Cannabinoids for Medical Use
A Systematic Review and Meta-analysis

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IMPORTANCE Cannabis and cannabinoid drugs are widely used to treat disease or alleviate symptoms, but their efficacy for specific indications is not clear.

OBJECTIVE To conduct a systematic review of the benefits and adverse events (AEs) of cannabinoids.

DATA SOURCES Twenty-eight databases from inception to April 2015.

STUDY SELECTION Randomized clinical trials of cannabinoids for the following indications: nausea and vomiting due to chemotherapy, appetite stimulation in HIV/AIDS, chronic pain, spasticity due to multiple sclerosis or paraplegia, depression, anxiety disorder, sleep disorder, psychosis, glaucoma, or Tourette syndrome.

DATA EXTRACTION AND SYNTHESIS Study quality was assessed using the Cochrane risk of bias tool. All review stages were conducted independently by 2 reviewers. Where possible, data were pooled using random-effects meta-analysis.

MAIN OUTCOMES AND MEASURES Patient-relevant/disease-specific outcomes, activities of daily living, quality of life, global impression of change, and AEs.

RESULTS A total of 79 trials (6462 participants) were included; 4 were judged at low risk of bias. Most trials showed improvement in symptoms associated with cannabinoids but these associations did not reach statistical significance in all trials. Compared with placebo, cannabinoids were associated with a greater average number of patients showing a complete nausea and vomiting response (47% vs 20%; odds ratio [OR], 3.82 [95% CI, 1.55-9.42]; 3 trials), reduction in pain (37% vs 31%; OR, 1.41 [95% CI, 0.99-2.00]; 8 trials), a greater average reduction in numerical rating scale pain assessment (on a 0-10-point scale; weighted mean difference [WMD], −0.46 [95% CI, −0.80 to −0.11]; 6 trials), and average reduction in the Ashworth spasticity scale (WMD, −0.12 [95% CI, −0.24 to 0.01]; 5 trials). There was an increased risk of short-term AEs with cannabinoids, including serious AEs. Common AEs included dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, and hallucination.

CONCLUSIONS AND RELEVANCE There was moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity. There was low-quality evidence suggesting that cannabinoids were associated with improvements in nausea and vomiting due to chemotherapy, weight gain in HIV infection, sleep disorders, and Tourette syndrome. Cannabinoids were associated with an increased risk of short-term AEs.


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Cannabis is a generic term used for drugs produced from plants belonging to the genus Cannabis. It is one of the most popular recreational drugs; worldwide, an estimated 178 million people aged 15 to 64 years used cannabis at least once in 2012. Cannabis was included as a controlled drug in the United Nations’ Single Convention on Narcotic Drugs, held in 1961, and its use is illegal in most countries.

Medical cannabis refers to the use of cannabis or cannabinoids as medical therapy to treat disease or alleviate symptoms. Cannabinoids can be administered orally, sublingually, or topically; they can be smoked, inhaled, mixed with food, or made into tea. They can be taken in herbal form, extracted naturally from the plant, gained by isomerisation of cannabidiol, or manufactured synthetically. Prescribed cannabinoids include dronabinol capsules, nabilone capsules, and the oromucosal spray nabiximols. Some countries have legalized medicinal-grade cannabis for chronically ill patients. Canada and the Netherlands have government-run programs in which specialized companies supply quality-controlled herbal cannabis. In the United States, 23 states and Washington, DC (May 2015), have introduced laws to permit the medical use of cannabis; other countries have similar laws. The aim of this systematic review was to evaluate the evidence for the benefits and adverse events (AEs) of medical cannabinoids across a broad range of indications.

Methods

This review followed guidance published by the Centre for Reviews and Dissemination and the Cochrane Collaboration. We established a protocol for the review (eAppendix 1 in Supplement 1).

Study Eligibility Criteria

Randomized clinical trials (RCTs) that compared cannabinoids with usual care, placebo, or no treatment in the following indications were eligible: nausea and vomiting due to chemotherapy, appetite stimulation in HIV/AIDS, chronic pain, spasticity due to multiple sclerosis (MS) or paraplegia, depression, anxiety disorder, sleep disorder, psychosis, intraocular pressure in glaucoma, or Tourette syndrome. These indications were prespecified by the project funders, the Swiss Federal Office of Public Health. If no RCTs were available for a particular indication or outcome (eg, long-term AEs such as cancer, psychosis, depression, or suicide), nonrandomized studies including uncontrolled studies (such as case series) with at least 25 patients were eligible.

Identification and Selection of Studies

Twenty-eight databases and gray literature sources were searched from inception to April 2015 without language restriction (Embase search strategy and details of databases searched available in eAppendix 2 in Supplement 2). The search strategy was peer reviewed by a second information specialist. Reference lists of included studies were screened. Search results and full-text articles were independently assessed by 2 reviewers; disagreements were resolved through consensus or referral to a third reviewer.

