions and Limitations	Comments
[Scoping Review]	• "to (1) explore the therapeutic use of cannabis in improving appetite and related metabolic processes in cancer patients, (2) investigate potential reasons for inconsistency amongst available studies, and (3) examine implications of available evidence on current practice." (p. 437) **Health Endpoints** • Appetite	• Databases searched include Ovid MEDLINE, Ovid Embase Classic, Cochrane Central Register of Controlled Trials, and PsycINFO from May 1990 to July 2016 • Search restrictions include humans and English language • Key articles and reviews were also searched for references **Studies Included** • N = 8		tetrohydrocannabinol (THC) and appetite whereas large clinical trials (n = 2) suggest otherwise." (p. 435)	• "Despite anecdotal observations suggesting the potential for cannabis to stimulate appetite, existing studies use various methods of administration and dosing, making it difficult to draw meaningful conclusions. Weak methodological choices in smaller studies have resulted in a high degree of variability in results. Further clinical trials that are well designed and carefully executed are essential to clearly define the role of these agents as appetite stimulants." (p. 435) **Authors' Reported Limitations** • "a detailed data extraction and quantitative synthesis was not performed." (p. 445) • "there is no guarantee that all cannabis interventions in CACS [cancer anorexia cachexia syndrome] were retrieved as a result of the limitation using MeSH terms. This may have contributed to the low number of results attained, and perhaps a more comprehensive search strategy could have generated further insight." (p. 445) • "Moreover, this review identified studies that used synthetic THC (dronabinol) instead of cannabis as the intervention; there may be differences in outcomes between herbal cannabis and	of a systematic review (i.e. multiple electronic databases searched, and search terms reported) • Review includes studies with active treatment, unknown active treatment status, and a possible mix of active/non-active treatment; however, conclusions do not distinguish between treatment status

Reference [Article Type]	Objective and Health Endpoint	Comprehensiveness	Meta-analysis	Results	Authors' Reported Conclusions and Limitations	Comments
					synthetic THC which could not be assessed in this study." (p. 445) • "as there is a dearth of studies in humans, future syntheses may consider including animal studies in order to increase the scope of the review and to better understand how cannabis could affect CACS." (p. 445)	

Original Studies

Table A3. Cannabis and benefits: Data abstraction table for original studies.

Study	Study Participants	Exposure	Outcome	Main Quantitative Results [Covariates Adjusted For]	Authors' Reported Conclusions and Limitations	Comments
Saadeh, 2018 Cross-sectional Study	**Study Sample** • Cancer patients (≥18 years of age) from a community cancer center, undergoing intravenous and/or oral chemotherapy **Sample Size (N) = 175** • Early-stage cancers N = 56 • Advanced-stage cancers N = 119 **Median Age in Years (range)** • 61 (20 – 86)	**Exposure** • "marijuana use within the last 30 days were considered current marijuana users" (p. e567) **Ascertainment** • Questionnaire **Use/Month; N (%)** • Once/month = 4 (12.5) • Twice/month = 1 (3.1)	**Outcome** • Pain • Tiredness • Drowsiness • Nausea • Appetite • Depression • Anxiety • Overall well-being **Ascertainment** • Edmonton Symptom Assessment Scale from 1 –	**Average Edmonton Symptom Assessment Scale score** • <u>Pain</u> Nonusers: 2.45 Users: 4.03 P: 0.003 • <u>Tiredness</u> Nonusers: 3.31 Users: 3.84 P: 0.186 • <u>Drowsiness</u> Nonusers: 2.45 Users: 2.91 P: 0.391 • <u>Nausea</u> Nonusers: 1.21 Users: 2.25 P: 0.019	**Authors' Reported Conclusions** • "Patients who used marijuana tended to rate their pain, nausea, lack of appetite, and anxiety worse on a scale of 1 to 10 than patients who did not use marijuana... No statistical differences were seen in other symptoms that patients were asked to rate (tiredness, drowsiness, depression, or overall well-being)." (p. e568) **Authors' Reported Limitations** • "Patients were recruited during a fairly short period of time—8 weeks—to participate	• None

