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

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Authors' objectives
To quantify the anti-emetic efficacy and adverse effects of cannabis used for chemotherapy-induced sickness.

Searching
Two authors searched MEDLINE and EMBASE to August 2000 using different search strategies. The keywords used were: 'cannabis', 'cannabinoids', 'marihuana', nabilone', tetrahydrocannabinoid', THC', 'marijuana', levonantradol', 'dronabinol', 'randomised', 'randomized' and 'human'. The Cochrane Library (Issue 3, 2000) was also searched, and bibliographies were examined. Studies reported in any language were considered, and only full publications in peer-reviewed journals were eligible. Authors and manufacturers were not contacted.

Study selection

Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible. Parallel group and crossover RCTs were included.

Specific interventions included in the review
Comparisons of cannabinoids with any anti-emetic or placebo control in chemotherapy were eligible. The three different cannabinoids used were oral nabilone (16 studies), oral dronabinol (13 studies) and intramuscular levonantradol (1 study). The following control treatments were used: placebo (10 studies), prochlorperazine (12 studies), metoclopramide (4 studies), chlorpromazine (2 studies), domperidone (2 studies), thiethylperazine (1 study), haloperidol (1 study) and alizapride (1 study).

Participants included in the review
Patients undergoing chemotherapy were eligible. The participants included adults and children with various tumours including lung cancer, osteogenic sarcoma, gynaecological, testicular and gastrointestinal tumours, lymphomas, and paediatric malignancies. The chemotherapy regimens included ones with low, moderate and high emetogenic substances.

Outcomes assessed in the review
Studies that assessed anti-emetic efficacy were eligible. Dichotomous data that were closest to complete control of nausea or vomiting in the first 24 hours were extracted. A secondary outcome was the number of patients who, after completion of the trials, expressed a preference for cannabis or control for future chemotherapy cycles. Adverse outcomes were also assessed when these were reported in dichotomous form.

How were decisions on the relevance of primary studies made?
One author checked all identified reports according to the inclusion criteria and excluded those judged to be definitely not relevant.

Assessment of study quality
Validity was assessed and scored according to the 3-item, 5-point Oxford score that considers the adequacy of randomisation and blinding, and the description of withdrawals (see Other Publications of Related Interest). All authors independently assessed study validity and met to reach a consensus.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.
The following information were tabulated in the review: the characteristics of patients; chemotherapy regimen; active and control treatments; the number of patients; and relevant end points. Relative risks (RR) with 95% confidence intervals (CIs) were calculated for a difference between the cannabis and control treatments.

**Methods of synthesis**

**How were the studies combined?**
The pooled RRs and 95% CI for cannabis versus control treatments were estimated using a fixed-effect model. The clinical relevance of the treatment effect was expressed as the number-needed-to-treat (NNT), along with 95% CIs.

**How were differences between studies investigated?**
L'Abbe plots of event rates for nausea and vomiting were created for the control versus the cannabinoid-treated groups. A sensitivity analysis was conducted by separately analysing the data from active controlled trials with medium event rates (25 to 75%) and extreme event rates (less than 25% and greater than 75%) in control treatment groups. A dose-response relationship was sought in the data from clinically homogeneous subgroups.

**Results of the review**
Thirty RCTs were included (1,760 patients were randomised but 394 patients were subsequently excluded by the original authors, leaving 1,366 evaluable patients).

The average sample size was 46 patients (range: 8 to 139).

**Anti-emetic efficacy (10 RCTs).**

There was wide variability in event rates with both cannabinoids and controls. The scatter in the event rates suggested increased efficacy with cannabinoids and relative homogeneity of the data.

Cannabinoids versus active control. Cannabinoids were more effective than active comparators for complete control of nausea (7 RCTs) and for complete control of vomiting (6 RCTs); the RRs were 1.38 (95% CI: 1.18, 1.62; NNT=6.4) and 1.28 (95% CI: 1.08, 1.51; NNT=8.0), respectively.

Cannabinoids versus placebo control. Cannabinoids were more effective than placebo for complete control of nausea (4 RCTs) and for complete control of vomiting (4 RCTs); the RRs were 1.21 (95% CI: 1.03, 1.42; NNT=8.0) and 1.84 (95% CI: 1.42, 2.38; NNT=3.3), respectively.

