National Institute for Health and Care Excellence

Final

Cannabis-based medicinal products:

[A] Evidence review for intractable nausea and vomiting

NICE guideline NG144

Evidence review underpinning recommendations 1.1.1 and 1.1.2 in the NICE guideline

November 2019

Final

These evidence reviews were developed by NICE Guideline Updates Team

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN: 978-1-4731-3578-9

Contents

Effectiveness of cannabis-based medicinal products for the treatment of intractable nausea and vomiting

Introduction

Intractable nausea or vomiting is defined as persistent nausea or vomiting that does not respond fully to standard antiemetic treatment. Intractable nausea and vomiting can be caused by a number of factors such as chemotherapy, radiotherapy, surgery, pregnancy and by medicines such as opioids.

Conventional antiemetics include domperidone, dopamine antagonists (for example prochlorperazine and chlorpromazine), 5-HT_3-receptor antagonists (for example ondansetron, granisetron and palonosetron) and neurokinin 1-receptor antagonists (for example aprepitant, fosaprepitant and rolapitant). Depending on the cause of nausea and vomiting, other medicines such as dexamethasone and lorazepam can be used alone or alongside the antiemetics described above. Combinations of medicines can be used in people whose symptoms do not respond to a single antiemetic. When combination antiemetic treatment has failed to control symptoms or has not been tolerated, there may be limited treatment options.

The aim of this review is to find out how effective cannabis-based medicinal products are in managing intractable nausea and vomiting, particularly when conventional antiemetic treatment options have not fully responded or not been tolerated. The review will also look into the safety profile (including complications and contraindications) and examine what individual patient requirements, treatments durations and reviewing and stopping criteria need to be considered when prescribing cannabis-based medicinal products.

Review question

What is the clinical and cost effectiveness of cannabis-based medicinal products for people with intractable nausea and vomiting?

This review question will also answer the following as part of the evidence review:

- What are the adverse effects or complications of cannabis-based medicinal products for people with intractable nausea and vomiting?
- What are the contraindications, potential interactions and risks and cautions for use of cannabis-based medicinal products for people with intractable nausea and vomiting?
- What are the individual patient monitoring requirements, treatment durations, reviewing and stopping criteria, including how should treatment be withdrawn or stopped, for use of cannabis-based medicinal products for people with intractable nausea and vomiting?

The review protocol for this review question is in Appendix A. The PICO table below formed part of the search strategy to identify studies associated with intractable nausea and vomiting.

PICO table

Population	Adults, young people, children and babies with intractable nausea or vomiting. Specific considerations will be given to: • Young people, children and babies • Pregnant women and women who are breastfeeding • People with existing substance abuse • People with hepatic and renal failure Intractable nausea or vomiting can be defined as persistent nausea or vomiting that does not respond fully to standard antiemetic treatment.
Interventions	Cannabis-based medicinal product
Comparator	• Placebo • Any relevant antiemetic treatment • Combination of treatments • Usual or standard care.
Outcomes	• Reduction of nausea and vomiting • Reduction of nausea • Reduction of vomiting • Reduction in retching • Participant reported improvement on a global impression change (PGIC) scale • Quality of life scores • Serious adverse events • Adverse events including but not limited to sleep problems, fatigue, road traffic accidents, psychological distress, dizziness, headache, confusion state, paranoia, psychosis, substance dependence, diarrhoea at the start of treatment • Withdrawals due to adverse events • Complications due to adverse events • Substance abuse due to the use of cannabis-based medicinal product. • Misuse/diversion • Hepatic and renal failure Outcomes requiring a narrative synthesis: • Contraindications as listed in exclusion criteria • Monitoring requirements, treatment durations, reviewing and stopping criteria, including how should treatment be withdrawn stopped as discussed in the methods of included studies.

This evidence review looked for cannabis-based medicinal products as the intervention. At the time of writing this evidence review, only nabilone had a UK marketing authorisation for treating intractable nausea, and vomiting. THC:CBD spray is available in the UK, but it is not licensed for the treatment of nausea and vomiting.

Evidence review

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual (2018). A review protocol was developed to

encompass the four review questions around effectiveness, adverse events, contraindications and monitoring requirements. This review protocol can be found in Appendix A. Methods specific to the review questions are described in the review protocol in Appendix B.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

A broad search strategy was used to identify all studies that examined the effectiveness of cannabis-based medicinal products in the treatment of intractable nausea and vomiting, chronic pain, spasticity and severe treatment-resistant epilepsy. Review protocol highlighted in Table 1 and Appendix A was used to identify studies associated with intractable nausea and vomiting.

For the adult population, randomised controlled trials (RCTs) and systematic review of RCTs were considered. The committee noted that a minimum of 5 RCTs were required to provide adequate evidence. If fewer than 5 RCTs were identified, prospective cohort studies would also be considered for inclusion.

For children, RCTs and systematic reviews of RCTs were a considered. The review protocol also specified that in the event of fewer than 5 RCTs being identified, prospective and retrospective cohort studies would also be considered for inclusion.

Additional information on safety concerns and contraindications were obtained from the Summary of Product Characteristics and other relevant sources, such as the U.S Food and Drugs Administration.

Studies were also excluded if they examined the use of:

- Synthetic cannabinoids in schedule 1 of the 2001 regulations,
- Smoked cannabis-based products
- Studies which do not report the doses or the concentration of cannabinoid constituents.

Additionally, crossover RCTs with washout periods of less than 1 week were excluded.

The review protocol also specifies that where possible, subgroup analyses would be conducted to explore the effectiveness of cannabis-based medicinal products in young people, children and babies, pregnant women and women who are breastfeeding, people with existing substance abuse and people with hepatic and renal failure.

Protocol deviations

The review protocol stated that if fewer than 5 RCTs were identified then prospective cohort studies would be included. However, full-text screening of observational studies found no prospective cohort studies that met the inclusion criteria. It was therefore agreed to deviate from the protocol and include non-comparative study designs as part of the review. This resulted in the inclusion of 1 non-comparative observational study which included children. The committee also considered this study to be reflective of current practice.

Clinical evidence

A total of 19,491 RCTs and systematic reviews were identified from the search. After removing duplicates, 9,341 references were screened on their titles and abstracts.

102 studies were obtained and reviewed against the inclusion criteria as described in the review protocol for intractable nausea and vomiting (Appendix A). Overall, 27 RCTs (6 parallel and 21 crossover) were included (see Appendix E for evidence tables). 75 references were excluded because they did not meet the eligibility criteria.

As fewer than 5 RCTs were identified which included children, an additional search was conducted for observational studies. A total of 5,975 observational studies were identified from the search. After removing duplicates, 4,028 references were screened on their titles and abstracts. 7 studies were obtained and reviewed against the inclusion criteria as described in the review protocol for intractable nausea and vomiting (Appendix A). Following full text review, 1 observational study was included. This study was identified as a non-comparative retrospective observational study. Overall, 24 studies included adults and 4 studies (3 RCTs and 1 non-comparative study) included children. See tables 2 and 3 for summary of included studies.

No studies were identified which included the following subgroups:

- Pregnant women and women who are breastfeeding
- People with hepatic or renal failure.

One additional study was identified which included evidence on people with some experience of illicit drug use.

See Appendix E for evidence tables and Appendix J for excluded studies.

Quality assessment of clinical studies included in the evidence review

In this review, parallel RCTs and crossover RCTs were identified. The quality of the evidence was initially graded as high. Majority of the evidence was identified for chemotherapy induced nausea and vomiting, with only 1 study looking at radiotherapy induced nausea and vomiting.

With regards to crossover studies, the committee identified 1 week as an adequate washout period. However, during the review of the crossover RCTs, a number of studies were identified which did not state the wash out period. Upon discussions with the committee, it was agreed with the studies examining chemotherapy induced nausea and vomiting, information on chemotherapy regimens could be used to ascertain washout period. The committee also highlighted most cycles have a gap of 1 to 3 weeks. Additionally, studies which did not state the washout period or chemotherapeutic agents used, were downgraded for risk of bias.

Studies were also downgraded for indirectness if the study did not report the population to have previously experienced nausea and vomiting or had nausea and vomiting at baseline. Results from these studies were not interpreted as a reduction in symptoms.

One non-comparative study was also included. This study was downgraded for insufficient information on how patients were recruited and for not specifying relevant outcomes a priori. This study was also downgraded for indirectness as the study design did not match the protocol for this review question.

See Appendix H for full GRADE tables and Appendix F for forest plots in situations where data have been meta-analysed.

Interventions

Of the 28 studies included, 27 studies looked at management of chemotherapy induced nausea and vomiting, and 1 study looked at radiotherapy induced nausea and vomiting. The included studies looked at the following interventions:

- Tetrahydrocannabinol (THC) (9 studies)
- Tetrahydrocannabinol (THC) plus prochlorperazine (1 study)
- Dronabinol (2 studies)
- Dronabinol plus prochlorperazine (1 study)
- Nabilone (14 studies)

At the time of writing this evidence review, with the exception of nabilone, most cannabis-based medicinal products such as tetrahydrocannabinol and dronabinol (both a schedule 2 controlled drug) did not have a UK marketing authorisation for treating intractable nausea and vomiting. The interventions were compared with treatments that are no longer considered as standard therapy (with the exception of ondansetron). Comparators included metoclopramide, prochlorperazine, domperidone and haloperidol.

Summary of clinical studies included in the evidence review

Table 2: summary of included adult studies

Reference	Population	Intervention/ comparator	Outcomes	Limitations
Frytak 1979 (USA) Parallel RCT	Patients undergoing their initial chemotherapy exposure to either as 2 or 3 combination chemotherapy agents Age at least over 21 years Duration: Patients were exposed to a strong emetic stimulus (emustine plus 5-flurouracil) on day 1 and a weaker stimulus (5-flurouracil) on days 2-4. Follow-up: 24 hours after chemotherapy and days 2-4 after chemotherapy	THC vs prochlorperazine (n=117) On day 1, the initial dose of antiemetic was given orally 2 hours before the initiation of chemotherapy. Subsequent doses were given 2 h and 8h after the initiation of chemotherapeutic treatment. On the remaining 3 days, the antiemetic agents were given 3times daily, ½ h before each regular meal	No nausea and vomiting Adverse events	Prochlorperazine not current standard practice Emetogenicity of chemotherapy agents varied Exclusion criteria specified that patients could not be experiencing nausea and vomiting before entry into study
Gralla 1984 (USA) Parallel RCT	Patients who had a white blood count (wbc) equal to or greater than 4000 cells/mm^3, platelet count equal to or greater than 120,000/mm^3, creatinine clearance equal to or greater than 65 ml/minute and a serum bilirubin less than 2.0 mg/dl. Duration: Patients were hospitalised to receive cisplatin at a dose of 120 mg/m^2 IV in a 20-minute infusion. Follow- up: 24 hours after cisplatin administration	THC vs metoclopramide (n= 31) THC given at a dose of 10 mg/m^2 orally. THC was given 1.5 hours before cisplatin and 1.5, 4.5, 7.5 and 10.5 hours after chemotherapy- total dose of 50 mg/m^2 of THC during the study period.	Adverse events Major emetic response (0-2 episodes)	Metoclopramide not current standard practice Study did not specify if people had previously experienced nausea and/ or vomiting or had showed signs at baseline
Lane 1991 (USA)	Patients between the ages of 18 and 69 years being treated for cancer with	Dronabinol vs prochlorperazine vs Dronabinol + prochlorperazine	Adverse events	Prochlorperazine not current standard practice

Reference	Population	Intervention/ comparator	Outcomes	Limitations
Parallel RCT	chemotherapy other than investigational agents or high dose (>60 mg/m^2) cisplatin. Duration: Patients could receive treatment regimens lasting up to 5 days. Follow up: Antiemetics were continued for 24 hours after the last dose of chemotherapy, up to a total of 6 days (1 day prior and up to 5 days on chemotherapy)	(n= 62) Dronabinol: Dronabinol 10 mg plus placebo 10 mg of dronabinol plus placebo was administered orally every 6 hours. Dronabinol + prochlorperazine: 10 mg of each were administered orally every 6 hours.	Withdrawals due to adverse events Two or fewer episodes of N&V No nausea and vomiting (complete response)	Emetogenicity of chemotherapy agents varied
Meiri 2007 (USA) Parallel RCT	Patents aged 18 years and older were required to have malignancy that did not involve the bone marrow Duration: 5-day study Follow up: efficacy evaluated on days 2-5.	Dronabinol vs Ondansetron vs placebo (n=64) Dronabinol: The dronabinol doses (2.5 mg and 5 mg orally 4 times daily) used in the fixed (day 2) and flexible (day 3-5) dosing phases of the study were based on the standard recommended antiemetic dose of 5mg orally 3 times daily or 4 times daily. For days 3-5 subjects took 2 or 4 capsules 4 times daily based on tolerance.	Incidence of Total response Complete response for vomiting/ retching Patients with at least one severe TEAE Patients with at least one SAE Patients with at least one TEAE Absence of delayed nausea Withdrawals due to adverse events	People with history of anticipatory nausea were excluded from the study

Reference	Population	Intervention/ comparator	Outcomes	Limitations
Pomeroy 1986 (Ireland) Parallel RCT	Patients undergoing chemotherapy for advanced malignant disease. Duration: The chemotherapy regiments remained constant for the two cycles of antiemetic. Follow up: Each day of chemotherapy	Nabilone vs domperidone (n= 38) Patients received 2 cycles of nabilone 1 mg 3 times daily.	Withdrawals due to adverse events Adverse events	Domperidone not current standard practice. Study did not specify if people had previously experienced nausea and/ or vomiting or had showed signs at baseline
Ahmedzai 1983 (UK) Crossover RCT	Patients with small cell bronchial carcinoma who were eligible for chemotherapy Duration: All patients received two 21-day cycles of combination chemotherapy Follow up: 3 treatment days	Nabilone vs prochlorperazine (n=34) 1 mg - 2 capsules of nabilone taken at 10am and 10pm.	No nausea No retching No retching Adverse events	Prochlorperazine not current standard practice Study did not specify if people had previously experienced nausea and/ or vomiting or had showed signs at baseline
Crawford 1986 (UK) Crossover RCT	Patients receiving cisplatin for treatment of adenocarcinoma of the ovary or germ cell tumours Duration: They were scheduled to receive two courses of nabilone capsules with placebo and two courses of metoclopramide with placebo. Follow up: Within 24 hours of the end of each course of therapy	Nabilone vs metoclopramide (n=32) 1 capsule when waking up, 2 capsules 2 hours before cisplatin therapy, 1 capsule before falling asleep, 1 capsule every 8 hours as required (up to 2 doses)	Adverse events	Metoclopramide not current standard practice
Einhorn 1981 (USA)	Patients receiving combination chemotherapy for neoplastic disease	Nabilone vs prochlorperazine (n=80)	Adverse events	Prochlorperazine not current standard practice

Reference	Population	Intervention/ comparator	Outcomes	Limitations
Crossover RCT	Duration: 2 courses of chemotherapy Follow up: 5 days	2 mg of nabilone. Initially first dose taken 30 mins before start of chemotherapy. Changed for last 44 patients - 3 doses beginning 12 hours before start of chemotherapy Then every 6 hours as required		
Herman 1981 (USA) Crossover RCT	Patients receiving repeated courses of chemotherapy on entry into the trial and previously experienced severe, drug-induced nausea and vomiting. Duration: 2 courses of identical chemotherapy Follow up: Dependant on type of cancer treatment (range 1.5 - 5.5 days)	Nabilone vs prochlorperazine (n=113) 2 mg of nabilone. 2 capsules orally every 8 hours, beginning 2 doses before start of chemotherapy or 2 capsules orally every 6 hours, beginning 30 mins before chemotherapy.	Complete response (no vomiting) Partial response Withdrawals due to adverse events	Prochlorperazine not current standard practice
Johansson 1982 (Finland) Crossover RCT	Adult patients with an age range of 18-70 years, with a good performance status (less than 2 on the ECOG scale), receiving the same cycles of cancer chemotherapy as previously, who had uncontrolled nausea and vomiting despite the use of standard antiemetic drugs. Duration: Patients received 2 consecutive cycles chemotherapy. Follow up: Daily	Nabilone vs prochlorperazine (n= 18 evaluable for efficacy, 26 patients remain evaluable for side effects) 2 mg twice daily. Antiemetic treatment was given every 12h for 4 consecutive doses, with the first dose on the night before chemotherapy and the last dose the morning after. On the day of chemotherapy, the drugs were taken between 1 and 3h before the anticancer treatment in order to ensure correct absorption of the drug.	Vomiting episodes (none) Severity of nausea (none) Withdrawals due to adverse events Adverse events	Prochlorperazine not current standard practice

Reference	Population	Intervention/ comparator	Outcomes	Limitations
Jones 1982 (USA) Crossover RCT	Adults without other serious contraindications to nabilone, who agreed to participate after informed consent, and who were likely to receive at least 2 identical courses of chemotherapy Duration: 2 courses of chemotherapy Follow up: 24h after chemotherapy	Nabilone vs placebo (n=24) 2 mg of nabilone administered the evening before, the morning of chemotherapy and every 12h thereafter for at least 24 hours.	Adverse events Withdrawals due to adverse events Less vomiting Less nausea	Study did not specify if people had previously experienced nausea and/ or vomiting or had showed signs at baseline
Kleinman 1983 Crossover RCT	Patients receiving chemotherapy known to cause acute gastrointestinal toxicity and had already experienced vomiting as a side effect Duration: 4 courses of antiemetic treatment. Follow up: 24 hours following chemotherapy	THC+ prochlorperazine vs prochlorperazine+ placebo (n=16) 15 mg of THC plus prochlorperazine. Patients received this combination one hour prior to the administration of chemotherapy. The same drugs were given four hours later, and a third final dose in another 4 hours. This sequence of three doses of prochlorperazine was defined as one course of ant-emetic treatment.	Withdrawals due to adverse events Adverse events	Prochlorperazine not current standard practice
Levitt 1982 Crossover RCT	Patients had lung cancer, ovarian cancer, breast cancer and a variety of cancers Duration: Patients received 2 cycles of chemotherapy. Follow up: Not reported	Nabilone vs prochlorperazine (n=36)	Less vomiting Less nausea Withdrawals due to adverse events Adverse events	Prochlorperazine not current standard practice Study did not specify if people had previously experienced nausea and/ or vomiting or had showed signs at baseline

Reference	Population	Intervention/ comparator	Outcomes	Limitations
McCabe 1988 (USA) Crossover RCT	People aged 18 years and experienced severe nausea and vomiting that was refractory to standard antiemetics Duration: Patients received each study drug twice in randomly allocated sequence. Follow up: 24 hours	THC vs prochlorperazine (n= 36) 15 mg/m² 1 hour prior to chemotherapy then every 4 hours for 24 hours	Complete response No nausea and vomiting Partial response Adverse events	Prochlorperazine not current standard practice
Neidhart 1981 (USA) Crossover RCT	Patients receiving a single injection or infusion of a cancer chemotherapeutic agent likely to induce intolerable vomiting and experiencing incapacitating vomiting refractory to standard antiemetic agents with any prior cancer chemotherapy Duration: Study included 2 courses of therapy with each antiemetic agent. Follow up: Not reported	THC vs haloperidol (n= 37) 10 mg At 2 hours and at 30 mins before start of chemotherapy followed by 3 to 4 hour intervals for maximum 8 doses	No vomiting Adverse events Moderate to severe adverse events	Haloperidol not current standard practice Data presented by number of courses not by number of people in study.
Niiranen 1985 (Finland) Crossover RCT	Patients with lung cancer who had been listed for treatment with at least 2 identical consecutive cycles of chemotherapy Duration: Patients had 2 consecutive cycles of chemotherapy Follow up: Up to 24 hours after chemotherapy	Nabilone vs prochlorperazine (n= 32) 1 mg given orally Initial dose the night before chemotherapy then 1 hour before chemotherapy and at 12 hour intervals up to 24 hours after chemotherapy	Adverse events No nausea	Prochlorperazine not current standard practice Study did not specify if people had previously experienced nausea and/ or vomiting or had showed signs at baseline

Reference	Population	Intervention/ comparator	Outcomes	Limitations
Orr 1980 (USA) Crossover RCT	Patients with a variety of neoplasms requiring drug therapy. All patients had previously demonstrated repeated vomiting from anticancer agents commonly known to induce emesis, and had failed standard antiemetic therapy Duration: not reported Follow up: 24 hours after drug ingestion	THC vs prochlorperazine (n=55) 7 mg/ $m^2$of THC orally every 4 hours for 4 doses.	No nausea Adverse events	Prochlorperazine not current standard practice
Priestman 1987 (UK) Crossover RCT	People with radiation induced nausea and vomiting, which has at least 5 treatments remaining of their course of radiotherapy. Duration: Antiemetic therapy was continued until either the completion of 30 days treatment Follow up: Daily	Nabilone vs metoclopramide (n= 20) 1 mgnabilone was given with a placebo capsule at midday. The interval between starting radiotherapy and starting antiemetic therapy varied considerably, with some patients preferring to cope with mild nausea for some days before requesting treatment. Mean time for nabilone patients = 9.5 days (± 6.29).	Serious adverse events Adverse events	Metoclopramide not current standard practice
Sallan 1975 (USA) Crossover RCT	Patients known to have a variety of neoplasms Duration: Patients received 3 one day courses of the drug. Follow up: Day after treatment.	THC vs placebo (n=15 courses) Initial dose was 15 mg given every 4 hours for three doses Because of some variability in responses, the dose was changed to 10 mg/m^2body surface area per dose.	Complete response (no vomiting) Partial response (50% reduction in vomiting) Adverse events	Data presented by number of courses not by number of people in study.

Reference	Population	Intervention/ comparator	Outcomes	Limitations
Sallan 1980 (USA) Crossover RCT	Patients known to have a variety of neoplasms Duration: Each patient was to receive three one-day courses of the study drug Follow up: Day after treatment	THC vs prochlorperazine (n= 79 courses) 10 mg -15 mg 5 patients with body surface area less than 1m² each received 10 mg of THC.	Adverse events Withdrawals due to adverse events No nausea and vomiting (complete response) Partial response	Prochlorperazine not current standard practice Age ranged from 8- 70 years but data not separated out for children Data presented by number of courses not by number of people in study.
Steele 1980 (USA) Crossover RCT	Patients receiving 2 consecutive, identical chemotherapy treatments Duration: 2 consecutive, identical chemotherapy treatments Follow up: Within 24h of completion of each cycle	Nabilone vs prochlorperazine (n=37) Nabilone 2 mg. Each anti-emetic was given every 12 hours for 3 to 5 doses with the first dose given the night before chemotherapy.	Adverse events	Prochlorperazine not current standard practice
Ungerleider 1982 (USA) Crossover RCT	People at least 18 years of age, not pregnant, English speaking, and not receiving concurrent radiation nor having a history of allergy or severe side effects to prochlorperazine. Duration: Varied depending on chemotherapeutic regimen Follow up: 24h after taking study medication	THC vs prochlorperazine (n=133) Dose calculated based on body surface area: SA <1.4m² = 7.5 mg SA <1.4m²-1.8m² = 10 mg SA >1.8m² = 12.5 mg	Relative nausea reduction Less nausea	Prochlorperazine not current standard practice

Reference	Population	Intervention/ comparator	Outcomes	Limitations
Ungerleider 1985 (USA) Crossover RCT	Study reports further findings from Ungerleider 1982. Study used to extract data on people with some experience of illicit drug use.	This study reports further findings from Ungerleider 1982.	Relative nausea reduction	Study did not state if people had existing substance abuse.
Wada 1982 (USA) Crossover RCT	Patients receiving a variety of chemotherapy regimens Duration: 2 consecutive cycles of cancer chemotherapy. Follow up: Daily	Nabilone vs placebo (n= 92) Nabilone 2 mg. One capsule was taken at 8am the preceding evening and one at 8am on the morning of the administration of chemotherapy. Chemotherapy was given 1-3 h after the 8am dose of nabilone.	Less vomiting Less nausea Withdrawals due to adverse events Adverse events	Study did not specify if people had previously experienced nausea and/ or vomiting or had showed signs at baseline
WBC: White blood cell count THC: Tetrahydrocannabinol SA: Surface area ECOG: Eastern Cooperative Oncology Group (ECOG) performance status				

Table 3: Summary of included children studies

Reference	Population	Intervention/ comparator	Outcomes	Limitations
Ekert (1979) (Australia) *Parallel RCT*	Children with various neoplastic diseases requiring chemotherapy **Age range:** 5-19 years **Duration:** THC group (1)- 17 courses Metoclopramide group- 25 courses THC group (2)- 18 courses Prochlorperazine group – 18 courses Follow up not reported	(1) THC vs metoclopramide (n=19) (2) THC vs prochlorperazine (n=14) THC capsules, 10 mg/m² with a maximum dose of 15 mg. This was given 2 hours before chemotherapy, and at 4,8,16 and 24 hours after the first dose.	Adverse events No vomiting	Prochlorperazine and metoclopramide not current standard practice Emetogenicity of chemotherapy agents varied Data presented by number of courses not by number of people in study.
Chan 1987 (Canada) *Crossover RCT*	Children receiving chemotherapy for various paediatric malignancies, receiving repeated courses of chemotherapy and experienced severe drug-induced nausea and vomiting but had never received nabilone or prochlorperazine **Age (mean and range):** 11.8 years (3.5 - 17.8) **Duration:** All patients in the study received two identical consecutive cycles of the same doses of chemotherapy. **Follow up:** Within 24 hours of completion of each cycle	**Nabilone vs prochlorperazine** (n=40) 1 mg nabilone 8-12 hours before the start of chemotherapy. Repeated 2 or 3 times daily depending on body weight.	Adverse events Complete relief of nausea and vomiting Less nausea Less vomiting Overall rate of improvement of retching and vomiting Serious adverse events	Prochlorperazine not current standard practice Chemotherapeutic agents not explicitly listed

Reference	Population	Intervention/ comparator	Outcomes	Limitations
Dalzell 1986 (UK) *Crossover RCT*	Consecutive children 17 years old or less undergoing emetogenic antieoplastic chemotherapy for malignant disease **Age (range):** 0.8-17 years **Duration:** Patient has to be scheduled to receive two identical courses of emetogenic chemotherapy **Follow up:** After completion of study (length not specified)	**Nabilone vs Domperidone** (n=18) Dose dependent on weight of patient. Patients received 3 (or 6) identical capsules daily, or in case of some of the very young, three identical looking white powders from broken capsules.	Adverse events	Follow up period no explicitly detailed Domperidone not current standard practice
Polito 2018 (Canada) *Non-comparative study*	Patients aged ≤18 years, receiving nabilone for the purpose of CINV prevention as an inpatient between 1st December 2010 - 30th November 2015 and receiving a dose of nabilone before the administration of the first chemotherapy dose of a chemotherapy block. **Age (median and range):** 14.0 years (1.14 - 18.00) **Duration:** First chemotherapy dose **Follow up:** Acute phase. Until 24 hours after administration of last antineoplastic dose of the block or until discharge	**Nabilone** Mean initial nabilone dose: Once daily – 19 micrograms/kg/ dose (2.30- 3.09) Twice daily – 17 micrograms/kg/ dose (5.00- 38.80) Three times daily- 14 micrograms/kg/ dose (9.10- 19.40)	Adverse events Number of vomits Complete vomiting control Partial vomiting control Withdrawal due to adverse events	Single arm study
THC: Tetrahydrocannabinol CINV: Chemotherapy induced nausea and vomiting				

See Appendix E for evidence tables and Appendix I for further information on adverse events.

As part of this evidence review, in addition to reviewing efficacy and safety data, studies were reviewed for information about patient monitoring and reviewing and stopping criteria when cannabis-based medicinal products were prescribed.

The interventions, doses, monitoring and stopping criteria are summarised in tables 4 and 5 below:

Table 4: Summary of interventions and doses in the included studies with adult population

Intervention (number of studies, n)	Indication	Dose and duration	Patient monitoring	Stopping criteria
Nabilone (n= 10)	CINV	1-2 mg Some studies reported administering nabilone evening before, morning of or between 30 minutes to 2 hours before chemotherapy. Frequency of dose ranged 3 times a day to every 12 hours for 4 consecutive doses.	In most of the studies blood pressure was monitored before and after the antiemetic was given. In some studies blood count and urinalysis was conducted.	Stopping criteria not specified these studies but some studies did report that patients were withdrawn from studies due to: Adverse events associated nabilone Patient choice
Nabilone (n=1)	RINV	1 mg given twice a day. Nabilone was given at midday.	Not reported	Not reported
THC (n=8)	CINV	Most studies based dose on surface area. Dose ranged from 7 mg to 15 mg. Initial dose was given 1-2 hours before chemotherapy. Number of doses ranged from 3 times daily, 4 doses every 4 hours to a maximum of 8 doses.	A number of studies did not report the how patients were monitored. One study reported that patients were seen by a physician each day and queried about side effects, one study reported that patients kept a diary and one study reported that Prior to each dose, patient or carer completed a vomiting and toxicity checklist. If toxicity interfered with function, next dose was delayed until toxicity reduced.	None of the studies reported a stopping criterion in the methods section. However, studies highlighted that patients were withdrawn from studies due to the following reasons: Due to THC toxicity and side effects such as dysphoric reactions and central nervous system side effects Patients removed themselves from the study (individuals felt after reconsideration that the use of marijuana was morally incorrect)
THC+ prochlorperazine	CINV	15 mg THC given	Not reported	Not reported

Intervention (number of studies, n)	Indication	Dose and duration	Patient monitoring	Stopping criteria
(n=1)		Combination was received 1 hour prior to chemotherapy and the 2 more doses given 4 hours apart.		
Dronabinol (n=2)	CINV	10 mg One study also administered as flexible dose of 10-20 mg/ day. One study administered dronabinol every 6 hours (1 day prior and up to 5 days during chemotherapy).	In one study side effects were monitored. Physical and clinical laboratory examination was conducted.	None of the studies reported a stopping criterion in the methods section. However, studies highlighted that patients were withdrawn from studies due to the following reasons: Adverse events
Dronabinol+ prochlorperazine (n=1)	CINV	10 mg Combination was administered dronabinol every 6 hours (1 day prior ad up to 5 days during chemotherapy).	Not reported	Not reported
CINV: Chemotherapy induced nausea and vomiting RINV: Radiotherapy induced nausea and vomiting THC: Tetrahydrocannabinol				

Table 5: Summary of interventions and doses in the included studies with children

Intervention (number of studies, n)	Indication	Dose and duration	Patient monitoring	Stopping criteria
Nabilone (n= 3)	CINV	0.5 – 1 mg In these studies frequency of dose was dependent on the	CBC count, urinalysis and SMA-12 conducted before each cycle. Blood pressure was also taken before and	None of the studies reported a stopping criterion in the methods section. However, studies highlighted that patients were

Intervention (number of studies, n)	Indication	Dose and duration	Patient monitoring	Stopping criteria
		boy weight and ranged from 2 or 3 times daily. In one study, nabilone was given in combination with other antiemetics such as 5-HT3 antagonists, dexamethasone and dimenhydrinate.	after each antiemetic was administered.	withdrawn from studies due to the following reasons: Adverse events Inefficacy
THC (n=1)	CINV	10mg /m² with a maximum dose of 15 mg. This was given 2 hours before chemotherapy, and at 4,8,16 and 24 hours after the first dose.	Not reported	Not reported
CBC: complete blood count SMA-12: Sequential multiple analysis 5-HT3 antagonists: Serotonin receptor antagonists				

See Appendix E for evidence tables.

Economic evidence

Included studies

A systematic review of the economic literature was conducted. 1,863 number of studies were retrieved by the search. No economic studies were identified which were applicable to this review question and no full-text copies of articles were requested.

Excluded studies

No full-text copies of articles were requested for this review and so there is no excluded studies list.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Summary of evidence

The summary of evidence reflects the evidence on effectiveness of cannabis-based medicinal products. Evidence summarises are stratified by population and reflect evidence that was statistically significant. Further information on adverse events is also provided. The format of the summary of evidence is explained in the methods in Appendix B. Further information on adverse events is provided in Appendix I.

Clinical evidence

Chemotherapy induced nausea and vomiting in adults

Effectiveness and safety of tetrahydrocannabinol (THC)

THC versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Absence of nausea and vomiting – after strong emetic stimulus (higher values favour THC)					
1 (Frytak 1979)	Parallel RCT	75 people	RR 2.23 (1.04, 4.78)	Very low	Favours THC
Complete reduction in nausea (higher values favour THC)					
1 (Orr 1981)	Crossover RCT	55 people	RR 8.00 (3.42, 18.74)	Moderate	Favours THC
Adverse events – number of participants experiencing adverse events (lower values favour THC)					
1 (Sallan 1975)	Crossover RCT	29 courses	RR 25.31 (1.65, 389.42)	Low	Favours placebo

Commonly reported adverse events for THC highlighted in the studies include, feeling 'high', sedation, coordination problems, loss of emotional control and somnolence.

THC versus metoclopramide

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Major emetic response (defined as between 0 and 2 episodes) (higher values favour THC)					
1 (Gralla 1984)	Parallel RCT	30 people	RR 0.36 (0.15, 0.89)	Low	Favours metoclopramide

Commonly reported adverse events for THC highlighted in the studies include, sedation, orthostatic hypotension, dizziness, dry mouth and feeling of 'high'.

THC versus prochlorperazine

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Complete reduction in nausea (higher values favour THC)					
1 (Orr 1981)	Crossover RCT	55 people	RR 5.00 (2.58, 9.68)	Moderate	Favours THC
Complete reduction in nausea and vomiting – all emetic risks (higher values favour THC)					
2 (McCabe 1988, Sallan 1980)	Crossover RCTs	115 (people and no. of antiemetic courses)	RR 2.73 (1.67, 4.45)	Low	Favours THC
Complete reduction in nausea and vomiting – greatest emetic risk (higher values favour THC)					
1 (Sallan 1980)	Crossover RCT	38 courses	RR 2.44 (1.16, 5.13)	Low	Favours THC
Partial reduction in nausea and vomiting – 50% reduction (higher values favour THC)					
1 McCabe (1988)	Crossover RCT	36 people	RR 14.00 (1.94, 100.94)	Low	Favours THC
Relative nausea reduction (reduction in severity) – in participants with some experience of illicit drug use (higher values favour THC)					
1 (Ungerleider 1985)	Crossover RCT	70 people	RR 1.72 (1.07, 2.78)	Very low	Favours THC

Commonly reported adverse events for THC highlighted in the studies include, sedation, coordination problems and feeling of 'high'.

THC versus haloperidol

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Moderate to severe adverse events (lower values favour THC)					
1 Neidhart 1981	Crossover RCT	109 courses	RR 4.58 (1.38, 15.17)	Low	Favours Haloperidol

Commonly reported adverse events for THC highlighted in the study include, drowsiness, feeling faint, feeling 'high', spasms or tremors.

Effectiveness and safety of THC+ prochlorperazine

THC+ prochlorperazine versus prochlorperazine+ placebo

Commonly reported adverse events for THC+ prochlorperazine highlighted in the study include, euphoria, mood alterations, sedation, increased food intake, adverse psychiatric reactions.

Effectiveness and safety of dronabinol

Dronabinol versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Absence of delayed nausea (higher values favour Dronabinol)					
1 Meiri 2007	Parallel RCT	27 people	RR 4.64 (1.24, 17.33)	Low	Favours dronabinol

Commonly reported adverse events for dronabinol highlighted in the study included diarrhoea, asthenia, fatigue, chest pain, constipation and dizziness.

Dronabinol (+placebo) versus prochlorperazine (+placebo)

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Adverse events (lower values favour Dronabinol+ placebo)					
1 Lane 1991	Parallel RCT	42 people	RR 2.29 (1.19, 4.38)	Moderate	Favours prochlorperazine + placebo
Withdrawals due to adverse events (lower values favour Dronabinol+ placebo)					
1 Lane 1991	Parallel RCT	42 people	RR 21.00 (1.31, 336.75)	Moderate	Favours prochlorperazine + placebo

Commonly reported adverse events for dronabinol highlighted in the study included neurological side effects such as dizziness, somnolence and vision disturbance, digestive side effects such as dry mouth and diarrhoea and cardiovascular side effects such as tachycardia.

Dronabinol versus ondansetron

Commonly reported adverse events for dronabinol highlighted in the study included diarrhoea, asthenia, fatigue, chest pain, constipation and dizziness.

Effectiveness and safety of dronabinol+ prochlorperazine

Dronabinol+ prochlorperazine versus prochlorperazine (+placebo)

Commonly reported adverse events for dronabinol + prochlorperazine highlighted in the study included neurological side effects such as dizziness, somnolence and vision disturbance, digestive side effects such as dry mouth, respiratory side effects such as dyspnoea and headache.

Effectiveness and safety of nabilone

Nabilone versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Complete relief in nausea and vomiting (higher values favour Nabilone)					
1 Wada 1982	Crossover RCT	92 people	RR 3.20 (1.67, 6.12)	Very low	Favours nabilone
Patients with less vomiting compared to comparator (higher values favour Nabilone)					
2 Leviit 1982, Wada 1982	Crossover RCTs	128 people	RR 4.08 (1.58, 10.57)	Very low	Favours nabilone
Patients with less nausea compared to comparator (higher values favour Nabilone)					
2 Leviit 1982, Wada 1982	Crossover RCTs	128 people	RR 7.45 (4.17, 13.32)	Very low	Favours nabilone
Relative reduction in nausea (less nausea compared to comparator) (higher values favour Nabilone)					
1 Jones 1982	Crossover RCT	24 people	RR 15.00 (2.15, 104.75)	Very low	Favours nabilone
Relative reduction in vomiting (less vomiting compared to comparator) (higher values favour Nabilone)					
1 Jones 1982	Crossover RCT	24 people	RR 6.33 (2.15, 18.62)	Very low	Favours nabilone
Withdrawals due to AEs (lower values favour Nabilone)					
3 Jones 1982, Levitt 1982, Wada 1982	Crossover RCTs	196 people	RR 8.33 (2.63, 26.42)	Low	Favours placebo

Commonly reported adverse events for nabilone highlighted in these studies include dizziness or vertigo, drowsiness, dry mouth and depersonalisation syndrome.

Nabilone versus prochlorperazine

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Absence of retching (higher values favour Nabilone)					
1 Ahmedzai 1983	Crossover RCT	56 people	RR 1.81 (1.20, 2.75)	Very low	Favours nabilone
Complete reduction in nausea and vomiting (total absence of nausea and vomiting) (higher values favour Nabilone)					
1 Herman 1979	Crossover RCT	113 people	RR 19.00 (1.12, 322.59)	Low	Favours nabilone
Partial reduction in nausea and vomiting (equal to or greater than 50% reduction in the duration or severity of nausea and number of vomiting episodes) (higher values favour Nabilone)					
1 Herman 1979	Crossover RCT	113 people	RR 2.25 (1.68, 3.02)	Low	Favours nabilone

Commonly reported adverse events for nabilone highlighted in these studies included dry mouth, drowsiness, decreased co-ordination, dizziness and drowsiness.

Nabilone versus domperidone

Commonly reported adverse events for nabilone highlighted in the study included drowsiness, dizziness, dry mouth, postural hypotension and headache.

Chemotherapy induced nausea and vomiting in children

Effectiveness and safety of tetrahydrocannabinol (THC)

THC versus metoclopramide

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Absence of vomiting – in children (higher values favour THC)					
1 (Ekert 1979)	Parallel RCT	42 courses	RR 3.53 (1.52, 8.19)	Very low	Favours THC

Commonly reported adverse event for THC highlighted in the study was drowsiness.

THC versus prochlorperazine

Commonly reported adverse event for THC highlighted in the study was drowsiness.

Effectiveness and safety of nabilone

Very low-quality evidence from 1 single arm study, including 110 children, showed that over half the children demonstrated complete vomiting control after taking nabilone. 34% of the children also had adverse events. These included sedation, dizziness, euphoria, headache, constipation, abdominal pain and tachycardia.

Nabilone versus prochlorperazine

No. of studies	Study design	Sample size	Effect size (95% CI)	Quality	Interpretation of effect
Overall Rate of improvement in retching and vomiting (higher values favour Nabilone) – in children					
1 Chan 1987	Crossover RCT	30 children	RR 2.33 (1.29, 4.23)	Low	Favours nabilone
Adverse events (lower values favour Nabilone) – in children					
1 Chan 1987	Crossover RCT	30 children	RR 2.29 (1.49, 3.50)	Low	Favours prochlorperazine

Commonly reported adverse events for nabilone highlighted in the study included drowsiness, dizziness, mood alteration, ocular swelling and irritation and orthostatic hypotension.

Nabilone versus domperidone

Commonly reported adverse events for nabilone highlighted in the study included drowsiness, dizziness, dry mouth, postural hypotension and headache.

Radiotherapy induced nausea and vomiting in adults

Effectiveness and safety of nabilone

Nabilone versus metoclopramide

Commonly reported adverse events for nabilone highlighted in the study included vertigo, dry mouth, disorientation and fatigue.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee identified outcomes such as complete or partial reduction in nausea or vomiting as important outcomes. The committee were also interested in the adverse events which were associated with the use of CBMPs. Additionally, the committee examined the information presented in individual studies around the dose, contraindications, monitoring requirements and stopping criteria for the different cannabis-based products identified in this review.

The quality of the evidence

Overall, the committee noted that the studies included in the review were of low to very low quality, with moderate- quality evidence for some outcomes. In this review, 6 parallel RCTs and 21 crossover RCTs were identified. The majority of these studies were also conducted in the 1970s and 80s. This meant that these studies used practices and antiemetics that were now out-dated.

Only one RCT [Meiri 2007] was identified which employed a practice that was similar to clinical practice in the UK. In this study, people received a pre-chemotherapy and post- chemotherapy treatment followed by study medication (dronabinol) on day 2. Additionally, a non-comparative retrospective study [Polito 2018] was identified in which children received nabilone as an adjunct to other antiemetic treatments which were reflective of the current UK practice. While this study did not match our review protocol in terms of study design, the committee noted that this study should be included as it was the only study which represented the current antiemetic practice for chemotherapy inducted nausea and vomiting (CINV). .

In terms of risk of bias, the majority of the RCTs were downgraded for risk of bias due to unclear random sequence generation and allocation concealment. Additionally, while the committee had identified one to three weeks as an adequate wash out period, the majority of the studies did not specify washout periods. The committee highlighted that in studies which specified the chemotherapy agents used, a washout period could be estimated. Therefore, studies which stated the chemotherapy agents used were not downgraded for risk of bias due to unclear washout period. However, the majority of the studies did not report data from the first period and the end of trial data was used in the review. Therefore, in these studies it is unclear if there was any carry over effect.

Furthermore, the committee took into account the indirectness of the evidence and highlighted that a number of studies do not focus on the population of interest. Several studies did not specify if people had persistent nausea or vomiting at baseline. Therefore, outcomes for which these studies contributed evidence were downgraded for indirectness as these could not be interpreted as a reduction in the outcomes of interest.

Due to these limitations, the committee did not feel they could make strong recommendations. However, based on the effectiveness data, the committee felt these interventions may still have a place in the treatment pathway as an add-on therapy. With limited information on the use of CBMPs in people with persistent nausea or vomiting, the committee drafted further research recommendations to examine the effectiveness of these products in people who have not fully responded

to optimal treatment. Separate questions were drafted for the adult population as well as babies, children and young adults.

Benefits and harms

Nausea and vomiting are common side effects of chemotherapy which can be unpleasant. While anti-emetic agents are available, some people can exhibit persistent nausea and vomiting that does not respond to optimal treatment. The evidence bases highlighted that nabilone was effective in some outcomes when compared to placebo and prochlorperazine. Therefore, it could provide some relief to patients with persistent nausea and vomiting.

However, keeping in line with current clinical practice and the availability of new antiemetics, the committee recommended for nabilone to be considered as an add-on therapy to optimised conventional antiemetics in people in with persistent chemotherapy- induced nausea and vomiting. If useful, this could help improve quality of life for patients as well as overall treatment experience.

One of the main concerns with the use of CBMPs was the potential for adverse events. The evidence base for delta-9-tetrahydrocannabinol (THC) highlighted that as well as having poor effectiveness data, more adverse events occurred in the THC arm when compared to placebo. Similar results were also identified in children. Most commonly reported adverse events in people in whom THC was administered included a feeling of 'high', sedation and dizziness. While the committee noted that sedation might not necessarily be considered an untoward effect in this patient population, feeling of high and dizziness can be disorientating to people.

THC is the psychoactive constituent of cannabis. While the committee noted that CBMPs would be used for a short period of time in people with CINV, they agreed that it is important to understand the impact of THC on the development of psychological disorders such as psychosis and schizophrenia as well as dependence. However, there was a lack of data reporting these events. Due to this the committee were unable to make a recommendation for the use of THC for persistent nausea and vomiting due to chemotherapy.

The evidence base for dronabinol was also poor in terms of effectiveness data. Furthermore, studies examining the use of dronabinol commonly reported side effects such as dizziness, somnolence, digestive side effects such as diarrhoea and dry mouth. With a lack of information on adverse events, the committee were unable to make a recommendation for the use of dronabinol for persistent nausea and vomiting due to chemotherapy.

Studies which examined the use of nabilone in adults showed that nabilone resulted in more adverse events when compared to placebo. Additionally, the most commonly reported adverse events included drowsiness, dizziness and dry mouth. A similar trend was identified in studies which included children. While one study found that use of nabilone resulted in the overall rate of improvement in retching and vomiting, greater number of adverse events also occurred in this arm. Studies that included children also reported adverse events such as mood changes [Dalzell 1986 and Chan 1987]. There was a lack of evidence on the development of psychological disorders and dependence. This was also a concern as the use CBMPs may be repeated in patients undergoing multiple cycles of chemotherapy.

The summary of product characteristics (SPC) for nabilone also identified similar adverse events to those highlighted in the studies included in the review. The SPC also highlighted other commonly reported adverse events which included: visual disturbance, concentration difficulties, sleep disturbance, dysphoria, hypotension,

headache and nausea. The committee also noted that the SPC specifies that nabilone is an abusable substance and therefore prescriptions should be limited to the amount necessary for a single cycle of chemotherapy. The committee further noted that the physical dependence capability of nabilone is still unknown.

Considering the adverse events and the uncertainty around dependence and development of psychological disorders, the committee noted that strong recommendations could not be made for the use of nabilone. Therefore, the committee recommended for nabilone to be considered as an adjunct treatment in adults.

Additionally, the evidence base for the use of nabilone in children was poor. It was also identified that nabilone is not currently licenced in children younger than 18 years of age as it's safety and efficacy have not been established. Therefore, the committee did not make recommendations for the use of nabilone in children. In order to further understand the adverse events associated with the use of CBMPs the committee made further research recommendations in the adult population and in babies and children.

Cost effectiveness and resource use

No published economic evidence was identified, and this topic was not prioritised for de novo economic modelling. Other topics were agreed to be higher priority for original modelling because the patient population is likely to be relatively small compared to other indications considered in this guideline. In addition, patients with intractable nausea and vomiting often receive treatment for a finite period of time (for example a cycle of chemotherapy), meaning that the resource impact per patient is likely to be lower than in other indications where treatment may be provided indefinitely.

In the absence of any published economic evidence or de novo analysis, the committee made a qualitative assessment about the cost effectiveness of medicinal cannabis for adults with chemotherapy-induced nausea and vomiting, which persists despite the use of conventional optimal antiemetic treatments.

Albeit low quality, the clinical review provided some evidence for the benefit of nabilone in reducing chemotherapy-induced nausea and vomiting.