Data Collection and Study Appraisal

We extracted data about baseline characteristics and outcomes (patient-relevant and disease-specific outcomes, activities of daily living, quality of life, global impression of change, and specified AEs). For dichotomous data such as number of patients with at least 30% improvement in pain, we calculated the odds ratio (OR) and 95% CI. For categorical data, we extracted details about each category assessed and the numbers of patients with an outcome in each category. Continuous data such as the Ashworth spasticity score were extracted as means and SDs at baseline, follow-up, and the change from baseline and used to calculate mean differences with 95% CIs. Results (mean difference, 95% CIs, and P values) from the between-group statistical analyses reported by the study were also extracted. All relevant sources were used for data extraction including full-text journal articles, abstracts, and clinical trial registry entries. Where available, the journal article was used as the primary publication because it had been peer reviewed.

RCTs were assessed for methodological quality using the Cochrane Risk of Bias tool. If at least one of the domains was rated as high, the trial was considered at high risk of bias. If all domains were judged as low, the trial was considered at low risk of bias. Otherwise, the trial was considered as having unclear risk of bias. Data extraction and risk-of-bias assessment were performed independently by 2 reviewers; disagreements were resolved by a third reviewer.

Synthesis

Clinical heterogeneity was assessed by grouping studies by indication, cannabinoid, and outcome. If there were 2 or more trials within a single grouping, data were pooled using random-effects meta-analysis. For continuous outcomes, we analyzed the mean difference in change from baseline; if this was not reported and could not be calculated from other data, we used the mean difference at follow-up. For dichotomous data, we used the OR. In order to avoid double counting, we selected a single data set from each study to contribute to the analysis. For studies evaluating multiple interventions, we selected the intervention or dose that was most similar to the other interventions being evaluated in the same analysis. Heterogeneity was investigated using forest plots and the I² statistic. Where data were considered too heterogeneous to pool or not reported in a format suitable for pooling (eg, data reported as medians), we used a narrative synthesis.

Sensitivity analyses were used to assess the statistical effect of trial design. The primary analysis included only parallel-group trials, results from crossover trials were included in an additional analysis. For the analysis of AEs, data for all conditions were combined. We conducted stratified analyses and meta-regression to investigate whether associations varied according to type of cannabinoid, study design (parallel group vs crossover trial), indication (each of the indication categories included in this report), compar-
Results

The searches identified 23 754 hits (records) of which 505 were considered potentially relevant, based on title and abstract screening, and obtained as full-text studies. A total of 79 studies (6462 participants), available as 151 reports, were included; 3 studies (6 reports) were included in multiple indication categories (Figure 1). Thirty-four studies were parallel-group trials (4436 participants), and 45 were crossover trials (2026 participants). Four studies were available only as an abstract,15-18 a further 3 were available only as abstracts19-21 but with additional details available on trial registries including full results in one,19 and details of 2 trials (including full trial results) were available only as trial registry entries22,23; all other trials were reported in full-length journal articles. Where reported, the proportion of participants who were men ranged from 0% to 100% (median, 50% [57 studies]), and the proportion of white participants ranged from 50% to 99% (median, 78% [18 studies]). Publication dates ranged from 1975 to 2015 (median, 2004 [with one-third of trials published before 1990]). Studies were conducted in a wide range of countries. A variety of cannabinoids were evaluated and compared with various different active comparators or placebo; most active comparators were included in the nausea and vomiting indication (Table 1). eAppendices 3 to 12 in Supplement 1 provide an overview of the included studies and their findings.

Four (5%) trials were judged at low risk of bias, 55 (70%) were judged at high risk of bias, and 20 (25%) at unclear risk of bias (eAppendix 13 in Supplement 2). The major potential source of bias in the trials was incomplete outcome data. More than 50% of trials reported substantial withdrawals and did not adequately account for this in the analysis. Selective outcome reporting was a potential risk of bias in 16% of trials. These studies did not report data for all outcomes specified in the trial register, protocol, or methods section or changed the primary outcome from that which was prespecified. Most studies reported being double-blinded but only 57% reported that appropriate methods had been used for participant binding and only 24% reported that outcome assessors had been appropriately blinded.

Full results from included studies are presented in eAppendices 3-12 in Supplement 2; pooled results and GRADE ratings are presented in Table 2.

- Nausea and Vomiting Due to Chemotherapy

Nausea and vomiting due to chemotherapy was assessed in 28 studies (37 reports; 1772 participants).15,16,24-58 Fourteen studies assessed nabilone and there were 3 for dronabinol, 1 for nabiximols, 4 for levonantradol, and 6 for THC. Two studies also included a combination therapy group of dronabinol with ondansetron or prochlorperazine. Eight studies included a placebo control, 3 of these also included an active comparator, and 20 studies included only an active comparator. The most common active comparators were prochlorperazine (15 studies), chlorpromazine (2 studies) and domperidone (2 studies). Other comparators (alizapride, hydroxyzine, metoclopramide and ondansetron) were evaluated in single studies (Table 1). Of all 28 studies,

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Figure 1. Flow of Studies Through the Review Process

| 23754 | Titles and abstracts screened (duplicates removed) |
| 17319 | RCT searches |
| 5397  | Depression searches |
| 1038  | AE searches |

- 505 Full reports assessed
- 354 Excluded reports
- 49 SRs used as source of studies6
- 47 AEs of recreational cannabis
- 44 Results not yet available, trial registry entries6
- 42 No outcomes of interest
- 36 Not primary studies or SRs
- 32 Not RCT and did not report long-term AE
- 17 Evaluated treatment withdrawal
- 16 No results data
- 13 Inappropriate population
- 13 Inappropriate controls
- 11 Background report
- 11 Crossover trial, unbalanced design
- 7 Unobtainable
- 6 Duplicate records
- 5 Did not evaluate cannabis
- 5 Terminated before results were available

AE indicates adverse event; RCT, randomized controlled trial; and SR, systematic review.

