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

Martin R Tramèr, Dawn Carroll, Fiona A Campbell, D John M Reynolds, R Andrew Moore, Henry J McQuay

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, thiemithylperazine, 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.

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Results

Included and excluded trials

We screened 198 reports; 51 were potentially relevant randomised controlled trials. Twenty one were subsequently excluded. Seven were not primarily studies of cannabinoids or had no relevant information,3–9 Four were in other clinical settings (radiotherapy,10–13 surgery,14 or AIDS15). Five randomised trials (four reports) were excluded because they reported emesis data per chemotherapy cycle only and no other relevant data could be extracted,16 the data could not be analysed,17 the study design was unclear,18 or the study used only physiological measurements.19 Finally, five reports (or parts of them20) were duplicates—that is, they contained data that had previously been published as full reports.21–25 We analysed data from 30 randomised controlled trials published between 1975 and 1997 (table 1). 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). The median quality score was 4 (range 1 to 4); 17 scored 4, eight 3, two 2, and three 1. The method of blinding was adequate in 21 (70%) trials—for example, identical tablets. Twenty five trials (83%) used a crossover design. Since the results from crossover trials were usually reported as if they had come from a parallel group trial we used the data accordingly. The median number of chemotherapy cycles was two (range one to six). Two trials were in children,11–13 and one in both children and adults.26 All other trials were in adults only. Various tumours were treated. Chemotherapy was with a variety of cytotoxic regimens with different emetogenic potencies (table 1). Five trials reported on the number of patients with a history of cannabis use.27–30 In nine trials, all patients were reported not to have used cannabis previously.28–30 In the other 16 trials, it was unclear whether patients had used cannabis previously.

Three different cannabinoids were tested. Oral nabiline was tested in 31 trials, oral dronabinol in 13, and intramuscular leonantradiol in one. Nabilone doses ranged from 1 mg per 24 hours in children29 to 8 mg per 24 hours in adults;23 the commonest dose was 4 mg per 24 hours. Dronabinol regimens were most often given according to body surface area in m². Doses ranged from 10 mg/m² twice daily29 to 15 mg/m² six times a day.30 Inhaled cannabis was not tested in these trials; however, in one trial comparing dronabinol with placebo, cannabis cigarettes were used as a rescue treatment in the event of a vomiting episode.31 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

In 14 trials, the observation period was clearly defined as 24 hours. In the other trials, chemotherapy cycles may have lasted longer, but it was unclear how long observations continued for antiemetic efficacy. We had to assume for all these trials that they reported antiemetic efficacy per patient within 24 hours—that is, acute antiemetic efficacy. In one trial, additional effi-
cacy data were clearly defined for days 2 to 4—that is, delayed antiemetic efficacy. This was not considered for combined analyses. Twelve trials reported antiemetic efficacy with various scoring systems, but we could not extract dichotomous data on the number of patients who were completely free of nausea or vomiting.

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. 55-36 41 48 55-55

Complete control of nausea or vomiting
Across all trials, cannabinoids were more effective than active comparators and placebo (table 2). 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.

Table 1 Characteristics of studies included in systematic review of cannabinoids for chemotherapy induced nausea and vomiting

