Therapeutic use of *Cannabis sativa* on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis

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This paper aims to evaluate the anti-emetic efficacy of cannabinoids in cancer patients receiving chemotherapy using a systematic review of literature searched within electronic databases such as PUBMED, EMBASE, PSYCINFO, LILACS, and 'The Cochrane Collaboration Controlled Trials Register'. Studies chosen were randomized clinical trials comprising all publications of each database until December 2006. From 12 749 initially identified papers, 30 fulfilled the inclusion criteria for this review, with demonstration of superiority of the anti-emetic efficacy of cannabinoids compared with conventional drugs and placebo. The adverse effects were more intense and occurred more often among patients who used cannabinoids. Five meta-analyses were carried out: (1) dronabinol versus placebo [$n = 185$; relative risk (RR) = 0.47; confidence interval (CI) = 0.19–1.16]; (2) Dronabinol versus neuroleptics [$n = 325$; RR = 0.67; CI = 0.47–0.96; number needed to treat (NNT) = 3.4]; (3) nabilone versus neuroleptics ($n = 277$; RR = 0.88; CI = 0.72–1.08); (4) levonantradol versus neuroleptics ($n = 194$; RR = 0.94; CI = 0.75–1.18); and (5) patients' preference for cannabis or other drugs ($n = 1138$; RR = 0.33; CI = 0.24–0.44; NNT = 1.8). The superiority of the anti-emetic efficacy of cannabinoids was demonstrated through meta-analysis.

Keywords: cancer, cannabis, chemotherapy, meta-analysis, randomized clinical trial, systematic review.

INTRODUCTION

Marijuana has been used by throughout human history for many purposes (Karniol 2000). It was listed on the American pharmacopoeia until 1944 (Bonnie & Whitebread 1974), when it was removed due to political pressure to ban its use in the US (Walsh *et al*. 2003).

Although marijuana has not returned to the American pharmacopoeia, in 1986 the Food and Drug Administration authorised the use of its active element, delta-9-tetrahydrocannabinol (THC), for medical purposes (Walsh *et al*. 2003) to treat nausea and vomiting side effects in patients receiving chemotherapy.

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Cannabinoids interact with various neurotransmitters and neuromodulators, such as gamma-aminobutyric acid (GABA), histamine, serotonin, dopamine, glutamate, norepinephrine, prostaglandins and opioid peptides (Grotenhermen 2002b).

Aside from these neurotransmitters, there seems to exist in the brain a 'cannabinoid system' (Karniol 2000). This system probably interacts with the classic neurotransmission systems to produce the pharmacological actions of *Cannabis sativa* (Pertwee 1990; Adams & Martin 1996; Mallet & Beninger 1996; Felder & Glass 1998). The existence of a cannabinoid neurotransmission system in the central nervous system, the function of which is still unknown, opens a wide potential for the discovery of therapeutic drugs with action on it (Karniol 2000).

Nausea and vomiting, which can be 'acute', 'retarded' or 'anticipatory' reactions (Fiori & Gralla 1984), are the chemotherapy side effects considered by patients as the most stressful (Barowski 1984). Up to three-fourths of all cancer patients experience chemotherapy-related emesis (Schwartzberg 2007). Chemotherapy-induced nausea and vomiting also have the potential to cause depression, anxiety and a feeling of helplessness (Wilcox *et al.* 1982; Dodds 1985).

Today, there are three synthetic cannabinoid drugs that have been evaluated in clinical trials for the treatment of nausea and vomiting in patients receiving chemotherapy: delta-9-THC, nabilone and levonantradol (Walsh *et al.* 2003).

Up until now, two medications, Marinol (dronabinol, delta-9-THC) and Cesamet (nabilone), have been approved to be prescribed for nausea and vomiting associated with chemotherapy in cancer patients. Marinol has also been approved for use in cases of anorexia and cachexia in AIDS patients (Grotenhermen 2002a).

This study describes a systematic research for evaluation of cannabis as a therapeutic agent for treating chemotherapy-induced nausea and vomiting in cancer patients.

OBJECTIVE

This review aims to evaluate, through a systematic literature review, interventions using *C. sativa* in the treatment of nausea and vomiting in patients with any type of cancer receiving chemotherapy, tested in randomized clinical trials and compared with any type of control group.

METHODS

Systematic review

Criteria for inclusion in this review

Type of study All randomized clinical trials about the subject published in the literature were objects for this study.

Type of participant People with any type of cancer receiving chemotherapeutic treatment, irrespective of gender, age and place of treatment. The chemotherapeutic schemes included those of low, moderate and high emetic potential.

Type of intervention Pharmacological interventions based on substances derived from *C. sativa* and/or smoked cannabis, irrespective of the time of intervention and of the association with other types of therapy for nausea and vomiting in cancer patients receiving chemotherapy.

Search strategy for study identification

Searches were made on the electronic databases MEDLINE (PUBMED), EMBASE, PSYCINFO, LILACS and 'The Cochrane Collaboration Controlled Trials Register'. The bibliographic search strategy comprised the initial period of the databases until December 2006. The first authors of the selected studies were contacted, and the bibliographies and references of these papers were also examined. There was no language restriction, but only complete papers published in peer-reviewed journals were considered. Data related to other clinical settings (e.g. radiotherapy) were not considered.

The search expression was based on the following Medical Subject Heading terms and categories: 'therapeutics', 'drug therapy', 'chemical and pharmacologic phenomena', 'neoplasms', 'antineoplastic and immunosuppressive agents', 'marijuana abuse', '*Cannabis*', 'randomized controlled trials', 'double-blind method', 'single-blind method', 'clinical trials', 'placebos', 'research design', 'comparative study', 'evaluation studies', 'follow-up studies', 'prospective studies' and 'random allocation'. Adjustments were made to the terms used according to the electronic database consulted.

Study description

The characteristics of the included studies are shown in Table 1.

