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Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy (Review)

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[Intervention Review]

Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy

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ABSTRACT

Background

Cannabis has a long history of medicinal use. Cannabis-based medications (cannabinoids) are based on its active element, delta-9-tetrahydrocannabinol (THC), and have been approved for medical purposes. Cannabinoids may be a useful therapeutic option for people with chemotherapy-induced nausea and vomiting that respond poorly to commonly used anti-emetic agents (anti-sickness drugs). However, unpleasant adverse effects may limit their widespread use.

Objectives

To evaluate the effectiveness and tolerability of cannabis-based medications for chemotherapy-induced nausea and vomiting in adults with cancer.

Search methods

We identified studies by searching the following electronic databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, PsycINFO and LILACS from inception to January 2015. We also searched reference lists of reviews and included studies. We did not restrict the search by language of publication.

Selection criteria

We included randomised controlled trials (RCTs) that compared a cannabis-based medication with either placebo or with a conventional anti-emetic in adults receiving chemotherapy.

Data collection and analysis

At least two review authors independently conducted eligibility and risk of bias assessment, and extracted data. We grouped studies based on control groups for meta-analyses conducted using random effects. We expressed efficacy and tolerability outcomes as risk ratio (RR) with 95% confidence intervals (CI).

Main results

We included 23 RCTs. Most were of cross-over design, on adults undergoing a variety of chemotherapeutic regimens ranging from moderate to high emetic potential for a variety of cancers. The majority of the studies were at risk of bias due to either lack of allocation concealment or attrition. Trials were conducted between 1975 and 1991. No trials involved comparison with newer anti-emetic drugs such as ondansetron.

Comparison with placebo
People had more chance of reporting complete absence of vomiting (3 trials; 168 participants; RR 5.7; 95% CI 2.6 to 12.6; low quality evidence) and complete absence of nausea and vomiting (3 trials; 288 participants; RR 2.9; 95% CI 1.8 to 4.7; moderate quality evidence) when they received cannabinoids compared with placebo. The percentage of variability in effect estimates that was due to heterogeneity rather than chance was not important (I^2 = 0% in both analyses).

People had more chance of withdrawing due to an adverse event (2 trials; 276 participants; RR 6.9; 95% CI 1.96 to 24; I^2 = 0%; very low quality evidence) and less chance of withdrawing due to lack of efficacy when they received cannabinoids, compared with placebo (1 trial; 228 participants; RR 0.05; 95% CI 0.0 to 0.89; low quality evidence). In addition, people had more chance of 'feeling high' when they received cannabinoids compared with placebo (3 trials; 137 participants; RR 31; 95% CI 6.4 to 152; I^2 = 0%).

People reported a preference for cannabinoids rather than placebo (2 trials; 256 participants; RR 4.8; 95% CI 1.7 to 13; low quality evidence).

Comparison with other anti-emetics
There was no evidence of a difference between cannabinoids and prochlorperazine in the proportion of participants reporting no nausea (5 trials; 258 participants; RR 1.5; 95% CI 0.67 to 3.2; I^2 = 63%; low quality evidence), no vomiting (4 trials; 209 participants; RR 1.11; 95% CI 0.86 to 1.44; I^2 = 0%; moderate quality evidence), or complete absence of nausea and vomiting (4 trials; 414 participants; RR 2.0; 95% CI 0.74 to 5.4; I^2 = 60%; low quality evidence). Sensitivity analysis where the two parallel group trials were pooled after removal of the five cross-over trials showed no difference (RR 1.1; 95% CI 0.70 to 1.7) with no heterogeneity (I^2 = 0%).

People had more chance of withdrawing due to an adverse event (5 trials; 664 participants; RR 3.9; 95% CI 1.3 to 12; I^2 = 17%; low quality evidence), due to lack of efficacy (1 trial; 42 participants; RR 3.5; 95% CI 1.4 to 8.9; very low quality evidence) and for any reason (1 trial; 42 participants; RR 3.5; 95% CI 1.4 to 8.9; low quality evidence) when they received cannabinoids compared with prochlorperazine.

People had more chance of reporting dizziness (7 trials; 675 participants; RR 2.4; 95% CI 1.8 to 3.1; I^2 = 12%), dysphoria (3 trials; 192 participants; RR 7.2; 95% CI 1.3 to 39; I^2 = 0%), euphoria (2 trials; 280 participants; RR 18; 95% CI 2.4 to 133; I^2 = 0%), 'feeling high' (4 trials; 389 participants; RR 6.2; 95% CI 3.5 to 11; I^2 = 0%) and sedation (8 trials; 947 participants; RR 1.4; 95% CI 1.2 to 1.8; I^2 = 31%), with significantly more participants reporting the incidence of these adverse events with cannabinoids compared with prochlorperazine.

People reported a preference for cannabinoids rather than prochlorperazine (7 trials; 695 participants; RR 3.3; 95% CI 2.2 to 4.8; I^2 = 51%; low quality evidence).

In comparisons with metoclopramide, domperidone and chlorpromazine, there was weaker evidence, based on fewer trials and participants, for higher incidence of dizziness with cannabinoids.

Two trials with 141 participants compared an anti-emetic drug alone with a cannabinoid added to the anti-emetic drug. There was no evidence of differences between groups; however, the majority of the analyses were based on one small trial with few events.

Quality of the evidence
The trials were generally at low to moderate risk of bias in terms of how they were designed and do not reflect current chemotherapy and anti-emetic treatment regimens. Furthermore, the quality of evidence arising from meta-analyses was graded as low for the majority of the outcomes analysed, indicating that we are not very confident in our ability to say how well the medications worked. Further research is likely to have an important impact on the results.

Authors' conclusions

Cannabis-based medications may be useful for treating refractory chemotherapy-induced nausea and vomiting. However, methodological limitations of the trials limit our conclusions and further research reflecting current chemotherapy regimens and newer anti-emetic drugs is likely to modify these conclusions.

PLAIN LANGUAGE SUMMARY

Cannabis-based medicine for nausea and vomiting in people treated with chemotherapy for cancer

Background
As many as three-quarters of people who receive chemotherapy experience nausea (feeling sick) and vomiting (being sick), which many find distressing. While conventional anti-sickness medicines are effective, they do not work for everyone, all of the time. Therapeutic drugs based on the active ingredient of cannabis, known as THC (delta-9-tetrahydrocannabinol), have been approved for use as anti-sickness medicines in some countries.

Review question
This review evaluated how well cannabis-based medicines work for treating nausea and vomiting due to chemotherapy treatment in people with cancer, and what the side effects were.

Main findings

This review of 23 randomised controlled trials (clinical studies where people are randomly put into one of two or more treatment groups) found that fewer people who received cannabis-based medicines experienced nausea and vomiting than people who received placebo (a pretend medicine). The proportion of people who experienced nausea and vomiting who received cannabis-based medicines was similar to conventional anti-nausea medicines. However, more people experienced side effects such as 'feeling high', dizziness, sedation (feeling relaxed or sleepy) and dysphoria (feeling uneasy or dissatisfied) and left the study due to the side effects with cannabis-based medicines, compared with either placebo or other anti-nausea medicines. In trials where people received cannabis-based medicines and conventional medicines in turn, overall people preferred the cannabis-based medicines.

Quality of the evidence

The trials were of generally of low to moderate quality and reflected chemotherapy treatments and anti-sickness medicines that were around in the 1980s and 1990s. Also, the results from combining studies on the whole were of low quality. This means that we are not very confident in our ability to say how well the anti-sickness medicines worked, and further research reflecting modern treatment approaches is likely to have an important impact on the results.

Cannabis-based medicines may be useful for treating chemotherapy-induced nausea and vomiting that responds poorly to commonly used anti-sickness medicines.

Summary of findings 1. Cannabinoids compared with placebo for chemotherapy-induced nausea and vomiting

Cannabinoids compared with placebo for chemotherapy-induced nausea and vomiting

Patient or population: people with chemotherapy-induced nausea and vomiting

Intervention: cannabinoids

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Cannabinoids				
Absence of nausea (follow-up)	3 per 100	6 per 100 (1 to 63)	**RR 2.0** (0.2 to 21)	96 (2)	⊕⊕⊖⊖ **low**[3,5]	RR **> 1** indicates treatment favours cannabinoids
Absence of vomiting (follow-up)	6 per 100	34 per 100 (16 to 76)	**RR 5.7** (2.6 to 12.6)	168 (3)	⊕⊕⊖⊖ **low**[3,5]	RR **> 1** indicates treatment favours cannabinoids
Absence of nausea and vomiting (follow-up)	11 per 100	32 per 100 (20 to 52)	**RR 2.9** (1.8 to 4.7)	288 (3)	⊕⊕⊕⊖ **moderate**[3]	RR **> 1** indicates treatment favours cannabinoids
Participant preference (follow-up)	Low-risk value[2]		**RR 4.8** (1.7 to 13)	256 (2)	⊕⊕⊖⊖ **low**[3,4]	RR **> 1** indicates treatment favours cannabinoids
	8 per 100	38 per 100 (14 to 104)				
	High-risk value[2]					
	22 per 100	106 (37 to 286)				
Withdrawal any reason	10 per 1000	3 per 1000	**RR 0.31** (0.01 to 7)	33 (1)	⊕⊖⊖⊖ **very low**[1,3,5]	RR **< 1** indicates treatment favours cannabinoids

(follow-up)		(0.1 to 7)				
Withdrawal due to adverse event (follow-up)	80 per 1000	4 per 1000 (0.0 to 72)	**RR 6.9** (1.96 to 24)	276 (2)	⊕⊖⊖⊖ **very low**[1,3,5]	RR **< 1** indicates treatment favours cannabinoids

*The **assumed risk** for all outcomes is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Sparse data.
[2] The low- and high-risk values are the two extreme proportions of people with a preference for one drug over another.
[3] Limitations in the design (cross-over study) and high attrition.
[4] Unexplained heterogeneity.
[5] Imprecision.

Summary of findings 2. Cannabinoids compared with other anti-emetic agent for chemotherapy-induced nausea and vomiting

Cannabinoids compared with other anti-emetic agent for chemotherapy-induced nausea and vomiting

Patient or population: people with chemotherapy-induced nausea and vomiting

Intervention: cannabinoids

Comparison: other anti-emetic agent

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Other anti-emetic agent	Cannabinoids				
Absence of nausea	37 per 100	56 per 100	**RR 1.46** (0.67 to 3.15)	258 (5)	⊕⊕⊖⊖ **low**[3,4]	RR **> 1** indicates treatment favours cannabinoids

(follow-up)		(25 to 118)					
Absence of vomiting (follow-up)	Low-risk value[2]		**RR 1.1** (0.86 to 1.4)	209 (4)	⊕⊕⊕⊖ **moderate[3]**	RR **> 1** indicates treatment favours cannabinoids	
	10 per 1 000	11 per 1 000 (9 to 14)					
	High-risk value[2]						
	70 per 100	77 per 100 (60 to 98)					
Absence of nausea and vomiting (follow-up)	Low-risk value[2]		**RR 2.0** (0.74 to 5.4)	414 (4)	⊕⊕⊖⊖ **low[3,4]**	RR **> 1** indicates treatment favours cannabinoids	
	1 per 100	2 per 100 (1 to 5)					
	High-risk value[2]						
	42 per 100	84 per 100 (31 to 227)					
Participant preference (follow-up)	23 per 100	64 per 100 (44 to 92)	**RR 2.8** (1.9 to 4.0)	799 (9)	⊕⊕⊖⊖ **low[3,4]**	RR **> 1** indicates treatment favours cannabinoids	
Withdrawal any reason (follow-up)	19 per 100	67 per 100 (27 to 171)	**RR 3.5** (1.4 to 9.0)	42 (1)	⊕⊕⊖⊖ **low[1,3]**	RR **< 1** indicates treatment favours cannabinoids	
Withdrawal due to lack of efficacy (follow-up)	20 per 100	19 per 100 (1 to 420)	**RR 0.97** (0.04 to 21)	118 (2)	⊕⊖⊖⊖ **very low[1,3,4]**	RR **< 1** indicates treatment favours cannabinoids	
Withdrawal due to adverse event (follow-up)	3 per 100	10 per 100 (4 to 24)	**RR 3.2** (1.3 to 8.0)	740 (6)	⊕⊕⊖⊖ **low[3,5]**	RR **< 1** indicates treatment favours cannabinoids	

*The **assumed risk** for all outcomes is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio.

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Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Sparse data.
[2] The low- and high-risk values are the two extreme proportions of people with a preference for one drug over another.
[3] Limitations in the design (cross-over study) and high attrition.
[4] Unexplained heterogeneity.
[5] Imprecision.

Summary of findings 3. Cannabinoid plus other anti-emetic agent compared with other anti-emetic monotherapy for chemotherapy-induced nausea and vomiting

Cannabinoid plus other anti-emetic agent compared with other anti-emetic monotherapy for chemotherapy-induced nausea and vomiting

Patient or population: people with chemotherapy-induced nausea and vomiting

Intervention: cannabinoid plus other anti-emetic agent

Comparison: anti-emetic monotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Anti-emetic monotherapy	Cannabinoid plus other anti-emetic agent				
Absence of nausea (follow-up)	1 per 100	10 per 100 (0 to 183)	**RR 10** (0.61 to 183)	37 (1)	⊕⊖⊖⊖ **very low[1,2,3]**	RR **> 1** indicates treatment favours cannabinoids
Absence of vomiting (follow-up)	29 per 100	44 per 100 (20 to 90)	**RR 1.5** (0.69 to 3.1)	89 (2)	⊕⊕⊖⊖ **low[1,2]**	RR **> 1** indicates treatment favours cannabinoids

Absence of nausea and vomiting (follow-up)	30 per 100	48 per 100 (20 to 108)	**RR 1.6** (0.68 to 3.6)	37 (1)	⊕⊕⊖⊖ **low**[1,2]	RR **> 1** indicates treatment favours cannabinoids
Withdrawal any reason (follow-up)	20 per 100	26 per 100 (8 to 84)	**RR 1.3** (0.41 to 4.2)	41 (1)	⊕⊕⊖⊖ **low**[1,2]	RR **< 1** indicates treatment favours cannabinoids
Withdrawal due to adverse event (follow-up)	1 per 100	7 per 100 (1 to 55)	**RR 7.0** (0.88 to 55)	105 (2)	⊕⊖⊖⊖ **very low**[1,2,3]	RR **< 1** indicates treatment favours cannabinoids
Withdrawal due to lack of efficacy (follow-up)	20 per 100	2 per 100 (0 to 40)	**RR 0.12** (0.01 to 2.0)	41 (1)	⊕⊕⊖⊖ **low**[1,2]	RR **< 1** indicates treatment favours cannabinoids

*The **assumed risk** for all outcomes is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio.

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Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Sparse data.
[2] Limitations in the design (cross-over study) and high attrition.
[3] Imprecision.

BACKGROUND

Description of the condition

Nausea and vomiting are considered the most stressful adverse effects of chemotherapy by people with cancer (Barowski 1984; de Boer-Dennert 1997; Russo 2014). Up to 75% of all people with cancer experience chemotherapy-related nausea and vomiting (Schwartzberg 2007), which can lead to depression, anxiety and a feeling of helplessness, lower quality of life and may affect chemotherapy adherence (Dodds 1985; Janelsins 2013; Wilcox 1982).

Guidelines that inform standard protocols and algorithms ensure best practice in managing chemotherapy-induced nausea and vomiting (Basch 2011; NCCN 2014; Roila 2010). However, standardised care and clinical decision-making occurs within the context of individualised care, where focus on a person's preference is key to reducing chemotherapy-related stress in people with cancer. People's preference for cancer treatment is illustrated by several studies that report people's preferences for specific chemotherapy regimens based on quality of life (reduced treatment toxicity), rather than treatment efficacy (increased predicted survival) (Beusterien 2014; Dubey 2005; Kuchuk 2013; Sun 2002). Therefore, it is important to consider use of all approved anti-emetics that treat chemotherapy-induced nausea and vomiting, where people may have a preference for one or another type of treatment.

During the 1990s, serotonin (5-HT3) receptor antagonists, combined with dexamethasone, became the gold standard in the prevention of vomiting caused by chemotherapy (Gralla 1999; MASCC 1998). Episodes of chemotherapy-induced nausea and vomiting are classified by distinct clinical phases: acute - within the first 24 hours of treatment; delayed - following the first 24 hours of treatment and anticipatory - a learned response where refractory nausea and vomiting have been experienced during previous chemotherapy cycles, which results in nausea and vomiting prior to a subsequent treatment cycle (Roila 2010). Nowadays, the anti-emetics indicated for chemotherapy with high emesis-inducing potential are 5-HT3 receptor antagonists, dexamethasone and aprepitant given during the acute emetic phase (Basch 2011; Gralla 2013; NCCN 2014; Olver 2004). However, if there is failure to respond, or there is an increase in vomiting, this cannot be corrected by increasing the dose or frequency of administration of the prophylactic anti-emetics (5-HT3 receptor antagonists, dexamethasone and aprepitant). People who experience refractory nausea and vomiting (i.e. people who do not respond to first-line prophylactic anti-emetics) can have additional anti-emetics added to their existing prophylactic anti-emetic regimen, such as a dopamine antagonist (metoclopramide, domperidone), a phenothiazine (prochlorperazine or levomepromazine), an antihistamine (cyclizine) or a butyrophenone (haloperidol) anti-emetic (Gralla 1999; Gralla 2013). Benzodiazepines (lorazepam) can also be added to the prophylactic anti-emetic regimen for refractory people, particularly those who are anxious or experience anticipatory nausea and vomiting (Gralla 1999). Dexamethasone is one of the most effective anti-emetics for delayed nausea and vomiting, so people experiencing delayed refractory emesis can be prescribed an extended course of dexamethasone on a reducing dosage (Gralla 1999; Huang 2004; Ioannidis 2000). More recently, there have been reports of olanzapine being an effective adjunctive treatment for refractory nausea and vomiting (Gralla 2013). A second-generation 5HT3 receptor antagonist, palonosetron, is effective in refractory nausea and vomiting to substitute for a first-generation 5HT3 receptor antagonist (Gralla 2013). In addition, if people are unable to tolerate oral 5HT3 receptor antagonists, other formulations can be considered such as a 24-hour granisetron transdermal patch, an orally disintegrating ondansetron melt, or ondansetron oral film (Gralla 2013). Consideration should also be made for other formulations of adjunctive anti-emetics, such as buccal or rectal formulations (Gralla 2013).

According to Walsh 2003, cannabinoids, the active agents derived from cannabis (marijuana), may be considered for controlling nausea and vomiting as fourth-line agents. They have been recommended in international anti-emetic guidelines for the prevention of chemotherapy-induced nausea and vomiting (Gralla 1999). Cannabinoids are thought to work through different mechanisms to other agents given for nausea and vomiting (see: How the intervention might work) and may be effective in people with cancer who respond poorly to commonly used agents (Machado Rocha 2008).

Description of the intervention

Cannabis has been used for medicinal purposes throughout history (Karniol 2001). It was listed on the American pharmacopoeia until 1944 (Bonnie 1974), when it was removed due to political pressure and was banned in the USA (Walsh 2003). Although cannabis has not been re-listed on the American pharmacopoeia, in 1986 the Food and Drug Administration (FDA) authorised the use of its active element, delta-9-tetrahydrocannabinol (delta-9-THC), for medical purposes (Walsh 2003), to treat the adverse effects of nausea and vomiting in people with cancer receiving chemotherapy (Gralla 1999).

Currently, there are two synthetic delta-9-THC (cannabinoid) agents that have been evaluated in clinical trials that are approved for the treatment of nausea and vomiting in people with cancer treated with chemotherapy. These are oral formulations of trans(+)-3-(1,1-dimethylheptyl)-6,6a,7,8,10,10a-hexahydro-1-hydroxy-6,6-dimethyl-9H-dibenzo(b,d),pyran-9-one, nabilone, and l(6aR-trans)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol, dronabinol.

How the intervention might work

Cannabinoids affect the user by interacting with various receptors in different areas of the brain (Grotenhermen 2002). To date, two types of cannabinoid receptors have been identified, termed CB1 and CB2. Two substances naturally occurring in the brain that bind to and activate CB1 receptors are anandamide (Devane 1992) and 2-arachidonoylglycerol (2-AG) (Mechoulam 1995; Sugiura 1995). The cannabinoid receptors, and other naturally occurring substances that bind to them, are collectively termed the 'endocannabinoid system' (Rodríguez de Fonseca 2005). The blockage of CB1 cannabinoid receptors induces vomiting, suggesting the existence of cannabinoid receptors within the areas of the brain related to nausea and vomiting. This also suggests that the delta-9-THC anti-emetic activity may be due to stimulation of the CB1 receptor (Darmani 2001).

Why it is important to do this review

A systematic review of randomised controlled trials (RCTs) published up to the year 2000 concluded that cannabinoids

may be useful for controlling chemotherapy-induced nausea and vomiting, but that harmful adverse effects may limit their widespread use (Tramer 2001). This meta-analysis pooled placebo-controlled and active controlled trials together. Furthermore, a more recently published systematic review came to a similar conclusion regarding effectiveness, but did not report on the adverse effects (Machado Rocha 2008). Cannabinoids are currently rarely used in clinical practice, and the publication of a systematic review of cannabinoids in highly emetic chemotherapy will provide an evidence base for their use in people with refractory nausea and vomiting.

OBJECTIVES

To evaluate the effectiveness and tolerability of cannabis-based medications for chemotherapy-induced nausea and vomiting in adults with cancer.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs of cross-over or parallel group design with active or placebo control groups, or both.

Types of participants

Adults aged 18 years and over presenting with any type of cancer and receiving chemotherapeutic treatment, independent of gender and clinical setting. The chemotherapeutic regimens include drugs with low, moderate or high emetic potential.

We excluded children and young people aged under 18 years, since prevention and treatment of chemotherapy-induced nausea and vomiting, including use of cannabinoids, has been reported in this population in another Cochrane Review (Phillips 2010).

For the purpose of this review, chemotherapeutic treatments were those containing cytotoxic systemic anti-cancer treatments.

Two review authors (VL and NS) independently classified chemotherapeutic regimens, containing one or more chemotherapy agents as low, moderate, moderate to high, or high emetic potential using both American Society of Clinical Oncology (ASCO) guidelines (Basch 2011) and MASCC (Multinational Association of Supportive Care in Cancer)/European Society for Medical Oncology (ESMO) guidelines (Roila 2010). We resolved differences in assessment by discussion.

Types of interventions

Experimental arm: licensed pharmacological interventions based on cannabinoids derived from cannabis: nabilone and dronabinol used either as monotherapy or adjunct to conventional dopamine antagonists.

Control arm: placebo or conventional dopamine antagonists.

Types of outcome measures

Primary outcomes

- Complete control of nausea and vomiting (absence of episodes of nausea and vomiting without use of rescue medication) in the acute phase (within 24 hours of treatment with chemotherapy) and in the delayed phase (after 24 hours' treatment with chemotherapy) of nausea and vomiting.
- Complete control of vomiting (absence of episodes of vomiting without use of rescue medication) in the acute and delayed phases of nausea and vomiting.
- Complete control of nausea (absence of episodes of nausea without use of rescue medication) in the acute and delayed phases of nausea and vomiting.

