

Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review

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Abstract

Objective To quantify the antiemetic efficacy and adverse effects of cannabis used for sickness induced by chemotherapy.

Design Systematic review.

Data sources Systematic search (Medline, Embase, Cochrane library, bibliographies), any language, to August 2000.

Studies 30 randomised comparisons of cannabis with placebo or antiemetics from which dichotomous data on efficacy and harm were available (1366 patients). Oral nabilone, oral dronabinol (tetrahydrocannabinol), and intramuscular levonantradol were tested. No cannabis was smoked. Follow up lasted 24 hours.

Results Cannabinoids were more effective antiemetics than prochlorperazine, metoclopramide, chlorpromazine, thiethylperazine, haloperidol, domperidone, or alizapride: relative risk 1.38 (95% confidence interval 1.18 to 1.62), number needed to treat 6 for complete control of nausea; 1.28 (1.08 to 1.51), NNT 8 for complete control of vomiting. Cannabinoids were not more effective in patients receiving very low or very high emetogenic chemotherapy. In crossover trials, patients preferred cannabinoids for future chemotherapy cycles: 2.39 (2.05 to 2.78), NNT 3. Some potentially beneficial side effects occurred more often with cannabinoids: "high" 10.6 (6.86 to 16.5), NNT 3; sedation or drowsiness 1.66 (1.46 to 1.89), NNT 5; euphoria 12.5 (3.00 to 52.1), NNT 7. Harmful side effects also occurred more

often with cannabinoids: dizziness 2.97 (2.31 to 3.83), NNT 3; dysphoria or depression 8.06 (3.38 to 19.2), NNT 8; hallucinations 6.10 (2.41 to 15.4), NNT 17; paranoia 8.58 (6.38 to 11.5), NNT 20; and arterial hypotension 2.23 (1.75 to 2.83), NNT 7. Patients given cannabinoids were more likely to withdraw due to side effects 4.67 (3.07 to 7.09), NNT 11.

Conclusions In selected patients, the cannabinoids tested in these trials may be useful as mood enhancing adjuvants for controlling chemotherapy related sickness. Potentially serious adverse effects, even when taken short term orally or intramuscularly, are likely to limit their widespread use.

Introduction

Sections of the medical establishment have pleaded for legalisation of cannabis (marijuana) for medical use.^{1 2} Interest in cannabis and its active constituents, cannabinoids, as therapeutic agents has increased recently.³ Dronabinol (Δ^9 -tetrahydrocannabinol, one of the main ingredients in cannabis) and the synthetic cannabinoid compound nabilone are available by prescription in some countries.

A Medline search using the terms cannabis, cannabinoids, marijuana, and marijuana smoking found 6059 articles from 1975 to 1996; most were on the antiemetic properties of cannabis.⁴ Surveys of oncologists' choices of treatment for emesis caused by chemotherapy came to divergent results.⁴ In one, 63% of responding oncologists agreed with the statement affirming the efficacy of cannabis for treatment of

emesis.⁵ In another, oncologists ranked dronabinol or smoked cannabis only ninth out of nine choices for mild nausea, and sixth out of nine for severe nausea.⁶ An early literature review on cannabinoids and emesis concluded that orally administered dronabinol represented a major advance in antiemetic therapy.⁷

We searched systematically for the strongest evidence of efficacy and harm of cannabis in patients having chemotherapy. We examined whether there is any evidence that cannabis is antiemetic when given concomitantly with emetogenic chemotherapy, how well cannabis works in this setting compared with placebo or conventional antiemetics, the evidence for a dose-response relation, and the profile of adverse effects.

Methods

Search strategy

We searched Medline, Embase, and the *Cochrane Library* systematically for randomised controlled comparisons of the antiemetic efficacy of cannabis (experimental intervention) with any antiemetic or placebo (control) in chemotherapy. Only full publications in peer reviewed journals were considered.

Critical appraisal

All retrieved reports were checked for inclusion criteria by one author, and those definitely not relevant were excluded at this stage. All potentially relevant reports were then read by all authors independently to assess adequacy of randomisation and blinding and description of withdrawals according to the validated three item, five point Oxford score.⁸ The maximum score of an included randomised controlled trial was five and the minimum was one. Authors met to reach a consensus.

Data extraction

From relevant reports we obtained information on patients, dose of cannabis and control treatments, chemotherapy regimens, and relevant end points. The end point of primary interest was antiemetic efficacy. Because of inconsistency in definitions we extracted only dichotomous data that came closest to complete control (that is, absence) of nausea or vomiting in the first 24 hours of chemotherapy. The end point of secondary interest was the number of patients who, after completion of the trial, expressed preference for cannabis or control for future chemotherapy cycles. Data on adverse effects were extracted when reported in dichotomous form.