Methodological quality of the included studies

The methodological quality evaluation of the clinical studies is considered of vital importance for conducting

Table 1 Characteristics of the included studies

Study	Methods	Participants	Interventions and therapeutic schedules	Outcomes	Chemotherapic agents	Methodologic quality
Ahmedzai *et al.* (1983)	Randomized, cross-over and double-blind	Patients with lung cancer (small cell bronchial carcinoma)	Nabilone 2 mg × 2 (27) vs prochlorperazine 10 mg × 3 (30)	Nausea, vomiting, anorexia, adverse effects and preference	Cyclophosphamide, adriamycin, etoposide, methotrexate, vincristin	B
Chan *et al.* (1987)	Randomized, cross-over and double-blind	Children with various paediatric malignancies	Nabilone 1–4 mg (30) vs prochlorperazine 5–20 mg (30)	Vomiting, adverse effects and preference	Doxorubicin, cyclophosphamide fluorouracil, methotrexate, vincristin, etoposide; cisplatin was not used	B
Chang *et al.* (1979)	Randomized, double-blind and paired (dronabinol-placebo or placebo-dronabinol)	Patients with osteogenic sarcoma	Dronabinol 10 mg/m2 × 4 (15) vs placebo (15)	Nausea, vomiting, food intake, adverse effects and THC plasma avaliation	High dose of methotrexate	B
Chang *et al.* (1981)	Randomized, double-blind and paired (dronabinol-placebo or placebo-dronabinol)	Patients with sarcoma	Dronabinol 10 mg/m2 × 4 (8) vs placebo (8)	Nausea, vomiting, adverse effects and THC plasma avaliation	Combination of doxorubucin and cyclophosphamide	B
Colls *et al.* (1980)	Randomized, double-blind, cross-over and multicentric	Patients with solid tumours	Dronabinol 12 mg/m2 × 2 (35) vs metoclopramide 4, 5 mg/m2 × 1 intravenous (35) vs thiethylperazine 6, 6 mg/m2 × 3 (35)	Nausea, vomiting and adverse effects	Cyclophosphamide, mustine, and others	B
Crawford and Buckman (1986)	Randomized, double-blind, cross-over	Patients with adenocarcinoma of the ovary or germ cell tumours	Nabilone 1 mg × 5 (37) vs metoclopramide 1 mg/kg × 5 (39)	Nausea, vomiting, adverse effects and preference	Cisplatin, cyclophosphamide, adriamycin, methotrexate, vincristin, bleomycin	B
Dalzell *et al.* (1986)	Randomized, double-blind, cross-over	Children with various tumours	Nabilone 1–3 mg (18) vs domperidone 15–45 mg (18)	Nausea, vomiting, adverse effects and preference	Cisplatin, cyclophosphamide, vincristin	B
Einhorn *et al.* (1981)	Randomized, double-blind, cross-over	Adults with various tumours	Nabilone 2 mg × 4 (80) vs prochlorperazine 10 mg × 4 (80)	Nausea, vomiting, appetite, adverse effects and preference	Cisplatin, cyclophosphamide, bleomycin, vincristin	B
Fritak *et al.* (1979)	Randomized, double-blind and paralell	Patients with gastrointestinal tumours	Dronabinol 15 mg × 2 (38) vs prochlorperazine 10 mg × 2 (41) vs placebo (37)	Nausea, vomiting and adverse effects	Vincristin, doxorubicin, fluorouracil, and others	A
George *et al.* (1983)	Randomized, double-blind, double-placebo, and cross-over	Women with advanced gynaecological cancer	Nabilone 1 mg × 3 (18) vs chlorpromazine 12,5 mg × 1–2 intramuscular (IM) (18)	Nausea, vomiting, adverse effects and preference	Cisplatin, cyclophosphamide, adriamycin	B
Gralla *et al.* (1984)	Randomized, double-blind and paired (the patients were exposed to both drugs)	Patients with various tumours	Dronabinol 10 mg/m2 × 5 (15) vs metoclopramide 2 mg/kg × 5 endovenous (15)	Nausea, vomiting, adverse effects and 'high'	High dose cisplatin	B
Herman *et al.* (1979)	Randomized, double-blind and cross-over	Patients with various tumours	Nabilone 2 mg × 3–4 (113) vs prochlorperazine 10 mg × 3–4 (113)	Nausea, vomiting, adverse effects and preference	Cisplatin, cyclophosphamide, vinblastin, bleomycin, and others	A
Hutcheon *et al.* (1983)	Randomized, paralell and blind	Patients with various tumours	Levonantradol 0,5 mg × 3 IM (27) vs levonantradol 0,75 mg × 3 IM (28) vs Levonantradol 1,0 mg × 3 IM (26) vs chlorpromazine 25 mg × 3 IM (27)	Nausea, vomiting, appetite and adverse effects	Cisplatin, cyclophosphamide, fluorouracil, vincristin	B
a (0.5 mg)	Randomized, paralell and blind	Patients with various tumours	Levonantradol 0,5 mg × 3 IM (27) vs chlorpromazine 25 mg × 3 IM (27)	Nausea, vomiting, appetite and adverse effects	Cisplatin, cyclophosphamide, fluorouracil, vincristin	B
b (0.75 mg)	Randomized, paralell and blind	Patients with various tumours	Levonantradol 0,75 mg ×3 IM (28) vs chlorpromazine 25 mg × 3 (27)	Nausea, vomiting, appetite and adverse effects	Cisplatin, cyclophosphamide, fluorouracil, vincristin	B
Johansson *et al.* (1982)	Randomized, double-blind and cross-over	Patients with various tumours	Nabilone 2 mg × 2 (18) vs prochlorperazine 10 mg × 2 (18)	Nausea, vomiting, appetite, adverse effects and preference	Cisplatin (50 mg/m2), adriamycin (40 mg/m2), cyclophosphamide (500 mg/m2), vinblastin, vincristin	B
Jones *et al.* (1982)	Randomized, double-blind and cross-over	Patients with various tumours (breast, lymphoma, ovary, lung e others)	Nabilone 2 mg × 2 (24) vs placebo (24)	Nausea, vomiting, adverse effects and preference	Cisplatin, adriamycin, and others	B
Kluin-Neleman *et al.* (1979)	Randomized, double-blind and cross-over	Patients with Hodgkin and non Hodgkin lymphomas	Dronabinol 10 mg/m2 ×2 (11) vs placebo (11)	Nausea, vomiting, adverse effects and THC plasma avaliation	MOPP	B