Secondary outcomes

- Withdrawal due to adverse effects of anti-emetic.
- Withdrawal due to any anti-emetic-related reason.
- Withdrawal due to lack of anti-emetic efficacy.
- Cross-over studies only: participant preference for one or other of the interventions (cannabis or control).
- Incidence of particular adverse effects: 'feeling high', sedation, euphoria, dizziness, heightened sense of anxiety or agitation (dysphoria), depression, hallucinations, paranoia, hypotension, focal dystonia, extrapyramidal effects and oculogyric crisis.

Search methods for identification of studies

We sought papers in all languages and carried out translations wherever necessary.

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, 2015, Issue 1), MEDLINE accessed via Ovid (from 1966 to January week 3 2015), EMBASE accessed via Ovid (from 1980 to January week 3 2015), PsycINFO accessed via Ovid (from inception to January week 2 2015) and LILACS (from inception to January 2015). Appendix 1, Appendix 2, Appendix 3, Appendix 4, and Appendix 5 show the search strategies.

All relevant articles were identified on PubMed and, using the 'related articles' feature, we carried out a further search for newly published articles.

Searching other resources

Unpublished and grey literature

We searched metaRegister (www.controlled-trials.com/rct), Physicians Data Query (www.nci.nih.gov), wwwclinicaltrials.gov, and www.cancer.gov/clinicaltrials for ongoing trials. We searched for conference proceedings and abstracts through ZETOC (zetoc.mimas.ac.uk) and WorldCat Dissertations.

Handsearching

We examined bibliographical references of all the relevant studies in detail in order to find studies not identified in the electronic search, and handsearched key textbooks and previous systematic reviews and reports of conferences (i.e. ESMO and ASCO).

Data collection and analysis

Selection of studies

We downloaded all the titles and abstracts retrieved by electronic searching to a reference management database; we removed duplicates and three review authors (LS, FA, SB) independently examined the remaining references. We excluded those studies that clearly did not meet the inclusion criteria and we obtained copies of

the full text of potentially relevant references. Three review authors (LS, FA, SB) independently assessed the eligibility of the retrieved papers. The review authors were not blinded to the authors' names, institutions and journals of publication. We resolved disagreements by discussion and documented the reasons for exclusion in the Characteristics of excluded studies table.

Data extraction and management

For the included studies, two review authors (FA, LS) independently abstracted data on characteristics of study participants (inclusion criteria, age, gender, type of cancer and stage of disease, co-morbidities, co-interventions and chemotherapy regimens); dose, frequency, route of administration and duration of experimental and control interventions; risk of bias (see Assessment of risk of bias in included studies); outcomes (see Types of outcome measures) and deviations from the protocol onto a data abstraction form specially designed for the review and checked by a third author (SB). We resolved disagreements by discussion or by appeal.

For dichotomous outcomes (such as number of people with chemotherapy-induced nausea and vomiting per treatment group that did not present with symptoms of nausea and vomiting, described as absence of episodes of nausea and vomiting, to the end of the period of study; or withdrawals), we extracted the number of participants in each treatment arm who experienced the outcome of interest and the number of participants assessed in order to estimate a risk ratio (RR).

Wherever possible, all data extracted were those relevant to an intention-to-treat analysis, in which participants were analysed in the groups to which they were assigned. For cross-over studies, we extracted information on the number of cross-over periods, duration of washout periods and whether a paired design had been taken into consideration in the analysis.

We notes the time points at which outcomes were collected and reported.

Unit of analysis

For cross-over studies, we extracted the number of events as the numerator and the number analysed as the denominator for each treatment period.

Assessment of risk of bias in included studies

We assessed the risk of bias in included RCTs using the Cochrane's 'Risk of bias' tool (Higgins 2011). This included assessment of:

- method used for generating the randomisation sequence allocation of participants to the treatment arms;
- allocation concealment;
- blinding (of participants, healthcare providers and outcome assessors);
- reporting of incomplete outcome data (studies were considered at high risk of bias if more than 80% of people were assessed for primary outcomes): proportion of losses to follow-up and association with treatment arms, reasons for drop-out and association of drop-outs with treatment arms;
- selective reporting of outcomes;
- any other sources of bias that were pre-defined as carry-over effects and unbiased data available for analysis for cross-over trials.

Three review authors independently applied the 'Risk of bias' tool and resolved differences by discussion. We summarised results in both a 'Risk of bias' graph and a 'Risk of bias' summary. We interpreted results of meta-analyses in light of the findings with respect to risk of bias.

Measures of treatment effect

For dichotomous outcomes, we calculated the RR and its respective 95% confidence interval (CI). We incorporated cross-over trials in the meta-analyses using reported summary effect estimates. Where the carry-over effects were evident for a particular study, then we only used the data for the first period for the meta-analysis.

Unit of analysis issues

None expected.

Dealing with missing data

We did not impute missing outcome data for any of the outcomes. If contact details could be obtained, we contacted trial authors and requested missing data.

Assessment of heterogeneity

We assessed the heterogeneity between the trials by visual inspection of forest plots, by estimation of the percentage heterogeneity between trials that could not be ascribed to sampling variation (Higgins 2003), and by a formal statistical test of the significance of the heterogeneity (Deeks 2001). We interpreted the I^2 value according to recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* as follows (Higgins 2011):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Where there was evidence of substantial heterogeneity, we investigated and reported the possible reasons for this.

Assessment of reporting biases

We examined funnel plots corresponding to meta-analysis of the primary outcome if there were at least 10 trials included in the meta-analysis to assess the potential for small-study effects such as publication bias.

Data synthesis

Where we judged the trials sufficiently similar, we pooled their results in a meta-analysis. For dichotomous outcomes, we combined the RR for each study. We used random-effects models with inverse variance weighting for all meta-analyses due to the clinical and methodological diversity of the studies (see Characteristics of included studies table).

If trials had multiple treatment groups, we divided the 'shared' comparison group into the number of treatment groups and treated comparisons between each treatment group and the split comparison group as independent comparisons.

Subgroup analysis and investigation of heterogeneity

We conducted the following subgroup analyses for the primary outcome if sufficient trials were available:

- history of cannabis use, naive users versus prior users of cannabis;
- history of exposure to chemotherapy, chemotherapy naive versus prior chemotherapy treatment;
- type of cannabinoid agent, nabilone versus dronabinol.

Sensitivity analysis

We carried out sensitivity analyses for the primary outcome, if sufficient trials were available, excluding trials at high risk of bias and trials of a cross-over design. We also analysed the influence of the following factors on estimates of treatment effect:

- repeating the analysis excluding trials where chemotherapeutic regimens had low or low-moderate emetic potential, or the emetic potential was unclassifiable;
- repeating the analysis excluding trials where the primary outcome data were gathered after more than 24 hours of chemotherapeutic treatment.

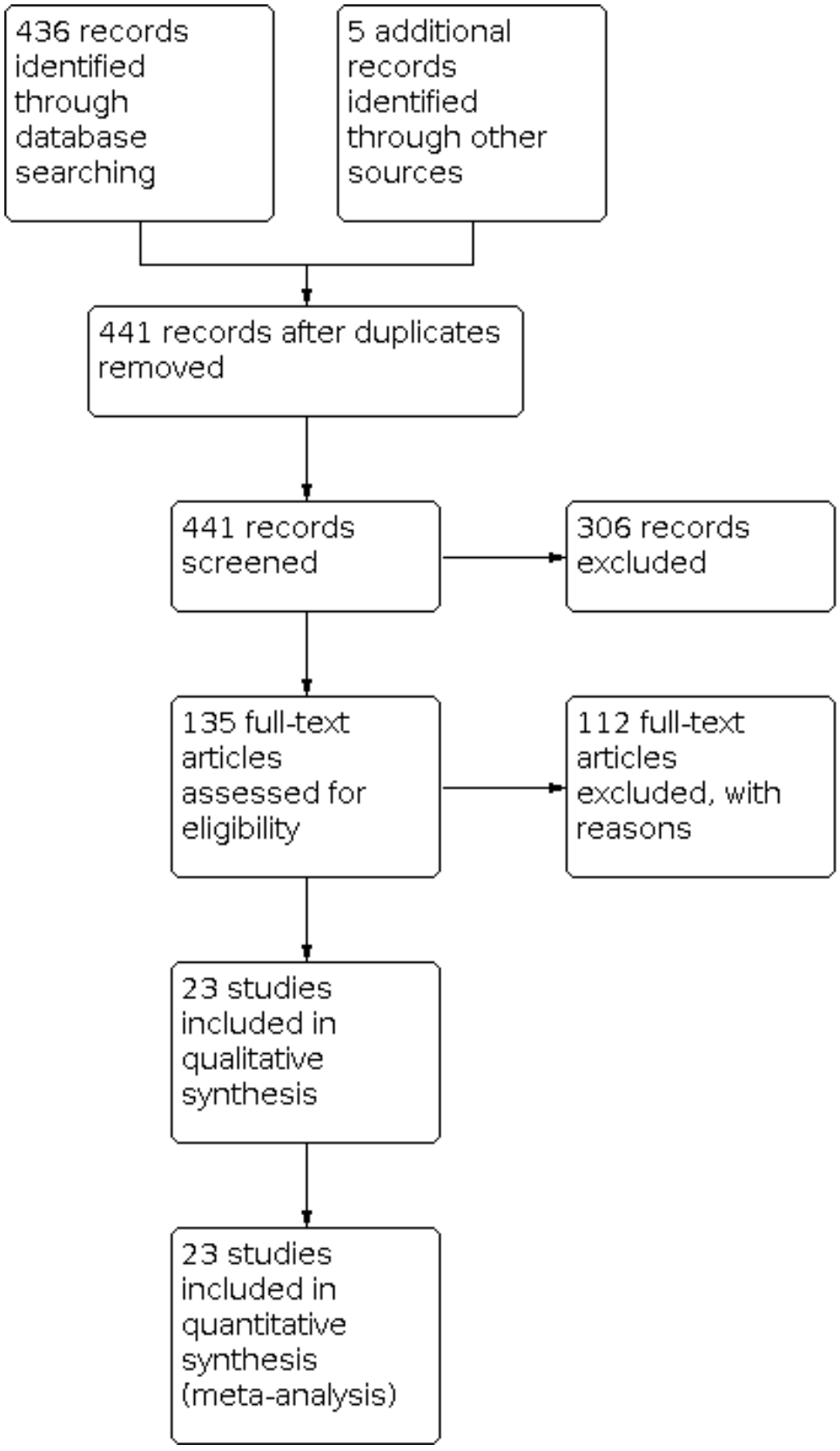
RESULTS

Description of studies

Results of the search

The search identified 441 records of which 135 were potentially eligible. We obtained hard copies of the full article of these articles for further consideration and excluded 112 (Figure 1). We identified no unpublished data.

Figure 1. Identification and selection of randomised controlled trials for review inclusion.



Included studies

Of the 23 included RCTs, the majority (19) were of cross-over design with four that were of parallel group design (Frytak 1979; Gralla 1984; Lane 1991; Pomeroy 1986).

The RCTs included people with a variety of cancers undergoing different chemotherapy regimens ranging from moderate to high anti-emetic potential, except for one of low emetic potential (Chang 1979a); five were unclassifiable as reporting of chemotherapy regimen was unclear (Kleinman 1983; Lane 1991; Levitt 1982; Sallan 1975a; Ungerleider 1982). Four trials were conducted on participants who were cannabis naive (Ahmedzai 1983; Frytak 1979; Johansson 1982; Lane 1991), one where 88% of participants were naive (Chang 1981), and one where 27% of participants were naive (Chang 1979a). One study excluded current users of cannabis (McCabe 1988), and in the other trials previous exposure to cannabinoids was unclear.

Nine RCTs compared cannabinoids given as monotherapy compared with placebo (Chang 1979a; Chang 1981; Frytak 1979; Jones 1982; Kluin-Neleman 1979; Levitt 1982; McCabe 1988; Sallan 1975a; Wada 1982), with another anti-emetic agent (prochlorperazine) in 11 RCTs (Ahmedzai 1983; Einhorn 1981; Frytak 1979; Herman 1979; Johansson 1982; Lane 1991; McCabe 1988; Niiranen 1985; Orr 1981; Steele 1980; Ungerleider 1982), metoclopramide in two RCTs (Crawford 1986; Gralla 1984), domperidone in one RCT (Pomeroy 1986), and chlorpromazine in one RCT (George 1983). Cannabinoids were also given as co-therapy with another anti-emetic agent compared with an anti-emetic agent alone in two RCTs (Kleinman 1983; Lane 1991). Two different cannabis-based medications were tested: nabilone in 12 RCTs (Ahmedzai 1983; Crawford 1986; Einhorn 1981; George 1983; Herman 1979; Johansson 1982; Jones 1982; Levitt 1982; Niiranen 1985; Pomeroy 1986; Steele 1980; Wada 1982), and dronabinol in 11 RCTs (Chang 1979a; Chang 1981; Frytak 1979; Gralla 1984; Kleinman 1983; Kluin-Neleman 1979; Lane 1991; McCabe 1988; Orr 1981; Sallan 1975a; Ungerleider 1982).

Dosing schedules varied across trials. Nabilone when given as monotherapy was administered most commonly as a fixed dose of 2 mg twice daily with lower doses administered when given as co-therapy. Dronabinol was mainly given at doses according to body surface area and ranged from 10 mg/m^2 twice daily to 15 mg/m^2 six times daily. Both were given as an oral formulations. In two trials, oral dronabinol was replaced with cannabis-based cigarettes if the participants vomited (Chang 1979a; Chang 1981).

The majority of the nausea or vomiting (or both) outcomes were reported for those that occurred within a 24-hour period. However, for some trials, it was unclear when outcomes were assessed and they may have been reported for a longer time-period (Herman 1979; Johansson 1982; Jones 1982; Kluin-Neleman 1979; Lane 1991; Levitt 1982). Trials were conducted between 1975 and 1991.

Excluded studies

We excluded 112 studies for reasons described in the Characteristics of excluded studies table. The main reasons were due to not being a primary study (i.e. a review, editorial or letter) (64) or were a non-randomised single-arm study (eight). RCTs were excluded due to not being an eligible treatment group (six); comparison (six) or a relevant outcome (one); recruited children (three); only presenting preliminary (three) or subsidiary results (one); having no extractable data (eight) or a duplicate of an existing study (10). Two were unobtainable.

Risk of bias in included studies

The trials were of variable quality ranging from low to moderate (Figure 2; Figure 3).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included trials.

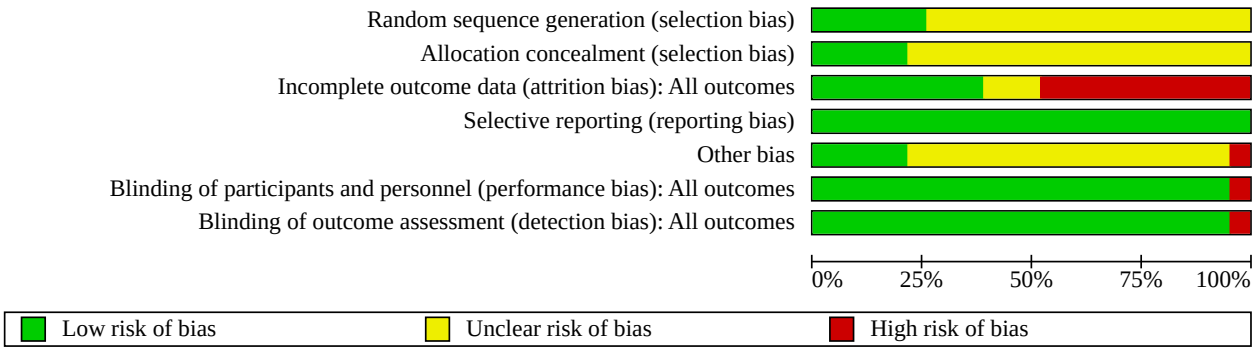


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included trial.

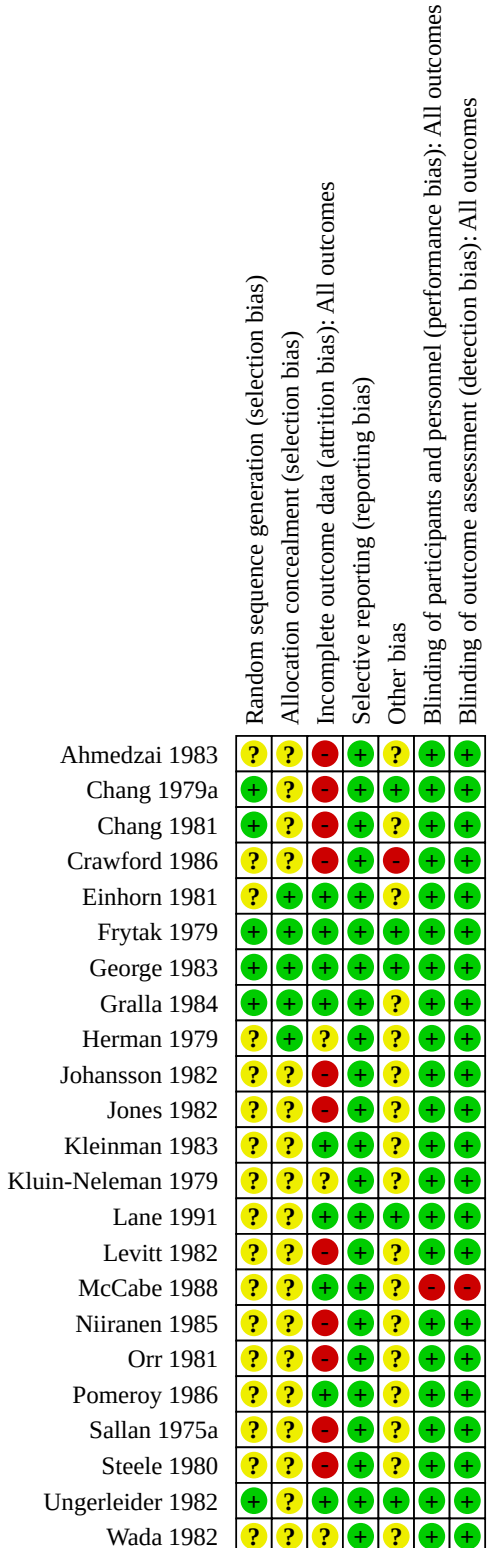
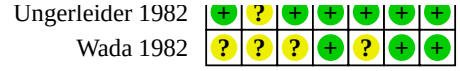


Figure 3. (Continued)



Allocation

Six trials adequately reported how the randomisation sequence was generated (Chang 1979a; Chang 1981; Frytak 1979; George 1983; Gralla 1984; Ungerleider 1982); the remaining 17 trials were unclear. Concealment of allocation was adequate in five trials (Einhorn 1981; Frytak 1979; George 1983; Gralla 1984; Herman 1979), and unclear in the remaining 18 trials.

Blinding

The majority of the trials were described as double-blind, which was implemented by using identical tablets. Eight were reported as double-blind, but it was unclear how this was achieved (Crawford 1986; Johansson 1982; Jones 1982; Lane 1991; Levitt 1982; Steele 1980; Ungerleider 1982; Wada 1982), and one study made no attempt at blinding (McCabe 1988).

Incomplete outcome data

Most trials were prone to attrition bias with only 9/23 trials judged as low risk of bias.

Selective reporting

All of the trials reported on the incidence of nausea or vomiting (or both); however, not all contributed to the meta-analyses. We were unable to include data for trials if they only reported results for nausea and vomiting as mean frequency of episodes, rather than the proportion of participants with and without nausea or vomiting (or both). While a reduction in severity of nausea or a reduction in vomiting episodes (or both) may be considered a worthwhile outcome for people with chemotherapy-induced nausea and vomiting, in these included trials, nausea severity was not measured with a validated instrument and episodes of vomiting were not analysed using standard methods for such (count) data. Therefore, we have not reported these data.

Other potential sources of bias

A large proportion of the trials were of cross-over design. We a*ssumed that the washout period was sufficient* and there were no carry-over effects of treatment due to the gap between chemotherapy treatment cycles, which would typically be around three weeks. The main potential source of bias was due to lack of information reported on whether a paired analysis was performed or not, and it was unclear if the groups were balanced at baseline.

Effects of interventions

See: **Summary of findings 1** Cannabinoids compared with placebo for chemotherapy-induced nausea and vomiting; **Summary of findings 2** Cannabinoids compared with other anti-emetic agent for chemotherapy-induced nausea and vomiting; **Summary of findings 3** Cannabinoid plus other anti-emetic agent compared with other anti-emetic monotherapy for chemotherapy-induced nausea and vomiting

Cannabinoids versus placebo

Nine trials with 819 participants compared cannabinoids with placebo (Chang 1979a; Chang 1981; Frytak 1979; Jones 1982; Kluin-Neleman 1979; Levitt 1982; Orr 1981; Sallan 1975a; Wada 1982), although not all trials contributed data for each outcome.

Primary outcome - anti-emetic efficacy

Two trials involving 96 participants showed no evidence of a difference between groups in the proportion of participants reporting complete absence of nausea with cannabinoids compared with placebo (RR 2.0; 95% CI 0.19 to 21; Analysis 1.1).

Three trials involving 168 participants showed that people had more chance of reporting complete absence of vomiting when they received cannabinoids compared with when they received placebo (RR 5.7; 95% CI 2.6 to 13). The percentage of the variability in effect estimates that was due to heterogeneity rather than chance was not important (I^2 = 0%, Tau^2 = 0.0, Chi^2 test for heterogeneity P value = 0.33; Analysis 1.2).

Three trials involving 288 participants showed that people had more chance of reporting complete absence of nausea and vomiting when they received cannabinoids compared with placebo (RR 2.9; 95% CI 1.8 to 4.7). The percentage of the variability in effect estimates that was due to heterogeneity rather than chance was not important (I^2 = 0%, Tau^2 = 0.0, Chi^2 test for heterogeneity P value = 0.50; Analysis 1.3).

Subgroup analyses, comparing results in trials with cannabis-naive people to trials where participants either had previous experience with cannabis or where previous use was unclear, showed no evidence of a difference between the two subgroups (P value = 0.4) with respect to absence of nausea and vomiting.

Secondary outcome - participant preference

Two trials involving 256 participants showed that people had more chance of reporting a preference for cannabinoids compared with placebo (RR 4.8; 95% CI 1.7 to 13) with substantial heterogeneity (I^2 = 71%, Tau^2 = 0.43, Chi^2 test for heterogeneity P value = 0.06; Analysis 1.9).

Secondary outcomes - tolerability and adverse events

One trial involving 33 participants showed no evidence of a difference between groups in the proportion of participants withdrawing for any reason (RR 0.31; 95% CI 0.01 to 7.21; Analysis 1.10).

Participants had more chance of withdrawing due to an adverse event when they received cannabinoids compared with placebo (2 trials; 226 participants; RR 6.9; 95% CI 2.0 to 24; Analysis 1.11), and less chance of withdrawing due to lack of efficacy (1 trial; 228 participants; RR 0.05; 95% CI 0.0 to 0.89; Analysis 1.12).

Participants had more chance of reporting 'feeling high' (3 trials; 137 participants; RR 31; 95% CI 6.4 to 152). The percentage of the variability in effect estimates that is due to heterogeneity rather than chance was not important (I^2 = 0%, Tau^2 = 0.0, Chi^2 test for heterogeneity P value = 0.95; Analysis 1.6).