Quantitative analysis

As an estimate of the significance of a difference between cannabis and control treatments we calculated relative risks with 95% confidence intervals.⁹ For combined data, a fixed effect model was used because heterogeneity tests lack sensitivity and because we pooled data only when they were clinically homogeneous.¹⁰ Clinical relevance of treatment effect was expressed as numbers needed to treat and 95% confidence intervals.¹¹ When the 95% confidence interval of the relative risk excluded 1, the 95% confidence interval for the number needed to treat ranged from a positive limit to a negative limit, indicating that the confidence interval includes infinity.¹²

We looked for a dose-response relation in data from clinically homogeneous subgroups. Such subgroups had to report comparisons of different doses of one cannabinoid (for instance, nabilone) with one comparator (for instance, placebo), have a similar underlying emetogenic risk (for instance, highly emetogenic chemotherapy with cisplatin), and have a well defined end point (for instance, complete control of vomiting).

Results

Included and excluded trials

We screened 198 reports; 51 were potentially relevant randomised controlled trials. Twenty one were subsequently excluded. We analysed data from 30 randomised controlled trials published between 1975 and 1997 (see *BMJ's* website for details). In the 30 trials, 1760 patients were randomised, but subsequently 394 (22%) were excluded by the original trialists. Thus, efficacy data from 1366 patients could be analysed. The average trial size was 46 patients (range 8 to 139).

Three different cannabinoids were tested. Oral nabilone was tested in 16 trials, oral dronabinol in 13, and intramuscular levonantradol in one.

Commonest controls were prochlorperazine (12 trials), and placebo (10 trials). Other comparators were metoclopramide (four), chlorpromazine (two), thiethylperazine (one), haloperidol (one), domperidone (two), and alizapride (one).

Antiemetic efficacy

The 10 trials that reported dichotomous data on nausea or vomiting showed a wide variability in event rates with both cannabinoids and controls (fig 1); the event rate scatter suggested increased efficacy with cannabinoids and relative homogeneity of the data.¹³⁻²¹

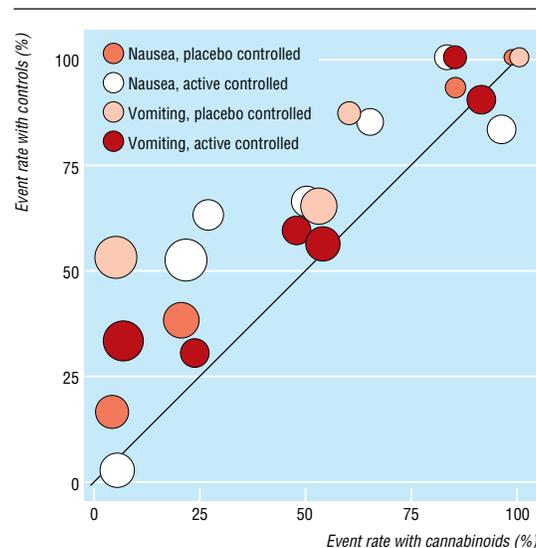


Fig 1 Incidences of nausea and vomiting with cannabinoids and control treatments. Each symbol represents one trial. Data are from 10 trials that reported separate dichotomous data on nausea or vomiting. Two trials had two comparators (active and placebo) and nine trials had data on both nausea and vomiting. Symbol sizes are proportional to trial sizes. The solid line represents equality

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Table 1 Control of nausea and vomiting and patients' preference for treatment in trials of cannabinoid against active antiemetic or control treatment