Table 1 *Continued*

Study	Methods	Participants	Interventions and therapeutic schedules	Outcomes	Chemotherapic agents	Methodologic quality
Lane *et al.* (1991)	Randomized, double-blind, paralell and multicentric	Patients with various tumours (breast, colon, lymphoma, lung and others)	Dronabinol 10 mg ×4 (17) vs prochlorperazine 10 mg × 4 (20) vs dronabinol 10 mg × 4 mais prochlorperazine 10 mg × 4 (17)	Nausea, vomiting and adverse effects	Cyclophosphamide, doxorubicin, 5-fluorouracil, vincristin, etoposide	B
Levitt (1982)	Randomized, double-blind and cross-over	Patients with various tumours (lung, ovary, breast, and others)	Nabilone 2 mg × 2 (36) vs placebo (36)	Nausea, vomiting, appetite, adverse effects and preference	Cisplatin, adriamycin, cyclophosphamide, fluorouracil, methotrexate, vincristin, and others	B
McCabe *et al.* (1988)	Randomized, comparative and cross-over	Patients with various tumours	Dronabinol 15 mg/m2 ×6 (36) vs prochlorperazine 10 mg × 6 (36)	Nausea, vomiting, adverse effects and preference	Cyclophosphamide, doxorubicin, fluorouracil, vincristin, and others	B
Neidhart *et al.* (1981)	Randomized, double-blind and cross-over	Patients with various tumours	Dronabinol 10 mg × 4 (average) (37) vs haloperidol 2 mg × 5 (average) (36)	Nausea, vomiting, adverse effects and preference	Cisplatin, adriamycin, and others	A
Niederle *et al.* (1986)	Randomized and cross-over	Patients with nonseminomatous testicular cancer	Nabilone 2 mg × 2 (20) vs alizapride 150 mg × 3 (20)	Nausea, vomiting, appetite, adverse effects and preference	Low dose cisplatin and adriamycin	B
Niiranen and Mattson (1985)	Randomized, double-blind and cross-over	Patients with lung cancer	Nabilone 1 mg × 2 (24) vs prochlorperazine 7,5 mg × 2 (24)	Nausea, vomiting, appetite, adverse effects and preference	Cisplatin, cyclophosphamide, adriamycin, vincristin, vindesine e etoposide	A
Orr and McKernan (1980)	Randomized, double-blind and cross-over	Patients with various tumours	Dronabinol 7 mg/m2 × 4 (55) vs prochlorperazine 7 mg/m2 × 4 (55) vs placebo (55)	Nausea, vomiting and adverse effects	Cyclophosphamide, doxorubicin, fluorouracil, and others	B
Pomeroy *et al.* (1986)	Randomized, double-blind and paralell	Patients with various tumours	Nabilone 1 mg × 3 (19) vs domperidone 20 mg × 3 (19)	Nausea, vomiting, appetite and adverse effects	Cisplatin in 70%, adriamycin in 19%, and others	B
Sallan *et al.* (1975)	Randomized, double-blind and paired (the patients were exposed to both drugs)	Patients with various tumours	Dronabinol 15 mg or 10 mg/m2 × 3 (20) vs placebo (20)	Nausea, vomiting, appetite and adverse effects	Various agents	B
Sallan *et al.* (1980)	Randomized, double-blind and cross-over	Patients with various tumours	Dronabinol 15 mg or 10 mg/m2 × 3 (73) vs prochlorperazine 10 mg × 3 (73)	Nausea, vomiting, appetite, development of 'high' and preference	Cisplatin, cyclophosphamide, methotrexate, and others	B
Sheidler *et al.* (1984)	Randomized, double-blind and cross-over	Patients with various kinds of cancer (solid tumours and haematologic malignancies)	Levonantradol 1,0 mg × 3 IM (16) vs prochlorperazine 10 mg × 3 IM (16)	Nausea, vomiting, adverse effects and preference	High doses cisplatin, cyclophosphamide and/or adriamycin	A
Steele *et al.* (1980)	Randomized, double-blind and cross-over	Patients with various tumours	Nabilone 2 mg × 2 (37) vs prochlorperazine 10 mg × 2 (37)	Nausea, vomiting, adverse effects and preference	High doses cisplatin, low doses cisplatin, mechlorethamine, streptozotocin, actinomycin D, or DTIC	B
Ungerleider *et al.* (1982)	Randomized, double-blind and paired (the patients were exposed to both drugs)	Patients with various tumours (carcinomas, sarcomas, lymphomas, and others)	Dronabinol 7,5–12,5 mg ×3 (181) vs prochlorperazine 10 mg × 3 (172)	Nausea, vomiting, Nausea, vomiting, appetite, mood, anxiety, concentration, activity, interaction, adverse effects and preference	Various agents: 66% with high emetic potencial; 27% with moderate; and 7% with low emetic potencial	A
Wada *et al.* (1982)	Randomized, double-blind and cross-over	Patients with various tumours	Nabilone 2 mg × 2 (84) vs placebo (84)	Nausea, vomiting, adverse effects and preference	Cisplatin, adriamycin	B

systematic reviews and for searching the best available evidence of the therapeutic effect of an intervention. The critical evaluation of each clinical trial to be included in a systematic review is vital to limit potential biases or systematic errors, to help possible comparisons to be made, and to serve as a guide to the interpretation of the final findings (Mulrow & Oxman 1997). This is made through a careful analysis of the random distribution processes as well as through verification of how individuals who left the study before it ended were treated by the statistical analysis (treatment intention analysis). In a meta-analysis, the double-blind follow-up and the treatment intention analysis are fundamental to reduce the so-called confusing factors of results.