There was no evidence of a difference between groups in the proportion of participants reporting depression (1 trial; 16 participants; RR 3.8; 95% CI 0.18 to 80; Analysis 1.4), dysphoria (2 trials; 96 participants; RR 9.0; 95% CI 0.50 to 161; Analysis 1.5), paranoia (1 trial; 64 participants; RR 3.0; 95% CI 0.13 to 71; Analysis 1.7), or sedation (2 trials; 139 participants; RR 4.5; 95% CI 0.35 to 58; Analysis 1.8) with substantial heterogeneity (I^2 = 72%, Tau^2 = 2.65, Chi^2 test for heterogeneity P value = 0.06).

The CIs for the estimates shown above are wide reflecting the uncertainty of these estimates.

Cannabinoids versus prochlorperazine

Nine trials with 1221 participants compared cannabinoids with prochlorperazine (Ahmedzai 1983; Frytak 1979; Herman 1979; Johansson 1982; Lane 1991; McCabe 1988; Niiranen 1985; Steele 1980; Ungerleider 1982), although not all trials contributed data for each outcome.

Primary outcome - anti-emetic efficacy

Five trials involving 258 participants showed no evidence of a difference between groups in the proportion of participants reporting no nausea (RR 1.5; 95% CI 0.67 to 3.2) with substantial heterogeneity (I^2 = 58%, Tau^2 = 0.33, Chi^2 test for heterogeneity P value = 0.05; Analysis 2.1).

Four trials involving 209 participants showed no evidence of a difference between groups in the proportion of participants reporting no vomiting (RR 1.1; 95% CI 0.86 to 1.4). The percentage of the variability in effect estimates that was due to heterogeneity rather than chance was not important (I^2 = 0%, Tau^2 = 0.0, Chi^2 test for heterogeneity P value = 0.53; Analysis 2.3).

Four trials involving 414 participants showed no evidence of a difference between groups in the proportion of participants reporting absence of nausea and vomiting (RR 2.0; 95% CI 0.74 to 5.4) with substantial heterogeneity (I^2 = 60%, Tau^2 = 0.51, Chi^2 test for heterogeneity P value = 0.06; Analysis 2.5). Sensitivity analysis, where the two parallel group trials were pooled after removal of the five cross-over trials, had an RR of 1.1 (95% CI 0.70 to 1.7) with no heterogeneity(I^2 = 0%, Tau^2 = 0.0, Chi^2 test for heterogeneity P value = 0.56).

Subgroup analyses - comparing results in trials with cannabis-naive people to trials where participants either had previous experience with cannabis or where previous use was unclear, showed no evidence of a difference between the two subgroups with respect to absence of nausea (P value = 0.11), but a difference between the subgroups for absence of nausea and vomiting with a smaller effect in people with no previous cannabis use (P value = 0.007). We were unable to conduct a subgroup analysis for absence of vomiting as all trials were of people who were cannabis naive (Analysis 2.6).

In addition, there was no evidence of a difference between subgroups comprised of different cannabinoid medications for absence of nausea (P value = 0.54), absence of vomiting (P value = 0.60) or absence of nausea and vomiting (P value = 0.10). The subgroup analyses did not explain the source of heterogeneity. There were insufficient data to perform other subgroup analyses listed in methods of analysis.

Secondary outcome - participant preference

Seven trials involving 695 participants showed participants had more chance of reporting a preference for cannabinoids compared with prochlorperazine (RR 3.2; 95% CI 2.2 to 4.7) with substantial heterogeneity (I^2 = 53%, Tau^2 = 0.13, Chi^2 test for heterogeneity P value = 0.05; Analysis 2.17).

Secondary outcomes - tolerability and adverse events

Based on one trial with 42 participants, participants had more chance of withdrawing for any reason (RR 3.5; 95% CI 1.4 to 8.9; Analysis 2.18), and due to lack of anti-emetic efficacy (RR 3.5; 95% CI 1.4 to 8.9; Analysis 2.20) when they received cannabinoids compared with prochlorperazine.

Five trials with 664 participants showed participants had more chance of withdrawing due to an adverse event when they received cannabinoids compared with prochlorperazine (RR 3.9; 95% CI 1.3 to 12) with unimportant heterogeneity(I^2 = 17%, Tau^2 = 0.31, Chi^2 test for heterogeneity P value = 0.31; Analysis 2.19).

Participants had more chance of reporting the following adverse events when they received cannabinoids compared with prochlorperazine: dizziness (7 trials; 675 participants; RR 2.4; 95% CI 1.8 to 3.1; unimportant heterogeneity: I^2 = 12%, Tau^2 = 0.02, Chi^2 test for heterogeneity P value = 0.34; Analysis 2.8), dysphoria (3 trials; 192 participants; RR 7.2; 95% CI 1.3 to 39; unimportant heterogeneity: I^2 = 0%, Tau^2 = 0.0, Chi^2 test for heterogeneity P value = 0.75; Analysis 2.9), euphoria (2 trials; 280 participants; RR 18; 95% CI 2.4 to 133; unimportant heterogeneity: I^2 = 0%, Tau^2 = 0.00, Chi^2 test for heterogeneity P value = 0.47; Analysis 2.10), 'feeling high' (4 trials; 389 participants; RR 6.2; 95% CI 3.5 to 11; unimportant heterogeneity: I^2 = 0%, Tau^2 = 0.0, Chi^2 test for heterogeneity P value = 0.75; Analysis 2.11), and sedation (8 trials; 947 participants; RR 1.4; 95% CI 1.2 to 1.8; moderate heterogeneity: I^2 = 31%, Tau^2 = 0.02, Chi^2 test for heterogeneity P value = 0.18; Analysis 2.15).

There was no evidence of a difference between groups in the proportion of participants reporting depression (3 trials; 317 participants; RR 0.81; 95% CI 0.51 to 1.3; unimportant heterogeneity: I^2 = 0%, Tau^2 = 0.0, Chi^2 test for heterogeneity P value = 0.47; Analysis 2.16), hallucinations (2 trials; 144 participants; RR 5.4; 95% CI 0.66 to 44; unimportant heterogeneity: I^2 = 0%, Tau^2 = 0.0, Chi^2 test for heterogeneity P value = 0.80; Analysis 2.12), postural hypotension (3 trials; 305 participants; RR 1.2; 95% CI 0.52 to 2.9; moderate heterogeneity: I^2 = 41%, Tau^2 = 0.29, Chi^2 test for heterogeneity P value = 0.18; Analysis 2.13), or paranoia (1 trial; 42 participants; RR 3.0; 95% CI 0.13 to 70; Analysis 2.14).

Cannabinoid versus metoclopramide

Two trials with 57 participants compared cannabinoid with metoclopramide (Crawford 1986; Gralla 1984), although both trials did not contribute data for each outcome.

Primary outcome - anti-emetic efficacy

Neither trial reported data for the proportion of participants with absence of nausea or vomiting (or both) (Crawford 1986; Gralla 1984).

Secondary outcome - participant preference

One trial involving 64 participants showed no evidence of a difference between groups in the proportion of participants reporting a preference for cannabinoids (RR 1.2; 95% CI 0.61 to 2.4; Analysis 2.17).

Secondary outcomes - tolerability and adverse events

Neither trial reported withdrawals.

Participants had more chance of reporting dizziness (1 trial, 30 participants; RR 12; 95% CI 1.8 to 81; Analysis 2.8), and postural hypotension (1 trial, 30 participants; RR 17; 95% CI 1.1 to 270; Analysis 2.13) when they received cannabinoids compared with metoclopramide. The CIs for these estimates were very wide reflecting the uncertainty of these estimates.

There was no evidence of a difference between groups in the proportion of participants reporting 'feeling high' (1 trial, 30 participants; RR 3.0; 95% CI 0.35 to 26; Analysis 2.11), or sedation (1 trial; 30 participants; RR 0.93; 95% CI 0.73 to 1.2; Analysis 2.15).The CIs for these estimates were very wide reflecting the uncertainty of these estimates. There were no dystonic reactions in either treatment group.

Cannabinoids versus domperidone

One trial with 38 participants compared cannabinoids versus domperidone (Pomeroy 1986).

Primary outcome - anti-emetic efficacy

The trial did not report data for the proportion of participants with absence of nausea or vomiting (or both).

Secondary outcome - participant preference

The trial did not report data for participant preference.

Secondary outcomes - tolerability and adverse events

There was no evidence of a difference between groups in the proportion of participants withdrawing due to lack of efficacy (RR 0.14; 95% CI 0.01 to 2.7; Analysis 2.20) or withdrawal due to an adverse event (RR 0.14; 95% CI 0.01 to 2.7; Analysis 1.11), with both estimates based on very low event rates.

Participants had more chance of reporting dizziness when they received cannabinoids compared with domperidone (RR 2.8; 95% CI 1.1 to 7.1; Analysis 2.8).

There was no evidence of a difference between groups in the proportion of participants reporting euphoria (RR 5.0; 95% CI 0.26 to 98; Analysis 2.10), postural hypotension (RR 4.0; 95% CI 0.49 to 33; Analysis 2.13) or sedation (RR 1.2; 95% CI 0.66 to 2.3; Analysis 2.15).

Cannabinoids versus chlorpromazine

One trial with 20 participants compared cannabinoids with chlorpromazine (George 1983).

Primary outcome - anti-emetic efficacy

The trial did not report data for anti-emetic efficacy.

Secondary outcome - participant preference

There was no evidence of a difference between groups in participants' preferences for treatment with cannabinoids or chlorpromazine (RR 2.0; 95% CI 0.83 to 4.8; Analysis 2.17).

Secondary outcomes - tolerability and adverse events

The trial did not report data for withdrawals.

There was no evidence of a difference between groups in the proportion of participants reporting euphoria (RR 3.0; 95% CI 0.13 to 70; Analysis 2.10), postural hypotension (RR 7.0; 95% CI 0.95 to 52; Analysis 2.13), or sedation (RR 1.7; 95% CI 0.85 to 3.4; Analysis 2.15), with few events giving rise to wide CIs around the point estimates.

Cannabinoid plus other anti-emetic agent versus other anti-emetic agent monotherapy

Two trials with 105 participants compared cannabinoid plus other anti-emetic agent with other anti-emetic agent monotherapy (Kleinman 1983; Lane 1991), although neither trial contributed data for all outcomes. The majority of the analyses were based on one small trial with few events (Lane 1991).

Primary outcome - anti-emetic efficacy

There was no evidence of a difference between groups in the proportion of participants reporting no nausea (RR 11; 95% CI 0.61 to 182; Analysis 3.1).

There was no evidence of a difference between groups in the proportion of participants reporting no vomiting (RR 1.5; 95% CI 0.69 to 3.1; Analysis 3.2).

There was no evidence of a difference between groups in the proportion of participants reporting no nausea or vomiting (RR 1.6; 95% CI 0.68 to 3.6; Analysis 3.3).

Secondary outcome - participant preference

The trials did not report data for participant preference.

Secondary outcomes - tolerability and adverse events

There was no evidence of a difference between groups in the proportion of participants withdrawing due to any reason (RR 1.3; 95% CI 0.41 to 4.2; Analysis 3.9).

There was no evidence of a difference between groups in the proportion of participants withdrawing due to an adverse event (RR 7.0; 95% CI 0.88 to 55; Analysis 3.10).

There was no evidence of a difference between groups in the proportion of participants withdrawing due to lack of efficacy (RR 0.12; 95% CI 0.01 to 2.0; Analysis 3.11).

There was no evidence of a difference between groups in the proportion of participants reporting depression (no participants in either group; Analysis 3.4), dizziness (RR 2.1; 95% CI 0.21 to 21; Analysis 3.5), dysphoria (RR 7.3; 95% CI 0.40 to 134; Analysis 3.6), paranoia (RR 5.2; 95% CI 0.27 to 103; Analysis 3.7), or sedation (RR 1.8; 95% CI 0.48 to 6.4; Analysis 3.8).

DISCUSSION

Summary of main results

The included trials showed that cannabinoids were more effective than placebo and were similar to conventional anti-emetics for treating chemotherapy-induced nausea and vomiting. However, despite causing more adverse events than placebo, overall there was weak evidence that people receiving chemotherapy for cancer preferred cannabinoids to placebo with stronger evidence that people preferred them to other anti-emetics.

Cannabinoids were highly effective. When compared with placebo, participants who received cannabinoids were five times as likely to report complete absence of vomiting, and three times as likely to report complete absence of nausea and vomiting. Although, some participants were six times more likely to withdraw from the study due to an adverse event with cannabinoids, other participants were more likely to withdraw due to lack of efficacy with placebo. Adverse events associated with cannabinoids were reported, however, the only one with evidence of a difference between cannabinoids and placebo was 'feeling high'. Overall, there was weak evidence that participants preferred cannabinoids to placebo.

When cannabinoids were compared with conventional anti-emetic drugs, there was no evidence of a difference for nausea, vomiting, or nausea and vomiting. The majority of the data for these analyses were from comparison with prochlorperazine. However, participants were three or four times more likely to withdraw due to an adverse event with cannabinoids than prochlorperazine. Dizziness, dysphoria, 'feeling high' and sedation were all more likely with cannabinoids. Dizziness in particular was more likely with cannabinoids compared with metoclopramide and domperidone. Overall, there was evidence that participants preferred cannabinoids to conventional anti-emetics; however, the majority of the trials were of prochlorperazine.

There may be an additional benefit of administering a cannabinoid with another anti-emetic agent. These benefits include reduced nausea, vomiting, and nausea and vomiting. Adverse events were similar to those for comparisons with anti-emetics given as monotherapy, but there were insufficient data to make firm conclusions.

Overall completeness and applicability of evidence

The trials included in this review were on adults with a wide variety of cancers undergoing a wide range of chemotherapy regimens. Many of the trials included participants who were refractory to conventional anti-emetic medications. The synthetic cannabis-based compounds were given orally and were either dronabinol or nabilone. The most informative RCTs were the ones that compared a cannabis-based medication with a conventional anti-emetic, rather than placebo. These trials showed that cannabis-based medications had similar anti-emetic effects compared with prochlorperazine and metoclopramide.

Nowadays, people receiving moderate to highly emetogenic chemotherapy regimens will be prescribed combination prophylactic anti-emetic regimens including a 5-HT_3 antagonist and steroid, and perhaps also include a neurokinin-1 (NK-1) inhibitor for very highly emetogenic regimens (NCCN 2015). In the event of a person experiencing breakthrough or refractory, acute chemotherapy-induced nausea and vomiting, an additional agent from a different pharmacological class of anti-emetics would be recommended, such as metoclopramide, prochlorperazine or lorazepam (NCCN 2015). Cannabis-based anti-emetics offer an alternative additional anti-emetic agent for breakthrough or refractory acute chemotherapy-induced nausea and vomiting. Since there is a lack of studies that compare the use of cannabinoids to 5-HT_3 antagonists and NK-1 inhibitors, this review found no evidence to support the use of cannabinoids in place of current prophylactic combination anti-emetic regimens.

Quality of the evidence

Overall, the trials were of variable quality (very low to moderate by Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach). Strengths included the use of blinding by using double-dummy preparations by the majority of the trials. However, it is possible that the trials were at risk of observer bias, due to the characteristic adverse effect profile of cannabinoids. The risk of bias from selective reporting of the primary outcome was low. The majority of the trials were unclear with respect to methods used to generate randomisation sequence and whether randomisation was concealed, so may be at risk of selection bias. A major weakness lies in the fact that a large proportion of the trials were of cross-over design, and we were unable to adjust the data to take into account the paired data, which will result in narrower CIs around effect estimates. Another weakness was high risk of bias from attrition from the trials. This was largely due to participants being excluded from analyses in the cross-over trials if they did not complete all cross-over periods. The summary of findings are shown in Summary of findings 1; Summary of findings 2; and Summary of findings 3. The quality of the evidence for most outcomes was generally of low quality. The main reasons were due to risk of bias, imprecise results due to few studies or few events (or both) and unexplained heterogeneity. The impact of the downgrading decisions means that further research is likely to influence the confidence in our estimates of effects and may change the estimates.

Potential biases in the review process

Some trials only reported episodes of nausea and vomiting, rather than the proportion of participants with no nausea and vomiting, therefore we did not include these results in meta-analyses. We also analysed dichotomous outcomes from the cross-over studies without adjusting the analyses, which potentially gives rise to more precise (narrower CIs) estimates of effect.

In order to avoid publication bias, we searched for ongoing trials in clinical trial registry databases; however, we identified no further trials.

Agreements and disagreements with other studies or reviews

Our findings are in broad agreement with previously published systematic reviews (Machado Rocha 2008; Tramer 2001). We have updated and extended these earlier reviews by pooling placebo-controlled trials separately from trials with active comparison groups, and where cannabis was given as co-therapy with another anti-emetic, and reporting on tolerability as well as efficacy outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

The widespread use of cannabis-based medicines for management of nausea and vomiting with chemotherapy is unlikely due to the adverse effects they cause. However, cannabinoids are a useful adjunctive treatment to consider for people on moderately or highly emetic chemotherapy that are refractory to other anti-emetic treatments, when all other options of therapy have been tried. Consideration needs to be made of the adverse effect profile of the cannabinoids, and how the adverse effects may be exacerbated with other concurrent anti-emetic treatments, as well as the age of the person. This systematic review will be valuable evidence for clinicians and future development of international guidelines to summarise the evidence available.

Implications for research

Adequate study design is important for anti-emetic studies, ideally using a double-blind trial design that is stratified for known prognostic factors, such as gender, age, alcohol intake, previous experience of chemotherapy, emetic potential of chemotherapy and a person's susceptibility to motion sickness (De Mulder 1992; Olver 1992a; Olver 1992b; Pater 1984). It is preferable for people to be chemotherapy naive and receiving the same chemotherapy regimens, or, if that is not possible, to receive those of the same emetogenicity as classified by international guidelines. Uniform anti-emetic regimens should be used, when comparing an adjunctive anti-emetic being added to the regimen in one arm (Rhodes 1984). Studies that compare the use of newer anti-emetics that have efficacy for treating refractory nausea and vomiting (olanzapine and palonosetron) with cannabinoids would also be informative. It is difficult to compare anti-emetic studies (Martin 1992), due to the variation in anti-emetic doses, routes of administration, time periods of assessment of nausea and vomiting, assessment of episodes of nausea and vomiting, and any additional anti-emetics that may have been administered. It also needs to be clear whether acute or delayed (or both) nausea and vomiting is being assessed, and there is also a variation in the definitions of complete response across studies, which impacts on comparing studies (Pater 1984). In the original anti-emetic trials, assessment of nausea and vomiting has been inconsistent where no reliable and valid measures have been used, which also impacts on their analysis and interpretation (Pater 1984; Rhodes 1984).

While cross-over trials are attractive to evaluate this type of therapy, they are susceptible to loss of participants if not all cross-over to the second and subsequent phases of the trial. Following recommendations of the CONSORT (Consolidated Standards of Reporting Trials) statement for cross-over studies would improve interpretation of such studies.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ahmedzai 1983

Study characteristics	
Methods	Randomised, double-blinded, 2-period cross-over study
Participants	34 people (19 (56%) men/15 (44%) women), median age 58 years. All cannabis naive Tumour types: small cell bronchial carcinoma Chemotherapy regimen: 2 x 21-day cycles. Cyclophosphamide 1 g/m^2, doxorubicin 40 mg/m^2 and etoposide (VP-16) 100 mg/m^2 day 1; etoposide 100 mg/m^2 days 2 and 3; vincristine 2 mg with methotrexate 50 mg/m^2 day 10 followed by folinic acid rescue. Cyclophosphamide and doxorubicin given IV bolus; VP-16 IV over 1-2 hours Chemotherapy emetogenicity: High
Interventions	Nabilone 2 mg orally twice daily x 3 days, n = 34 Prochlorperazine 10 mg orally 3 times daily x 3 days, n = 34
Outcomes	Episodes and frequency of nausea and vomiting day 1; withdrawal due to adverse effects; withdrawals due to death; participant preference due to adverse effects; incidence of feeling high, euphoria, postural dizziness, dysphoria
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported

Ahmedzai 1983 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	8/34 (24%) participants withdrew
Selective reporting (reporting bias)	Low risk	Data reported for primary outcome
Other bias	Unclear risk	Approximately 10 days' washout period. Unclear if paired analysis was performed. Unclear if groups were balanced at baseline
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double dummy tablet"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding assumed as study reported as "double-blind" and dummy tablet used

Chang 1979a

Study characteristics	
Methods	Randomised, double-blind, 3-period cross-over, placebo-controlled trial
Participants	15 people (10/15 (67%) men/5/15 (33%) women) aged 15-49 years (median = 24 years). 4/15 (27%) participants were cannabis naive Tumour type: osteogenic sarcoma Chemotherapy regimens: methotrexate 250 mg/kg with leucovorin calcium rescue every 3 weeks for 18 months Chemotherapy emetogenicity: low
Interventions	Dronabinol 10 mg/m^2 orally every 3 hours for total 5 doses (Phase I), n = 15. If participant vomited during this period oral dose was replaced with THC cigarette for remaining doses Placebo, n = 15
Outcomes	Episodes of nausea and vomiting on day of therapy; frequency and severity of nausea; episodes of sedation, euphoria, dizziness, depression, paranoia
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Order of THC-placebo administration was randomized into three paired trials"

Chang 1979a *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	58/77 (75%) participants received THC, 39/53 (74%) participants received placebo
Selective reporting (reporting bias)	Low risk	Data reported for primary outcome
Other bias	Low risk	Groups balanced at baseline
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Identical gelatin capsules with sesame oil". "Identical cigarettes, the odour and taste of a lit placebo cigarette were identical to those of cannabis cigarette"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding assumed as study reported as "double-blind"

Chang 1981

Study characteristics	
Methods	Randomised, double-blind, 3-period cross-over trial
Participants	8 people (6/8 (75%) men/2/8 (25%) women) aged 17-58 years (median = 41 years), 7/8 (88%) participants were cannabis naive Tumour types: resected soft tissue sarcoma Chemotherapy regimen: adjuvant doxorubicin and cyclophosphamide every 4 weeks until a total cumulative doxorubicin dose of 500-550 mg/m^2 Doxorubicin (70 mg/m^2)and cyclophosphamide (700 mg/m^2) were given at constant doses for all participants Chemotherapy emetogenicity: high
Interventions	Dronabinol 10 mg/m^2 orally every 3 hours for total 5 doses, if vomited then participant given marijuana cigarettes 900 mg, containing THC 1.93% (approximately 17.4 mg), n = 8 Placebo, n = 8
Outcomes	Episodes of nausea and vomiting on day of therapy
Notes	
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Order of THC-placebo administration was randomized into paired trials"

Chang 1981 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	17/27 (63%) participants received THC, 16/27 (59%) participants received placebo
Selective reporting (reporting bias)	Low risk	Data reported for primary outcome
Other bias	Unclear risk	Assumed washout period sufficient. Paired analysis was performed. Unclear if groups balanced at baseline
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Identical gelatin capsules with sesame oil. Identical cigarettes, the odour and taste of a lit placebo cigarette were identical to those of cannabis cigarette"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding assumed as study reported as "double-blind". "Neither patients nor nursing staff was [sic] informed which drug was administered"

