TITLE: Nabilone for Non-chemotherapy Associated Nausea and Weight Loss due to Medical Conditions: A Review of the Clinical Effectiveness and Guidelines

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CONTEXT AND POLICY ISSUES

Cannabis has been used medically for its antiemetic, sedative, and analgesic effects and for its ability to stimulate appetite.[1] The major psychoactive ingredient of cannabis is delta-9-tetrahydrocannabinol (THC).[1] Nabilone is a synthetic cannabinoid analog of THC[1] and is approved for use in Canada for the treatment of severe nausea and vomiting associated with chemotherapy in adults over the age of 18 years.[2] For its approved indication, nabilone (1 mg to 2 mg) is used short-term, administered the night before and one to three hours prior to chemotherapy and can be continued up to 24 hours following chemotherapy. A systematic review of randomized controlled trials (RCTs) found that 70% of patients undergoing chemotherapy who received cannabinoids had complete control of nausea compared to 57% of placebo patients (RR 1.21; 95% CI 1.03 to 1.42).[3] As well, 66% of patients had complete control of vomiting with cannabinoids compared to 36% of patients treated with placebo (RR 1.84; 95% CI 1.42 to 2.38).[3]

Nabilone exerts its therapeutic effect by acting as an agonist at the CB1 cannabinoid receptor, a receptor that has a role in the regulation of nausea and vomiting, appetite, movement, and pain.[4] As such, nabilone has the potential to be used 'off-label' for a number of conditions, for example, in the management of nausea and vomiting attributed to factors other than chemotherapy. In addition, the appetite stimulating properties of cannabinoids have been used to manage problematic or excessive weight loss secondary to medical conditions, such as AIDS and cancers.[5] This report will review the evidence of clinical effectiveness and safety of nabilone when used for the treatment of non-chemotherapy related nausea and vomiting and to manage weight loss attributed to medical conditions.

RESEARCH QUESTIONS

1. What is the clinical effectiveness and safety of nabilone for use in the treatment of non-chemotherapy associated nausea and vomiting?

2. What is the clinical effectiveness and safety of nabilone for use in the treatment of weight loss due to medical conditions?

3. What are the evidence-based guidelines regarding the use of nabilone in the treatment of non-chemotherapy associated nausea and vomiting?

4. What are the evidence-based guidelines regarding the use of nabilone in the treatment of weight loss due to medical conditions?

KEY FINDINGS

One low quality RCT, one low quality retrospective cohort study and two case reports suggest that nabilone may be effective in preventing nausea and vomiting following surgery, treating intractable vomiting associated with HIV/AIDS, and treating weight loss in patients with hepatitis C virus undergoing treatment with interferon-ribavirin. However, given the limitations of these studies, it is difficult to draw strong conclusions about the effectiveness of nabilone in these conditions. No evidence-based guidelines addressing the use of nabilone in the treatment of weight loss due to medical conditions or for the treatment of non-chemotherapy associated nausea and vomiting were identified.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including Medline, Embase, PubMed, The Cochrane Library (2014, Issue 8), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied to limit retrieval by publication type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 1982 and August 8, 2014.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications to determine if they were relevant to the review. The same reviewer evaluated the full-text publications for the final article selection into the report based upon the criteria identified in Table 1.

Table 1: Selection Criteria

Population	Adults and adolescents (Age ≥ 13 years old) with non-chemotherapy associated nausea and vomiting Adults and adolescents (Age ≥ 13 years old) with weight loss due to a medical condition (such as anorexia, HIV, etc.)
Intervention	Nabilone
Comparator	Placebo, no treatment, or active alternative treatments
Outcomes	Clinical effectiveness (e.g. reduced nausea, reduced vomiting, change in weight) Safety (adverse events, abuse and misuse) Guidelines and recommendations
Study Designs	Health technology assessments (HTA), systematic reviews (SR), meta-analyses (MA), randomized controlled trials (RCTs), non-RCTs, and guidelines.