- These excluded reports were screened as full-text articles/reports.
- The number of included RCTS does not sum because some were included in more than 1 indication category.
Table 1. Evaluation of Interventions by Included Studies

<table>
<thead>
<tr>
<th>Intervention</th>
<th>US Legal Status and Approved Use</th>
<th>Cannabis-Related Properties</th>
<th>Administration Method</th>
<th>Dose Evaluated</th>
<th>Comparator</th>
<th>No. of Studies*</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ajulemic acid (JBT-101, CT3)</td>
<td>Not currently in clinical use</td>
<td>Synthetic nonpsychoactive cannabinoid Derivative of the THC metabolite 11-nor-9-carboxy-THC</td>
<td>Capsules (oral)</td>
<td>Maximum 40 mg 2 ×/d</td>
<td>Placebo</td>
<td>1</td>
<td>Pain</td>
</tr>
<tr>
<td>CBD</td>
<td>Use does not appear to be explicitly restricted</td>
<td>Active cannabinoid part of cannabis</td>
<td>Capsules (oral)</td>
<td>200-800 mg/d</td>
<td>Placebo</td>
<td>2</td>
<td>Psychosis, anxiety</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Amsulpiride</td>
<td>1</td>
<td>Psychosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Oromuscosal spray</td>
<td>20 mg 1 ×/d or 40 mg 1 ×/d (2 doses evaluated)</td>
<td>Placebo</td>
<td>1</td>
</tr>
<tr>
<td>Cannabis (marijuana)</td>
<td>Regulated under Schedule I of the Controlled Substances Act 1970 Legal for medical use in 23 states</td>
<td>Numerous active cannabinoids that will vaporize at different temperatures</td>
<td>Vaporized</td>
<td>Two concentrations: 1.29% and 3.53% 4 puffs after 1 h then 4-8 puffs after 3 h</td>
<td>Placebo</td>
<td>1</td>
<td>Pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Smoked</td>
<td>Maximum 3 cigarettes/d</td>
<td>Placebo</td>
<td>1</td>
</tr>
<tr>
<td>Dronabinol</td>
<td>Licensed for treatment of anorexia associated with weight loss in patients with AIDS Also for nausea and vomiting associated with cancer chemotherapy (United States and Germany)</td>
<td>Synthetic THC</td>
<td>Capsules (oral)</td>
<td>Maximum 5-30 mg/d 1-4 doses/d (most common, 2 doses)</td>
<td>Placebo</td>
<td>10</td>
<td>Nausea and vomiting, pain, spasticity, HIV, sleep</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Megestrol acetate</td>
<td>1</td>
<td>HIV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dronabinol + prochlorperazine or prochlorperazine</td>
<td>1</td>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dronabinol + ondansetron, ondansetron, or placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levonantradol</td>
<td>Not currently in clinical use</td>
<td>Synthetic analogue of dronabinol</td>
<td>Capsules (oral)</td>
<td>Maximum 5 mg/d 1 mg 2 hours before chemotherapy then 1 mg every 4 hours</td>
<td>Prochlorperazine</td>
<td>1</td>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intramuscular</td>
<td>Maximum 1.5 mg -6 mg 0.5 mg-1 mg, 1-2 h before chemotherapy then every 4 h</td>
<td>Prochlorperazine</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Chlorpromazine</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Metoclopramide</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Nabilone</td>
<td>Approved by the US FDA in 1985 for treatment of chemotherapy-induced nausea and vomiting that has not responded to conventional antiemtics Also marketed in the United Kingdom, Mexico, and Austria</td>
<td>Synthetic cannabinoid derivate mimicking THC</td>
<td>Capsules (oral)</td>
<td>Maximum 0.5 mg-8 mg Most common dose 2 mg 2 ×/d</td>
<td>Placebo</td>
<td>7*</td>
<td>Spasticity, pain, sleep, nausea and vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dihydrocodeine</td>
<td>1</td>
<td>Pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Amitriptyline</td>
<td>1</td>
<td>Pain, sleep</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Chlorpromazine</td>
<td>1</td>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Alizapride</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Domperidone</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prochlorperazine</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Nabiximols</td>
<td>Licensed for use in the United Kingdom, Spain, Czech Republic, Germany, Denmark, Sweden, Italy, Austria, Canada, Poland, France (for spasticity due to multiple sclerosis) Not currently licensed in the United States Initial target indication for US FDA approval is cancer pain</td>
<td>Each mL contains 27 mg THC and 25 mg CBD Oromuscosal spray</td>
<td>Titrated to a maximum of 4-48 sprays/24 h Most common maximum was 8 sprays/3 h or 48 sprays/24 h</td>
<td>Placebo</td>
<td>19</td>
<td>Spasticity, pain, nausea and vomiting</td>
<td></td>
</tr>
<tr>
<td>ECP002A</td>
<td>No current marketing authorization</td>
<td>Pure (≥98%) Natural Δ9-THC</td>
<td>Oral tablet</td>
<td>Individualized dose</td>
<td>Placebo</td>
<td>1</td>
<td>Spasticity</td>
</tr>
</tbody>
</table>