Crawford 1986

Study characteristics	
Methods	Randomised, 2-period cross-over study
Participants	32 people Tumour type: adenocarcinoma of the ovary or germ cell tumours. Chemotherapy regimen: cisplatin 100 mg/m^2, cyclophosphamide and doxorubicin (for people with adenocarcinoma of ovary), cisplatin 120 mg/m^2, methotrexate and vincristine (for people with germ cell tumours). No information on doses reported Chemotherapy emetogenicity: high
Interventions	Nabilone 1 mg orally every 8 hours, n = 32 Metoclopramide 1 mg/kg IV every 3 hours, n = 32
Outcomes	Episodes of vomiting during 24 hours, nausea, dizziness, euphoria and drowsiness
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

Crawford 1986 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	7/32 (22%) participants received the 4 planned treatment and only 37/64 (58%) participants received 1 or 2 treatment episodes of nabilone and 39/64 (61%) participants received 1 or 2 treatment episodes of metochlopramide
Selective reporting (reporting bias)	Low risk	Data reported for primary outcome
Other bias	High risk	Assumed washout period sufficient. Paired analysis was not performed. Unclear if groups were balanced at baseline
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reported as "double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding assumed as study reported as "double-blind"

Einhorn 1981

Study characteristics	
Methods	Randomised, prospective, double-blind, 2-period cross-over study
Participants	100 people aged 15-74 years, mean = 28 years Tumour type; sarcoma (1 person), Hodgkin's disease (2 people), lymphoma (4 people), bladder carcinoma (3 people), testicular carcinoma (70 people) Chemotherapy regimens: doxorubicin hydrochloride and cyclophosphamide (1 person), nitrogen mustard, vincristine, prednisone and procarbazine (2 people), cyclophosphamide, doxorubicin hydrochloride, vincristine and prednisone (4 people), cisplatin, doxorubicin hydrochloride and 5-fluorouracil (3 people), cisplatin, vinblastine and bleomycin (45 people), cisplatin, vinblastine, bleomycin and doxorubicin hydrochloride (25 people). No information on doses reported Chemotherapy emetogenicity: high
Interventions	Nabilone 2 mg, orally every 6 hours, n = 100 Prochlorperazine 10 mg, orally every 6 hours, n = 100
Outcomes	Episodes of nausea and vomiting during 24 hours of therapy; frequency of vomiting; withdrawal due to adverse effects; withdrawal due to early death and change of chemotherapy; episodes of 'feeling high', depression, hallucination, paranoia, hypotension
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported

Einhorn 1981 *(Continued)*

Allocation concealment (selection bias)	Low risk	"Identical capsules used"
Incomplete outcome data (attrition bias) All outcomes	Low risk	80/100 (80%) participants received nabilone, 80/100 (80%) participants received prochlorperazine
Selective reporting (reporting bias)	Low risk	Data reported for primary outcome
Other bias	Unclear risk	Assumed washout period sufficient. Unclear if paired analysis was performed. Unclear if groups were balanced at baseline
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reported as "double-blind", identical capsules used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding assumed as study reported as "double-blind", identical capsules used

Frytak 1979

Study characteristics	
Methods	Randomised, double-blind, parallel group trial
Participants	116 people, median age = 61 years. All cannabis naive. THC n = 38 (22 men/16 women), prochlorperazine n = 41 (21 men/20 women), placebo n = 37 (27 men/10 women) Tumour types: colorectal cancer (28 people), gastric cancer (7 people), liver cancer (2 people), miscellaneous (1 person), gastric surgery (5 people), hepatic metastasis (20 people) Chemotherapy regimens: 5-fluorouracil and semustine or 5-fluorouracil and semustine plus triazinate, razoxane, doxorubicin or vincristine. 5-fluorouracil 300-350 mg/m^2 IV for 5 days. Semustine 110-175 mg/m^2 day 1 only Chemotherapy emetogenicity: moderate
Interventions	Dronabinol 15 mg on day 1, 2 hours prior to chemotherapy, then 2 and 8 hours after initiation of chemotherapy. Then 3 times daily x 3 days orally, n = 38 Prochlorperazine 10 mg on day 1, 2 hours prior to chemotherapy, then 2 and 8 hours after initiation of chemotherapy. Then 3 times daily x 3 days orally, n = 41 Placebo n = 37
Outcomes	Episodes of nausea and vomiting during 24 hours, sedation, feeling high; withdrawal due to intolerable central nervous system toxicity or excessive vomiting
Notes	
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

Frytak 1979 *(Continued)*

Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Low risk	Drugs dispensed in individual packets identified by code number
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1/117 (0.8%) participants withdrew. After day 1, 10/38 (26%) participants withdrew in THC group, 5/41 (12%) participants withdrew in prochlorperazine group, 3/37 (8%) participants withdrew in placebo group
Selective reporting (reporting bias)	Low risk	Data reported for primary outcome
Other bias	Low risk	Groups were balanced at baseline
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Identical opaque gelatin capsules"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding assumed as study reported as "double-blind"

George 1983

Study characteristics	
Methods	Randomized double-blind 2-period cross-over study
Participants	20 people, mean age 54.1 years Tumour type: advanced gynaecological cancer who vomited during the first chemotherapy treatment Chemotherapy regimen: cis-platinum (50 mg/m^2) with hydration. Vomited during the first treatment. Doxorubicin (40 mg/m^2), cyclophosphamide (600 mg/m^2) and cis-platinum (11 people); cyclophosphamide 600 mg and cis-platinum (3 people); cis-platinum (6 people) Chemotherapy emetogenicity: high
Interventions	Nabilone 1 mg 24 hours before chemotherapy then 1 mg 3 times daily orally Chlorpromazine 12.5 mg IM before chemotherapy with additional dose if requested
Outcomes	Number of vomiting episodes in 24 hours, participant preference, adverse events
Notes	Translated from French

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomly allocated by lottery

George 1983 *(Continued)*

Allocation concealment (selection bias)	Low risk	Identical placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	All people were included in the analysis
Selective reporting (reporting bias)	Low risk	Data reported for primary outcome
Other bias	Low risk	There was no evident difference caused by the order of administration of the drugs
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo, double-dummy tablets used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding assumed as study reported as double-blind

Gralla 1984

Study characteristics	
Methods	Randomised, double-blinded parallel group trial
Participants	31 people (23 men/ 5 women). THC n = 15 (13 men/2 women), aged 39-72 years (median = 58 years); metoclopramide n = 16 (11 men/5 women), aged 45-70 years (median = 58 years) Tumour types: bronchogenic carcinoma (12 people), oesophageal carcinoma (2 people), head and neck carcinoma head and neck carcinoma (1 person) Chemotherapy regimens: all receiving first course of cisplatin 120 mg/m^2 IV Chemotherapy emetogenicity: high
Interventions	Dronabinol 10 mg/m^2 1.5 hours prior to chemotherapy, then at 1.5, 4.5, 7.5 and 10.5 hours after chemotherapy orally, n = 15 Metoclopramide, 2 mg/kg 30 minutes prior to chemotherapy, then 1.5, 3.5, 5.5 and 8.5 hours after chemotherapy IV, n = 16
Outcomes	Episodes of nausea and vomiting during 24 hours, sedation, dizziness, orthostatic hypotension, feeling high
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Paired design in which one patient in every pair was randomly assigned to each treatment"

Gralla 1984 *(Continued)*

Allocation concealment (selection bias)	Low risk	"Identical vials and capsules used"
Incomplete outcome data (attrition bias) All outcomes	Low risk	15/15 (100%) participants received THC, 15/16 (94%) participants received metoclopramide
Selective reporting (reporting bias)	Low risk	Data reported for primary outcome
Other bias	Unclear risk	Unclear if groups were balanced at baseline
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Identical vials and capsules used"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding assumed as study reported as "double-blind"

Herman 1979

Study characteristics	
Methods	Randomised, double-blinded, 2-period cross-over study
Participants	152 people (126 men/26 women) aged 15-74 years (median = 33 years) Tumour type: testicular carcinoma (70 people), non-Hodgkin's disease (12 people), Hodgkin's disease (11 people) Chemotherapy regimen: cisplatin daily for 5 days, vinblastine and bleomycin (70 people); cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP 12 people); nitrogen mustard (mechlorethamine?), vincristine, procarbazine and prednisone (MOPP 11 people); other regimens included dactinomycin, dacarbazine, 5-fluorouracil, melphalan and nitrosourea compounds. No information on doses reported Chemotherapy emetogenicity: high
Interventions	Nabilone 2 mg, every 8 hours orally, n = 152 Prochlorperazine 10 mg, every 8 hours orally, n = 152
Outcomes	Episodes of nausea and vomiting daily during chemotherapy; withdrawal due to adverse effects; episodes of somnolence, dizziness, depression, euphoria, preference
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported

Herman 1979 *(Continued)*

Allocation concealment (selection bias)	Low risk	"Drugs packaged in identical containers marked only with a number code"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	113/152 (74%) participants received nabilone, 113/152 (74%) participants received prochlorperazine
Selective reporting (reporting bias)	Low risk	Data reported for primary outcome
Other bias	Unclear risk	Assumed washout period sufficient. Unclear if paired analysis was performed. Unclear if groups were balanced at baseline
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Identical containers marked only with a number code"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding assumed as study reported as "double-blind" and "identical containers marked only with a number code"

Johansson 1982

Study characteristics	
Methods	Randomised, double-blind, 2-period cross-over study
Participants	27 people aged 18-70 years Tumour types: cervical cancer (2 people), cancer of fallopian tubes (2 people), ovarian cancer (13 people), testicular cancer (2 people), head and neck cancer (1 person), bronchus cancer (1 person), histiocytoma (1 person), fibrosarcoma (1 person), oligodendroma (1 person), lymphoma (2 people) Chemotherapy regimens: doxorubicin 40 mg/m^2, cyclophosphamide 500 mg/m^2 and cisplatinum 50 mg/m^2 (11 people) in combination with vinblastine, vincristine or ftorafur (tegfur-uracil). Cyclophosphamide 750-1000 mg/m^2 and cisplatinum 75 mg/m^2 when given as sole agents Chemotherapy emetogenicity: high
Interventions	Nabilone 2 mg twice daily x 4 days orally, n = 27 Prochlorperazine 10 mg twice daily x 4 days orally, n = 27
Outcomes	Episodes of nausea and vomiting assessed daily and reported for follow-up at end of anti-emetic therapy; withdrawal due to lack of efficacy; withdrawal due to hypotension, vertigo and headache; participant preference; episodes of drowsiness, dizziness, depression, hypotension
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported

Johansson 1982 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	18/27 (67%) participants received nabilone, 18/27 (67%) participants received prochlorperazine
Selective reporting (reporting bias)	Low risk	Data reported for primary outcome
Other bias	Unclear risk	Assumed washout period sufficient. Unclear if paired analysis was performed. Unclear if groups were balanced at baseline
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reported as "double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding assumed as study reported as "double-blind"

Jones 1982

Study characteristics	
Methods	Prospective, randomised, double-blind, 2-period cross-over trial
Participants	54 people; aged 20-37 years (n = 9), 38-57 years (n = 23), > 58 years (n = 22) Tumour types: breast cancer (15 people), lymphoma (12 people), ovarian cancer (8 people), lung cancer (7 people), melanoma (3 people), testicular cancer (2 people), miscellaneous (7 people) Chemotherapy regimens: adriamycin-based regimens (25 people), cisplatinum-based regimens (14 people), other combinations (12 people). No information on doses reported Chemotherapy emetogenicity: high
Interventions	Nabilone 2 mg every 12 hours orally, n = 54 Placebo, n = 54
Outcomes	Episodes of nausea and vomiting unclear time period of results unclear; withdrawal due to severe nausea and vomiting; episodes of drowsiness, euphoria, hallucination, hypotension
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

Jones 1982 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	24/54 (44%) participants received nabilone, 24/54 (44%) participants received placebo
Selective reporting (reporting bias)	Low risk	Data reported for primary outcome
Other bias	Unclear risk	Assumed washout period sufficient. Unclear if paired analysis was performed. Unclear if groups were balanced at baseline
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reported as "double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding assumed as study reported as "double-blind"

Kleinman 1983

Study characteristics	
Methods	Randomised, double-blind, 4-period cross-over study
Participants	16 people (9 men/7 women) aged 18-53 years (median = 38 years) Tumour types: not reported Chemotherapy regimens: "Cancer chemotherapy known to cause acute gastrointestinal toxicity" Chemotherapy emetogenicity: unable to classify
Interventions	Prochlorperazine 10 mg + dronabinol 15 mg x 2 courses orally, n = 16 Prochlorperazine + placebo orally, n = 16
Outcomes	Episodes of nausea and vomiting 24 hours after chemotherapy, euphoria, sedation
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	28/32 (87.5%) participants received prochlorperazine + THC, 24/32 (75%) participants received prochlorperazine + placebo (overall 52/64 (81%) participants received either of the 2 courses)

Kleinman 1983 *(Continued)*

Selective reporting (reporting bias)	Low risk	Data reported for primary outcome
Other bias	Unclear risk	Assumed washout period sufficient. Unclear if paired analysis was performed. Unclear if groups were balanced at baseline
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reported as "double-blind" and "identical capsules used"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding assumed as study reported as "double-blind and identical capsules used"

Kluin-Neleman 1979

Study characteristics	
Methods	Randomised, double-blind, 2-period cross-over study
Participants	11 people (10 men/1 woman) aged 21-53 years Tumour types: Hodgkin's or non-Hodgkin's lymphoma Chemotherapy regimens: mitoxine 6 mg/m^2 (maximum 10 mg), vincristine 1.4 mg/m^2 (maximum 2 mg) IV on days 1 and 8. Procarbazine 100 mg/m^2 and prednisone 40 mg/m^2 oral days 1-14 for 6 cycles with intervals of 2 weeks Chemotherapy emetogenicity: high
Interventions	Dronabinol 10 mg/m^2 orally, n = 11 Placebo, n = 11
Outcomes	Episodes of nausea and vomiting at end of day of therapy, feeling high, dizziness, hallucinations
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	17 participants received THC, 11 participants received placebo
Selective reporting (reporting bias)	Low risk	Data reported for primary outcome

Kluin-Neleman 1979 *(Continued)*

Other bias	Unclear risk	Washout period 2 weeks. Unclear if paired analysis was performed. Unclear if groups were balanced at baseline
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Identical gelatin capsules were used"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding assumed as study reported as "double-blind" and "identical gelatin capsules used"

Lane 1991

Study characteristics	
Methods	Randomised, double-blind, parallel group study
Participants	Dronabinol n = 21 (10 men/11 women) aged 20-68 years (median = 47 years), prochlorperazine n = 21 (10 men/11 women) aged 22-64 years (median = 49 years), dronabinol plus prochlorperazine n = 20 (9 men/11 women) aged 25-65 years (median = 55.5 years). Total n = 62 (29 men/33 women) aged 20-68 years (median = 52 years) All cannabis naive Tumour types: breast cancer (24 people), colon cancer (3 people), lung cancer (8 people), lymphoma (17 people), miscellaneous (10 people) Chemotherapy regimens: cyclophosphamide and doxorubicin (26 people), 5-fluorouracil (14 people), vincristine (13 people), etoposide (10 people), No information on doses reported. 48/62 participants received chemotherapy with high emetogenic potential Chemotherapy emetogenicity: unable to classify
Interventions	Dronabinol 10 mg every 6 hours orally, n = 21 Prochlorperazine 10 mg every 6 hours orally, n = 21 Dronabinol 10 mg + prochlorperazine 10 mg orally, n = 20
Outcomes	Episodes of nausea and vomiting during chemotherapy treatment; withdrawal due to adverse effects; episodes of somnolence, dizziness, paranoid reaction, depression
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

Lane 1991 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	17/21 (81%) participants received dronabinol, 20/21 (95%) participants received prochlorperazine, 17/20 (85%) participants received dronabinol + prochlorperazine
Selective reporting (reporting bias)	Low risk	Data reported for primary outcome
Other bias	Low risk	Groups were balanced at baseline
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reported as "double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding assumed as study reported as "double-blind"

Levitt 1982

Study characteristics	
Methods	Randomised, double-blind, 2-period cross-over study
Participants	58 people aged 17-78 years Tumour types: lung cancer (21 people), ovarian cancer (11 people), breast cancer (10 people), other cancers (16 people) Chemotherapy regimens: combinations of doxorubicin, bleomycin, cisplatinum, cyclophosphamide, dactinomycin, melphalan, mitomycin C, methotrexate, vincristine, etoposide, 5-fluorouracil. No information on doses reported Chemotherapy emetogenicity: unable to classify
Interventions	Nabilone, n = 58 Placebo, n = 58
Outcomes	Episodes of nausea and vomiting time of assessment unclear, frequency and severity of nausea, withdrawal due to lack of efficacy, adverse effects, episodes of drowsiness
Notes	Dose and duration not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	High risk	36/58 (62%) participants received nabilone, 36/58 (62%) participants received placebo

Levitt 1982 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	Data reported for primary outcome
Other bias	Unclear risk	Assumed washout period sufficient. Unclear if paired analysis was performed. Unclear if groups were balanced at baseline
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reported as "double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding assumed as study reported as "double-blind"

McCabe 1988

Study characteristics	
Methods	Randomised, 2-period cross-over trial
Participants	36 (9 men/27 women) aged 18-69 years (median = 48 years) Tumour types: breast cancer (11 people), haematological malignancies (9 people), sarcomas (6 people), gastrointestinal malignancies (5 people), melanoma (2 people), ovarian cancer (2 people), testicular cancer (1 person) Chemotherapy regimens: doxorubicin (13 people), cyclophosphamide, methotrexate and 5-fluorouracil (7 people), nitrogen mustard, vincristine, procarbazine and prednisone (7 people), platinum combinations (4 people), DTIC (2 people), 5-fluorouracil combinations (2 people), 5-azacytadine (1 person). No information on doses reported Chemotherapy emetogenicity: moderate to high
Interventions	Dronabinol 15 mg/m^2 1 hour prior to chemotherapy, then every 4 hours for 24 hours after chemotherapy orally, n = 36 Prochlorperazine 10 mg 1 hour prior to chemotherapy, then every 4 hours for 24 hours after chemotherapy orally, n = 36
Outcomes	Episodes of nausea and vomiting during 24 hours, feeling high, dizziness, dysphoria, hallucination, paranoia
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

McCabe 1988 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All people were analysed
Selective reporting (reporting bias)	Low risk	Data reported for primary outcome
Other bias	Unclear risk	Assumed washout period sufficient. Unclear if paired analysis was performed. Unclear if groups were balanced at baseline
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Blinding not achieved"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Study not blinded

Niiranen 1985

Study characteristics	
Methods	Randomised, double-blind, 2-period cross-over study
Participants	32 people (20 men/4 women) aged 48-78 years, mean = 61 years Tumour type: lung cancer Chemotherapy regimen: cyclophosphamide 1.2 g/m^2 day 1, etoposide 150 mg/m^2 IV day 1, 250 mg/m^2 orally day 3, and vincristine 1.3 mg/m^2 days 1 and 8 (5 people); cyclophosphamide 400 mg/m^2, adriamycin 40 mg/m^2, cisplatinum 40 mg/m^2 every 28 days (8 people); cisplatinum 90 mg/m^2 day 1 and vindesine 3 mg/m^2 5 x weekly then twice monthly every 28 days (2 people); cisplatinum 90 mg/m^2 day 1 and etoposide 50 mg/m^2 days 1-5 every 28 days (9 people); cisplatinum 60 mg/m^2 day 1 and etoposide 150 mg/m^2 IV day 1 and 200 mg/m^2 orally day 3 every 28 days (1 person) Chemotherapy emetogenicity: high
Interventions	Nabilone 1 mg orally night before chemotherapy, 1 hour before chemotherapy and every 12 hours up to 24 hours as required orally, n = 32 Prochlorperazine 7.5 mg orally night before chemotherapy, 1 hour before chemotherapy and every 12 hours up to 24 hours as required orally, n = 32
Outcomes	Episodes, frequency and severity of nausea and vomiting at 24 hours; withdrawal due to adverse effects; participant preference; episodes of drowsiness, hallucination, hypotension
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported

Niiranen 1985 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	24/32 (75%) participants received nabilone, 24/32 (75%) participants received prochlorperazine
Selective reporting (reporting bias)	Low risk	Data reported for primary outcome
Other bias	Unclear risk	Assumed washout period sufficient. Unclear if paired analysis was performed. Unclear if groups were balanced at baseline
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Identical appearing capsules used"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding assumed as study reported as "double-blind" and "identical appearing capsules used"

Orr 1981

Study characteristics	
Methods	Randomised double-blind 2-period cross-over
Participants	79 people (28 men/51 women) aged 22-71 years, mean = 46 years Tumour type: variety of neoplasms Chemotherapy regimen: doxorubicin, cyclophosphamide, 5-fluorouracil (with methotrexate), nitrogen mustard, imidazole carboxamide, nitrosaurea and cytosine arabinoside. No information on doses reported Chemotherapy emetogenicity: high (5-fluorouracil + methotrexate low risk but only 3/55 people)
Interventions	Dronabinol 7 mg/m^2 every 4 hours x 4 doses orally, n = 79 Prochlorperazine 7 mg every 4 hours x 4 doses orally, n = 79
Outcomes	Nausea 24 hours post treatment and adverse events
Notes	
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

Orr 1981 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	55/79 (69%) participants in both groups analysed
Selective reporting (reporting bias)	Low risk	Data reported for primary outcome
Other bias	Unclear risk	Assumed washout period sufficient. Unclear if paired analysis was performed. Unclear if groups were balanced at baseline
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Identical capsule used"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	States "double-blind"

Pomeroy 1986

Study characteristics	
Methods	Randomised, double-blind parallel group trial
Participants	38 people (23 men/15 women) aged 21-66 years (median = 42 years) Tumour types: ovarian cancer (11 people), testicular cancer (9 people), bronchus carcinoma (8 people), non-Hodgkin's lymphoma (3 people), Hodgkin's disease (2 people), sarcoma (2 people), breast cancer (1 person), melanoma (1 person), nephroblastoma (1 person) Chemotherapy regimens: cisplatin (10 people); cisplatin and treosulphan (7 people); cisplatin, vincristine, methotrexate and bleomycin (4 people), cisplatin, actinomycin D and etoposide (2 people); cisplatin, vinblastine and bleomycin (2 people); cisplatin and vindesine (1 person); adriamycin, bleomycin, vincristine and DTIC (2 people); adriamycin, vincristine and cyclophosphamide (2 people); adriamycin, vincristine, cyclophosphamide and prednisone (2 people); adriamycin, vincristine and etoposide (1 person); ifosfamide (2 people); vincristine, methotrexate and 5-fluorouracil (1 person); vindesine, DTIC and 1-(2-chloroethyl)3-cyclohexyl-1-nitrosurea (CCNU) (1 person). No information on doses reported Chemotherapy emetogenicity: high
Interventions	Nabilone 1 mg 3 times daily x 2 cycles orally, n = 19 Domperidone 20 mg 3 times daily x 2 cycles orally, n = 19
Outcomes	Episodes of vomiting daily, withdrawal due to adverse effects, lack of efficacy, episodes of drowsiness, dizziness, hypotension, euphoria
Notes	2 cycles of chemotherapy evaluated
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

Pomeroy 1986 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	32/38 (84%) participants received nabilone, 33/38 (87%) participants received domperidone
Selective reporting (reporting bias)	Low risk	Data reported for primary outcome
Other bias	Unclear risk	Unclear if groups were balanced at baseline
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Identical capsules used"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding assumed as study reported as "double-blind" and "identical capsules used"