HIV – Human Immunodeficiency Virus; HTA - Health technology assessment; MA - Meta-analysis; RCT - Randomized controlled trial;
SR - Systematic review

Exclusion Criteria

Articles were excluded if they did not meet the predefined selection criteria as outlined in Table 1 or were outside of the timeframe of the search. As well, review articles that were not based upon a systematic literature search and guidance documents or consensus statements that did not include a description of the methodology used in their development or were not clearly evidence-based were excluded from the report.

Critical Appraisal of Individual Studies

The included randomized controlled trial (RCT) and retrospective cohort study were critically appraised using the SIGN50 Checklist relevant to each study design.[6,7] Items from the checklists were considered in assessing the quality of the included literature and results of the critical appraisal are discussed narratively. Numeric scores from these tools were not calculated. Case studies were not critically appraised formally using a specific tool or instrument. The quality of these studies will be discussed in the limitations section.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 266 citations. After screening citations from the database and grey literature searches, 16 potentially relevant studies were obtained for full-text review. One RCT,[8] one retrospective cohort study[9] and two case reports[10,11] met the selection criteria and were included in the review. The PRISMA flowchart in Appendix 1 details the process of the study selection.

Summary of Study Characteristics

1. *What is the clinical effectiveness and safety of nabilone for use in the treatment of non-chemotherapy associated nausea and vomiting?*

One RCT[8] and two case reports[10,11] were identified in which nabilone was used for the treatment or prevention of nausea and vomiting unrelated to chemotherapy in inpatient settings (Appendix 2, Table 2 and Table 3). The included RCT[8] was conducted in the United Kingdom and compared the efficacy of nabilone 2 mg with 10mg of metoclopramide administered 90 minutes prior to surgery in the prevention of post-operative nausea and vomiting in 60 patients who underwent abdominal hysterectomy. Patients were followed for 24 hours post-surgery and were permitted to have prochlorperazine as a co-intervention; however actual use was not reported. Demographic characteristics of the patients were not reported. Other outcomes assessed included pain control, adverse effects, relaxation, and sedation. The two case reports, both from North America (one from the United States and one from Canada) involved male patients with AIDS who were treated with nabilone 1 mg to 2 mg twice daily to manage intractable nausea and vomiting after failure of other alternatives such as scopolamine, prochlorperazine, dimenhydrinate, and metoclopramide, or inability to tolerate these drugs.[10,11] Both patients were near end of life at the time of treatment.

2. *What is the clinical effectiveness and safety of nabilone for use in the treatment of weight loss due to medical conditions?*

One retrospective cohort study evaluated the effectiveness of the oral cannabinoids (OCs) nabilone and dronabinol in the management of weight loss, nausea, and vomiting in patients who initiated combination therapy with interferon and ribavirin for hepatitis C virus (HCV) (Appendix 2, Table 3).[9] The study was conducted in Canada and included a total of 191 patients, of which 25 were exposed to treatment with either nabilone (n=16) or dronabinol (n=9) at variable dosages, the details of which were not reported. Outcomes were compared between OC users (the 25 patients who received nabilone or dronabinol) and non-users (166 patients who were treated at the same clinic during the study period but were not given an OC). Outcomes included subjective relief of anorexia, nausea, vomiting, and insomnia, and trends in weight loss and persistence with HCV therapy. Results were reported for nabilone and dronabinol combined only.

3. *What are the evidence-based guidelines regarding the use of nabilone in the treatment of non-chemotherapy associated nausea and vomiting?*

No relevant evidence-based guidelines were identified.

4. *What are the evidence-based guidelines regarding the use of nabilone in the treatment of weight loss due to medical conditions?*

No relevant evidence-based guidelines were identified.

Summary of Critical Appraisal

Details of the critical appraisal of the included clinical studies are summarized in Appendix 3, Table 4.