Considering the importance of the methodological quality evaluation of the included studies, the criteria used were those described by Mulrow and Oxman (1997) and the Jadad Scale (Jadad *et al*. 1996). Two independent reviewers evaluated the quality of the included studies (FCMR and SCS).

The trials included in this review were rated as quality A or B according to the randomization procedure of allocation concealment, following the Cochrane Collaboration Manual for methodological quality evaluation (Mulrow & Oxman 1997). They are as follows:

A 'Low risk of bias'. Adequate allocation concealment (e.g. central computer-generated randomisation).
B 'Moderate bias risk'. Unclear or doubtful allocation concealment.
C 'High bias risk'. Inadequate allocation concealment (e.g. the use of alternate numbers, date of birth, etc.).

RESULTS

Using the search strategy, we identified 12 749 papers. Their titles were scanned to exclude papers that did not satisfy the objectives of this review. A total of 735 abstracts were evaluated in detail. Most of them were excluded because they did not satisfy the objectives of this review. Finally, 96 complete papers were analysed. Thirty randomized clinical trials using *C. sativa* to treat chemotherapy-induced nausea and vomiting were identified.

Most studies used a 'cross-over' design, although Fritak *et al*. (1979), Hutcheon *et al*. (1983), Pomeroy *et al*. (1986) and Lane *et al*. (1991) used 'parallel' design studies.

In the individual studies, the size of most samples was small: 17 studies had fewer than 50 patients, seven studies had between 50 and 100 patients, and only six studies had 100 patients or more. In total, the studies included 1 719 patients who had different types of cancer, were of different ages and receiving different types of chemotherapeutic agents. Many studies used some form of standard design (mostly the 'cross-over' ones); however, since the studies were reviewed over a long period of time, there was considerable variation in their designs.

In many studies, the dose of anti-emetic medication was adjusted during the research, either to increase its efficacy or to reduce the side effects. There were also studies wherein the protocol allowed the administration of an anti-emetic other than the studied drugs to patients who required them or who presented with unbearable nausea and vomiting.

Of the 30 studies included in the systematic review, 17 were excluded from the meta-analysis on the anti-emetic efficacy due to a number of reasons (see Table 2).

Finally, it was possible to include in this meta-analysis data related to 13 randomized clinical trials on the use of cannabis for treating nausea and vomiting in cancer patients receiving chemotherapy (total anti-emetic efficacy). Eighteen clinical trials were included for the outcome 'preference for one of the study drugs'.

All studies included in this meta-analysis, except three (Niederle *et al*. 1986, which used alizapride; Hutcheon *et al*. 1983, which used chlorpromazine; and Dalzell *et al*. 1986, which used domperidone) compared cannabis with prochlorperazine, a neuroleptic, as the control drug.

Thirty-one papers were excluded for failing to meet the study criteria (Appendix 1).

The category shown in Figure 1 comprises two studies. In terms of anti-emetic efficacy, there was not a statistically significant difference in favour of dronabinol [n = 185; relative risk (RR) = 0.47; confidence interval (CI) = 0.19–1.16; P = 0.10].

The category shown in Figure 2 comprises five studies. In terms of anti-emetic efficacy, there was a statistically significant difference in favour of dronabinol [n = 325; RR = 0.67; CI = 0.47–0.96; P = 0.03; number needed to treat (NNT) = 3.4].

The category shown in Figure 3 comprised six studies. In terms of anti-emetic efficacy, there was not a statistically significant difference in favour of nabilone (n = 277; RR = 0.88; CI = 0.72–1.08; P = 0.21).

The category shown in Figure 4 comprised two studies. One of them allowed three comparisons: three different doses of levonantradol (0.5 mg, 0.75 mg and 1.0 mg) were compared with a neuroleptic (Hutcheon *et al*. 1983). In terms of anti-emetic efficacy, there was not a statistically significant difference in favour of levonantradol (n = 194; RR = 0.94; CI = 0.75–1.18; P = 0.60).

The category shown in Figure 5 comprised 18 studies. In terms of preference for one of the drugs, there was a

Table 2. Studies excluded from the meta-analysis (outcome: total anti-emetic efficacy)

Number of studies	Reasons	Articles
2 studies	The studies exposed dichotomic data on the total anti-emetic efficacy via number of chemotherapy sequences, not number of patients.	Neidhart *et al.* (1981); Sallan *et al.* (1975)
3 studies	The studies exposed dichotomic data on the partial anti-emetic efficacy, not total.	Jones *et al.* (1982); Levitt (1982); Wada *et al.* (1982)
1 study	The period analysed was 5 days, while the other meta-analysis studies evaluated the acute anti-emetic efficacy during a period of up to 24 h.	Herman *et al.* (1979)
2 studies	Did not present dichotomic data on the total anti-emetic efficacy; Compared equal outcomes, the different variable being the chemotherapeutic drug used.	Chang *et al.* (1979); *1981
9 studies	Failed to present dichotomic data on the total anti-emetic efficacy.	Pomeroy *et al.* (1986); George *et al.* (1983); Colls (1980); Crawford and Buckman (1986); Einhorn *et al.* (1981); Steele *et al.* (1980); Gralla *et al.* (1984); Ungerleider *et al.* (1982); Kluin-Neleman *et al.* (1979).