(continued)

risk of bias was high for 23 or unclear for 5. All studies suggested a greater benefit of cannabinoids compared with both active comparators and placebo, but these did not reach statistical significance in all studies. The average number of patients showing a complete nausea and vomiting response was greater with cannabinoids (dronabinol or nabiximols) than placebo (OR, 3.82 [95% CI, 1.55-9.42]; 3 trials). There was no evidence of heterogeneity for this
Abbreviations: CBD, cannabidiol; US FDA, US Food and Drug Administration; THC, tetrahydrocannabinol.

The active nolfoundsignificantlygreaterweightgainwithbothformsof
in single studies and associations failed to reach statistical
percentage of body fat, reduced nausea, and improved func-
thatitmayalsobeassociatedwithincreasedappetite,greater
ies were at high risk of bias. There was some evidence that
marijuana), and 1 compared with megastrol acetate. All stud-
aminolevaluatednabiloneas an adjunctivetogabapentin.121Theconditionscausingthechronicpainvar-
cluded neuropathic pain (central, peripheral, or not specified; 12 studies), 3 for cancer pain, 3 for diabetic peripheral neuropathy, 2 for
HIV-associated sensory neuropathy, and 1 study for each of
the following indications: refractory pain due to MS or other
neurological conditions, for rheumatoid arthritis, for non-
cancer pain (nociceptive and neuropathic), central pain (not
specified further), musculoskeletal problems, and
chemotherapy-induced pain.

Two studies were at low risk of bias, 9 at unclear risk, and
17 at high risk of bias. Studies generally suggested improve-
ments in pain measures associated with cannabinoids but
these did not reach statistical significance in most individual
studies.

The average number of patients who reported a reduc-
tion in pain of at least 30% was greater with cannabinoids
than with placebo (OR, 1.41 [95% CI, 0.99-2.00]; 8 trials; Figure 2). One trial assessed smoked THC77 and reported the
greatest beneficial effect (OR, 3.43 [95% CI, 1.03-11.48]), and
7 trials assessed nabiximols (Figure 2). Pain conditions
evaluated in these trials were neuropathic pain (OR, 1.38
[95% CI, 0.93-2.03]; 6 trials) and cancer pain (OR, 1.41 [95%
CI, 0.99-2.00]; 2 trials), with no clear differences between
pain conditions. Nabiximols was also associated with a
greater average reduction in the Numerical Rating Scale
(NRS; 0-10 scale) assessment of pain (weighted mean differ-
ence [WMD], −0.46 [95% CI, −0.80 to −0.11]; 6 trials), brief
pain inventory-short form, severity composite index (WMD,
−0.17 [95% CI, −0.50 to 0.16]; 3 trials), neuropathic pain
scale (WMD, −3.89 [95% CI, −7.32 to −0.47]; 5 trials), and
the proportion of patients reporting improvement on a global
impression of change score (OR, 2.08 [95% CI, 1.21 to 3.59];
6 trials) compared with placebo. There was some evidence to
support this based on continuous data but this was not
consistent across trials. There was no difference in average
quality-of-life scores as measured by the EQ-5D health sta-
tus index (WMD, −0.01 [95% CI, −0.05 to 0.02]; 3 trials)
between nabiximols and placebo. Two of the studies
included in the meta-analysis for the NRS (0-10 scale)

### Analysis

The pain assessment in 28 studies (63 reports; 2454
participants).19,20,22,23,63-120 Thirteen studies evaluated
nabiximols, 4 were for smoked THC, 5 for nabilone, 3 for
THC oromucosal spray, 2 dronabinol, 1 vaporized cannabis
(included 2 doses), 1 for ajuvencic acid capsules, and 1 for
oral THC. One trial compared nabilone with amitriptyline64;
all other studies were placebo controlled. One of these
studies evaluated nabilone as an adjunctive treatment to
gabapentin.123 The conditions causing the chronic pain var-

### Chronic Pain

Chronic pain was assessed in 28 studies (63 reports; 2454
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all other studies were placebo controlled. One of these
studies evaluated nabilone as an adjunctive treatment to
gabapentin.123 The conditions causing the chronic pain varied
between studies and included neuropathic pain (central,
peripheral, or not specified; 12 studies), 3 for cancer pain, 3 for
diabetic peripheral neuropathy, 2 for fibromyalgia, 2 for