1. *What is the clinical effectiveness and safety of nabilone for use in the treatment of non-chemotherapy associated nausea and vomiting?*

The included RCT[8] addressed a clearly focused research question, blinded medical staff to treatment allocation and had complete follow-up in 88% of patients overall. However, there were a number of limitations to this study, including a lack of reporting of the methods of randomization and allocation concealment. Further, it was unclear if the patients were blinded to treatment allocation, which could potentially be problematic given the subjective nature of some of the outcome variables, such as pain. Moreover, it was unclear how the blinding was maintained as the authors did not report using matching placebos or other method of masking the allocated treatment. No baseline characteristics were reported, making it unclear if the treatment groups were similar at the start of the study and it did not appear that an intention to treat analysis was carried out. As actual use of prochlorperazine was not reported, it is unclear if usage was balanced between groups and, if not, what potential confounding effect that it may have had on the observed study outcomes.

2. *What is the clinical effectiveness and safety of nabilone for use in the treatment of weight loss due to medical conditions?*

While the included retrospective cohort study had an appropriate and focused research question, the interpretation of the results and confidence in the study's findings are limited by a number of methodological issues. A greater proportion of patients who initiated treatment with OCs were white, had more advanced liver biopsy stages, had a history of drug or alcohol abuse and were more likely to have a co-infection with HCV. These baseline differences and other possible confounding variables were not accounted for in the statistical analysis and confidence intervals were not reported. A database was used to retrospectively capture OC use over a 3.5 year period. It is possible that some individuals may have had exposure to OCs from other sources not captured in the database, making misclassification on exposure possible. Further, the dose and duration of the OC regimens were not reported, thus, the actual regimen or regimens evaluated was unclear. Outcomes were not clearly defined and it was uncertain as to how some of the key patient-reported outcomes would have been captured retrospectively.

Summary of Findings

1. *What is the clinical effectiveness and safety of nabilone for use in the treatment of non-chemotherapy associated nausea and vomiting?*

The included RCT[8] found no statistical difference in the clinical effectiveness of nabilone and metoclopramide in preventing post-operative nausea (23% with nabilone versus 30% with metoclopramide; *P* > 0.05) and vomiting (15% with nabilone versus 22% with metoclopramide; *P* > 0.05) following hysterectomy (Appendix 4, Table 5). Patient ratings of nausea and vomiting using visual analog scales (VAS) were also numerically similar between groups and did not differ statistically. The authors concluded that at the dosages used (which were standard dosages for both drugs), nabilone was no more effective than metoclopramide in preventing post-operative nausea and vomiting.

The two case reports[10,11] of nabilone use in patients with HIV/AIDS who experienced intractable nausea and vomiting found rapid resolution of symptoms with treatment. In both case reports, patients had failed to respond to treatment with other antiemetic prior to nabilone use. Drowsiness[11] and pleasant hallucinations[10] were observed as side effects.[11]

2. *What is the clinical effectiveness and safety of nabilone for use in the treatment of weight loss due to medical conditions?*

In the retrospective cohort study[9] in which nabilone or dronabinol was used for the management of anorexia, nausea, and weight loss in patients with chronic HCV, weight loss stabilized with OC treatment after about one month of treatment (Appendix 4, Table 5). An average of 4.5 kg weight loss was observed prior to initiation, which was reduced to 0.5 kg following initiation. No statistical comparison was made between users and non-users of OCs. As well, a greater proportion of OC users were able to complete treatment with interferon and ribavirin, which the authors attributed to better side effect management. Subjective improvement in symptoms was reported in 64% of oral cannabinoid users. No assessment of subjective improvement in symptoms was made in non-users of OCs. The authors concluded that OCs were effective for the management of anorexia, nausea and vomiting in patients with HCV who are taking interferon and ribavirin in combination.

3. *What are the evidence-based guidelines regarding the use of nabilone in the treatment of non-chemotherapy associated nausea and vomiting?*

No relevant evidence-based guidelines were identified.

4. *What are the evidence-based guidelines regarding the use of nabilone in the treatment of weight loss due to medical conditions?*

No relevant evidence-based guidelines were identified.