<table>
<thead>
<tr>
<th>Setting</th>
<th>Chemotherapy</th>
<th>Active v control (No of patients)*</th>
<th>Oxford score (random/blinding/ drop outs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults, small cell bronchial carcinoma 24</td>
<td>Dexamethasone, cyclophosphamide, methotrexate, vincristine, etoposide</td>
<td>Nabilone 2 mg (27) v prochlorperazine 10 mg (30)</td>
<td>1/2/1</td>
</tr>
<tr>
<td>Children, age 3.5 to 17.8 years, various paediatric malignances 25-28</td>
<td>Dexamethasone, cyclophosphamide, fluorouracil, methotrexate, vincristine, etoposide</td>
<td>Nabilone 1-4 mg (30) v prochlorperazine 5-20 mg (39)</td>
<td>1/2/1</td>
</tr>
<tr>
<td>Adults, osteogenic sarcoma 29-32</td>
<td>High dose methotrexate</td>
<td>Dronabinol 10 mg/m² x (15) v placebo (15)</td>
<td>1/2/1</td>
</tr>
<tr>
<td>Adults, various tumours 33</td>
<td>Dexamethasone, cyclophosphate</td>
<td>Dronabinol 10 mg/m² x (8) v placebo (8)</td>
<td>1/2/1</td>
</tr>
<tr>
<td>Adults, solid tumours 34</td>
<td>Cyclophosphamide, mustine</td>
<td>Dronabinol 10 mg/m² x (35) v metoclopromide 4.5 mg/m² x (35) v thiethylperazine 6.6 mg/m² x (35)</td>
<td>1/2/0</td>
</tr>
<tr>
<td>Adults, adenocarcinoma of the ovary, germ cell tumours 34</td>
<td>Dexamethasone, cisplatin, cyclophosphamide, methotrexate, vincristine, etoposide</td>
<td>Nabilone 1 mg (37) v metoclopromide 1 mg/kg x (38) v intravenous (38)</td>
<td>1/2/0</td>
</tr>
<tr>
<td>Adults, various tumours 35</td>
<td>Cisplatin, cyclophosphamide, vincristine</td>
<td>Nabilone 1-3 mg (18) v domperidone 15-45 mg (18)</td>
<td>1/2/1</td>
</tr>
<tr>
<td>Adults, 15 to 74 years, various tumours 36</td>
<td>Bleomycin, cisplatin, cyclophosphamide, vincristine</td>
<td>Nabilone 2 mg (30) v prochlorperazine 10 mg (30)</td>
<td>1/2/1</td>
</tr>
<tr>
<td>Adults, 17 to 89 years, various tumours 36</td>
<td>Bleomycin, cyclophosphamide, vincristine</td>
<td>Nabilone 2 mg (50) v placebo (50)</td>
<td>1/2/1</td>
</tr>
<tr>
<td>Adults, median age 61 years, gastrointestinal tumours 37</td>
<td>Dexamethasone, fluorouracil, vincristine</td>
<td>Dronabinol 15 mg (2) v prochlorperazine 10 mg (21) v placebo (21)</td>
<td>1/2/1</td>
</tr>
<tr>
<td>Adults, 39 to 73 years, various tumours 38</td>
<td>Dexamethasone, cyclophosphamide, vincristine</td>
<td>Dronabinol 10 mg/m² x (5) v metoclopromide 10 mg/kg x (15)</td>
<td>1/2/1</td>
</tr>
<tr>
<td>Adults, median age 53 (range 15 to 74) years, various tumours 39</td>
<td>Bleomycin, cyclophosphamide, cisplatin, vincristine</td>
<td>Nabilone 2 mg (13) v prochlorperazine 10 mg/kg x (13) v intravenous (13)</td>
<td>1/2/1</td>
</tr>
<tr>
<td>Adults, mean age 50 (range 17 to 80) years, various tumours 40</td>
<td>Cisplatin, cyclophosphamide, fluorouracil, vincristine</td>
<td>Levonantradol 0.5 mg (27) v levonantradol 0.75 mg (28) v levonantradol 1.0 mg (29) v intramuscular (29)</td>
<td>1/0/0</td>
</tr>
<tr>
<td>Adults, aged 18 to 70 years, various tumours 41</td>
<td>Dexamethasone, cisplatin, cyclophosphamide, vincristine</td>
<td>Nabilone 2 mg (18) v prochlorperazine 10 mg (18)</td>
<td>1/0/1</td>
</tr>
<tr>
<td>Adults, aged 20 to 58 years, various tumours 42</td>
<td>Dexamethasone, cisplatin</td>
<td>Nabilone 2 mg (24) v placebo (24)</td>
<td>1/1/1</td>
</tr>
<tr>
<td>Adults, Hodgkin’s or non-Hodgkin’s lymphoma 43</td>
<td>Vincristine, chlorpromazine</td>
<td>Dronabinol 10 mg/m² x (11) v placebo (11)</td>
<td>1/2/0</td>
</tr>
<tr>
<td>Adults, aged 20 to 68 years, various tumours 44</td>
<td>Cisplatin (not high dose)</td>
<td>Dronabinol 10 mg (17) v prochlorperazine 10 mg 28 v placebo (28)</td>
<td>1/1/1</td>
</tr>
<tr>
<td>Adults, 50th centile = 57 years, various tumours 45</td>
<td>Dexamethasone, cisplatin, cyclophosphamide, fluorouracil, vincristine</td>
<td>Nabilone 2 mg (36) v placebo (36)</td>
<td>1/0/0</td>
</tr>
<tr>
<td>Adults, aged 18 to 69 years, various tumours, history of emesis due to chemotherapy 46</td>
<td>Cyclophosphamide, dexamethasone, fluorouracil, vincristine</td>
<td>Dronabinol 15 mg/m² x (36) v prochlorperazine 10 mg (36)</td>
<td>1/0/0</td>
</tr>
<tr>
<td>Adults, mean age 41-45 years, various tumours 47</td>
<td>Cisplatin, dexamethasone</td>
<td>Dronabinol 10 mg (4) v placebo (4)</td>
<td>1/2/0</td>
</tr>
<tr>
<td>Adults aged 19 to 45 years, testicular cancer 48</td>
<td>Dexamethasone, cisplatin</td>
<td>Nabilone 1 mg (20) v placebo (20)</td>
<td>1/0/0</td>
</tr>
<tr>
<td>Adults, aged 48 to 78 years, lung cancer 49</td>
<td>Dexamethasone, cisplatin, cyclophosphamide, vincristine</td>
<td>Nabilone 2 mg (24) v prochlorperazine 7.5 mg (24)</td>
<td>1/2/1</td>
</tr>
<tr>
<td>Adults, aged 22 to 71 years, various tumours 50</td>
<td>Cyclophosphamide, doxorubicin, fluorouracil</td>
<td>Dronabinol 7 mg (55) v prochlorperazine 7 mg/m² x (55) v placebo (55)</td>
<td>1/2/1</td>
</tr>
<tr>
<td>Adults, aged 21 to 66 years, various tumours 51</td>
<td>Doxorubicin, cisplatin</td>
<td>Nabilone 1 mg (36) v placebo (36)</td>
<td>1/1/1</td>
</tr>
<tr>
<td>Adults, aged 18 to 78 years, various tumours 52</td>
<td>No data</td>
<td>Dronabinol 15 mg or 10 mg/m² x (30) v placebo (30)</td>
<td>1/2/1</td>
</tr>
<tr>
<td>Children and adults, aged 9 to 70 years, various tumours 53</td>
<td>Cisplatin, cyclophosphamide, methotrexate</td>
<td>Dronabinol 15 mg or 10 mg/m² x (37) v prochlorperazine 10 mg x (37)</td>
<td>1/2/1</td>
</tr>
<tr>
<td>Adults aged 19 to 65 years, various tumours 54</td>
<td>Cisplatin</td>
<td>Nabilone 2 mg (27) v prochlorperazine 10 mg (27)</td>
<td>1/1/1</td>
</tr>
<tr>
<td>Adults, aged 18 to 82 years, various tumours 55</td>
<td>Dronabinol 7.5 to 12.5 mg (172) v prochlorperazine 10 mg (181)</td>
<td>2/1/1</td>
<td></td>
</tr>
<tr>
<td>Adults aged 18 to 81 years, various tumours 56</td>
<td>Nabilone 2 mg (84) v placebo (84)</td>
<td>1/2/1</td>
<td></td>
</tr>
</tbody>
</table>