Study	Study Participants	Exposure	Outcome	Main Quantitative Results [Covariates Adjusted For]	Authors' Reported Conclusions and Limitations	Comments
	Sex; N (%) Males • 57 (32.6)	• Once/week = 2 (6.3) • 1-2 days/week = 4 (12.5) • 3-4 days/week = 5 (15.6) • 5-7 days/week = 16 (50) **Routes** (p. e570) • "Joint or cigar with marijuana in it" • "Vaporizer or other electronic device" • "Bong, water pipe, or hookah" • "Bowl or glass pipe" • "Baked or cooked or prepared in food or candy, or other edible" • "By mouth in form of an oil, capsule, or other liquid" • "Topical in form of an ointment or cream" • "Other"	10 (where 10 is the worst)	• <u>Lack of Appetite</u> Nonusers: 2.36 Users: 4.09 P: 0.008 • <u>Depression</u> Nonusers: 1.96 Users: 2.34 P: 0.302 • <u>Anxiety</u> Nonusers: 2.21 Users: 3.34 P: 0.014 • <u>Overall Well-being</u> Nonusers: 2.33 Users: 2.88 P: 0.123	in this research, which limited the sample size." (p. 557) • "Those who consented to participate in this survey may have been more biased in their responses, especially if they were marijuana users and were benefiting from marijuana use." (p. 557) • More patients who used marijuana reported pain, nausea, appetite issues, and anxiety compared with those who did not use marijuana. It is not known if these patients inherently had higher baseline scores for these symptoms and sought out marijuana use for better symptom management or if it could be argued that marijuana did not help these particular patients better control these symptoms." (p. e571) • "Statistical and clinical significance could not be determined from this study." (p. e571) • "we did not correlate the route of marijuana administration to symptom indication. The bioavailability and half-life of marijuana may differ according to whether the patient inhales or ingests the product." (p. e571) • "Surprisingly, no difference was noted between nonusers	

Study	Study Participants	Exposure	Outcome	Main Quantitative Results [Covariates Adjusted For]	Authors' Reported Conclusions and Limitations	Comments
					and users in terms of tiredness or drowsiness, an expected adverse effect associated with marijuana use. It is not known, however, what time of day marijuana was used and whether this would have affected patient adverse effects or not." (p. e571)	
Côté, 2016 Randomized Double-Blind Placebo-Controlled Trial [Canada]	**Study Sample** • Adult patients (18 – 80 years of age) with head and neck cancer recruited from the Hôtel-Dieu de Québec hospital who are undergoing treatment (radiotherapy, postoperative radiotherapy, radiochemotherapy, or postoperative radiochemotherapy) **Sample Size Randomized (N) = 56** • Nabilone = 28 • Placebo = 28 **Sample Size at Week 7** • Nabilone = 19 • Placebo = 13 **Mean Age** • Nabilone = 63.5 • Placebo = 63.8	**Exposure** • Nabilone vs. placebo **Administration** • Day prior to radiotherapy: one Nabilone pill (0.5 mg) at bedtime • During 1st week: same dose of Nabilone (0.5 mg) • During 2nd week: 2 Nabilone pills /day (0.5 mg) • 3rd week – end of radiotherapy: up to 4 Nabilone pills/day (1 mg)	**Outcome** • 15-point Improvement in global quality of life scale • Pain • Number of other antalgic medications used • Weight fluctuation • Number of days without feeding tube/ gastrostomy • Appetite • Nausea • Number of anti-emetic medication used • Nabilone toxicity **Ascertainment**	**Nabilone vs. Placebo** • <u>Quality of life improvement:</u> No significant difference (p = 0.4270) • <u>Pain based on VAS:</u> No significant difference (p = 0.6048) • <u>Antalgic medication use:</u> No significant difference (p = 0.6671) • <u>Time needed for 20% increase in pain:</u> No significant difference (p = 0.4614) • <u>Appetite:</u> No significant difference (p = 0.3295) • <u>Weight fluctuation:</u> No significant difference (p = 0.1454) • <u>Need for feeding tube:</u> No significant difference • <u>Nausea:</u> No significant difference (p = 0.7105) • <u>Anti-emetic medication use:</u> No significant difference (p = 0.6124)	**Authors' Reported Conclusions** • "Even though nabilone was not potent enough to improve patients' quality of life over placebo, we can undoubtedly conclude that nabilone's toxicity is limited and that this medication is well tolerated by patients receiving radiotherapy treatments." (p. 323) **Authors' Reported Limitations** • "Most of the dropouts (12/15) in the placebo group were receiving radiochemotherapy treatments. Since the remaining patients in the placebo group were treated mostly with radiotherapy alone (with or without surgery), it is possible that the effect of nabilone on appetite was underestimated." (p. 323) • "sample size was relatively small and from a single center, which could have prevented the detection of differences for secondary outcomes…	• 9 – 11 weeks follow-up • "Concomitant use of anti-emetics (metoclopramide only) and antalgics (only acetaminophen/ codeine, hydromorphone, or transdermal fentanyl) was permitted." (p. 318)