End point	No of trials	Event rate (No of patients)		Relative risk (95% CI)	No needed to treat (95% CI)
		Cannabis (%)	Control (%)		
Control of nausea and vomiting					
Complete control of nausea v placebo	4	70 (81/116)	57 (66/115)	1.21 (1.03 to 1.42)	8.0 (4.0 to 775)
Complete control of vomiting v placebo	4	66 (76/116)	36 (41/115)	1.84 (1.42 to 2.38)	3.3 (2.4 to 5.7)
Complete control of nausea v active	7	59 (122/207)	43 (93/215)	1.38 (1.18 to 1.62)	6.4 (4.0 to 16)
Complete control of vomiting v active	6	57 (111/194)	45 (90/201)	1.28 (1.08 to 1.51)	8.0 (4.5 to 38)
Sensitivity analysis (cannabinoids v active)					
Complete control of nausea:					
Event rate in controls 25% to 75%	3	70 (75/107)	41 (46/112)	1.70 (1.32 to 2.18)	3.4 (2.4 to 6.1)
Event rate in controls <25% or >75%	4	47 (47/100)	46 (47/103)	1.06 (0.88 to 1.27)	73 (6.6 to -8.1)
Complete control of vomiting					
Event rate in controls 25% to 75%	4	72 (105/146)	57 (87/153)	1.26 (1.07 to 1.48)	6.6 (3.9 to 23)
Event rate in controls <25% or >75%	2	13 (6/48)	6 (3/48)	1.86 (0.53 to 6.47)	16 (5.6 to -19)
Patients' rating					
Preference for cannabinoid v placebo	4	76 (153/202)	13 (27/202)	5.67 (3.95 to 8.15)	1.6 (1.4 to 1.8)
Preference for cannabinoid v active	14	61 (371/604)	26 (156/608)	2.39 (2.05 to 2.78)	2.8 (2.4 to 3.3)

Active=prochlorperazine, metoclopramide, chlorpromazine, tiethylperazine, haloperidol, domperidone, alizapride.

Complete control of nausea or vomiting

Across all trials, cannabinoids were more effective than active comparators and placebo (table 1). Six to eight patients needed to be treated with cannabinoids for one to benefit who would have vomited or had nausea had they all received a conventional antiemetic.

Sensitivity analyses

One trial reported very low event rates in the control groups: 16% of patients felt nauseous with placebo and 2% with prochlorperazine.¹⁷ Chemotherapy was mainly with low emetogenic substances (vincristine, fluorouracil) (table 1).

Six trials reported event rates above 75% in the control group (fig 1). In two nausea rates with placebo were 93% and 100%, respectively, and vomiting rates were 87% and 100%.^{15 16} Chemotherapy was with high dose methotrexate¹⁵ or with doxorubicin and cytoxan.¹⁶ In one trial rates of nausea and vomiting were 100% despite prochlorperazine¹⁸; chemotherapy was with cisplatin. In two trials, the nausea rate was 85% despite alizapride²⁰ and 83% despite prochlorperazine²¹; again, the chemotherapy regimen contained cisplatin. Finally, in one trial 90% of controls receiving prochlorperazine vomited; chemotherapy was with moderately emetogenic drugs (cyclophosphamide, methotrexate, fluorouracil).¹⁴

When data from active controlled trials with medium event rates in controls (25% to 75%) were combined, cannabinoids were superior to conventional antiemetics, and numbers needed to treat were below 4 to prevent nausea and below 7 to prevent vomiting (table 1). When data from active controlled trials with extreme event rates in control groups (<25% and 75% >) were combined, there were no significant differences between cannabinoids and active comparators (table 1). It became clear that cannabinoids were antiemetic only when the components of the chemotherapy regimen and the event rates in control patients suggested a medium emetogenic setting.

Patients' preference

At the end of 18 crossover trials, patients were asked which treatment they preferred for further chemotherapy cycles. Between 38% and 90% of patients preferred cannabinoids (fig 2). In four placebo controlled

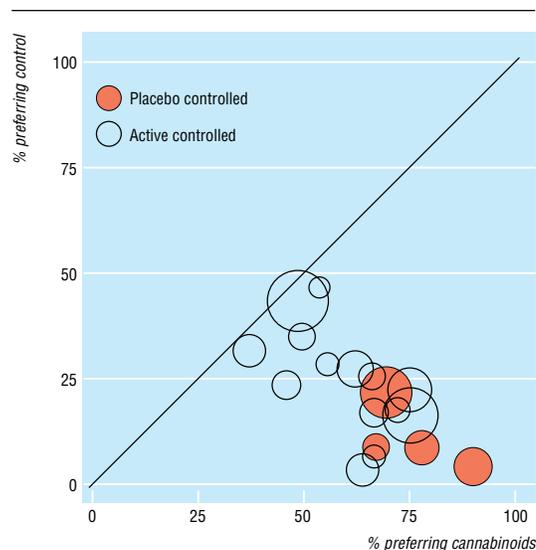


Fig 2 Percentages of patients preferring cannabinoids or control for future chemotherapy. Each symbol represents one trial. Symbol sizes are proportional to trial sizes. The solid line represents equality

crossover trials preference for placebo was between 4% and 22%.²²⁻²⁵ The difference in favour of cannabinoids was significant (table 2). In 14 active controlled crossover trials 3% to 46% of patients preferred the standard antiemetic.^{13 14 18 20 26-34} The difference in favour of cannabinoids was significant (table 1).