### Appetite Stimulation in HIV/AIDS Infection

Appetite stimulation in HIV/AIDS was assessed in 4 studies
(4 reports; 255 participants).59-62 All studies assessed dron-
abinol, 3 compared with placebo (1 of which also assessed
marijuana), and 1 compared with megastrol acetate. All studies
were at high risk of bias. There was some evidence that
dronabinol is associated with an increase in weight when
compared with placebo. More limited evidence suggested that
it may also be associated with increased appetite, greater
percentage of body fat, reduced nausea, and improved func-
tional status. However, these outcomes were mostly assessed
in single studies and associations failed to reach statistical
significance. The trial that evaluated marijuana and dronabi-
nol found significantly greater weight gain with both forms of
cannabinoid when compared with placebo.59 The active
comparison trial found that megastrol acetate was associated
with greater weight gain than dronabinol and that combining
dronabinol with megastrol acetate did not lead to additional
weight gain.60

### Table 1. Evaluation of Interventions by Included Studies (continued)

<table>
<thead>
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<th>Dose Evaluated</th>
<th>Comparator</th>
<th>No. of Studies*</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>THC/CBD</td>
<td>See individual components</td>
<td>Combination of CBD and THC</td>
<td>Capsules (oral)</td>
<td>Maximum 10 mg-60 mg/d, given as 2 doses</td>
<td>Placebo</td>
<td>4</td>
<td>Spasticity</td>
</tr>
</tbody>
</table>

Abbreviations: CBD, cannabidiol; US FDA, US Food and Drug Administration; THC, tetrahydrocannabinol.

* The number of studies does not sum to 79 because some reported more than 2 treatment groups and were accounted more than once.

One trial evaluated nabilone as an adjunctive to gabapentin.