The committee noted that the size of the eligible population and length of use varied, depending on different chemotherapies. In most cases clinicians would only offer nabilone for relieving nausea and vomiting for a limited period of time during cycles of chemotherapy.

They acknowledged that there might be some resource impact on the NHS as a result of their recommendation. The cost of nabilone was estimated to be £20-59 per day of treatment. They considered that any resource impact would be unlikely to be significant as nabilone would typically not be offered continuously. Given that persistent chemotherapy-induced nausea and vomiting could lead to additional health care resources, such as a hospital stay and patients would be unlikely to continue treatment for long if it was not providing benefit, the committee concluded that nabilone could be a cost-effective add-on treatment option. This was in contrast to other reviews in this guideline, where the more modest effect sizes and/or the long term nature of the treatment rendered CBMPs unlikely to be cost-effective.

Other factors the committee took into account

Dose, treatments duration, monitoring requirements and stopping criteria

The evidence base showed that nabilone demonstrated effectiveness in some outcomes such as complete reduction in nausea and vomiting. However, the committee noted that information on dose, treatments duration, monitoring requirements and stopping criteria would be important for healthcare professionals to consider when administering nabilone.

In terms of dosage, studies that examined the use of nabilone for CINV typically administered 1-2mg nabilone. Furthermore, doses were usually given the night before chemotherapy, on the day of chemotherapy and then repeated for at least 24 hours after chemotherapy was stopped. In terms of patient monitoring, several studies stated that blood pressure was taken in the erect and supine position after taking nabilone as well as laboratory monitoring, such as platelet count and urinalysis. A stopping criterion was not specified in these studies, but people withdrew from studies mainly due to intercurrent illness, inefficacy and adverse events.

Due to the lack of information, the committee were unable to make specific recommendations on dose, treatment duration, monitoring requirements and stopping criteria. However, the committee noted that this information can be obtained from the SPC, which is used as part of current practice.

Contraindications

The committee also noted that studies did not provide adequate information on contraindications such as drug interactions. Drug interactions are a concern because CBMPs can act as enzyme inhibitors of the cytochrome P-450 isoenzymes and can reduce the excretion of drugs such as opioids, which can lead to drug toxicity. Furthermore, people may be using different prescribed medications as well as using food supplements obtained from health food shops. Therefore, it is important to highlight any potential interactions.

The SPC also states that nabilone should be administered with caution in people who are also taking other psychoactive drugs or CNS depressants, including alcohol, barbiturates and narcotic analgesics. Nabilone has also been shown to have an additive CNS depressant effect when given with diazepam, secobarbital, alcohol or opioids. Due to these concerns, the committee recommended that potential adverse drug interactions should be considered particularly when prescribing nabilone with central nervous system depressants and other centrally active drugs.

Furthermore, due to lack of information on other contraindications, the committee were unable to make specific recommendations. However, this information can be obtained from the SPC which highlights that caution should be taken when considering use of nabilone in people with a history of psychiatric disorder, including manic-depressive illness and schizophrenia as well as the elderly with hypotension and heart disease.

Additionally, overarching recommendations have been made on factors that need to be considered when prescribing which include, mental health history and the potential for interaction with other medicines.

Subgroups

The committee identified young people, children and babies, pregnant women and women who were breastfeeding, people with existing substance abuse and people

with hepatic and renal failure as important subgroups. Overall, 3 studies [Ekert 1979, Chan 1987 and Dalzell 1986] were identified which explored the effects of CBMPs in children and young people. However, only 1 study [Chan 1979] contributed effectiveness data on the use of nabilone. This study showed no significant reduction in retching and vomiting or complete reduction in retching and vomiting. This study also demonstrated that more adverse events occurred in children taking nabilone compared to those taking prochlorperazine.

Additionally, no studies were identified which examined the effectiveness of CBMPs in babies, pregnant women and women who are breastfeeding, in people with hepatic or renal failure or in people with existing substance abuse. However, it should be noted that one study [Ungerleider 1985] was identified which conducted subgroup analyses in people with some experience of illicit drug use, but the study did not further specify the substances which people had used. The committee also further noted that several studies excluded people with hepatic or renal disease or with previous experience of, or regular use of, marijuana, or drug addiction.

The committee were unable to make specific recommendations for these subgroups but noted that this information is available in the SPC. Additionally, overarching recommendations have been made on factors that need to be considered when prescribing which include, current and past use of cannabis, history of substance misuse, pregnancy and breastfeeding and medical history, in particular liver impairment, renal impairment, cardiovascular disease.

The committee also drafted research recommendations to further explore the effectiveness of CBMPs as an add-on treatment to optimised conventional antiemetics in adults with persistent CINV as well as in people with persistent nausea or vomiting not caused by chemotherapy. Pregnant women and women who are breastfeeding, people with existing substance abuse and people with hepatic and renal failure were included as subgroups of interest. Additionally, a separate research recommendation on the clinical and cost effectiveness of cannabis-based medicinal products as an add-on treatment in babies, children and young adults with persistent chemotherapy-induced nausea or vomiting was drafted.

Other causes of persistent nausea and vomiting

In this review, 28 studies were included, with only 1 study [Priestman 1987] focusing on radiotherapy-induced nausea and vomiting. However, this study did not provide effectiveness data on the use of nabilone. Due to a lack of evidence, the committee were unable to make recommendations for the use of CBMPs in people with radiotherapy induced nausea and vomiting.

The committee noted that there are cancer and non-cancer causes of persistent nausea and vomiting, however due to a lack of evidence, recommendations could only be made on the use of CBMPs in people with CINV. However, the committee did identify this as an important area for research and therefore drafted research recommendations to further explore the effectiveness of CBMPs in other populations.

This evidence review supports recommendations 1.1.1 and 1.1.2 and the research recommendations on chemotherapy-induced intractable nausea and vomiting in adults, chemotherapy-induced intractable nausea and vomiting in babies, children and young people and intractable nausea and vomiting not caused by chemotherapy.

Glossary

Cannabis-based medicinal products
In this guideline cannabis-based medicinal products include:

- cannabis-based products for medicinal use as set out by the UK Government in the 2018 Regulations
- the licensed products delta-9-tetrahydrocannibinol and cannabidiol (Sativex) and nabilone
- plant-derived cannabinoids such as pure cannabidiol (CBD)
- synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC), for example, dronabinol.

Conventional optimal antiemetics
These are treatments that are commonly used in practice at an optimum tolerated dose to manage nausea and vomiting.

Appendix A – Review protocols

Review protocol for clinical effectiveness, cost effectiveness, contraindications, potential interactions, individual patient monitoring requirements, treatment durations, reviewing and stopping criteria for cannabis based medicinal products

Field (based on PRISMA-P	Content
Review question	What is the clinical and cost effectiveness of cannabis-based medicinal products for people with intractable nausea and vomiting? What are the adverse effects or complications of cannabis-based medicinal products for people with intractable nausea and vomiting? What are the contraindications, potential interactions and risks and cautions for use of cannabis-based medicinal products for people with intractable nausea and vomiting? What are the individual patient monitoring requirements, treatment durations, reviewing and stopping criteria, including how should treatment be withdrawn or stopped, for use of cannabis-based medicinal products for people with intractable nausea and vomiting?
Type of review question	Intervention
Objective of the review	To determine the effectiveness, harms and cost-effectiveness of cannabis based medicinal products in reducing intractable nausea and vomiting.

Field (based on PRISMA-P	Content
Eligibility criteria – population/disease/condition/issue/domain	Adults, young people, children and babies with intractable nausea or vomiting. Specific considerations will be given to: Young people, children and babies Pregnant women and women who are breastfeeding People with existing substance misuse People with hepatic and renal failure Intractable nausea or vomiting can be defined as persistent nausea or vomiting that does not respond fully to standard antiemetic treatment. The terms intractable and persistent can be used interchangeably. Intractable nausea or vomiting can be induced by chemotherapy, radiotherapy and other non-cancer causes.
Eligibility criteria – intervention	Cannabis-based products for medicinal use (as per government definition): A cannabis-based product for medicinal use that is a preparation or other product, other than one to which paragraph 5 of part 1 of schedule 4 applies, which: is or contains cannabis, cannabis resin, cannabinol or a cannabinol derivative (not being dronabinol or its stereoisomers) is produced for medicinal use in humans; and is a medicinal product, or a substance or preparation for use as an ingredient of, or in the production of an ingredient of, a medicinal product (MDR 2018 regulations)

Field (based on PRISMA-P	Content
	Synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC) for example dronabinol Licensed products Sativex and nabilone Plant-derived cannabinoids such as pure cannabidiol For the purpose of this guideline, all the interventions above will be classed as cannabis-based medicinal products.
Eligibility criteria – comparator	Placebo Any relevant antiemetic treatment Combination of treatments Usual or standard care.
Outcomes	Reduction of nausea and vomiting Reduction of nausea Reduction of vomiting Reduction in retching Participant reported improvement on a global impression change (PGIC) scale Quality of life scores Serious adverse events Adverse events including but not limited to sleep problems, fatigue, road traffic accidents, psychological distress, dizziness, headache, confusion state, paranoia, psychosis, substance dependence, diarrhoea at the start of treatment Withdrawals due to adverse events Complications due to adverse events Substance abuse due to the use of cannabis-based medicinal product.

Field (based on PRISMA-P	Content
	Misuse/diversion Hepatic and renal failure Outcomes requiring a narrative synthesis: Contraindications as listed in exclusion criteria Monitoring requirements, treatment durations, reviewing and stopping criteria, including how should treatment be withdrawn stopped as discussed in the methods of included studies.
Eligibility criteria – study design	For adults: RCTs Systematic reviews of RCTs The committee noted that a minimum of 5 RCTs were required to provide adequate evidence. If less than five RCTs identified, prospective cohort studies will be used. For children: RCTs Systematic reviews of RCTs If less than five RCTs identified, prospective and retrospective cohort studies will be used. Additional information on safety concerns and contraindications will be obtained from the Summary of Product Characteristics and other relevant sources, such as the U.S Food and Drugs Administration.

Field (based on PRISMA-P	Content
Other inclusion/exclusion criteria	Inclusion Cannabis-based products for the medicinal use when other treatments haven't helped or have been discounted. Exclusion Synthetic cannabinoids In schedule 1 of the 2001 regulations, Smoked cannabis-based products Studies which do not report the doses or the concentration of cannabinoid constituents. For randomised crossover studies, washout periods of less than 1 week.
sub-group analysis	Subgroups, where possible, will include: Young people, children and babies Pregnant women and women who are breastfeeding People with existing substance abuse
Selection process – duplicate screening/selection/analysis	10% of the abstracts will be reviewed by two reviewers, with any disagreements will be resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements are found between the different reviewers, a further 10% of the abstracts will be reviewed by two reviewers, with this process continuing until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer.
Data management (software)	See Appendix B.

Field (based on PRISMA-P	Content
Information sources – databases and dates	Sources to be searched Clinical searches - Medline, Medline in Process, Medline EPub Ahead of Print, Embase, Cochrane CDSR, CENTRAL, DARE (legacy records), HTA, MHRA. Economic searches - Medline, Medline in Process, Medline EPub Ahead of Print, Embase, Econlit, NHS EED (legacy records) and HTA, with economic evaluations and quality of life filters applied. Supplementary search techniques None identified Limits Studies reported in English Study design RCT, SR and Observational filter will be applied (as agreed) Animal studies will be excluded from the search results Conference abstracts will be excluded from the search results No date limit will be set.
Identify if an update	N/A
Author contacts	Guideline updates team
Highlight if amendment to previous protocol	This is a new protocol.
Search strategy – for one database	For details please see Appendix C of relevant chapter.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as Appendix D (clinical evidence tables) or H (economic evidence tables).

Field (based on PRISMA-P	Content
Data items – define all variables to be collected	For details please see evidence tables in Appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Study checklists were used to critically appraise individual studies. For details please see Appendix H Developing NICE guidelines: the manual The following checklists will be used: Risk of bias of intervention studies - systematic reviews and meta-analyses will be assessed using the Risk of Bias in Systematic Reviews (ROBIS) checklist Risk of bias of intervention studies – randomised controlled trials (individual or cluster) will be assessed using the Cochrane risk of bias (RoB) 2.0 tool Risk of bias of cohort studies will be assessed using Cochrane ROBINS-I The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see section 6 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the methods and process section of the main file.

Field (based on PRISMA-P	Content
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review in the main file.
Describe contributions of authors and guarantor	A multidisciplinary committee [add link to history page of the guideline] developed the evidence review. The committee was convened by NICE Guideline Updates Team and chaired by Steve Pilling in line with section 3 of Developing NICE guidelines: the manual. Staff from NICE undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.

Appendix B - Methods

1.1 Priority screening

The reviews undertaken for this guideline all made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. This uses a machine learning algorithm (specifically, an SGD classifier) to take information on features (1, 2 and 3 word blocks) in the titles and abstract of papers marked as being 'includes' or 'excludes' during the title and abstract screening process, and re-orders the remaining records from most likely to least likely to be an include, based on that algorithm. This re-ordering of the remaining records occurs every time 25 additional records have been screened.

As an additional check to ensure this approach did not miss relevant studies, the included studies list of included systematic reviews were searched to identify any papers not identified through the primary search.

1.2 Evidence synthesis and meta-analyses

Where possible, meta-analyses were conducted to combine the results of quantitative studies for each outcome. Dichotomous outcomes were reported as risk ratios.

1.3 Evidence of effectiveness of interventions

Quality assessment

Parallel RCTs were quality assessed using the Cochrane Risk of Bias Tool for randomised trials (RoB 2.0). For crossover RCTs, Cochrane Risk of Bias Tool (RoB 2.0) for crossover trials was used.

Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Some concern around risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

The review protocol stated that if fewer than 5 RCTs were identified then prospective cohort studies would be included. However, full-text screening of observational studies found no prospective cohort studies that met the inclusion criteria. It was therefore agreed to deviate from the protocol and include non-comparative study designs as part of the review. This resulted in the inclusion of 1 non-comparative observational study which included children. The committee also identified this study to be reflective of current practice.

This study was quality assessed using the Institute of Health Economics (IHE) Quality Appraisal Checklist. Studies were assessed on the methods of participant recruitment, retention and outcome measurement (as appropriate), with each individual study classified into one of the following three groups:

- Low risk of bias – The true result for the study is likely to be close to the estimated result
- Moderate risk of bias – There is a possibility the true result for the study is substantially different to the estimated result.

- High risk of bias – It is likely the true result for the study is substantially different to the estimated result.

Each individual study, both RCTs and observational studies were also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Methods for combining intervention evidence

Meta-analyses of interventional data were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event. Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the pooled risk in the comparator arm of the meta-analysis (all pooled trials).

Fixed- and random-effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken.
- The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

Meta-analyses were performed in Cochrane Review Manager V5.3.

Due to the nature of the evidence, GRADE approach was not applied to data from the single arm study. Table summarising the evidence was included in the evidence review.

Minimal clinically important differences (MIDs)

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus MID could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required a MID to be defined to act as a non-inferiority margin.

No MIDs were not identified through the COMET database or by the Guideline Committee. Therefore, it was agreed with the committee that the line of no effect was used to assess imprecision.

When decisions were made in situations where MIDs were not available, the 'Evidence to Recommendations' section of that review should make explicit the committee's view of the expected clinical importance and relevance of the findings. In particular, this includes consideration of whether the whole effect of a treatment (which may be felt across multiple independent outcome domains) would be likely to be clinically meaningful, rather than simply whether each individual sub outcome might be meaningful in isolation.

GRADE for pairwise meta-analyses of interventional evidence

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2018)'. Data from all study designs was initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in Table 1

Table 1: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.

GRADE criteria	Reasons for downgrading quality
Imprecision	If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

The quality of evidence for each outcome was upgraded if any of the following three conditions were met:

- Data from non-randomised studies showing an effect size sufficiently large that it cannot be explained by confounding alone.
- Data showing a dose-response gradient.
- Data where all plausible residual confounding is likely to increase our confidence in the effect estimate.

Summary of evidence

The evidence is presented in the form of a table because the committee agreed in advance that effect sizes would be an important consideration. Summary of evidence is stratified by population and reflects evidence that was statistically significant.

Where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), and the magnitude of that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the evidence showed that there is an effect. In all other cases, we state that the evidence could not differentiate between the comparators.

Appendix C - Literature search strategies

A single systematic search was conducted for all of the questions within this evidence review between 19th December 2018 and 21st January 2019. The following databases were searched MEDLINE, MEDLINE in Process, MEDLINE e pub Ahead of print, Embase, (all via the Ovid platform), Cochrane Database of Systematic Reviews CENTRAL (all via the Wiley platform), and the HTA and DARE databases (both via the CRD platform). NICE inhouse RCT, systematic review, and observational filters were attached where appropriate.

The MEDLINE strategy is presented below. This was translated for other databases

1 Medical Marijuana/

2 cannabinoids/ or cannabidiol/ or cannabinol/ or cannabis/

3 ((cannabi* or hemp or marijuana or marihuana) adj4 (medicine* or medicinal or medical or oil or oils or product* or extract* or therap* or CBD or vap* or spray* or inhal* or compound* or resin* or derivative*)).tw.

4 (epidiolex* or cannabidiol* or cannabinoid*).tw.

5 (sativex or nabiximols or tetrabinex or nabidiolex).tw.

6 (nabilone or cesamet).tw.

7 (tilray* or bedrocan* or bedrobinol* or bedica* or bediol* or bedrolite*).tw.

8 Dronabinol/

9 (dronabinol* or marinol* or syndros*).tw.

10 (9-ene-tetrahydrocannabinol* or 9enetetrahydrocannabinol*).tw.

11 (THC or tetrahydrocannabinol*).tw.

12 ("delta(1)-thc*" or "delta(1)-tetrahydrocannabinol*" or "delta(9)-thc*" or "delta(9)-tetrahydrocannabinol*").tw.

13 (9-delta-tetra-hydrocannabinol* or "9-delta-THC*" or "9 delta tetra hydrocannabinol*" or "9 delta THC*").tw.

14 (1-delta-tetra-hydrocannabinol* or "1-delta-THC*" or "1 delta tetra hydrocannabinol" or "1 delta thc*").tw.

15 THCa.tw.

16 CBDa.tw.

17 cannabinol*.tw.

18 cannabigerol*.tw.

19 cannabichromene*.tw.

20 (tetrahydrocannabivarin* or THCV).tw.

21 (cannabidivarin* or CBDV).tw.

22 or/1-21

23 animals/ not humans/

24 22 not 23

25 limit 24 to english language

26 Randomized Controlled Trial.pt.

27 Controlled Clinical Trial.pt.

28 Clinical Trial.pt.

29 exp Clinical Trials as Topic/

30 Placebos/

31 Random Allocation/

32 Double-Blind Method/

33 Single-Blind Method/

34 Cross-Over Studies/

35 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw.

36 (random$ adj3 allocat$).tw.

37 placebo$.tw.

38 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.

39 (crossover$ or (cross adj over$)).tw.

40 or/20-33

41 Meta-Analysis.pt.

42 Network Meta-Analysis/

43 Meta-Analysis as Topic/

44 Review.pt.

45 exp Review Literature as Topic/

46 (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw.

47 (review$ or overview$).ti.

48 (systematic$ adj5 (review$ or overview$)).tw.

49 ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw.

50 ((studies or trial$) adj2 (review$ or overview$)).tw.

51 (integrat$ adj3 (research or review$ or literature)).tw.

52 (pool$ adj2 (analy$ or data)).tw.

53 (handsearch$ or (hand adj3 search$)).tw.

54 (manual$ adj3 search$).tw.

55 or/35-48

56 34 or 49

57 19 and 50

58 Observational Studies as Topic/

59 Observational Study/

60 Epidemiologic Studies/

61 exp Case-Control Studies/

62 exp Cohort Studies/

63 Cross-Sectional Studies/

64 Controlled Before-After Studies/

65 Historically Controlled Study/

66 Interrupted Time Series Analysis/

67 Comparative Study.pt.

68 case control$.tw.

69 case series.tw.

70 (cohort adj (study or studies)).tw.

71 cohort analy$.tw.

72 (follow up adj (study or studies)).tw.

73 (observational adj (study or studies)).tw.

74 longitudinal.tw.

75 prospective.tw.

76 retrospective.tw.

77 cross sectional.tw.

78 or/26-45

79 25 and 46

80 57 or 79

Searches to identify economic evidence were run on 20th December 2018 in MEDLINE, MEDLINE in Process, MEDLINE e pub Ahead of print, Econlit and Embase (all va the Ovid platform), NHS EED and the Health Technology Assessment Database (via the CRD platform). NICE inhouse economic evaluation and Quality of Life filters were attached to lines 1 to 25 of the core strategy (lines 1 to 25 of the MEDLINE version shown above) in the MEDLINE and Embase databases. The MEDLINE version of the filters is displayed below.

Economic evaluations

Economics/

exp "Costs and Cost Analysis"/

Economics, Dental/

exp Economics, Hospital/

exp Economics, Medical/

Economics, Nursing/

Economics, Pharmaceutical/

Budgets/

exp Models, Economic/

Markov Chains/

Monte Carlo Method/

Decision Trees/

econom$.tw.

cba.tw.

cea.tw.

cua.tw.

markov$.tw.

(monte adj carlo).tw.

(decision adj3 (tree$ or analys$)).tw.

(cost or costs or costing$ or costly or costed).tw.

(price$ or pricing$).tw.

budget$.tw.

expenditure$.tw.

(value adj3 (money or monetary)).tw.

(pharmacoeconomic$ or (pharmaco adj economic$)).tw.

or/1-25

Quality of Life

1. "Quality of Life"/
2. quality of life.tw.
3. "Value of Life"/
4. Quality-Adjusted Life Years/
5. quality adjusted life.tw.
6. (qaly$ or qald$ or qale$ or qtime$).tw.

7. disability adjusted life.tw.
8. daly$.tw.
9. Health Status Indicators/
10. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
11. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
12. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
13. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
14. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
15. (euroqol or euro qol or eq5d or eq 5d).tw.
16. (qol or hql or hqol or hrqol).tw.
17. (hye or hyes).tw.
18. health$ year$ equivalent$.tw.
19. utilit$.tw.
20. (hui or hui1 or hui2 or hui3).tw.
21. disutili$.tw.
22. rosser.tw.
23. quality of wellbeing.tw.
24. quality of well-being.tw.
25. qwb.tw.
26. willingness to pay.tw.
27. standard gamble$.tw.
28. time trade off.tw.
29. time tradeoff.tw.
30. tto.tw.
31. or/1-30

A search of the MHRA was undertaken on the 24th January 2019 to look for safety updates, alerts and recalls. The search terms are displayed below.

Sativex

Dronabinol

Epidiolex

Nabiximols

Abalone

Tetrabinex

Nabidiolex

Cesamet

Tilray

Bedrocan

Bedrobinol

Bedica

Bediol

Bedrolite

Marinol

Syndros

THC

Tetrahydrocannabinol

Cannabinol

Cannibigerol

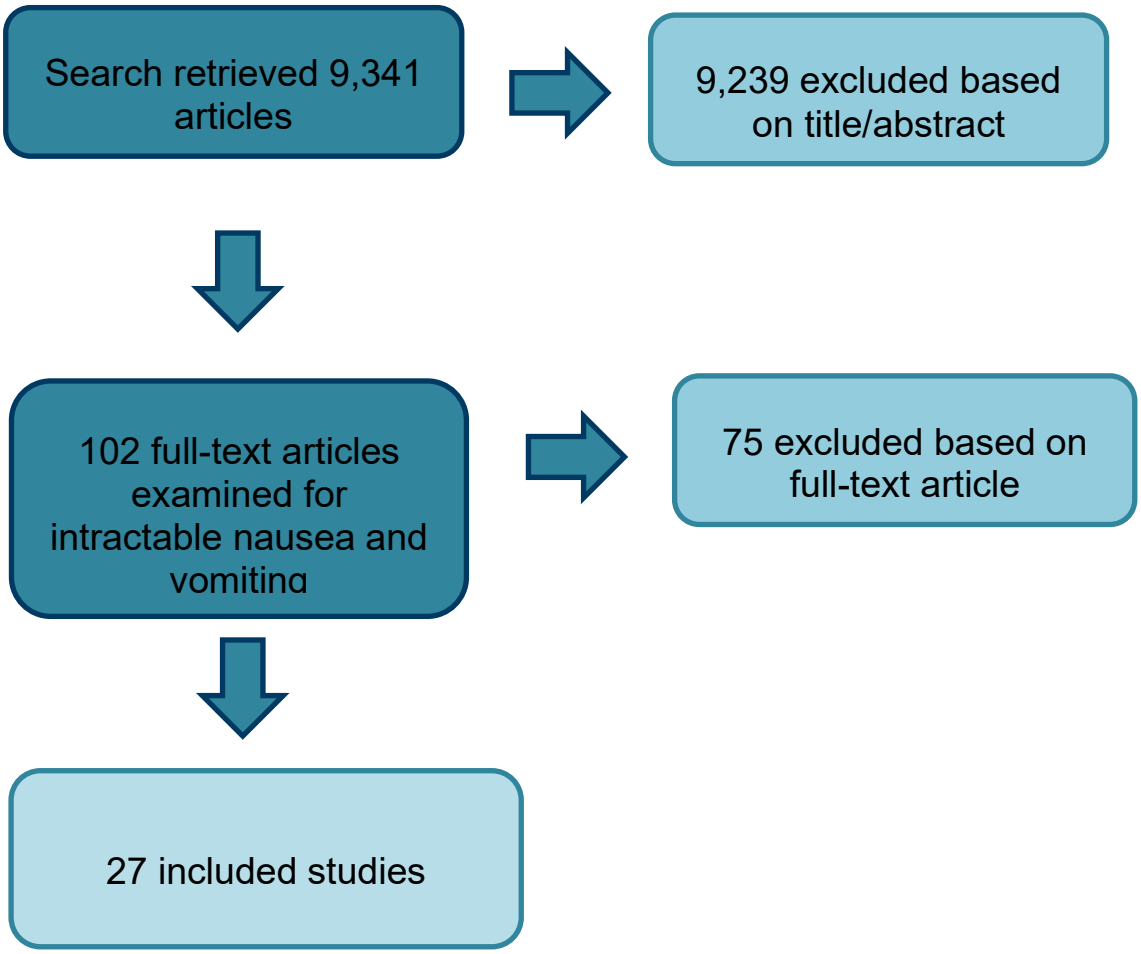
Cannabichromene

Tetrahydrocannabivarin

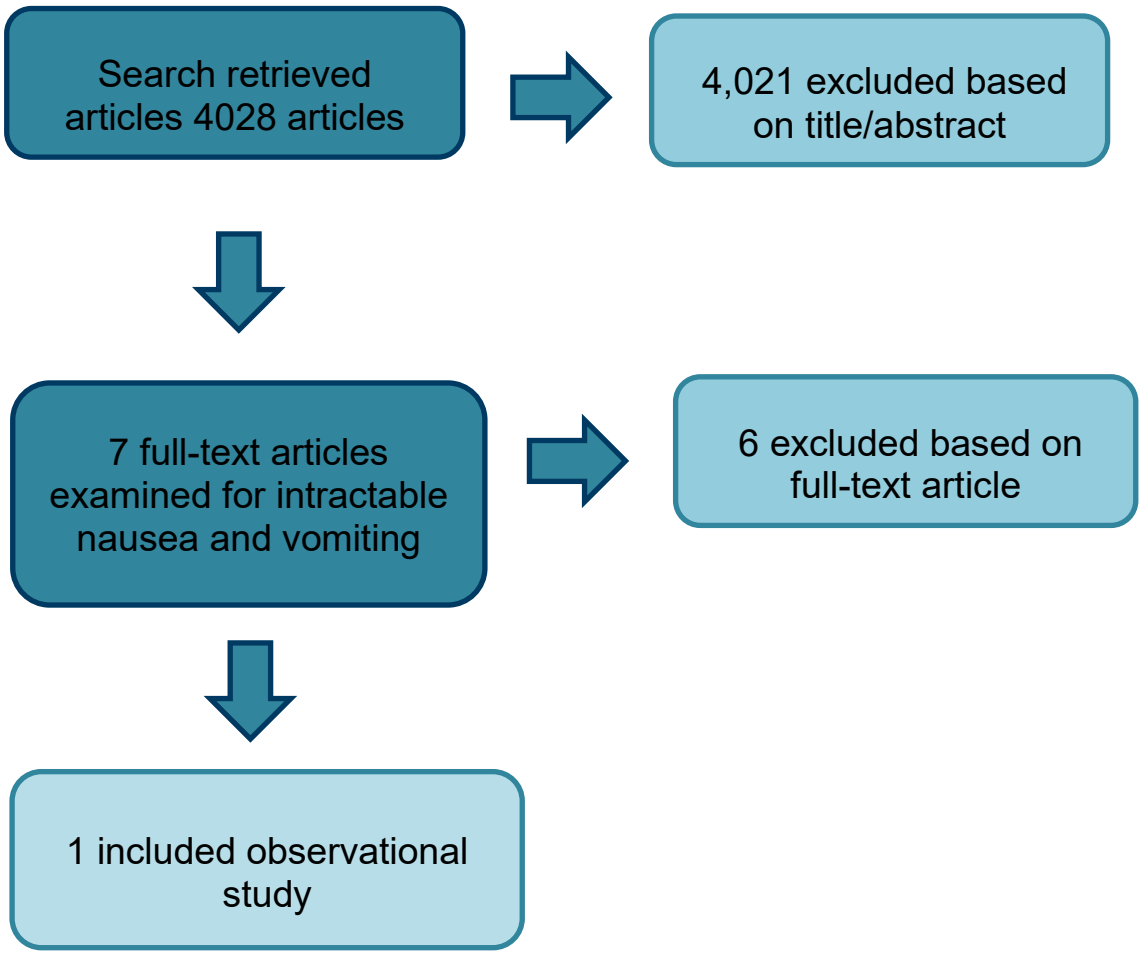
Cannabidivarin

Appendix D – Clinical evidence study selection

RCTs and systematic reviews of RCTs search



Observational studies search



Appendix E – Clinical evidence table

E.1 Parallel RCTs

Ekert 1979

Ekert, 1979	
Bibliographic Reference	Ekert, H.; Waters, K. D.; Jurk, I. H.; Mobilia, J.; Loughnan, P.; Amelioration of cancer chemotherapy-induced nausea and vomiting by delta-9-tetrahydrocannabinol; The Medical journal of Australia; 1979; vol. 2 (no. 12); 657-659

Study details

Study type	Randomised controlled trial (RCT)
Study location	Melbourne, Australia
Study setting	Department of Clinical Haematology and Oncology, Pharmacy, and Clinical Pharmacology
Study dates	Not specified
Duration of follow-up	Not specified
Sources of funding	Research Technology Branch, National Institute of Drug Abuse, (Maryland, USA) supplied THC. R.P Scherer Pty Ltd. (Melborne) supplied the placebo syrup. Beecham (Australia) Pty. Ltd. supplied metoclopramide syrup. Protea Pharaceuticals Pty Ltd. Syndey supplied prochlorperazine tablets. Rotary Tabeting Cooperation Pty Ltd Melbourne supplied placebo tablets.
Inclusion criteria	Children with various neoplastic diseases requiring chemotherapy
Exclusion criteria	Not stated

Study type	Randomised controlled trial (RCT)
Sample size	THC vs metochlopramide 19 children THC vs prochlorperazine 14 children
Loss to follow-up	Not reported
Symptom specific characteristics	Chemotherapy induced nausea and vomiting. Patients received single agents (e.g. methotrexate) and combination chemotherapy: vincristine, doxorubicin. dacarbazine vincristine, cyclophosphamide, doxorubicin, prednisolone cytosine arabinoside, cyclophosphamide, asparaginase cytosine arabinoside, 6-thioguanine 5-fluouracil, doxorubicin, actinomycin D Vincristine, Lomustin
Intervention 1	THC plus placebo
Intervention 2	Metoclopramide plus placebo
Intervention 3	THC

Study type	Randomised controlled trial (RCT)
	plus placebo
Intervention 4	Prochlorperazine plus placebo
Outcome measures	Adverse events No vomiting

Study arms

THC (N = 17)

17 courses of anticancer chemotherapy were randomised. Placebo syrup

Split between study groups	17 courses
% Female	21% (overall)
Mean age (SD)	Overall Median age: 11 years Range- 5- 19 years
Formulation	5mg and 2.5mg capsules Patient took THC with placebo syrup.
How dose was titrated up	Not reported
What the maintenance dose was	10mg/m² with a maximum dose of 15 mg.

How long the maintenance dose was sustained for	This was given 2 hours before chemotherapy, and at 4,8,16 and 24 hours after the first dose.
Monitoring/reviewing procedure	Not reported
Stopping criteria	Not reported

THC (N = 18)

18 courses of anticancer chemotherapy were randomised. placebo tablet

Split between study groups	**18 courses**
% Female	Overall 50%
Mean age (SD)	Overall Median age: 14 years Range: 6-19 years
Symptom specific characteristics	Chemotherapy induced nausea and vomiting. Patients received single agents (e.g. methotrexate) and combination chemotherapy.
Formulation	5mg and 2.5mg capsules
How dose was titrated up	Not reported
What the maintenance dose was	10mg/m² with a maximum dose of 15 mg.

How long the maintenance dose was sustained for	This was given 2 hours before chemotherapy, and at 4,8,16 and 24 hours after the first dose.
Monitoring/reviewing procedure	Not reported
Stopping criteria	Not reported

Metoclopramide (N = 25)

25 courses of anticancer chemotherapy were randomised. placebo

Split between study groups	**25 courses**
% Female	21% (overall)
Mean age (SD)	Overall Median age: 11 years Range- 5- 19 years
Symptom specific characteristics	Chemotherapy induced nausea and vomiting. Patients received single agents (e.g. methotrexate) and combination chemotherapy.
Formulation	syrup at a concentration of 1 mg/mL Placebo capsules made of soft gelatin containing peanut oil was also administered
How dose was titrated up	Based on surface area

What the maintenance dose was	10 mg for patients with body surface area greater than 0.7m² and in a dose of 5mg for patients with body surface area less than 0.7m² . It was given on the same time schedule as THC but to prevent neurological toxicity, the 4 hour dose was always a placebo
How long the maintenance dose was sustained for	This was given 2 hours before chemotherapy, and at 4,8,16 and 24 hours after the first dose.
Monitoring/reviewing procedure	Not reported
Stopping criteria	Not reported

Prochlorperazine (N = 18)

18 courses of anticancer chemotherapy were randomised. placebo

Split between study groups	**18 courses**
% Female	Overall 50%
Mean age (SD)	Overall Median age: 14 years Range: 6-19 years
Formulation	5- 10 mg prochlorperazine
How dose was titrated up	Based on surface area

What the maintenance dose was	The doses of prochlorperazine were as follows; for children with SA 0.7 to 1.1 m² = 5 mg at 2 hours before chemotherapy, 8, 16, 24 hours after chemotherapy; for children with SA 1.1 to 1.4 m² = 10 mg at 2 hours before chemotherapy, 8 hours and 5 mg at 16, 24 hours after chemotherapy and for children with SA > 1.4 m² = 10 mg given at 2 hours before chemotherapy, 8, 16, 24 hours after chemotherapy. Placebo was also given to these children at 4 hours after chemotherapy.
How long the maintenance dose was sustained for	r children with SA 0.7 to 1.1 m² = 2 hours before chemotherapy, 8, 16, 24 hours after chemotherapy; for children with SA 1.1 to 1.4 m² = 2 hours before chemotherapy, 8 hours and 5 mg at 16, 24 hours after chemotherapy for children with SA > 1.4 m² = 2 hours before chemotherapy, 8, 16, 24 hours after chemotherapy. Placebo was also given to these children at 4 hours after chemotherapy.
Monitoring/reviewing procedure	Not reported
Stopping criteria	Not reported

Cochrane Risk of Bias Tool 2.0
Domain 1: Bias arising from the randomization process
Risk of bias judgement for this domain
High
(Insufficient information on random sequence generation, allocation concealment and baseline differences between intervention groups. Study only provided information on the chemotherapy regimens followed in each arm.)
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for this domain
Low
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for this domain
This question has not yet been answered.

Cochrane Risk of Bias Tool 2.0
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for this domain
Low
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for this domain
Low
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement domain
Low
Overall bias and Directness
Risk of bias judgement
High
(Insufficient information on random sequence generation, allocation concealment and baseline differences between intervention groups. Study also does not state number of children allocated to each arm but instead reports the number of chemotherapy regimens randomised. Study only provided information on the chemotherapy regimens followed in each arm.)
Overall Directness
Partially applicable
(Study does not report if patients have previously experienced nausea and vomiting.)

Frytak 1979Frytak, 1979	
Bibliographic Reference	Frytak, S.; Moertel, C. G.; O'Fallon, J. R.; Rubin, J.; Creagan, E. T.; O'Connell, M. J.; Schutt, A. J.; Schwartau, N. W.; Delta-9-tetrahydrocannabinol as an antiemetic for patients receving cancer chemotherapy. A comparison with prochlorperazine and a placebo; Annals of Internal Medicine; 1979; vol. 91 (no. 6); 825-830

Study details

Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Department of Oncology

Study type	Randomised controlled trial (RCT)
Study dates	Not specified
Duration of follow-up	24 hours after chemotherapy Days 2-4 after chemotherapy
Sources of funding	Not specified
Inclusion criteria	Patients undergoing their initial chemotherapy exposure to combined 5- fluorouracil and semustine (methyl CCNU) either as a two drug combination or in three drug combinations with vincristine, doxorubicin (Adriamycin), razoane (ICRF 159) or triazinate. Patients at least 21 years old with unresectable gastrointestinal cancer or were participants in gastrointestinal cancer surgical adjuvant programs.
Exclusion criteria	Patients could not have been experiencing nausea or vomiting before entry into the study. Patients taking psychotherapeutic agents A past history of drug dependence or a significant psychological disturbance
Sample size	117 patients
Symptom specific characteristics	Chemotherapy induced nausea and vomiting. Patients were exposed to a strong emetic stimulus (emustine plus 5-flurouracil) on Day 1 and a weaker stimulus (5-flurouracil) on Days 2-4. Patients could not have been experiencing nausea and vomiting before entry into study.
Intervention 1	THC 15 mg of THC was administered. On day 1, the initial dose of antiemetic was given 2 hours before the initiation of chemotherapy. Subsequent doses were given 2 h and 8h after the initiation of chemotherapeutic treatment. On the remaining 3 days, the antiemetic agents were given three-time daily, ½ h before each regular meal
Intervention 2	Prochlorperazine 10 mg of prochlorperazine was administered. On day 1, the initial dose of antiemetic was given 2 hours before the initiation of chemotherapy. Subsequent doses were given 2 h and 8h after the initiation of chemotherapeutic treatment. On the remaining 3 days, the antiemetic agents were given three-time daily, ½ h before each regular meal.
Intervention 3	Placebo (lactose) -On day 1, the initial dose of antiemetic was given 2 hours before the initiation of chemotherapy. Subsequent doses were given 2 h and 8h after the initiation of chemotherapeutic treatment. On the remaining 3 days, the antiemetic agents were given three-time daily, ½ h before each regular meal

Study type	Randomised controlled trial (RCT)
Outcome measures	Adverse events Sedation, Coordination problems (any abnormality that upset the smooth, synchronous, relation between mind and body necessary for the normal functioning of the person) and 'high' (defined as a euphoric, dreamy, floating types of feeling). No nausea or vomiting during day 1 and Days 2-4

Study arms

THC (delta-9-tetrahydrocannabinol) (N = 38)

Loss to follow-up	18 studies dropped from the study after Day 1 because of intolerable central nervous system toxicity or excessive vomiting (10 from THC group)
% Female	42%
Mean age (SD)	21- 39: 3, 40-49:2, 50-59:14, 60-69:10, 70+: 9
Formulation	15 mg of THC was given to patients. The dosage was chosen to duplicate that previously used by Sallan and colleagues.
How dose was titrated up	Not reported.
What the maintenance dose was	15 mg
How long the maintenance dose was sustained for	On day 1, the initial dose of antiemetic was given 2 hours before the initiation of chemotherapy. Subsequent doses were given 2 h and 8h after the initiation of chemotherapeutic treatment. On the remaining 3 days, the antiemetic agents were given three-time daily, ½ h before each regular meal.

Monitoring/reviewing procedure	Study reports that patients were seen by physician each day and queried about side effects.
Stopping criteria	Stopping criteria not specified in method section. However, patients have refused to continue on study because of intolerable central nervous side effects.

Prochlorperazine (N = 41)

Loss to follow-up	**18 studies dropped from the study after Day 1 because of intolerable central nervous system toxicity or excessive vomiting (5 to prochlorperazine)**
% Female	49%
Mean age (SD)	21- 39: 3, 40-49: 4, 50-59: 10, 60-69: 17, 70+: 7
Formulation	10 mg of prochlorperazine
How dose was titrated up	Not reported.
What the maintenance dose was	10 mg
How long the maintenance dose was sustained for	On day 1, the initial dose of antiemetic was given 2 hours before the initiation of chemotherapy. Subsequent doses were given 2 h and 8h after the initiation of chemotherapeutic treatment. On the remaining 3 days, the antiemetic agents were given three-time daily, ½ h before each regular meal.
Monitoring/reviewing procedure	Study reports that patients were seen by physician each day and queried about side effects.
Stopping criteria	Stopping criteria not specified in method section. However, patients have refused to continue on study because of intolerable central nervous side effects.

Placebo (N = 27)

Loss to follow-up	**18 studies dropped from the study after Day 1 because of intolerable central nervous system toxicity or excessive vomiting (3 to placebo)**
% Female	27%
Mean age (SD)	21- 39:2, 40-49: 4, 50-59: 15, 60-69: 10, 70+: 6
How long the maintenance dose was sustained for	On day 1, the initial dose of antiemetic was given 2 hours before the initiation of chemotherapy. Subsequent doses were given 2 h and 8h after the initiation of chemotherapeutic treatment. On the remaining 3 days, the antiemetic agents were given three-time daily, ½ h before each regular meal.
Monitoring/reviewing procedure	Study reports that patients were seen by physician each day and queried about side effects.
Stopping criteria	Stopping criteria not specified in method section. However, patients have refused to continue on study because of intolerable central nervous side effects.

Cochrane Risk of Bias Tool 2.0
Domain 1: Bias arising from the randomization process
Risk of bias judgement for this domain
Low
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for this domain
Some Concerns
(No information provided for analysis methods)
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for this domain

Cochrane Risk of Bias Tool 2.0
This question has not yet been answered. **Domain 3. Bias due to missing outcome data** Risk-of-bias judgement for this domain High (Higher proportion of patients excluded from THC arm than Prochlorperazine or placebo arms. Reasons for exclusion may have been because of adverse events which may have been a reaction to the drug) **Domain 4. Bias in measurement of the outcome** Risk-of-bias judgement for this domain Some concerns (Outcomes based on patient-reported questionnaire which may result in subjective results) **Domain 5. Bias in selection of the reported result** Risk-of-bias judgement domain Low **Overall bias and Directness** Risk of bias judgement High (No information provided for analysis methods. Higher proportion of patients excluded from THC arm than Prochlorperazine or placebo arms. Reasons for exclusion may have been because of adverse events which may have been a reaction to the drug) **Overall Directness** Directly applicable (Adverse events) Partially applicable (No nausea or vomiting: Study specified that patients could not be experiencing nausea and vomiting before study, therefore cannot determine reduction)

Gralla 1984

Gralla, 1984	
Bibliographic Reference	Gralla, R. J.; Tyson, L. B.; Bordin, L. A.; Clark, R. A.; Kelsen, D. P.; Kris, M. G.; Kalman, L. B.; Groshen, S.; Antiemetic therapy: a review of recent studies and a report of a random assignment trial comparing metoclopramide with delta-9-tetrahydrocannabinol; Cancer treatment reports; 1984; vol. 68 (no. 1); 163-72

Study details

Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Hospital setting
Study dates	Not reported.
Duration of follow-up	24 hours after cisplatin administration
Sources of funding	Supported in part by a grant from the A.H Robins Co. and by Public Health Service grant from the National Cancer Institute.
Inclusion criteria	Patients who had a wbc equal to or greater than 4000 cells/mm3, platelet count equal to or greater than 120,000/mm3, creatinine clearance equal to or greater than 65 ml/minute and a serum bilirubin less than 2.0mg/dl. Receiving their first course cisplatin at a dose of 120 mg/m2 IV. Performance status >50% (Karnofsky scale) Patients with histologically confirmed malignancy
Exclusion criteria	Not stated
Sample size	31 patients
Symptom specific characteristics	Chemotherapy induced nausea and vomiting All patients were hospitalised to receive cisplatin at a dose of 120 mg/m² IV in a 20 minute infusion. Patients with lung or osophageal cancers also received a vinca alkaloid (vindesine or vinblastine) during the treatment period; these agents generally do not induce emesis. Not reported if patients had previously experienced nausea and vomiting.
Intervention 1	THC (1) 1) Delta-9-tetrahydrocannabinol. Supplied in 5- and 2.5 mg capsules
Intervention 2	Metoclopramide (2) 2) Supplied in 50- and 2ml vials, containing 150 and 10 mg of the agent
Outcome measures	Adverse events (3) 3) Sedation: graded as none, mild (patient lethargic but aroused by verbal stimuli and completely oriented when awakened), moderate (patient aroused only by physical stimuli and completely oriented when awakened) and marked (patient aroused only by physical stimuli and disoriented when awakened). Presence or absence of 'high', orthostatic hypotension (decrease ≥ 20 mm Hg), dry mouth, number of bowel movements and dystonic reactions. major antiemetic response (4)

Study type	Randomised controlled trial (RCT)
	4) (0-2 episodes)

Study arms

Delta-9 tetrahydrocannabinol (THC) (N = 15)

Loss to follow-up	No loss to follow-up
% Female	13%
Mean age (SD)	Median: 58 Range: 39-72
Formulation	THC given at a dose of 10mg/m² orally. THC was given 1.5 hours before cisplatin and 1.5, 4.5, 7.5 and 10.5 hours after chemotherapy- total dose of 50mg/m² of THC during the study period. Patients also received placebo via IV.
How dose was titrated up	Not reported.
What the maintenance dose was	Total dose of 50 mg/m² throughout study period.
How long the maintenance dose was sustained for	Up to 10.5 hours after chemotherapy.
Monitoring/reviewing procedure	All patients were observed in the hospital. Study does not give details of factors that were reviewed.
Stopping criteria	Not reported

Metoclopramide (N = 15)

Study type	Randomised controlled trial (RCT)
Loss to follow-up	One patient with lung cancer and a history of athrosclerotic cardiovascular disease experienced the onset of atrial 1 hour after receiving cisplatin. The patient had been given only the initial dose of metoclopramide.

% Female	33%
Mean age (SD)	Median: 58 Range: 45-70
Formulation	2mg/kg was added to 50 mil of 0.9% sodium chloride and infused over 15 minutes at the time of each dose. The dosage was kept constant throughout each trial and was administered at the following times: 30 minutes prior to cisplatin and 1.5,3.5,5.5 and 8.5 hours after therapy. The total dose of metoclopramide was 10mg/kg during the study period.
How dose was titrated up	Not reported.
What the maintenance dose was	10mg/kg during the study period.
How long the maintenance dose was sustained for	8.5 hours after chemotherapy.
Monitoring/reviewing procedure	All patients were observed in the hospital. Study does not give details of factors that were reviewed.
Stopping criteria	Not reported.