Limitations

The evidence of clinical effectiveness of nabilone for the treatment of non-chemotherapy associated nausea and vomiting or weight loss due to medical conditions was sparse, limited to one RCT,[8] one retrospective cohort study[9] and two case reports.[8,10] The included RCT had a number of limitations as previously noted, which could potentially compromise its internal validity. Further, in the RCT, patients were followed for 24 hours post-surgery. As such, this study does not provide evidence of longer term safety of nabilone when used off-label to treat nausea and vomiting unrelated to chemotherapy. Moreover, in the included RCT, nabilone was used for prevention (rather than active treatment). It is unclear if similar results would be observed if nabilone was used to treat (rather than prevent) nausea and vomiting in patients following surgery or due to other underlying causes. The two case reports suggested that nabilone was effective in resolving intractable nausea and vomiting in patients with HIV/AIDS. However, it is difficult to make any inferences or draw any conclusions about treatment effect from case reports as they are quite limited in their internal and external validity. Case reports reflect the experience of single patients and are not generalizable beyond the specific patient under study. Further, as they do not have a control or comparison group, the treatment effect cannot be specifically attributed to the intervention received. Statistical analysis cannot be carried out and the impact of potential confounding factors on the observed outcome cannot be controlled or adjusted for. Moreover, the patients and investigators in the included case reports were unblinded, which can potentially lead to reporting or observer bias. Case reports are also vulnerable to placebo effects that cannot be controlled for. In both case reports, the patients were near end of life and had failed on treatment with a number of other alternatives. Thus, the context of these case reports was very specific to certain circumstances and of unclear generalizability. The included retrospective cohort also had a number of limitations (previously described) which potentially compromised the ability to make conclusions about the effectiveness of OCs in the treatment of weight loss. Further, outcome reporting in this study was generally unclear and without comparison to the non-exposed group. Moreover, outcomes were reported for nabilone and dronabinol combined. While 64% of the included patients were taking nabilone, the observed results could potentially differ for nabilone alone. It should be noted that outcome data reflected only a small group of patients (n=16) who were taking nabilone, which could limit the generalizability of the findings to a more broad population. No evidence was identified that assessed the impact of nabilone on weight loss related to medical conditions other than HCV, and no evidence-based guidelines regarding the use of nabilone in the treatment of weight loss due to medical conditions or for the treatment of non-chemotherapy associated nausea and vomiting.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

One low quality RCT and one low quality cohort study assessed the clinical effectiveness of nabilone in the treatment of non-chemotherapy associated nausea and vomiting or weight loss related to medical conditions, respectively. While both studies supported the use of nabilone for these indications, they had multiple limitations that potentially compromised their internal validity. This makes it difficult to make strong conclusions about the effectiveness of nabilone for the indications assessed. Two case reports also described the use of nabilone in patients with HIV/AIDS who had intractable nausea and vomiting and reported one resolution of symptoms with its use; however, these case reports again are limited quality and would be considered hypothesis generating for further evaluation in the clinical trial context. Overall, based on the included evidence, no conclusions about the effectiveness of nabilone for non-chemotherapy

related nausea and vomiting or weight loss due to medical conditions can be made. No evidence-based guidelines regarding the use of nabilone in the treatment of weight loss due to medical conditions or for the treatment of non-chemotherapy associated nausea and vomiting were identified.