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**Figure 2**

One trial assessed smoked THC77 and reported the
greatest beneficial effect (OR, 3.43 [95% CI, 1.03-11.48]), and
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included in the meta-analysis for the NRS (0-10 scale)
<table>
<thead>
<tr>
<th>Indication</th>
<th>No. of Studies</th>
<th>Cannabinoid (No. of Studies)</th>
<th>Comparator</th>
<th>Outcome</th>
<th>Summary Estimate</th>
<th>Favors</th>
<th>I², %</th>
<th>GRADE Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting due to chemotherapy</td>
<td>3 (102)</td>
<td>Dronabinol (2), Nabiximols (1)</td>
<td>Placebo</td>
<td>Nausea and vomiting Complete response</td>
<td>OR (95% CI), 3.82 (1.55 to 9.42)</td>
<td>CBM 0</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>1 (88)</td>
<td>Dronabinol</td>
<td>Placebo</td>
<td>Weight gain No. of patients who gained ≥2 kg within 6 weeks</td>
<td>OR (95% CI), 2.2 (0.68 to 7.27)</td>
<td>CBM NA</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Chronic pain (neuropathic and cancer pain)</td>
<td>8 (1370)</td>
<td>Smoked THC (1), Nabiximols (7)</td>
<td>Placebo</td>
<td>Pain reduction ≥30% NRS or VAS scores Follow-up 2-15 weeks</td>
<td>OR (95% CI), 1.41 (0.99 to 2.00)</td>
<td>CBM 48</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 (948)</td>
<td>Nabiximols (6)</td>
<td>Placebo</td>
<td>Pain NRS scores (0-10) Follow-up 2-14 weeks</td>
<td>WMD (95% CI), -0.46 (-0.80 to -0.11)</td>
<td>CBM 59</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 (613)</td>
<td>Nabiximols (3)</td>
<td>Placebo</td>
<td>Pain Brief Pain Inventory-Short Form scale (0 to 10) Follow-up 3-15 weeks</td>
<td>WMD (95% CI), -0.17 (-0.50 to 0.16)</td>
<td>CBM 0</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 (267)</td>
<td>Nabiximols (5), Nabilone (1)</td>
<td>Placebo</td>
<td>Patient global impression of change Follow-up 3-14 weeks</td>
<td>OR (95% CI), 2.08 (1.21 to 3.59)</td>
<td>CBM 68</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 (764)</td>
<td>Nabiximols (5)</td>
<td>Placebo</td>
<td>Neuropathic pain Neuropathic Pain Scale (0-100) Follow-up 5-15 weeks</td>
<td>WMD (95% CI), -3.89 (-7.32 to -0.47)</td>
<td>CBM 41</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 (573)</td>
<td>Nabiximols (3)</td>
<td>Placebo</td>
<td>Quality of life EQ-5D scale (0 to 100) Follow-up 12-15 weeks</td>
<td>WMD (95% CI), -0.01 (-0.05 to 0.02)</td>
<td>Placebo 0</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Spasticity due to multiple sclerosis or paraplegia</td>
<td>2 (519)</td>
<td>Nabiximols (2)</td>
<td>Placebo</td>
<td>50% Reduction in spasticity symptoms NRS (0-10) Follow-up 6-14 weeks</td>
<td>OR (95% CI), 1.40 (0.81 to 2.41)</td>
<td>CBM 0</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 (519)</td>
<td>Nabiximols (2)</td>
<td>Placebo</td>
<td>30% Reduction in spasticity symptoms NRS Follow-up 6-14 weeks</td>
<td>OR (95% CI), 1.64 (0.95 to 2.83)</td>
<td>CBM 44</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 (1244)</td>
<td>Nabiximols (4), THC/CBD (1), Dronabinol (1)</td>
<td>Placebo</td>
<td>Spasticity Ashworth Spasticity Scale Follow-up 3-15 weeks</td>
<td>WMD (95% CI), -0.11 (-0.23 to 0.02)</td>
<td>CBM 0</td>
<td>Moderate</td>
<td></td>
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<tr>
<td></td>
<td>3 (698)</td>
<td>Nabiximols (2), Nabilone (1)</td>
<td>Placebo</td>
<td>Spasticity NRS or VAS scores Follow-up 3-15 weeks</td>
<td>WMD (95% CI), -0.76 (-1.38 to -0.14)</td>
<td>CBM 73</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 (1433)</td>
<td>Nabilone (2), Dronabinol (1), THC/CBD (1)</td>
<td>Placebo</td>
<td>ADLs Barthel Index of ADL</td>
<td>WMD (95% CI), -0.58 (-1.73 to 0.56)</td>
<td>Placebo 0</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 (497)</td>
<td>Nabiximols (2)</td>
<td>Placebo</td>
<td>Walking speed as assessed by timing</td>
<td>WMD (95% CI), -0.86 (-3.08 to 1.36)</td>
<td>CBM 24</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 (461)</td>
<td>Nabiximols</td>
<td>Placebo</td>
<td>Global Impression Patient global impression of change</td>
<td>OR (95% CI), 1.44 (1.07 to 1.94)</td>
<td>CBM 0</td>
<td>Low</td>
<td></td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Indication</th>
<th>No. of Studies (No. of Patients)</th>
<th>Cannabinoid (No. of Studies)</th>
<th>Comparator</th>
<th>Outcome</th>
<th>Summary Estimate</th>
<th>Favors</th>
<th>I², %</th>
<th>GRADE Rating</th>
</tr>
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<tbody>
<tr>
<td>Depression</td>
<td>1 (66)</td>
<td>Nabiximols</td>
<td>Placebo</td>
<td>Depression Hospital Anxiety and Depression Scale (0-52) Follow-up 5 weeks</td>
<td>Mean difference (95% CI), 0.15 (−1.0 to 1.31)</td>
<td>Placebo</td>
<td>NA</td>
<td>Very low</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>1 (24)</td>
<td>Cannabidiol</td>
<td>Placebo</td>
<td>Anxiety Visual Analogue Mood Scale (anxiety factor scale; 0-100) Follow-up 107 minutes</td>
<td>Mean difference, −16.52</td>
<td>CBM</td>
<td>NA</td>
<td>Very low</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>1 (22)</td>
<td>Nabilone</td>
<td>Placebo</td>
<td>Sleep apnea/hypopnea Apnea Hypopnea Index Follow-up 3 weeks</td>
<td>Mean difference, −19.64</td>
<td>P value = .02</td>
<td>CBM</td>
<td>NA</td>
</tr>
<tr>
<td>Psychosis</td>
<td>1 (35)</td>
<td>Cannabidiol</td>
<td>Amisulpride</td>
<td>Mental health Brief Psychiatric Rating Scale Follow-up 4 weeks</td>
<td>Mean difference (95% CI), −0.10 (−9.20 to 8.90)</td>
<td>CBM</td>
<td>NA</td>
<td>Low</td>
</tr>
<tr>
<td>Tourette syndrome</td>
<td>1 (17)</td>
<td>THC capsules</td>
<td>Placebo</td>
<td>Tic severity Shapiro Tourette Syndrome Severity Scale (0-6) Follow-up 6 weeks</td>
<td>Mean difference (95% CI), 1 (−12.60 to 14.60)</td>
<td>THC</td>
<td>NA</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>1 (17)</td>
<td>THC capsules</td>
<td>Placebo</td>
<td>Tic severity Tourette syndrome symptom list (tic rating) Follow-up 6 weeks</td>
<td>Mean difference, −16.2</td>
<td>P value &lt; .05</td>
<td>THC</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>1 (18)</td>
<td>THC capsules</td>
<td>Placebo</td>
<td>Tic severity Yale Global Tic Severity Scale (0-100) Follow-up 6 weeks</td>
<td>Mean difference, −12.03</td>
<td>P value = .061</td>
<td>THC</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: ADL, activities of daily living; CBM, cannabis based medicine; EQ-5D, EuroQol Five Dimension Scale; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NA, not applicable; NRS, numerical rating scale; OR, odds ratio; THC, tetrahydrocannabinol; VAS, visual analog scale; WMD, weighted mean difference.

* No studies for glaucoma were included in the study estimate. The authors note that THC and cannabidiol were the interventions used in the reviewed glaucoma studies.

**Outcome includes the specific indication that was assessed, the means by which assessment was made, and follow-up (not shown for all studies).
assessed patients with cancer pain, all other studies assessed patients with neuropathic pain. There were no clear differences based on cause of pain in the meta-analysis of NRS. Sensitivity analyses that included crossover trials showed results consistent with those based on parallel-group trials alone.