Cochrane Risk of Bias Tool 2.0
Domain 1: Bias arising from the randomization process
Risk of bias judgement for this domain
Some concerns
(Limited information about the randomisation process or allocation concealment)
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for this domain
Some Concerns
(Unclear if people delivering the interventions were aware of assigned intervention)
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Cochrane Risk of Bias Tool 2.0
Risk of bias judgement for this domain This question has not yet been answered. **Domain 3. Bias due to missing outcome data** Risk-of-bias judgement for this domain Low **Domain 4. Bias in measurement of the outcome** Risk-of-bias judgement for this domain Some concerns (Unclear whether outcome assessors were aware of intervention) **Domain 5. Bias in selection of the reported result** Risk-of-bias judgement domain Low **Overall bias and Directness** Risk of bias judgement Some concerns (Limited information on randomisation process and unclear whether outcome assessors were aware of the assigned intervention) **Overall Directness** Partially applicable (The study did not report if patients had previously experienced or exhibited intractable nausea and vomiting, therefore cannot determine reduction)

Lane 1991

Lane, 1991	
Bibliographic Reference	Lane, M.; Vogel, C. L.; Ferguson, J.; Krasnow, S.; Saiers, J. L.; Hamm, J.; Salva, K.; Wiernik, P. H.; Holroyde, C. P.; Hammill, S.; Shepard, K.; Plasse, T.; Original article. Dronabinol and prochlorperazine in combination for treatment of cancer chemotherapy-induced nausea and vomiting; Journal of Pain and Symptom Management; 1991; vol. 6 (no. 6); 352-359

Study details

Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Mutlicentre – 9 centres in total
Study dates	Not specified.
Duration of follow-up	Antiemetics were continued for 24 hours after the last dose of chemotherapy, up to a total of 6 days (1day prior and up to 5 days on chemotherapy.
Sources of funding	Study was supported by Rozane Laboratories and UNIMED. Inc.
Inclusion criteria	Age (1) 1) Patients between the ages of 18 and 69 years Being treated for cancer with chemotherapy other than investigational agents or high dose (>60mg/m2) cisplatin.
Exclusion criteria	Patients with central nervous system primaries or metastases
Sample size	62 patients
Symptom specific characteristics	Chemotherapy induced nausea and vomiting. All patients received prior chemotherapy and prior antiemetic therapy. Approximately one-half of each group had previously received either prochlorperazine, no patients had previously received dronabinol or any other cannabinoid. 27% of patients had experienced fewer than 2 episodes of nausea and vomiting with their prior chemotherapy/ antiemetic regiment. 52% has experienced between 2 and 10 episodes and 21% had experienced more than 10 episodes of nausea and vomiting. Patients included were on high (total 48) and low emetogenic agents (8). The most commonly used drugs were cyclophosphamide and doxorubicin (26 patients), 5-fluorouracil (14 patients), vincristine (13 patients) and etoposide (10 patients). Patients could receive treatment regimens lasting up to 5 days.
Intervention 1	Dronabinol +placebo (2) 2) Dronabinol 10 mg plus placebo 10 mg of dronabinol plus placebo was administered by mouth every 6 hours.
Intervention 2	Placebo plus Prochlorperazine (3) 3) Placebo plus Prochlorperazine 10 mg of prochlorperazine plus placebo was administered by mouth every 6 hours.
Intervention 3	Dronabinol + Prochlorperazine (5) 5) 10 mg of each were administered by mouth every 6 hours.
Outcome measures	Adverse events (4)

Study type	Randomised controlled trial (RCT)
	4) Patients were questioned at each visit regarding the occurrence of side effects Withdrawals due to adverse events two or fewer episodes of N&V No nausea and vomiting (complete response)

Study arms

Dronabinol (N = 21)

With prochlorperazine placebo

Loss to follow-up	**Withdrawn prior to chemotherapy: 3** **Side effects:10** **Insufficient therapeutic effect: 2** **Other: 2- intercurrent illness, protocol violation**
% Female	52%
Mean age (SD)	Median: 47 Range: 20-68
Formulation	Dronabinol 10 mg plus placebo was administered by mouth every 6 hours.
How dose was titrated up	Not reported
What the maintenance dose was	Dronabinol 10 mg
How long the maintenance dose was sustained for	Anti-emetic continued 2h hours after the last dose of chemotherapy, up to a total of 6 days (1 days prior and up to 5 days on chemotherapy)
Monitoring/reviewing procedure	Not reported.

Stopping criteria	Not reported.

Prochlorperazine (N = 21)

With dronabinol placebo

Study type	Randomised controlled trial (RCT)
Loss to follow-up	Withdrawn prior to chemotherapy: 1 Side effects:0 Insufficient therapeutic effect:2 Other: 2- protocol violation, non-compliance
% Female	52%
Mean age (SD)	Median: 49 Range: 22-64
Formulation	10 mg of prochlorperazine plus placebo was administered by mouth every 6 hours
How dose was titrated up	Not reported
What the maintenance dose was	10 mg
How long the maintenance dose was sustained for	Antiemetics were continued for 24 hours after the last dose of chemotherapy, up to a total of 6 days (1day prior and up to 5 days on chemotherapy.
Monitoring/reviewing procedure	Not reported
Stopping criteria	Not reported

Dronabinol+ Prochlorperazine (N = 20)

Study type	Randomised controlled trial (RCT)
Loss to follow-up	Withdrawn prior to chemotherapy: 2 4 intercurrent illness Side effects: Insufficient therapeutic effect: 0 Other: 1=
% Female	55%
Mean age (SD)	Median: 55.5 Range: 25-65
Formulation	10 mg of dronabinol and 10 mg of prochlorperazine administered by mouth every 6 hours.
How dose was titrated up	Not reported
What the maintenance dose was	10 mg of dronabinol 10 mg of prochlorperazine
How long the maintenance dose was sustained for	Antiemetics were continued for 24 hours after the last dose of chemotherapy, up to a total of 6 days (1day prior and up to 5 days on chemotherapy)
Monitoring/reviewing procedure	Not reported
Stopping criteria	Not reported

Cochrane Risk of Bias Tool 2.0
Domain 1: Bias arising from the randomization process Risk of bias judgement for this domain Some concerns (No information for randomisation, allocation concealment or baseline differences)

Cochrane Risk of Bias Tool 2.0
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for this domain
Some Concerns
(Unclear whether participants and people delivering the interventions were aware of assigned intervention)
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for this domain
This question has not yet been answered.
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for this domain
Some concerns
(More people excluded/withdrawn from study for dronabinol than prochlorperazine)
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for this domain
Some concerns
(Potentially subjective responses with patient-reported questionnaire)
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement domain
Low
Overall bias and Directness
Risk of bias judgement
Some concerns
(No information on randomisation or whether patients were aware of intervention. More patients excluded from the dronabinol than prochlorperazine arm)
Overall Directness
Directly applicable

Meiri 2007

Meiri, 2007	
Bibliographic Reference	Meiri, Eyal; Jhangiani, Haresh; Vredenburgh, James J.; Barbato, Luigi M.; Carter, Frederick J.; Yang, Hwa-Ming; Baranowski, Vickie; Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting; Current medical research and opinion; 2007; vol. 23 (no. 3); 533-43

Study details

Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Hospital setting
Study dates	Not specified
Duration of follow-up	5 day study with efficacy being evaluated on days 2-5.
Sources of funding	The study was supported by Solvay Pharmaceuticals
Inclusion criteria	Patents aged 18 years and older were required to have malignancy that did not involve the bone marrow Patients need to undergoing chemotherapy including a moderately to highly emetogenic regimen, ocaliplatin at doses employed for the treatment of colon cancer, or the combination of doxorubicin with cyclophosphamide with or without taxanes for the treatment of breast cancer. Patients could be receiving concomitant radiation therapy other than abdominal radiation Patients could be changing from prior chemotherapy to a new moderately or highly emetogenic agent alone or in combination with other agents. Women were eligible for enrolment if they had a negative pregnancy test at baseline and would not become pregnant during the trial Patients had to have an estimated life expectancy of at least 6 weeks post chemotherapy. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 at screening.
Exclusion criteria	Patients could not have received anti-emetic therapy in the 7 days pre-chemotherapy Patients with a history of anticipatory nausea and/ or vomiting were excluded Patients with primary malignancy of the brain, spinal cord, or nervous system; metastases to these sites; or leukemias or lymphomas involving the bone marrow were excluded Patients were ineligible for enrolled if they had a history of brain surgery, moderate to severe brain trauma, or any other neurological disorder likely to affect central nervous system functioning.

Study type	Randomised controlled trial (RCT)
	Patients who were prescribed opiates, propoxyphene, or benzodiazepines by the treating physician whose dosage were not stable for 2 weeks before stud entry were excluded from the study. Patients with conditions that might interfere with study participation were excluded, including patients who has a history or current diagnosis of psychotic disorder, had evidence if substance abuse disorder, had taken opiates or benzodiazepines not at a stable dose for 2 weeks, or had unstable medical conditions.
Sample size	64 patients
Symptom specific characteristics	Study focused on delayed cancer induced nausea and vomiting, defined as nausea and vomiting occurring more than 24 hours after chemotherapy and lasting for up to 1 week. Patients were receiving chemotherapy of moderate to high emetic risk. Nausea defined as an unpleasant feeling in the abdomen or stomach usually associated with an aversion to food, vomiting defined as the forcible or violent ejection of the stomach content through the mouth, usually as coordinated, involuntary spasms of the respiratory and abdominal muscles and retching defined as dry heaves which is the attempt to vomit, consisting of brief spasmodic contractions of the diaphragm, thoracic muscles, and abdominal muscles)
Intervention 1	Dronabinol Medication was administered in the morning. The dronabinol doses (2.5 mg and 5 mg PO QID) used in the fixed (day 2) and flexible (3-5) dosing phases of the study were based on the standard recommended antiemetic dose of 5mg PO TID or QID. For day 3-5 subjects took 2 or 4 capsules QID based on tolerance.
Intervention 2	Ondansetron Medication was administered in the morning. The oral doses of ondansetron (4 mg and 8 mg BID) used in the fixed (day 2) and flexible (3-5) dosing phases of the study were based on the standard recommended dose of 8mg BID for the treatment of emesis associated with moderately emetogenic chemotherapy. All patients took 4 capsules QID
Outcome measures	Incidence of Total response (No delayed vomiting and/ or retching, intensity of nausea <5mm on a 100-mm VAS, and no use of rescue medication) Complete response for vomiting/ retching (No delayed vomiting and/ or retching, intensity of nausea <5mm on a 100-mm VAS, and no use of rescue medication) Patients with at least one severe TEAE Patients with at least one SAE Patients with at least one TEAE Absence of delayed nausea

Study type	Randomised controlled trial (RCT)
	Withdrawals due to adverse events
Intervention 3	Placebo In the placebo group, medication was administered in the morning. Placebo was received QID. All patients took 4 capsules QID. For day 3-5 subjects took 2 or 4 capsules QID based on tolerance.
Intervention 4	Dronabinol + Ondansetron Medication was administered in the morning. Subjects received dronabinol 2.5 mg QID (10 mg/day) plus ondansetron 8 mg (16 mg/day). For day 3-5 subjects took 2 or 4 capsules QID based on tolerance.

Study arms

Dronabinol (N = 17)

Patients also received a standard prechemotherapy regimen of dexamethasone (20 mg PO) and ondansetron (16 mg IV) and dronabinol (2.5 mg PO) prechemotherapy. Also received dronabinol (2.5 mg PO) postchemotherapy. (Day 1)

Loss to follow-up	4 : (adverse events (1), protocol violation (2), other (1))
% Female	47%
Mean age (SD)	61.6 (14.2)
Formulation	Fixed day (Day 2): All subjects took four capsules QID. 2.5 mg PO QID (10mg/day) Flexible day (Days 3-5): All subjects took two or four capsules QID based on tolerance. 2.5- 5mg QID (10-20mg/day).
How dose was titrated up	Study drug doses could be adjusted on day 2 through 5, based on tolerability. In the event that four capsules of study medication QID were not tolerated for day 3 through day 5, the dose could be cut in half by instructing subjects to take capsules from Row 1 and Row 3 only for each dose.

What the maintenance dose was	Fixed day (Day 2): 10mg/day Flexible day (Days 3-5): 10-20mg/day
How long the maintenance dose was sustained for	Days 2- 5
Monitoring/reviewing procedure	Symptoms of intolerance monitored, which included chest discomfort, dizziness or lightheadedness, dysphoria or excessive sedation. To assess the safety of the active treatments, physical examination (screening and follow-up), 12- lead electrocardiograph with rhythm strip (screening), clinical laboratory analysis (screening day, day, follow up) were conducted. Adverse events and concomitant medications were also assessed throughout the trial.
Stopping criteria	Stopping criteria not explained in methods section. However, study specified that patients had discontinued study medication because of treatment emergent adverse event.

Ondansetron (N = 16)

Patients also received a standard prechemotherapy regimen of dexamethasone (20 mg PO) and ondansetron (16 mg IV) and dronabinol (2.5 mg PO) prechemotherapy. Also received dronabinol (2.5 mg PO) postchemotherapy. (Day 1)

Loss to follow-up	**4: (adverse events (2), protocol violation (1), other (1))**
% Female	71%
Mean age (SD)	55.6 (16.1)
Formulation	Fixed day (Day 2): All subjects took four capsules QID. 8mg BID (16 mg/day). Also recieved placebo to for the middle two doses. Flexible day (Days 3-5): All subjects took two or four capsules QID based on tolerance. 2.5- 5mg QID (10-20mg/day).

How dose was titrated up	Study drug doses could be adjusted on day 2 through 5, based on tolerability. In the event that four capsules of study medication QID were not tolerated for day 3 through day 5, the dose could be cut in half by instructing subjects to take capsules from Row 1 and Row 3 only for each dose.
What the maintenance dose was	Fixed day (Day 2): 16mg/day Flexible day (Days 3-5): 8-16mg/day
How long the maintenance dose was sustained for	Days 2- 5
Monitoring/reviewing procedure	Symptoms of intolerance monitored, which included chest discomfort, dizziness or light-headedness, dysphoria or excessive sedation. To assess the safety of the active treatments, physical examination (screening and follow-up), 12- lead electrocardiograph with rhythm strip (screening), clinical laboratory analysis (screening day, day, follow up) were conducted. Adverse events and concomitant medications were also assessed throughout the trial.
Stopping criteria	Stopping criteria not explained in methods section. However, study specified that patients had discontinued study medication because of treatment emergent adverse event.

Dronabinol + Ondansetron (N = 17)

Patients also received a standard prechemotherapy regimen of dexamethasone (20 mg PO) and ondansetron (16 mg IV) and dronabinol (2.5 mg PO) prechemotherapy. Also received dronabinol (2.5 mg PO) postchemotherapy. (Day 1) Data from this arm not included in analysis.

Split between study groups	**17 patients**
Loss to follow-up	4: adverse events (3), other (1))
% Female	65%
Mean age (SD)	56.8 (10.9)

Formulation	Fixed day (Day 2): All subjects took four capsules QID. 2.5mg QID (10mg/day) dronabinol plus odansetron 8mg BID (16mg/ day) Flexible day (Days 3-5): All subjects took two or four capsules QID based on tolerance. 2.5- 5mg QID (10-20mg/day) dronabinol plus 4-8mg BID(8-16mg/day) odansetron.
How dose was titrated up	For Days 3 to 5 (flexible dosing),
What the maintenance dose was	Fixed day (Day 2): 10mg/day dronabinol + 6mg/ day ondansetron Flexible day (Days 3-5): 10-20mg/day dronabinol + 8-16mg/day ondansetron
How long the maintenance dose was sustained for	Days 2- 5
Monitoring/reviewing procedure	Symptoms of intolerance monitored, which included chest discomfort, dizziness or light-headedness, dysphoria or excessive sedation. To assess the safety of the active treatments, physical examination (screening and follow-up), 12- lead electrocardiograph with rhythm strip (screening), clinical laboratory analysis (screening day, day, follow up) were conducted. Adverse events and concomitant medications were also assessed throughout the trial.
Stopping criteria	Stopping criteria not explained in methods section. However, study specified that patients had discontinued study medication because of treatment emergent adverse event.

Placebo (N = 14)

Patients also received a standard prechemotherapy regimen of dexamethasone (20 mg PO) and ondansetron (16 mg IV) and placebo (PO) prechemotherapy. Also received placebo (PO) postchemotherapy. (Day 1)

Split between study groups	**14 patients**
Loss to follow-up	3 : (withdrew consent (2), other (1))
% Female	62%
Mean age (SD)	57.2 (8.6)
Formulation	Group received placebo QID

How dose was titrated up	NA
What the maintenance dose was	Group received placebo QID
How long the maintenance dose was sustained for	Days 2- 5
Monitoring/reviewing procedure	Symptoms of intolerance monitored, which included chest discomfort, dizziness or light-headedness, dysphoria or excessive sedation. To assess the safety of the active treatments, physical examination (screening and follow-up), 12- lead electrocardiograph with rhythm strip (screening), clinical laboratory analysis (screening day, day, follow up) were conducted. Adverse events and concomitant medications were also assessed throughout the trial.
Stopping criteria	Stopping criteria not explained in methods section. However, study specified that patients had discontinued study medication because of treatment emergent adverse event.

Cochrane Risk of Bias Tool 2.0
Domain 1: Bias arising from the randomization process
Risk of bias judgement for this domain
Some concerns
(No information on randomisation or allocation concealment)
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)
Risk of bias for this domain
Low
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for this domain
This question has not yet been answered.
Domain 3. Bias due to missing outcome data
Risk-of-bias judgement for this domain
Low

Cochrane Risk of Bias Tool 2.0
Domain 4. Bias in measurement of the outcome
Risk-of-bias judgement for this domain
Some concerns
(Potentially subjective outcomes)
Domain 5. Bias in selection of the reported result
Risk-of-bias judgement domain
Low
Overall bias and Directness
Risk of bias judgement
Some concerns
(No information on randomisation or sequence allocation and potentially subjective outcomes)
Overall Directness
Directly applicable
(All other outcomes)
Partially applicable
(Complete response, total response and absence of nausea: Patients with a history of anticipatory nausea and vomiting were excluded)

Pomeroy 1986

Pomeroy, 1986	
Bibliographic Reference	Pomeroy, M.; Fennelly, J. J.; Towers, M.; Prospective randomized double-blind trial of nabilone versus domperidone in the treatment of cytotoxic-induced emesis; Cancer chemotherapy and pharmacology; 1986; vol. 17 (no. 3); 285-8

Study details

Study type	Randomised controlled trial (RCT)
Study location	Dublin, Ireland
Study setting	Department of Clinical Oncology
Study dates	Not specified
Duration of follow-up	Each day of chemotherapy.

Study type	Randomised controlled trial (RCT)
Sources of funding	Not reported
Inclusion criteria	Patients undergoing chemotherapy for advanced malignant disease (1) 1) Tumour types included: ovary, testis, bronchus, non-Hodgkin's lymphoma, Hodgkin's disease, sarcoma, breast, melanoma, nephroblastoma.
Exclusion criteria	Not stated
Sample size	38 patients
% Female	39.5% overall
Mean age (SD)	Mean age: 42 years (range 21-66 years) - overall
Symptom specific characteristics	Chemotherapy induced nausea and vomiting. The chemotherapy regiments remained constant for the two cycles of antiemetic and included cisplatin in 70% patients, Adriamycin in 19%, and ifofamide in 5% of the patients. Study did not report if patients had previously experienced nausea and vomiting.
Intervention 1	Nabilone (2) 2) Patients received 2 cycles of nabilone 1mg t.d.s
Intervention 2	Domperiodone (3) 3) Patients received 2 cycles of domperidone 20mg t.d.s
Outcome measures	Withdrawals due to adverse events Adverse events

Study arms

Nabilone (N = 19)

% Female	39.5% overall
Mean age (SD)	Mean age: 42 years (range 21-66 years) - overall
Formulation	1 mg t.d.s given during Cycle 1 and Cycle 2. An additional dose of nabilone (1 mg) was given the night before each cyle of chemotherapy.
How dose was titrated up	Not reported.

What the maintenance dose was	1 mg
How long the maintenance dose was sustained for	2 cycles of chemotherapy
Monitoring/reviewing procedure	Adverse events recorded. Erect and supine blood pressure and pulse rate measurements were taken 2-4 hours after the morning dose of antiemetic.
Stopping criteria	Not reported.

Domperidone (N = 19)

% Female	**39.5% overall**
Mean age (SD)	Mean age: 42 years (range 21-66 years) - overall
Formulation	20 mg t.d.s given during Cycle 1 and Cycle 2. An additional dose of domperidone (20 mg) was given the night before each cycle of chemotherapy.
How dose was titrated up	Not reported
What the maintenance dose was	20
How long the maintenance dose was sustained for	2 cycles of chemotherapy
Monitoring/reviewing procedure	Adverse events recorded. Erect and supine blood pressure and pulse rate measurements were taken 2-4 hours after the morning dose of antiemetic.
Stopping criteria	Not reported.

Cochrane Risk of Bias Tool 2.0
Domain 1: Bias arising from the randomization process Risk of bias judgement for this domain

Cochrane Risk of Bias Tool 2.0
Some concerns (No information on randomisation, allocation concealment or baseline values) **Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)** Risk of bias for this domain Low **Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)** Risk of bias judgement for this domain This question has not yet been answered. **Domain 3. Bias due to missing outcome data** Risk-of-bias judgement for this domain Low **Domain 4. Bias in measurement of the outcome** Risk-of-bias judgement for this domain Low **Domain 5. Bias in selection of the reported result** Risk-of-bias judgement domain Low **Overall bias and Directness** Risk of bias judgement Some concerns (No information on randomisation, allocation concealment or baseline values) **Overall Directness** Directly applicable (Adverse events) Partially applicable (Withdrawals due to AEs: Study did not specify if patients had previously experienced nausea and/or vomiting or has shown signs at baseline)

E.2 Crossover RCTs

1987

Chan, 1987	
Bibliographic Reference	Chan, H. S.; Correia, J. A.; MacLeod, S. M.; Nabilone versus prochlorperazine for control of cancer chemotherapy-induced emesis in children: a double-blind, crossover trial; Pediatrics; 1987; vol. 79 (no. 6); 946-52

Study details

Study type	Cross-over randomised controlled trial
Study location	Toronto, Canada
Study setting	The Hospital for Sick Children
Study dates	February 1982 - April 1983
Duration of follow-up	Within 24 hours of completion of each cycle
Sources of funding	Eli Lilly
Inclusion criteria	Receiving chemotherapy for various paediatric malignancies Receiving repeated courses of chemotherapy and experienced severe drug-induced nausea and vomiting but had never received nabilone or prochlorperazine
Exclusion criteria	Patients who had not previously experienced chemotherapy-associated nausea and vomiting
Sample size	40
Split between study groups	Cross-over trial (all patients completed both arms)
Loss to follow-up	10
% Female	Not reported
Mean age (SD)	Mean (range): 11.8 (3.5 - 17.8)
Symptom specific characteristics	All patients in the study received two identical consecutive cycles of the same doses of chemotherapy. All chemotherapeutic agents or combinations prescribed in this study had been previously shown to produce moderate to severe nausea and vomiting in the study subjects. None of the patients received cis-platinum based regimens. Specific chemotherapeutic agents not specified.

Study type	Cross-over randomised controlled trial
Intervention 1	Nabilone
Intervention 2	Prochlorperazine
Outcome measures	Adverse events Complete relief of nausea and vomiting Less nausea Less vomiting Overall rate of improvement of retching and vomiting Serious adverse events

Study arms

Nabilone (N = 30)

Formulation	Nabilone 1 mg capsules
How dose was titrated up	Not reported
What the maintenance dose was	1 mg 8-12 hours before the start of chemotherapy. Repeated two or three times daily depending on body weight: 18-27 kg - 1 bid 27.1-36 kg - 1 tid >36 kg - 2 bid Dose was reduced after 10 months of the trial due to major adverse events of dizziness and drowsiness after nabilone: <18 - 0.5 bid 18-30 kg - 1 tid >30 kg - 1 bid
How long the maintenance dose was sustained for	Varied depending on how long antiemetic coverage was needed after each type of chemotherapy regimen
Monitoring/reviewing procedure	CBC count, urinalysis and SMA-12 obtained before each cycle. Supine and standing blood pressure measurements recorded before and 4 hours after each antiemetic agent was administered

	During every cycle of chemotherapy, every episode of retching or vomiting was recorded. Patients asked to reported side effects and rate their severity
Stopping criteria	Patients who experienced severe dizziness and drowsiness were excluded from the rest of the study

Prochlorperazine (N = 30)

Formulation	Prochlorperazine 5 mg, identical appearance to nabilone
How dose was titrated up	Not reported
What the maintenance dose was	5 mg 8-12 hours before the start of chemotherapy. Repeated two or three times daily depending on body weight 18-27 kg - 5 bid 27.1-36 kg - 5 tid >36 kg – 10 bid Dose was reduced after 10 months of the trial due to major adverse events of dizziness and drowsiness after nabilone: <18 - 2.5 bid 18-30 kg - 5 tid >30 kg - 5 bid
How long the maintenance dose was sustained for	Varied depending on how long antiemetic coverage was needed after each type of chemotherapy regimen
Monitoring/reviewing procedure	CBC count, urinalysis and SMA-12 obtained before each cycle. Supine and standing blood pressure measurements recorded before and 4 hours after each antiemetic agent was administered During every cycle of chemotherapy, every episode of retching or vomiting was recorded. Patients asked to reported side effects and rate their severity
Stopping criteria	Patients who experienced severe dizziness and drowsiness were excluded from the rest of the study

Cochrane Risk of Bias Tool 2.0 for Crossover Trials
Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process

Cochrane Risk of Bias Tool 2.0 for Crossover Trials
Some concerns (No information on baseline values. Results not separated by phases which could have masked period effects) **Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)** Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention) Some concerns (Washout period not specified.) **Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)** Risk of bias judgement for deviations from intended interventions (effect of adhering to intervention) This question has not yet been answered. **Domain 3. Bias due to missing outcome data** Risk of bias judgement for missing outcome data Low **Domain 4. Bias in measurement of the outcome** Risk of bias judgement for measurement of the outcome Low **Domain 5. Bias in selection of the reported result** Risk of bias judgement for selection of the reported result Some concerns (No information on whether a statistical test for carry-over was performed) **Overall bias and Directness** Risk of bias judgement High (No information on whether a statistical test for carry-over was performed. No information on washout period. No information on baseline values. Results not separated by phases which could have masked period effects) **Overall Directness** Directly applicable

Ahmedzai 1983

Ahmedzai, 1983	
Bibliographic Reference	Ahmedzai, S.; Carlyle, D. L.; Calder, I. T.; Moran, F.; Anti-emetic efficacy and toxicity of nabilone, a synthetic cannabinoid, in lung cancer chemotherapy; British journal of cancer; 1983; vol. 48 (no. 5); 657-63

Study details

Study type	**Cross-over randomised controlled trial** **2 period cross over study**
Study location	UK
Study setting	Department of Pharmacy
Study dates	Not reported
Duration of follow-up	3 treatment days
Sources of funding	Nabilone and placebo capsules were supplied by Lily Research ltd.
Inclusion criteria	Patients with small cell bronchial carcinoma who were eligible for chemotherapy
Exclusion criteria	Not stated
Sample size	34 patients
Symptom specific characteristics	Chemotherapy induced nausea and vomiting All patients received two 21-day cycles of combination chemotherapy comprising of Cyclophosphamide (CTX) 1 gm², Adriamycin 40mgm² & Etoposide (VP-16) 1OOmgm-2 on Day 1; VP-16 1OOmgm-2 on Days 2 and 3 and Vincristine 2mg with Methotrexate 50mgm-2 on Day 10, followed by folinic acid rescue. Day 1-3 chemotherapy pulses were given on an in-patient basis, with CTX and ADR administered as i.v. boluses and VP-16 as an i.v. infusion over 1-2 h.
Intervention 1	Nabilone 2 x 1 mg capsules at 10am & 10pm
Intervention 2	Prochlorperazine 2 x 5 mg tablets at 6am, 2pm & 10pm
Outcome measures	No nausea No retching No retching

Study type	Cross-over randomised controlled trial 2 period cross over study
	Adverse events

Study arms

Nabilone (N = 34)

% Female	44%
Mean age (SD)	Median: 58 Range 27-72
Formulation	2 x 1mg capsules
How dose was titrated up	Not reported
What the maintenance dose was	1 mg - 2 capsules taken at 10 am and 10 pm.
How long the maintenance dose was sustained for	3 treatment days The anti-emetics under study were restricted to Day 1-3 pulses
Monitoring/reviewing procedure	Blood pressure in the erect and supine positions and pulse rate were recorded just before the first dose of ant-emetic at 10 pm on Day 0, 1 h afterwards and thereafter twice daily.
Stopping criteria	Stopping criteria not specified in methods section. However, study highlighted that one patient was withdrawn from study after review of histology, and 2 patients did not complete a course due to adverse effects.

Prochlorperazine (N = 34)

% Female	44%
Mean age (SD)	Median: 58 Range 27-72
Formulation	2 x 5mg tablets
How dose was titrated up	Not reported
What the maintenance dose was	2 x 5mg tablets given at 6 am, 2 pm, and 10 pm. The anti-emetics under study were restricted to Day 1-3 pulses.

How long the maintenance dose was sustained for	3 treatment days The anti-emetics under study were restricted to Day 1-3 pulses
Monitoring/reviewing procedure	Blood pressure in the erect and supine positions and pulse rate were recorded just before the first dose of ant-emetic at 10 pm on Day 0, 1 h afterwards and thereafter twice daily.
Stopping criteria	Stopping criteria not specified in methods section. However, study highlighted that one patient was withdrawn from study after review of histology, and 2 patients did not complete a course due to adverse effects.

Cochrane Risk of Bias Tool 2.0 for Crossover Trials

Domain 1: Bias arising from the randomisation process

Risk of bias judgement for the randomisation process

Some concerns

(No information on randomisation, allocation concealment or baseline values. Results not separated by phases which could have masked period effects)

Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)

Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)

Low

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Risk of bias judgement for deviations from intended interventions (effect of adhering to intervention)

This question has not yet been answered.

Domain 3. Bias due to missing outcome data

Risk of bias judgement for missing outcome data

High

(outcome data not available for all participants. Only people who completed cycles were included in analysis.)

Domain 4. Bias in measurement of the outcome

Risk of bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk of bias judgement for selection of the reported result

Some concerns

Cochrane Risk of Bias Tool 2.0 for Crossover Trials
(No information on whether a statistical test for carry-over was performed) **Overall bias and Directness** Risk of bias judgement High (All outcomes: due to high risk of bias associated with missing outcome data and some concerns with random sequence generation and allocation concealment.) **Overall Directness** Partially applicable (Outcomes: no nausea, no vomiting, no vomiting- study does not specify if all patients had previously experienced nausea and/or vomiting or had showed signs at baseline. This does not allow us to identify a reduction in symptoms.)

Crawford 1986

Crawford, 1986	
Bibliographic Reference	Crawford, S. M.; Buckman, R.; Nabilone and metoclopramide in the treatment of nausea and vomiting due to cisplatinum: a double blind study; Medical oncology and tumor pharmacotherapy; 1986; vol. 3 (no. 1); 39-42

Study details

Study type	Cross-over randomised controlled trial
Study location	UK
Study setting	Hospital setting
Study dates	Not reported
Duration of follow-up	Within 24 hours of the end of each course of therapy
Sources of funding	Eli Lilly
Inclusion criteria	Patients receiving cisplatin for treatment of adenocarcinoma of the ovary or germ cell tumours
Exclusion criteria	Not stated
Sample size	32
Split between study groups	Cross-over trial (all patients completed both arms)

Study type	Cross-over randomised controlled trial
Loss to follow-up	Not reported
% Female	Not reported
Mean age (SD)	Not reported
Symptom specific characteristics	Chemotherapy induced nausea and vomiting Patients received cisplatin for the treatment of adenocarcinoma of the ovary or germ cell tumours. The former group also received cyclophosphamide and adriamycin. The latter group received methotrexate, vincristine and bleomycin. They were scheduled to receive two courses of nabilone capsules with placebo and two courses of metoclopramide with placebo.
Intervention 1	Nabilone
Intervention 2	Metoclopramide
Outcome measures	Adverse events

Study arms

Nabilone (N = 32)

Formulation	Nabilone capsule
How dose was titrated up	Not reported
What the maintenance dose was	One capsule when waking up, 2 capsules 2 hours before cisplatin therapy, 1 capsule before falling asleep, 1 capsule every 8 hours as required (up to 2 doses)
How long the maintenance dose was sustained for	Not reported
Monitoring/reviewing procedure	Nursing staff recorded the occurrence and quantity of each emesis episode Patients completed a questionnaire to report nausea and side-effects within 24 hours of each course of therapy
Stopping criteria	Not reported

Metoclopramide (N = 32)

Formulation	Metoclopramide infusions
How dose was titrated up	Not reported
What the maintenance dose was	1 infusion 30 minutes before cisplatin therapy, 1 infusion at 3.5 hours and 6.5 hours after therapy. 1 infusion every 3 hours as required up to 3 doses

Cochrane Risk of Bias Tool 2.0 for Crossover Trials
Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process
Some concerns
(Unclear random sequence generation, allocation concealment and baseline imbalances)
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)
Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)
Some concerns
(Unclear if participants and personnel were aware of assigned intervention.)
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from intended interventions (effect of adhering to intervention)
This question has not yet been answered.
Domain 3. Bias due to missing outcome data
Risk of bias judgement for missing outcome data
High
(Outcome data not available for all patients. Unclear if missing outcome data is proportional between the two study arms.)
Domain 4. Bias in measurement of the outcome
Risk of bias judgement for measurement of the outcome
Low
Domain 5. Bias in selection of the reported result
Risk of bias judgement for selection of the reported result

Cochrane Risk of Bias Tool 2.0 for Crossover Trials
Some concerns (No information on statistical test for carry over) **Overall bias and Directness** Risk of bias judgement High (Unclear random sequence generation, allocation concealment and baseline imbalances. Unclear if participants and personnel were aware of assigned intervention. Outcome data not available for all patients. Unclear if missing outcome data is proportional between the two study arms. No information on statistical test for carry over.) **Overall Directness** Directly applicable

Dalzell 1986

Dalzell, 1986	
Bibliographic Reference	Dalzell, A. M.; Bartlett, H.; Lilleyman, J. S.; Nabilone: an alternative antiemetic for cancer chemotherapy; Archives of disease in childhood; 1986; vol. 61 (no. 5); 502-5

Study details

Study type	Cross-over randomised controlled trial
Study location	UK
Study setting	Children's hospital
Study dates	16 months (dates not provided)
Duration of follow-up	After completion of study (length not specified)
Sources of funding	Eli Lily supported and helped with study design and analysis.
Inclusion criteria	Consecutive children 17 years old or less undergoing emetogenic antieoplastic chemotherapy for malignant disease Patient has to be scheduled to receive two identical courses of emetogenic chemotherapy
Exclusion criteria	Not stated
Sample size	18 children

Study type	Cross-over randomised controlled trial
Symptom specific characteristics	Chemotherapy induced nausea and vomiting Chemotherapy regimens included vincristine, antinomycin & cyclophosphamide; cisplatinum VP16; mustine, vincristine, procarbazine & prednisolone; M-AMSA, VP16, 5-Azacytidine; high dose cytarabine; cyclophosphamide, cisplatinum, VM26; daunorubican, cytarabine, thioguanine. Study does not report if children had previously experienced nausea and vomiting. If vomiting was severe enough to prevent effectively oral antiemetic therapy then parenteral domperidone was allowed in addition to the prescribed drug.
Intervention 1	Nabilone Patients received three (or six) identical capsules daily, or in case of some of the very young, three identical looking white powders from broken capsules. Dose dependent on weight of patient.
Intervention 2	Domperidone Patients received three (or six) identical capsules daily, or in case of some of the very young, three identical looking white powders from broken capsules. Dose dependent on weight of patient.
Outcome measures	Adverse events

Study arms

Nabilone (N = 18)

% Female	22% (overall)
Mean age (SD)	Range: 0.8-17 years (overall)
Formulation	Dependent on weight of patient Patients received three (or six) identical capsules daily, or in case of some of the very young, three identical looking white powders from broken capsules.
How dose was titrated up	Not reported.
What the maintenance dose was	Weight of patient (kg): <18: 0.5mg twice a day

	18-36: 1mg twice a day >36: 1 mg three times a day
How long the maintenance dose was sustained for	The first dose in all cases was taken the night before beginning chemotherapy, and the last dose 24 hours after stopping it.
Monitoring/reviewing procedure	Not reported
Stopping criteria	Stopping criteria not specified in methods section. However, study highlighted that 2 patients were withdrawn by their parents because vomiting was considered uncontrolled.

Domperidone (N = 18)

% Female	**22% (overall)**
Mean age (SD)	Range: 0.8-17 years (overall)
Formulation	Weight pf patient (kg): <18: 5mg three times a day 18-36: 10mg three times a day >36: 15 mg three times a day Patients received three (or six) identical capsules daily, or in case of some of the very young, three identical looking white powders from broken capsules.
How dose was titrated up	Not reported
What the maintenance dose was	Weight pf patient (kg): <18: 5mg three times a day 18-36: 10mg three times a day >36: 15 mg three times a day
How long the maintenance dose was sustained for	The first dose in all cases was taken the night before beginning chemotherapy, and the last dose 24 hours after stopping it.

Monitoring/reviewing procedure	Not reported
Stopping criteria	Stopping criteria not specified in methods section. However, study highlighted that 2 patients were withdrawn by their parents because vomiting was considered uncontrolled.

Cochrane Risk of Bias Tool 2.0 for Crossover Trials

Domain 1: Bias arising from the randomisation process

Risk of bias judgement for the randomisation process

Some concerns

(No information on randomisation, allocation concealment or baseline values. Results not separated by phases which could have masked period effects)

Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)

Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)

Low

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Risk of bias judgement for deviations from intended interventions (effect of adhering to intervention)

This question has not yet been answered.

Domain 3. Bias due to missing outcome data

Risk of bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome

Risk of bias judgement for measurement of the outcome

Low

Domain 5. Bias in selection of the reported result

Risk of bias judgement for selection of the reported result

Some concerns

(No information on whether a statistical test for carry-over was performed)

Overall bias and Directness

Risk of bias judgement

Cochrane Risk of Bias Tool 2.0 for Crossover Trials
Some concerns (No information on whether a statistical test for carry-over was performed. No information on randomisation, allocation concealment or baseline values. Results not separated by phases which could have masked period effects.) **Overall Directness** Directly applicable

Einhorn 1981

Einhorn, 1981	
Bibliographic Reference	Einhorn, L. H.; Nagy, C.; Furnas, B.; Williams, S. D.; Nabilone: an effective antiemetic in patients receiving cancer chemotherapy; Journal of clinical pharmacology; 1981; vol. 21 (no. s1); 64S-69S

Study details

Study type	Cross-over randomised controlled trial
Study location	USA
Study setting	Medical centre
Study dates	Not reported
Duration of follow-up	5 days
Sources of funding	Not reported
Inclusion criteria	Receiving combination chemotherapy for neoplastic disease
Sample size	100
Split between study groups	Cross-over study (all patients completed both treatment arms)
Loss to follow-up	Not reported
% Female	Not reported
Mean age (SD)	Median (range): 28 (15 - 74)
Symptom specific characteristics	Chemotherapy induced nausea and vomiting. Patients received combination of chemotherapy for neoplastic disease: Sarcoma

Study type	Cross-over randomised controlled trial
	Chemotherapeutic agents: Doxorubicin hydrochloride + cyclophosphamide **Consecutive number of days on chemotherapy:** 1 **Weeks between cycles:** 3 Hodgkin's disease **Chemotherapeutic agents:** nitrogen mustard (HN2) + vincristine + prednisone + procarbazine **Consecutive number of days on chemotherapy:** 1 and 8 **Weeks** between cycles: 4 Lymphoma **Chemotherapeutic agents:** Doxorubicin hydrochloride + cyclophosphamide + vincristine + prednisone **Consecutive number of days on chemotherapy:** 1 **Weeks between cycles:** 3 Bladder **Chemotherapeutic agents**: cisplatin + Doxorubicin hydrochloride +5-flourouracil **Consecutive number of days on chemotherapy:** 1 and 5 **Weeks between cycles:** 3 and 4 Testicular **Chemotherapeutic agents:** cisplatin + vinblastine +bleomycin **Consecutive number of days on chemotherapy:** 5 **Weeks between cycles:** 3 Patients received 2 courses of chemotherapy
Intervention 1	Nabilone
Intervention 2	Prochlorperazine
Outcome measures	Adverse events

Study arms

Nabilone (N = 80)

Formulation	Nabilone 2 mg orally
How dose was titrated up	Not reported
What the maintenance dose was	2 mg Initially first dose taken 30 mins before start of chemotherapy. Changed for last 44 patients - 3 doses beginning 12 hours before start of chemotherapy Then every 6 hours as required
How long the maintenance dose was sustained for	Not reported
Monitoring/reviewing procedure	Before starting treatment and at the end of each cycle: complete blood count, SMA-12 and urinalysis. In hospitalised patients sitting and standing blood pressures were recorded before initial dose of nabilone and every 6 hours afterwards Every 24 hours patients completed a case report rating severity of nausea, number of vomits, presence of depression, drowsiness, anxiety, relaxation, light-headedness, feeling high and altered food intake
Stopping criteria	Stopping criteria not specified in methods section. However, study highlighted that 3 patients failed to complete study because of nabilone toxicity.

Prochlorperazine (N = 80)

Formulation	10 mg
How dose was titrated up	Not reported
What the maintenance dose was	10 mg Initially first dose taken 30 mins before start of chemotherapy. Changed for last 44 patients - 3 doses beginning 12 hours before start of chemotherapy Then every 6 hours as required
Monitoring/reviewing procedure	Before starting treatment and at the end of each cycle: complete blood count, SMA-12 and urinalysis. In hospitalised patients sitting and standing blood pressures were recorded before initial dose of nabilone and every 6 hours afterwards Every 24 hours patients completed a case report rating severity of nausea, number of vomits, presence of depression, drowsiness, anxiety, relaxation, light-headedness, feeling high and altered food intake

Stopping criteria	Stopping criteria not specified in methods section. However, study highlighted that 3 patients failed to complete study because of nabilone toxicity.

Cochrane Risk of Bias Tool 2.0 for Crossover Trials

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process
Some concerns
(No information on randomisation, allocation concealment or baseline values)
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)
Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)
Low
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from intended interventions (effect of adhering to intervention)
This question has not yet been answered.
Domain 3. Bias due to missing outcome data
Risk of bias judgement for missing outcome data
Some concerns
(Unclear if the number of withdrawals was similar between treatment arms)
Domain 4. Bias in measurement of the outcome
Risk of bias judgement for measurement of the outcome
Low
Domain 5. Bias in selection of the reported result
Risk of bias judgement for selection of the reported result
Low
Overall bias and Directness
Risk of bias judgement
Some concerns
(No information on randomisation, allocation concealment or baseline values. Unclear if the number of withdrawals was similar between treatment arms.)

Cochrane Risk of Bias Tool 2.0 for Crossover Trials
Overall Directness Directly applicable

Herman 1979

Herman, 1979	
Bibliographic Reference	Herman, T. S.; Einhorn, L. H.; Jones, S. E.; Nagy, C.; Chester, A. B.; Dean, J. C.; Furnas, B.; Williams, S. D.; Leigh, S. A.; Dorr, R. T.; Moon, T. E.; Superiority of nabilone over prochlorperazine as an antiemetic in patients receiving cancer chemotherapy; The New England journal of medicine; 1979; vol. 300 (no. 23); 1295-7

Study details

Study type	Cross-over randomised controlled trial
Study location	USA
Study setting	University of Arizona Cancer Centre Indiana University School of Medicine
Study dates	Not reported
Duration of follow-up	Dependant on type of cancer treatment (range 1.5 - 5.5 days)
Sources of funding	Eli Lilly
Inclusion criteria	Receiving repeated courses of chemotherapy on entry into the trial Previously experienced severe, drug-induced nausea and vomiting
Exclusion criteria	History of psychiatric or cardiovascular disease
Sample size	152
Split between study groups	Cross-over trial (all patients completed both arms)
Loss to follow-up	Not reported
% Female	17%
Mean age (SD)	Median (range): 33 (15 - 74)

Study type	Cross-over randomised controlled trial
Symptom specific characteristics	Chemotherapy induced nausea and vomiting Upon entry all patients were receiving repeated courses of chemotherapy and all had experienced severe, drug induced nausea and vomiting. Chemotherapy regimens used: cisplatin; vinblastine & bleomycin; cyclophosphamide, doxorubicin, vincristine & prednisone; nitrogen mustard, vincristine, procarbazine & prednisone. Patients received 2 courses of identical chemotherapy.
Intervention 1	Nabilone
Intervention 2	Prochlorperazine
Outcome measures	Complete response (no vomiting) Total absence of nausea and vomiting Partial response Equal to or greater than 50% reduction in the duration or severity of nausea and number of vomiting episodes Withdrawals due to adverse events

Study arms

Nabilone (N = 113)

Formulation	1 mg capsules
How dose was titrated up	Not reported
What the maintenance dose was	2 mg University of Arizona Medical Centre: 2 capsules orally every 8 hours, beginning 2 doses before start of chemotherapy Indiana University School of Medicine: 2 capsules orally every 6 hours, beginning 30 mins before chemotherapy
How long the maintenance dose was sustained for	Varied depending on type of cancer treatment
Monitoring/reviewing procedure	Patients completed daily questionnaire during treatment to rate nausea & vomiting and 16 possibly drug-related side-effects on scale of 0 (none) to 3 (severe). Patients asked to estimate the duration of symptoms and number of times they occurred. At the end of each cycle of treatment, patients compared level of nausea & vomiting with that experienced before taking nabilone

Stopping criteria	Stopping criteria not specified in methods section. However, study highlighted that 9 patients stopped antiemetic therapy because of the early occurrence of unacceptable side effects.

Prochlorperazine (N = 113)

Formulation	**5 mg capsules**
How dose was titrated up	Not reported
What the maintenance dose was	5 mg University of Arizona Medical Centre: 2 capules orally every 8 hours, beginning 2 doses before start of chemotherapy Indiana University School of Medicine: 2 capsules orally evey 6 hours, beginning 30 mins before chemotherapy
How long the maintenance dose was sustained for	Varied depending on type of cancer treatment
Monitoring/reviewing procedure	Patients completed daily questionnaire during treatment to rate nausea & vomiting and 16 possibly drug-related side-effects on scale of 0 (none) to 3 (severe). Patients asked to estimate the duration of symptoms and number of times they occurred. At the end of each cycle of treatment, patients compared level of nausea & vomiting with that experienced before taking nabilone
Stopping criteria	Stopping criteria not specified in methods section. However, study highlighted that 9 patients stopped antiemetic therapy because of the early occurrence of unacceptable side effects.