Sallan 1975a

Study characteristics	
Methods	Randomised, double-blind, 2-period cross-over study
Participants	22 people (10 men/12 women) aged 18-76 years (median = 29.5 years) Tumour types: variety of neoplasms Chemotherapy regimen: adriamycin, 5-azacytidine, nitrogen mustard, imidazole carboxamide, procarbazine, high-dose cyclophosphamide or high-dose methotrexate or combinations. No information on doses reported Chemotherapy emetogenicity: unable to classify
Interventions	Dronabinol 15 mg, later changed to 10 mg/m^2, every 4 hours x 3 doses orally, n = 33 Placebo, n = 33
Outcomes	Episodes of nausea and vomiting on day after treatment, withdrawal due to adverse effects, episodes of feeling high, somnolence, paranoia, hallucination
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported

Sallan 1975a *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	20/33 (61%) participants received THC, 22/33 (67%) participants received placebo
Selective reporting (reporting bias)	Low risk	Data reported for primary outcome
Other bias	Unclear risk	Assumed washout period sufficient. Unclear if paired analysis was performed. Unclear if groups were balanced at baseline
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Identical gelatin capsules used"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding assumed as study reported as "double-blind" and "identical gelatin capsules used"

Steele 1980

Study characteristics	
Methods	Randomised, double-blind, 2-period cross-over study
Participants	55 people aged 19-65 years Tumour types: not reported Chemotherapy regimen: high-dose *cis*-dichlorodiammineplatinum 120 mg/m^2 ± vindesine 3 mg/m^2 every 4-6 weeks; low-dose *cis*-dichlorodiammineplatinum 60 mg/m^2 ± vindesine 3 mg/m^2, every 4-6 weeks; low-dose *cis*-dichlorodiammineplatinum 60 mg/m^2 ± adriamycin 45 mg/m^2 every 3-4 weeks; mechlorethamine 6 mg/m^2 + vincristine 1.4 mg/m^2 + procarbazine orally x 14 days 100 mg/m^2 every 4 weeks days 1-8; streptozotocin 500 mg/m^2 every week; actinomycin D 1 mg/m^2 ± vinblastine 4 mg/m$_2$ + chlorambucil orally x 14 days 4 mg/m^2 or 0.15 mg/kg every 3-4 weeks; DTIC 800 mg/m^2 ± cyclophosphamide orally x 14 days 100 mg/m^2 every 4 weeks. All drugs IV unless otherwise stated Chemotherapy emetogenicity: high
Interventions	Nabilone 2 mg every 12 hours x 3-5 doses orally, n = 55 Prochlorperazine 10 mg every 12 hours x 3-5 doses orally, n = 55
Outcomes	Episodes of nausea and vomiting during 24 hours; withdrawal due to adverse effects; lack of efficacy, episodes of somnolence, dizziness, feeling high, postural hypotension, dysphoria, hallucination
Notes	
Risk of bias	
Bias	**Authors' judgement** / **Support for judgement**

Steele 1980 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	37/55 (67%) participants received nabilone, 37/55 (67%) participants received prochlorperazine
Selective reporting (reporting bias)	Low risk	Data reported for primary outcome
Other bias	Unclear risk	Assumed washout period sufficient. Unclear if paired analysis was performed. Unclear if groups were balanced at baseline
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reported as "double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding assumed as study reported as "double-blind"

Ungerleider 1982

Study characteristics	
Methods	Randomised, double-blind, 2-period cross-over study
Participants	214 people (107 men/107 women) aged 18-82 years (median = 47 years) Tumour types: "wide variety of neoplasms" Chemotherapy regimens: antibiotics (70 people), nitrosoureas (21 people), alkylating agents (119 people), antimetabolites (82 people), vinca-alkaloids (60 people), hormones (13 people), miscellaneous (33 people) and combinations. Rated as high for 66% of people, moderate for 27% of people or low for 7% of people emetic potential Chemotherapy emetogenicity: unable to classify - unknown combinations
Interventions	Dronabinol 7.5 mg for < 1.4/m^2, 10 mg for 1.4-1.8 m^2 or 12.5 mg for > 1.8 m^2 orally, n = 214 Prochlorperazine 10 mg 1 hour prior to chemotherapy, then every 4 hours x 4 doses per day x all chemotherapy days orally, n = 214
Outcomes	Episodes of nausea and vomiting during 24 hours; withdrawal due to adverse effects; episodes of sedation, depression, feeling high
Notes	
Risk of bias	

Bias	**Authors' judgement**	**Support for judgement**

Ungerleider 1982 *(Continued)*

Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	172/214 (80%) participants received THC, 181/214 (85%) received prochlorperazine
Selective reporting (reporting bias)	Low risk	Data reported for primary outcome
Other bias	Low risk	Washout period 1-3 weeks. Paired analysis was performed. Groups were balanced at baseline
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reported as "double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding assumed as study reported as "double-blind"

Wada 1982

Study characteristics	
Methods	Randomised, double-blind, 2-period cross-over trial
Participants	114 people (47 men/67 women) aged 18-81 years (median = 57 years) Tumour types: lung cancer (23 people), breast cancer (18 people), ovarian cancer (16 people), lymphoma (including Hodgkin's) (12 people), colonic cancer (7 people), prostatic cancer (5 people), adenocarcinoma (5 people), bladder cancer (3 people), melanoma (3 people), pancreatic cancer (3 people), oesophageal cancer (3 people), stomach cancer (3 people), sarcoma (2 people), testicular cancer (2 people), others (9 people) Chemotherapy regimens: adriamycin (66 people), carmustine (2 people), bleomycin (7 people), cisplatinum (40 people), cytoxan (46 people), dactinomycin (1 person), DTIC (7 people), 5-fluorouracil (29 people), mustine (4 people), MCCNU (6 people), melphalan (1 person), methotrexate (14 people), mitomycin (17 person), procarbazine (7 people), streptozotocin (1 person), tamoxifen (1 person), vinblastine (5 person), vincristine (16 people), VP-16 (1 person)
Interventions	Nabilone 2 mg night prior and 1-3 hours before chemotherapy and then every 12 hours orally, n = 114 Placebo, n = 114
Outcomes	Episodes of nausea and vomiting during 24 hours; withdrawal due to adverse effects; lack of efficacy; progressive disease; death; participant preference; episodes of dizziness, drowsiness, euphoria, dysphoria, hypotension, hallucination
Notes	
Risk of bias	

Wada 1982 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	84/114 (74%) participants completed both the courses, 92/114 (81%) participants were evaluable for efficacy
Selective reporting (reporting bias)	Low risk	Data reported for primary outcome
Other bias	Unclear risk	Assumed washout period sufficient. Unclear if paired analysis was performed. Unclear if groups were balanced at baseline
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reported as "double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding assumed as study reported as "double-blind"

DTIC: 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide; HN2: ; IM: intramuscular; IV: intravenous; MCCNU: methyl lomustine; n: number; THC: delta-9-tetrahydrocannabinol.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aapro 1981	Not a primary study - editorial
Allan 1987	Not a primary study - review
Anderson 1981	Not a primary study - review
Artim 1983	Participants received chemotherapy and radiotherapy
Bateman 1982	Not a primary study - letter
Ben 2006	Not a primary study - review
Biedrzycki 2007	Not a primary study - conference presentation
Broder 1982	Lacks data - abstract of preliminary findings, participant age and characteristics not reported
Carey 1983	Not a primary study - review
Chan 1987	Randomised controlled trial involving children
Chang 1979b	Duplicate of Chang 1979a

Study	Reason for exclusion
Citron 1985	Cross route comparison of intramuscular versus oral cannabinoid
Cocchetto 1981	Not a primary study - review
Colls 1980a	Letter - lacks detail on study methods, participant groups, control intervention and results
Colls 1980b	Did not report data for primary outcome, measurement of nausea and vomiting using a non-validated measure. No details on participants reported
Cone 1982	Not randomised - single-arm study
Costa 2007	Not a primary study - review
Cotter 2009	Not a primary study - review
Cronin 1981	Not randomised - single-arm cross-over study
Croxford 2003	Not a primary study - review
Cunningham 1985	Control group was cannabinoid monotherapy and not conventional anti-emetic
Cunningham 1988	Sub-therapeutic dose of prochlorperazine used
Dalzell 1986	Randomised controlled trial involving children
Darmani 2010	Not a primary study - review
Davis 2007	Not a primary study - review
Davis 2008	Not a primary study - review
Devine 1987	Not randomised - single-arm cross-over study
Dodds 1985	Not a primary study - review from thesis
Dow 1984	Not a primary study - letter
Duran 2010	Not an approved formulation of delta-9-tetrahydrocannabinol
Ekert 1979	Randomised controlled trial involved children not adults
Ettinger 2007	Not a primary study - clinical practice guidelines
Feyer 2011	Not a primary study - review
Fiore 1984	Not a primary study - review
Fox 1979	Not a primary study - letter
Galal 2009	Not a primary study - review
Gallego 1984	Not a primary study - review
Gerhartz 1983	Not randomised - single-arm study

Study	Reason for exclusion
Gerra 2010	Not a primary study - review
Goodman 1997	Not a primary study - review
Gorter 1999	Not randomised
Grunberg 1989	Not a primary study - review
Guzman 2003	Not a primary study - review
Heim 1984	Evaluates a non-approved formulation of delta-9-tetrahydrocannabinol
Herrstedt 1998	Not a primary study - review
Herrstedt 2008	Not a primary study - review
Higi 1982	Pilot study
Hiller 1984	Not a primary study - review
Hutcheon 1983	Evaluates a non-approved formulation of delta-9-tetrahydrocannabinol
Jordan 2007	Not a primary study - review
Jordan 2011	Not a primary study - review guideline
Kearsley 1985	Not a primary study - review
Kenny 1982	Non-randomised single-arm study
Kluin-Nelemans 1981a	Duplicate to included
Kluin-Nelemans 1981b	Not randomised. Abstract with scant details of methods reported
Krasnow 1991	Not a primary study - review
Kreutz 2007	Not a primary study - review
Lane 1989	Duplicate Lane 1991
Lane 1990	Duplicate data. Single-centre study included in Lane 1991
Laszlo 1982	Not a primary study - review
Levitt 1981	Evaluates ophthalmological outcomes. Nausea and vomiting not evaluated
Levitt 1984	Cross-route comparison of oral versus smoked cannabis
Lohr 2008	Not a primary study - review
Long 1982	Preliminary data presented
Machado 2008	Not a primary study - systematic review and meta-analysis
Mechoulam 1978	Not a primary study - drug development

Study	Reason for exclusion
Mechoulam 1999	Not a primary study - review
Mechoulam 2001	Not a primary study - review
Meiri 2007	Not acute nausea and vomiting but evaluating delayed nausea and vomiting
Murakami 1986	Not a primary study - review
Musty 2001	Not a primary study - review
Nagy 1978	Scanty data in an abstract - no extractable data
Navari 2009a	Not a primary study - review
Navari 2009b	Not a primary study - review
Niederle 1986	Evaluates a non-eligible anti-emetic (alizapride)
Niiranen 1987	Control group was cannabinoid monotherapy and not conventional anti-emetic
Nyman 1982	Not a primary study - review
Orr 1980	Duplicate of Orr 1981
Penta 1981	Not a primary study - review
Perwitasari 2011	Not a primary study - review
Phillips 2010	Not a primary study - review
Plasse 1991	Not a primary study - expert opinion
Porta 2002	Not a primary study - review
Poster 1981	Not a primary study - review
Reynolds 2002	Not a primary study - letter
Sallan 1975b	Duplicate study of Sallan 1975a
Sallan 1980	Participants aged 9-70 years; number or percent of children included not reported
Schuette 1985	Duplicate study reported in Niederle 1986
Sheidler 1984	Evaluates a non-approved formulation of delta-9-tetrahydrocannabinol
Slatkin 2007	Not a primary study - review
Smith 2007	Not a primary study - review
Stambaugh 1982	Cross-route comparison of intramuscular versus oral cannabinoid
Stambaugh 1984	Evaluates a non-approved formulation of delta-9-tetrahydrocannabinol
Steele 1979	Duplicate study reported in Steele 1980

Study	Reason for exclusion
Stewart 1990	Not a primary study - review
Stuart 1982	Not randomised - single-arm study
Stuart-Harris 1983	Not randomised
Sweet 1980	Not a primary study - letter
Toth 2008	Not a primary study - review
Tramer 2001	Not a primary study - review
Ungerleider 1985	Sub-group analysis of study reported in Ungerleider 1982
Venner 1986	Preliminary results - ongoing study
Vincent 1983	Not a primary study - review
Voth 1997	Not a primary study - review
Wang 2008	Not a primary study - review
Ward 1985	Not a primary study - drug evaluation
Ware 2008	Not a primary study - review
Zuardi 2008	Not a primary study - review

Characteristics of studies awaiting classification *[ordered by study ID]*

Citron 1983

Methods	Double-blind, randomised, crossover study
Participants	People reciveing chemotherapy
Interventions	IM levonantradol, a synthetic cannabinoid, given at a dose of 1 mg every 4 hours versus oral delta-9-tetrahydrocannabinol (THC) given at a dose of 15 mg every 4 hours
Outcomes	Nausea, emetic episodes
Notes	

Earhart 1983

Methods	RCT
Participants	Cancer patients receiving cisplatin chemotherapy
Interventions	Evonantradol versus prochlorperazine as parenteral antiemetics

Earhart 1983 *(Continued)*

Outcomes	Nausea and vomiting
Notes	

Harden-Harrison 2012

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Jhangiani 2005

Methods	Double-blind, placebo-controlled study
Participants	Patients receiving moderately to highly emetogenic chemotherapy
Interventions	Dronabinol alone or in combination with ondansetron versus ondansetron alone
Outcomes	Nausea and vomiting intensity
Notes	

Mersiades A, 2018

Methods	
Participants	
Interventions	
Outcomes	
Notes	

Neidhart 1981

Methods	A prospective, randomized and double-blinded trial
Participants	All patients are receiving chemotherapeutic agents known to induce severe vomiting
Interventions	Effects of delta-9-tetrahydrocannabinol and haloperidol

Neidhart 1981 *(Continued)*

Outcomes	Nausea and vomiting
Notes	

DATA AND ANALYSES

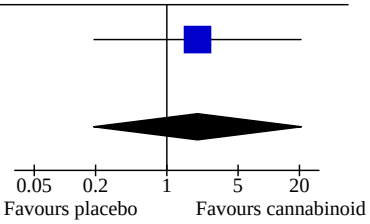
Comparison 1. Cannabinoid versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Absence of nausea	2	96	Risk Ratio (IV, Random, 95% CI)	2.00 [0.19, 20.97]
1.2 Absence of vomiting	3	168	Risk Ratio (IV, Random, 95% CI)	5.69 [2.56, 12.64]
1.2.1 Nabilone	1	72	Risk Ratio (IV, Random, 95% CI)	7.25 [2.84, 18.52]
1.2.2 Dronabinol	2	96	Risk Ratio (IV, Random, 95% CI)	3.00 [0.65, 13.76]
1.3 Absence of nausea and vomiting	3	288	Risk Ratio (IV, Random, 95% CI)	2.86 [1.76, 4.65]
1.3.1 Cannabis naive	1	75	Risk Ratio (IV, Random, 95% CI)	2.23 [1.04, 4.78]
1.3.2 Prior cannabis use	2	213	Risk Ratio (IV, Random, 95% CI)	3.40 [1.80, 6.39]
1.4 Depression	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.5 Dysphoria	2	96	Risk Ratio (IV, Random, 95% CI)	9.00 [0.50, 160.59]
1.6 'Feeling high'	3	137	Risk Ratio (IV, Random, 95% CI)	31.10 [6.37, 151.85]
1.7 Paranoia	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.8 Sedation	2	139	Risk Ratio (IV, Random, 95% CI)	4.47 [0.35, 57.81]
1.9 Participant preference	2	256	Risk Ratio (IV, Random, 95% CI)	4.82 [1.74, 13.36]
1.10 Withdrawal for any reason	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.11 Withdrawal due to adverse event	2	276	Risk Ratio (IV, Random, 95% CI)	6.85 [1.96, 23.99]
1.12 Withdrawal due to lack of efficacy	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1: Cannabinoid versus placebo, Outcome 1: Absence of nausea

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Chang 1979a	2	32	1	32	100.0%	2.00 [0.19 , 20.97]
Chang 1981	0	16	0	16		Not estimable
Total (95% CI)		**48**		**48**	**100.0%**	**2.00 [0.19 , 20.97]**
Total events:	2		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.56)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Cannabinoid versus placebo, Outcome 2: Absence of vomiting

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
1.2.1 Nabilone						
Levitt 1982	29	36	4	36	72.5%	7.25 [2.84 , 18.52]
Subtotal (95% CI)		**36**		**36**	**72.5%**	**7.25 [2.84 , 18.52]**
Total events:	29		4			

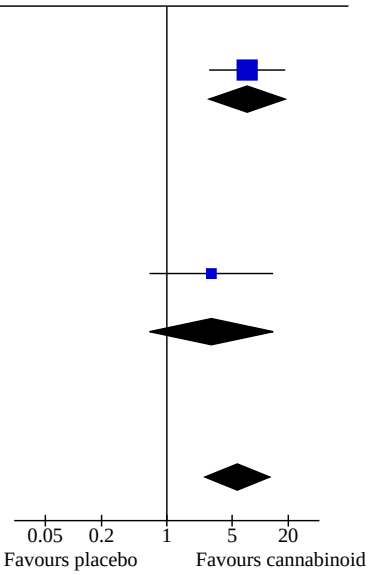
Heterogeneity: Not applicable
Test for overall effect: Z = 4.14 (P < 0.0001)

1.2.2 Dronabinol						
Chang 1979a	6	32	2	32	27.5%	3.00 [0.65 , 13.76]
Chang 1981	0	16	0	16		Not estimable
Subtotal (95% CI)		**48**		**48**	**27.5%**	**3.00 [0.65 , 13.76]**
Total events:	6		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.41 (P = 0.16)

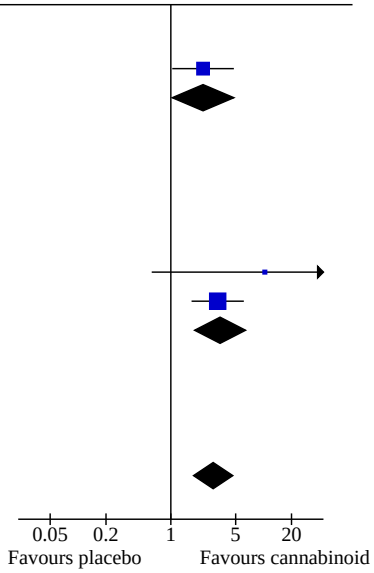
Total (95% CI)		**84**		**84**	**100.0%**	**5.69 [2.56 , 12.64]**
Total events:	35		6			

Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 1 (P = 0.33); I² = 0%
Test for overall effect: Z = 4.27 (P < 0.0001)
Test for subgroup differences: Chi² = 0.93, df = 1 (P = 0.33), I² = 0%



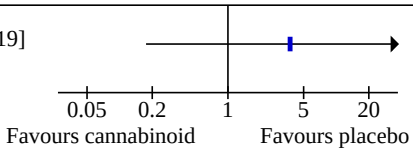
Analysis 1.3. Comparison 1: Cannabinoid versus placebo, Outcome 3: Absence of nausea and vomiting

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
1.3.1 Cannabis naive						
Frytak 1979	16	38	7	37	40.6%	2.23 [1.04 , 4.78]
Subtotal (95% CI)		**38**		**37**	**40.6%**	**2.23 [1.04 , 4.78]**
Total events:	16		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.05 (P = 0.04)						
1.3.2 Prior cannabis use						
Sallan 1975a	5	15	0	14	3.0%	10.31 [0.62 , 170.96]
Wada 1982	32	92	10	92	56.4%	3.20 [1.67 , 6.12]
Subtotal (95% CI)		**107**		**106**	**59.4%**	**3.40 [1.80 , 6.39]**
Total events:	37		10			
Heterogeneity: Tau² = 0.00; Chi² = 0.63, df = 1 (P = 0.43); I² = 0%						
Test for overall effect: Z = 3.79 (P = 0.0001)						
Total (95% CI)		**145**		**143**	**100.0%**	**2.86 [1.76 , 4.65]**
Total events:	53		17			
Heterogeneity: Tau² = 0.00; Chi² = 1.33, df = 2 (P = 0.51); I² = 0%						
Test for overall effect: Z = 4.23 (P < 0.0001)						
Test for subgroup differences: Chi² = 0.70, df = 1 (P = 0.40), I² = 0%						



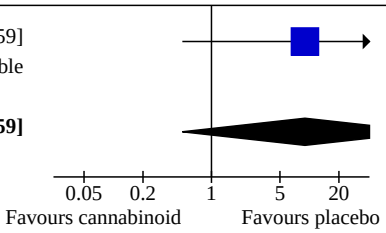
Analysis 1.4. Comparison 1: Cannabinoid versus placebo, Outcome 4: Depression

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Placebo Events	Placebo Total	Risk Ratio IV, Random, 95% CI
Chang 1979a	1	7	0	9	3.75 [0.18 , 80.19]



Analysis 1.5. Comparison 1: Cannabinoid versus placebo, Outcome 5: Dysphoria

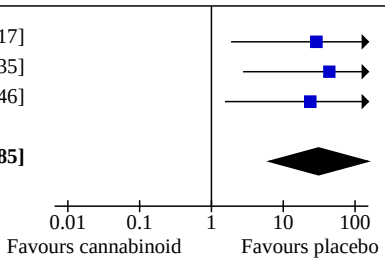
Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Chang 1979a	4	32	0	32	100.0%	9.00 [0.50 , 160.59]
Chang 1981	0	16	0	16		Not estimable
Total (95% CI)		**48**		**48**	**100.0%**	**9.00 [0.50 , 160.59]**
Total events:	4		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.49 (P = 0.14)						
Test for subgroup differences: Not applicable						



Analysis 1.6. Comparison 1: Cannabinoid versus placebo, Outcome 6: 'Feeling high'

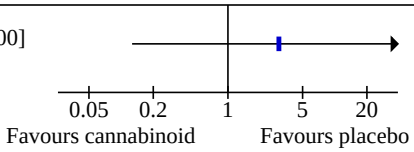
Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Chang 1981	14	16	0	16	33.5%	29.00 [1.88 , 448.17]
Frytak 1979	22	38	0	37	32.9%	43.85 [2.76 , 697.35]
Sallan 1975a	13	16	0	14	33.6%	23.82 [1.54 , 367.46]
Total (95% CI)		**70**		**67**	**100.0%**	**31.10 [6.37 , 151.85]**
Total events:	49		0			

Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 2 (P = 0.95); I² = 0%
Test for overall effect: Z = 4.25 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Cannabinoid versus placebo, Outcome 7: Paranoia

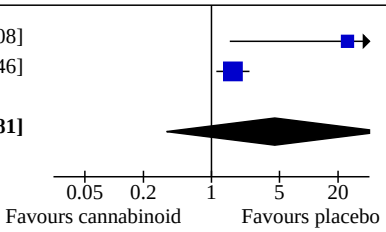
Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Placebo Events	Placebo Total	Risk Ratio IV, Random, 95% CI
Chang 1979a	1	32	0	32	3.00 [0.13 , 71.00]