**Spasticity Due to MS or Paraplegia**

Fourteen studies (33 reports; 2280 participants) assessed spasticity due to MS or paraplegia.17,19,65,87,91,122-149 Eleven studies (2138 participants) included patients with MS and 3 included patients with paraplegia (142 participants) caused by spinal cord injury. Six studies assessed nabiximols, 3 for dronabinol, 1 for nabilone, 4 for THC/CBD (2 of these also assessed dronabinol), and 1 each for ECP002A and smoked THC. All studies included a placebo control group; none included an active comparator. Two studies were at low risk of bias, 5 were at unclear risk of bias, and 7 were at high risk of bias. Studies generally suggested that cannabinoids were associated with improvements in spasticity, but this failed to reach statistical significance in most studies. There were no clear differences based on type of cannabinoid. Only studies in MS patients reported sufficient data to allow summary estimates to be generated. Cannabinoids (nabiximols, dronabinol, and THC/CBD) were associated with a greater average improvement on the Ashworth scale for spasticity compared with placebo, although this did not reach statistical significance (WMD, −0.12 [95% CI, −0.24 to 0.01]; 5 trials; **Figure 3**). Cannabinoids (nabilone and nabiximols) were also associated with a greater average improvement in spasticity assessed using numerical rating scales (mean difference, −0.76 [95% CI, −1.38 to −0.14]; 3 trials). There was no evidence of a difference in association according to type of cannabinoid for either analysis. Other measures of spasticity also suggested a greater benefit of cannabinoid but did not reach statistical significance (Table 2). The average number of patients who reported an improvement on a global impression of change score was also greater with nabiximols than placebo (OR, 1.44 [95% CI, 1.07 to 1.94]; 3 trials); this was supported by a further crossover trial of dronabinol and oral THC/CBD that provided continuous data for this outcome.132 Sensitivity analyses that included crossover trials showed results consistent with those based on parallel group trials alone.

**Depression**

No studies evaluating cannabinoids for the treatment of depression fulfilled inclusion criteria. Five studies included for other indications reported depression as an outcome measure; 4 evaluated chronic pain and 1 evaluated spasticity in MS patients.57,73,75,80,129 One trial assessed dronabinol (2 doses), 3 assessed nabiximols, and 1 assessed nabilone. Two studies were rated as having unclear risk of bias and 3 as having high risk of bias. Three studies suggested no difference between cannabinoids (dronabinol and nabiximols) and placebo in depression outcomes. One parallel-group trial that compared different doses of nabilomixols with placebo reported a negative effect of nabiximols for the highest dose (11-14 sprays per day) compared with placebo (mean difference from baseline, 2.50 [95% CI, 0.38 to 4.62]) but no difference between placebo and the 2 lower doses.67

**Anxiety Disorder**

One small parallel-group trial, judged at high risk of bias, evaluated patients with generalized social anxiety disorder.150 The trial reported that cannabidiol was associated with a greater improvement on the anxiety factor of a visual analogue mood scale (mean difference from baseline, −16.52; P value = .01) compared with placebo during a simulated public speaking test. Additional data about anxiety outcomes provided by 4 studies (1 parallel group) in patients with chronic pain also sug-
gested a greater benefit of cannabinoids (dronabinol, nabilone, and nabiximols) than placebo but these studies were not restricted to patients with anxiety disorders.73-75,80

Sleep Disorder

Two studies (5 reports; 54 participants) evaluated cannabinoids (nabilone) specifically for the treatment of sleep problems. One was a parallel-group trial judged at high risk of bias. This reported a greater benefit of nabiximol compared with placebo on the sleep apnea/hypopnea index (mean difference from baseline, −19.64; P = .02). The other was a crossover trial judged at low risk of bias in patients with fibromyalgia and compared nabilone with amitriptyline. This suggested that nabilone was associated with improvements in insomnia (mean difference from baseline, −19.64; P value = .02). The other was a crossover trial judged at low risk of bias in patients with fibromyalgia and compared nabilone with amitriptyline. This suggested that nabilone was associated with improvements in insomnia (mean difference from baseline, −19.64; P value = .02).

Glaucoma

One very small crossover trial (6 participants)159 judged at unclear risk of bias compared tetrahydrocannabinol (THC; 5 mg), cannabidiol (20 mg), cannabidiol (40 mg) oromucosal spray, and placebo. This trial found no difference between placebo and cannabinoids on measures of intraocular pressure in patients with glaucoma.

Movement Disorders Due to Tourette Syndrome

Two small placebo-controlled studies (4 reports; 36 participants)160-163 suggested that THC capsules may be associated with a significant improvement in tic severity in patients with Tourette syndrome.

Adverse Events

Data about AEs were reported in 62 studies (127 reports). Meta-regression and stratified analysis showed no evidence for a difference in the association of cannabinoids with the incidence of “any AE” based on type of cannabinoid, study design, indication, comparator, or duration of follow-up; further analyses were conducted for all studies combined. Figure 4 shows the results of the meta-analyses for the number of participants experiencing any AE compared when compared with controls, stratified according to cannabinoid. Cannabinoids were associated with a much greater risk of any AE, serious AE, withdrawals due to AE, and a number of specific AEs (Table 3). No studies evaluating the long-term AEs of cannabinoids were identified, even when searches were extended to lower levels of evidence.