Cochrane Risk of Bias Tool 2.0 for Crossover Trials
Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process
Some concerns
(No information on randomisation or baseline values. Results not separated by phases which could have masked period effects)
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)
Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)
Low
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Cochrane Risk of Bias Tool 2.0 for Crossover Trials
Risk of bias judgement for deviations from intended interventions (effect of adhering to intervention) This question has not yet been answered. **Domain 3. Bias due to missing outcome data** Risk of bias judgement for missing outcome data Some concerns (Unclear if the reason for missing outcome data was the same between groups or whether results were robust to missing data) **Domain 4. Bias in measurement of the outcome** Risk of bias judgement for measurement of the outcome Low **Domain 5. Bias in selection of the reported result** Risk of bias judgement for selection of the reported result Some concerns (No information on whether a statistical test for carry-over was performed) **Overall bias and Directness** Risk of bias judgement High (No information on randomisation or baseline values. Results not separated by phases which could have masked period effects. Unclear if the reason for missing outcome data was the same between groups or whether results were robust to missing data. No information on whether a statistical test for carry-over was performed) **Overall Directness** Directly applicable

Johansson 1982

Johansson, 1982	
Bibliographic Reference	Johansson, R.; Kilkku, P.; Groenroos, M.; A double-blind, controlled trial of nabilone vs. prochlorperazine for refractory emesis induced by cancer chemotherapy; Cancer treatment reviews; 1982; vol. 9supplb; 25-33

Study details

Study type	Cross-over randomised controlled trial
Study location	Finland
Study setting	Hospital setting
Study dates	September 1981 and April 1982
Duration of follow-up	Daily
Sources of funding	Not reported
Inclusion criteria	Adult patients with an age range of 18-70 years, with a good performance status (less than 2 on the ECOG scale) , receiving the same cycles of cancer chemotherapy as previously, who had uncontrolled nausea and vomiting despite the use of standard antiemetic drugs.
Exclusion criteria	Patients with known psychotic or cardiovascular diseases, currently under medication, or with previous usage of marijuana
Sample size	27
Symptom specific characteristics	Chemotherapy induced nausea and vomiting. Patients receiving the same cycles of cancer chemotherapy who had uncontrolled nausea and vomiting despite the use of standard antiemetic drugs. Chemotherapy included the following agents as the emetogenic stimuli: cis-platinum, Adriamycin, cyclophosphamide (in combination with vinblastine, vincristine or ftorafur). Patients received 2 consecutive cycles chemotherapy.
Intervention 1	Nabilone
Intervention 2	Prochlorperazine
Outcome measures	Vomiting episodes (none) Severity of nausea (none) Withdrawals due to adverse events Adverse events

Study arms

Nabilone (N = 27)

Loss to follow-up	9 patients had insufficient data, change of chemotherapy regime during crossover, concomitant antiemetic therapy, failure to complete the crossover.
% Female	Not reported
Mean age (SD)	Age range = 18 to 70 years.
Formulation	Nabilone 2 mg b.i.d
How dose was titrated up	Not reported
What the maintenance dose was	2 mg b.i.d
How long the maintenance dose was sustained for	Antiemetic treatment was given every 12h for 4 consecutive doses, with the first dose on the night before chemotherapy and the last dose the morning after. On the day of chemotherapy, the drugs were taken between 1 and 3h before the anticancer treatment in order to ensure correct absorption of the drug.
Monitoring/reviewing procedure	Prior to entry into the study and following each cycle, a blood count, platelet count, urinalysis and SMA-12 were obtained. Pulse and recumbent and standing blood pressure were recorded before the initial dose of the study drug was given and subsequently 4 and 2 hours prior to each dose and then each hour during the first 4 hours after the morning dose of the anti-emetic drug
Stopping criteria	Not specified.

Prochlorperazine (N = 27)

Split between study groups	18 evaluable for efficacy 26 patients remain evaluable for side effects
Loss to follow-up	9 patients had insufficient data, change of chemotherapy regime during crossover, concomitant antiemetic therapy, failure to complete the crossover.
% Female	Not reported
Mean age (SD)	Age range = 18 to 70 years.
Formulation	10 mg b.i.d
How dose was titrated up	Not reported

What the maintenance dose was	10mg b.i.d
How long the maintenance dose was sustained for	Antiemetic treatment was given every 12h for 4 consecutive doses, with the first dose on the night before chemotherapy and the last dose the morning after. On the day of chemotherapy, the drugs were taken between 1 and 3h before the anticancer treatment in order to ensure correct absorption of the drug.
Monitoring/reviewing procedure	Antiemetic treatment was given every 12h for 4 consecutive doses, with the first dose on the night before chemotherapy and the last dose the morning after. On the day of chemotherapy, the drugs were taken between 1 and 3h before the anticancer treatment in order to ensure correct absorption of the drug.
Stopping criteria	Not reported.

Cochrane Risk of Bias Tool 2.0 for Crossover Trials

Domain 1: Bias arising from the randomisation process

Risk of bias judgement for the randomisation process

Some concerns

(No information on randomisation, allocation concealment or baseline values. Results not separated by phases which could have masked period effects)

Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)

Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)

Some concerns

(Unclear blinding)

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Risk of bias judgement for deviations from intended interventions (effect of adhering to intervention)

This question has not yet been answered.

Domain 3. Bias due to missing outcome data

Risk of bias judgement for missing outcome data

Some concerns

(Data missing for over half of participants and not clear if reasons for missing data were similar between groups)

Domain 4. Bias in measurement of the outcome

Cochrane Risk of Bias Tool 2.0 for Crossover Trials
Risk of bias judgement for measurement of the outcome
Low
Domain 5. Bias in selection of the reported result
Risk of bias judgement for selection of the reported result
Some concerns
(No information on whether a statistical test for carry-over was performed)
Overall bias and Directness
Risk of bias judgement
High
(No information on whether a statistical test for carry-over was performed. Data missing for over half of participants and not clear if reasons for missing data were similar between groups. No information on randomisation, allocation concealment or baseline values. Results not separated by phases which could have masked period effects.)
Overall Directness
Directly applicable

Jones 1982

Jones, 1982	
Bibliographic Reference	Jones, S. E.; Durant, J. R.; Greco, F. A.; Robertone, A.; A multi-institutional Phase III study of nabilone vs. placebo in chemotherapy-induced nausea and vomiting; Cancer treatment reviews; 1982; vol. 9supplb; 45-8

Study details

Study type	Cross-over randomised controlled trial
Study location	USA
Study setting	3 Cancer centres
Study dates	Not specified
Duration of follow-up	24h after chemotherapy
Sources of funding	Grants from Eli Lilly

Study type	Cross-over randomised controlled trial
Inclusion criteria	Adults without other serious contraindications to nabilone, who agreed to participate after informed consent, and who were likely to receive at least 2 identical courses of chemotherapy
Exclusion criteria	Not stated
Sample size	54
Symptom specific characteristics	Chemotherapy induced nausea and vomiting. Patients undergoing a variety of types of chemotherapy. Chemotherapy regimens used: Adriamycin-based; cis-platinum-based; other (not stated). No other antiemetics were permitted. Patients underwent 2 identical courses of chemotherapy Study did not state if patients had previously experienced nausea and vomiting
Intervention 1	Nabilone
Intervention 2	Placebo
Outcome measures	Adverse events Withdrawals due to adverse events Less vomiting Less nausea

Study arms

Nabilone (N = 24)

Split between study groups	24
Loss to follow-up	6 patients were unevaluable due to protocol violations and 24 due to insufficient therapy.
% Female	Overall 35%

Mean age (SD)	Overall 20-37 = 9 38-57 = 23 >58 = 22
Formulation	2mg Nabilone
How dose was titrated up	Not reported
What the maintenance dose was	2mg
How long the maintenance dose was sustained for	Administered the evening before, the morning of chemotherapy and every 12h thereafter for at least 24 hours.
Monitoring/reviewing procedure	Routine blood pressure and laboratory monitoring conducted.
Stopping criteria	Stopping criteria not specified in methods section. However, study highlighted that 25 patients terminated study early, due to adverse events, severe nausea and vomiting during the first course of chemotherapy (placebo group), change in chemotherapy, progressive cancer and patients choice.

Placebo (N = 24)

Split between study groups	**24**
Loss to follow-up	6 patients were unevaluable due to protocol violations and 24 due to insufficient therapy.
% Female	Overall 35%
Mean age (SD)	Overall 20-37 = 9 38-57 = 23

	>58 = 22
Formulation	Placebo
Monitoring/reviewing procedure	Routine blood pressure and laboratory monitoring conducted.
Stopping criteria	Stopping criteria not specified in methods section. However, study highlighted that 25 patients terminated study early, due to adverse events, severe nausea and vomiting during the first course of chemotherapy (placebo group), change in chemotherapy, progressive cancer and patients choice.

Cochrane Risk of Bias Tool 2.0 for Crossover Trials

Domain 1: Bias arising from the randomisation process

Risk of bias judgement for the randomisation process

Some concerns

(No information on randomisation, allocation concealment or baseline values. Results not separated by phases which could have masked period effects)

Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)

Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)

Some concerns

(No information on whether participants and personnel were aware of intervention and no information on whether a statistical test for carry-over was performed)

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Risk of bias judgement for deviations from intended interventions (effect of adhering to intervention)

This question has not yet been answered.

Domain 3. Bias due to missing outcome data

Risk of bias judgement for missing outcome data

Some concerns

(30 people withdrew from the study. Unclear if the number of withdrawals was similar between treatment arms)

Domain 4. Bias in measurement of the outcome

Risk of bias judgement for measurement of the outcome

Low

Cochrane Risk of Bias Tool 2.0 for Crossover Trials
Domain 5. Bias in selection of the reported result
Risk of bias judgement for selection of the reported result
Some concerns
(No information on whether a statistical test for carry-over was performed)
Overall bias and Directness
Risk of bias judgement
High
(Some concerns with random sequence generation, allocation concealment, blinding and No information on whether a statistical test for carry-over was performed.)
Overall Directness
Partially applicable
(Partially direct for following outcomes: less nausea, less vomiting. Directly applicable for withdrawals due to AEs and adverse events)

Kleinman 1983

Kleinman, 1983	
Bibliographic Reference	Kleinman, S.; Weitzman, S. A.; Cassem, N.; Andrews, E.; Double blind trial of delta-9-tetrahydrocannabinol (THC) versus placebo as an adjunct to prochlorperazine for chemotherapy-induced vomiting; Current Therapeutic Research - Clinical and Experimental; 1983; vol. 33 (no. 6i); 1014-1017

Study details

Study type	Cross-over randomised controlled trial 4 period cross over study
Study location	Not reported
Study setting	Not reported
Study dates	Not reported
Duration of follow-up	24 hours following chemotherapy

Study type	Cross-over randomised controlled trial 4 period cross over study
Sources of funding	THC supplied by the National Institute of Drug Abuse
Inclusion criteria	Patients receiving chemotherapy known to cause acute gastrointestinal toxicity and had already experienced vomiting as a side effect
Exclusion criteria	Severely debilitated patients Those with psychoactive difficulties or histories of untoward reactions or problems with psychoactive drugs
Sample size	16
Symptom specific characteristics	Chemotherapy induced nausea and vomiting. Study did not specify chemotherapeutic agent. Patients had already experienced vomiting as a side effect. Each patient in the study was scheduled the receive 4 courses of antiemetic treatment.
Intervention 1	Prochlorperazine + THC
Intervention 2	Prochlorperazine + placebo
Outcome measures	Withdrawals due to adverse events Adverse events

Study arms

Prochlorperazine + THC (N = 16)

Study type	Cross-over randomised controlled trial
Loss to follow-up	14 patients completed three or four courses of anit-emetic treatment, and 2 dropped out after one course.
% Female	43.75%
Mean age (SD)	Median age: 38 Age range: 18 to 53 years
Formulation	10mg capsule of prochlorperazine plus 15 mg of THC
How dose was titrated up	Not reported

What the maintenance dose was	10 mg of prochlorperazine plus 15mg of THC Patients received this combination one hour prior to the administration of chemotherapy. The same drugs were given four hours later, and a third final dose in another 4 hours. This sequence of three doses of prochlorperazine was defined as one course of ant-emetic treatment.
How long the maintenance dose was sustained for	Four hours after chemotherapy, and a third final dose in another 4 hours.
Monitoring/reviewing procedure	Not reported
Stopping criteria	Not reported

Prochlorperazine + placebo (N = 16)

Study type	**Cross-over randomised controlled trial**
Loss to follow-up	14 patients completed three or four courses of anit-emetic treatment, and 2 dropped out after one course.
% Female	43.75%
Mean age (SD)	Median age: 38 Age range: 18 to 53 years
Formulation	10 mg of prochlorperazine plus placebo
How dose was titrated up	How dose was titrated up Not reported
What the maintenance dose was	10mg capsule of prochlorperazine plus placebo Patients received this combination one hour prior to the administration of chemotherapy. The same drugs were given four hours later, and a third final dose in another 4 hours. This sequence of three doses of prochlorperazine was defined as one course of ant-emetic treatment.
How long the maintenance dose was sustained for	Four hours after chemotherapy, and a third final dose in another 4 hours.

Monitoring/reviewing procedure	Not reported
Stopping criteria	Not reported

Cochrane Risk of Bias Tool 2.0 for Crossover Trials
Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process
Some concerns
(unclear random sequence generation and allocation concealment.)
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)
Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)
Some concerns
(Unclear crossover period. No information provided on chemotherapeutic agents used, therefore crossover period could not be determined.)
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from intended interventions (effect of adhering to intervention)
This question has not yet been answered.
Domain 3. Bias due to missing outcome data
Risk of bias judgement for missing outcome data
Low
Domain 4. Bias in measurement of the outcome
Risk of bias judgement for measurement of the outcome
Low
Domain 5. Bias in selection of the reported result
Risk of bias judgement for selection of the reported result
Low
Overall bias and Directness
Risk of bias judgement
High

Cochrane Risk of Bias Tool 2.0 for Crossover Trials
(Outcomes: Withdrawals due to AEs and adverse events. Due to unclear random sequence generation and allocation concealment. Unclear crossover period.) **Overall Directness** Directly applicable

Levitt 1982

Levitt, 1982	
Bibliographic Reference	Levitt, M.; Nabilone vs. placebo in the treatment of chemotherapy-induced nausea and vomiting in cancer patients; Cancer treatment reviews; 1982; vol. 9supplb; 49-53

Study details

Study type	Cross-over randomised controlled trial
Study location	Canada
Study setting	Not reported
Study dates	Not reported
Duration of follow-up	Not reported
Sources of funding	Not reported
Exclusion criteria	Not stated
Sample size	58
Symptom specific characteristics	Chemotherapy induced nausea and vomiting. Patients had lung cancer, ovarian cancer, breast cancer and a variety of cancers. Their chemotherapy consisted of a variety of treatment regimens which included the antioplastic agents including Adriamycin, bleomycin, ciplatinym, cyclophosphamide, dactinomycin, melphalan, mitomycin C, methotrexate, tamoxifen, vincristine, VP-16, 5- fluorouracil. Study does not state if patients had previously experienced nausea and vomiting. Patients received 2 cycles of chemotherapy.
Intervention 1	Nabilone
Intervention 2	Prochlorperazine

Study type	Cross-over randomised controlled trial
Outcome measures	Less vomiting Less nausea Withdrawals due to adverse events Adverse events

Study arms

Nabilone (N = 36)

Split between study groups	36
Loss to follow-up	20 patients did not complete the study, only 7 study terminations were attributable to the study drugs. The majority of the reasons for early terminations were unrelated to either nabilone or placebo administration.
% Female	Overall 66%
Mean age (SD)	Overall 17-37 = 8 38-57 = 21 58-77 = 28 ≥ 78 = 1
Formulation	Nabilone
How dose was titrated up	Not specified
What the maintenance dose was	Not specified
How long the maintenance dose was sustained for	Not specified

Monitoring/reviewing procedure	Not specified
Stopping criteria	Stopping criteria not specified in methods section. However, study highlighted that study terminations were due to side effects, lack of efficacy, intercurrent illness, change in chemotherapy and patient decision.

Prochlorperazine (N = 36)

Split between study groups	**36**
Loss to follow-up	20 patients did not complete the study, only 7 study terminations were attributable to the study drugs. The majority of the reasons for early terminations were unrelated to either nabilone or placebo administration.
% Female	Overall 66%
Mean age (SD)	Overall 17-37 = 8 38-57 = 21 58-77 = 28 ≥ 78 = 1
Formulation	Not specified
How dose was titrated up	Not specified
What the maintenance dose was	Not specified
How long the maintenance dose was sustained for	Not specified
Monitoring/reviewing procedure	Not specified

Stopping criteria	Stopping criteria not specified in methods section. However, study highlighted that study terminations were due to side effects, lack of efficacy, intercurrent illness, change in chemotherapy and patient decision.

Cochrane Risk of Bias Tool 2.0 for Crossover Trials

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process
Some concerns
(No information on randomisation, allocation concealment or baseline values. Results not separated by phases which could have masked period effects)
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)
Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)
Some concerns
(Insufficient information on blinding.)
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from intended interventions (effect of adhering to intervention)
This question has not yet been answered.
Domain 3. Bias due to missing outcome data
Risk of bias judgement for missing outcome data
Some concerns
(Limited information on missing outcome data and withdrawals)
Domain 4. Bias in measurement of the outcome
Risk of bias judgement for measurement of the outcome
Some concerns
(Insufficient information on blinding.)
Domain 5. Bias in selection of the reported result
Risk of bias judgement for selection of the reported result
Some concerns
(No information on whether a statistical test for carry-over was performed)
Overall bias and Directness

Cochrane Risk of Bias Tool 2.0 for Crossover Trials
Risk of bias judgement High (Outcomes: less vomiting, less nausea and withdrawals due to AE. Some concerns for AEs) No information on randomisation, allocation concealment or baseline values. Insufficient information on blinding. Limited information on missing outcome data and withdrawals. No information on whether a statistical test for carry-over was performed.) **Overall Directness** Partially applicable (Partially direct for following outcomes: less nausea and less vomiting. Directly applicable for withdrawals due to AEs and adverse events)

McCabe 1988

McCabe, 1988	
Bibliographic Reference	McCabe, M.; Smith, F. P.; Macdonald, J. S.; Woolley, P. V.; Goldberg, D.; Schein, P. S.; Efficacy of tetrahydrocannabinol in patients refractory to standard antiemetic therapy; Investigational new drugs; 1988; vol. 6 (no. 3); 243-6

Study details

Study type	Cross-over randomised controlled trial
Study location	USA
Study setting	Vincent T Lombardi Cancer Research Centre
Study dates	Not reported
Duration of follow-up	24 hours
Sources of funding	National Institute of Drug Abuse
Inclusion criteria	Age ≥18 years Experienced severe nausea and vomiting that was refractory to standard antiemetics No history of psychiatric illness or pre-existing cardiac disease
Exclusion criteria	Not stated
Sample size	36

Study type	Cross-over randomised controlled trial
Split between study groups	Cross-over trial (all patients completed both arms)
Loss to follow-up	Not reported
% Female	75%
Mean age (SD)	Median (range): 48 (18-69)
Symptom specific characteristics	Chemotherapy induced nausea and vomiting All patients in the study group had experienced severe nausea and vomiting that was refractory to standard antiemetics. 34 patients had received prochlorperazine in the past and the remaining 2 patients had received thiethylperazine as an antiemetic. Chemotherapy regimens used: CMF, MOPP, combinations of platinum, 5-FU, doxorubicin, DTIC & 5-azacytdaine Patients received each study drug twice in randomly allocated sequence.
Intervention 1	THC
Intervention 2	Prochlorperazine
Outcome measures	Complete response (no vomiting) No nausea and vomiting Partial response 50% decrease Adverse events

Study arms

THC (N = 36)

Cross-over trial (all patients completed both arms)

Formulation	THC (Gelatine capsule)
How dose was titrated up	Not reported
What the maintenance dose was	15 mg/m² 1 hour prior to chemotherapy then every 4 hours for 24 hours
How long the maintenance dose was sustained for	24 hours
Monitoring/reviewing procedure	Patient diary for 24 hours recording frequency, duration and intensity of nausea and/or vomiting (including retching). Side effects also described
Stopping criteria	Not reported

Prochlorperazine (N = 36)

Cross-over trial (all patients completed both arms)

Formulation	Prochlorperazine (Tablet)
How dose was titrated up	Not reported
What the maintenance dose was	10 mg 1 hour prior to chemotherapy then every 4 hours for 24 hours
How long the maintenance dose was sustained for	24 hours

Cochrane Risk of Bias Tool 2.0 for Crossover Trials
Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process
Some concerns

Cochrane Risk of Bias Tool 2.0 for Crossover Trials
(No information on randomisation, allocation concealment or baseline values. Results not separated by phases which could have masked period effects)
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)
Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)
Some concerns
(Unclear if participants and personnel were aware of assignment.)
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from intended interventions (effect of adhering to intervention)
This question has not yet been answered.
Domain 3. Bias due to missing outcome data
Risk of bias judgement for missing outcome data
Some concerns
(No information provided for missing outcome data)
Domain 4. Bias in measurement of the outcome
Risk of bias judgement for measurement of the outcome
Low
Domain 5. Bias in selection of the reported result
Risk of bias judgement for selection of the reported result
Some concerns
(No information on whether a statistical test for carry-over was performed)
Overall bias and Directness
Risk of bias judgement
High
(No information on randomisation, allocation concealment or baseline values. Results not separated by phases which could have masked period effects. Unclear if participants and personnel were aware of assignment. No information on whether a statistical test for carry-over was performed. No information provided for missing outcome data.)
Overall Directness
Directly applicable

Neidhart 1981

Neidhart, 1981	
Bibliographic Reference	Neidhart, J. A.; Gagen, M. M.; Wilson, H. E.; Young, D. C.; Comparative trial of the antiemetic effects of THC and haloperidol; Journal of clinical pharmacology; 1981; vol. 21 (no. 89suppl); 38S-42S

Study details

Study type	Cross-over randomised controlled trial
Study location	USA
Study setting	Hospital
Study dates	Not reported
Duration of follow-up	Not reported
Sources of funding	National Cancer Institute
Inclusion criteria	Patients receiving a single injection or infusion of a cancer chemotherapeutic agent likely to induce intolerable vomiting Patients experiencing incapacitating vomiting refractory to standard antiemetic agents with any prior cancer chemotherapy
Exclusion criteria	Not stated
Sample size	52
Split between study groups	THC: 37 Haloperidol: 36
Loss to follow-up	Not reported
% Female	THC: 43% Haloperidol: 42%
Mean age (SD)	THC: 41.0 Haloperidol: 44.8
Symptom specific characteristics	Chemotherapy induced nausea and vomiting. Patients had experienced incapacitating vomiting refractory to standard antiemetic agents with prior cancer chemotherapy. Chemotherapy regimens used: cisplatin; doxorubicin; nitrogen mustard; cisplatin & doxorubicin; other (not stated). Study included 2 courses of therapy with each antiemetic agent.
Intervention 1	THC

Study type	Cross-over randomised controlled trial
Intervention 2	Haloperidol
Outcome measures	No vomiting Adverse events Moderate to severe adverse events

Study arms

THC (N = 52)

Cross-over study (all patients completed both arms)

Formulation	10 mg THC in 0.12 ml sesame oil
How dose was titrated up	Not reported
What the maintenance dose was	10 mg At 2 hours and at 30 mins before start of chemotherapy followed by 3 to 4 hour intervals for maximum 8 doses
How long the maintenance dose was sustained for	Not reported
Monitoring/reviewing procedure	Prior to each dose, patient or carer completed a vomiting and toxicity checklist. If toxicity interfered with function, next dose was delayed until toxicity reduced
Stopping criteria	Not reported

Haloperidol (N = 52)

1 hour prior to chemotherapy then every 4 hours for 24 hours

Formulation	2 mg tablet in opaque capsule filled with powdered lactose
How dose was titrated up	Not reported
What the maintenance dose was	2 mg At 2 hours and at 30 mins before start of chemotherapy followed by 3 to 4 hour intervals for maximum 8 doses
How long the maintenance dose was sustained for	Not reported
Monitoring/reviewing procedure	Prior to each dose, patient or carer completed a vomiting and toxicity checklist. If toxicity interfered with function, next dose was delayed until toxicity reduced
Stopping criteria	Not reported.

Cochrane Risk of Bias Tool 2.0 for Crossover Trials
Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process
Some concerns
(Unclear if allocation was concealed until participants were recruited to intervention.)
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)
Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)
Low
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from intended interventions (effect of adhering to intervention)
This question has not yet been answered.
Domain 3. Bias due to missing outcome data
Risk of bias judgement for missing outcome data
Some concerns
(No information on missing data.)
Domain 4. Bias in measurement of the outcome

Cochrane Risk of Bias Tool 2.0 for Crossover Trials
Risk of bias judgement for measurement of the outcome Low **Domain 5. Bias in selection of the reported result** Risk of bias judgement for selection of the reported result Some concerns (Unclear if test for carryover was conducted. Unclear which period the data is from) **Overall bias and Directness** Risk of bias judgement High (Unclear if allocation was concealed until participants were recruited to intervention. No information on missing data. Unclear if test for carryover was conducted. Unclear which period the data is from.) **Overall Directness** Directly applicable

Niiranen 1985

Niiranen, 1985	
Bibliographic Reference	Niiranen, A.; Mattson, K.; A cross-over comparison of nabilone and prochlorperazine for emesis induced by cancer chemotherapy; American journal of clinical oncology; 1985; vol. 8 (no. 4); 336-40

Study details

Study type	Cross-over randomised controlled trial
Study location	Finland
Study setting	Hospital
Study dates	Not reported
Duration of follow-up	Up to 24 hours after chemotherapy
Sources of funding	Lilly Research
Inclusion criteria	Patients with lung cancer who had been listed for treatment with at least 2 identical consecutive cycles of chemotherapy
Exclusion criteria	Clinically significant hepatic, renal or central nervous system disease

Study type	Cross-over randomised controlled trial
	Alcoholism Drug addiction
Sample size	32
Split between study groups	Cross-over trial (all patients completed both arms)
Loss to follow-up	Not reported
% Female	17%
Mean age (SD)	Mean (range): 72 (56-97)
Symptom specific characteristics	Chemotherapy induced nausea and vomiting. Patients received various chemotherapeutic drugs: cyclophosphamide, etoposide, vincristine, adriamycin, cisplatin and vindesine. Patients had 2 consecutive cycles of chemotherapy
Intervention 1	Nabilone
Intervention 2	Prochlorperazine
Outcome measures	Adverse events No nausea

Study arms

Nabilone (N = 32)

Cross-over trial (all patients completed both arms)

Formulation	1 mg capsule
How dose was titrated up	Not reported
What the maintenance dose was	1 mg given orally Initial dose the night before chemotherapy then 1 hour before chemotherapy and at 12 hour intervals up to 24 hours after chemotherapy

How long the maintenance dose was sustained for	Up to 24 hours after chemotherapy
Monitoring/reviewing procedure	Nausea, vomiting and appetite during the 24 hours after chemotherapy were assessed by the patient using a self-administered questionnaire and by the investigators. Side effects also recorded. Before study entry and after the last dose of each cycle a CBC, SMA-12 and urinalysis were conducted. Blood pressure and heart rate when sitting down and standing were recorded before the initial nabilone dose, immediately before chemotherapy and 3-4 hours after taking nabilone
Stopping criteria	Stopping criteria not described in methods. But study did report that one

Prochlorperazine (N = 32)

Cross-over trial (all patients completed both arms)

Formulation	**7.5 mg capsules**
How dose was titrated up	Not reported
What the maintenance dose was	7.5 mg given orally Initial dose the night before chemotherapy then 1 hour before chemotherapy and at 12 hour intervals up to 24 hours after chemotherapy
How long the maintenance dose was sustained for	Up to 24 hours after chemotherapy
Monitoring/reviewing procedure	Nausea, vomiting and appetite during the 24 hours after chemotherapy were assessed by the patient using a self-administered questionnaire and by the investigators. Side effects also recorded. Before study entry and after the last dose of each cycle a CBC, SMA-12 and urinalysis were conducted. Blood pressure and heart rate when sitting down and standing were recorded before the initial nabilone dose, immediately before chemotherapy and 3-4 hours after taking nabilone

Cochrane Risk of Bias Tool 2.0 for Crossover Trials
Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process
Some concerns
(No information on randomisation, allocation concealment or baseline values. Results not separated by phases which could have masked period effects)
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)
Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)
Low
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from intended interventions (effect of adhering to intervention)
This question has not yet been answered.
Domain 3. Bias due to missing outcome data
Risk of bias judgement for missing outcome data
Some concerns
(Study does not specify if proportion of missing data is equal among the two arms.)
Domain 4. Bias in measurement of the outcome
Risk of bias judgement for measurement of the outcome
Low
Domain 5. Bias in selection of the reported result
Risk of bias judgement for selection of the reported result
Some concerns
(Limited information on statistical test for carry-over)
Overall bias and Directness
Risk of bias judgement
High
(No information on randomisation, allocation concealment or baseline values. Results not separated by phases which could have masked period effects. Study does not specify if proportion of missing data is equal among the two arms. Limited information on statistical test for carry-over.)
Overall Directness
Partially applicable

Cochrane Risk of Bias Tool 2.0 for Crossover Trials
(Outcomes: no nausea. Study did not specify if patients previously experienced nausea and/or vomiting or had showed signs at baseline)

Orr 1980

Orr, 1980	
Bibliographic Reference	Orr, L. E.; McKernan, J. F.; Bloome, B.; Antiemetic effect of tetrahydrocannabinol. Compared with placebo and prochlorperazine in chemotherapy-associated nausea and emesis; Archives of Internal Medicine; 1980; vol. 140 (no. 11); 1431-1433

Study details

Study type	Cross-over randomised controlled trial
Study location	USA
Study setting	Hospital setting
Study dates	Not reported
Duration of follow-up	24 hours after drug ingestion
Sources of funding	THC supplied by National Institute of Drug Abuse
Inclusion criteria	Patients with a variety of neoplasms requiring drug therapy. All patients had previously demonstrated repeated vomiting from anticancer agents commonly known to induce emesis, and had failed standard antiemetic therapy
Exclusion criteria	Pregnant women, those receiving abdominal radiation and those individuals with a short life expectancy
Sample size	79
Symptom specific characteristics	Chemotherapy induced nausea and vomiting. Patients with a variety of neoplasms and previously demonstrated repeated vomiting from anticancer agents commonly known to induce emesis, and had failed standard antiemetic therapy, including phelothiazines, antihistamines and sedatives. Chemotherapeutic agents used included doxorubicin hydrochloride, cyclophosphamide, fluorouracil (with methotrexate), mechlorethamine hydrochloride, decarbazine nitrosureas, and cytarabine given as a continuous infusion.
Intervention 1	THC
Intervention 2	Prochlorperazine
Intervention 3	Placebo

Study type	Cross-over randomised controlled trial
Outcome measures	No nausea Adverse events

Study arms

THC (N = 55)

Split between study groups	55
Loss to follow-up	24 individuals voluntarily removed themselves from the study for various reasons after having been partially studied.
% Female	Overall 65%
Mean age (SD)	Overall Average: 46 years Range: 22-71 years
Formulation	THC suspended in 0.12 mL of sesame oil
How dose was titrated up	Not reported, but dose chosen because authors felt that higher doses might produce sedation sufficient to impair normal activities.
What the maintenance dose was	7mg/ sq m of THC orally every 4 hours for 4 doses.
How long the maintenance dose was sustained for	All drugs were administered one hour before chemotherapy and then given every 4 hours for 4 doses.
Monitoring/reviewing procedure	Not reported
Stopping criteria	Stopping criteria not specified in methods section. However, study highlighted that two patients repeatedly vomited the study drugs before chemotherapy could be administered and removed themselves from the study. 3 individuals felt after reconsideration that the

	use of marijuana was morally incorrect and abandoned the investigation. 2 patients were also disqualified before completion because of untoward dysphoric reactions due to THC.

Prochlorperazine (N = 55)

Split between study groups	55
Loss to follow-up	24 individuals voluntarily removed themselves from the study for various reasons after having been partially studied.
% Female	Overall 65%
Mean age (SD)	Overall Average: 46 years Range: 22-71 years
Formulation	Prochlorperazine
How dose was titrated up	Not reported, but dose chosen because authors felt that higher doses might produce sedation sufficient to impair normal activities.
What the maintenance dose was	7 mg/sq m of prochlorperazine orally every 4 hours for 4 doses
How long the maintenance dose was sustained for	All drugs were administered one hour before chemotherapy and then given every 4 hours for 4 doses.
Monitoring/reviewing procedure	Not reported
Stopping criteria	Stopping criteria not specified in methods section. However, study highlighted that two patients repeatedly vomited the study drugs before chemotherapy could be administered and removed themselves from the study. 3 individuals felt after reconsideration that the use of marijuana was morally incorrect and abandoned the investigation. 2 patients were also disqualified before completion because of untoward dysphoric reactions due to THC.

Placebo (N = 55)

Split between study groups	55
Loss to follow-up	24 individuals voluntarily removed themselves from the study for various reasons after having been partially studied.
% Female	Overall 65%
Mean age (SD)	Overall Average: 46 years Range: 22-71 years
Formulation	Placebo
How long the maintenance dose was sustained for	All drugs were administered one hour before chemotherapy and then given every 4 hours for 4 doses.
Monitoring/reviewing procedure	Not reported
Stopping criteria	Stopping criteria not specified in methods section. However, study highlighted that two patients repeatedly vomited the study drugs before chemotherapy could be administered and removed themselves from the study. 3 individuals felt after reconsideration that the use of marijuana was morally incorrect and abandoned the investigation. 2 patients were also disqualified before completion because of untoward dysphoric reactions due to THC.

Cochrane Risk of Bias Tool 2.0 for Crossover Trials
Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process
Some concerns
(No information on randomisation, allocation concealment or baseline values. Results not separated by phases which could have masked period effects)
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)
Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)

Cochrane Risk of Bias Tool 2.0 for Crossover Trials
Low
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from intended interventions (effect of adhering to intervention)
This question has not yet been answered.
Domain 3. Bias due to missing outcome data
Risk of bias judgement for missing outcome data
Some concerns
(Greater amount of missing outcome data for the placebo group)
Domain 4. Bias in measurement of the outcome
Risk of bias judgement for measurement of the outcome
Low
Domain 5. Bias in selection of the reported result
Risk of bias judgement for selection of the reported result
Some concerns
(No information on whether a statistical test for carry-over was performed)
Overall bias and Directness
Risk of bias judgement
Some concerns
(No information on randomisation, allocation concealment or baseline values. Results not separated by phases which could have masked period effects. No information on whether a statistical test for carry-over was performed)
Overall Directness
Directly applicable

Priestman 1987

Priestman, 1987	
Bibliographic Reference	Priestman, S. G.; Priestman, T. J.; Canney, P. A.; A double-blind randomised cross-over comparison of nabilone and metoclopramide in the control of radiation-induced nausea; Clinical radiology; 1987; vol. 38 (no. 5); 543-4

Study details

Study type	Cross-over randomised controlled trial 2 period cross over study
Study location	UK
Study setting	Hospital setting
Study dates	Not reported
Duration of follow-up	Daily
Sources of funding	Eli Lilley and Co supplied nabilone.
Inclusion criteria	People with radiation induced nausea and vomiting, which has at least 5 treatments remaining of their course of radiotherapy.
Sample size	40
Symptom specific characteristics	Radiation induced nausea and vomiting Radiotherapy received not specified but study reports that patients received treatment on pelvis, abdomen, thorax, head and neck and other treatment sites. Patients had already experienced vomiting as a side effect.
Intervention 1	Nabilone Plus placebo
Intervention 2	Metoclopramide
Outcome measures	Serious adverse events Adverse events

Study arms

Nabilone (N = 40)

Plus placebo

Split between study groups	20
Loss to follow-up	40 patients entered the study but 1 declined to take the prescribed anti-emetic
% Female	45%
Mean age (SD)	Mean age: 61.9 years
Formulation	1mg bd given with placebo.
How dose was titrated up	Not reported
What the maintenance dose was	1mg Nabilone was given with a placebo capsule at midday. The interval between starting radiotherapy and starting antiemetic therapy varied considerably, with some patients preferring to cope with mild nausea for some days before requesting treatment. Mean time for nabilone patients = 9.5 days (± 6.29).
How long the maintenance dose was sustained for	Antiemetic therapy was continued until either the completion of 30 days treatment, the completion of radiotherapy or evidence of failure to respond to anti-emetic therapy, which ever was soonest.
Monitoring/reviewing procedure	Not reported
Stopping criteria	Not reported

Metoclopramide (N = 40)

Sample size	19
Loss to follow-up	40 patients entered the study but 1 declined to take the prescribed anti-emetic
% Female	53%
Mean age (SD)	Mean age: 54.5 years
Formulation	10 mg tds
How dose was titrated up	Not reported

What the maintenance dose was	10 mg Metoclopramide was given with a placebo capsule at midday. The interval between starting radiotherapy and starting antiemetic therapy varied considerably, with some patients preferring to cope with mild nausea for some days before requesting treatment. Mean time for nabilone patients = 8.36 days (± 5.18).
How long the maintenance dose was sustained for	Antiemetic therapy was continued until either the completion of 30 days treatment, the completion of radiotherapy or evidence of failure to respond to anti-emetic therapy, which ever was soonest.
Monitoring/reviewing procedure	Not reported
Stopping criteria	Not reported

Cochrane Risk of Bias Tool 2.0 for Crossover Trials

Domain 1: Bias arising from the randomisation process

Risk of bias judgement for the randomisation process

Some concerns

(unclear random sequence generation and allocation concealment.)

Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)

Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)

Some concerns

(study did not state washout period.)

Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)

Risk of bias judgement for deviations from intended interventions (effect of adhering to intervention)

This question has not yet been answered.

Domain 3. Bias due to missing outcome data

Risk of bias judgement for missing outcome data

Low

Domain 4. Bias in measurement of the outcome

Risk of bias judgement for measurement of the outcome

Cochrane Risk of Bias Tool 2.0 for Crossover Trials
Low **Domain 5. Bias in selection of the reported result** Risk of bias judgement for selection of the reported result Some concerns (Study does not specify which period the data is from. and does not mention test for carry-over) **Overall bias and Directness** Risk of bias judgement High (Outcomes: Serious AEs and side effects- Some concerns identified in randomisation process and insufficient information on washout period. Study does not specify which period the data is from. and does not mention test for carry-over) **Overall Directness** Directly applicable

Sallan 1975

Sallan, 1975	
Bibliographic Reference	Sallan, S. E.; Zinberg, N. E.; Frei, E., 3rd; Antiemetic effect of delta-9-tetrahydrocannabinol in patients receiving cancer chemotherapy; The New England journal of medicine; 1975; vol. 293 (no. 16); 795-7

Study details

Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Hospital setting
Study dates	Not specified
Duration of follow-up	Day after treatment.
Sources of funding	THC supplied by the National Institute on Drug Abuse.
Inclusion criteria	Patients known to have a variety of neoplasms
Exclusion criteria	Pregnant women and patients with a past history of emotional instability or untoward reactions to psychoactive drugs were not eligible
Sample size	22

Study type	Randomised controlled trial (RCT)
Symptom specific characteristics	Chemotherapy induced nausea and vomiting. Chemotherapeutic agents not reported. Patients included had previously experienced nausea and vomiting. Patients received 3 one day courses of the drug.
Intervention 1	THC
Intervention 2	Placebo
Outcome measures	Complete response (no vomiting) Partial response 50% reduction in vomiting Adverse events

Study arms

THC (N = 15 courses)

Loss to follow-up	11 patients completed three courses of treatment, two completed two courses and nine completed one course. one of the 11 never vomited and was excluded from analysis because the dose of cancer chemotherapy agent was reduced by 50%.
% Female	55% overall
Mean age (SD)	Overall median: 29.5 years Range: 18 and 76 years.
Formulation	THC suspended in 0.12ml of sesame oil
How dose was titrated up	Initial dose was 15mg given every 4 hours for three doses Because of some variability in responses, the dose was changed to 10mg per square metre body surface area per dose.
What the maintenance dose was	19 patients received 15mg doses and 3 received 20mg doses.

How long the maintenance dose was sustained for	Each course consisted of three doses of drug, the first taken 2 hours before and the other 2 and 6 hours after chemotherapy
Monitoring/reviewing procedure	Not reported
Stopping criteria	Stopping criteria not specified in methods section. However, study highlighted that one patient decided to smoke marijuana and became ineligible to continue.

Placebo (N = 14 courses)

Formulation	**Placebo** **Identical appearing placebo capsules containing only sesame oil**
How long the maintenance dose was sustained for	Each course consisted of three doses of drug, the first taken 2 hours before and the other 2 and 6 hours after chemotherapy
Monitoring/reviewing procedure	Not reported
Stopping criteria	Stopping criteria not specified in methods section. However, study highlighted that one patient decided to smoke marijuana and became ineligible to continue.

Cochrane Risk of Bias Tool 2.0 for Crossover Trials
Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process
Some concerns
(No information on randomisation, allocation concealment or baseline values. Results not separated by phases which could have masked period effects)
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)
Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)
High
(Crossover period not defined.)

Cochrane Risk of Bias Tool 2.0 for Crossover Trials
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from intended interventions (effect of adhering to intervention)
This question has not yet been answered.
Domain 3. Bias due to missing outcome data
Risk of bias judgement for missing outcome data
Some concerns
(outcome data not available for all participants. Only people who completed cycles were included in analysis.)
Domain 4. Bias in measurement of the outcome
Risk of bias judgement for measurement of the outcome
Low
Domain 5. Bias in selection of the reported result
Risk of bias judgement for selection of the reported result
Some concerns
(Unclear statistical test for crossover.)
Overall bias and Directness
Risk of bias judgement
High
(No information on whether a statistical test for carry-over was performed. No information on washout period. No information on random sequence generation, allocation concealment and baseline values. Results not separated by phases which could have masked period effects)
Overall Directness
Directly applicable

Sallan 1980

Sallan, 1980	
Bibliographic Reference	Sallan, S. E.; Cronin, C.; Zelen, M.; Zinberg, N. E.; Antiemetics in patients receiving chemotherapy for cancer. A randomized comparison of delta-9-tetrahydrocannabinol and prochlorperazine; New England Journal of Medicine; 1980; vol. 302 (no. 3); 135-138

Study details

Study type	Cross-over randomised controlled trial
Study location	USA
Study setting	Hospital setting
Study dates	Not reported
Duration of follow-up	Day after treatment
Sources of funding	THC supplied by National Institute on Drug Abuse
Inclusion criteria	Patients known to have a variety of neoplasms
Exclusion criteria	Pregnant women and patients with a past history of emotional instability or untoward reactions to psychoactive drugs were not eligible
Symptom specific characteristics	Chemotherapy induced nausea and vomiting. Patients received chemotherapy of: - Greatest emetic activity- combination of agents including cisplatin, dacarbazine, doxorubicin and cyclophosphamide - Moderate emetic activity- combinations of agents including high-dose methotrexate, cyclophosphamide, doxorubicin, and actinomycin D. Cisplatin and high dose actinomycin D as single agents. - Low emetic activity- Single agent including high dose methotrexate, cyclophosphamide and doxorubicin Patients had previously experienced nausea and vomiting. Each patient was to receive three one-day courses of the study drug (2 courses with one drug and 1 course with the other)
Intervention 1	THC
Intervention 2	Prochlorperazine
Outcome measures	Adverse events Withdrawals due to adverse events No nausea and vomiting (complete response) Partial response

Study arms

THC (N = 79 courses)

Split between study groups	79
Loss to follow-up	27 patients received only one course and were removed from the study: 2 died of cancer, 4 had THC toxicity, one refused to accept the risk of vomiting with subsequent courses of other antiemetic after having a complete response to THC, seven had changes in chemotherapy regiments, 13 patients vomited during the first course and chose to quit the study.
% Female	Overall 39%
Mean age (SD)	Overall Average age: 32.5 years Range 9-70 years
Formulation	10- 15mg THC Suspended in 0.12ml of sesame oil
How dose was titrated up	Based on body surface area.
What the maintenance dose was	10mg -15mg 5 patients with body surface area less than 1m² each received 10mg of THC.
How long the maintenance dose was sustained for	three one-day courses
Monitoring/reviewing procedure	Not reported
Stopping criteria	Stopping criteria not specified in methods section. However, study highlighted that patients were removed from the study due to THC toxicity, one patient refused to accept the risk of vomiting with subsequent courses of anti-emetic and change in chemotherapy.

Prochlorperazine (N = 78 courses)

Split between study groups	78
Loss to follow-up	27 patients received only one course and were removed from the study: 2 died of cancer, 4 had THC toxicity, one refused to accept the risk of vomiting with subsequent courses of other antiemetic after having a complete response to THC, seven had changes in chemotherapy regiments, 13 patients vomited during the first course and chose to quit the study.
% Female	Overall 39%
Mean age (SD)	Overall Average age: 32.5 years Range 9-70 years
Formulation	Prochlorperazine 10 mg
How dose was titrated up	Not reported
What the maintenance dose was	10 mg
How long the maintenance dose was sustained for	three one-day courses
Monitoring/reviewing procedure	Not reported
Stopping criteria	Stopping criteria not specified in methods section. However, study highlighted that patients were removed from the study due to THC toxicity, one patient refused to accept the risk of vomiting with subsequent courses of anti-emetic and change in chemotherapy.

Cochrane Risk of Bias Tool 2.0 for Crossover Trials
Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process
Some concerns

Cochrane Risk of Bias Tool 2.0 for Crossover Trials
(No information on randomisation, allocation concealment or baseline values. Results not separated by phases which could have masked period effects)
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)
Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)
Low
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from intended interventions (effect of adhering to intervention)
This question has not yet been answered.
Domain 3. Bias due to missing outcome data
Risk of bias judgement for missing outcome data
Low
Domain 4. Bias in measurement of the outcome
Risk of bias judgement for measurement of the outcome
Low
Domain 5. Bias in selection of the reported result
Risk of bias judgement for selection of the reported result
Some concerns
(No information on whether a statistical test for carry-over was performed)
Overall bias and Directness
Risk of bias judgement
Some concerns
(No information on whether a statistical test for carry-over was performed. No information on randomisation, allocation concealment or baseline values. Results not separated by phases which could have masked period effects.))
Overall Directness
Directly applicable

Steele 1980

Steele, 1980	
Bibliographic Reference	Steele, N.; Gralla, R. J.; Braun, D. W., Jr.; Young, C. W.; Double-blind comparison of the antiemetic effects of nabilone and prochlorperazine on chemotherapy-induced emesis; Cancer treatment reports; 1980; vol. 64 (no. 23); 219-24

Study details

Study type	Cross-over randomised controlled trial
Study location	USA
Study setting	Hospital setting
Study dates	April 1978 to January 1979
Duration of follow-up	Within 24h of completion of each cycle
Sources of funding	Not reported
Exclusion criteria	Patients were not eligible if they had known cardiac disease or psychotic episodes or had regularly used marijuana.
Sample size	55
Symptom specific characteristics	Chemotherapy induced nausea and vomiting Patients receiving 2 consecutive, identical chemotherapy treatments Chemotherapy regimens used: High-dose DDP & vindesine (frequency = 4-6 weeks) ; Low-dose DDP & vindesine (frequency = 4-6 weeks); Low-dose DDP & adriamycin (frequency = 3-4 weeks); Mechlorethamine, vincristine & procarbazine(frequency = 4 weeks - days 1 and 8); streptozotocin (frequency = 3- 4 weeks); Actinomycin D, vinblastine & chlorambucil (frequency = 3- 4 weeks); DTIC & cyclophosphamide (frequency = 4 weeks) It is not reported if patients had either previously experienced nausea and vomiting, or had it at baseline.
Intervention 1	Nabilone
Intervention 2	Prochlorperazine
Outcome measures	Adverse events

Study arms

Nabilone (N = 37)

Split between study groups	37
Loss to follow-up	18 patients were excluded from evaluation.
Mean age (SD)	Overall

	Median: 50 Range: 19 to 65 years
Formulation	2mg oral nabilone
How dose was titrated up	Not reported
What the maintenance dose was	2 mg
How long the maintenance dose was sustained for	Each anti-emetic was given every 12 hours for 3 to 5 doses with the first dose given the night before chemotherapy.
Monitoring/reviewing procedure	A cbc, platelet count, urinalysis, SMA-12 and electrocardiogram (ECG) were conducted. Supine and standing blood pressures were monitored every 4 hours during waking hours.
Stopping criteria	Stopping criteria not specified in methods section. However, study highlighted that 4 patients withdrew from the study after taking nabilone due to intolerable adverse events.