After the exclusion of studies in which the control groups showed extreme event rates (less than 25% or greater than 75%), cannabinoids were superior to conventional anti-emetics. The RRs for complete control of nausea and complete control of vomiting were 1.70 (95% CI: 1.32, 2.18; NNT=3.4) and 1.26 (95% CI: 1.07, 1.48; NNT=6.6), respectively.

After limiting the analysis to those trials with extreme event rates in the control group, there was no significant difference between cannabinoids and active comparators. These studies included one RCT that used low emetogenic drugs (vincristine and fluorouracil) and had low rates (less than 25%) of nausea in the control group, and 6 RCTs that had high rates (greater than 75%) of nausea in the placebo control groups. The latter 6 RCTs used regimes involving the following: high-dose methotrexate; doxorubicin and cytoxan; cisplatin; or a combination of cyclophosphamide, methotrexate and fluorouracil.

**Patients' preference (18 crossover RCTs).**

Significantly more patients expressed a preference to be treated with cannabinoids for further chemotherapy cycles rather than either placebo or active comparator. The RR versus placebo (4 RCTs) was 5.67 (95% CI: 3.95, 8.15; NNT=1.6) and the RR versus active control (14 RCTs) was 2.39 (95% CI: 2.05, 2.78; NNT=2.8).

**Side-effects.**
Side-effects were significantly more common with cannabinoids. The potentially beneficial side-effects found were 'high' (RR 10.6, 95% CI: 6.86, 16.5), sedation or drowsiness (RR 1.66, 95% CI: 1.46, 1.89), and euphoria (RR 12.5, 95% CI: 3.00, 52.1). The definitely harmful side-effects found were as follows: dysphoria or depression (RR 8.06, 95% CI: 3.38, 19.2), dizziness (RR 2.97, 95% CI: 2.31, 3.83), hallucinations (RR 6.10, 95% CI: 2.41, 15.4), paranoia (RR 8.58, 95% CI: 6.38, 11.5), and arterial hypotension (RR 2.23, 95% CI: 1.75, 2.83).

Withdrawals due to side-effects were significantly more common with cannabinoids than with the control; the RR was 4.67 (95% CI: 3.07, 7.09; NNT=11).

Authors' conclusions
The cannabinoids tested in these trials may be useful as mood-enhancing adjuncts for controlling chemotherapy-related sickness in selected patients. Potentially serious side-effects, even when cannabinoids are taken orally or intramuscularly in the short term, are likely to limit their widespread use.

CRD commentary
The aims were stated and the inclusion criteria were defined in terms of the study design, intervention, participants and outcome. Several relevant sources were searched but different search strategies were mentioned in the abstract, the introduction and the methods section. Thus, it was difficult to ascertain which actual search strategy had been pursued.

The methods used to select the studies were described and no language restrictions were applied. It appears that no attempt was made to locate unpublished material, which raises the possibility of publication bias. The validity of the included studies was assessed using a validated scale and was reported in the tables. The methods used to assess validity were described. Relevant data were extracted and tabulated, but the methods used to extract the data were not reported. The studies were grouped by comparator and the data were combined in a meta-analysis. Heterogeneity of the results was assessed by plotting event rates in the control group against those in experimental treatment groups. A sensitivity analysis was performed to explore the influence of the event rate of the control group on the results. Side-effects and patients' preferences were both evaluated.

With the exception of the search strategy, this was a clearly written and presented review. The evidence presented supports the authors' conclusions.

Implications of the review for practice and research
Practice: The authors state that oral nabilone and dronabinol and intramuscular levonantradol are superior to conventional anti-emetics in chemotherapy, but that side-effects (some potentially beneficial and some harmful) are common with cannabinoids.

Research: The authors state that priority should be given to trials of cannabinoids for indications where there are few competing drugs, such as spasticity in multiple sclerosis. They also state that research is required to identify the patients who are most likely to benefit from the anti-emetic effect of cannabinoids, and who are least likely to suffer from neuropsychiatric adverse events. They suggest further trials in chemotherapy to establish the usefulness of cannabinoids as adjuncts to modern anti-emetics, using minimal effective doses.

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Other publications of related interest

These additional published commentaries may also be of interest. Kinzbrunner BM. Review: cannabinoids control chemotherapy-induced nausea and vomiting but increase the risk of side effects. Evid Based Med 2002;7:24-5. Barnes J. Systematic review of cannabinoids for cancer chemotherapy-induced nausea and vomiting. FACT 2002;7:144-5.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.