*Drugs taken orally unless stated otherwise.
In one trial rates of nausea and vomiting were 100%; chemotherapy was with high emetogenic substances (vincristine, doxorubicin and cyclophosphamide). In two trials, nausea rates were 85% despite prochlorperazine; chemotherapy was with low emetogenic substances (vincristine, methotrexate, fluorouracil). In one trial nausea and vomiting rates were 93% and 100%, respectively, and vomiting rates were 87% and 100%.

Sensitivity analyses

One trial reported very low event rates in the control groups: 16% of patients felt nauseous with placebo and 2% with prochlorperazine. 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 95% and 100%, respectively, and vomiting rates were 87% and 100%. Chemotherapy was with high dose methotrexate or with doxorubicin and cytoxan. In one trial rates of nausea and vomiting were 100% despite prochlorperazine; chemotherapy was with cisplatin. In two trials, the nausea rate was 85% despite alizapride and 83% despite prochlorperazine; 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).

When data from active controlled trials with medium control event rates (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 2). 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 2).

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. We therefore tried to test for dose responsiveness after excluding trials that reported extreme event rates in control groups. The largest clinically homogeneous subgroup contained just two trials, which compared dronabinol 30 mg per day with prochlorperazine 20 mg or with doxorubicin 28 mg/m² with prochlorperazine 30 mg/m². No sensible conclusion on dose-response relations with cannabinoids could be drawn. For the same reason, no conclusion could be drawn on the relative efficacy of nabilone, dronabinol, or levonantradol.

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 crossover trials preference for placebo was between 4% and 22%.

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. The difference in favour of cannabinoids was significant (table 2). A subgroup analysis, taking into account history of cannabis use, was not possible since this was inconsistently reported.

In the only parallel group trial that reported preference as an end point, 78% of the patients who had received chlorpromazine and 58% of those who had received levonantradol wished to receive the same treatment.