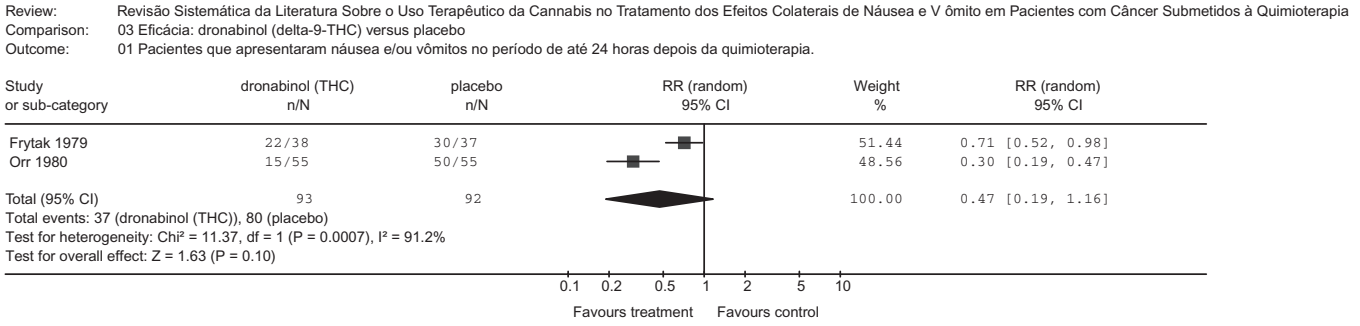

Figure 1. Dronabinol (delta-9-tetrahydrocannabinol) versus placebo.

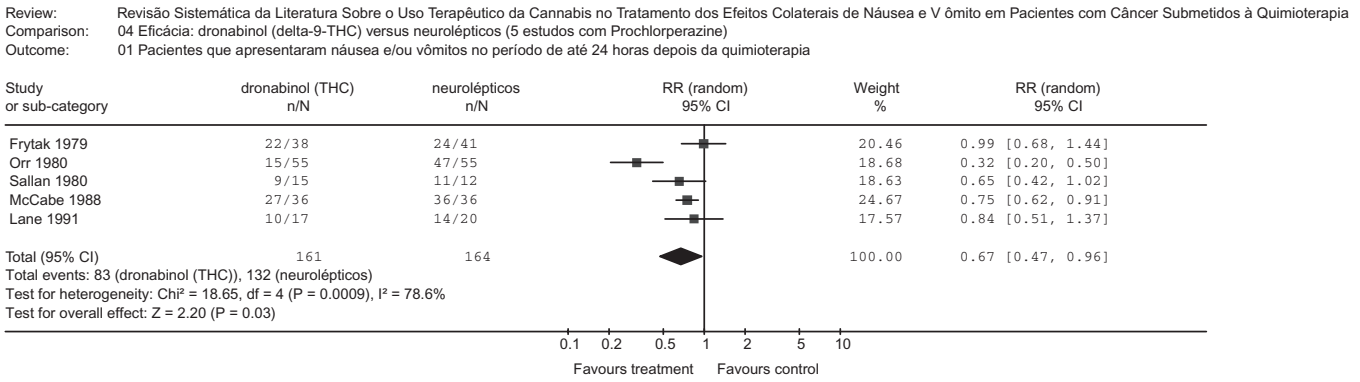

Figure 2. Dronabinol (delta-9-tetrahydrocannabinol) versus neuroleptics.

statistically significant difference in favour of the *Cannabis* components ($n = 1138$; RR = 0.33; CI = 0.24–0.44; $P < 0.00001$; NNT = 1.8).

Figure 6 shows the 'Funnel Plot' of the risk difference versus the sample size. It shows some measure of symmetry and normal distribution (Gaussian), suggesting that there is no systematic error (bias) due to paper omission generated by languages other than English, multiplicity of issues generated by a single study, poor methodology, inaccurate analysis or fraud. Also, the absence of perfect symmetry suggests clinical and methodological heterogeneity inherent to the execution of the trials by different

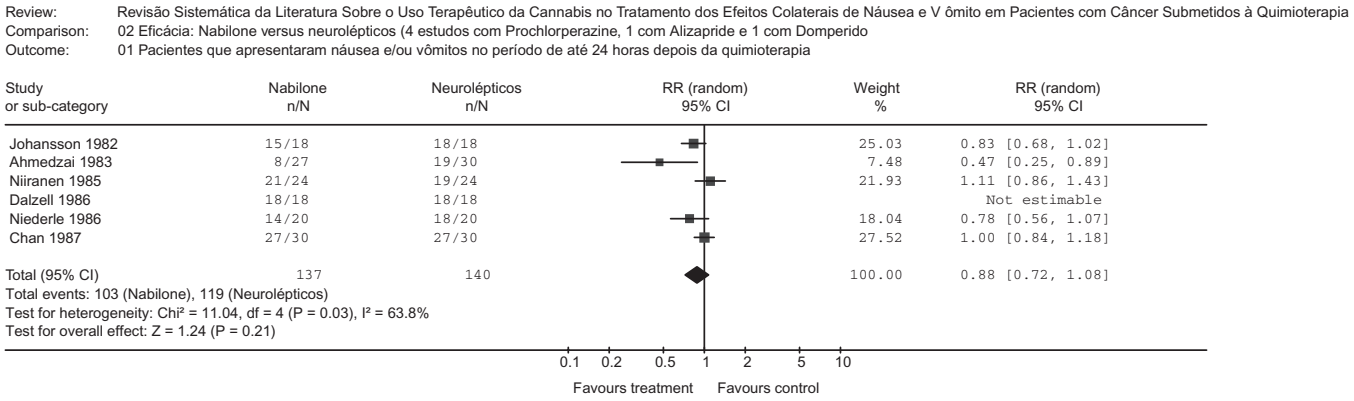

Figure 3. Nabilone versus neuroleptics.