Prochlorperazine (N = 37)

Split between study groups	**37**
Loss to follow-up	18 patients were excluded from evaluation.
Mean age (SD)	Overall Median: 50 Range: 19 to 65 years
Formulation	10 mg oral slow-release prochlorperazine
How dose was titrated up	Not reported
What the maintenance dose was	10 mg

How long the maintenance dose was sustained for	Each antiemetic was given every 12 hours for three to five doses, with the first dose given the night before chemotherapy.
Monitoring/reviewing procedure	A cbc, platelet count, urinalysis, SMA-12 and electrocardiogram were obtained in hospitalised patients. Supine and standing blood pressues were monitored every 4 hours during waking hours.
Stopping criteria	Stopping criteria not specified in methods section. However, study highlighted that 4 patients withdrew from the study after taking nabilone due to intolerable adverse events.

Cochrane Risk of Bias Tool 2.0 for Crossover Trials

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process
Some concerns
(Unclear random sequence generation. No information on baseline values. Results not separated by phases which could have masked period effects.)
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)
Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)
High
(participant aware of assignment.)
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from intended interventions (effect of adhering to intervention)
This question has not yet been answered.
Domain 3. Bias due to missing outcome data
Risk of bias judgement for missing outcome data
Some concerns
(outcome data not available for all participants)
Domain 4. Bias in measurement of the outcome
Risk of bias judgement for measurement of the outcome
High

Cochrane Risk of Bias Tool 2.0 for Crossover Trials
(study states that antiemetic treatment was instituted the night before chemotherapy and 15-18 hours often elapsed before chemotherapy was administered. Because of this pre-treatment, a significant number of patients were able to determine which drug they were receiving before chemotherapy because of the side effects)
Domain 5. Bias in selection of the reported result
Risk of bias judgement for selection of the reported result
Some concerns
(No information on whether a statistical test for carry-over was performed)
Overall bias and Directness
Risk of bias judgement
High
(Unclear random sequence generation. No information on baseline values. Results not separated by phases which could have masked period effects. participant aware of assignment. outcome data not available for all participants. No information on whether a statistical test for carry-over was performed)
Overall Directness
Directly applicable

Ungerleider 1982

Ungerleider, 1982	
Bibliographic Reference	Ungerleider, J. T.; Andrysiak, T.; Fairbanks, L.; Cannabis and cancer chemotherapy. A comparison of oral delta-9-THC and prochlorperazine; Cancer; 1982; vol. 50 (no. 4); 636-645

Study details

Study type	Cross-over randomised controlled trial
Study location	USA
Study setting	Hospital setting
Study dates	July 1st 1977- March 1st 1980
Duration of follow-up	24h after taking study medication
Sources of funding	THC provided by the National Institute on Drug Abuse

Study type	Cross-over randomised controlled trial
Inclusion criteria	at least 18 years of age, not pregnant, English speaking, and not receiving concurrent radiation nor having a history of allergy or severe side effects to prochlorperazine. Women of childbearing potential were permitted in the study after the first six months, after FDA approved protocol amendment Patients must either have received a course of chemotherapy associated with documented history of nausea and vomiting, or be on the first course of chemotherapy of a drug with a high emetic potential
Exclusion criteria	Not stated
Sample size	214
Loss to follow-up	Study states that 75 patients terminated (at their request) from the study during or following their first cycle.
Symptom specific characteristics	Chemotherapy induced nausea and vomiting Patients with a wide variety of neoplasms and chemotherapeutic regimens. Patients had previously experienced nausea and vomiting. Patients had to agree to not use other anti-emetics during study period.
Intervention 1	THC
Intervention 2	Prochlorperazine
Outcome measures	Relative nausea reduction Less nausea

Study arms

THC (N = 133)

Split between study groups	133
Loss to follow-up	Study states that 75 patients terminated (at their request) from the study during or following their first cycle.
% Female	50%
Mean age (SD)	Mean: 47 years Range: 18-82 years
Formulation	THC

How dose was titrated up	Based on body surface area
What the maintenance dose was	SA <1.4m² = 7.5 mg SA <1.4m²-1.8m² = 10 mg SA >1.8m² = 12.5 mg
How long the maintenance dose was sustained for	Study drugs were administered orally 1 hour before chemotherapy and every4 hours thereafter for a total of 4 doses per day on each day of chemotherapy.
Monitoring/reviewing procedure	Not reported
Stopping criteria	Not reported

Prochlorperazine (N = 133)

Split between study groups	**133**
Loss to follow-up	Study states that 75 patients terminated (at their request) from the study during or following their first cycle.
% Female	50%
Mean age (SD)	Mean: 47 years Range: 18-82 years
Formulation	Prochlorperazine - 10 mg
How dose was titrated up	Not reported
What the maintenance dose was	Fixed dose of 10 mg
How long the maintenance dose was sustained for	Study drugs were administered orally 1 hour before chemotherapy and every4 hours thereafter for a total of 4 doses per day on each day of chemotherapy.

Monitoring/reviewing procedure	Not reported
Stopping criteria	Not reported

Cochrane Risk of Bias Tool 2.0 for Crossover Trials
Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process
Some concerns
(No information on baseline imbalances.)
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)
Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)
Some concerns
(Unclear if participants were aware of assignment.)
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from intended interventions (effect of adhering to intervention)
This question has not yet been answered.
Domain 3. Bias due to missing outcome data
Risk of bias judgement for missing outcome data
Some concerns
(People who withdrew reported fewer effects of the drug than those who completed the study)
Domain 4. Bias in measurement of the outcome
Risk of bias judgement for measurement of the outcome
Low
Domain 5. Bias in selection of the reported result
Risk of bias judgement for selection of the reported result
Some concerns
(No information on whether a statistical test for carry-over was performed. Results not separated by phases which could have masked period effects)
Overall bias and Directness

Cochrane Risk of Bias Tool 2.0 for Crossover Trials
Risk of bias judgement High (Unclear if participants were aware of assignment. People who withdrew reported fewer effects of the drug than those who completed the study, No information on whether a statistical test for carry-over was performed. Results not separated by phases which could have masked period effects.) **Overall Directness** Directly applicable

Ungerleider 1985

Ungerleider, 1985	
Bibliographic Reference	Ungerleider, J. T.; Sarna, G.; Fairbanks, L. A.; Goodnight, J.; Andrysiak, T.; Jamison, K.; THC or Compazine for the cancer chemotherapy patient--the UCLA study. Part II: Patient drug preference; American journal of clinical oncology; 1985; vol. 8 (no. 2); 142-7

Study details

Study location	USA
Study setting	Hospital setting
Study dates	July 1st 1977- March 1st 1980
Duration of follow-up	24h after taking study medication
Sources of funding	THC provided by the National Institute on Drug Abuse
Sample size	139 patients. 50% of patients in the sample reported a past history of some illegal drug use, predominantly marijuana (Overall 70 patients)
Symptom specific characteristics	Study reports further findings from Ungerleider 1982. Study used to extract data on people with some experience of illicit drug use. Study states that a prestudy interview was conducted with each patient to obtain a thorough psychological history emphasising licit and illicit drug use. 50% of patients in the sample reported a past history of some illegal drug use, predominantly marijuana.
Intervention 1	Nabilone
Intervention 2	Prochlorperazine
Outcome measures	Relative nausea reduction

Study arms

THC **This study reports further findings from Ungerleider 1982. Study used to extract data on people with some experience of illicit drug use.** **Prochlorperazine** **This study reports further findings from Ungerleider 1982. Study used to extract data on people with some experience of illicit drug use.**

Cochrane Risk of Bias Tool 2.0 for Crossover Trials
Refer to Ungerleider 1982 for information on individual domains. **Overall bias and Directness** Risk of bias judgement High (Unclear if participants were aware of assignment. People who withdrew reported fewer effects of the drug than those who completed the study, No information on whether a statistical test for carry-over was performed. Results not separated by phases which could have masked period effects.) **Overall Directness** Partially applicable: study states that people had history of illicit drug use but does not state if people had existing substance abuse.

Wada 1982

Wada, 1982	
Bibliographic Reference	Wada, J. K.; Bogdon, D. L.; Gunnell, J. C.; Hum, G. J.; Gota, C. H.; Rieth, T. E.; Double-blind, randomized, crossover trial of nabilone vs. placebo in cancer chemotherapy; Cancer treatment reviews; 1982; vol. 9supplb; 39-44

Study details

Study type	**Cross-over randomised controlled trial**
Study location	USA
Study setting	Hospital setting
Study dates	Not reported
Duration of follow-up	Daily
Sources of funding	Nabilone supplied by Eli Lilly

Study type	Cross-over randomised controlled trial
Exclusion criteria	Patients with significant cardiovascular, hepatic, renal or central nervous system disease and patients with known psychosis or alcohol or drug addiction
Symptom specific characteristics	Chemotherapy induced nausea and vomiting Patients receiving a variety of chemotherapy regimens. 2 consecutive cycles of cancer chemotherapy. Chemotherapy agents used: Adriamycin, BCNU, Bleomycin, Cis-platinum, Cytoxan, Dactinomycin, DTIC, 5-Fluorouracil, HN2, MCCNU, Melphalan, Methotrexate, Mitomycin, Procarbazine, Streptozotocin, Tamoxifen, Vinblastine, Vincristine, VP-16. Study does not state if patients had previously experienced nausea and vomiting.
Intervention 1	Nabilone
Intervention 2	Placebo
Outcome measures	Complete relief of nausea and vomiting Less vomiting Less nausea Withdrawals due to adverse events Adverse events

Study arms

Nabilone (N = 114)

Split between study groups	92 evaluable for efficacy 104 for adverse experiences
Loss to follow-up	30 patients terminated the study early. 8 cases were due to nabilone- related adverse experiences, 9 patients discontinued due to lack of efficacy of the placebo, 4 had progressive cancer with required a change or discontinuation of chemotherapy, and 3 patients had cancer related deaths. 4 were lost to follow up. 2 changed their minds and decided not the participate in the study after randomisation, but before actually starting on treatment.
% Female	Overall 59%
Mean age (SD)	Overall Mean : 57

	Age range: 18-81 years
Formulation	Nabilone 2 mg
How dose was titrated up	Not reported
What the maintenance dose was	2 mg - one capsule One capsule was taken at 8 am the preceding evening and one at 8 am on the morning of the administration of chemotherapy. Chemotherapy was given 1-3 h after the 8 am dose of nabilone.
How long the maintenance dose was sustained for	The study drug was continued on a 12h schedule for 1 dose after the final administration of chemotherapy.
Monitoring/reviewing procedure	Blood pressure were measured before each cycles of chemotherapy, and 3-4 hours after each morning dose of the study medication.
Stopping criteria	Stopping criteria not specified in methods section. However, study highlighted that 30 patients terminated the study early due to nabilone related adverse experiences, lack of efficacy (of placebo), progressive cancer, change or discontinued chemotherapy.

Placebo (N = 114)

Split between study groups	**92 evaluable for efficacy 104 for adverse experiences**
Loss to follow-up	30 patients terminated the study early. 8 cases were due to nabilone- related adverse experiences, 9 patients discontinued due to lack of efficacy of the placebo, 4 had progressive cancer with required a change or discontinuation of chemotherapy, and 3 patients had cancer related deaths. 4 were lost to follow up. 2 changed their minds and decided not the participate in the study after randomisation, but before actually starting on treatment.
% Female	Overall 59%
Mean age (SD)	92 evaluable for efficacy 104 for adverse experiences
Formulation	Placebo

Stopping criteria	Stopping criteria not specified in methods section. However, study highlighted that 30 patients terminated the study early due to nabilone related adverse experiences, lack of efficacy (of placebo), progressive cancer, change or discontinued chemotherapy.

Cochrane Risk of Bias Tool 2.0 for Crossover Trials

Domain 1: Bias arising from the randomisation process
Risk of bias judgement for the randomisation process
Some concerns
(No information on randomisation, allocation concealment or baseline values. Results not separated by phases which could have masked period effects)
Domain 2: Risk of bias due to deviations from intended interventions (effect of assignment to intervention)
Risk of bias judgement for deviations from intended interventions (effect of assignment to intervention)
Some concerns
(No information on whether participants and personnel were aware of intervention or if a statistical test for carry-over was performed)
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)
Risk of bias judgement for deviations from intended interventions (effect of adhering to intervention)
This question has not yet been answered.
Domain 3. Bias due to missing outcome data
Risk of bias judgement for missing outcome data
Some concerns
(30 people withdrew from the study. Unclear if the number of withdrawals was similar between treatment arms)
Domain 4. Bias in measurement of the outcome
Risk of bias judgement for measurement of the outcome
Low
Domain 5. Bias in selection of the reported result
Risk of bias judgement for selection of the reported result
Some concerns
(No information on whether a statistical test for carry-over was performed)
Overall bias and Directness
Risk of bias judgement

Cochrane Risk of Bias Tool 2.0 for Crossover Trials
High (No information on randomisation, allocation concealment or baseline values. Results not separated by phases which could have masked period effects. Missing data, No information on whether participants and personnel were aware of intervention or if a statistical test for carry-over was performed) **Overall Directness** Partially applicable (Partially direct for outcomes: complete relief of nausea and vomiting, less nausea, less vomiting. Directly applicable for other outcomes.)

E.3 Observational study

Polito 2018

Polito, 2018	
Bibliographic Reference	Polito, Samantha; MacDonald, Tamara; Romanick, Marcel; Jupp, Jennifer; Wiernikowski, John; Vennettilli, Ashlee; Khanna, Mila; Patel, Priya; Ning, Winnie; Sung, Lillian; Dupuis, L. Lee; Safety and efficacy of nabilone for acute chemotherapy-induced vomiting prophylaxis in pediatric patients: A multicenter, retrospective review; Pediatric blood & cancer; 2018; vol. 65 (no. 12); e27374

Study details

Study location	Canada
Study setting	5 institutions (SickKids, Toronto; Hamilton Health Sciences Centre, Hamilton; Alberta Children's Hospital, Calgary; Stollery Children's Hospital, Edmonton; IWK Health Centre, Halifax
Study dates	December 1 2010 - November 30 2015
Duration of follow-up	Acute phase. Until 24 hours after administration of last antineoplastic dose of the block or until discharge
Sources of funding	None reported
Inclusion criteria	Age (1) 1) ≤18 years Received nabilone for the purpose of CINV prevention as an inpatient between 1st December 2010 - 30th November 2015 Received a dose of nabilone before the administration of the first chemotherapy dose of a chemotherapy block
Exclusion criteria	Receiving nabilone for any purpose other than CINV Received the first nabilone dose of the course after administration of the first chemotherapy dose of the chemotherapy block

Study location	Canada
Sample size	110
Split between study groups	110 (single arm study)
% Female	41%
Mean age (SD)	Median (range): 14.0 (1.14 - 18.00)
Condition specific characteristics	Emetogenicity (%) (2) 2) High (75%), Moderate (23%, Low (0%), Minimal (0.1%)
Interventions	Nabilone Some patients also received nabilone in combination with other antiemetics such as 5-HT3 antagonists, dexamethasone and dimenhydrinate.
Outcome measures	Adverse events Number of vomits Complete vomiting control (3) 3) No vomiting and no rescue therapy during the acute phase Partial vomiting control (4) 4) 1 to 2 vomits during any 24 hour period of acute phase Withdrawal due to adverse events
Formulation	Mean initial nabilone dose: Once daily - 19 µg/kg/ dose (2.30- 3.09?) Twice daily - 17 µg/kg/ dose (5.00- 38.80) Three times daily- 14 µg/kg/ dose (9.10- 19.40)
How dose was titrated up	No information provided
What the maintenance dose was	Once daily - 5% Twice daily - 83% Three times daily - 3% 9 patients received dose of 60 µg/kg/day or higher

Study location	Canada
How long the maintenance dose was sustained for	During acute phase. Until 24 hours after administration of last antineoplastic dose of the block or until discharge
Stopping criteria	Nabilone discontinued in 10 patients due to adverse events

IHE Quality Appraisal Checklist for Case Series Studies
Study objective *Was the hypothesis/aim/objective of the study clearly stated?* Partial **Study design** *Was the study conducted prospectively?* No *Were the cases collected in more than one centre?* Yes *Were patients recruited consecutively?* Unclear **Study population** *Were the characteristics of the patients included in the study described?* Partial *Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?* Yes *Did patients enter the study at a similar point in the disease?* Unclear **Intervention and co-intervention** *Was the intervention of interest clearly described?* Partial *Were additional interventions (co-interventions) clearly described?*

IHE Quality Appraisal Checklist for Case Series Studies
Partial
Outcome measure
Were relevant outcome measures established a priori?
Yes
Were outcome assessors blinded to the intervention that patients received?
Unclear
Were the relevant outcomes measured using appropriate objective/subjective methods?
Partial
Were the relevant outcome measures made before and after the intervention?
No
Statistical analysis
Were the statistical tests used to assess the relevant outcomes appropriate?
Yes
Results and conclusions
Was follow-up long enough for important events and outcomes to occur?
Yes
Were losses to follow-up reported?
No
Did the study provide estimates of random variability in the data analysis of relevant outcomes?
No
Were the adverse events reported?
Yes
Were the conclusions of the study supported by results?
Yes
Competing interests and sources of support
Were both competing interests and sources of support for the study reported?
Partial
Overall Risk of Bias

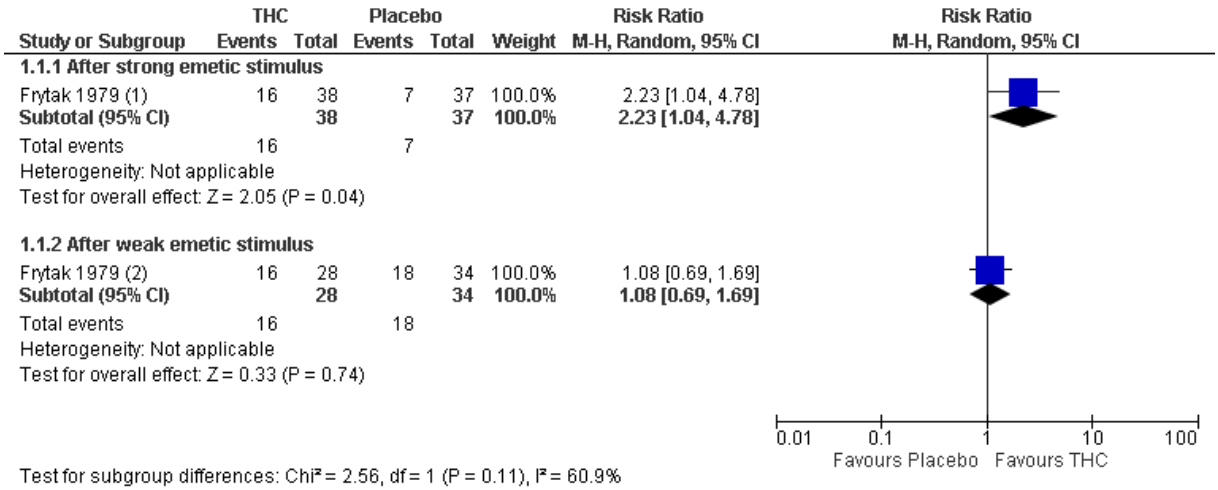
IHE Quality Appraisal Checklist for Case Series Studies
Risk of Bias
High
Applicability
Partially directly applicable

Appendix F – Forest plots

F. 1 Chemotherapy induced nausea and vomiting

Tetrahydrocannabinol (THC) vs placebo

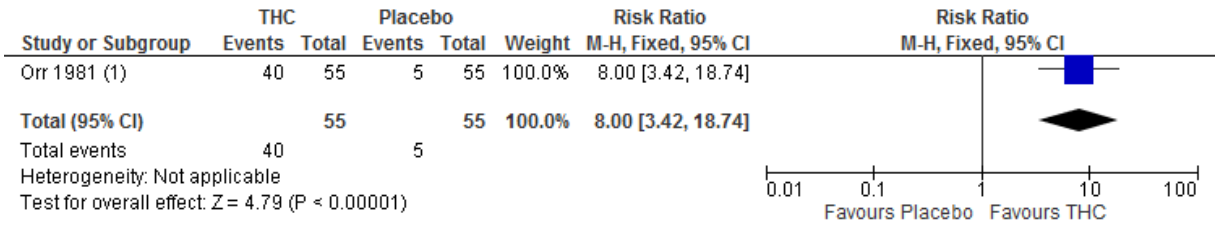
Absence of nausea and vomiting



Test for subgroup differences: $Chi^2 = 2.56$, df = 1 (P = 0.11), $I^2 = 60.9\%$

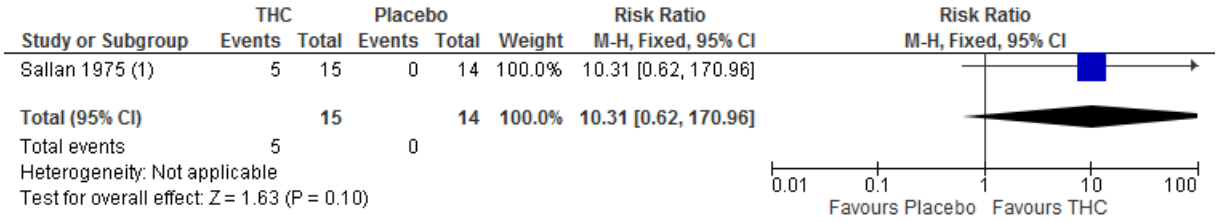
Footnotes
(1) Day 1
(2) Days 2-4

Complete reduction in nausea



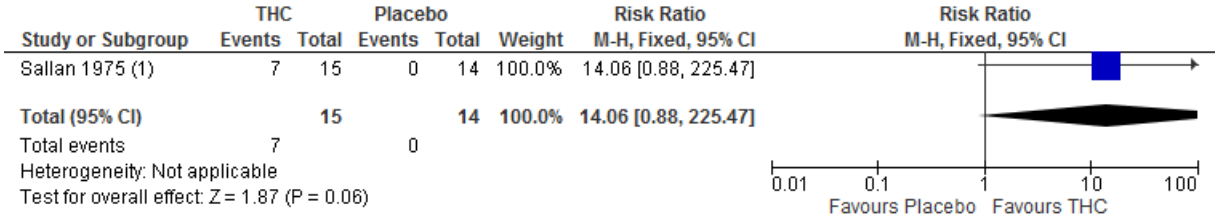
Footnotes
(1) Patients had previously demonstrated repeated vomiting from anticancer agents and had failed standard antiemetic therapy.

Complete reduction in vomiting



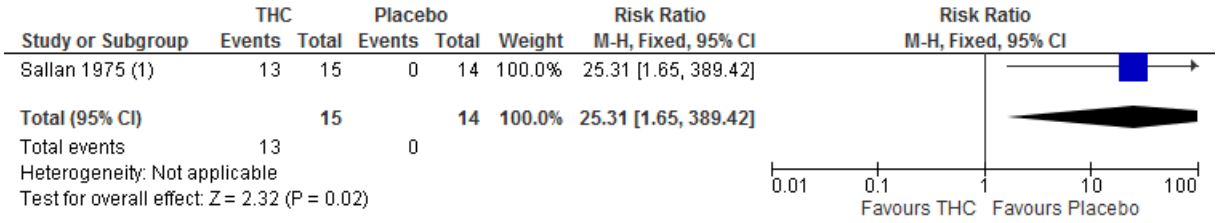
Footnotes
(1) Patients included had previously experienced nausea and vomiting. No. of events = number of courses

Partial reduction in vomiting (50% reduction)



Footnotes
(1) Patients included had previously experienced nausea and vomiting. No. of events = number of courses

Adverse events

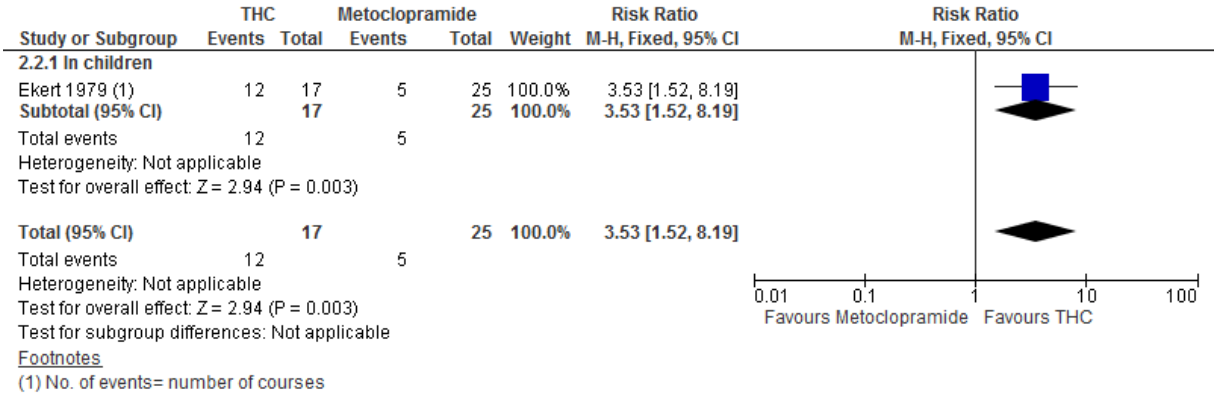


Footnotes
(1) Includes feeling 'high', somnolence, paranoid ideation, apprehension, fear, panic and visual distortion.

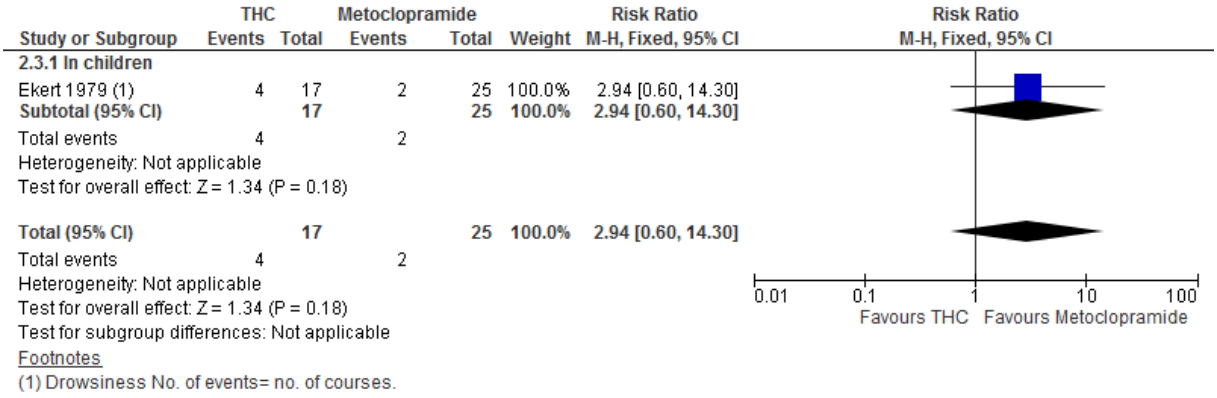
Tetrahydrocannabinol (THC) vs Metoclopramide

Major antiemetic response (defined as between 0-2 episodes)

Absence of vomiting

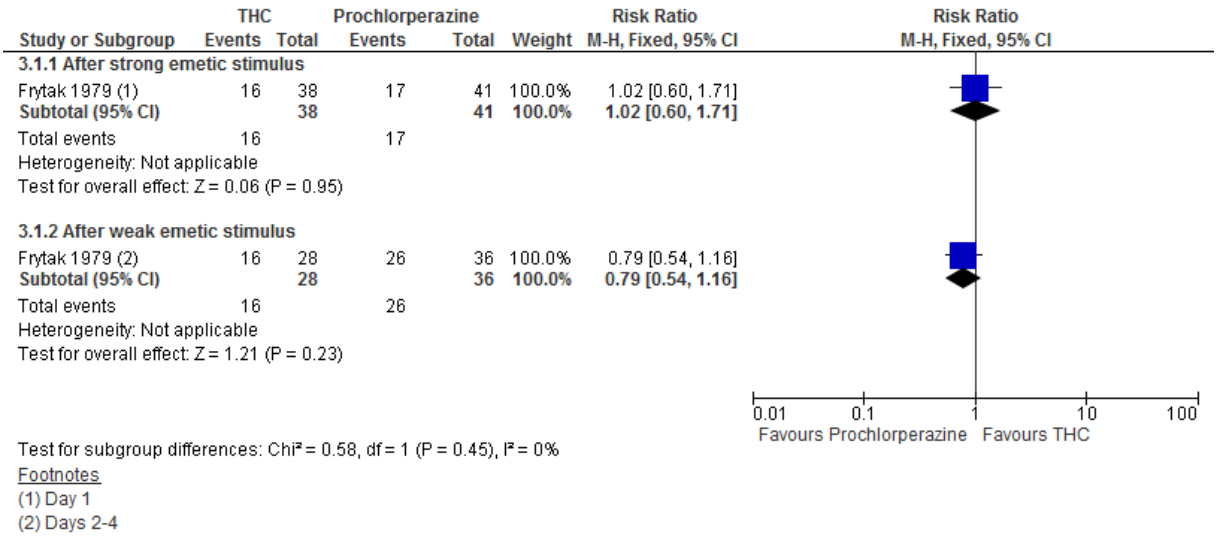


Adverse events



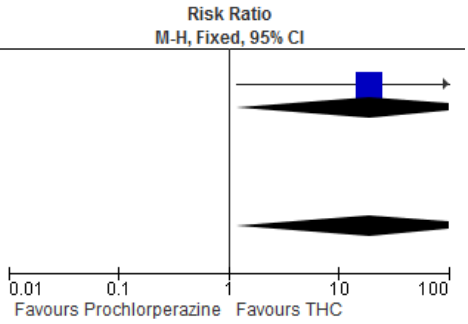
Tetrahydrocannabinol (THC) vs Prochlorperazine

Absence of nausea and vomiting



Absence of vomiting

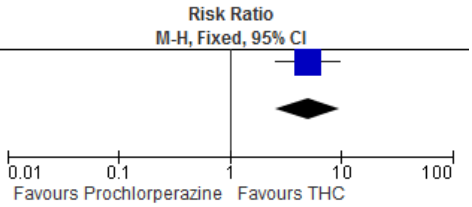
Study or Subgroup	THC Events	Total	Prochlorperazine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 In children						
Ekert 1979 (1)	9	18	0	18	100.0%	19.00 [1.19, 303.76]
Subtotal (95% CI)		**18**		**18**	**100.0%**	**19.00 [1.19, 303.76]**
Total events	9		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.08 (P = 0.04)						
Total (95% CI)		**18**		**18**	**100.0%**	**19.00 [1.19, 303.76]**
Total events	9		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.08 (P = 0.04)						
Test for subgroup differences: Not applicable						



Footnotes
(1) No. of events= number of courses

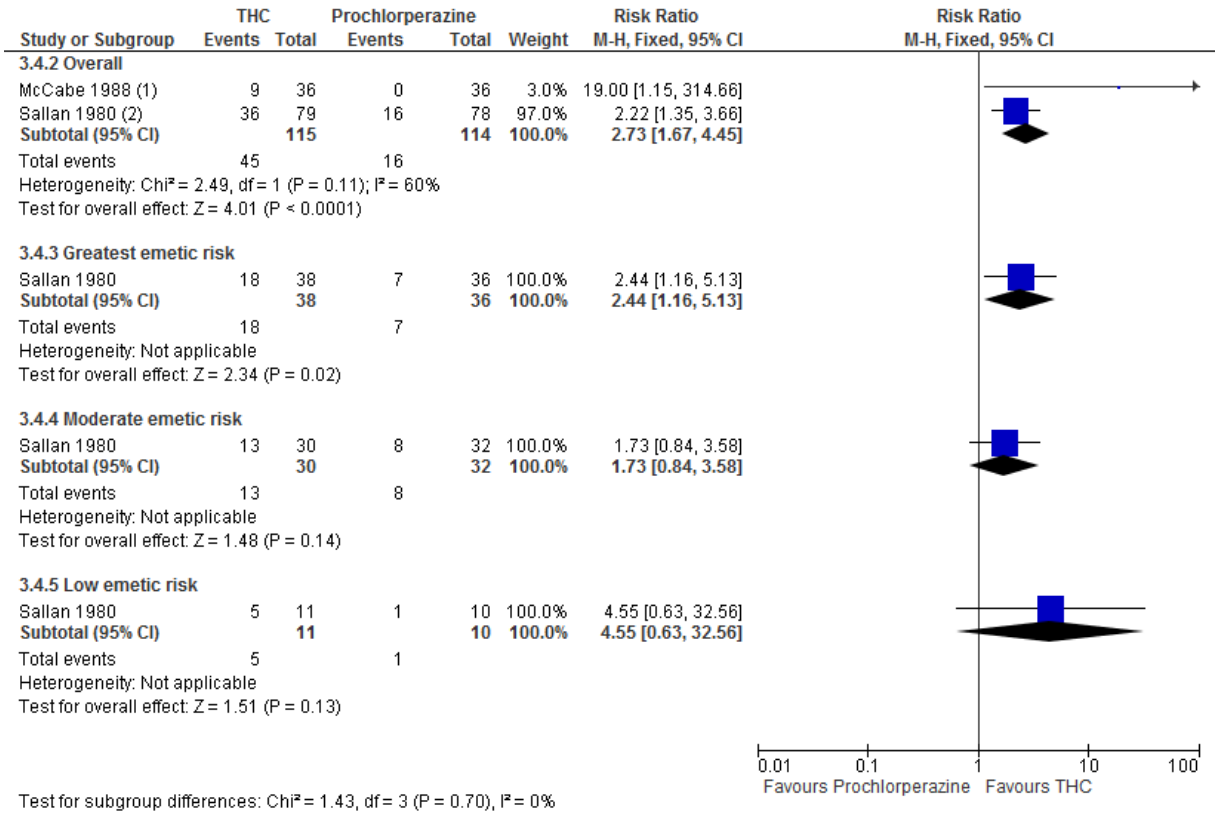
Complete reduction in nausea

Study or Subgroup	THC Events	Total	Prochlorperazine Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Orr 1981 (1)	40	55	8	55	100.0%	5.00 [2.58, 9.68]
Total (95% CI)		**55**		**55**	**100.0%**	**5.00 [2.58, 9.68]**
Total events	40		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.77 (P < 0.00001)						



Footnotes
(1) Patients had previously demonstrated repeated vomiting from anticancer agents and had failed standard antiemetic therapy.

Complete reduction in nausea and vomiting



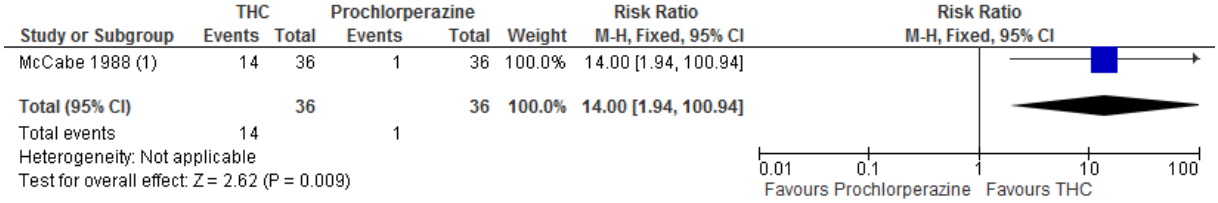
Test for subgroup differences: Chi² = 1.43, df = 3 (P = 0.70), I² = 0%

Footnotes

(1) Patients in the study group had experienced severe nausea and vomiting that was refractory to standard antiemetics

(2) Patients had previously experienced nausea and vomiting. no of events= no. of antiemetic courses

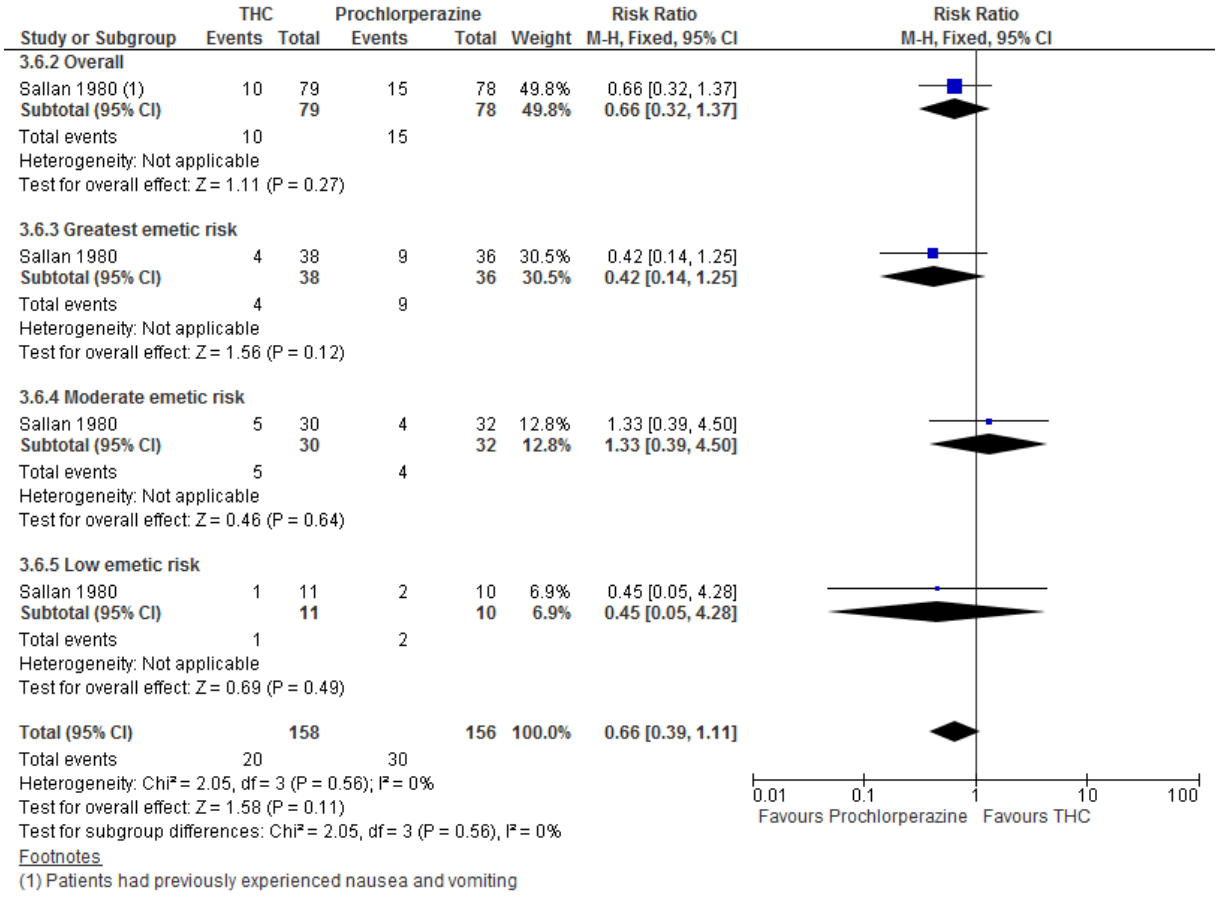
Partial reduction in nausea and vomiting (50% decrease)



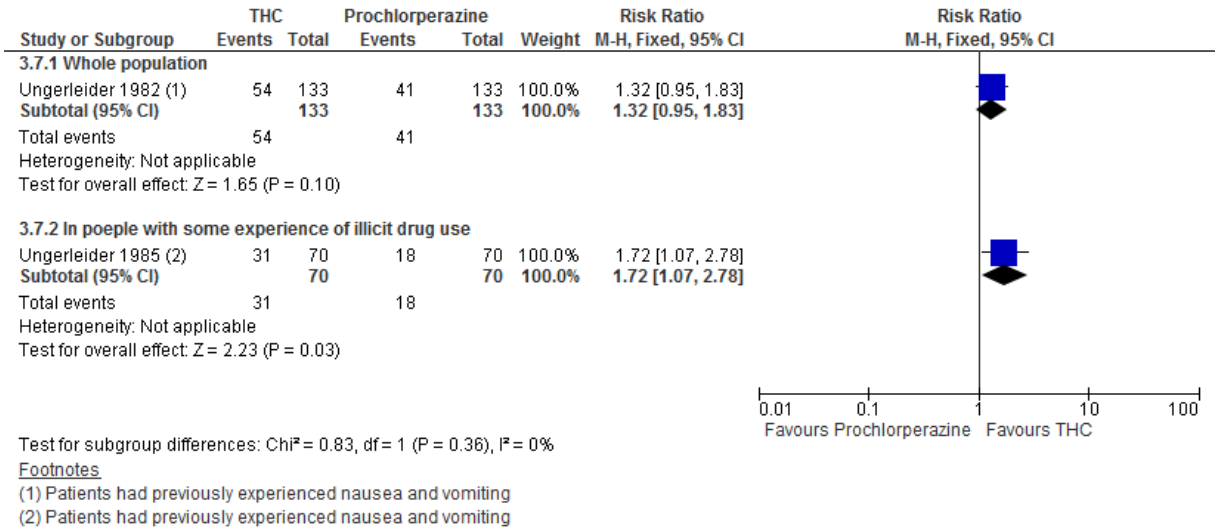
Footnotes

(1) Patients in the study group had experienced severe nausea and vomiting that was refractory to standard antiemetics

Partial reduction in nausea and vomiting (reduction in severity of nausea and vomiting)

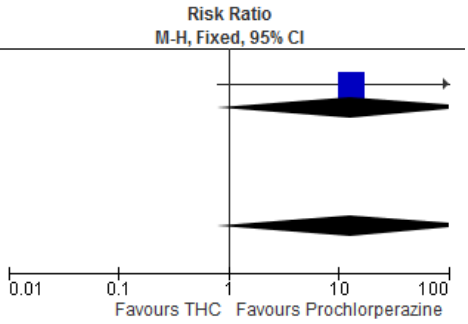


Relative reduction in nausea (less nausea compared to comparator)



Adverse events

Study or Subgroup	THC Events	THC Total	Prochlorperazine Events	Prochlorperazine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.8.1 In children						
Ekert 1979 (1)	6	18	0	18	100.0%	13.00 [0.79, 214.91]
Subtotal (95% CI)		**18**		**18**	**100.0%**	**13.00 [0.79, 214.91]**
Total events	6		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.79 (P = 0.07)						
Total (95% CI)		**18**		**18**	**100.0%**	**13.00 [0.79, 214.91]**
Total events	6		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.79 (P = 0.07)						
Test for subgroup differences: Not applicable						

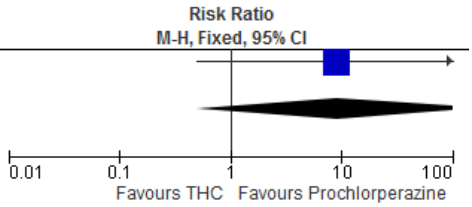


Footnotes

(1) Drowsiness. No. of events= no. of courses.

Withdrawals due to adverse events

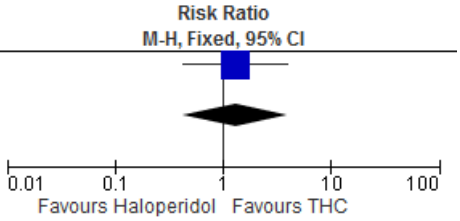
Study or Subgroup	THC Events	THC Total	Prochlorperazine Events	Prochlorperazine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sallan 1980	4	84	0	84	100.0%	9.00 [0.49, 164.59]
Total (95% CI)		**84**		**84**	**100.0%**	**9.00 [0.49, 164.59]**
Total events	4		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.48 (P = 0.14)						



Tetrahydrocannabinol (THC) vs Haloperidol

Complete reduction in vomiting

Study or Subgroup	THC Events	THC Total	Haloperidol Events	Haloperidol Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Neidhart 1981 (1)	6	50	5	54	100.0%	1.30 [0.42, 3.98]
Total (95% CI)		**50**		**54**	**100.0%**	**1.30 [0.42, 3.98]**
Total events	6		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.45 (P = 0.65)						

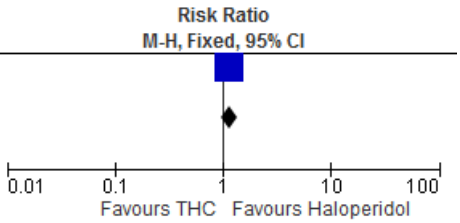


Footnotes

(1) Patients had experienced incapacitating vomiting refractory to standard antiemetic agents. No. of events = no. of courses

Adverse events

Study or Subgroup	THC Events	THC Total	Haloperidol Events	Haloperidol Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Neidhart 1981 (1)	48	53	44	56	100.0%	1.15 [0.98, 1.36]
Total (95% CI)		**53**		**56**	**100.0%**	**1.15 [0.98, 1.36]**
Total events	48		44			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.72 (P = 0.09)						



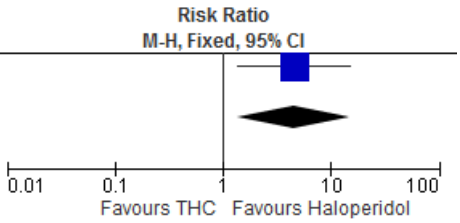
Footnotes

(1) No. of events = no. of courses. Adverse event defined as any toxicity

Moderate to severe adverse events

Study or Subgroup	THC Events	THC Total	Haloperidol Events	Haloperidol Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Neidhart 1981 (1)	13	53	3	56	100.0%	4.58 [1.38, 15.17]
Total (95% CI)		**53**		**56**	**100.0%**	**4.58 [1.38, 15.17]**
Total events	13		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.49 (P = 0.01)



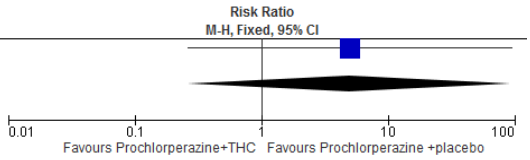
Footnotes
(1) No. of events = no. of courses.

Prochlorperazine +THC vs Prochlorperazine +placebo

Withdrawals due to adverse events

Study or Subgroup	Prochlorperazine+THC Events	Prochlorperazine+THC Total	Prochlorperazine +placebo Events	Prochlorperazine +placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kleinman 1983	2	14	0	14	100.0%	5.00 [0.26, 95.61]
Total (95% CI)		**14**		**14**	**100.0%**	**5.00 [0.26, 95.61]**
Total events	2		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.07 (P = 0.29)

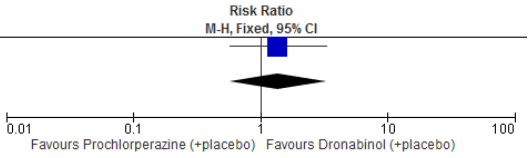


Dronabinol (+ placebo) vs prochlorperazine (+placebo)

Complete reduction in nausea and vomiting

Study or Subgroup	Dronabinol (+placebo) Events	Dronabinol (+placebo) Total	Prochlorperazine (+placebo) Events	Prochlorperazine (+placebo) Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lane 1991 (1)	7	17	6	20	100.0%	1.37 [0.57, 3.30]
Total (95% CI)		**17**		**20**	**100.0%**	**1.37 [0.57, 3.30]**
Total events	7		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.71 (P = 0.48)

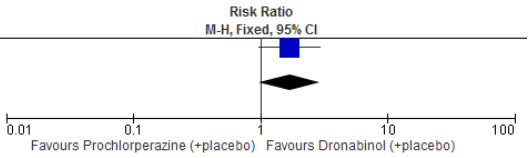


Footnotes
(1) All patients received prior chemotherapy and prior antiemetic therapy and had experienced nause and vomiting.