Study	Study Participants	Exposure	Outcome	Main Quantitative Results [Covariates Adjusted For]	Authors' Reported Conclusions and Limitations	Comments
	Sex; N Males • Nabilone = 26 • Placebo = 20		• European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 • EORTC QLQ H&N35 • Questionnaire for appetite • Questionnaire for nausea • Questionnaire for toxicity • Visual analog scale (VAS) for pain	• <u>Sleep:</u> No significant different (p = 0.4438) • <u>Mood:</u> No significant difference (p = 0.3214) • Note: "All the analyses were also carried out while adjusting for site, treatment, and tumor size." (p. 319)	considering the small number of participants, the number of secondary outcomes was large." (p. 323) • "We did not expect that such an important part of our study population would drop out of the trial before its completion; 24 patients quit, which brings a possible lost to follow-up bias." (p. 323) • "Further analyses of our study population revealed an unbalanced distribution of patients with an advanced lesion. Consequently, patients receiving combined modality treatments were unequally represented in both groups… Considering that the negative treatment repercussions on patients' well-being are cumulative when radiotherapy and chemotherapy are combined, we can suppose that patients in the control group were more affected by their treatment." (p. 323)	
Lynch, 2014 Double-Blind, Placebo-Controlled, Crossover Pilot Trial	**Study Sample** • Patients with neuropathic pain for 3 months following chemotherapy, and with an average pain intensity over a 7-day period of at least 4 on a 11-point scale.	**Exposure** • Nabiximols (oral mucosal spray) vs. Placebo **Administration** • Begin with 1 spray prior to bedtime	**Primary Outcome** • Chemotherapy-induced neuropathic pain **Secondary Outcomes**	**Mean NRS-PI Scores** • Mean pre-treatment score: 6.75 (6.17 – 7.33) <u>Mid-treatment period</u> • Active treatment score: 5.5 (4.43 – 6.57) • Placebo treatment score: 6.31 (5.58 – 7.04) <u>End of 4 weeks</u> • Active treatment score:	**Authors' Reported Conclusions** • "When examining the whole group, there was no statistically significant difference between the treatment and the placebo groups. Responder analysis nonetheless demonstrated that five participants reported a two-point or greater	• Between study medications, patients underwent a washout phase of 2-weeks • Article also reported on an extension trial which occurred

Study	Study Participants	Exposure	Outcome	Main Quantitative Results [Covariates Adjusted For]	Authors' Reported Conclusions and Limitations	Comments
	Sample Size (N) • N randomized = 18 • N completed RCT = 16 **Age in Years (SD)** • 56 (10.80) **Sex; N Male:Female** • 3:15	• Increase by 1-2 sprays/day until effective dose reached (maximum dose of 12 sprays/day) • Dose kept stable for 4 weeks; if maximum dose not effective, then a 1-week stable dose period was permitted	• Health-related quality of life: physical and mental • Allodynia and hyeralgesia **Ascertainment** • Outcome measured following 2- and 4-weeks during stable dose period • Numeric rating scale for pain intensity (NRS-PI) from 0-10 • Short Form-36 Health Survey (SF-36) for health-related quality of life • Quantitative Sensory Testing (QST)	6.00 (6.98 – 5.02) • Placebo treatment score: 6.38 (5.67 – 7.09) **Responder analysis among patients with at least a 2-point decrease in pain scores during treatment (N = 5)** • Mean baseline score: 6.00 (4.92 – 7.08) • Nabiximols: 3.40 (2.40 – 4.40) • Placebo: 5.40 (4.07 – 6.73) **Secondary outcomes (physical/mental quality of life, allodynia, and hyperalgesia)** • No statistically significant differences between groups	reduction in their pain according to NRS-PI, which trended toward statistical significance." (p. 171) • "In conclusion, this pilot trial supports that it will be worthwhile to study nabiximols in a full randomized controlled trial of chemotherapy-induced neuropathic pain. Our studies also raise the possibility that nabiximols may be useful as an adjunctive therapy for treating chemotherapy-induced neuropathic pain." (p. 172) **Authors' Reported Limitations** • "statistically underpowered small pilot trial…" (p. 171)	following completion of RCT