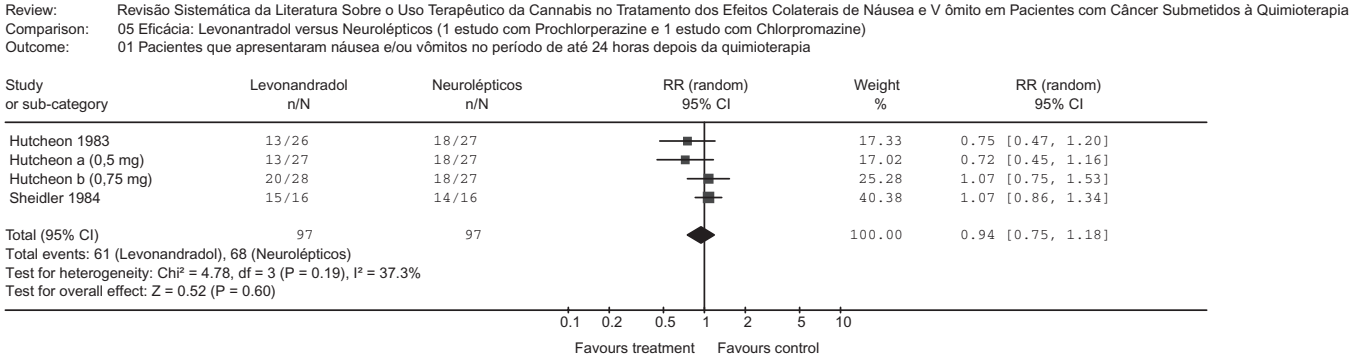

Figure 4. Levonantradol versus neuroleptics.

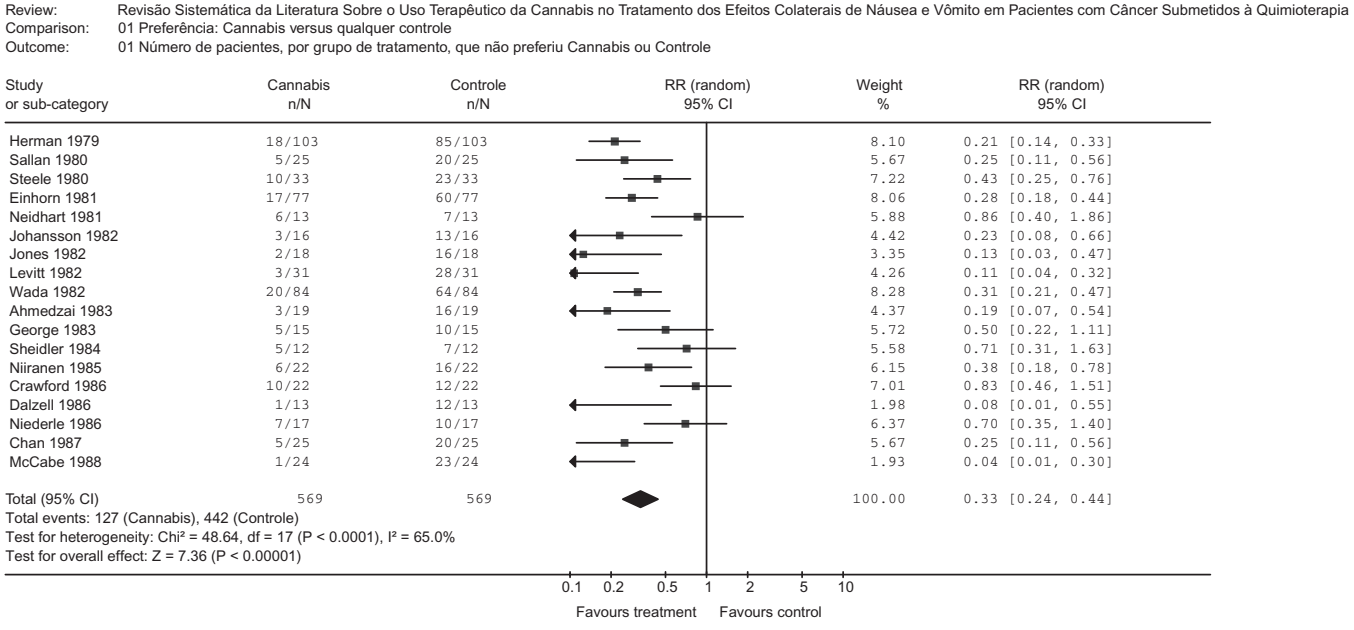

Figure 5. Preference for cannabis or control.

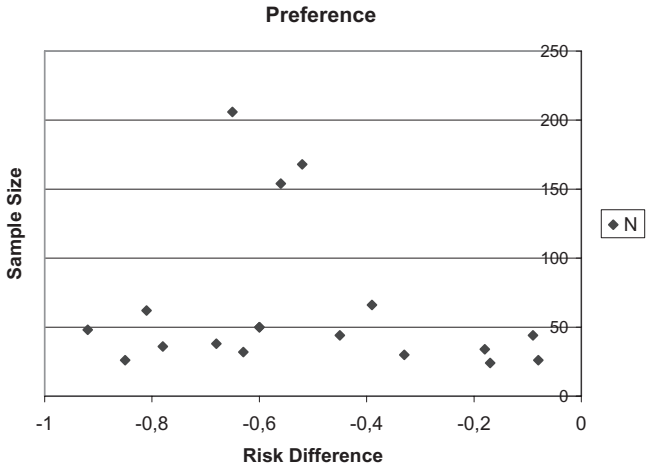

Figure 6. 'Funnel plot' of the risk difference versus sample size.

authors, in different geographical regions and dealing with methodological and clinical peculiarities.