2 or fewer episodes of nausea and vomiting

Study or Subgroup	Dronabinol (+placebo) Events	Dronabinol (+placebo) Total	Prochlorperazine (+placebo) Events	Prochlorperazine (+placebo) Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lane 1991 (1)	13	17	9	20	100.0%	1.70 [0.98, 2.95]
Total (95% CI)		**17**		**20**	**100.0%**	**1.70 [0.98, 2.95]**
Total events	13		9			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.88 (P = 0.06)

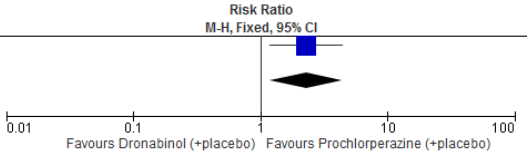


Footnotes
(1) All patients received prior chemotherapy and prior antiemetic therapy and had experienced nause and vomiting

Adverse events

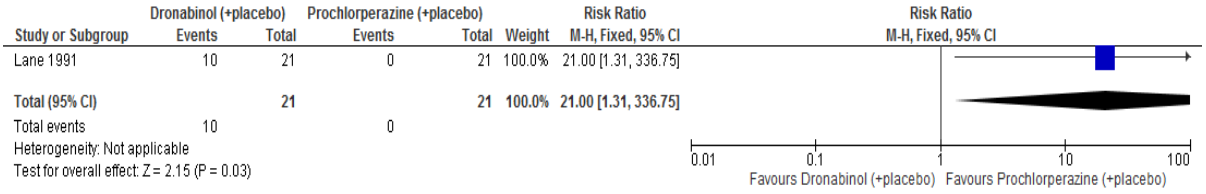
Study or Subgroup	Dronabinol (+placebo) Events	Dronabinol (+placebo) Total	Prochlorperazine (+placebo) Events	Prochlorperazine (+placebo) Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Lane 1991 (1)	16	21	7	21	100.0%	2.29 [1.19, 4.38]
Total (95% CI)		**21**		**21**	**100.0%**	**2.29 [1.19, 4.38]**
Total events	16		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.49 (P = 0.01)



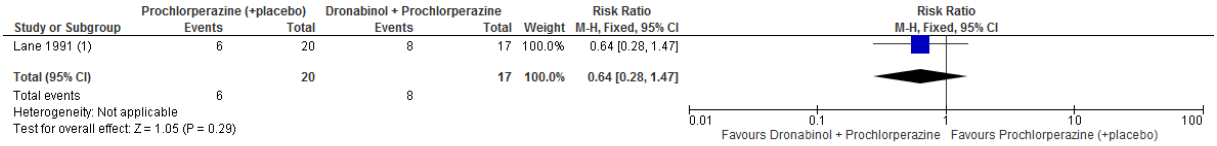
Footnotes
(1) Included neurological, digestive, cardiovascular, respiratory and other events including other body systems

Withdrawals due to adverse events



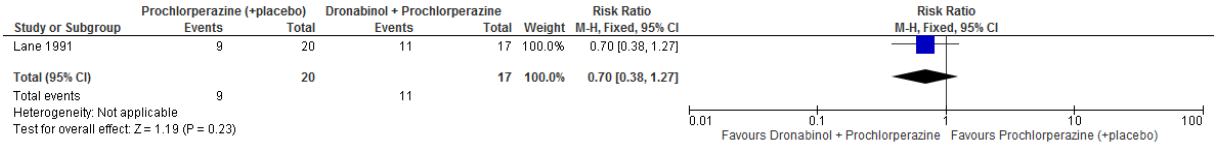
Dronabinol + prochlorperazine vs Prochlorperazine (+ placebo)

Complete reduction in nausea and vomiting

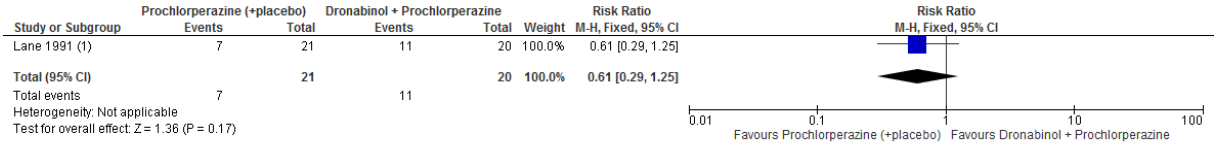


Footnotes
(1) All patients received prior chemotherapy and prior antiemetic therapy and had experienced nause and vomiting

2 or fewer episodes of nausea and vomiting



Adverse events

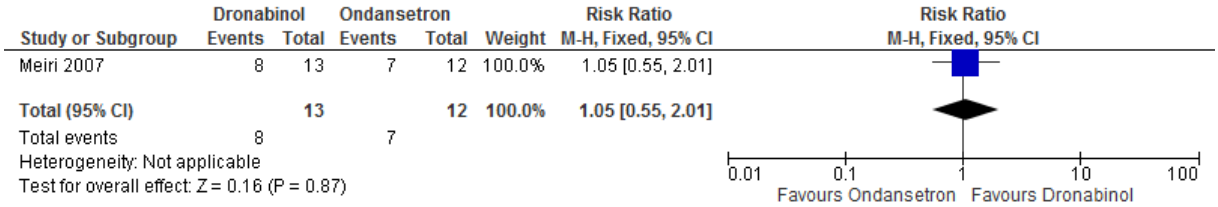


Footnotes
(1) Included neurological, digestive, cardiovascular, respiratory and other events including other body systems

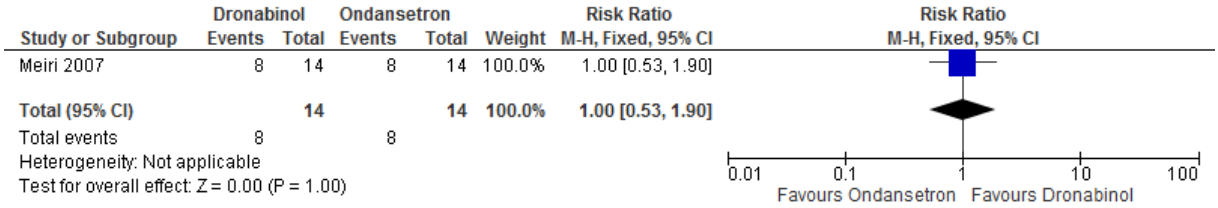
Withdrawals due to adverse events

Dronabinol vs Ondansetron

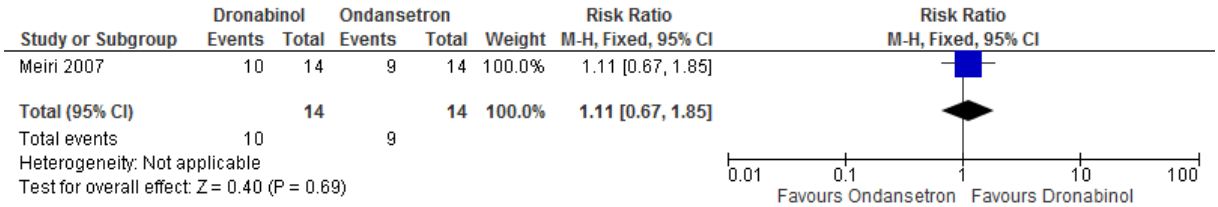
Complete response (no delayed vomiting/ retching, intensity of nausea of ≤30 mm on the VAS, and no use of rescue medication)



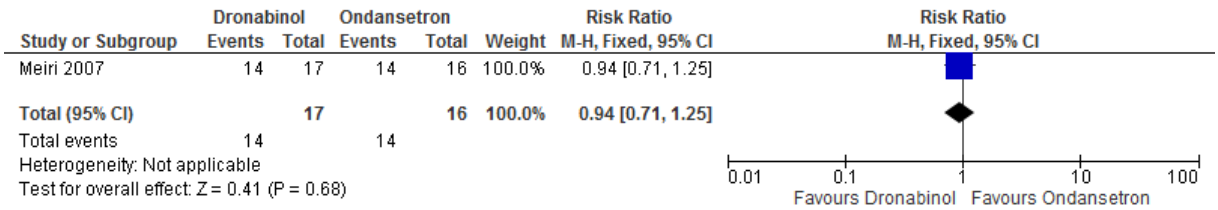
Total response (No delayed vomiting and/ or retching, intensity of nausea <5mm on a 100-mm VAS, and no use of rescue medication)



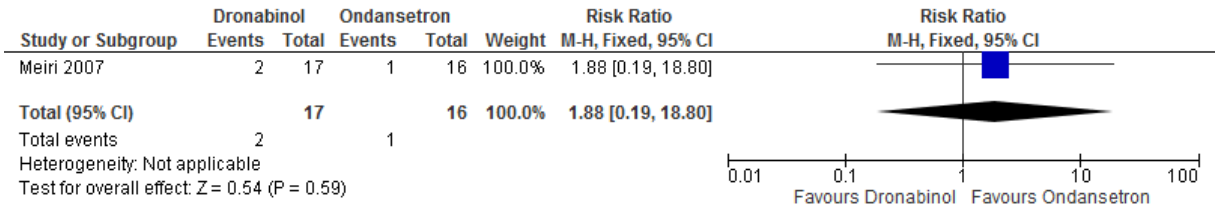
Absence of delayed nausea



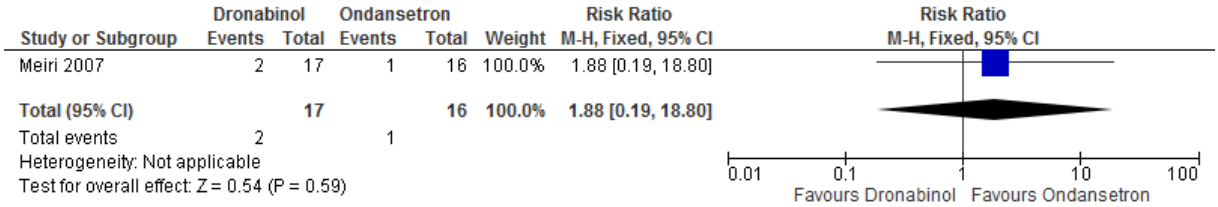
Patient with at least one TEAE



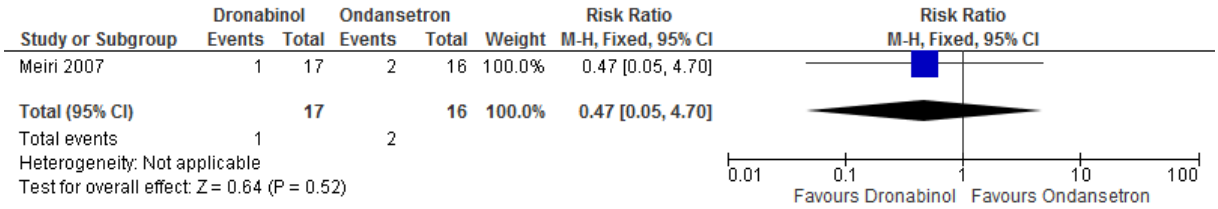
Patient with at least one SAE



Patient with at least one severe TEAE

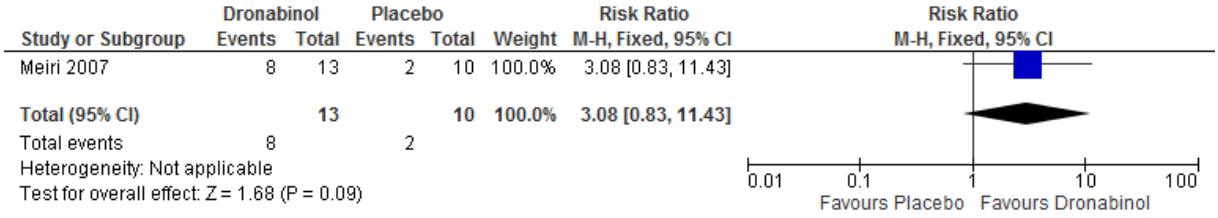


Withdrawals due to adverse events

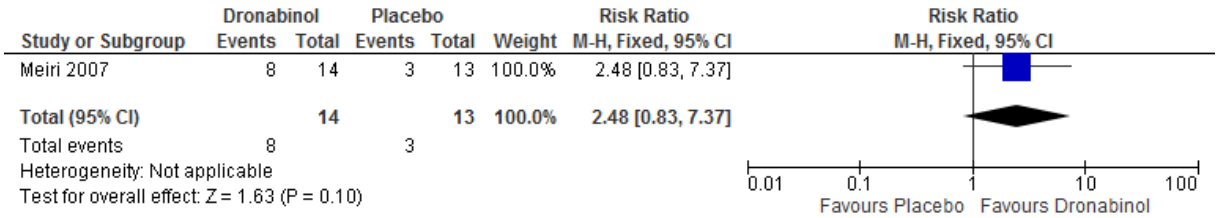


Dronabinol vs placebo

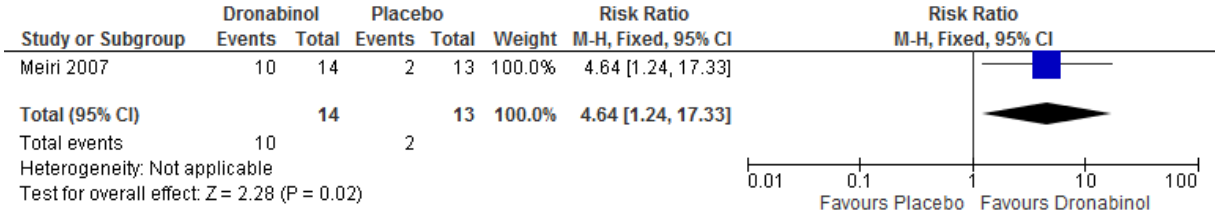
Complete response (no delayed vomiting/ retching, intensity of nausea of ≤30 mm on the VAS, and no use of rescue medication)



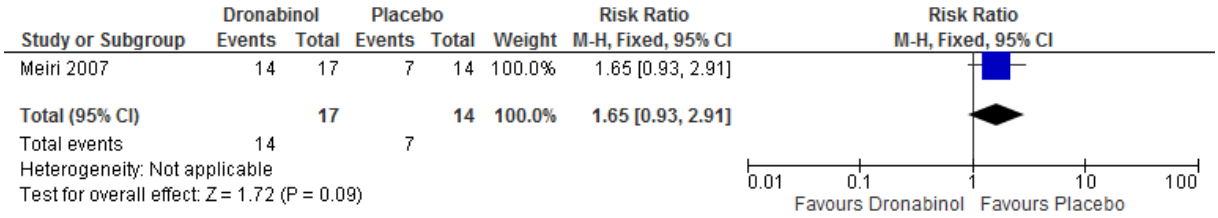
Total response (No delayed vomiting and/ or retching, intensity of nausea <5mm on a 100-mm VAS, and no use of rescue medication)



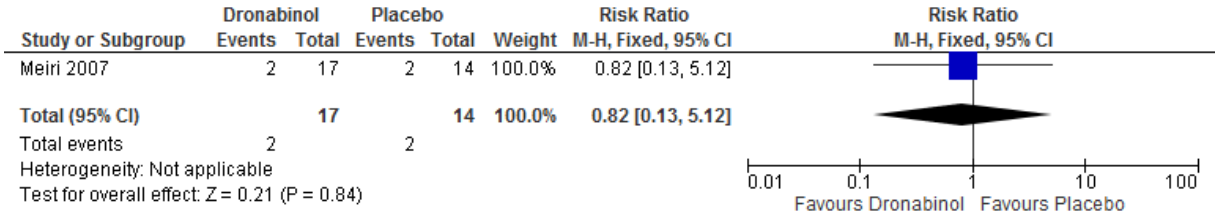
Absence of delayed nausea



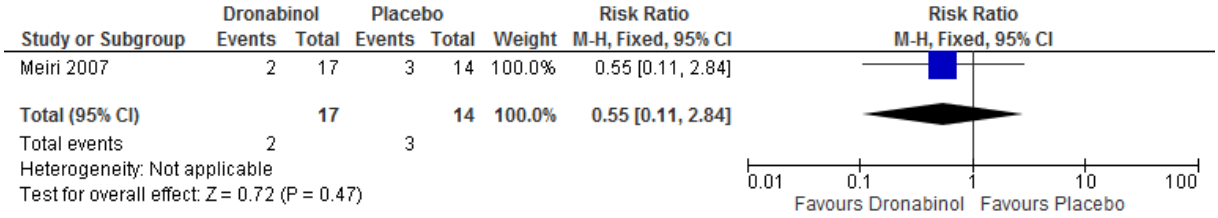
Patient with at least one TEAE



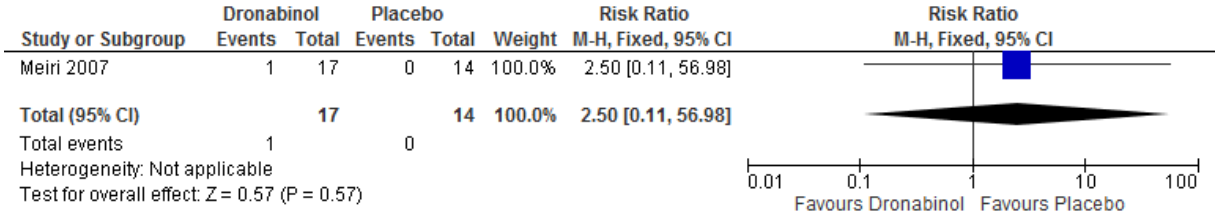
Patient with at least one SAE



Patient with at least one severe TEAE

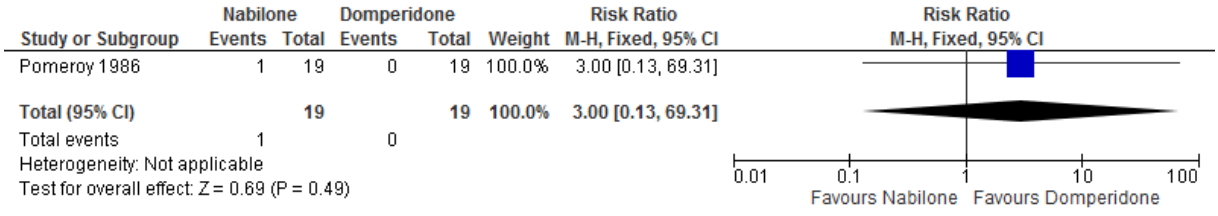


Withdrawals due to adverse events



Nabilone vs Domperidone

Withdrawals due to adverse events

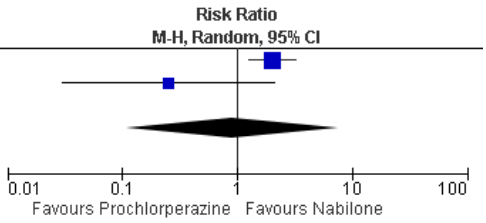


Nabilone vs Prochlorperazine

Absence of nausea

Study or Subgroup	Nabilone Events	Nabilone Total	Prochlorperazine Events	Prochlorperazine Total	Weight	Risk Ratio M-H, Random, 95% CI
Ahmedzai 1983 (1)	21	26	12	30	61.2%	2.02 [1.25, 3.25]
Niiranen 1985	1	24	4	24	38.8%	0.25 [0.03, 2.08]
Total (95% CI)		**50**		**54**	**100.0%**	**0.90 [0.11, 7.50]**
Total events	22		16			

Heterogeneity: Tau² = 1.86; Chi² = 4.03, df = 1 (P = 0.04); I² = 75%
Test for overall effect: Z = 0.10 (P = 0.92)

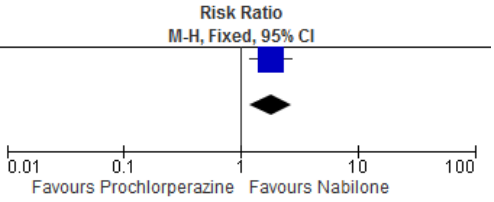


Footnotes
(1) Data from Day 3

Absence of retching

Study or Subgroup	Nabilone Events	Nabilone Total	Prochlorperazine Events	Prochlorperazine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ahmedzai 1983 (1)	22	26	14	30	100.0%	1.81 [1.20, 2.75]
Total (95% CI)		**26**		**30**	**100.0%**	**1.81 [1.20, 2.75]**
Total events	22		14			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.80 (P = 0.005)

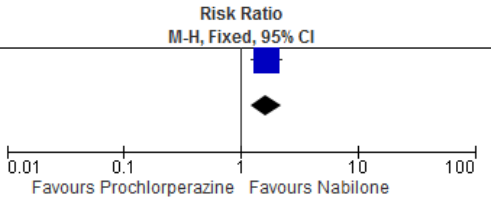


Footnotes
(1) Data from Day 3

Absence of vomiting

Study or Subgroup	Nabilone Events	Nabilone Total	Prochlorperazine Events	Prochlorperazine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ahmedzai 1983 (1)	26	26	18	30	100.0%	1.64 [1.23, 2.21]
Total (95% CI)		**26**		**30**	**100.0%**	**1.64 [1.23, 2.21]**
Total events	26		18			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.32 (P = 0.0009)



Footnotes
(1) Data from Day 3

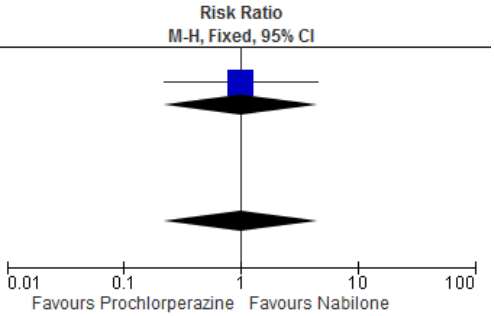
Complete reduction in retching and vomiting

Study or Subgroup	Nabilone Events	Nabilone Total	Prochlorperazine Events	Prochlorperazine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.4.1 In children						
Chan 1987 (1)	3	30	3	30	100.0%	1.00 [0.22, 4.56]
Subtotal (95% CI)		**30**		**30**	**100.0%**	**1.00 [0.22, 4.56]**
Total events	3		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

Total (95% CI)		**30**		**30**	**100.0%**	**1.00 [0.22, 4.56]**
Total events	3		3			

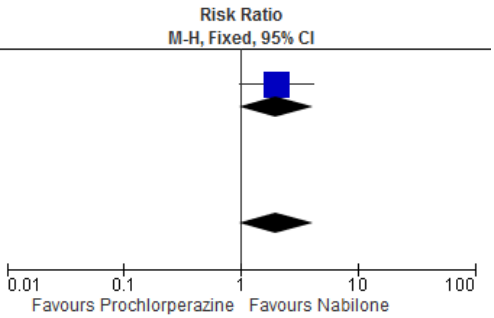
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



Footnotes
(1) Chemotherapeutic agents had previously shown to produce produce moderate to severe nausea and vomiting in the study subjects

Reduction in retching and vomiting (less retching and vomiting)

Study or Subgroup	Nabilone Events	Nabilone Total	Prochlorperazine Events	Prochlorperazine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.5.1 In children						
Chan 1987 (1)	18	30	6	20	100.0%	2.00 [0.96, 4.15]
Subtotal (95% CI)		**30**		**20**	**100.0%**	**2.00 [0.96, 4.15]**
Total events	18		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.86 (P = 0.06)						
Total (95% CI)		**30**		**20**	**100.0%**	**2.00 [0.96, 4.15]**
Total events	18		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.86 (P = 0.06)						
Test for subgroup differences: Not applicable						

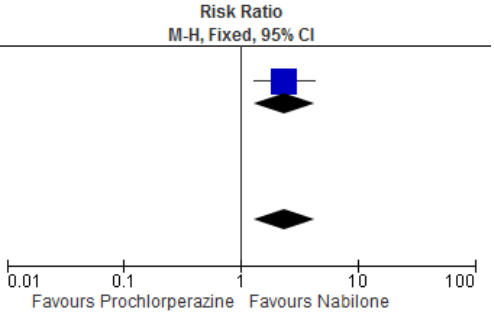


Footnotes

(1) Chemotherapeutic agents had previously shown to produce produce moderate to severe nausea and vomiting in the study subjects

Overall Rate of improvement of retching and vomiting

Study or Subgroup	Nabilone Events	Nabilone Total	Prochlorperazine Events	Prochlorperazine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.6.1 In children						
Chan 1987 (1)	21	30	9	30	100.0%	2.33 [1.29, 4.23]
Subtotal (95% CI)		**30**		**30**	**100.0%**	**2.33 [1.29, 4.23]**
Total events	21		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.79 (P = 0.005)						
Total (95% CI)		**30**		**30**	**100.0%**	**2.33 [1.29, 4.23]**
Total events	21		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.79 (P = 0.005)						
Test for subgroup differences: Not applicable						

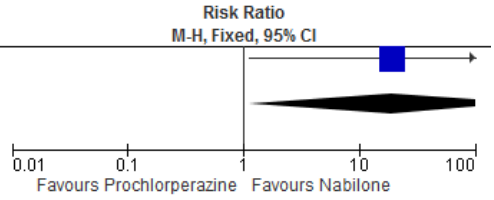


Footnotes

(1) Chemotherapeutic agents had previously shown to produce produce moderate to severe nausea and vomiting in the study subjects

Complete reduction in nausea and vomiting (total absence of nausea and vomiting)

Study or Subgroup	Nabilone Events	Nabilone Total	Prochlorperazine Events	Prochlorperazine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Herman 1979 (1)	9	113	0	113	100.0%	19.00 [1.12, 322.59]
Total (95% CI)		**113**		**113**	**100.0%**	**19.00 [1.12, 322.59]**
Total events	9		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.04 (P = 0.04)						

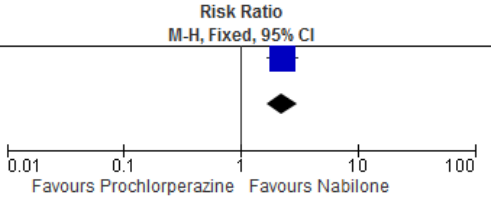


Footnotes

(1) Patients previously experienced severe, drug-induced nausea and vomiting

Partial reduction in nausea and vomiting (equal to or greater than 50% reduction in the duration or severity of nausea and number of vomiting episodes)

Study or Subgroup	Nabilone Events	Nabilone Total	Prochlorperazine Events	Prochlorperazine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Herman 1979 (1)	81	113	36	113	100.0%	2.25 [1.68, 3.02]
Total (95% CI)		**113**		**113**	**100.0%**	**2.25 [1.68, 3.02]**
Total events	81		36			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.42 (P < 0.00001)						



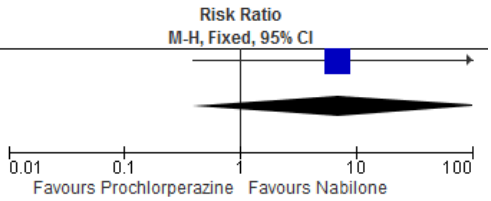
Footnotes

(1) Patients previously experienced severe, drug-induced nausea and vomiting

Complete reduction in nausea

Study or Subgroup	Nabilone Events	Nabilone Total	Prochlorperazine Events	Prochlorperazine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Johansson 1982 (1)	3	18	0	18	100.0%	7.00 [0.39, 126.48]
Total (95% CI)		**18**		**18**	**100.0%**	**7.00 [0.39, 126.48]**
Total events	3		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.32 (P = 0.19)

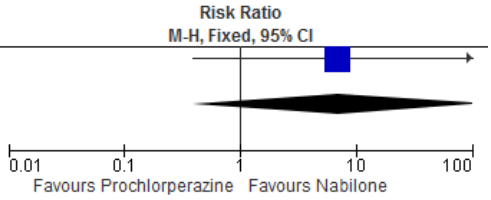


Footnotes
(1) Patients had uncontrolled nausea and vomiting despite the use of standard antiemetic drugs

Complete reduction in vomiting

Study or Subgroup	Nabilone Events	Nabilone Total	Prochlorperazine Events	Prochlorperazine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Johansson 1982 (1)	3	18	0	18	100.0%	7.00 [0.39, 126.48]
Total (95% CI)		**18**		**18**	**100.0%**	**7.00 [0.39, 126.48]**
Total events	3		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.32 (P = 0.19)



Footnotes
(1) Patients had uncontrolled nausea and vomiting despite the use of standard antiemetic drugs

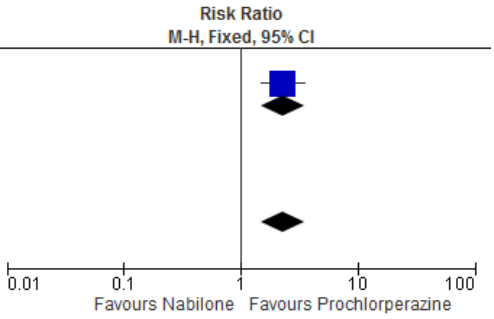
Adverse events

Study or Subgroup	Nabilone Events	Nabilone Total	Prochlorperazine Events	Prochlorperazine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.7.1 In children						
Chan 1987 (1)	32	36	14	36	100.0%	2.29 [1.49, 3.50]
Subtotal (95% CI)		**36**		**36**	**100.0%**	**2.29 [1.49, 3.50]**
Total events	32		14			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.81 (P = 0.0001)

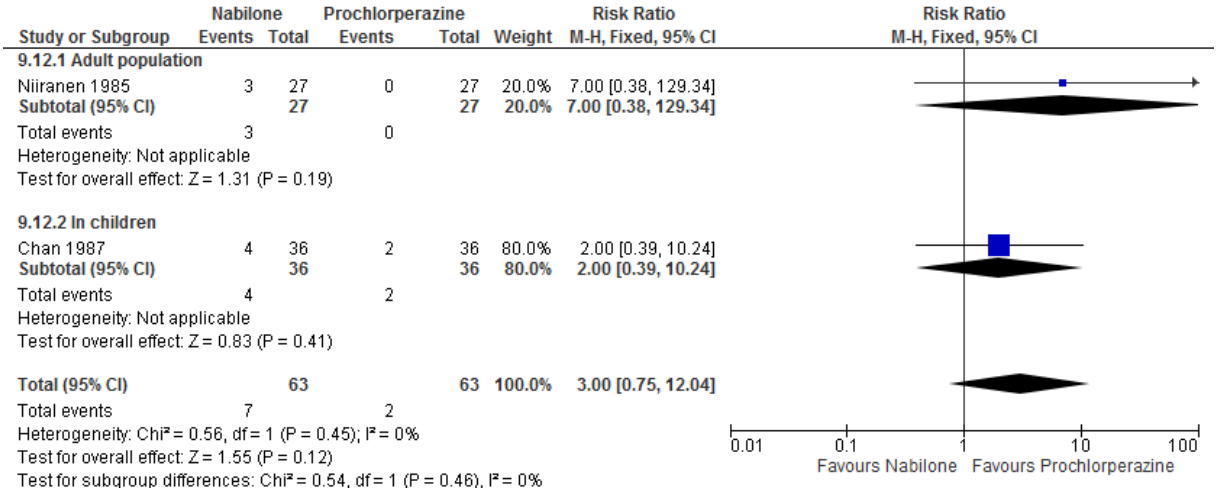
Total (95% CI)		**36**		**36**	**100.0%**	**2.29 [1.49, 3.50]**
Total events	32		14			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.81 (P = 0.0001)
Test for subgroup differences: Not applicable

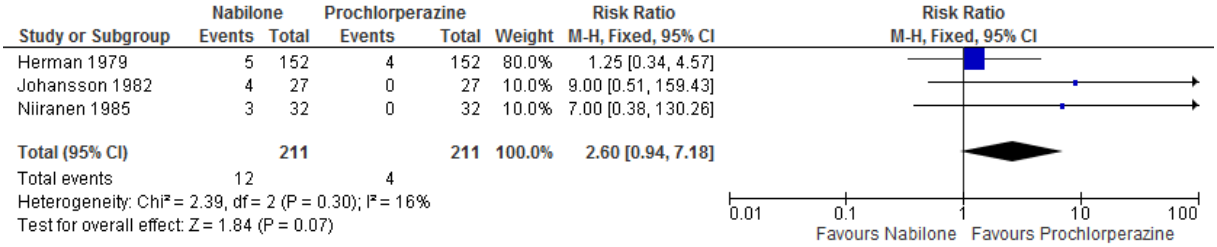


Footnotes
(1) Dizziness, drowsness, mood alteration, ocular swelling and irritation, orthostatic hypotension, muscle twitching and increase appetite

Serious AEs

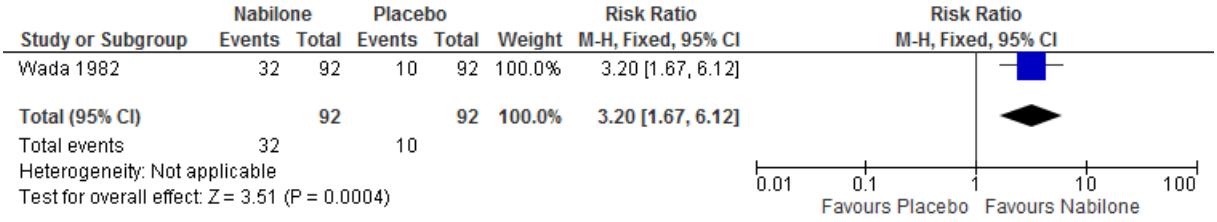


Withdrawals due to adverse events

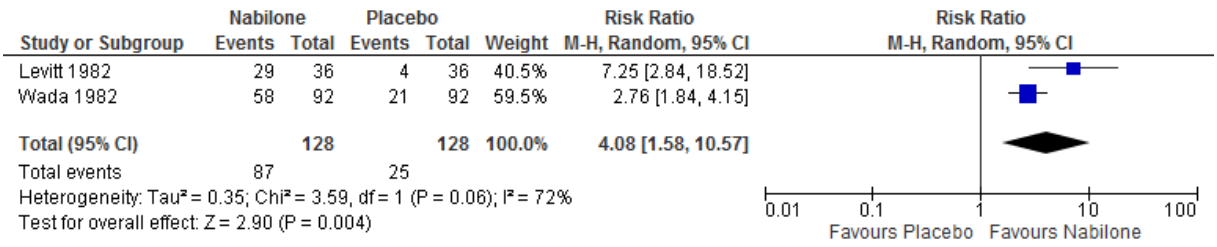


Nabilone vs Placebo

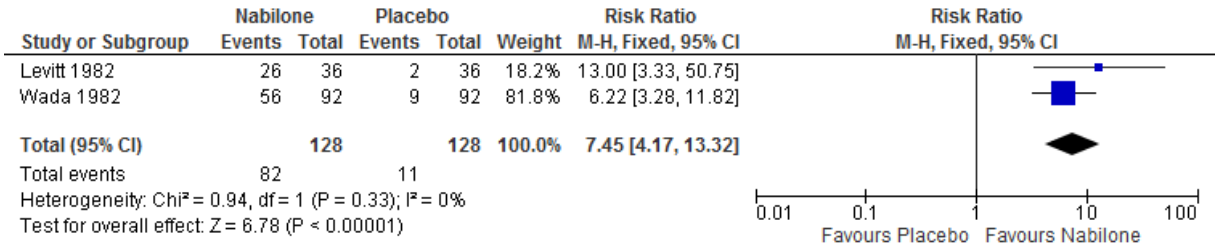
Complete relief of nausea and vomiting



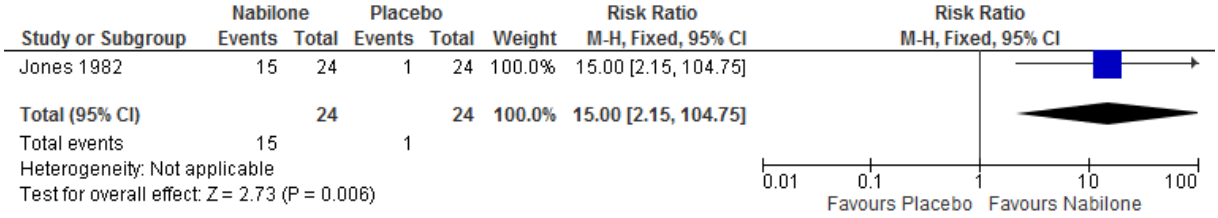
Patients with less vomiting compared to comparator



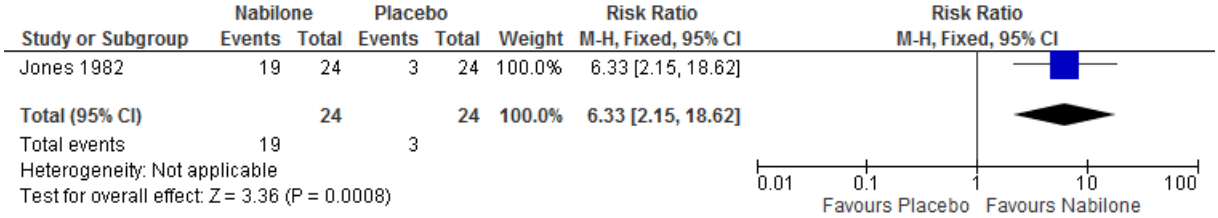
Patients with less nausea compared to comparator



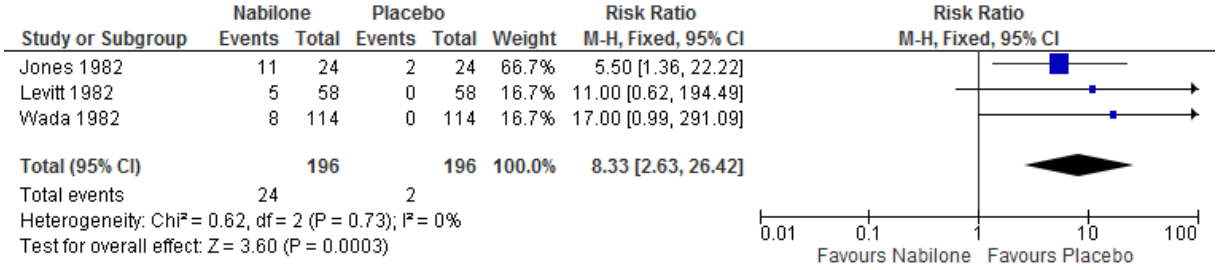
Relative reduction in nausea (less nausea compared to comparator)



Relative reduction in vomiting (less vomiting compared to comparator)



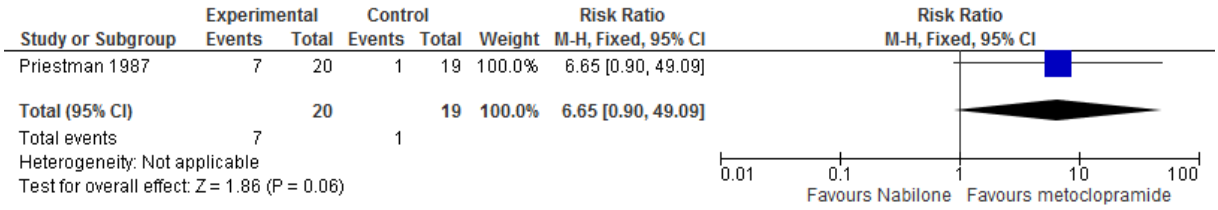
Withdrawals due to AEs



F. 2 Radiotherapy induced nausea and vomiting

Nabilone vs Metoclopramide

Severe AEs



Appendix G – Observational study data

Outcome	n (%)	Quality
Total adverse events	37 (34%)	Very low
Withdrawal due to adverse events	10 (9%)	Very low

	n (%)			Quality
Outcome	Moderately emetogenic chemotherapy	Highly emetogenic chemotherapy	All patients	
Complete vomiting control (no vomiting and no rescue therapy)	14 (54%)	42 (51%)	57 (52%)	Very low
Partial vomiting control (1-2 vomits per 24 hours)	7 (27%)	28 (34%)	35 (31%)	Very low

Appendix H - GRADE tables

H.1 Chemotherapy-induced nausea and vomiting

Tetrahydrocannabinol (THC) versus placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Absence of nausea and vomiting – after strong emetic stimulus (higher values favour THC)										
1 (Frytak 1979)	Parallel RCT	75 people	RR 2.23 (1.04, 4.78)	19 per 100 people	42 per 100 people (20, 90)	Very serious[1]	N/A[2]	Serious[3]	No serious	Very low
Absence of nausea and vomiting – after weak emetic stimulus (higher values favour THC)										
1 (Frytak 1979)	Parallel RCT	62 people	RR 1.08 (0.69, 1.69)	53 per 100 people	57 per 100 people (37, 89)	Very serious[1]	N/A[2]	Serious[3]	Serious[4]	Very low
Complete reduction in nausea (higher values favour THC)										
1 (Orr 1981)	Crossover RCT	55 people	RR 8.00 (3.42, 18.74)	5 per 100 people	73 per 100 people (31,170)	Serious[5]	N/A[2]	No serious	No serious	Moderate
Complete reduction of vomiting (higher values favour THC)										
1 (Sallan 1975)	Crossover RCT	29 courses	RR 10.31 (0.62, 170.96)	0 per 100 people	0 per 100 people	Very serious[6]	N/A[2]	No serious	Serious[4]	Very low
Partial reduction in vomiting (50% reduction) (higher values favour THC)										
1 (Sallan 1975)	Crossover RCT	29 courses	RR 14.06 (0.88, 225.47)	0 per 100 people	0 per 100 people	Very serious[6]	N/A[2]	No serious	Serious[4]	Very low
Adverse events – number of participants experiencing adverse events (lower values favour THC)										
1 (Sallan 1975)	Crossover RCT	29 courses	RR 25.31 (1.65, 389.42)	0 per 100 people	0 per 100 people	Very serious[6]	N/A[2]	No serious	No serious	Low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality

1. High risk of bias as study did not provide information for analysis methods. Higher proportion of patients excluded from THC arm than Prochlorperazine or placebo arms. Reasons for exclusion may have been because of adverse events which may have been a reaction to the drug. Downgrade 2 levels for very serious risk of bias.

2. N/A Inconsistency not applicable to single study.

3. Study specified that patients could not be experiencing nausea and vomiting before study. Downgrade 1 level for serious indirectness.

4. Downgrade 1 level for serious imprecision. Confidence interval crosses the line of no effect.

5. Some concerns around risk of bias as no information on randomisation, allocation concealment or baseline values were provided. Results not separated by phases which could have masked period effects. No information on whether a statistical test for carry-over was performed. Downgrade 1 level for serious risk of bias

6. High risk of bias as study did not state whether a statistical test for carry-over was performed. No information on washout period. No information on random sequence generation, allocation concealment and baseline values. Results not separated by phases which could have masked period effects. Downgrade 2 levels for very serious risk of bias.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

Tetrahydrocannabinol (THC) versus metoclopramide

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Major emetic response (defined as between 0 and 2 episodes) (higher values favour THC)										
1 (Gralla 1984)	Parallel RCT	30 people	RR 0.36 (0.15, 0.89)	73 per 100 people	26 per 100 people (11, 65)	Serious[1]	N/A[2]	Serious[3]	No serious	Low
Absence of vomiting – in children (higher values favour THC)										
1 (Ekert 1979)	Parallel RCT	42 courses	RR 3.53 (1.52, 8.19)	20 per 100 people	71 per 100 people (30, 164)	Very serious[5]	N/A[2]	Serious[3]	No serious	Very low
Adverse events (lower values favour THC)										
1 Ekert 1979	Parallel RCT	42 courses	RR 2.94 (0.60, 14.30)	8 per 100 people	24 per 100 people (5, 114)	Very serious[5]	N/A[2]	No serious	Serious[4]	Very low

1. Some concerns around risk of bias as study provided limited information on randomisation process and unclear whether outcome assessors were aware of the assigned intervention. Downgrade 1 level for serious risk of bias.