Analysis 1.8. Comparison 1: Cannabinoid versus placebo, Outcome 8: Sedation

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Chang 1979a	12	32	0	32	36.5%	25.00 [1.54 , 405.08]
Frytak 1979	29	38	17	37	63.5%	1.66 [1.12 , 2.46]
Total (95% CI)		**70**		**69**	**100.0%**	**4.47 [0.35 , 57.81]**
Total events:	41		17			

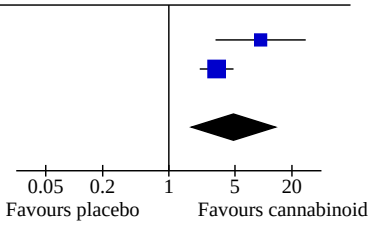
Heterogeneity: Tau² = 2.65; Chi² = 3.57, df = 1 (P = 0.06); I² = 72%
Test for overall effect: Z = 1.15 (P = 0.25)
Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1: Cannabinoid versus placebo, Outcome 9: Participant preference

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Levitt 1982	28	36	3	36	38.2%	9.33 [3.11 , 27.97]
Wada 1982	64	92	20	92	61.8%	3.20 [2.12 , 4.82]
Total (95% CI)		**128**		**128**	**100.0%**	**4.82 [1.74 , 13.36]**
Total events:	92		23			

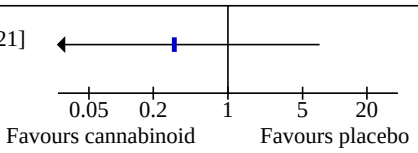
Heterogeneity: Tau² = 0.39; Chi² = 3.21, df = 1 (P = 0.07); I² = 69%
Test for overall effect: Z = 3.02 (P = 0.003)
Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1: Cannabinoid versus placebo, Outcome 10: Withdrawal for any reason

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Placebo Events	Placebo Total	Risk Ratio IV, Random, 95% CI
Chang 1981	0	17	1	16	0.31 [0.01 , 7.21]

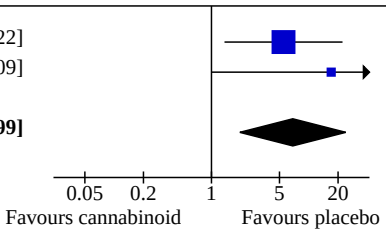
Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1: Cannabinoid versus placebo, Outcome 11: Withdrawal due to adverse event

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Placebo Events	Placebo Total	Weight	Risk Ratio IV, Random, 95% CI
Jones 1982	11	24	2	24	80.5%	5.50 [1.36 , 22.22]
Wada 1982	8	114	0	114	19.5%	17.00 [0.99 , 291.09]
Total (95% CI)		**138**		**138**	**100.0%**	**6.85 [1.96 , 23.99]**
Total events:	19		2			

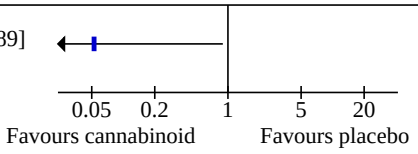
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.49$, df = 1 (P = 0.48); $I^2 = 0\%$
Test for overall effect: Z = 3.01 (P = 0.003)
Test for subgroup differences: Not applicable



Analysis 1.12. Comparison 1: Cannabinoid versus placebo, Outcome 12: Withdrawal due to lack of efficacy

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Placebo Events	Placebo Total	Risk Ratio IV, Random, 95% CI
Wada 1982	0	114	9	114	0.05 [0.00 , 0.89]

Test for subgroup differences: Not applicable



Comparison 2. Cannabinoid versus other anti-emetic agent

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Absence of nausea	5	258	Risk Ratio (IV, Random, 95% CI)	1.46 [0.67, 3.15]
2.1.1 Prochlorperazine	5	258	Risk Ratio (IV, Random, 95% CI)	1.46 [0.67, 3.15]
2.2 Absence of nausea (subgroup analysis 2)	5		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.2.1 Nabilone	3	141	Risk Ratio (IV, Random, 95% CI)	1.41 [0.33, 6.03]
2.2.2 Dronabinol	2	117	Risk Ratio (IV, Random, 95% CI)	2.38 [0.21, 26.91]
2.3 Absence of vomiting	4	209	Risk Ratio (IV, Random, 95% CI)	1.11 [0.86, 1.44]

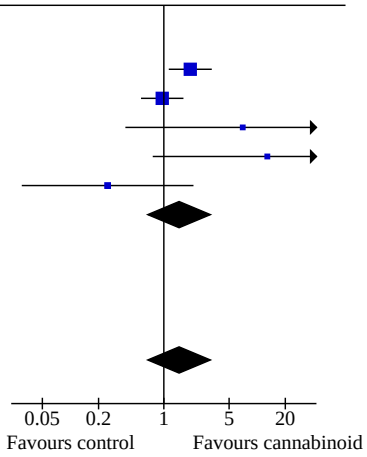
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3.1 Prochlorperazine	4	209	Risk Ratio (IV, Random, 95% CI)	1.11 [0.86, 1.44]
2.4 Absence of vomiting (subgroup analysis 2)	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.4.1 Nabilone	2	93	Risk Ratio (IV, Random, 95% CI)	1.55 [0.39, 6.24]
2.4.2 Dronabinol	2	116	Risk Ratio (IV, Random, 95% CI)	1.05 [0.64, 1.71]
2.5 Absence of nausea and vomiting	4	414	Risk Ratio (IV, Random, 95% CI)	2.00 [0.74, 5.38]
2.5.1 Prochlorperazine	4	414	Risk Ratio (IV, Random, 95% CI)	2.00 [0.74, 5.38]
2.6 Absence of nausea and vomiting (subgroup analysis 1)	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.6.1 Cannabis naive	2	116	Risk Ratio (IV, Random, 95% CI)	1.10 [0.70, 1.72]
2.6.2 Prior cannabis use	2	298	Risk Ratio (IV, Random, 95% CI)	17.98 [2.44, 132.43]
2.7 Absence of nausea and vomiting (subgroup analysis 2)	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.7.1 Nabilone	1	226	Risk Ratio (IV, Random, 95% CI)	17.00 [0.99, 291.06]
2.7.2 Dronabinol	3	188	Risk Ratio (IV, Random, 95% CI)	1.44 [0.62, 3.31]
2.8 Dizziness	9	743	Risk Ratio (IV, Random, 95% CI)	2.54 [1.91, 3.37]
2.8.1 Domperidone	1	38	Risk Ratio (IV, Random, 95% CI)	2.75 [1.06, 7.12]
2.8.2 Prochlorperazine	7	675	Risk Ratio (IV, Random, 95% CI)	2.36 [1.82, 3.07]
2.8.3 Metoclopramide	1	30	Risk Ratio (IV, Random, 95% CI)	12.00 [1.78, 81.06]
2.9 Dysphoria	3	192	Risk Ratio (IV, Random, 95% CI)	7.17 [1.33, 38.84]
2.9.1 Prochloperazine	3	192	Risk Ratio (IV, Random, 95% CI)	7.17 [1.33, 38.84]
2.10 Euphoria	4	358	Risk Ratio (IV, Random, 95% CI)	8.89 [2.05, 38.63]
2.10.1 Domperidone	1	38	Risk Ratio (IV, Random, 95% CI)	5.00 [0.26, 97.70]
2.10.2 Prochlorperazine	2	280	Risk Ratio (IV, Random, 95% CI)	17.97 [2.42, 133.37]
2.10.3 Chlorpromazine	1	40	Risk Ratio (IV, Random, 95% CI)	3.00 [0.13, 69.52]
2.11 'Feeling high'	5	419	Risk Ratio (IV, Random, 95% CI)	5.90 [3.42, 10.17]
2.11.1 Prochlorperazine	4	389	Risk Ratio (IV, Random, 95% CI)	6.18 [3.52, 10.85]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.11.2 Metoclopramide	1	30	Risk Ratio (IV, Random, 95% CI)	3.00 [0.35, 25.68]
2.12 Hallucinations	2	144	Risk Ratio (IV, Random, 95% CI)	5.39 [0.66, 43.68]
2.12.1 Prochlorperazine	2	144	Risk Ratio (IV, Random, 95% CI)	5.39 [0.66, 43.68]
2.13 Postural hypotension	6	413	Risk Ratio (IV, Random, 95% CI)	2.40 [0.88, 6.53]
2.13.1 Domperidone	1	38	Risk Ratio (IV, Random, 95% CI)	4.00 [0.49, 32.57]
2.13.2 Prochlorperazine	3	305	Risk Ratio (IV, Random, 95% CI)	1.22 [0.52, 2.89]
2.13.3 Metoclopramide	1	30	Risk Ratio (IV, Random, 95% CI)	17.00 [1.07, 270.41]
2.13.4 Chlorpromazine	1	40	Risk Ratio (IV, Random, 95% CI)	7.00 [0.95, 51.80]
2.14 Paranoia	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.14.1 Prochlorperazine	1	42	Risk Ratio (IV, Random, 95% CI)	3.00 [0.13, 69.70]
2.15 Sedation	11	1055	Risk Ratio (IV, Random, 95% CI)	1.33 [1.08, 1.64]
2.15.1 Domperidone	1	38	Risk Ratio (IV, Random, 95% CI)	1.22 [0.66, 2.25]
2.15.2 Prochlorperazine	8	947	Risk Ratio (IV, Random, 95% CI)	1.44 [1.18, 1.76]
2.15.3 Metoclopramide	1	30	Risk Ratio (IV, Random, 95% CI)	0.93 [0.73, 1.18]
2.15.4 Chlorpromazine	1	40	Risk Ratio (IV, Random, 95% CI)	1.71 [0.85, 3.44]
2.16 Depression	3	317	Risk Ratio (IV, Random, 95% CI)	0.81 [0.51, 1.28]
2.16.1 Prochlorperazine	3	317	Risk Ratio (IV, Random, 95% CI)	0.81 [0.51, 1.28]
2.17 Participant preference	9	799	Risk Ratio (IV, Random, 95% CI)	2.76 [1.88, 4.03]
2.17.1 Prochlorperazine	7	695	Risk Ratio (IV, Random, 95% CI)	3.24 [2.23, 4.72]
2.17.2 Metoclopramide	1	64	Risk Ratio (IV, Random, 95% CI)	1.20 [0.61, 2.37]
2.17.3 Chlorpromazine	1	40	Risk Ratio (IV, Random, 95% CI)	2.00 [0.83, 4.81]
2.18 Withdrawal for any reason	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
2.18.1 Prochlorperazine	1	42	Risk Ratio (IV, Random, 95% CI)	3.50 [1.38, 8.89]
2.19 Withdrawal due to adverse event	6	740	Risk Ratio (IV, Random, 95% CI)	3.16 [1.26, 7.93]
2.19.1 Domperidone	1	76	Risk Ratio (IV, Random, 95% CI)	3.00 [0.13, 71.40]
2.19.2 Prochlorperazine	5	664	Risk Ratio (IV, Random, 95% CI)	3.90 [1.25, 12.20]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.20 Withdrawal due to lack of efficacy	2	118	Risk Ratio (IV, Random, 95% CI)	0.97 [0.04, 20.93]
2.20.1 Domperidone	1	76	Risk Ratio (IV, Random, 95% CI)	0.14 [0.01, 2.67]
2.20.2 Prochlorperazine	1	42	Risk Ratio (IV, Random, 95% CI)	3.50 [1.38, 8.89]

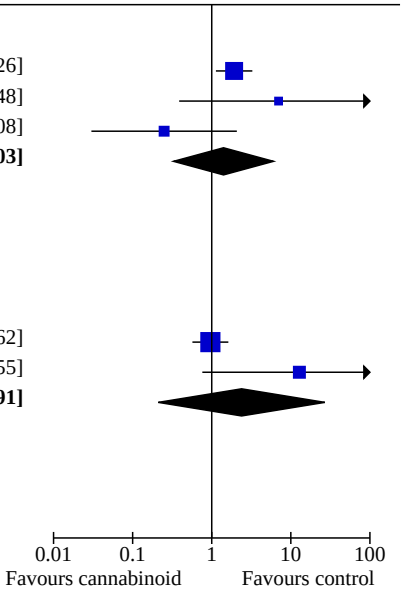
Analysis 2.1. Comparison 2: Cannabinoid versus other anti-emetic agent, Outcome 1: Absence of nausea

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
2.1.1 Prochlorperazine						
Ahmedzai 1983	19	27	11	30	38.4%	1.92 [1.13 , 3.26]
Frytak 1979	17	42	16	38	38.6%	0.96 [0.57 , 1.62]
Johansson 1982	3	18	0	18	6.2%	7.00 [0.39 , 126.48]
Lane 1991	5	17	0	20	6.4%	12.83 [0.76 , 216.55]
Niiranen 1985	1	24	4	24	10.3%	0.25 [0.03 , 2.08]
Subtotal (95% CI)		**128**		**130**	**100.0%**	**1.46 [0.67 , 3.15]**
Total events:	45		31			
Heterogeneity: Tau² = 0.33; Chi² = 9.42, df = 4 (P = 0.05); I² = 58%						
Test for overall effect: Z = 0.96 (P = 0.34)						
Total (95% CI)		**128**		**130**	**100.0%**	**1.46 [0.67 , 3.15]**
Total events:	45		31			
Heterogeneity: Tau² = 0.33; Chi² = 9.42, df = 4 (P = 0.05); I² = 58%						
Test for overall effect: Z = 0.96 (P = 0.34)						
Test for subgroup differences: Not applicable						



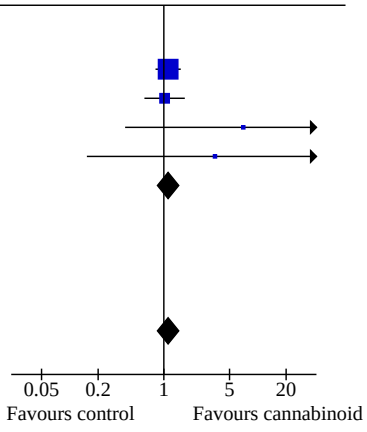
Analysis 2.2. Comparison 2: Cannabinoid versus other anti-emetic agent, Outcome 2: Absence of nausea (subgroup analysis 2)

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
2.2.1 Nabilone						
Ahmedzai 1983	19	27	11	30	55.8%	1.92 [1.13 , 3.26]
Johansson 1982	3	18	0	18	17.8%	7.00 [0.39 , 126.48]
Niiranen 1985	1	24	4	24	26.4%	0.25 [0.03 , 2.08]
Subtotal (95% CI)		**69**		**72**	**100.0%**	**1.41 [0.33 , 6.03]**
Total events:	23		15			
Heterogeneity: Tau² = 0.91; Chi² = 4.24, df = 2 (P = 0.12); I² = 53%						
Test for overall effect: Z = 0.46 (P = 0.64)						
2.2.2 Dronabinol						
Frytak 1979	17	42	16	38	64.9%	0.96 [0.57 , 1.62]
Lane 1991	5	17	0	20	35.1%	12.83 [0.76 , 216.55]
Subtotal (95% CI)		**59**		**58**	**100.0%**	**2.38 [0.21 , 26.91]**
Total events:	22		16			
Heterogeneity: Tau² = 2.28; Chi² = 3.12, df = 1 (P = 0.08); I² = 68%						
Test for overall effect: Z = 0.70 (P = 0.48)						
Test for subgroup differences: Chi² = 0.13, df = 1 (P = 0.72), I² = 0%						



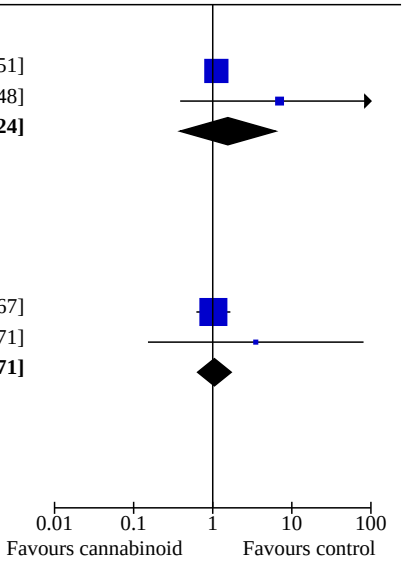
Analysis 2.3. Comparison 2: Cannabinoid versus other anti-emetic agent, Outcome 3: Absence of vomiting

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
2.3.1 Prochlorperazine						
Ahmedzai 1983	21	27	21	30	70.8%	1.11 [0.82 , 1.51]
Frytak 1979	17	38	18	41	27.7%	1.02 [0.62 , 1.67]
Johansson 1982	3	18	0	18	0.8%	7.00 [0.39 , 126.48]
Lane 1991	1	17	0	20	0.7%	3.50 [0.15 , 80.71]
Subtotal (95% CI)		**100**		**109**	**100.0%**	**1.11 [0.86 , 1.44]**
Total events:	42		39			
Heterogeneity: Tau² = 0.00; Chi² = 2.18, df = 3 (P = 0.53); I² = 0%						
Test for overall effect: Z = 0.78 (P = 0.43)						
Total (95% CI)		**100**		**109**	**100.0%**	**1.11 [0.86 , 1.44]**
Total events:	42		39			
Heterogeneity: Tau² = 0.00; Chi² = 2.18, df = 3 (P = 0.53); I² = 0%						
Test for overall effect: Z = 0.78 (P = 0.43)						
Test for subgroup differences: Not applicable						



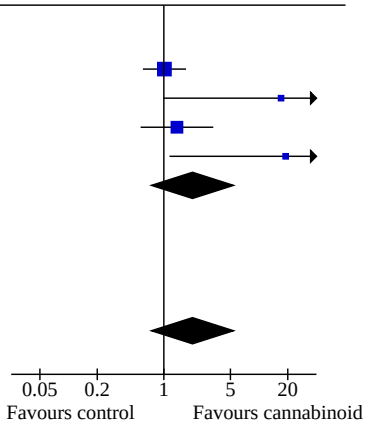
Analysis 2.4. Comparison 2: Cannabinoid versus other anti-emetic agent, Outcome 4: Absence of vomiting (subgroup analysis 2)

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
2.4.1 Nabilone						
Ahmedzai 1983	21	27	21	30	81.8%	1.11 [0.82 , 1.51]
Johansson 1982	3	18	0	18	18.2%	7.00 [0.39 , 126.48]
Subtotal (95% CI)		**45**		**48**	**100.0%**	**1.55 [0.39 , 6.24]**
Total events:	24		21			
Heterogeneity: Tau² = 0.59; Chi² = 1.54, df = 1 (P = 0.22); I² = 35%						
Test for overall effect: Z = 0.62 (P = 0.54)						
2.4.2 Dronabinol						
Frytak 1979	17	38	18	41	97.6%	1.02 [0.62 , 1.67]
Lane 1991	1	17	0	20	2.4%	3.50 [0.15 , 80.71]
Subtotal (95% CI)		**55**		**61**	**100.0%**	**1.05 [0.64 , 1.71]**
Total events:	18		18			
Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 1 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.20 (P = 0.84)						
Test for subgroup differences: Chi² = 0.27, df = 1 (P = 0.60), I² = 0%						



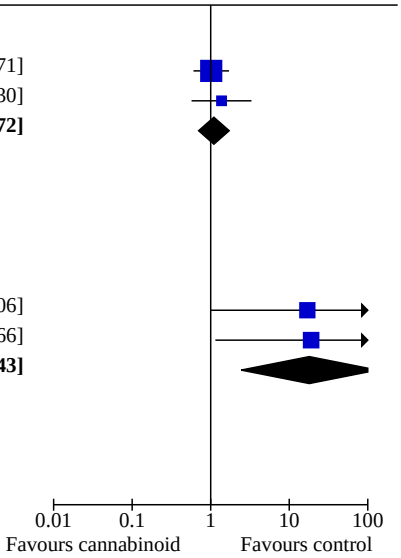
Analysis 2.5. Comparison 2: Cannabinoid versus other anti-emetic agent, Outcome 5: Absence of nausea and vomiting

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
2.5.1 Prochlorperazine						
Frytak 1979	16	38	17	41	44.2%	1.02 [0.60 , 1.71]
Herman 1979	8	113	0	113	9.8%	17.00 [0.99 , 291.06]
Lane 1991	7	17	6	20	36.1%	1.37 [0.57 , 3.30]
McCabe 1988	9	36	0	36	10.0%	19.00 [1.15 , 314.66]
Subtotal (95% CI)		**204**		**210**	**100.0%**	**2.00 [0.74 , 5.38]**
Total events:	40		23			
Heterogeneity: Tau² = 0.51; Chi² = 7.51, df = 3 (P = 0.06); I² = 60%						
Test for overall effect: Z = 1.37 (P = 0.17)						
Total (95% CI)		**204**		**210**	**100.0%**	**2.00 [0.74 , 5.38]**
Total events:	40		23			
Heterogeneity: Tau² = 0.51; Chi² = 7.51, df = 3 (P = 0.06); I² = 60%						
Test for overall effect: Z = 1.37 (P = 0.17)						
Test for subgroup differences: Not applicable						



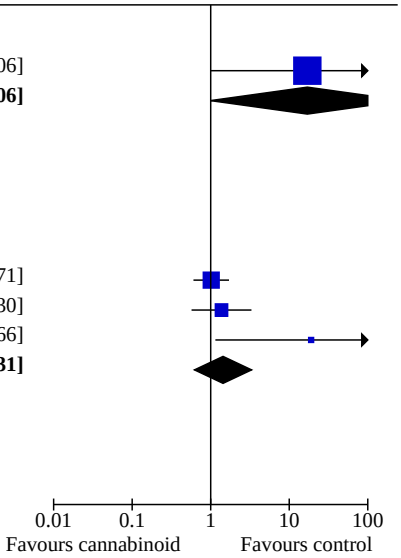
Analysis 2.6. Comparison 2: Cannabinoid versus other anti-emetic agent, Outcome 6: Absence of nausea and vomiting (subgroup analysis 1)

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
2.6.1 Cannabis naive						
Frytak 1979	16	38	17	41	74.0%	1.02 [0.60 , 1.71]
Lane 1991	7	17	6	20	26.0%	1.37 [0.57 , 3.30]
Subtotal (95% CI)		**55**		**61**	**100.0%**	**1.10 [0.70 , 1.72]**
Total events:	23		23			
Heterogeneity: Tau² = 0.00; Chi² = 0.33, df = 1 (P = 0.56); I² = 0%						
Test for overall effect: Z = 0.41 (P = 0.68)						
2.6.2 Prior cannabis use						
Herman 1979	8	113	0	113	49.4%	17.00 [0.99 , 291.06]
McCabe 1988	9	36	0	36	50.6%	19.00 [1.15 , 314.66]
Subtotal (95% CI)		**149**		**149**	**100.0%**	**17.98 [2.44 , 132.43]**
Total events:	17		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.96); I² = 0%						
Test for overall effect: Z = 2.84 (P = 0.005)						
Test for subgroup differences: Chi² = 7.17, df = 1 (P = 0.007), I² = 86.1%						