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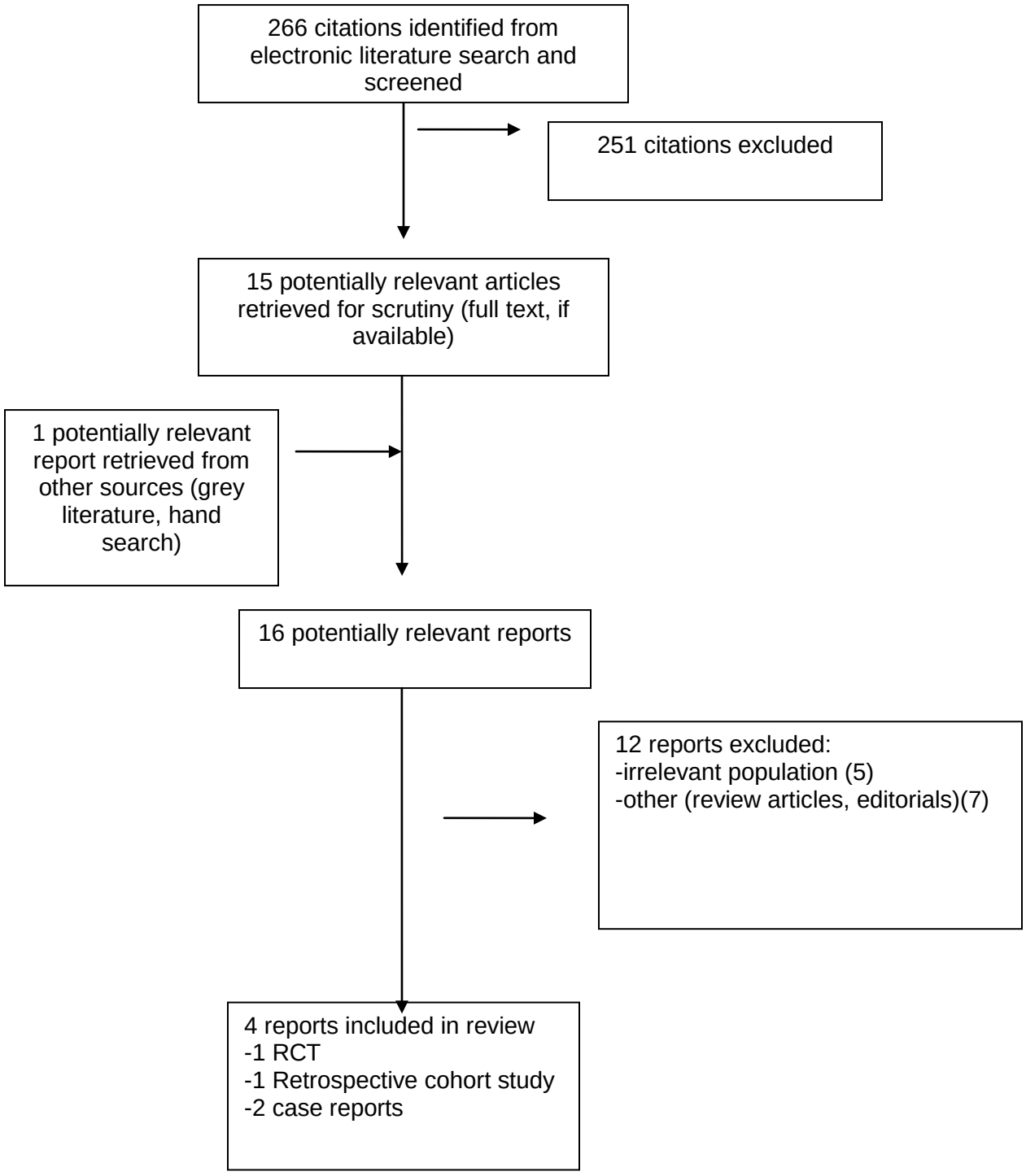
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Summary of Individual Study Characteristics