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
2. N/A Inconsistency not applicable to single study 3. Study did not report if patients had previously experienced or exhibited intractable nausea and vomiting. Downgrade 1 level for serious indirectness. 4. Downgrade 1 level for serious imprecision. Confidence interval crosses the line of no effect. 5. High risk of bias due to insufficient information on random sequence generation, allocation concealment and baseline differences between intervention groups. Study also does not state number of children allocated to each arm but instead reports the number of chemotherapy regimens randomised. Study only provided information on the chemotherapy regimens followed in each arm. Downgrade 2 levels for very serious risk of bias. * Derived by taking the overall number of event/ total number of participants and multiplying by 100										

Tetrahydrocannabinol (THC) versus prochlorperazine

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Absence of nausea and vomiting – after strong emetic stimulus (higher values favour THC)										
1 (Frytak 1979)	Parallel RCT	79 people	RR 1.02 (0.60, 1.71)	41 per 100 people	42 per 100 people (24, 71)	Very serious[1]	N/A[2]	Serious[3]	Serious[4]	Very low
Absence of nausea and vomiting – after strong emetic stimulus (higher values favour THC)										
1 (Frytak 1979)	Parallel RCT	64 people	RR 0.79 (0.54, 1.16)	72 per 100 people	57 per 100 people (39, 84)	Very serious[1]	N/A[2]	Serious[3]	Serious[4]	Very low
Absence of vomiting – in children (higher values favour THC)										
1 (Ekert 1979)	Parallel RCT	36 courses	RR 19.00 (0.79, 303.76)	0 per 100 people	0 per 100 people	Very serious[5]	N/A[2]	Serious[6]	Serious[4]	Very low
Complete reduction in nausea (higher values favour THC)										
1 (Orr 1981)	Crossover RCT	55 people	RR 5.00	15 per 100 people	73 per 100 people (38, 141)	Serious[7]	N/A[2]	No serious	No serious	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
			(2.58, 9.68)							
Complete reduction in nausea and vomiting – all emetic risks (higher values favour THC)										
2 (McCabe 1988, Sallan 1980)	Crossover RCTs	115 (people and no. of antiemetic courses)	RR 2.73 (1.67, 4.45)	14 per 100 people	38 per 100 people (23, 62)	Serious[8]	Serious[9]	No serious	No serious	Low
Complete reduction in nausea and vomiting – greatest emetic risk (higher values favour THC)										
1 (Sallan 1980)	Crossover RCT	38 courses	RR 2.44 (1.16, 5.13)	19 per 100 people	47 per 100 people (23, 100)	Serious[10]	Serious[9]	No serious	No serious	Low
Complete reduction of nausea and vomiting – moderate emetic risk (higher values favour THC)										
1 (Sallan 1980)	Crossover RCT	32 courses	RR 1.73 (0.84, 3.58)	25 per 100 people	43 per 100 people (21, 90)	Serious[10]	N/A[2]	No serious	Serious[4]	Low
Complete reduction in nausea and vomiting – low emetic risk (higher values favour THC)										
1 (Sallan 1980)	Crossover RCT	11 courses	RR 4.55 (0.63, 32.56)	10 per 100 people	46 per 100 people (6, 326)	Serious[10]	N/A[2]	No serious	Serious[4]	Low
Partial reduction in nausea and vomiting – 50% reduction (higher values favour THC)										
1 McCabe (1988)	Crossover RCT	36 people	RR 14.00 (1.94, 100.94)	3 per 100 people	39 per 100 people (5, 280)	Very serious[11]	N/A[2]	No serious	No serious	Low
Partial reduction in nausea and vomiting (reduction in severity of nausea and vomiting) – overall emetic risk (higher values favour THC)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 (Sallan 1980)	Crossover RCT	79 courses	RR 0.66 (0.32, 1.37)	19 per 100 people	13 per 100 people (6, 26)	Serious[10]	N/A[2]	No serious	Serious[4]	Low
Partial reduction in nausea and vomiting (reduction in severity of nausea and vomiting) – greatest emetic risk (higher values favour THC)										
1 (Sallan 1980)	Crossover RCT	38 courses	RR 0.42 (0.14, 1.25)	25 per 100 people	19 per 100 people (4, 31)	Serious[10]	N/A[2]	No serious	Serious[4]	Low
Partial reduction in nausea and vomiting (reduction in severity of nausea and vomiting) – moderate emetic risk (higher values favour THC)										
1 (Sallan 1980)	Crossover RCT	32 courses	RR 1.33 (0.39, 4.50)	13 per 100 people	17 per 100 people (5, 56)	Serious[10]	N/A[2]	No serious	Serious[4]	Low
Partial reduction in nausea and vomiting (reduction in severity of nausea and vomiting) – low emetic risk (higher values favour THC)										
1 (Sallan 1980)	Crossover RCT	11 courses	RR 0.45 (0.05, 4.28)	20 per 100 people	9 per 100 people (1, 86)	Serious[10]	N/A[2]	No serious	Serious[4]	Low
Relative nausea reduction (reduction in severity) – all participants (higher values favour THC)										
1 (Ungerleider 1982)	Crossover RCT	133 people	RR 1.32 (0.95, 1.83)	31 per 100 people	41 per 100 people (29, 56)	Very serious[12]	N/A[2]	No serious	Serious[4]	Very low
Relative nausea reduction (reduction in severity) – in participants with some experience of illicit drug use (higher values favour THC)										
1 (Ungerleider 1985)	Crossover RCT	70 people	RR 1.72 (1.07, 2.78)	26 per 100 people	44 per 100 people (28, 71)	Very serious[12]	N/A[2]	No serious	Serious[13]	Very low
Adverse events (lower values favour THC)										
1 (Ekert 1979)	Parallel RCT	36 courses	RR 13.00	0 per 100 people	0 per 100 people	Very serious[5]	N/A[2]	No serious	Serious[4]	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
			(0.79, 214.91)							
Withdrawals due to adverse events (lower values favour THC)										
1 (Sallan 1980)	Crossover RCT	84 people	RR 9.00 (0.49, 164.59)	0 per 100 people	0 per 100 people	Serious[10]	N/A[2]	No serious	Serious[4]	Low

1. High risk of bias as study did not provide information for analysis methods. Higher proportion of patients excluded from THC arm than Prochlorperazine or placebo arms. Reasons for exclusion may have been because of adverse events which may have been a reaction to the drug. Downgrade 2 levels for very serious risk of bias.
2. N/A Inconsistency not applicable to single study.
3. Study specified that patients could not be experiencing nausea and vomiting before study. Downgrade 1 level for serious indirectness.
4. Downgrade 1 level for serious imprecision. Confidence interval crosses the line of no effect.
5. High risk of bias due to insufficient information on random sequence generation, allocation concealment and baseline differences between intervention groups. Study also does not state number of children allocated to each arm but instead reports the number of chemotherapy regimens randomised. Study only provided information on the chemotherapy regimens followed in each arm. Downgrade 2 levels for very serious risk of bias.
6. Study did not report if patients had previously experienced or exhibited intractable nausea and vomiting. Downgrade 1 level for serious indirectness.
7. Some concerns around risk of bias as no information on randomisation, allocation concealment or baseline values were provided. Results not separated by phases which could have masked period effects. No information on whether a statistical test for carry-over was performed. Downgrade 1 level for serious risk of bias
8. Downgrade 1 level for serious risk of bias. Greater than 33.3% of weight in meta-analysis came from study which demonstrated some concerns regarding risk of bias.
9. Downgrade 1 level for serious inconsistency. The I2 was between 33.3% and 66.7%
10. Some concerns around risk of bias no information on whether a statistical test for carry-over was performed was provided. No information on randomisation, allocation concealment or baseline values. Results not separated by phases which could have masked period effects.
11. High risk of bias as no information on randomisation, allocation concealment or baseline values was provided. Results not separated by phases which could have masked period effects. Unclear if participants and personnel were aware of assignment. No information on whether a statistical test for carry-over was performed. No information provided for missing outcome data. Downgrade 2 levels for very serious risk of bias.
12. High risk of bias as it was unclear if participants were aware of assignment. People who withdrew reported fewer effects of the drug than those who completed the study, no information on whether a statistical test for carry-over was performed. Results not separated by phases which could have masked period effects. Downgrade 2 levels for very serious risk of bias.
13. Study states that people had history of illicit drug use but does not state if people had existing substance abuse. Downgrade 1 level for serious indirectness.

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
* Derived by taking the overall number of event/ total number of participants and multiplying by 100										

Tetrahydrocannabinol (THC) versus Haloperidol

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Complete reduction in vomiting (higher values favour THC)										
1 Neidhart 1981	Crossover RCT	104 courses	RR 1.30 (0.42, 3.98)	9 per 100 people	12 per 100 people (4, 37)	Very serious[1]	N/A[2]	No serious	Serious[3]	Very low
Adverse events (lower values favour THC)										
1 Neidhart 1981	Crossover RCT	109 courses	RR 1.15 (0.98, 1.36)	79 per 100 people	90 per 100 people (77, 1.07)	Very serious[1]	N/A[2]	No serious	Serious[3]	Very low
Moderate to severe adverse events (lower values favour THC)										
1 Neidhart 1981	Crossover RCT	109 courses	RR 4.58 (1.38, 15.17)	5 per 100 people	25 per 100 people (7, 81)	Very serious[1]	N/A[2]	No serious	No serious	Low

1. High risk of bias as unclear if allocation was concealed until participants were recruited to intervention. No information on missing data. Unclear if test for carryover was conducted. Unclear which period the data is from. Downgrade for very serious risk of bias.
2. N/A Inconsistency not applicable to single study.
3. Downgrade 1 level for serious imprecision. Confidence interval crosses the line of no effect.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

Prochlorperazine + Tetrahydrocannabinol (THC) versus Prochlorperazine + placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Withdrawals due to adverse events (lower values favour THC)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 Kleinman 1983	Crossover RCT	16 people	RR 5.00 (0.26, 95.61)	0 per 100 people	0 per 100 people	Very serious[1]	N/A[2]	No serious	Serious[3]	Very low

1. High risk of bias due to unclear random sequence generation, allocation concealment and crossover period. Downgrade 2 levels for very serious risk of bias,
2. N/A Inconsistency not applicable to single study
3. Downgrade 1 level for serious imprecision. Confidence interval crosses the line of no effect.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

Dronabinol (+ placebo) versus prochlorperazine (+ placebo)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Complete reduction in nausea and vomiting (higher values favour Dronabinol + placebo)										
1 Lane 1991	Parallel RCT	37 people	RR 1.37 (0.57, 3.30)	30 per 100 people	41 per 100 people (17, 99)	Serious[1]	N/A2	No serious	Serious[3]	Low
2 or fewer episodes of nausea and vomiting (higher values favour Dronabinol+ placebo)										
1 Lane 1991	Parallel RCT	37 people	RR 1.70 (0.98, 2.95)	45 per 100 people	77 per 100 people (44,133)	Serious[1]	N/A[2]	No serious	Serious[3]	Low
Adverse events (lower values favour Dronabinol+ placebo)										
1 Lane 1991	Parallel RCT	42 people	RR 2.29 (1.19, 4.38)	33 per 100 people	76 per 100 people (40, 146)	Serious[1]	N/A[2]	No serious	No serious	Moderate
Withdrawals due to adverse events (lower values favour Dronabinol+ placebo)										
1 Lane 1991	Parallel RCT	42 people	RR 21.00 (1.31, 336.75)	0 per 100 people	0 per 100 people	Serious[1]	N/A[2]	No serious	No serious	Moderate

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality

1. Some concerns around study not reporting randomisation process or whether patients were aware of intervention. Downgrade 1 level for serious risk of bias. More patients excluded from the dronabinol than prochlorperazine arm.
2. N/A Inconsistency not applicable to single study.
3. Downgrade 1 level for serious imprecision. Confidence interval crosses the line of no effect.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

Dronabinol + prochlorperazine versus Prochlorperazine (+ placebo)

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Complete reduction in nausea and vomiting (higher values favour Prochlorperazine+ placebo)										
1 Lane 1991	Parallel RCT	27 people	RR 0.64 (0.28, 1.47)	47 per 100 people	30 per 100 people (13, 69)	Serious[1]	N/A[2]	No serious	Serious[3]	Low
2 or fewer episodes of nausea and vomiting (higher values favour Prochlorperazine+ placebo)										
1 Lane 1991	Parallel RCT	27 people	RR 0.70 (0.38, 1.27)	65 per 100 people	45 per 100 people (25, 82)	Serious[1]	N/A[2]	No serious	Serious[3]	Low
Adverse events (lower values favour Prochlorperazine+ placebo)										
1 Lane 1991	Parallel RCT	41 people	RR 0.61 (0.29, 1.25)	55 per 100 people	6 per 100 people (16, 69)	Serious[1]	N/A[2]	No serious	Serious[3]	Low
Withdrawals due to adverse events (lower values favour Prochlorperazine+ placebo)										
1 Lane 1991	Parallel RCT	41people	RR 0.11 (0.01, 1.85)	20 per 100 people	2 per 100 people (0,37)	Serious[1]	N/A[2]	No serious	Serious[3]	Low

1. Some concerns around study not reporting randomisation process or whether patients were aware of intervention. Downgrade 1 level for serious risk of bias. More patients excluded from the dronabinol than prochlorperazine arm.
2. N/A Inconsistency not applicable to single study.
3. Downgrade 1 level for serious imprecision. Confidence interval crosses the line of no effect.

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
* Derived by taking the overall number of event/ total number of participants and multiplying by 100										

Dronabinol versus Ondansetron

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Complete response (no delayed vomiting/ retching, intensity of nausea of ≤30 mm on the VAS, and no use of rescue medication) (higher values favour Dronabinol)										
1 Meiri 2007	Parallel RCT	25 people	RR 1.05 (0.55, 2.01)	58 per 100 people	61 per 100 people (32, 117)	Serious[1]	N/A[2]	Serious[3]	Serious[4]	Very low
Total response (No delayed vomiting and/ or retching, intensity of nausea <5mm on a 100-mm VAS, and no use of rescue medication) (higher values favour Dronabinol)										
1 Meiri 2007	Parallel RCT	28 people	RR 1.00 (0.53, 1.90)	57 per 100 people	57 per 100 people (30, 109)	Serious[1]	N/A[2]	Serious[3]	Serious[4]	Very low
Absence of delayed nausea (higher values favour Dronabinol)										
1 Meiri 2007	Parallel RCT	28 people	RR 1.11 (0.67, 1.85)	64 per 100 people	71 per 100 people (43, 119)	Serious[1]	N/A[2]	Serious[3]	Serious[4]	Very low
Patient with at least one TEAE (lower values favour Dronabinol)										
1 Meiri 2007	Parallel RCT	33 people	RR 0.94 (0.71, 1.25)	88 per 100 people	82 per 100 people (62, 109)	Serious[1]	N/A[2]	No serious	Serious[4]	Low
Patient with at least one SAE (lower values favour Dronabinol)										
1 Meiri 2007	Parallel RCT	33 people	RR 1.88 (0.19, 18.80)	6 per 100 people	12 per 100 people (1, 118)	Serious[1]	N/A[2]	No serious	Serious[4]	Low
Patient with at least one severe TEAE (lower values favour Dronabinol)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 Meiri 2007	Parallel RCT	33 people	RR 1.88 (0.19, 18.80)	6 per 100 people	12 per 100 people (1, 118)	Serious[1]	N/A[2]	No serious	Serious[4]	Low
Withdrawals due to adverse events (lower values favour Dronabinol)										
1 Meiri 2007	Parallel RCT	33 people	RR 0.47 (0.05, 4.70)	13 per 100 people	6 per 100 people (1, 59)	Serious[1]	N/A[2]	No serious	Serious[4]	Low

1. Some concerns as no information on randomisation or sequence allocation was provided and potentially subjective outcomes. Downgrade 1 level for serious risk of bias.
2. N/A Inconsistency not applicable to single study
3. Downgrade 1 level for serious indirectness. Study is partially applicable as patients with a history of anticipatory nausea were excluded from the study.
4. Downgrade 1 level for serious imprecision. Confidence interval crosses the line of no effect.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

Dronabinol versus Placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Complete response (no delayed vomiting/ retching, intensity of nausea of ≤30 mm on the VAS, and no use of rescue medication) (higher values favour Dronabinol)										
1 Meiri 2007	Parallel RCT	23 people	RR 3.08 (0.83, 11.43)	20 per 100 people	62 per 100 people (17, 229)	Serious[1]	N/A[2]	Serious[3]	Serious[4]	Very low
Total response (No delayed vomiting and/ or retching, intensity of nausea <5mm on a 100-mm VAS, and no use of rescue medication) (higher values favour Dronabinol)										
1 Meiri 2007	Parallel RCT	27 people	RR 2.48 (0.83, 7.37)	23 per 100 people	57 per 100 people (19, 170)	Serious[1]	N/A[2]	Serious[3]	Serious[4]	Very low
Absence of delayed nausea (higher values favour Dronabinol)										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 Meiri 2007	Parallel RCT	27 people	RR 4.64 (1.24, 17.33)	15 per 100 people	69 per 100 people (19, 267)	Serious[1]	N/A[2]	Serious[3]	No serious	Low
Patient with at least one TEAE (lower values favour Dronabinol)										
1 Meiri 2007	Parallel RCT	31 people	RR 1.65 (0.93, 2.91)	50 per 100 people	83 per 100 people (47, 146)	Serious[1]	N/A[2]	No serious	Serious[4]	Low
Patient with at least one SAE (lower values favour Dronabinol)										
1 Meiri 2007	Parallel RCT	31 people	RR 0.82 (0.13, 5.12)	14 per 100 people	12 per 100 people (2, 73)	Serious[1]	N/A[2]	No serious	Serious[4]	Low
Patient with at least one severe TEAE (lower values favour Dronabinol)										
1 Meiri 2007	Parallel RCT	31 people	RR 0.55 (0.11, 2.84)	21 per 100 people	12 per 100 people (2, 61)	Serious[1]	N/A[2]	No serious	Serious[4]	Low
Withdrawals due to adverse events (lower values favour Dronabinol)										
1 Meiri 2007	Parallel RCT	31 people	RR 2.50 (0.11, 56.98)	0 per 100 people	0 per 100 people	Serious[1]	N/A[2]	No serious	Serious[4]	Low

1. Some concerns as no information on randomisation or sequence allocation was provided and potentially subjective outcomes. Downgrade 1 level for serious risk of bias.
2. N/A Inconsistency not applicable to single study
3. Downgrade 1 level for serious indirectness. Study is partially applicable as patients with a history of anticipatory nausea were excluded from the study.
4. Downgrade 1 level for serious imprecision. Confidence interval crosses the line of no effect.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

Nabilone versus Domperidone

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Withdrawals due to adverse events (lower values favour Nabilone)										
1 Pomeroy 1986	Crossover RCT	19	RR 3.00 (0.13, 69.31)	0 per 100 people	0 per 100 people	Serious[1]	N/A[2]	No serious	Serious[3]	Low

1. Some concerns as no information on randomisation, allocation concealment or baseline values were provided in the study. Downgrade 1 eve for serious risk of bias.
2. N/A Inconsistency not applicable to single study
3. Downgrade 1 level for serious imprecision. Confidence interval crosses the line of no effect.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

Nabilone versus Prochlorperazine

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Absence of nausea (higher values favour Nabilone)										
2 Ahmedzai 1983, Niiranen 1985	Crossover RCT	80 people	RR 0.90 (0.11, 7.50)	30 per 100 people	27 per 100 people (3, 222)	Very serious[1]	Very serious[2]	Serious[3]	Serious[4]	Very low
Absence of retching (higher values favour Nabilone)										
1 Ahmedzai 1983	Crossover RCT	56 people	RR 1.81 (1.20, 2.75)	47 per 100 people	84 per 100 people (56, 128)	Very serious[5]	N/A[6]	Serious[7]	No serious	Very low
Absence of vomiting (higher values favour Nabilone)										
1 Ahmedzai 1983	Crossover RCT	56 people	RR 1.64 (1.23, 2.21)	60 per 100 people	98 per 100 people (74, 133)	Very serious[5]	N/A[6]	Serious[7]	No serious	Very low
Complete reduction in retching and vomiting (higher values favour Nabilone) – in children										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 Chan 1987	Crossover RCT	30 children	RR 1.00 (0.22, 4.56)	10 per 100 people	10 per 100 people (2, 46)	Very serious[8]	N/A[6]	No serious	Serious[4]	Very low
Reduction in retching and vomiting (less retching and vomiting) (higher values favour Nabilone) – in children										
1 Chan 1987	Crossover RCT	30 children	RR 2.00 (0.96, 4.15)	30 per 100 people	60 per 100 people (29, 125)	Very serious[8]	N/A[6]	No serious	Serious[4]	Very low
Overall Rate of improvement in retching and vomiting (higher values favour Nabilone) – in children										
1 Chan 1987	Crossover RCT	30 children	RR 2.33 (1.29, 4.23)	30 per 100 people	70 per 100 people (39, 127)	Very serious[8]	N/A[6]	No serious	No serious	Low
Complete reduction in nausea and vomiting (total absence of nausea and vomiting) (higher values favour Nabilone)										
1 Herman 1979	Crossover RCT	113 people	RR 19.00 (1.12, 322.59)	0 per 100 people	0 per 100 people	Very serious[9]	N/A[6]	No serious	No serious	Low
Partial reduction in nausea and vomiting (equal to or greater than 50% reduction in the duration or severity of nausea and number of vomiting episodes) (higher values favour Nabilone)										
1 Herman 1979	Crossover RCT	113 people	RR 2.25 (1.68, 3.02)	32 per 100 people	72 per 100 people (54, 96)	Very serious[9]	N/A[6]	No serious	No serious	Low
Complete reduction in nausea (higher values favour Nabilone)										
1 Johansson 1982	Crossover RCT	18 people	RR 7.00 (0.39, 126.48)	0 per 100 people	0 per 100 people	Very serious[10]	N/A[6]	No serious	Serious[4]	Very low
Complete reduction in vomiting (higher values favour Nabilone)										
1 Johansson 1982	Crossover RCT	18 people	RR 7.00 (0.39, 126.48)	0 per 100 people	0 per 100 people	Very serious[10]	N/A[6]	No serious	Serious[4]	Very low
Adverse events (lower values favour Nabilone) – in children										

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 Chan 1987	Crossover RCT	30 children	RR 2.29 (1.49, 3.50)	39 per 100 people	89 per 100 people (58, 136)	Very serious[8]	N/A[6]	No serious	No serious	Low
Serious AEs (lower values favour Nabilone)- whole population										
2 Niiranen 1985, Chan 1987	Crossover RCTs	63 people	RR 3.00 (0.75, 12.04)	3 per 100 people	10 per 100 people (2, 38)	Very serious[1]	No serious	No serious	Serious[4]	Very Low
Subgroup analysis – In children - Serious AEs (lower values favour Nabilone)										
1 Chan 1987	Crossover RCT	30 children	RR 2.00 (0.39, 10.24)	6 per 100 people	11 per 100 people (2, 57)	Very serious[8]	N/A[6]	No serious	Serious[4]	Very low
Withdrawals due to adverse events (lower values favour Nabilone)										
3 Herman 1979, Johansson 1982, Niiranen 1985	Crossover RCTs	211 people	RR 2.06 (0.94, 7.18)	2 per 100 people	5 per 100 people (2, 14)	Very serious[1]	No serious	No serious	Serious[4]	Very low

1. Downgrade 2 levels for very serious risk of bias. Greater than 33.3% of weight in meta-analysis came from study which demonstrated high risk of bias.
2. I^2 was greater than 66.7%. Downgrade 2 levels for very serious inconsistency.
3. Downgrade 1 level for serious indirectness. Studies did not state if patients had previously nausea and vomiting or exhibited these symptoms at baseline.
4. Downgrade 1 level for serious imprecision. Confidence interval crosses the line of no effect.
5. High risk of bias due to unclear random sequence generation, allocation concealment and baseline imbalances. Unclear if participants and personnel were aware of assigned intervention. Outcome data not available for all patients. Unclear if missing outcome data is proportional between the two study arms. No information on statistical test for carry over. Downgrade 2 levels for very serious risk of bias.
6. N/A Inconsistency not applicable due to single study
7. Downgrade 1 level for serious indirectness. Study did not state if patients had previously nausea and vomiting or exhibited these symptoms at baseline.
8. High risk of bias due to no information on whether a statistical test for carry-over was performed. No information on washout period. No information on baseline values. Results not separated by phases which could have masked period effects. Downgrade 2 levels for very serious risk of bias.

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality

9. High risk of bias due to no information on randomisation or baseline values. Results not separated by phases which could have masked period effects. Unclear if the reason for missing outcome data was the same between groups or whether results were robust to missing data. No information on whether a statistical test for carry-over was performed. Downgrade 2 levels due to very serious risk of bias.
10. High risk of bias due to no information on whether a statistical test for carry-over was performed. Data missing for over half of participants and not clear if reasons for missing data were similar between groups. No information on randomisation, allocation concealment or baseline values. Results not separated by phases which could have masked period effects. Downgrade 2 levels due to very serious risk of bias.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

Nabilone versus Placebo

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Complete relief in nausea and vomiting (higher values favour Nabilone)										
1 Wada 1982	Crossover RCT	92 people	RR 3.20 (1.67, 6.12)	11 per 100 people	35 per 100 people (18, 67)	Very serious[1]	N/A[2]	Serious[3]	No serious	Very low
Patients with less vomiting compared to comparator (higher values favour Nabilone)										
2 Leviit 1982, Wada 1982	Crossover RCTs	128 people	RR 4.08 (1.58, 10.57)	20 per 100 people	80 per 100 people (31, 61)	Very serious[4]	Very serious[5]	Serious[6]	No serious	Very low
Patients with less nausea compared to comparator (higher values favour Nabilone)										
2 Leviit 1982, Wada 1982	Crossover RCTs	128 people	RR 7.45 (4.17, 13.32)	9 per 100 people	64 per 100 people (36, 114)	Very serious[4]	No serious	Serious[6]	No serious	Very low
Relative reduction in nausea (less nausea compared to comparator) (higher values favour Nabilone)										
1 Jones 1982	Crossover RCT	24 people	RR 15.00 (2.15, 104.75)	4 per 100 people	63 per 100 people (*9, 436)	Very serious[7]	N/A[2]	Serious[8]	No serious	Very low

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Relative reduction in vomiting (less vomiting compared to comparator) (higher values favour Nabilone)										
1 Jones 1982	Crossover RCT	24 people	RR 6.33 (2.15, 18.62)	13 per 100 people	79 per 100 people (27, 233)	Very serious[7]	N/A[2]	Serious[8]	No serious	Very low
Withdrawals due to AEs (lower values favour Nabilone)										
3 Jones 1982, Levitt 1982, Wada 1982	Crossover RCTs	196 people	RR 8.33 (2.63, 26.42)	1 per 100 people	9 per 100 people (3, 27)	Very serious[4]	No serious	No serious	No serious	Low

1. High risk of bias due to no information on randomisation, allocation concealment or baseline values. Results not separated by phases which could have masked period effects. Missing data, no information on whether participants and personnel were aware of intervention or if a statistical test for carry-over was performed. Downgrade 2 levels for very serious risk of bias.
2. N/A Inconsistency not applicable to single study
3. Downgrade 1 level for serious indirectness. Study does not state if patients had previously nausea and vomiting or exhibited these symptoms at baseline.
4. Downgrade 2 levels for very serious risk of bias. Greater than 33.3% of weight in meta-analysis came from study which demonstrated high risk of bias
5. I^2 was greater than 66.7%. Downgrade 2 levels for very serious inconsistency.
6. Downgrade 1 level for serious indirectness. Greater than 33.3% of the weight in a meta-analysis came from partially indirect studies.
7. High risk of bias due to some concerns with random sequence generation, allocation concealment, blinding and no information on whether a statistical test for carry-over was performed. Downgrade 2 levels for very serious risk of bias.
8. Downgrade 1 level for serious indirectness. Studies did not state if patients had previously nausea and vomiting or exhibited these symptoms at baseline

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

H.2 Radiotherapy-induced nausea and vomiting

Nabilone versus Metoclopramide

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control *	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Adverse events (lower values favour THC)										
1 Priestman 1987	Crossover RCT	39	RR 6.65 (0.90, 40.09)	5 per 100 people	35 per 100 people (5, 258)	Very serious[1]	N/A[2]	No serious	Serious[3]	Very low

1. High risk of bias due to some concerns identified in randomisation process and insufficient information on washout period. Study does not specify which period the data is from. and does not mention test for carry-over. Downgrade 2 levels for very serious risk of bias.
2. N/A Inconsistency not applicable due to single study
3. Downgrade 1 level for serious imprecision. Confidence interval crosses the line of no effect.

* Derived by taking the overall number of event/ total number of participants and multiplying by 100

Appendix I – Adverse events

Chemotherapy induced nausea and vomiting

Nabilone

Study	Adverse events reported
Pomeroy 1986 (n=19)	Drowsiness (11), Dizziness (11), Dry mouth (10), Postural hypotension (4), Headache (2), light headedness (2), euphoria (2), confusion (1), difficulty talking (1), drunk feeling (1), weakness (1), constipation (1), nausea (1), dysepesia (1)
Dalzell 1986 (n=18 children)	Drowsiness (55%), dizziness (36%), mood changes (14%) – depression (1), weeping and clinging to mother (1), crying and hysterical laughter (1), heavy eyed (9%), pruritus (5%), dry mouth (5%), vagueness (5%), light headedness (5%), increased appetite (5%), hallucinations (5%)
Ahmedzai 1983 (n= 34)	Drowsiness- mild (43%), drowsiness-severe (14%), postural drowsiness- mild (28%), postural drowsiness- severe (7%), light-headedness- mild (4%), light-headedness- severe (4%), confusion/ disorientation (11%), dysphoria (7%), drunk-feeling- pleasant (7%), drunk-feeling- unpleasant (11%), euphoria (14%), 'high' (7%), dry mouth (11%), blurred vision (4%), paraesthesia/ numbness (7%), vertigo (4%), nausea (4%) headache (0%), itch (0%)
Steele 1980 (n= 37)	Somnolence (47%), Dizziness (35.8%), Dry mouth (24.6%), 'high' (18.9%), postural hypotension (16.9%), increased appetite(13.2%), 'drugged' or hangover effect (9.4%), light headedness (7.5%), decreased ability of concentrate (7.5%), relaxed, tranquil (5.6%), restlessness (5.2%), nausea (5.2%), dysphoria (3.7%), hallucinations (3.7%), time or space distortion (3.7%), lethargy (1.8%), headache (1.8%)
Chan 1987 (n= 30 children)	Dizziness (50%), Drowsiness (67%), Mood alteration (14%), Ocular swelling and irritation (11%), Orthostatic hypotension (8%), muscle twitching (6%), increased appetite (3%)
Einhorn 1981 (n=80)	(n): 'High' (40), feeling more relaxed (51), light-headedness (60), syncopal episode (2), Major alterations in mentation and perception (2)
Herman 1979 (n= 113)	Somnolence (85%), Dry mouth (84%), dizziness (69%), decreased co-ordination (68%), blurred vision (60%), decreased concentration (50%), depression (20%), euphoria (16%), tachycardia (11%), anxiety (3%) Study also reports that 1 patient exhibited orthostatic hypotension and fainted upon arising. Patient was hospitalised and remained lethargic for the next 12 hours by recovered fully. Two patients also experienced syncope during treatment with nabilone, but these episodes were considered mild. One patient woke with feelings of marked depersonalisation associated with visual hallucinations after the first 2mg capsule. This drug induced psychosis lasted approximately 8 hours, but recovery was complete. 2 patients also experienced visual hallucinations, and one became overtly paranoid. 1 patient also experienced nightmares, and one experienced lethargy.
Johansson 1982 (n=27)	Drowsiness, sleepiness (4%), dizziness, vertigo (23%), postural low BP (42%), increased appetite (4%), syncope (4%), headache (4%), depression (4%), powerless, general weakness (4%), mood change (8%)
Niiranen 1985 (n=32)	(n): vertigo (13), dryness of mouth (7), decreased coordination (3), hallucinations (3), drowsiness (2), headache (1).
Wada 1982	Dizziness (40%), Drowsiness (34%), Dry mouth (28%), euphoria (25%), dysphoria (10%), coordination disturbance, ataxia (9%), light-headedness (9%),

Study	Adverse events reported
(n=104)	hypotension (5%), disorientation, confusion (6%), nausea (2%), asthenia (1%), syncope (1%), hallucinations (1%), headache (1%)
Jones 1982 (n=24)	Dizziness (65%), Drowsiness (51%), Dry mouth (31%), euphoria (6%), ataxia (8%), sleep disturbance (14%)
Levitt 1982 (n=36)	Vertigo (67%), Drowsiness (61%), Depersonalisation syndrome (35%), disorientation (16%), headache (10%), inebriated feeling (10%), nausea (10%), vision disturbance (10%), concentration decreased (8%), sleep disturbance (6%)
Polito 2018 (n=110 children)	Sedation 20%; Dizziness 10%; Eupohoria 4%; Headache 3%; Constipation 2%; Abdominal pain 2%; Tachycardia 2%; Other (hypotension, anorexia, swollen eyelids, pruritus, hallucination, xerophalmia, bradycardia, hand cramp, chest pain) 8%

THC

Study	Adverse events reported
Gralla 1984 (n=15)	Sedation- mild (73%), moderate (13%), Orthostatic hypotension (53%), Dizziness (80%), Dry mouth (80%), 'High' (20%), dystonic reactions (0%), median no. of bowel movements (per patient over 24 hours) (0)
Frytak 1979 (n=38)	Sedation (76%), Coordination problems (72%), 'High' (58%) Other side effects (n): ataxia (7), Hypotension (3), visual hallucinations (2), Blurred vision (2), muddled thinking (2), paresthesias- face and extremities (2), depression (1), anxiety (1), nightmares (1), amnesia (1), fainting (1), slurred speech (10, faecal incontinence (1)
Orr 1981 (n=55)	Elevation of affect 'high' (82%), sedation (28%), loss of emotional or physical control (fear of irrational behaviour) (21%), nervousness (7%)
McCabe 1988 (n=36)	Dysphoria (52%)- consisting of dizziness, hallucinations, memory lapses and paranoia.
Ungerleider 1982 (n=133)	Sedation (45.3%), physiological (36.4%), psychological (34.3%), panic (3.5%)
Ungerleider 1985 (n=70)	In people with some experience of illegal drug use Sedation (51%), physiological (33%), psychological (33%), panic (3%), hunger (25%)
Sallan 1975 (n=11)	'High' – characterised by mood changes such as easy laughing, elation, heightened awareness, mild aberrations of fine motor co-ordination and minimal distortion of their activities and interactions with others. Somnolence, toxicity- characterised as paranoid ideation, apprehension, fear, panic and frightening visual hallucinations.
Neidhart 1981 (n=52)	Drowsiness (58%), feeling faint (55%), spasms or tremors (15%), silly (13%), depressed (12%), hallucinations or hysteria (8%), other- 'High' (40%)
Ekert 1979 (n=35)	Drowsiness was captured as part of adverse events and was common in children treated with THC. Study also reported at two patients also reported a 'high' while receiving THC. One patient had a bad 'trip'.

Prochlorperazine+ THC

Study	Adverse events reported
Kleinman 1983 (n=16)	Euphoria, mood alterations, sedation, increased food intake, adverse psychiatric reactions.

Dronabinol

Study	Adverse events reported
Lane 1991 (n=21)	(n): Neurologic (13) – Somnolence (4), Dizziness (7), Asthenia (2), Vision disturbances (3), Confusion (2), Depersonalisation (3), Paranoid reaction (1), Anxiety (1), Depression (2), Paresthesias (1). Digestive (5)- Dry mouth (2), Diarrhoea (2). Cardiovascular (3)- Tachycardia (2). Respiratory (0)- Dyspnea (0). Other body systems (3)- Headache (1)
Meiri 2007 (n=17)	(n): Diarrhoea (4), Asthenia (2), Fatigue (2) Chest pain (1), Constipation (1), Dizziness (1), Headache (0), Hyperglycaemia (0), Insomnia (0)

Dronabinol + Prochlorperazine

Study	Adverse events reported
Lane 1991 (n=20)	(n): Neurologic (11) – Somnolence (5), Dizziness (2), Asthenia (2), Vision disturbances (2), Confusion (1), Depersonalisation (0), Paranoid reaction (2), Anxiety (1), Depression (0), Paresthesias (0). Digestive (2)- Dry mouth (2), Diarrhoea (0). Cardiovascular (0)- Tachycardia (0). Respiratory (1)- Dyspnoea (1). Other body systems (1)- Headache (1)

Radiotherapy induced nausea and vomiting

Nabilone

Study	Adverse events reported
Priestman 1987 (n=40)	Vertigo (30%), dry mouth (15%), disorientation (20%), fatigue (25%), euphoria (5%), personality change (5%), loss of appetite (5%) Metoclopramide: vertigo (11%), dry mouth (5%), disorientation (5%), fatigue (5%), euphoria (0%), personality change (0%), loss of appetite (0%), fever (5%)

Appendix J – Excluded studies

Clinical studies

RCTS

Study	Code [Reason]
Ames, F. R. and Cridland, J. S. (1985) The antiemetic effect of Cannabis sativa during cytotoxic therapy. South african medical journal 68(11): 780-781	- Note to Editor
Badowski, Melissa E. (2017) A review of oral cannabinoids and medical marijuana for the treatment of chemotherapy-induced nausea and vomiting: a focus on pharmacokinetic variability and pharmacodynamics. Cancer chemotherapy and pharmacology 80(3): 441-449	- Review article. The bibliography was reviewed for possible includes
Beal, J. E., Olson, R., Laubenstein, L. et al. (1995) Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. Journal of pain and symptom management 10(2): 89-97	- Results not presented in an extractable format
Beal, J. and Flynn, N. (1995) AIDS-associated anorexia. Journal of the Physicians Association for AIDS Care 2(1): 19-22	- Narrative review
Broder, L. E.; Lean, N. L.; Hilsenbeck, S. G. (1982) A randomized blinded clinical trial comparing delta-9-tetrahydrocannabinol (THC) and hydroxizine (HZ) as antiemetics (AE) for cancer chemotherapy (CT). Proceedings of the American Association for Cancer Research vol23: 514	- Conference abstract
Cannabis In Cachexia Study, Group, Strasser, Florian, Luftner, Diana et al. (2006) Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: a multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the Cannabis-In-Cachexia-Study-Group. Journal of clinical Oncology : official journal of the American Society of Clinical Oncology 24(21): 3394-400	- No outcomes of interest
Chan, H. S.; MacLeod, S. M.; Correia, J. A. (1984) Nabilone vs. prochlorperazine for control of cancer chemotherapy-induced emesis in children. Proceedings of the American society of clinical oncology 3: 108, Abstract C-421	- This article is no longer available from any source
Chang, A. E.; Shiling, D. J.; Stillman, R. C. (1979) A prospective randomized trial of delta-9-tetrahydrocannabinol (THC) as an antiemetic in patients receiving high dose methotrexate (MTX). Proceedings of the American Association for Cancer Research vol20	- Conference abstract
Chang, A. E.; Shiling, D. J.; Stillman, R. C. (1979) Delta-9-tetrahydrocannabinol as an antiemetic in	- Study examined the use of THC capsules and cigarettes

Study	Code [Reason]
cancer patients receiving high-dose methotrexate. A prospective, randomized evaluation. Annals of Internal Medicine 91(6): 819-824	
Chang, A. E., Shiling, D. J., Stillman, R. C. et al. (1981) A prospective evaluation of delta-9-tetrahydrocannabinol as an antiemetic in patients receiving adriamycin and cytoxan chemotherapy. Cancer 47(7): 1746-1751	- Smoked THC
Chang, A. E., Shiling, D. J., Stillman, R. C. et al. (1979) Delata-9-tetrahydrocannabinol as an antiemetic in cancer patients receiving high-dose methotrexate. A prospective, randomized evaluation. Annals of internal medicine 91(6): 819-24	- Duplicate reference
Citron, M. L., Herman, T. S., Vreeland, F. et al. (1985) Antiemetic efficacy of levonantradol compared to delta-9-tetrahydrocannabinol for chemotherapy-induced nausea and vomiting. Cancer treatment reports 69(1): 109-12	- Study examined the use of levonantradol
Colls, B. M. (1980) Cannabis and cancer chemotherapy. Lancet 1(8179): 1187-1188	- Note to Editor
Colls, B. M.; Ferry, D. G.; Gray, A. J. (1980) The antiemetic activity of tetrahydrocannabinol versus metoclopramide and thiethylperazine in patients undergoing cancer chemotherapy. New Zealand Medical Journal 91(662): 449-451	- Results not presented in an extractable format
Cotter, Jayme (2009) Efficacy of Crude Marijuana and Synthetic Delta-9-Tetrahydrocannabinol as Treatment for Chemotherapy-Induced Nausea and Vomiting: A Systematic Literature Review. Oncology nursing forum 36(3): 345-352	- Review article. The bibliography was reviewed for possible includes
Cunngham, D., Bradley, C. J., Forrest, C. J. et al. (1987) A randomised trial of oral nabilone and prochlorperazine compared to intravenous metoclopramide and dexamethasone in treatment of emesis induced by chemotherapy regimens containing cis-platin of cis-platin analogues. Br-j-cancer 56: 226	- Conference abstract
Cunningham, D., Bradley, C. J., Forrest, G. J. et al. (1988) A randomized trial of oral nabilone and prochlorperazine compared to intravenous metoclopramide and dexamethasone in the treatment of nausea and vomiting induced by chemotherapy regimens containing cisplatin or cisplatin analogues. European journal of cancer & clinical oncology 24(4): 685-9	- Wrong intervention [Study examined the combined use of nabilone and prochloperazine]
Dupuis, L. Lee and Nathan, Paul C. (2003) Options for the prevention and management of acute chemotherapy-induced nausea and vomiting in children. Paediatric drugs 5(9): 597-613	- Narrative review
Duran, Marta, Perez, Eulalia, Abanades, Sergio et al. (2010) Preliminary efficacy and safety of an oromucosal standardized cannabis extract in	- Patients included in trial recieved different standard antiemetic therapy. Aim

Study	Code [Reason]
chemotherapy-induced nausea and vomiting. British journal of clinical pharmacology 70(5): 656-63	of review was not to compare different antiemetic therapies.
Frytak, S.; Moertel, C. G.; O'Fallon, J. R. (1979) A comparison of delta-9-tetrahydrocannabinol (THC), prochlorperazine (PCP) and placebo as antiemetics for cancer chemotherapy. Proceedings of the American Association for Cancer Research vol20	- Conference abstract
George, M.; Pejovic, M. H.; Thuaire, M. (1983) Randomized trial of nabilone as antimetic in cancer patients treated with cisplatin. BIOMED-PHARMACOTHER 37(1): 24-27	- Duplicate reference
George, M., Pejovic, M. H., Thuaire, M. et al. (1983) Randomized comparative trial of a new anti-emetic: nabilone, in cancer patients treated with cisplatin. Biomedecine & pharmacotherapie [Biomedicine & pharmacotherapy] 37(1): 24-27	- Non-English language article
Gilbert, C. J., Ohly, K. V., Rosner, G. et al. (1995) Randomized, double-blind comparison of a prochlorperazine-based versus a metoclopramide-based antiemetic regimen in patients undergoing autologous bone marrow transplantation. Cancer 76(11): 2330-7	- No outcomes of interest
Harden-Harrison, M. M., Munsell, M. F., Fisch, M. J. et al. (2012) Dronabinol for the prevention of nausea from cyclophosphamide and/or adriamycin. Supportive care in cancer. 20: S209-S210	- Conference abstract
Hartlapp, J. H., Illiger, H. J., Wolter, H. et al. (1984) Nabilone (Cesametic(R)) versus metoclopramide (Paspertin(R)). A double blind cross over study in cytostatic agent induced toxic vomitting of patients with testicular cancer. Journal of cancer research and clinical oncology 107(suppl): 24	- Conference abstract
Heim, M. E.; Queisser, W.; Altenburg, H. P. (1984) Randomized crossover study of the antiemetic activity of levonantradol and metoclopramide in cancer patients receiving chemotherapy. Cancer Chemotherapy and Pharmacology 13(2): 123-125	- Study examined the use of levonantradol
Hutcheon, A. W., Palmer, J. B., Soukop, M. et al. (1983) A randomised multicentre single blind comparison of a cannabinoid anti-emetic (levonantradol) with chlorpromazine in patients receiving their first cytotoxic chemotherapy. European journal of cancer & clinical oncology 19(8): 1087-90	- Study examined the use of levonantradol
Jatoi, Aminah, Windschitl, Harold E., Loprinzi, Charles L. et al. (2002) Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. Journal of clinical Oncology: official journal of the American Society of Clinical Oncology 20(2): 567-73	- Wrong comparison [Study compared dronabinol with megestrol acetate]
Jhangiani, H., Vredenburgh, J., Barbato, L. et al. (2005) Dronabinol or Ondansetron Alone and	- Conference abstract

Study	Code [Reason]
Combined for Delayed Chemotherapy-Induced Nausea and Vomiting (CINV). Blood 106(11part2): 477	
Jordan, Karin; Kasper, Christoph; Schmoll, Hans-Joachim (2005) Chemotherapy-induced nausea and vomiting: current and new standards in the antiemetic prophylaxis and treatment. European journal of cancer (Oxford, England: 1990) 41(2): 199-205	- Narrative review
Kleine-Brueggeney, Maren, Greif, Robert, Brenneisen, Rudolf et al. (2015) Intravenous Delta-9-Tetrahydrocannabinol to Prevent Postoperative Nausea and Vomiting: A Randomized Controlled Trial. Anesthesia and analgesia 121(5): 1157-64	- The relevant conditions are not included [Postoperative nausea and vomiting was not considered as being intractable.]
Kluin-Neleman, J. C., Neleman, F. A., Meuwissen Th, O. J. A. et al. (1979) Delta9-tetrahydrocannabinol (THC) as an antiemetic in patients treated with cancerchemotherapy: A double-blind cross-over trial against placebo. Veterinary and Human Toxicology 21(5): 338-340	- Results not presented in an extractable format
Kluin-Neleman, J. C., Neleman, F. A., Meuwissen, O. J. et al. (1979) delta 9-Tetrahydrocannabinol (THC) as an antiemetic in patients treated with cancerchemotherapy; a double-blind cross-over trial against placebo. Veterinary and human toxicology 21(5): 338-40	- Duplicate reference
Kluin-Nelemans, J. C., Meuwissen Th, O. J. A., Nelemans, F. A. et al. (1981) DELTA9-Tetrahydrocannabinol (THC) as an anti-emetic in patients treated with cancer chemotherapy. A double-blind cross-over trial against placebo. Netherlands Journal of Medicine 24(2): 90	- Conference abstract
Kluin-Nelemans, J. C., Meuwissen, OJATh, Nelemans, F. A. et al. (1981) Deltasup 9-Tetrahydrocannabinol (THC) as an anti-emetic in patients treated with cancer chemotherapy. A double-blind cross-over trial against placebo. Netherlands journal of medicine 24(2): 90	- Conference abstract
Lane, M., Smith, F. E., Sullivan, R. A. et al. (1990) Dronabinol and prochlorperazine alone and in combination as antiemetic agents for cancer chemotherapy. American Journal of Clinical Oncology: Cancer Clinical Trials 13(6): 480-484	- Duplicate results [Study only reports results from one center. Main results presented in Lane 1991]
Lane, M., Vogel, C. L., Ferguson, J. et al. (1989) Dronabinol and prochlorperazine in combination are better than either single agent alone for treatment of chemotherapy-induced nausea and vomiting. Proceedings of the american society of clinical oncology 8: 326abstract1269	- Conference abstract
Lane, M., Vogel, C. L., Ferguson, J. et al. (1991) Dronabinol and prochlorperazine in combination for treatment of cancer chemotherapy-induced nausea and vomiting. Journal of pain and symptom management 6(6): 352-359	- Duplicate reference

Study	Code [Reason]
Levin, D. N., Dulberg, Z., Chan, A. et al. (2016) A randomized controlled trial of nabilone for the prevention of postoperative nausea and vomiting in elective surgery. Anesthesia and analgesia. Conference: 2016 annual meeting of the international anesthesia research society, IARS 2016. United states. Conference start: 20160321. Conference end: 20160324 122(5supplement3): 463	- Conference abstract
Levin, David Neville, Dulberg, Zachary, Chan, An-Wen et al. (2017) A randomized-controlled trial of nabilone for the prevention of acute postoperative nausea and vomiting in elective surgery. Une etude randomisee controlee pour evaluer l'efficacite du nabilone pour la prevention des nausees et vomissements postoperatoires aigus lors de chirurgie non urgente. 64(4): 385-395	- The relevant conditions are not included [Study does not explore intractable nausea and vomiting]
Levitt, M., Faiman, C., Hawks, R. et al. (1984) Randomized double blind comparison of delta-9-tetrahydrocannabinol and marijuana as chemotherapy antiemetics. Proceedings of the american society of clinical oncology 3: 91, Abstract C-354	- This article is no longer available from any source
Levitt, M., Wilson, A., Bowman, D. et al. (1981) Physiologic observations in a controlled clinical trial of the antiemetic effectiveness of 5, 10, and 15 mg of delta 9-tetrahydrocannabinol in cancer chemotherapy. Ophthalmologic implications. Journal of clinical pharmacology 21(s1): 103S-109S	- No outcomes of interest
Lewis, I. H.; Campbell, D. N.; Barrowcliffe, M. P. (1994) Effect of nabilone on nausea and vomiting after total abdominal hysterectomy. British journal of anaesthesia 73(2): 244-6	- The relevant conditions are not included [Postoperative nausea and vomiting was not considered as being intractable.]
Long, A.; Mioduszewski, J.; Natale, R. (1982) A randomized double-blind cross-over comparison of the antiemetic activity of levonantradol and prochlorperazine. Proceedings of the American Society of Clinical Oncology vol1: C-220	- Conference abstract
Lucraft, H. H. and Palmer, M. K. (1982) Randomised clinical trial of levonantradol and chlorpromazine in the prevention of radiotherapy-induced vomiting. Clinical radiology 33(6): 621-2	- Study examined the use of levonantradol
Machado Rocha, F. C., Stefano, S. C., De Cassia Haiek, R. et al. (2008) Therapeutic use of Cannabis sativa on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. European journal of cancer care 17(5): 431-43	- Review article. The bibliography was reviewed for possible includes
Mersiades, A., Haber, P., Stockler, M. et al. (2017) Pilot and definitive randomized double-blind placebo-controlled trials evaluating anoral cannabinoid-rich THC/CBD cannabis extract for secondary prevention of chemotherapy-induced nausea and vomiting (CINV). Asia-pacific journal of clinical oncology. Conference:	- Conference poster