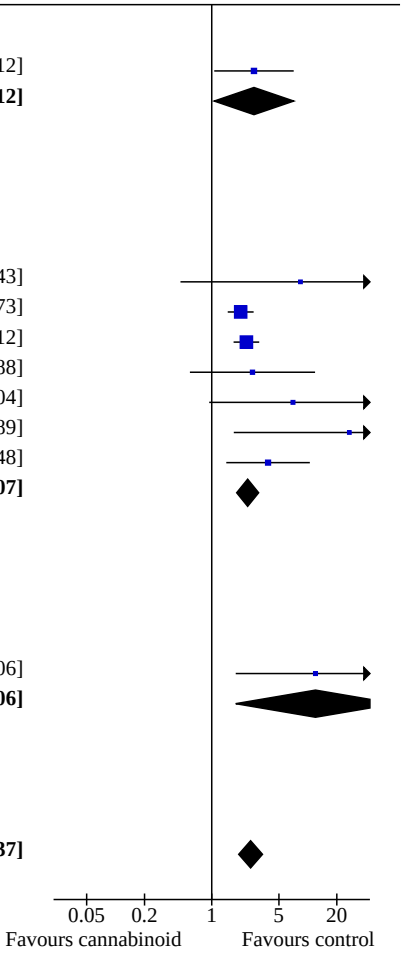
Analysis 2.7. Comparison 2: Cannabinoid versus other anti-emetic agent, Outcome 7: Absence of nausea and vomiting (subgroup analysis 2)

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
2.7.1 Nabilone						
Herman 1979	8	113	0	113	100.0%	17.00 [0.99 , 291.06]
Subtotal (95% CI)		**113**		**113**	**100.0%**	**17.00 [0.99 , 291.06]**
Total events:	8		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.96 (P = 0.05)						
2.7.2 Dronabinol						
Frytak 1979	16	38	17	41	53.5%	1.02 [0.60 , 1.71]
Lane 1991	7	17	6	20	38.7%	1.37 [0.57 , 3.30]
McCabe 1988	9	36	0	36	7.8%	19.00 [1.15 , 314.66]
Subtotal (95% CI)		**91**		**97**	**100.0%**	**1.44 [0.62 , 3.31]**
Total events:	32		23			
Heterogeneity: Tau² = 0.27; Chi² = 4.20, df = 2 (P = 0.12); I² = 52%						
Test for overall effect: Z = 0.85 (P = 0.40)						
Test for subgroup differences: Chi² = 2.68, df = 1 (P = 0.10), I² = 62.6%						



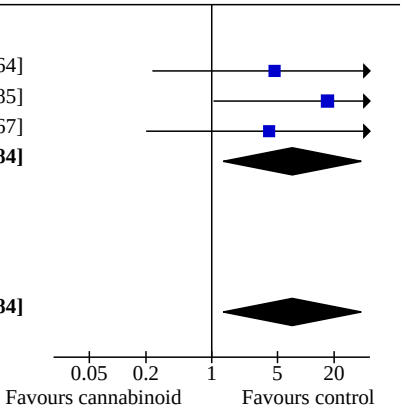
Analysis 2.8. Comparison 2: Cannabinoid versus other anti-emetic agent, Outcome 8: Dizziness

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
2.8.1 Domperidone						
Pomeroy 1986	11	19	4	19	7.9%	2.75 [1.06 , 7.12]
Subtotal (95% CI)		**19**		**19**	**7.9%**	**2.75 [1.06 , 7.12]**
Total events:	11		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.08 (P = 0.04)						
2.8.2 Prochlorperazine						
Ahmedzai 1983	4	28	0	26	1.0%	8.38 [0.47 , 148.43]
Einhorn 1981	60	80	30	80	37.5%	2.00 [1.47 , 2.73]
Herman 1979	78	113	34	113	37.8%	2.29 [1.69 , 3.12]
Johansson 1982	6	26	2	23	3.4%	2.65 [0.59 , 11.88]
Lane 1991	7	21	1	21	2.0%	7.00 [0.94 , 52.04]
Niiranen 1985	13	24	0	24	1.0%	27.00 [1.70 , 429.89]
Steele 1980	19	53	4	43	7.2%	3.85 [1.42 , 10.48]
Subtotal (95% CI)		**345**		**330**	**90.0%**	**2.36 [1.82 , 3.07]**
Total events:	187		71			
Heterogeneity: Tau² = 0.02; Chi² = 6.84, df = 6 (P = 0.34); I² = 12%						
Test for overall effect: Z = 6.42 (P < 0.00001)						
2.8.3 Metoclopramide						
Gralla 1984	12	15	1	15	2.1%	12.00 [1.78 , 81.06]
Subtotal (95% CI)		**15**		**15**	**2.1%**	**12.00 [1.78 , 81.06]**
Total events:	12		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.55 (P = 0.01)						
Total (95% CI)		**379**		**364**	**100.0%**	**2.54 [1.91 , 3.37]**
Total events:	210		76			
Heterogeneity: Tau² = 0.03; Chi² = 9.81, df = 8 (P = 0.28); I² = 18%						
Test for overall effect: Z = 6.42 (P < 0.00001)						
Test for subgroup differences: Chi² = 2.78, df = 2 (P = 0.25), I² = 28.2%						



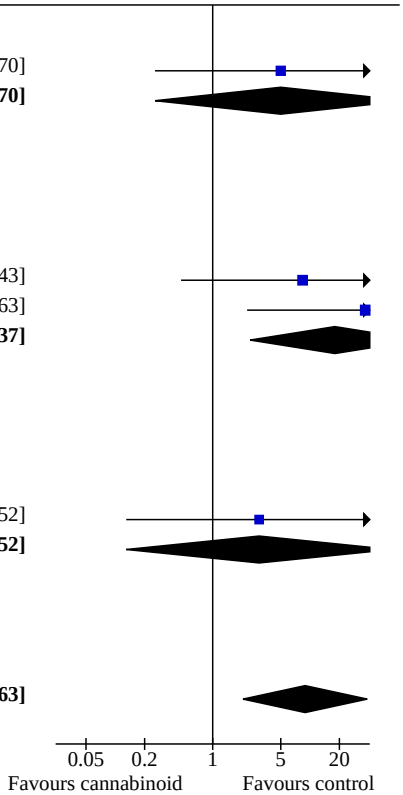
Analysis 2.9. Comparison 2: Cannabinoid versus other anti-emetic agent, Outcome 9: Dysphoria

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
2.9.1 Prochloperazine						
Ahmedzai 1983	2	28	0	26	31.9%	4.66 [0.23 , 92.64]
Lane 1991	8	21	0	21	36.6%	17.00 [1.04 , 276.85]
Steele 1980	2	53	0	43	31.5%	4.07 [0.20 , 82.67]
Subtotal (95% CI)		**102**		**90**	**100.0%**	**7.17 [1.33 , 38.84]**
Total events:	12		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 2 (P = 0.75); I² = 0%						
Test for overall effect: Z = 2.29 (P = 0.02)						
Total (95% CI)		**102**		**90**	**100.0%**	**7.17 [1.33 , 38.84]**
Total events:	12		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 2 (P = 0.75); I² = 0%						
Test for overall effect: Z = 2.29 (P = 0.02)						
Test for subgroup differences: Not applicable						



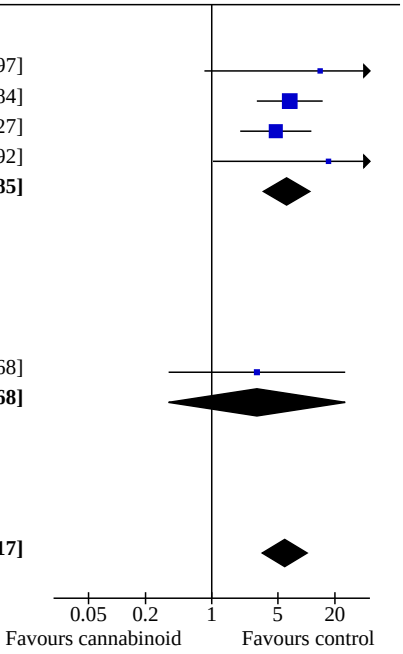
Analysis 2.10. Comparison 2: Cannabinoid versus other anti-emetic agent, Outcome 10: Euphoria

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
2.10.1 Domperidone						
Pomeroy 1986	2	19	0	19	24.4%	5.00 [0.26 , 97.70]
Subtotal (95% CI)		**19**		**19**	**24.4%**	**5.00 [0.26 , 97.70]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
2.10.2 Prochlorperazine						
Ahmedzai 1983	4	28	0	26	26.1%	8.38 [0.47 , 148.43]
Herman 1979	18	113	0	113	27.6%	37.00 [2.26 , 606.63]
Subtotal (95% CI)		**141**		**139**	**53.7%**	**17.97 [2.42 , 133.37]**
Total events:	22		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.53, df = 1 (P = 0.47); I² = 0%						
Test for overall effect: Z = 2.82 (P = 0.005)						
2.10.3 Chlorpromazine						
George 1983	1	20	0	20	21.9%	3.00 [0.13 , 69.52]
Subtotal (95% CI)		**20**		**20**	**21.9%**	**3.00 [0.13 , 69.52]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
Total (95% CI)		**180**		**178**	**100.0%**	**8.89 [2.05 , 38.63]**
Total events:	25		0			
Heterogeneity: Tau² = 0.00; Chi² = 1.60, df = 3 (P = 0.66); I² = 0%						
Test for overall effect: Z = 2.91 (P = 0.004)						
Test for subgroup differences: Chi² = 1.08, df = 2 (P = 0.58), I² = 0%						



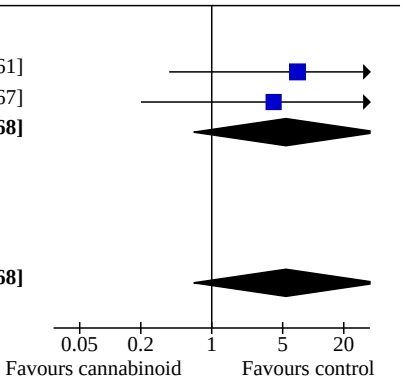
Analysis 2.11. Comparison 2: Cannabinoid versus other anti-emetic agent, Outcome 11: 'Feeling high'

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
2.11.1 Prochlorperazine						
Ahmedzai 1983	7	28	0	26	3.7%	13.97 [0.84 , 232.97]
Einhorn 1981	40	80	6	80	46.4%	6.67 [3.00 , 14.84]
Frytak 1979	22	38	5	41	39.7%	4.75 [2.00 , 11.27]
Steele 1980	10	53	0	43	3.8%	17.11 [1.03 , 283.92]
Subtotal (95% CI)		**199**		**190**	**93.6%**	**6.18 [3.52 , 10.85]**
Total events:	79		11			
Heterogeneity: Tau² = 0.00; Chi² = 1.22, df = 3 (P = 0.75); I² = 0%						
Test for overall effect: Z = 6.33 (P < 0.00001)						
2.11.2 Metoclopramide						
Gralla 1984	3	15	1	15	6.4%	3.00 [0.35 , 25.68]
Subtotal (95% CI)		**15**		**15**	**6.4%**	**3.00 [0.35 , 25.68]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.00 (P = 0.32)						
Total (95% CI)		**214**		**205**	**100.0%**	**5.90 [3.42 , 10.17]**
Total events:	82		12			
Heterogeneity: Tau² = 0.00; Chi² = 1.63, df = 4 (P = 0.80); I² = 0%						
Test for overall effect: Z = 6.38 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.41, df = 1 (P = 0.52), I² = 0%						



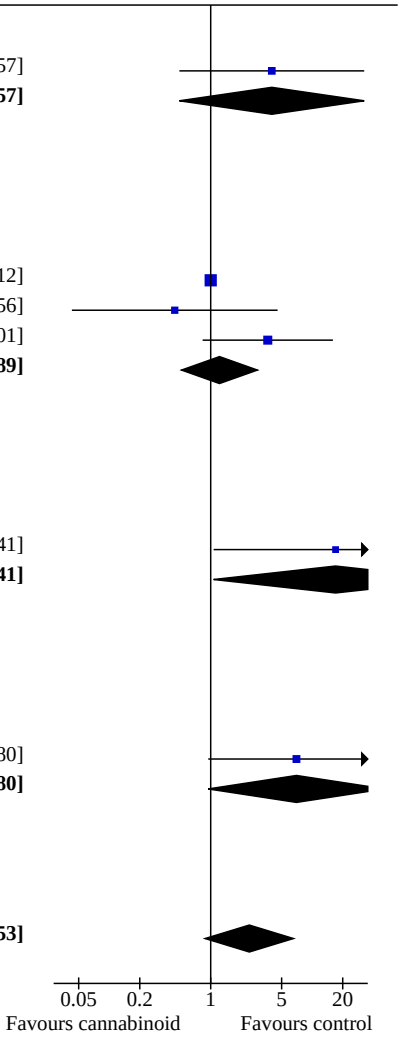
Analysis 2.12. Comparison 2: Cannabinoid versus other anti-emetic agent, Outcome 12: Hallucinations

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
2.12.1 Prochlorperazine						
Niiranen 1985	3	24	0	24	51.7%	7.00 [0.38 , 128.61]
Steele 1980	2	53	0	43	48.3%	4.07 [0.20 , 82.67]
Subtotal (95% CI)		**77**		**67**	**100.0%**	**5.39 [0.66 , 43.68]**
Total events:	5		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.80); I² = 0%						
Test for overall effect: Z = 1.58 (P = 0.11)						
Total (95% CI)		**77**		**67**	**100.0%**	**5.39 [0.66 , 43.68]**
Total events:	5		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.80); I² = 0%						
Test for overall effect: Z = 1.58 (P = 0.11)						
Test for subgroup differences: Not applicable						



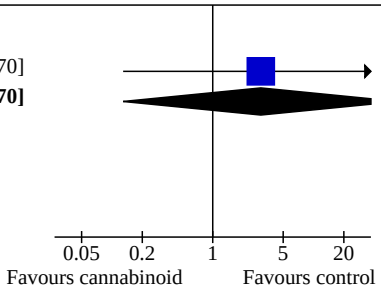
Analysis 2.13. Comparison 2: Cannabinoid versus other anti-emetic agent, Outcome 13: Postural hypotension

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
2.13.1 Domperidone						
Pomeroy 1986	4	19	1	19	13.4%	4.00 [0.49 , 32.57]
Subtotal (95% CI)		**19**		**19**	**13.4%**	**4.00 [0.49 , 32.57]**
Total events:	4		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.30 (P = 0.20)						
2.13.2 Prochlorperazine						
Einhorn 1981	70	80	70	80	32.4%	1.00 [0.89 , 1.12]
Johansson 1982	1	26	2	23	11.7%	0.44 [0.04 , 4.56]
Steele 1980	9	53	2	43	19.0%	3.65 [0.83 , 16.01]
Subtotal (95% CI)		**159**		**146**	**63.1%**	**1.22 [0.52 , 2.89]**
Total events:	80		74			
Heterogeneity: Tau² = 0.29; Chi² = 3.41, df = 2 (P = 0.18); I² = 41%						
Test for overall effect: Z = 0.45 (P = 0.65)						
2.13.3 Metoclopramide						
Gralla 1984	8	15	0	15	9.3%	17.00 [1.07 , 270.41]
Subtotal (95% CI)		**15**		**15**	**9.3%**	**17.00 [1.07 , 270.41]**
Total events:	8		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.01 (P = 0.04)						
2.13.4 Chlorpromazine						
George 1983	7	20	1	20	14.1%	7.00 [0.95 , 51.80]
Subtotal (95% CI)		**20**		**20**	**14.1%**	**7.00 [0.95 , 51.80]**
Total events:	7		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.91 (P = 0.06)						
Total (95% CI)		**213**		**200**	**100.0%**	**2.40 [0.88 , 6.53]**
Total events:	99		76			
Heterogeneity: Tau² = 0.80; Chi² = 12.62, df = 5 (P = 0.03); I² = 60%						
Test for overall effect: Z = 1.71 (P = 0.09)						
Test for subgroup differences: Chi² = 5.48, df = 3 (P = 0.14), I² = 45.2%						



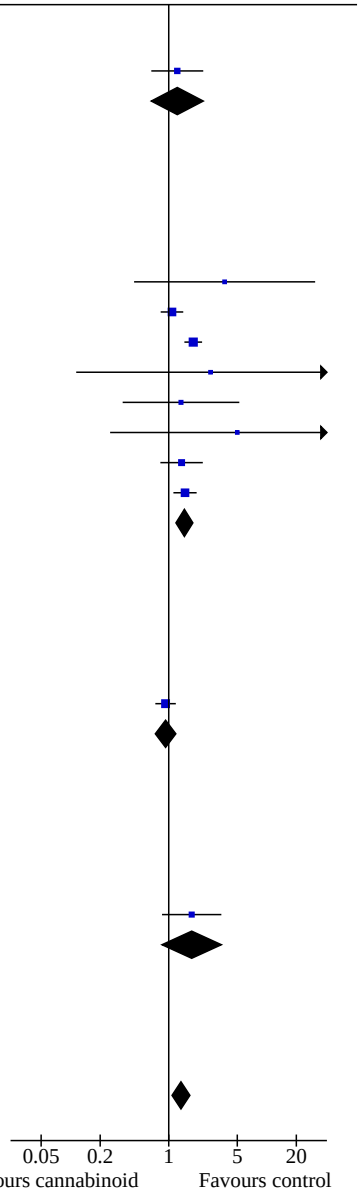
Analysis 2.14. Comparison 2: Cannabinoid versus other anti-emetic agent, Outcome 14: Paranoia

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
2.14.1 Prochlorperazine						
Lane 1991	1	21	0	21	100.0%	3.00 [0.13 , 69.70]
Subtotal (95% CI)		**21**		**21**	**100.0%**	**3.00 [0.13 , 69.70]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.49)						
Test for subgroup differences: Not applicable						



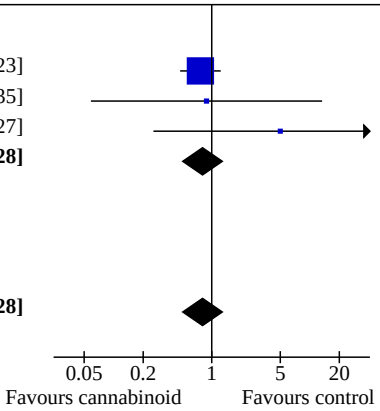
Analysis 2.15. Comparison 2: Cannabinoid versus other anti-emetic agent, Outcome 15: Sedation

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
2.15.1 Domperidone						
Pomeroy 1986	11	19	9	19	7.9%	1.22 [0.66 , 2.25]
Subtotal (95% CI)		**19**		**19**	**7.9%**	**1.22 [0.66 , 2.25]**
Total events:	11		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.65 (P = 0.52)						
2.15.2 Prochlorperazine						
Ahmedzai 1983	4	28	1	26	0.9%	3.71 [0.44 , 31.11]
Frytak 1979	29	38	29	41	17.2%	1.08 [0.83 , 1.41]
Herman 1979	96	113	54	113	19.3%	1.78 [1.44 , 2.19]
Johansson 1982	1	26	0	23	0.4%	2.67 [0.11 , 62.42]
Lane 1991	4	21	3	21	2.1%	1.33 [0.34 , 5.24]
Niiranen 1985	2	24	0	24	0.5%	5.00 [0.25 , 98.96]
Steele 1980	25	53	15	43	10.1%	1.35 [0.82 , 2.22]
Ungerleider 1982	78	172	56	181	16.9%	1.47 [1.12 , 1.92]
Subtotal (95% CI)		**475**		**472**	**67.5%**	**1.44 [1.18 , 1.76]**
Total events:	239		158			
Heterogeneity: Tau² = 0.02; Chi² = 10.10, df = 7 (P = 0.18); I² = 31%						
Test for overall effect: Z = 3.63 (P = 0.0003)						
2.15.3 Metoclopramide						
Gralla 1984	13	15	14	15	18.1%	0.93 [0.73 , 1.18]
Subtotal (95% CI)		**15**		**15**	**18.1%**	**0.93 [0.73 , 1.18]**
Total events:	13		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.60 (P = 0.55)						
2.15.4 Chlorpromazine						
George 1983	12	20	7	20	6.5%	1.71 [0.85 , 3.44]
Subtotal (95% CI)		**20**		**20**	**6.5%**	**1.71 [0.85 , 3.44]**
Total events:	12		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.52 (P = 0.13)						
Total (95% CI)		**529**		**526**	**100.0%**	**1.33 [1.08 , 1.64]**
Total events:	275		188			
Heterogeneity: Tau² = 0.05; Chi² = 21.40, df = 10 (P = 0.02); I² = 53%						
Test for overall effect: Z = 2.69 (P = 0.007)						
Test for subgroup differences: Chi² = 8.65, df = 3 (P = 0.03), I² = 65.3%						



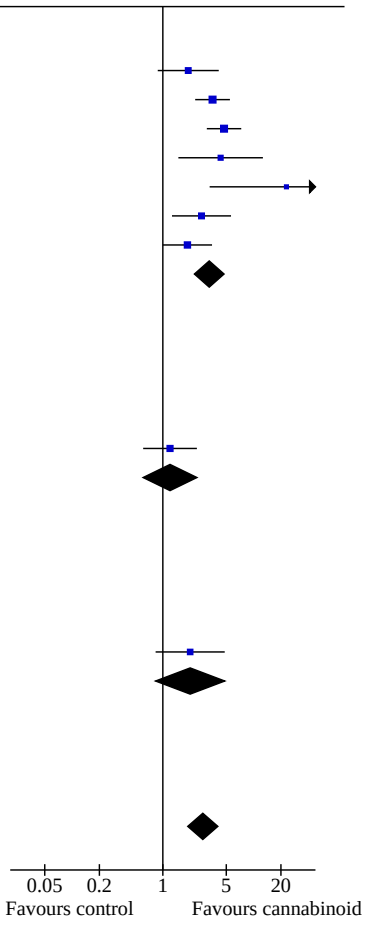
Analysis 2.16. Comparison 2: Cannabinoid versus other anti-emetic agent, Outcome 16: Depression

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
2.16.1 Prochlorperazine						
Herman 1979	23	113	30	113	94.7%	0.77 [0.48 , 1.23]
Johansson 1982	1	26	1	23	2.9%	0.88 [0.06 , 13.35]
Lane 1991	2	21	0	21	2.4%	5.00 [0.25 , 98.27]
Subtotal (95% CI)		**160**		**157**	**100.0%**	**0.81 [0.51 , 1.28]**
Total events:	26		31			
Heterogeneity: Tau² = 0.00; Chi² = 1.49, df = 2 (P = 0.47); I² = 0%						
Test for overall effect: Z = 0.91 (P = 0.36)						
Total (95% CI)		**160**		**157**	**100.0%**	**0.81 [0.51 , 1.28]**
Total events:	26		31			
Heterogeneity: Tau² = 0.00; Chi² = 1.49, df = 2 (P = 0.47); I² = 0%						
Test for overall effect: Z = 0.91 (P = 0.36)						
Test for subgroup differences: Not applicable						



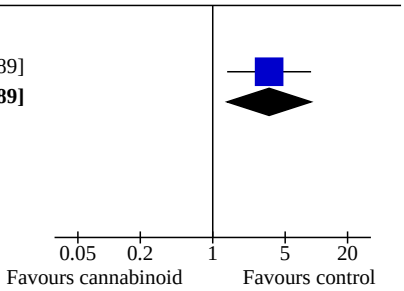
Analysis 2.17. Comparison 2: Cannabinoid versus other anti-emetic agent, Outcome 17: Participant preference