Table 2: Table of Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes
Non-chemotherapy Related Nausea and Vomiting					
Lewis, 1994[8] United Kingdom	Double- blind, RCT 24 hours post-surgery	Patients (n=60) undergoing elective total abdominal hysterectomy were randomized Patients were ASA I or II, less than 70 years of age (specific demographics not reported)	Nabilone 2mg administered 90 minutes prior to surgery along with 10 mg of diazepam Prochlorperazine permitted on an as needed basis every six hours post-operatively	Metoclopramide 10mg administered 90 minutes prior to surgery along with 10 mg of diazepam Prochlorperazine permitted on an as needed basis every six hours post-operatively	Incidence of post-operative nausea and vomiting for the first 24 hours following surgery. Retching was considered vomiting. Pain was measured on a visual analog scale. Adverse effects, relaxation and sedation were also monitored.
Weight Loss, Nausea and Vomiting					
Costiniuk 2008[9] Canada	Retrospective cohort design 24 to 48 weeks of follow-up (depending on genotype of hepatitis C virus) Total of 5189 person-weeks of follow-up	Patients with hepatitis C virus (n=191) who initiated treatment with interferon-ribavirin therapy between August 2003 and January 2007 were retrospectively identified and categorized as OC users or non-users. Age (mean ± SD) OC Users – 44 ± 7 OC Non-users – 43 ± 10 Weight, kg (mean ± SD)	OC use at variable dosages*(n=25) Nabilone (n=16) – 866 person-weeks Dronabinol (n=9) 4323 person weeks No description of co-interventions reported	No use of OCs (n=166) No description of co-interventions reported	Relief of anorexia, nausea, vomiting, and insomnia. Trends in weight loss, HCV therapy persistence

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes
		OC Users – 78 ± 19 OC Non-users – 79 ± 17 Male (%) OC Users – 72 OC Non-users – 75 HCV Genotype 1 (%) OC Users – 73 OC Non-users – 61 HCV Genotype 2 (%) OC Users – 8 OC Non-users – 12 HCV Genotype 3 (%) OC Users – 20 OC Non-users – 23 HCV Genotype 4 (%) OC Users – 0 OC Non-users – 3			

ASA – American Society of Anesthesiologists; HCV – Hepatitis C virus; OC – Oral cannabinoid; Kg – Kilogram; RCT – Randomized controlled trial
* Actual dosages or dosage ranges were not reported

Table 3: Table of Characteristics of Included Case Reports

First Author, Publication Year, Country	Patient Characteristics	Setting	Reason for Admission	Initial Treatment
Non-chemotherapy Related Nausea and Vomiting				
Flynn, 1992[10] Canada	38 year old male with a one-year history of AIDS and recurrent Pneumocystis carinii pneumonia HIV polyneuropathy, AIDs related dementia complex.	Palliative care unit	Intractable nausea and vomiting	Scopolamine disk every three days for six days Dimenhydrinate 50mg every four hours Intolerant to prochlorperazine
Green, 1989[11] United States	52 year old male with a one-year history of AIDS	Infectious Disease Unit	Intractable nausea and vomiting secondary to a cryptosporidial infection of the gastrointestinal tract	Failed on treatment with prochlorperazine, cyclizine, domperidone, high dose IV metoclopramide

AIDS – Acquired Immunodeficiency Syndrome; HIV – Human immunodeficiency virus; IV – Intravenous

APPENDIX 3: Summary of Critical Appraisal

*Table 4: Critical Appraisal of Included Studies of Clinical Effectiveness**

First Author, Publication Year	Strengths	Limitations
Randomized Controlled Trial (SIGN-50 Checklist RCTs)[6]		
Lewis, 1994[8]	• Appropriate and clearly focused research question • Assignment to treatment groups was randomized, although method of randomization was not described. • Anesthetist, recovery room staff and nursing staff were blinded to treatment allocation. • Follow-up was complete in 88% of patients and similar between groups.	• Method of allocation concealment was not described • Not reported if patient was blinded to treatment status. • Did not report using matching placebos to blind the treatment status, so unclear how the blinding was maintained. • Baseline demographics not reported, so unclear if treatment groups were comparable. • Unclear how nausea and vomiting were assessed (e.g., patient self-report, healthcare provider observed) and with what frequency of monitoring. • Analysis did not appear to be based on the intention to treat principle.
Cohort Studies (SIGN-50 Checklist for Cohort Studies)[7]		
Costiniuk 2008[9]	• Appropriate and clearly focused research question	• There were some imbalances in characteristics between OC Users and Non-OC Users (HCV genotype, ethnicity, liver biopsy stage, HIV co-infection, alcohol or drug abuse history) • It was possible that some patients may have used OCs prior to the time period captured in the database (although OCs were not typically used prior to the study period), creating the potential for misclassification on exposure. • Unclear if follow-up was complete for the entire course of therapy. As such, characteristics between full participants and those lost to follow-up were not made. • Details on exposure (dose and duration of OC use) were not reported. • Definitions of outcomes and method of assessment were not clear, particularly for subjective symptomatic relief given the retrospective design and data source. • Blinding to exposure status was unclear. This is particularly important for subjective outcomes. • Confounders were not accounted for in the analysis and confidence intervals were not reported.