Study	Code [Reason]
annual scientific meeting of the medical oncology group of australia incorporated, MOGA 2017. Australia 13: 67-68	
Mersiades, A., Tognela, A., Haber, P. S. et al. (2018) Pilot and definitive randomised double-blind placebo-controlled trials evaluating an oral cannabinoid-rich THC/CBD cannabis extract for chemotherapy-induced nausea and vomiting (CINV). Asia-pacific journal of clinical oncology. Conference: annual scientific meeting of the australian and new zealand urogenital and prostate, ANZUP 2018. Australia 14(supplement2): 66	- Conference abstract
Mersiades, A., Tognela, A., Haber, P. et al. (2017) Pilot and definitive randomised double-blind placebo-controlled trials evaluating an oral cannabinoid-rich THC/CBD cannabis extract for secondary prevention of chemotherapy-induced nausea and vomiting (CINV). Asia-pacific journal of clinical oncology. Conference: 44th annual scientific meeting of the clinical oncology society of australia, COSA 2017. Australia 13(supplement4): 165	- Conference poster
Mersiades, A., Tognela, A., Haber, P. et al. (2018) Pilot and definitive randomised double-blind placebo-controlled trials evaluating an oral cannabinoid-rich THC/CBD cannabis extract for secondary prevention of chemotherapyinduced nausea and vomiting (CINV). Supportive care in cancer. Conference: 2018 joint meeting of the multinational association of supportive care in cancer, MASCC and the international society of oral oncology, ISOO 2018. Austria 26(2supplement1): 78	- Conference abstract
Morales, Mariaignacia; Corsi, Oscar; Pena, Jose (2017) Are cannabinoids effective for the management of chemotherapy induced nausea and vomiting? Son efectivos los cannabinoides para el manejo de nauseas y vomitos inducidos por quimioterapia? 17(9): e7119	- Review article. The bibliography was reviewed for possible includes
Nagy, C. M., Furnas, B. E., Einhorn, L. H. et al. (1978) Nabilone (N) anti-emetic crossover study in cancer chemotherapy patients. Proceedings of the American Association for Cancer Research vol19	- This article is no longer available from any source
Niederle, N.; Schutte, J.; Schmidt, C. G. (1986) Crossover comparison of the antiemetic efficacy of nabilone and alizapride in patients with nonseminomatous testicular cancer receiving cisplatin therapy. Klinische Wochenschrift 64(8): 362-5	- Irrelevant comparator [Nabilone compared to alizapride.]
Niiranen, A. and Mattson, K. (1987) Antiemetic efficacy of nabilone and dexamethasone: a randomized study of patients with lung cancer receiving chemotherapy. American journal of clinical oncology 10(4): 325-9	- Wrong comparison [Study examined additive effect of dexamethasone with nabilone monotherapy]
Orr, L. E. and McKernan, J. F. (1981) Antiemetic effect of delta 9-tetrahydrocannabinol in chemotherapy-	- Duplicate reference

Study	Code [Reason]
associated nausea and emesis as compared to placebo and compazine. Journal of clinical pharmacology 21(89suppl): 76S-80S	
Penta, J. S., Poster, D. S., Bruno, S. et al. (1981) Clinical trials with antiemetic agents in cancer patients receiving chemotherapy. Journal of clinical pharmacology 21(s1): 11S-22S	- Review article. The bibliography was reviewed for possible includes [Review article was also out of date]
Phillips, Robert S., Friend, Amanda J., Gibson, Faith et al. (2016) Antiemetic medication for prevention and treatment of chemotherapy-induced nausea and vomiting in childhood. The Cochrane database of systematic reviews 2: cd007786	- Review article. The bibliography was reviewed for possible includes
Phillips, Robert S., Gopaul, Shireen, Gibson, Faith et al. (2010) Antiemetic medication for prevention and treatment of chemotherapy induced nausea and vomiting in childhood. The Cochrane database of systematic reviews: cd007786	- Review article. The bibliography was reviewed for possible includes
Sallan, S.; Zinberg, N.; Frei, E. (1975) Oral delta 9 tetrahydrocannabinol (THC) in the prevention of vomiting (V) associated with cancer chemotherapy (CC). Proceedings of the American Association for Cancer Research 16(66)	- Conference abstract
Schuette, J.; Niederle, N.; Krischke, W. (1985) Randomized crossover trial comparing the antiemetic efficacy of nabilone versus alizapride in patients (pts) with nonseminomatous testicular cancer (NSTC) receiving low-dose cisplatin therapy. Proceedings of the American Association for Cancer Research vol26	- This article is no longer available from any source
Schussel, Victor, Kenzo, Lucas, Santos, Andreia et al. (2018) Cannabinoids for nausea and vomiting related to chemotherapy: Overview of systematic reviews. Phytotherapy research: PTR 32(4): 567-576	- Review article. The bibliography was reviewed for possible includes
Sheidler, V. R., Ettinger, D. S., Diasio, R. B. et al. (1984) Double-blind multiple-dose crossover study of the antiemetic effect of intramuscular levonantradol compared to prochlorperazine. Journal of clinical pharmacology 24(4): 155-9	- Study examined the use of levonantradol
Smith, Lesley A., Azariah, Fredric, Lavender, Verna T. C. et al. (2015) Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. The Cochrane database of systematic reviews: cd009464	- Review article. The bibliography was reviewed for possible includes
Stambaugh, J. E., Jr.; McAdams, J.; Vreeland, F. (1984) Dose ranging evaluation of the antiemetic efficacy and toxicity of intramuscular levonantradol in cancer subjects with chemotherapy-induced emesis. Journal of clinical pharmacology 24(1112): 480-5	- Study examined the use of levonantradol
Stambaugh, J. E.; McAdams, J.; Vreeland, F. (1982) A phase II randomized trial of the antiemetic activity of levonantradol (CP-50,556) in cancer patients receiving chemotherapy. Proceedings of the American Society of Clinical Oncology vol1: C-240	- Study examined the use of levonantradol - Conference abstract

Study	Code [Reason]
Struwe, M., Kaempfer, S. H., Geiger, C. J. et al. (1993) Effect of dronabinol on nutritional status in HIV infection. The Annals of pharmacotherapy 27(78): 827-31	- No outcomes of interest
Stuart Harris, R. C.; Mooney, C. A.; Smith, I. E. (1983) Levonantradol: A synthetic cannabinoid in the treatment of severe chemotherapy-induced nausea and vomiting resistant to conventional anti-emetic therapy. Clinical Oncology 9(2): 143-146	- Study examined the use of levonantradol
Tafelski, S.; Hauser, W.; Schafer, M. (2016) Efficacy, tolerability, and safety of cannabinoids for chemotherapy-induced nausea and vomiting--a systematic review of systematic reviews. Schmerz (Berlin, Germany) 30(1): 14-24	- Review article. The bibliography was reviewed for possible includes
Tait, Robert J., Caldicott, David, Mountain, David et al. (2016) A systematic review of adverse events arising from the use of synthetic cannabinoids and their associated treatment. Clinical toxicology (Philadelphia, Pa.) 54(1): 1-13	- The relevant conditions are not included [Review also examined all synthetic cannabinoids.]
Tramer, M. R., Carroll, D., Campbell, F. A. et al. (2001) Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. BMJ (Clinical research ed.) 323(7303): 16-21	- Review article. The bibliography was reviewed for possible includes
Turcott, J., Guillen-Nunez, M. D. R., Flores, D. et al. (2018) The Effect of Nabilone on Appetite, Nutritional Status, and Quality of Life in Lung Cancer Patients: a Randomized, Double-Blind Clinical Trial. Journal of thoracic oncology. Conference: IASLC 19th world conference on lung cancer. Canada 13(10supplement): S360-S361	- Conference abstract
Tyson, L. B.; Gralla, R. J.; Clark, R. A. (1985) Phase 1 trial of levonantradol in chemotherapy-induced emesis. American Journal of Clinical Oncology: Cancer Clinical Trials 8(6): 528-532	- Study examined the use of levonantradol
Ungerleider, J. T., Andrysiak, T. A., Fairbanks, L. A. et al. (1984) Tetrahydrocannabinol vs. prochlorperazine. The effects of two antiemetics on patients undergoing radiotherapy. Radiology 150(2): 598-9	- Cross-over trial with inadequate washout period (<1 week)
van den Elsen, G. A. H., Ahmed, A. I. A., Lammers, M. et al. (2014) Efficacy and safety of medical cannabinoids in older subjects: a systematic review. Ageing research reviews 14: 56-64	- Review article. The bibliography was reviewed for possible includes
Wang, T., Collet, J. P., Shapiro, S. et al. (2008) Adverse effects of medical cannabinoids: A systematic review. CMAJ 178(13): 1669-1678	- Review article. The bibliography was reviewed for possible includes

Observational studies

Study	Code [Reason]
Ames, F. R. and Cridland, J. S. (1985) The antiemetic effect of Cannabis sativa during cytotoxic therapy. South African medical journal	- Not a relevant study design [Letter to the editor]

Study	Code [Reason]
= Suid-Afrikaanse tydskrif vir geneeskunde 68(11): 780-1	
Bar-Sela, Gil, Tauber, Dina, Mitnik, Inbal et al. (2019) Cannabis-related cognitive impairment: a prospective evaluation of possible influences on patients with cancer during chemotherapy treatment as a pilot study. Anti-cancer drugs 30(1): 91-97	- Observational study of adults
Ekert, H., Waters, K. D., Jurk, I. H. et al. (1979) Amelioration of cancer chemotherapy-induced nausea and vomiting by delta-9-tetrahydrocannabinol. The Medical journal of Australia 2(12): 657-659	- Not a relevant study design [Randomised cross-over trial]
Elder, Joshua J. and Knoderer, Holly M. (2015) Characterization of Dronabinol Usage in a Pediatric Oncology Population. The journal of pediatric pharmacology and therapeutics: JPPT: the official journal of PPAG 20(6): 462-7	- Not a relevant study design
Layeeque, Rakhshanda, Siegel, Eric, Kass, Rena et al. (2006) Prevention of nausea and vomiting following breast surgery. American journal of surgery 191(6): 767-72	- Observational study of adults
Russo, E., Mathre, M. L., Byrne, A. et al. (2002) Chronic cannabis use in the Compassionate Investigational New Drug program: An examination of benefits and adverse effects of legal clinical Cannabis. Journal of Cannabis Therapeutics 2(1): 3-57	- Observational study of adults

Economic studies

Appendix K- Research recommendations

1. **What is the clinical and cost effectiveness of cannabis-based medicinal products as an add-on treatment for adults with chemotherapy-induced nausea and vomiting which persists with optimised conventional antiemetics?**

27 studies were identified which examined the clinical effectiveness of cannabis-based medicinal products (CBMPs). While these studies did demonstrate effectiveness of interventions such as nabilone in treating chemotherapy induced nausea and vomiting (CINV), these studies were of low quality and were considered indirect as some studies did not include the population of interest and majority did not reflect current practice. Additionally, no studies were identified which examined the cost effectiveness of CBMPs in treating intractable nausea and vomiting.

Further research is needed using a robust study design such as a parallel RCT to explore the clinical and cost effectiveness of CBMPs as an adjunct to optimal therapy in adults with persistent nausea and vomiting caused by chemotherapy who haven't fully responded to optimal treatment. Studies should be UK based. Research in this area is essential to inform future updates of key recommendations in this guidance which in turn can help improve patient outcomes.

PICO	**Population:** Adults with persistent chemotherapy induced nausea and vomiting who haven't fully responded to optimal treatment Specific subgroups: • Pregnant women and women who are breastfeeding • People with existing substance abuse • People with hepatic and renal failure **Interventions:** Cannabis based product defined as: 1. A cannabis-based product for medicinal use that is a preparation or other product, other than one to which paragraph 5 of part 1 of schedule 4 applies, which: • is or contains cannabis, cannabis resin, cannabinol or a cannabinol derivative (not being dronabinol or its stereoisomers) • is produced for medicinal use in humans; and • is a medicinal product, or • a substance or preparation for use as an ingredient of, or in the production of an ingredient of, a medicinal product (MDR 2018 regulations) 2. Synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC) for example dronabinol 3. Licensed products Sativex and nabilone 4. Plant-derived cannabinoids such as pure cannabidiol

	Cannabis based product used as an adjunct to optimal therapy **Comparator:** Optimal therapy alone **Outcomes:** • Reduction of nausea and vomiting • Reduction of nausea • Reduction of vomiting • Participant reported improvement on a global impression change (PGIC) scale • Quality of life scores • Serious adverse events • Adverse events including but not limited to sleep problems, fatigue, road traffic accidents, psychological distress, dizziness, headache, confusion state, paranoia, psychosis, substance dependence, diarrhoea at the start of treatment • Withdrawals due to adverse events • Complications due to adverse events • Substance abuse due to the use of cannabis-based medicinal product. • Psychosis due to the use of cannabis-based medicinal product. Misuse/diversion • Hepatic and renal failure
Current evidence base	26 RCTS (6 parallel RCTS, 20 crossover RCTs) and 1 retrospective study
Study design	Randomised controlled trial
Other comments	Study should be adequately powered and have an adequate follow up period.

2. What is the clinical and cost effectiveness of cannabis-based medicinal products as an add-on treatment in babies, children and young people with chemotherapy-induced nausea or vomiting which persists with optimised conventional antiemetics?

Four studies were identified which examined the clinical effectiveness of cannabis-based medicinal products (CBMPs) in children. In 1 study two different parallel studies were conducted in which delta-9-tetrahydrocannabinol (THC) was compared to metoclopramide and prochlorperazine for the chemotherapy induced nausea and vomiting (CINV) in children. This study did show significant absence of vomiting in children who were given THC, but this study was underpowered. Only one study was identified which examined the efficacy and safety of nabilone in children. This study did demonstrate a significant overall rate of improvement in retching and vomiting but also adverse events. One retrospective study was also conducted in children. Due to the lack of evidence and potential adverse events associated with the use of CBMPs, no recommendations were made for the use of CBMPs in children.

Further research is needed using a robust study design such as a parallel RCT to explore the clinical and cost effectiveness of CBMPs as an adjunct to optimal therapy in babies, children and young adults with persistent nausea and vomiting caused by chemotherapy who haven't fully responded to optimal treatment. Studies should be UK based. Research in this area is essential to inform future updates of key recommendations in this guidance which in turn can help improve patient outcomes.

PICO	**Population:** babies, children and young people with persistent chemotherapy induced nausea and vomiting who haven't fully responded to optimal treatment Specific subgroups: • Babies, children and young people with existing substance abuse • Babies, children and young people with hepatic and renal failure **Interventions:** Cannabis based product defined as: 1. A cannabis-based product for medicinal use that is a preparation or other product, other than one to which paragraph 5 of part 1 of schedule 4 applies, which: • is or contains cannabis, cannabis resin, cannabinol or a cannabinol derivative (not being dronabinol or its stereoisomers) • is produced for medicinal use in humans; and • is a medicinal product, or • a substance or preparation for use as an ingredient of, or in the production of an ingredient of, a medicinal product (MDR 2018 regulations) 2. Synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC) for example dronabinol 3. Licensed products Sativex and nabilone

	4. Plant-derived cannabinoids such as pure cannabidiol **Cannabis based product used as an adjunct to optimal therapy** **Comparator:** Optimal therapy alone **Outcomes:** • Reduction of nausea and vomiting • Reduction of nausea • Reduction of vomiting • Participant reported improvement on a global impression change (PGIC) scale • Quality of life scores • Serious adverse events • Adverse events including but not limited to sleep problems, fatigue, road traffic accidents, psychological distress, dizziness, headache, confusion state, paranoia, psychosis, substance dependence, diarrhoea at the start of treatment • Withdrawals due to adverse events • Complications due to adverse events • Substance abuse due to the use of cannabis-based medicinal product. • Psychosis due to the use of cannabis-based medicinal product. Misuse/diversion • Hepatic and renal failure
Current evidence base	3 studies (1 parallel RCTs and 2 crossover RCTs), 1 retrospective study
Study design	Randomised controlled trial
Other comments	Study should be adequately powered and have an adequate follow up period.

3. What is the clinical and cost effectiveness of cannabis-based medicinal products as an add-on treatment for adults with persistent nausea or vomiting not caused by chemotherapy which hasn't fully responded to optimised conventional antiemetics?

Out of the 28 studies identified, only 1 study focused on radiotherapy induced nausea and vomiting (RINV) while the remaining studies focused on chemotherapy induced nausea and vomiting (CINV). Due to the lack of evidence on other causes of persistent nausea and vomiting, the committee were unable to make any recommendations.

Further research is needed using a robust study design such as a parallel RCT to explore the clinical and cost effectiveness of CBMPs as an adjunct to optimal therapy in people with cancer and non-cancer related persistent nausea and vomiting. Studies should be UK based. Research in this area is essential to inform future updates of key recommendations in this guidance which in turn can help improve patient outcomes.

PICO	**Population:** Adults with cancer and non-cancer related persistent induced nausea and vomiting not caused by chemotherapy who haven't fully responded to optimal treatment Specific subgroups: • Pregnant women and women who are breastfeeding • People with existing substance abuse • People with hepatic and renal failure **Interventions:** Cannabis based product defined as: 1. A cannabis-based product for medicinal use that is a preparation or other product, other than one to which paragraph 5 of part 1 of schedule 4 applies, which: • is or contains cannabis, cannabis resin, cannabinol or a cannabinol derivative (not being dronabinol or its stereoisomers) • is produced for medicinal use in humans; and • is a medicinal product, or • a substance or preparation for use as an ingredient of, or in the production of an ingredient of, a medicinal product (MDR 2018 regulations) 2. Synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC) for example dronabinol 3. Licensed products Sativex and nabilone 4. Plant-derived cannabinoids such as pure cannabidiol **Cannabis based product used as an adjunct to optimal therapy** **Comparator:** Optimal therapy alone **Outcomes:** • Reduction of nausea and vomiting

	• Reduction of nausea • Reduction of vomiting • Participant reported improvement on a global impression change (PGIC) scale • Quality of life scores • Serious adverse events • Adverse events including but not limited to sleep problems, fatigue, road traffic accidents, psychological distress, dizziness, headache, confusion state, paranoia, psychosis, substance dependence, diarrhoea at the start of treatment • Withdrawals due to adverse events • Complications due to adverse events • Substance abuse due to the use of cannabis-based medicinal product. • Psychosis due to the use of cannabis-based medicinal product. Misuse/diversion • Hepatic and renal failure
Current evidence base	1 RCT focusing on people with radiotherapy induced nausea and vomiting.
Study design	Randomised controlled trial
Other comments	Study should be adequately powered and have an adequate follow up period.

4. What is the clinical and cost effectiveness of cannabis-based medicinal products as an add-on treatment for babies, children and young people with persistent nausea or vomiting not caused by chemotherapy which hasn't fully responded to optimised conventional antiemetics?

In this review, only studies focusing on the use of cannabis-based medicinal products in babies, children and young people for chemotherapy induced nausea and vomiting (CINV) were identified. Due to the lack of evidence on other causes of persistent nausea and vomiting, the committee were unable to make any recommendations.

Further research is needed using a robust study design such as a parallel RCT to explore the clinical and cost effectiveness of CBMPs as an adjunct to optimal therapy in children with cancer and non-cancer related persistent nausea and vomiting. Studies should be UK based. Research in this area is essential to inform future updates of key recommendations in this guidance which in turn can help improve patient outcomes.

PICO	**Population:** Babies, children and young people with cancer and non-cancer related persistent induced nausea and vomiting not caused by chemotherapy who haven't fully responded to optimal treatment Specific subgroups: • Babies, children and young people with existing substance abuse • Babies, children and young people with hepatic and renal failure **Interventions:** Cannabis based product defined as: 1. A cannabis-based product for medicinal use that is a preparation or other product, other than one to which paragraph 5 of part 1 of schedule 4 applies, which: • is or contains cannabis, cannabis resin, cannabinol or a cannabinol derivative (not being dronabinol or its stereoisomers) • is produced for medicinal use in humans; and • is a medicinal product, or • a substance or preparation for use as an ingredient of, or in the production of an ingredient of, a medicinal product (MDR 2018 regulations) 2. Synthetic compounds which are identical in structure to naturally occurring cannabinoids such as delta-9-tetrahydrocannabinol (THC) for example dronabinol 3. Licensed products Sativex and nabilone 4. Plant-derived cannabinoids such as pure cannabidiol **Cannabis based product used as an adjunct to optimal therapy** **Comparator:** Optimal therapy alone **Outcomes:** • Reduction of nausea and vomiting • Reduction of nausea

	• Reduction of vomiting • Participant reported improvement on a global impression change (PGIC) scale • Quality of life scores • Serious adverse events • Adverse events including but not limited to sleep problems, fatigue, road traffic accidents, psychological distress, dizziness, headache, confusion state, paranoia, psychosis, substance dependence, diarrhoea at the start of treatment • Withdrawals due to adverse events • Complications due to adverse events • Substance abuse due to the use of cannabis-based medicinal product. • Psychosis due to the use of cannabis-based medicinal product. Misuse/diversion • Hepatic and renal failure
Current evidence base	1 RCT focusing on people with radiotherapy induced nausea and vomiting.
Study design	Randomised controlled trial
Other comments	Study should be adequately powered and have an adequate follow up period.

Appendix L - References

Included studies

RCTs

Ahmedzai, S., Carlyle, D. L., Calder, I. T. et al. (1983) Anti-emetic efficacy and toxicity of nabilone, a synthetic cannabinoid, in lung cancer chemotherapy. British journal of cancer 48(5): 657-63

Chan, H. S.; Correia, J. A.; MacLeod, S. M. (1987) Nabilone versus prochlorperazine for control of cancer chemotherapy-induced emesis in children: a double-blind, crossover trial. Pediatrics 79(6): 946-52

Crawford, S. M. and Buckman, R. (1986) Nabilone and metoclopramide in the treatment of nausea and vomiting due to cisplatinum: a double blind study. Medical oncology and tumor pharmacotherapy 3(1): 39-42

Dalzell, A. M.; Bartlett, H.; Lilleyman, J. S. (1986) Nabilone: an alternative antiemetic for cancer chemotherapy. Archives of disease in childhood 61(5): 502-5

Einhorn, L. H., Nagy, C., Furnas, B. et al. (1981) Nabilone: an effective antiemetic in patients receiving cancer chemotherapy. Journal of clinical pharmacology 21(s1): 64S-69S

Ekert, H., Waters, K. D., Jurk, I. H. et al. (1979) Amelioration of cancer chemotherapy-induced nausea and vomiting by delta-9-tetrahydrocannabinol. The Medical journal of Australia 2(12): 657-659

Frytak, S., Moertel, C. G., O'Fallon, J. R. et al. (1979) Delta-9-tetrahydrocannabinol as an antiemetic for patients receving cancer chemotherapy. A comparison with prochlorperazine and a placebo. Annals of Internal Medicine 91(6): 825-830

Gralla, R. J., Tyson, L. B., Bordin, L. A. et al. (1984) Antiemetic therapy: a review of recent studies and a report of a random assignment trial comparing metoclopramide with delta-9-tetrahydrocannabinol. Cancer treatment reports 68(1): 163-72

Herman, T. S., Einhorn, L. H., Jones, S. E. et al. (1979) Superiority of nabilone over prochlorperazine as an antiemetic in patients receiving cancer chemotherapy. The New England journal of medicine 300(23): 1295-7

Johansson, R.; Kilkku, P.; Groenroos, M. (1982) A double-blind, controlled trial of nabilone vs. prochlorperazine for refractory emesis induced by cancer chemotherapy. Cancer treatment reviews 9 suppl b: 25-33

Jones, S. E., Durant, J. R., Greco, F. A. et al. (1982) A multi-institutional Phase III study of nabilone vs. placebo in chemotherapy-induced nausea and vomiting. Cancer treatment reviews 9supplb: 45-8

Kleinman, S., Weitzman, S. A., Cassem, N. et al. (1983) Double blind trial of delta-9-tetrahydrocannabinol (THC) versus placebo as an adjunct to prochlorperazine for chemotherapy-induced vomiting. Current Therapeutic Research - Clinical and Experimental 33(6i): 1014-1017

Lane, M., Vogel, C. L., Ferguson, J. et al. (1991) Original article. Dronabinol and prochlorperazine in combination for treatment of cancer chemotherapy-induced nausea and vomiting. Journal of Pain and Symptom Management 6(6): 352-359

Levitt, M. (1982) Nabilone vs. placebo in the treatment of chemotherapy-induced nausea and vomiting in cancer patients. Cancer treatment reviews 9supplb: 49-53

McCabe, M., Smith, F. P., Macdonald, J. S. et al. (1988) Efficacy of tetrahydrocannabinol in patients refractory to standard antiemetic therapy. Investigational new drugs 6(3): 243-6

Meiri, Eyal, Jhangiani, Haresh, Vredenburgh, James J. et al. (2007) Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. Current medical research and opinion 23(3): 533-43

Neidhart, J. A., Gagen, M. M., Wilson, H. E. et al. (1981) Comparative trial of the antiemetic effects of THC and haloperidol. Journal of clinical pharmacology 21(89suppl): 38S-42S

Niiranen, A. and Mattson, K. (1985) A cross-over comparison of nabilone and prochlorperazine for emesis induced by cancer chemotherapy. American journal of clinical oncology 8(4): 336-40

Orr, L. E.; McKernan, J. F.; Bloome, B. (1980) Antiemetic effect of tetrahydrocannabinol. Compared with placebo and prochlorperazine in chemotherapy-associated nausea and emesis. Archives of Internal Medicine 140(11): 1431-1433

Pomeroy, M.; Fennelly, J. J.; Towers, M. (1986) Prospective randomized double-blind trial of nabilone versus domperidone in the treatment of cytotoxic-induced emesis. Cancer chemotherapy and pharmacology 17(3): 285-8

Priestman, S. G.; Priestman, T. J.; Canney, P. A. (1987) A double-blind randomised cross-over comparison of nabilone and metoclopramide in the control of radiation-induced nausea. Clinical radiology 38(5): 543-4

Sallan, S. E., Cronin, C., Zelen, M. et al. (1980) Antiemetics in patients receiving chemotherapy for cancer. A randomized comparison of delta-9-tetrahydrocannabinol and prochlorperazine. New England Journal of Medicine 302(3): 135-138

Sallan, S. E.; Zinberg, N. E.; Frei, E., 3rd (1975) Antiemetic effect of delta-9-tetrahydrocannabinol in patients receiving cancer chemotherapy. The New England journal of medicine 293(16): 795-7

Steele, N., Gralla, R. J., Braun, D. W., Jr. et al. (1980) Double-blind comparison of the antiemetic effects of nabilone and prochlorperazine on chemotherapy-induced emesis. Cancer treatment reports 64(23): 219-24

Ungerleider, J. T.; Andrysiak, T.; Fairbanks, L. (1982) Cannabis and cancer chemotherapy. A comparison of oral delta-9-THC and prochlorperazine. Cancer 50(4): 636-645

Ungerleider, J. T., Sarna, G., Fairbanks, L. A. et al. (1985) THC or Compazine for the cancer chemotherapy patient--the UCLA study. Part II: Patient drug preference. American journal of clinical oncology 8(2): 142-7

Wada, J. K., Bogdon, D. L., Gunnell, J. C. et al. (1982) Double-blind, randomized, crossover trial of nabilone vs. placebo in cancer chemotherapy. Cancer treatment reviews 9supplb: 39-44

Observational studies

Polito, Samantha, MacDonald, Tamara, Romanick, Marcel et al. (2018) Safety and efficacy of nabilone for acute chemotherapy-induced vomiting prophylaxis in pediatric patients: A multicenter, retrospective review. Pediatric blood & cancer 65(12): e27374

Excluded studies

RCTs

Ames, F. R. and Cridland, J. S. (1985) The antiemetic effect of Cannabis sativa during cytotoxic therapy. South african medical journal 68(11): 780-781

Badowski, Melissa E. (2017) A review of oral cannabinoids and medical marijuana for the treatment of chemotherapy-induced nausea and vomiting: a focus on pharmacokinetic variability and pharmacodynamics. Cancer chemotherapy and pharmacology 80(3): 441-449

Beal, J. E., Olson, R., Laubenstein, L. et al. (1995) Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. Journal of pain and symptom management 10(2): 89-97

Beal, J. and Flynn, N. (1995) AIDS-associated anorexia. Journal of the Physicians Association for AIDS Care 2(1): 19-22

Broder, L. E.; Lean, N. L.; Hilsenbeck, S. G. (1982) A randomized blinded clinical trial comparing delta-9-tetrahydrocannabinol (THC) and hydroxizine (HZ) as antiemetics (AE) for cancer chemotherapy (CT). Proceedings of the American Association for Cancer Research vol23: 514

Cannabis In Cachexia Study, Group, Strasser, Florian, Luftner, Diana et al. (2006) Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: a multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the Cannabis-In-Cachexia-Study-Group. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 24(21): 3394-400

Chan, H. S.; MacLeod, S. M.; Correia, J. A. (1984) Nabilone vs. prochlorperazine for control of cancer chemotherapy-induced emesis in children. Proceedings of the american society of clinical oncology 3: 108, Abstract C-421

Chang, A. E.; Shiling, D. J.; Stillman, R. C. (1979) A prospective randomized trial of delta-9-tetrahydrocannabinol (THC) as an antiemetic in patients receiving high dose methotrexate (MTX). Proceedings of the American Association for Cancer Research vol20

Chang, A. E.; Shiling, D. J.; Stillman, R. C. (1979) Delta-9-tetrahydrocannabinol as an antiemetic in cancer patients receiving high-dose methotrexate. A prospective, randomized evaluation. Annals of Internal Medicine 91(6): 819-824

Chang, A. E., Shiling, D. J., Stillman, R. C. et al. (1981) A prospective evaluation of delta-9-tetrahydrocannabinol as an antiemetic in patients receiving adriamycin and cytoxan chemotherapy. Cancer 47(7): 1746-1751

Chang, A. E., Shiling, D. J., Stillman, R. C. et al. (1979) Delata-9-tetrahydrocannabinol as an antiemetic in cancer patients receiving high-dose methotrexate. A prospective, randomized evaluation. Annals of internal medicine 91(6): 819-24

Citron, M. L., Herman, T. S., Vreeland, F. et al. (1985) Antiemetic efficacy of levonantradol compared to delta-9-tetrahydrocannabinol for chemotherapy-induced nausea and vomiting. Cancer treatment reports 69(1): 109-12

Colls, B. M. (1980) Cannabis and cancer chemotherapy. Lancet 1(8179): 1187-1188

Colls, B. M.; Ferry, D. G.; Gray, A. J. (1980) The antiemetic activity of tetrahydrocannabinol versus metoclopramide and thiethylperazine in patients undergoing cancer chemotherapy. New Zealand Medical Journal 91(662): 449-451

Cotter, Jayme (2009) Efficacy of Crude Marijuana and Synthetic Delta-9-Tetrahydrocannabinol as Treatment for Chemotherapy-Induced Nausea and Vomiting: A Systematic Literature Review. Oncology nursing forum 36(3): 345-352

Cunngham, D., Bradley, C. J., Forrest, C. J. et al. (1987) A randomised trial of oral nabilone and prochlorperazine compared to intravenous metoclopramide and dexamethasone in treatment of emesis induced by chemotherapy regimens containing cis-platin of cis-platin analogues. Br-j-cancer 56: 226

Cunningham, D., Bradley, C. J., Forrest, G. J. et al. (1988) A randomized trial of oral nabilone and prochlorperazine compared to intravenous metoclopramide and dexamethasone in the treatment of nausea and vomiting induced by chemotherapy regimens containing cisplatin or cisplatin analogues. European journal of cancer & clinical oncology 24(4): 685-9

Dupuis, L. Lee and Nathan, Paul C. (2003) Options for the prevention and management of acute chemotherapy-induced nausea and vomiting in children. Paediatric drugs 5(9): 597-613

Duran, Marta, Perez, Eulalia, Abanades, Sergio et al. (2010) Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting. British journal of clinical pharmacology 70(5): 656-63

Frytak, S.; Moertel, C. G.; O'Fallon, J. R. (1979) A comparison of delta-9-tetrahydrocannabinol (THC), prochlorperazine (PCP) and placebo as antiemetics for cancer chemotherapy. Proceedings of the American Association for Cancer Research vol20

George, M.; Pejovic, M. H.; Thuaire, M. (1983) Randomized trial of nabilone as antimetic in cancer patients treated with cisplatin. BIOMED-PHARMACOTHER 37(1): 24-27

George, M., Pejovic, M. H., Thuaire, M. et al. (1983) Randomized comparative trial of a new anti-emetic: nabilone, in cancer patients treated with cisplatin. Biomedecine & pharmacotherapie [Biomedicine & pharmacotherapy] 37(1): 24-27

Gilbert, C. J., Ohly, K. V., Rosner, G. et al. (1995) Randomized, double-blind comparison of a prochlorperazine-based versus a metoclopramide-based antiemetic regimen in patients undergoing autologous bone marrow transplantation. Cancer 76(11): 2330-7

Harden-Harrison, M. M., Munsell, M. F., Fisch, M. J. et al. (2012) Dronabinol for the prevention of nausea from cyclophosphamide and/or adriamycin. Supportive care in cancer. 20: S209-S210

Hartlapp, J. H., Illiger, H. J., Wolter, H. et al. (1984) Nabilone (Cesametic(R)) versus metoclopramide (Paspertin(R)). A double-blind cross over study in cytostatic agent induced toxic vomitting of patients with testicular cancer. Journal of cancer research and clinical oncology 107(suppl): 24

Heim, M. E.; Queisser, W.; Altenburg, H. P. (1984) Randomized crossover study of the antiemetic activity of levonantradol and metoclopramide in cancer patients receiving chemotherapy. Cancer Chemotherapy and Pharmacology 13(2): 123-125

Hutcheon, A. W., Palmer, J. B., Soukop, M. et al. (1983) A randomised multicentre single blind comparison of a cannabinoid anti-emetic (levonantradol) with chlorpromazine in patients receiving their first cytotoxic chemotherapy. European journal of cancer & clinical oncology 19(8): 1087-90

Jatoi, Aminah, Windschitl, Harold E., Loprinzi, Charles L. et al. (2002) Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 20(2): 567-73

Jhangiani, H., Vredenburgh, J., Barbato, L. et al. (2005) Dronabinol or Ondansetron Alone and Combined for Delayed Chemotherapy-Induced Nausea and Vomiting (CINV). Blood 106(11part2): 477

Jordan, Karin; Kasper, Christoph; Schmoll, Hans-Joachim (2005) Chemotherapy-induced nausea and vomiting: current and new standards in the antiemetic prophylaxis and treatment. European journal of cancer (Oxford, England: 1990) 41(2): 199-205

Kleine-Brueggeney, Maren, Greif, Robert, Brenneisen, Rudolf et al. (2015) Intravenous Delta-9-Tetrahydrocannabinol to Prevent Postoperative Nausea and Vomiting: A Randomized Controlled Trial. Anesthesia and analgesia 121(5): 1157-64

Kluin-Neleman, J. C., Neleman, F. A., Meuwissen Th, O. J. A. et al. (1979) Delta9-tetrahydrocannabinol (THC) as an antiemetic in patients treated with cancerchemotherapy: A double-blind cross-over trial against placebo. Veterinary and Human Toxicology 21(5): 338-340

Kluin-Neleman, J. C., Neleman, F. A., Meuwissen, O. J. et al. (1979) delta 9-Tetrahydrocannabinol (THC) as an antiemetic in patients treated with cancerchemotherapy; a double-blind cross-over trial against placebo. Veterinary and human toxicology 21(5): 338-40

Kluin-Nelemans, J. C., Meuwissen Th, O. J. A., Nelemans, F. A. et al. (1981) DELTA9-Tetrahydrocannabinol (THC) as an anti-emetic in patients treated with cancer chemotherapy. A double-blind cross-over trial against placebo. Netherlands Journal of Medicine 24(2): 90

Kluin-Nelemans, J. C., Meuwissen, OJATh, Nelemans, F. A. et al. (1981) Deltasup 9-Tetrahydrocannabinol (THC) as an anti-emetic in patients treated with cancer chemotherapy. A double-blind cross-over trial against placebo. Netherlands journal of medicine 24(2): 90

Lane, M., Smith, F. E., Sullivan, R. A. et al. (1990) Dronabinol and prochlorperazine alone and in combination as antiemetic agents for cancer chemotherapy. American Journal of Clinical Oncology: Cancer Clinical Trials 13(6): 480-484

Lane, M., Vogel, C. L., Ferguson, J. et al. (1989) Dronabinol and prochlorperazine in combination are better than either single agent alone for treatment of chemotherapy-induced nausea and vomiting. Proceedings of the american society of clinical oncology 8: 326abstract1269

Lane, M., Vogel, C. L., Ferguson, J. et al. (1991) Dronabinol and prochlorperazine in combination for treatment of cancer chemotherapy-induced nausea and vomiting. Journal of pain and symptom management 6(6): 352-359

Levin, D. N., Dulberg, Z., Chan, A. et al. (2016) A randomized controlled trial of nabilone for the prevention of postoperative nausea and vomiting in elective surgery. Anesthesia and analgesia. Conference: 2016 annual meeting of the international anesthesia research society, IARS 2016. United states. Conference start: 20160321. Conference end: 20160324 122(5supplement3): 463

Levin, David Neville, Dulberg, Zachary, Chan, An-Wen et al. (2017) A randomized-controlled trial of nabilone for the prevention of acute postoperative nausea and vomiting in elective surgery. Une etude randomisee controlee pour evaluer l'efficacite du nabilone pour la prevention des nausees et vomissements postoperatoires aigus lors de chirurgie non urgente. 64(4): 385-395

Levitt, M., Faiman, C., Hawks, R. et al. (1984) Randomized double blind comparison of delta-9-tetrahydrocannabinol and marijuana as chemotherapy antiemetics. Proceedings of the american society of clinical oncology 3: 91, Abstract C-354

Levitt, M., Wilson, A., Bowman, D. et al. (1981) Physiologic observations in a controlled clinical trial of the antiemetic effectiveness of 5, 10, and 15 mg of delta 9-tetrahydrocannabinol in cancer chemotherapy. Ophthalmologic implications. Journal of clinical pharmacology 21(s1): 103S-109S

Lewis, I. H.; Campbell, D. N.; Barrowcliffe, M. P. (1994) Effect of nabilone on nausea and vomiting after total abdominal hysterectomy. British journal of anaesthesia 73(2): 244-6

Long, A.; Mioduszewski, J.; Natale, R. (1982) A randomized double-blind cross-over comparison of the antiemetic activity of levonantradol and prochlorperazine. Proceedings of the American Society of Clinical Oncology vol1: C-220

Lucraft, H. H. and Palmer, M. K. (1982) Randomised clinical trial of levonantradol and chlorpromazine in the prevention of radiotherapy-induced vomiting. Clinical radiology 33(6): 621-2

Machado Rocha, F. C., Stefano, S. C., De Cassia Haiek, R. et al. (2008) Therapeutic use of Cannabis sativa on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. European journal of cancer care 17(5): 431-43

Mersiades, A., Haber, P., Stockler, M. et al. (2017) Pilot and definitive randomized double-blind placebo-controlled trials evaluating anoral cannabinoid-rich THC/CBD cannabis extract for secondary prevention of chemotherapy-induced nausea and vomiting (CINV). Asia-pacific journal of clinical oncology. Conference: annual scientific meeting of the medical oncology group of australia incorporated, MOGA 2017. Australia 13: 67-68

Mersiades, A., Tognela, A., Haber, P. S. et al. (2018) Pilot and definitive randomised double-blind placebo-controlled trials evaluating an oral cannabinoid-rich THC/CBD cannabis extract for chemotherapy-induced nausea and vomiting (CINV). Asia-pacific journal of clinical oncology. Conference: annual scientific meeting of the australian and new zealand urogenital and prostate, ANZUP 2018. Australia 14(supplement2): 66

Mersiades, A., Tognela, A., Haber, P. et al. (2017) Pilot and definitive randomised double-blind placebo-controlled trials evaluating an oral cannabinoid-rich THC/CBD cannabis extract for secondary prevention of chemotherapy-induced nausea and vomiting (CINV). Asia-pacific journal of clinical oncology. Conference: 44th annual scientific meeting of the clinical oncology society of australia, COSA 2017. Australia 13(supplement4): 165

Mersiades, A., Tognela, A., Haber, P. et al. (2018) Pilot and definitive randomised double-blind placebo-controlled trials evaluating an oral cannabinoid-rich THC/CBD cannabis extract for secondary prevention of chemotherapyinduced nausea and vomiting (CINV). Supportive care in cancer. Conference: 2018 joint meeting of the multinational association of supportive care in cancer, MASCC and the international society of oral oncology, ISOO 2018. Austria 26(2supplement1): 78

Morales, Mariaignacia; Corsi, Oscar; Pena, Jose (2017) Are cannabinoids effective for the management of chemotherapy induced nausea and vomiting? Son efectivos los cannabinoides para el manejo de nauseas y vomitos inducidos por quimioterapia? 17(9): e7119

Nagy, C. M., Furnas, B. E., Einhorn, L. H. et al. (1978) Nabilone (N) anti-emetic crossover study in cancer chemotherapy patients. Proceedings of the American Association for Cancer Research vol19

Niederle, N.; Schutte, J.; Schmidt, C. G. (1986) Crossover comparison of the antiemetic efficacy of nabilone and alizapride in patients with nonseminomatous testicular cancer receiving cisplatin therapy. Klinische Wochenschrift 64(8): 362-5

Niiranen, A. and Mattson, K. (1987) Antiemetic efficacy of nabilone and dexamethasone: a randomized study of patients with lung cancer receiving chemotherapy. American journal of clinical oncology 10(4): 325-9

Orr, L. E. and McKernan, J. F. (1981) Antiemetic effect of delta 9-tetrahydrocannabinol in chemotherapy-associated nausea and emesis as compared to placebo and compazine. Journal of clinical pharmacology 21(89suppl): 76S-80S

Penta, J. S., Poster, D. S., Bruno, S. et al. (1981) Clinical trials with antiemetic agents in cancer patients receiving chemotherapy. Journal of clinical pharmacology 21(s1): 11S-22S

Phillips, Robert S., Friend, Amanda J., Gibson, Faith et al. (2016) Antiemetic medication for prevention and treatment of chemotherapy-induced nausea and vomiting in childhood. The Cochrane database of systematic reviews 2: cd007786

Phillips, Robert S., Gopaul, Shireen, Gibson, Faith et al. (2010) Antiemetic medication for prevention and treatment of chemotherapy induced nausea and vomiting in childhood. The Cochrane database of systematic reviews: cd007786

Sallan, S.; Zinberg, N.; Frei, E. (1975) Oral delta 9 tetrahydrocannabinol (THC) in the prevention of vomiting (V) associated with cancer chemotherapy (CC). Proceedings of the American Association for Cancer Research 16(66)

Schuette, J.; Niederle, N.; Krischke, W. (1985) Randomized crossover trial comparing the antiemetic efficacy of nabilone versus alizapride in patients (pts) with nonseminomatous testicular cancer (NSTC) receiving low-dose cisplatin therapy. Proceedings of the American Association for Cancer Research vol26

Schussel, Victor, Kenzo, Lucas, Santos, Andreia et al. (2018) Cannabinoids for nausea and vomiting related to chemotherapy: Overview of systematic reviews. Phytotherapy research: PTR 32(4): 567-576

Sheidler, V. R., Ettinger, D. S., Diasio, R. B. et al. (1984) Double-blind multiple-dose crossover study of the antiemetic effect of intramuscular levonantradol compared to prochlorperazine. Journal of clinical pharmacology 24(4): 155-9

Smith, Lesley A., Azariah, Fredric, Lavender, Verna T. C. et al. (2015) Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. The Cochrane database of systematic reviews: cd009464

Stambaugh, J. E., Jr.; McAdams, J.; Vreeland, F. (1984) Dose ranging evaluation of the antiemetic efficacy and toxicity of intramuscular levonantradol in cancer subjects with chemotherapy-induced emesis. Journal of clinical pharmacology 24(1112): 480-5

Stambaugh, J. E.; McAdams, J.; Vreeland, F. (1982) A phase II randomized trial of the antiemetic activity of levonantradol (CP-50,556) in cancer patients receiving chemotherapy. Proceedings of the American Society of Clinical Oncology vol1: C-240

Struwe, M., Kaempfer, S. H., Geiger, C. J. et al. (1993) Effect of dronabinol on nutritional status in HIV infection. The Annals of pharmacotherapy 27(78): 827-31

Stuart Harris, R. C.; Mooney, C. A.; Smith, I. E. (1983) Levonantradol: A synthetic cannabinoid in the treatment of severe chemotherapy-induced nausea and vomiting resistant to conventional anti-emetic therapy. Clinical Oncology 9(2): 143-146

Tafelski, S.; Hauser, W.; Schafer, M. (2016) Efficacy, tolerability, and safety of cannabinoids for chemotherapy-induced nausea and vomiting--a systematic review of systematic reviews. Schmerz (Berlin, Germany) 30(1): 14-24

Tait, Robert J., Caldicott, David, Mountain, David et al. (2016) A systematic review of adverse events arising from the use of synthetic cannabinoids and their associated treatment. Clinical toxicology (Philadelphia, Pa.) 54(1): 1-13

Tramer, M. R., Carroll, D., Campbell, F. A. et al. (2001) Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. BMJ (Clinical research ed.) 323(7303): 16-21

Turcott, J., Guillen-Nunez, M. D. R., Flores, D. et al. (2018) The Effect of Nabilone on Appetite, Nutritional Status, and Quality of Life in Lung Cancer Patients: a Randomized, Double-Blind Clinical Trial. Journal of thoracic oncology. Conference: IASLC 19th world conference on lung cancer. Canada 13(10supplement): S360-S361

Tyson, L. B.; Gralla, R. J.; Clark, R. A. (1985) Phase 1 trial of levonantradol in chemotherapy-induced emesis. American Journal of Clinical Oncology: Cancer Clinical Trials 8(6): 528-532

Ungerleider, J. T., Andrysiak, T. A., Fairbanks, L. A. et al. (1984) Tetrahydrocannabinol vs. prochlorperazine. The effects of two antiemetics on patients undergoing radiotherapy. Radiology 150(2): 598-9

van den Elsen, G. A. H., Ahmed, A. I. A., Lammers, M. et al. (2014) Efficacy and safety of medical cannabinoids in older subjects: a systematic review. Ageing research reviews 14: 56-64

Wang, T., Collet, J. P., Shapiro, S. et al. (2008) Adverse effects of medical cannabinoids: A systematic review. CMAJ 178(13): 1669-1678

Observational studies

Ames, F. R. and Cridland, J. S. (1985) The antiemetic effect of Cannabis sativa during cytotoxic therapy. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde 68(11): 780-1

Bar-Sela, Gil, Tauber, Dina, Mitnik, Inbal et al. (2019) Cannabis-related cognitive impairment: a prospective evaluation of possible influences on patients with cancer during chemotherapy treatment as a pilot study. Anti-cancer drugs 30(1): 91-97

Ekert, H., Waters, K. D., Jurk, I. H. et al. (1979) Amelioration of cancer chemotherapy-induced nausea and vomiting by delta-9-tetrahydrocannabinol. The Medical journal of Australia 2(12): 657-659

Elder, Joshua J. and Knoderer, Holly M. (2015) Characterization of Dronabinol Usage in a Pediatric Oncology Population. The journal of pediatric pharmacology and therapeutics: JPPT : the official journal of PPAG 20(6): 462-7

Layeeque, Rakhshanda, Siegel, Eric, Kass, Rena et al. (2006) Prevention of nausea and vomiting following breast surgery. American journal of surgery 191(6): 767-72

Russo, E., Mathre, M. L., Byrne, A. et al. (2002) Chronic cannabis use in the Compassionate Investigational New Drug program: An examination of benefits and adverse effects of legal clinical Cannabis. Journal of Cannabis Therapeutics 2(1): 3-57