DISCUSSION

Using the statistical model of 'random effect', the meta-analysis shows that dronabinol cannabinoid had a better acute anti-emetic efficacy (remission) than conventional anti-emetic drugs on cancer patients treated with potentially emesis-inducing chemotherapeutic agents. Cannabinoids nabilone and levonantradol did not have superior acute anti-emetic efficacy when compared with the conventional anti-emetics in the studies included in this meta-analysis (statistically significant difference). However, they had a clinically significant difference towards the intervention. These results must be considered with caution due to the small number of studies and the small patient sample of each study.

Compared with placebo, dronabinol was not more effective in the total remission of nausea and/or vomiting (random statistical model), although due to ethical considerations, placebo should not be used for patients receiving chemotherapy.

In terms of partial improvement of nausea and/or vomiting, the random studies in this systematic review of data on the frequency of vomiting episodes and severity of nausea show that cannabinoids apparently had a better anti-emetic efficacy than conventional drugs when used in cancer patients who underwent chemotherapy using potentially emetic-inducing agents. However, the absence of data on the standard deviation in most studies makes this an arguable conclusion.

On the other hand, side effects (described below) occurred more frequently and more intensely in patients who used cannabinoids than in those who used control drugs.

The 'intention to treat' analysis was carried out for the majority of the studies. The side-effects analysis included the patients who abandoned the study before completion and therefore were not evaluated for anti-emetic efficacy.

It was not possible to establish a dose–response relationship for there was insufficient data quality in the original papers on this aspect. In some studies, the dose was adjusted during the study itself, either to attain a possible efficacy enhancement or to reduce the unwanted side effects.

The relationship described between the cannabinoid plasma concentration and its therapeutic effect was not clearly examined in the studies. In one study, the anti-emetic efficacy was related to the THC plasma concentration. In another study, there was no correlation between the THC plasma levels and the efficacy or the side effects.

In terms of medication safety, the systematic review showed that the cannabinoids were toxic for some patients even when the drugs were given orally and their use restricted (for 24 h). Some side effects occurred almost exclusively in patients who were exposed to the cannabinoid agents: 5% presented with paranoid delusions, 6% presented with hallucinations, and almost 13% presented with dysphoria and/or depression. The number of patients who left the study due to the occurrence of cannabinoid side effects is the main parameter of the eventual toxicity related to this substance.

During this review, it was observed that although the patients showed a higher number of collateral effects as well as a higher symptom intensity during the treatment with cannabinoids, most dropouts were not due to possible cannabinoid toxicity. These dropouts were responsible for almost 30% of the nearly 400 dropouts in all the studies included. The other reasons for dropping out were condition evolution, change of the chemotherapeutic strategy during the study, death due to cancer, protocol violation, use of concomitant anti-emetic medication, inadequate data and low efficacy using two drugs.

However, some side effects such as 'high' sensation, sleepiness, sedation and euphoria, which were more frequent when cannabinoids were used, would be potentially 'beneficial' for most patients; in other words, they would be pleasant during the chemotherapeutic treatment (Tramèr *et al*. 2001).

In the double-blind and cross-over studies included in this review, most patients preferred the cannabis-based treatment when asked about their preferred drug. This preference was significant in relation to the control drugs (prochlorperazine, chlorpromazine, domperidone, halo-

peridol, alizapride, metoclopramide, placebo) used in the studies. From this preference, it can be hypothesized that because nausea and vomiting during chemotherapy have such important impact and cause such discomfort to the patients, the patients prefer the cannabis side effects instead of the conventional anti-emetic medications that have lower efficacy.

In this review, it is important to consider some limitations because some analyses potentially overrate the cannabinoids' efficacy and underrate their damage.

According to the Cochrane Manual, the studies were of acceptable quality. Of all selected studies, 70% presented a proper mask method description. Most cross-over studies used a 'double dummy' design. The psychological effect of smoking a *C. sativa* cigarette was not an analysed factor since cannabis was given via orally ingested capsules.

However, the cannabinoids presented specific collateral effects, which were not presented by the control drugs, and these factors presented a high incidence. In a study on orally given nabilone, many patients identified which drug they had received because of the collateral effects experienced. In a series of 100 blinded treatment interventions using THC and placebo, the nurses identified the active drugs in 85% of the cases and the patients in 95% of the cases (Tramèr *et al*. 2001). Such high values allow us to hypothesise that there was some bias on the part of the observer in these studies.

Some studies selected groups of patients who had not responded to the anti-emetic treatment with conventional drugs in previous chemotherapy cycles. This could have introduced among the patients a bias in favour of cannabis and against the drugs they knew they were refractory to.

Some studies selected groups of patients with a previous history of smoking cannabis. In a study by Vinciguerra *et al*. (1988), it was claimed that young people with previous exposure to marijuana were predisposed to better anti-emetic efficacy. However, it is not clear whether this factor alone was a bias. There are a few studies similar to this situation, and in one of them, the patients who had no previous history of cannabis use demonstrated better efficacy when compared with the other group (Ungerleider *et al*. 1982).

The sample size can also be a source of criticism of the results of the studies. Of the 30 studies included in this review, 13 had more than 50 patients included, and only six had more than 100 patients. However, of the studies with numbers of patients available for analysis of anti-emetic efficacy, only nine had more than 50 patients analysed, and only four included more than 100 patients. Small samples have already shown an overrating of the effect under other circumstances (Moore *et al*. 1998), and this result tendency may have been repeated in this analysis.

Today, two anti-emetics that are prescribed demonstrate good efficacy in reducing acute emesis: selective antagonists for 5-hydroxytryptamine (5-HT) receptor and protachykinin (NK1) receptor. The latter retards vomiting caused by chemotherapy with high emesis-inducing potential (Olver 2004).

During the 1990s, 5-HT3 receptor antagonist combined with dexamethasone became the gold standard in acute emesis prophylaxis caused by chemotherapy (MASCC 1998). However, if there is failure to respond or there is an increase in emesis, this cannot be corrected by an increase in dosage or frequency of administration. It seems that other receptor mechanisms may be involved (Tattersall *et al*. 1994; Herstedt 1996). Besides, in cases of delayed emesis (from the second day onwards), the above combination rarely obtains 50% of the desired effect (Kris *et al*. 1985; Olver *et al*. 1996).