Table 2 Control of nausea and vomiting and patients' preference for treatment in trials of cannabinoid against active antiemetic or control treatment

<table>
<thead>
<tr>
<th>End point</th>
<th>No of trials</th>
<th>Cannabis (%)</th>
<th>Control (%)</th>
<th>Relative risk (95% CI)</th>
<th>No needed to treat (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control of nausea and vomiting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete control of nausea v placebo</td>
<td>4</td>
<td>70 (81/116)</td>
<td>57 (66/115)</td>
<td>1.21 (1.03 to 1.42)</td>
<td>8.0 (4.0 to 77.5)</td>
</tr>
<tr>
<td>Complete control of vomiting v placebo</td>
<td>4</td>
<td>66 (76/116)</td>
<td>36 (41/115)</td>
<td>1.84 (1.42 to 2.38)</td>
<td>3.3 (2.4 to 5.7)</td>
</tr>
<tr>
<td>Complete control of nausea v active</td>
<td>7</td>
<td>59 (122/207)</td>
<td>43 (93/215)</td>
<td>1.38 (1.18 to 1.62)</td>
<td>6.4 (4.0 to 16)</td>
</tr>
<tr>
<td>Complete control of vomiting v active</td>
<td>6</td>
<td>57 (111/194)</td>
<td>45 (90/201)</td>
<td>1.28 (1.08 to 1.51)</td>
<td>8.0 (4.5 to 15.6)</td>
</tr>
<tr>
<td>Sensitivity analysis (cannabinoids v active)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Complete control of nausea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event rate in controls 25% to 75%</td>
<td>3</td>
<td>70 (75/107)</td>
<td>41 (46/112)</td>
<td>1.70 (1.32 to 2.18)</td>
<td>3.4 (2.4 to 6.1)</td>
</tr>
<tr>
<td>Event rate in controls &lt;25% or &gt;75%</td>
<td>4</td>
<td>47 (47/100)</td>
<td>46 (47/103)</td>
<td>1.06 (0.88 to 1.27)</td>
<td>73 (6.6 to 81.1)</td>
</tr>
<tr>
<td>Complete control of vomiting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event rate in controls 25% to 75%</td>
<td>4</td>
<td>72 (105/146)</td>
<td>57 (87/153)</td>
<td>1.28 (1.07 to 1.48)</td>
<td>6.6 (3.9 to 23)</td>
</tr>
<tr>
<td>Event rate in controls &lt;25% or &gt;75%</td>
<td>2</td>
<td>13 (6/48)</td>
<td>6 (4/46)</td>
<td>1.86 (0.53 to 6.47)</td>
<td>16 (5.6 to 59)</td>
</tr>
<tr>
<td>Patients' rating</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preference for cannabinoid v placebo</td>
<td>4</td>
<td>76 (153/202)</td>
<td>13 (27/202)</td>
<td>5.87 (3.96 to 8.15)</td>
<td>1.6 (1.4 to 1.8)</td>
</tr>
<tr>
<td>Preference for cannabinoid v active</td>
<td>14</td>
<td>61 (371/604)</td>
<td>26 (156/608)</td>
<td>2.39 (2.05 to 2.78)</td>
<td>2.8 (2.4 to 3.3)</td>
</tr>
</tbody>
</table>

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

Active controls: prochlorperazine, metoclopramide, chlorpromazine, tiethylperazine, haloperidol, domperidone, alizapride.

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drug for future chemotherapy cycles. This difference that was not significant (relative risk 0.74, 95% confidence interval 0.50 to 1.09).

Side effects
Side effects happened significantly more often with cannabinoids (table 3). 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 3). In 19 trials, the number of patients who withdrew from the study due to intolerable adverse effects was significantly increased with cannabinoids (table 3).

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, metoclo-
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. We could not establish a dose-response relation, mainly because there were insufficient quality data from the original trials. In some trials, dose was adjusted during the trial. The relation between plasma concentration of a cannabinoid and its antiemetic efficacy is unclear. In one trial, antiemetic efficacy was related to the plasma concentration of dronabinol. Another trial found no correlation between dronabinol serum levels and efficacy or adverse reactions.

Defining an intervention’s usefulness includes estimates of the likelihood of 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. 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 3). 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. The trials we included were of acceptable quality according to the Oxford quality scale, with 25 of 30 trials scoring 3 or 4. In 70% of trials an adequate method of blinding was described. Most crossover trials used a double dummy design. 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. 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. We must therefore assume that most of these trials had some degree of observer bias.

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

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. The selection of refractory patients introduces bias against the regimens that do not include cannabinoids. Younger age and previous marijuana exposure have been identified as factors that predicted response to antiemetic treatment. Regular cannabis users may be more likely to believe in its antiemetic efficacy. They may also experience adverse effects of cannabis more positively than patients who have not previously taken cannabis (for instance, a “high” or somnolence). In one trial, where more than 50% of patients were regular cannabis users, only 6% did not believe that cannabis would reduce their nausea and vomiting symptoms.

In view of the numerous biases in these trials, “preference” and “satisfaction” are likely to be surrogate endpoints. These endpoints alone do not allow to judge with confidence on the usefulness of cannabinoids in the control of chemotherapy related emesis.

Finally, we have the problem of size. Small trials can be greatly affected by the random play of chance. 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, 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-HT₁ receptor antagonists). Minimal effective doses would then be needed. Identifi-
cation 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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