OC – Oral cannabinoid; SIGN – Scottish Intercollegiate Guidelines Network

APPENDIX 4: Results

Table 5: Table of Main Study Findings and Authors' Conclusions

First Author, Publication Year	Main Study Findings			Authors' Conclusions
Non-chemotherapy Related Nausea and Vomiting				
Randomized Controlled Trial				
Lewis, 1994[8]		Nabilone (n=26)	Metoclopramide (n=27)	*"At the doses used, nabilone is no more effective than metoclopramide as a postoperative antiemetic in women undergoing abdominal hysterectomy." p.245*
	Reported in Recovery Room – n (%) Nausea Vomiting Antiemetic use Opioid use*	 6(23) 4(15) 5(19) 5(19)	 8(30) 6(22) 5(19) 14 (52)	
	Reported on Ward – n (%) Nausea Vomiting Antiemetic use Opioid use	 19 (73) 14(54) 15 (58) 26(100)	 19 (70) 18 (67) 19 (70) 25 (93)	
	VAS scores (mean, range) Nausea Vomiting Pain	 3.0 (0-7) 1.5(0-8) 4.0 (0-6)	 3.5 (0-10) 3.0 (0-9) 5.0 (0-10)	
	Postoperative interview – n (%) Relaxed Sedated Side effects*** Would have same premedication	 24 (93) 20 (78) 0(0) 25 (96)	 26 (96) 13(48) 1(4) 26(96)	
Case Reports				
Flynn, 1992[10]	Patient was treated with nabilone 2mg twice daily and had rapid resolution of nausea and vomiting After seven days of treatment, the dose was reduced to 1 mg twice			*"…Nabilone is a viable therapeutic alternative in the treatment of AIDS-related intractable nausea and vomiting. Its use as a first-line therapy is somewhat restricted by its cost and by its side effects of*

First Author, Publication Year	Main Study Findings	Authors' Conclusions
	daily, which the patient took until his death, approximately three weeks after admission.	*hypotension and hallucinations." p.46*
Green, 1989[11]	Patient was treated with nabilone 1mg twice daily and had complete resolution of nausea and vomiting, but experienced drowsiness. He was maintained on nablione for four days, prior to dying due to septicemia.	*"…the apparent value of nablione as a therapeutic alternative in the treatment of intractable nausea in terminal AIDS should not be ignored and clearly warrants further investigation." p. 28*
Weight Loss, Nausea and Vomiting		
Costiniuk, 2008[9]	**Trends in weight loss for OC Users** Median weight loss after starting HCV therapy, but prior to OC initiation – 4.5 kg Median weight loss following initiation of HCV therapy – 0.5 kg** Showed stabilization one month after starting OC (week 12) **Full duration of HCV therapy completed*** OC Users – 78% OC Non-users – 49% **Subjective improvement in anorexia, nausea, vomiting or insomnia** OC Users – 64% OC Non-users – Not reported	OCs are effective for the management of therapy-related anorexia, nausea and weight loss. *"As a consequence of better side effect management, patients may be better able to complete a full course of treatment.."p.379*

AIDS - – Acquired Immunodeficiency Syndrome; HCV – Hepatitis C virus; OC – Oral cannabinoid
**P* < 0.05
** Weight loss in the non-OC group was not reported numerically but graphically appeared to continue at week 12
*** Reported as the presence or absence of any side effect