Nowadays, the anti-emetic indications for chemotherapy with high emesis-inducing potential are 5-HT3 receptor antagonists, dexamethasone and aprepitant during the acute emetic phase, and aprepitant and dexamethasone (for two more days) during the delayed emesis phase (Olver 2004). According to Walsh *et al*. (2003), cannabinoids are fourth-line agents to be considered when dealing with nausea and vomiting.

Some agents consider that when compared with modern anti-emetics, cannabinoids are 'only' modestly effective and because of this more research on cannabinoids would be indispensable.

However, cannabinoids seem to act through different mechanisms and can be effective for people who respond in an unsatisfactory way to the anti-emetic drugs used today.

There are at least two types of cannabinoid receptors, CB1 and CB2, to which potent and selective antagonists have been developed. The blockage of CB1 cannabinoid receptors induces vomiting, suggesting the existence of an endogenous cannabinoid system within the emetic circuits. This also suggests that the delta-9-THC anti-emetic activity would be due to the stimulation of the CB1 receptor (Darmani 2001).

Besides, delta-9-THC and its synthetic analogues (CP 55, 940 and WIN 55, 212–2) were able to prevent the inducing of this condition. However, it is not yet known whether the cannabinoid receptor antagonist can override or oppose the delta-9-THC capability of preventing vomiting caused by cisplatin chemotherapeutic agents.

Ferrari *et al.* (1999)reported that a number of cannabinoids (delta-9-THC, delta-8-THC, 7-hydroxy-delta-9-THC, nabilone, HU 210) seem to be effective in

preventing vomiting induced by cisplatin or apomorfin in cats and pigeons (Darmani 2001).

No clinical trials in humans comparing the action of cannabinoids with modern anti-emetics for nausea and/or vomiting in cancer patients receiving chemotherapy were found.

Today, cannabinoids alone would not be used as first-line medication for treating nausea and vomiting, but they seem promising because they have an auxiliary anti-emetic mechanism. The drugs' efficacy can be higher when combined with other anti-emetic drugs than when each drug is used alone. Because the cannabinoids' mechanism is different from other medications, they can benefit refractory patients or be used as auxiliaries to enhance the effect of existent anti-emetic medications if it is confirmed that the synergy among cannabinoids, 5-HT3 receptor antagonist and dexamethasone is similar to the synergy observed among cannabinoids and prochlorperazine.

Thus, smaller doses of cannabinoids in combination with modern anti-emetic medications might eventually not only enhance the anti-emetic efficacy, but also reduce the cannabinoids' collateral effects observed in this review.

Recent findings on cannabinoids and endocannabinoids receptors have opened a new era in research on their physiological and pharmacological uses, as well as research on the cannabinoids' molecular bases (Walsh *et al*. 2003). This information could help develop new synthetic cannabinoid antagonists for possible therapeutic use and could separate the desired effects from the unwanted ones (Pertwee 1999a,b).

CONCLUSIONS

1 The cannabinoid dronabinol had an anti-emetic efficacy superior to neuroleptics for cancer patients receiving chemotherapy.
2 Although there was not a statistically significant difference between the cannabinoid dronabinol and placebo for cancer patients receiving chemotherapy, a clinically significant difference in favour of dronabinol was observed.
3 Although there was not a statistically significant difference between the cannabinoid nabilone and neuroleptics in cancer patients receiving chemotherapy, a clinically significant difference in favour of nabilone was observed.
4 Although there was not a statistically significant difference between the cannabinoid levonantradol and neuroleptics in cancer patients receiving chemotherapy, a clinically significant difference in favour of levonantradol was observed.
5 The number of dropouts from studies due to unbearable collateral effects was significantly higher for patients who used cannabinoids. These dropouts were responsible for approximately one-third of the dropouts for all studies included in the systematic review.
6 Most dropouts occurred due to other causes than the collateral effects of the cannabinoids.
7 Patients showed a clear preference for cannabinoids as anti-emetic medication when receiving chemotherapy.
8. Possible use of cannabinoids to treat chemotherapy-induced nausea and vomiting.
9. This study demonstrates the need for further work to evaluate the use of cannabinoids and modern anti-emetics.

POTENTIAL INTERESTS CONFLICT

This paper has no conflict of interests.

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APPENDIX 1

Characteristics of the excluded studies:

- Six papers compared different doses of the same cannabinoid drug: Diasio *et al.* (1981); Laszlo *et al.* (1981); Higi *et al.* (1982); Welsh *et al.* (1983); Stambaugh *et al.* (1984); and Tyson *et al.* (1985).
- One study compared two cannabinoid drugs: Citron *et al.* (1985).
- Twenty studies were excluded because they were not the object of the present review (non-randomized, open-label, absence of comparison between cannabinoids and control drugs, correspondence, lack of relevant data, data on physiological measurements only): Ekert *et al.* (1979), Colls (1980); Garb *et al.* (1980); Lucas and Laszlo (1980); Rose (1980); Cronin *et al.* (1981); Heim *et al.* (1981); Levitt *et al.* (1981); Sweet *et al.* (1981); Cone *et al.* (1982); Kenny and Wilkinson (1982); Lucraft and Palmer (1982); Niamatali *et al.* (1984); Cunningham *et al.* (1985, 1988); Devine *et al.* (1987); Niiranen and Mattson (1987); Vinciguerra *et al.* (1988); Abrahamov *et al.* (1995);Gilbert *et al.* (1995).
- Four studies were duplicated completely or partially: Orr and McKernan (1981); Einhorn (1982); Ungerleider *et al.* (1985); and Lane *et al.* (1990).