Side effects

Side effects happened significantly more often with cannabinoids (table 2). Some side effects could be classified as potentially beneficial (for instance, a sensation of a "high," euphoria, and drowsiness, sedation, or somnolence) whereas others were definitely harmful (for instance, dysphoria and depression, hallucinations, or paranoia). Hallucinations and paranoia occurred exclusively with cannabinoids. Arterial hypotension (>20% decrease in blood pressure compared with baseline) was also more common with cannabinoids (table 2). In 19 trials, the number of patients who withdrew from the study due to intolerable adverse effects was significantly increased with cannabinoids (table 2).

Table 2 Rates of side effects among patients receiving cannabinoid antiemetic treatment compared with placebo or active control

End point	No of trials	Event rate (No of patients)		Relative risk (95% CI)	No needed to treat (95% CI)
		Cannabis (%)	Control (%)		
"Beneficial" central side effects:					
"High" sensation	8	35 (162/470)	3 (17/562)	10.6 (6.86 to 16.5)	3.2 (2.8 to 3.7)
Drowsiness, sedation, somnolence	15	50 (320/636)	30 (224/737)	1.66 (1.46 to 1.89)	5.0 (4.0 to 6.8)
Euphoria*	3	14 (24/168)	1 (1/168)	12.5 (3.00 to 52.1)	7.3 (5.2 to 12)
Harmful central side effects:					
Dizziness*	9	49 (173/357)	17 (57/344)	2.97 (2.31 to 3.83)	3.1 (2.6 to 3.9)
Dysphoria or depression	10	13 (39/312)	0.3 (1/378)	8.06 (3.38 to 19.2)	8.2 (6.3 to 12)
Hallucination	10	6 (26/435)	0 (0/424)	6.10 (2.41 to 15.4)	17 (12 to 27)
Paranoia	6	5 (14/285)	0 (0/286)	8.58 (6.38 to 11.5)	20 (13 to 42)
Hypotension	13	25 (124/497)	11 (53/485)	2.23 (1.75 to 2.83)	7.1 (5.3 to 11)
Withdrawal due to side effects	19	11 (108/1003)	2 (18/1108)	4.67 (3.07 to 7.09)	11 (8.9 to 14)

*No studies used a placebo control.

Discussion

The evidence we have from randomised trials shows cannabinoids to be slightly better than conventional antiemetics for treating chemotherapy induced emesis, and patients prefer them. They are also more toxic. Two extreme positions could be taken, perhaps using the following arguments.

Arguments for and against

The optimistic position favours cannabinoids. Overwhelmingly, patients preferred cannabinoids for future chemotherapy, even though cannabinoids were only slightly more effective than other antiemetics and only for moderately emetogenic chemotherapy. Patients' subjective view on preference is more important than the scientifically evaluated efficacy of that intervention. Although side effects occur more often with cannabinoids, these may be concentrated in a fairly small number of patients so that most patients find cannabinoids effective without undue adverse effects. There are even some potentially beneficial side effects. Of 100 cancer patients undergoing chemotherapy who received a cannabinoid 30 more would be sedated, 20 would feel a sensation of a "high," and 15 would feel euphoric compared with 100 who received a conventional antiemetic. Some patients may perceive a degree of sedation or somnolence as useful during chemotherapy. Thus, further clinical trials with cannabinoids in chemotherapy are justified.

The pessimistic position favours conventional antiemetics, as cannabinoids are not much better, and their toxicity is unacceptably high (dizziness, dysphoria, hallucinations, paranoia). The toxic effects may lead to study withdrawal. There were no comparisons of cannabinoids with a serotonin (5-HT₃) receptor antagonist, the best comparator for prevention of acute emesis in highly emetogenic chemotherapy. It is, however, unlikely that cannabinoids would be more effective and less toxic than a 5-HT₃ receptor antagonist.

The correct position is probably somewhere in the middle. Undoubtedly, most patients preferred cannabinoids for future chemotherapy cycles. One in two compared with placebo, and one in three compared with conventional antiemetics would have preferred to receive cannabinoids again. We do not know whether the incidence of cannabinoid related "beneficial" side effects was related to this overwhelming preference for cannabinoids for future chemotherapy.