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
2.17.1 Prochlorperazine						
Ahmedzai 1983	12	27	7	30	11.0%	1.90 [0.88 , 4.13]
Einhorn 1981	60	80	17	80	15.8%	3.53 [2.27 , 5.48]
Herman 1979	85	113	18	113	15.9%	4.72 [3.05 , 7.31]
Johansson 1982	13	18	3	18	7.8%	4.33 [1.48 , 12.66]
McCabe 1988	23	36	1	36	3.2%	23.00 [3.28 , 161.35]
Niiranen 1985	16	24	6	24	11.3%	2.67 [1.26 , 5.64]
Steele 1980	23	53	10	43	13.1%	1.87 [1.00 , 3.48]
Subtotal (95% CI)		**351**		**344**	**78.0%**	**3.24 [2.23 , 4.72]**
Total events:	232		62			
Heterogeneity: Tau² = 0.12; Chi² = 12.19, df = 6 (P = 0.06); I² = 51%						
Test for overall effect: Z = 6.15 (P < 0.00001)						
2.17.2 Metoclopramide						
Crawford 1986	12	32	10	32	12.2%	1.20 [0.61 , 2.37]
Subtotal (95% CI)		**32**		**32**	**12.2%**	**1.20 [0.61 , 2.37]**
Total events:	12		10			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.52 (P = 0.60)						
2.17.3 Chlorpromazine						
George 1983	10	20	5	20	9.7%	2.00 [0.83 , 4.81]
Subtotal (95% CI)		**20**		**20**	**9.7%**	**2.00 [0.83 , 4.81]**
Total events:	10		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.55 (P = 0.12)						
Total (95% CI)		**403**		**396**	**100.0%**	**2.76 [1.88 , 4.03]**
Total events:	254		77			
Heterogeneity: Tau² = 0.19; Chi² = 20.67, df = 8 (P = 0.008); I² = 61%						
Test for overall effect: Z = 5.21 (P < 0.00001)						
Test for subgroup differences: Chi² = 6.56, df = 2 (P = 0.04), I² = 69.5%						



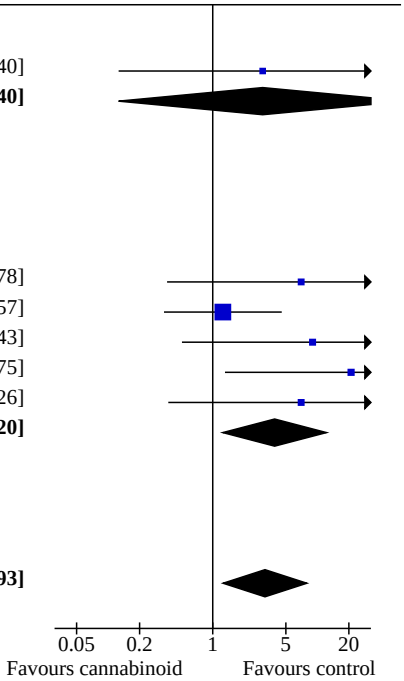
Analysis 2.18. Comparison 2: Cannabinoid versus other anti-emetic agent, Outcome 18: Withdrawal for any reason

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
2.18.1 Prochlorperazine						
Lane 1991	14	21	4	21	100.0%	3.50 [1.38 , 8.89]
Subtotal (95% CI)		**21**		**21**	**100.0%**	**3.50 [1.38 , 8.89]**
Total events:	14		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.63 (P = 0.008)						
Test for subgroup differences: Not applicable						

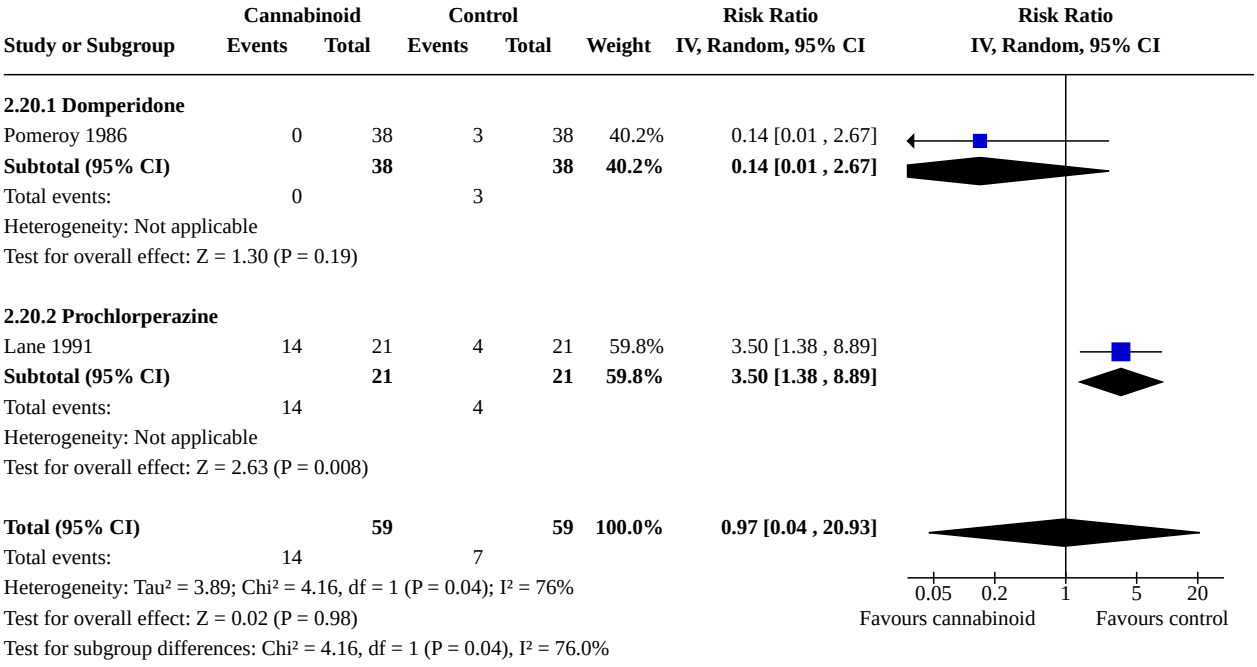


Analysis 2.19. Comparison 2: Cannabinoid versus other anti-emetic agent, Outcome 19: Withdrawal due to adverse event

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
2.19.1 Domperidone						
Pomeroy 1986	1	38	0	38	8.4%	3.00 [0.13 , 71.40]
Subtotal (95% CI)		**38**		**38**	**8.4%**	**3.00 [0.13 , 71.40]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
2.19.2 Prochlorperazine						
Einhorn 1981	3	100	0	100	9.8%	7.00 [0.37 , 133.78]
Herman 1979	5	152	4	152	50.6%	1.25 [0.34 , 4.57]
Johansson 1982	4	27	0	27	10.3%	9.00 [0.51 , 159.43]
Lane 1991	10	21	0	21	11.0%	21.00 [1.31 , 336.75]
Niiranen 1985	3	32	0	32	9.9%	7.00 [0.38 , 130.26]
Subtotal (95% CI)		**332**		**332**	**91.6%**	**3.90 [1.25 , 12.20]**
Total events:	25		4			
Heterogeneity: $Tau^2 = 0.31$; $Chi^2 = 4.83$, df = 4 (P = 0.31); $I^2 = 17\%$						
Test for overall effect: Z = 2.34 (P = 0.02)						
Total (95% CI)		**370**		**370**	**100.0%**	**3.16 [1.26 , 7.93]**
Total events:	26		4			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.83$, df = 5 (P = 0.44); $I^2 = 0\%$						
Test for overall effect: Z = 2.45 (P = 0.01)						
Test for subgroup differences: $Chi^2 = 0.02$, df = 1 (P = 0.88), $I^2 = 0\%$						



Analysis 2.20. Comparison 2: Cannabinoid versus other antiemetic agent, Outcome 20: Withdrawal due to lack of efficacy



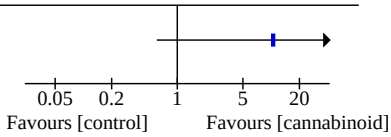
Comparison 3. Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Absence of nausea	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.2 Absence of vomiting	2	89	Risk Ratio (IV, Random, 95% CI)	1.47 [0.69, 3.13]
3.3 Absence of nausea and vomiting	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.4 Depression	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.5 Dizziness	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.6 Dysphoria	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.7 Paranoia	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.8 Sedation	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.9 Withdrawal for any reason	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
3.10 Withdrawal due to adverse event	2	105	Risk Ratio (IV, Random, 95% CI)	6.97 [0.88, 55.19]
3.11 Withdrawal due to lack of efficacy	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Analysis 3.1. Comparison 3: Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy, Outcome 1: Absence of nausea

Study or Subgroup	Cannabinoid cotherapy Events	Total	Control Events	Total	Risk Ratio IV, Random, 95% CI
Lane 1991	4	17	0	20	10.50 [0.61 , 182.09]

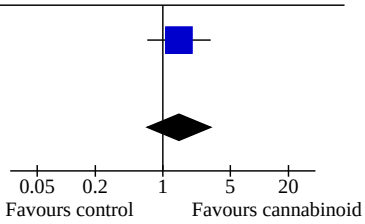
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy, Outcome 2: Absence of vomiting

Study or Subgroup	Cannabinoid Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Kleinman 1983	12	28	7	24	100.0%	1.47 [0.69 , 3.13]
Lane 1991	0	17	0	20		Not estimable
Total (95% CI)		**45**		**44**	**100.0%**	**1.47 [0.69 , 3.13]**
Total events:	12		7			

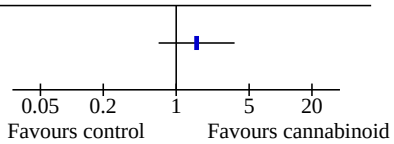
Heterogeneity: Not applicable
Test for overall effect: Z = 1.00 (P = 0.32)
Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3: Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy, Outcome 3: Absence of nausea and vomiting

Study or Subgroup	Cannabinoid Events	Total	Control Events	Total	Risk Ratio IV, Random, 95% CI
Lane 1991	8	17	6	20	1.57 [0.68 , 3.63]

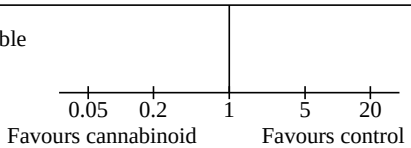
Test for subgroup differences: Not applicable



Analysis 3.4. Comparison 3: Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy, Outcome 4: Depression

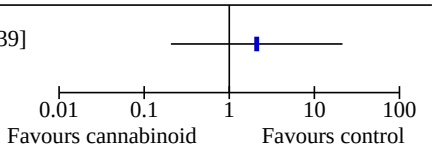
Study or Subgroup	Cannabinoid Events	Total	Control Events	Total	Risk Ratio IV, Random, 95% CI
Lane 1991	0	20	0	21	Not estimable

Test for subgroup differences: Not applicable



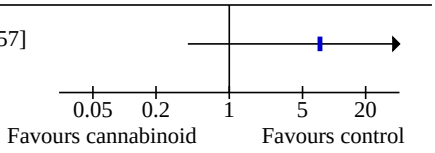
Analysis 3.5. Comparison 3: Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy, Outcome 5: Dizziness

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Control Events	Control Total	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Lane 1991	2	20	1	21	2.10 [0.21 , 21.39]	
Test for subgroup differences: Not applicable						



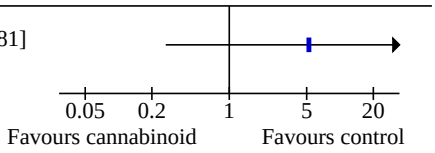
Analysis 3.6. Comparison 3: Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy, Outcome 6: Dysphoria

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Control Events	Control Total	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Lane 1991	3	20	0	21	7.33 [0.40 , 133.57]	
Test for subgroup differences: Not applicable						



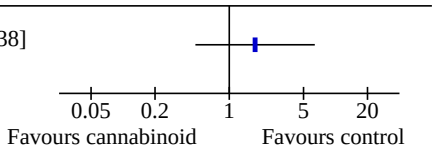
Analysis 3.7. Comparison 3: Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy, Outcome 7: Paranoia

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Control Events	Control Total	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Lane 1991	2	20	0	21	5.24 [0.27 , 102.81]	
Test for subgroup differences: Not applicable						



Analysis 3.8. Comparison 3: Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy, Outcome 8: Sedation

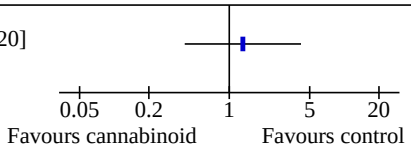
Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Control Events	Control Total	Risk Ratio IV, Random, 95% CI	Risk Ratio IV, Random, 95% CI
Lane 1991	5	20	3	21	1.75 [0.48 , 6.38]	
Test for subgroup differences: Not applicable						



Analysis 3.9. Comparison 3: Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy, Outcome 9: Withdrawal for any reason

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Control Events	Control Total	Risk Ratio IV, Random, 95% CI
Lane 1991	5	20	4	21	1.31 [0.41 , 4.20]

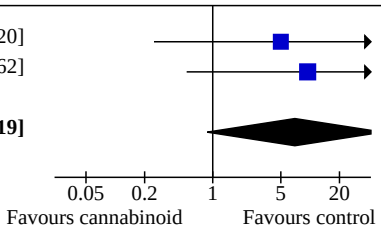
Test for subgroup differences: Not applicable



Analysis 3.10. Comparison 3: Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy, Outcome 10: Withdrawal due to adverse event

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Kleinman 1983	2	32	0	32	47.6%	5.00 [0.25 , 100.20]
Lane 1991	4	20	0	21	52.4%	9.43 [0.54 , 164.62]
Total (95% CI)		**52**		**53**	**100.0%**	**6.97 [0.88 , 55.19]**
Total events:	6		0			

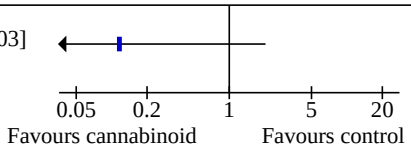
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.76); I² = 0%
Test for overall effect: Z = 1.84 (P = 0.07)
Test for subgroup differences: Not applicable



Analysis 3.11. Comparison 3: Cannabinoid plus other antiemetic agent versus other antiemetic monotherapy, Outcome 11: Withdrawal due to lack of efficacy

Study or Subgroup	Cannabinoid Events	Cannabinoid Total	Control Events	Control Total	Risk Ratio IV, Random, 95% CI
Lane 1991	0	20	4	21	0.12 [0.01 , 2.03]

Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Antineoplastic Agents] explode all trees
#2 MeSH descriptor: [Antineoplastic Combined Chemotherapy Protocols] explode all trees
#3 chemotherap*
#4 #1 or #2 or #3
#5 MeSH descriptor: [Nausea] explode all trees
#6 MeSH descriptor: [Vomiting] explode all trees
#7 nause* or vomit*
#8 emesis* or emetic* or antiemetic* or emetogenic*
#9 #5 or #6 or #7 or #8
#10 MeSH descriptor: [Cannabinoids] explode all trees
#11 MeSH descriptor: [Cannabis] explode all trees

#12 cannab*
#13 dronabinol
#14 nabilone
#15 tetrahydrocannabinol
#16 cesamet
#17 delta-9-THC
#18 delta-9-tetrahydrocannabinol
#19 marinol
#20 #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
#21 #4 and #9 and #20

Appendix 2. MEDLINE search strategy

1 exp Antineoplastic Agents/
2 exp Antineoplastic Combined Chemotherapy Protocols/
3 chemotherap*.mp.
4 1 or 2 or 3
5 exp Nausea/
6 exp Vomiting/
7 (nause* or vomit*).mp.
8 (emesis* or emetic* or antiemetic* or emetogenic*).mp.
9 5 or 6 or 7 or 8
10 exp Cannabinoids/
11 exp Cannabis/
12 cannab*.mp.
13 marinol.mp.
14 dronabinol.mp.
15 nabilone.mp.
16 tetrahydrocannabinol.mp.
17 cesamet.mp.
18 delta-9-THC.mp.
19 delta-9-tetrahydrocannabinol.mp.
20 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21 randomized controlled trial.pt.
22 controlled clinial trial.pt.
23 randomized.ab.
24 placebo.ab.
25 drug therapy.fs.
26 randomly.ab.
27 trial.ab.
28 groups.ab.
29 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30 4 and 9 and 20 and 29

Key: mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier

Appendix 3. EMBASE search strategy

1 exp chemotherapy/
2 exp antineoplastic agent/
3 chemotherap*.mp.
4 1 and 2 and 3
5 exp "nausea and vomiting"/
6 (nause* or vomit*).mp.
7 (emesis* or emetic* or antiemetic* or emetogenic*).mp.
8 5 or 6 or 7
9 exp cannabinoid/
10 cannabis/
11 cannab*.mp.
12 marinol.mp.
13 dronabinol.mp.
14 nabilone.mp.

15 tetrahydrocannabinol.mp.
16 cesamet.mp.
17 delta-9-THC.mp.
18 delta-9-tetrahydrocannabinol.mp.
19 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20 4 and 8 and 19
21 crossover procedure/
22 double-blind procedure/
23 randomized controlled trial/
24 single-blind procedure/
25 random*.mp.
26 factorial*.mp.
27 (crossover* or cross over* or cross-over*).mp.
28 placebo*.mp.
29 (double* adj blind*).mp.
30 (singl* adj blind*).mp.
31 assign*.mp.
32 allocat*.mp.
33 volunteer*.mp.
34 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35 20 and 34

Key: [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

Appendix 4. PsycInfo search strategy

1 antineoplastic drugs/
2 chemotherapy/
3 chemotherap*.mp.
4 1 or 2 or 3
5 nausea/
6 vomiting/
7 nause*.mp.
8 vomit*.mp.
9 (emesis or emetic* or antiemetic* or emetogenic*).mp
10 5 or 6 or 7 or 8 or 9
11 exp cannabinoids/
12 exp cannabis/
13 cannab*.mp.
14 marinol.mp.
15 dronabinol.mp.
16 nabilone.mp.
17 tetrahydrocannabinol.mp.
18 cesamet.mp.
19 delta-9-THC.mp.
20 delta-9-tetrahydrocannabinol.mp.
21 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22 4 and 10 and 21

key: [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]

Appendix 5. LILACS search strategy

((MH:D02.455.848.090$ OR MH:B01.650.940.800.575.100.175.500 OR cannab$ OR marinol OR dronabinol OR nabilone OR tetrahydrocannabinol OR cesamet OR delta-9-THC OR delta-9-tetrahydrocannabinol) AND (MH:nausea or MH:vomiting OR MH:emetics OR MH:antiemetics OR nausea$ OR vomit$ OR emesis OR emetic$ OR emetogenic$ OR antiemetic$) AND (MH:D27.505.954.248$ OR MH:E02.183.750.500 OR MH:E02319.077.500 OR MH:E02.319.310.037 OR chemotherap$))

WHAT'S NEW

Date	Event	Description
11 October 2021	Amended	Most recent search date 11 October 2021. No new studies identified for inclusion.

HISTORY

Protocol first published: Issue 11, 2011
Review first published: Issue 11, 2015

Date	Event	Description
27 November 2019	Amended	A search for studies on 14 November 2019 has identified 2 potentially relevant studies (see 'Characteristics of studies awaiting classification'). These studies have not yet been incorporated into this Cochrane Review.

CONTRIBUTIONS OF AUTHORS

- Lesley Smith: write protocol, screened studies for inclusion, extracted and analysed data, write final review.
- Fredric Azariah: screened searches, screened studies for inclusion, extracted data, contributed to drafts of the review.
- Verna Lavender: classified chemotherapy regimens, assessed nausea and vomiting measurements, contributed to drafts of the review.
- Nicola Stoner: classified chemotherapy regimens, assessed nausea and vomiting measurements, contributed to drafts of the review.
- Silvana Bettiol: screened searches, screened studies for inclusion, extracted data, contributed to drafts of the review.

DECLARATIONS OF INTEREST

The authors have no conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- Cochrane, UK

  Gynaecological Cancer Review Group

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Based on peer review feedback of a draft of the review and inclusion of clinical experts on the review team, we made a number of post-protocol amendments.

'Types of Participants' have changed from "*people* to "*Adults aged 18 years and over*".

We removed the plan for a subgroup analysis "*by emetic potential of the chemotherapy agent, high versus low emetogenic potentia*l" and added a new subgroup analysis "*by history of exposure to chemotherapy, chemotherapy naive versus prior chemotherapy treatment*".T

he primary outcomes we stated in the protocol are listed in the bullet points below. However, we were unable to analyse data for frequency and severity of nausea or vomiting (or both) due to use of non-valid and reliable measures, and inappropriate analysis of results reported in the primary studies. We focused on the proportion of people with cancer with complete absence of nausea or vomiting or both in common with other systematic reviews of treatments for nausea and vomiting.

- Absence of episodes of nausea and vomiting.
- Frequency of nausea and vomiting.

- Severity of nausea.

We also stated that we would only extract data for the outcome 'participant preference' for the first cross-over period only (erroneously), and, due to none of the trials reporting this, we extracted responses for the entire study period.

We added three additional adverse effects as secondary outcomes: focal dystonia, extrapyramidal effects and oculogyric crisis.

We did not contact pharmaceutical companies for data on file.

Methods for future updates

Data extraction and management

For continuous outcomes (severity of nausea measured using a validated symptom scale), we will extract the final value and standard deviation of the outcome of interest and the number of participants assessed in each treatment arm at the end of follow-up in order to estimate the mean difference between treatment arms (or standardised mean difference if measured on different scales) and its standard error.

Data for frequency of nausea or vomiting, or both, may be reported in a number of ways. For data presented as counts (number of nausea or vomiting (or both) episodes), we will extract the number of events and person-time at risk, if presented, in order to calculate a nausea and vomiting rate per treatment group. For data presented as continuous data, we will extract the mean number of events (nausea or vomiting (or both) episodes) in each treatment group. For data presented as categorical data (number of participants who experience at least five events), we will proceed as described above for dichotomous data.

Data collection and analysis

If the results are statistically significant, we will calculate the number needed to treat for an additional beneficial outcome (NNTB) or additional harmful outcome (NNTH). For continuous outcomes, we will calculate the difference in means between treatment arms at the end of follow-up. We will consider the magnitude of the effect of an intervention as at least moderate if the 'effect size' is superior to 0.5 (Cohen 1988). For outcomes reported as rates, we will calculate the rate ratio.

Wherever the data are missing or only imputed data are reported, we will contact the trial authors and request the data on the outcomes only among the participants who were assessed.

Where the trials have multiple treatment groups, we will divide the 'shared' comparison group into the number of treatment groups and treat comparisons between each treatment group and the split comparison group as independent comparisons.

Unit of analysis

In future updates it may be possible to:

- obtain data from study authors for each treatment period or summary statistics of the degree of agreement between each person's responses, or both;
- adjust the analyses for the dichotomous outcomes to take into account the paired data.

INDEX TERMS

Medical Subject Headings (MeSH)

Antiemetics [adverse effects] [*therapeutic use]; Antineoplastic Agents [adverse effects]; Cannabinoids [adverse effects] [*therapeutic use]; Chlorpromazine [adverse effects] [therapeutic use]; Dizziness [chemically induced]; Domperidone [adverse effects] [therapeutic use]; Euphoria; Metoclopramide [adverse effects] [therapeutic use]; Nausea [chemically induced] [*drug therapy]; Neoplasms [*drug therapy]; Prochlorperazine [adverse effects] [therapeutic use]; Randomized Controlled Trials as Topic; Vomiting [chemically induced] [*drug therapy]

MeSH check words

Adult; Humans