Efficacy and safety

Before a chemical compound can be recommended for medical use, both its efficacy and safety must be proved. Cannabinoids were more effective than conventional antiemetics (prochlorperazine, metoclopramide). Of 100 cancer patients treated with oral cannabinoids during chemotherapy, 16 will not be nauseated (number needed to treat 6.4) and 13 will not vomit (8) who would have done so had they all received a conventional antiemetic. Compared with placebo, cannabinoids were obviously better, although a placebo may not be an adequate comparator in patients having chemotherapy.

Defining an intervention's usefulness includes estimates of the likelihood for harm. The physical and neuropsychiatric adverse effects of long term use of cannabis are well established, based mainly on observations from long term marijuana smokers.³⁵ Our systematic review shows clearly that cannabinoids are toxic for many patients even when taken orally and acutely (for 24 hours). Some adverse effects occurred almost exclusively with cannabinoid exposure. For instance, 5% of patients had paranoia, 6% had hallucinations, and almost 13% had dysphoria or depression (table 2). The number of patients withdrawing from the studies due to intolerable side effects is the most reliable parameter of the severity of cannabinoid related toxicity. One in eleven patients treated with cannabinoids will stop treatment who would not have stopped treatment had they taken a placebo or another antiemetic. This is an important new message for doctors, policy makers, and patients.

These results should make us think hard about the ethics of clinical trials of cannabinoids when safe and effective alternatives are known to exist and when efficacy of cannabinoids is known to be marginal. The trials analysed here are likely to be the largest subgroup on the medical use of cannabinoids and therefore the single most important source of information on their potential for harm.

Effect of bias

This meta-analysis is open to some biases, and they all have the potential to overestimate the efficacy and to underestimate the harm of cannabinoids. Cannabinoids were given as tablets or intramuscular injection, so any psychological effect of smoking a joint was not a factor. However, cannabinoids showed specific adverse effects that control treatments did not, and their incidence was high. In one trial of oral nabilone, many

patients identified which drug they received because of the adverse effects experienced.³³ In a series of 100 blinded dronabinol and placebo treatments, nurses correctly identified the active treatment in 85% and patients in 95%; seven of the 10 errors were made by patients on the first drug trial of the study.³⁶ We must therefore assume that most of these trials had some degree of observer bias.

Some trials studied selected groups of patients who either had not responded to conventional antiemetic prophylaxis during previous chemotherapy cycles (“high risk” patients) or regularly used cannabis. Both subgroups introduce a bias in favour of cannabinoids.

Finally, we have the problem of size. Small trials can be greatly affected by the random play of chance.³⁷ Of the 30 studies available for analysis, only nine had over 50 analysable patients and only four more than 100. Small size has been shown to overestimate treatment effects in other circumstances,³⁸ and it is not possible to rule out similar effects here.

Implications

The research agenda needs to be clear. Priority should go to trials of cannabinoids for indications where there are few competing drugs, such as spasticity in multiple sclerosis. In chemotherapy, the combination of weak antiemetic efficacy with potentially beneficial side effects (sedation, euphoria) raises the question whether further trials should be designed to establish the usefulness of cannabinoids as adjuncts to modern antiemetics (for instance, 5-HT₃ receptor antagonists). Minimal effective doses would then be needed. Identification of patients who are most likely to profit from the antiemetic effect of cannabinoids and least likely to suffer from neuropsychiatric adverse effects is needed.

In conclusion, the cannabinoids reviewed here were slightly superior to conventional antiemetics after chemotherapy, and patients preferred them. However, potentially serious adverse effects, even when the drugs are taken short term orally or intramuscularly, are likely to limit their widespread use. In selected patients, cannabinoids may be useful as mood enhancing adjuncts for the control of chemotherapy related sickness.

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Contributors: MRT initiated the project, searched, extracted, and analysed the data and is the study guarantor. DC initiated the project, searched and cross checked extracted data. DJMR, FAC, RAM, and HJM cross checked extracted data. RAM and HJM provided the Excel template for data analyses. All authors participated in discussing the results and in writing the paper.

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What is already known on this topic

Requests have been made for legalisation of cannabis (marijuana) for medical use

Long term smoking of cannabis can have physical and neuropsychiatric adverse effects

Cannabis may be useful in the control of chemotherapy related sickness

What this study adds

Oral nabilone and dronabinol and intramuscular levonantradol are superior to conventional antiemetics (such as prochlorperazine or metoclopramide) in chemotherapy

Side effects are common with cannabinoids, and although some may be potentially beneficial (euphoria, “high,” sedation), others are harmful (dysphoria, depression, hallucinations)

Many patients have a strong preference for cannabinoids

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