Cannabinoids for Medical Use

Sleep Disorder

Two studies (5 reports; 54 participants) evaluated cannabinoids (nabilone) specifically for the treatment of sleep problems. One was a parallel-group trial judged at high risk of bias. This reported a greater benefit of nabiximol compared with placebo on the sleep apnea/hypopnea index (mean difference from baseline, −19.64; P = .02). The other was a crossover trial judged at low risk of bias in patients with fibromyalgia and compared nabilone with amitriptyline. This suggested that nabilone was associated with improvements in insomnia (mean difference from baseline, −19.64; P value = .02). The other was a crossover trial judged at low risk of bias in patients with fibromyalgia and compared nabilone with amitriptyline. This suggested that nabilone was associated with improvements in insomnia (mean difference from baseline, −19.64; P value = .02).
### Figure 4. Odds of Having Any Adverse Event With Cannabinoids Compared With Placebo, Stratified According to Cannabinoid

<table>
<thead>
<tr>
<th>Adverse Events With Cannabinoids vs Placebo by Cannabinoid, Indication, and Study</th>
<th>Cannabinoid Events</th>
<th>Placebo Events</th>
<th>Odds Ratio (95% CI)</th>
<th>More Adverse Events With Placebo</th>
<th>More Adverse Events With Cannabinoid</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dronabinol</strong></td>
<td></td>
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<tr>
<td>HIV</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Beal et al,62 1995</td>
<td>31</td>
<td>72</td>
<td>9</td>
<td>67</td>
<td>4.87 (2.10-11.32)</td>
<td></td>
</tr>
<tr>
<td>Timpone et al,60 1997</td>
<td>7</td>
<td>11</td>
<td>8</td>
<td>10</td>
<td>0.44 (0.06-3.16)</td>
<td></td>
</tr>
<tr>
<td><strong>Nabiximols</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lane et al,64 1991</td>
<td>21</td>
<td>21</td>
<td>7</td>
<td>21</td>
<td>6.40 (1.65-24.77)</td>
<td></td>
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<tr>
<td>Meiri et al,65 2007</td>
<td>2</td>
<td>17</td>
<td>3</td>
<td>14</td>
<td>0.49 (0.07-3.44)</td>
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<tr>
<td>Pain</td>
<td></td>
<td></td>
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<tr>
<td>Svensson et al,86 2004</td>
<td>23</td>
<td>24</td>
<td>11</td>
<td>24</td>
<td>27.18 (3.14-235.02)</td>
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<tr>
<td><strong>Nabilone</strong></td>
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<tr>
<td>Nausea and vomiting</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Chan et al,69 1987</td>
<td>32</td>
<td>36</td>
<td>14</td>
<td>36</td>
<td>12.57 (3.65-43.30)</td>
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<tr>
<td>George et al,70 1983</td>
<td>17</td>
<td>20</td>
<td>11</td>
<td>20</td>
<td>4.64 (1.02-21.00)</td>
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<tr>
<td>Johansson et al,71 1982</td>
<td>14</td>
<td>26</td>
<td>9</td>
<td>23</td>
<td>1.81 (0.58-5.66)</td>
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<tr>
<td>Pomeroy et al,72 1986</td>
<td>16</td>
<td>19</td>
<td>15</td>
<td>19</td>
<td>1.42 (0.27-7.44)</td>
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<tr>
<td>Multiple sclerosis</td>
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<tr>
<td>Collin et al,77 2007</td>
<td>102</td>
<td>124</td>
<td>46</td>
<td>65</td>
<td>1.92 (0.95-3.88)</td>
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<td>Collin et al,75 2010</td>
<td>156</td>
<td>167</td>
<td>132</td>
<td>170</td>
<td>4.08 (2.01-8.30)</td>
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<tr>
<td>Langford et al,64 2013</td>
<td>120</td>
<td>167</td>
<td>106</td>
<td>172</td>
<td>1.59 (1.01-2.51)</td>
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<td>Wade et al,74 2004</td>
<td>67</td>
<td>80</td>
<td>57</td>
<td>80</td>
<td>2.08 (0.97-4.47)</td>
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<tr>
<td>Nausea and vomiting</td>
<td></td>
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<tr>
<td>Duran et al,74 2010</td>
<td>6</td>
<td>7</td>
<td>6</td>
<td>9</td>
<td>3.00 (0.24-37.67)</td>
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</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
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<tr>
<td>Subtotal $i^2=69.1%$, ($P=0.01$)</td>
<td>79</td>
<td>145</td>
<td>38</td>
<td>136</td>
<td>10.24</td>
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<tr>
<td><strong>Levonantradol</strong></td>
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<tr>
<td>Nausea and vomiting</td>
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<td></td>
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<tr>
<td>Heim et al,75 1984</td>
<td>32</td>
<td>45</td>
<td>13</td>
<td>45</td>
<td>6.06 (2.43-15.08)</td>
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<td>Hutcheon et al,77 1983</td>
<td>23</td>
<td>26</td>
<td>20</td>
<td>27</td>
<td>2.68 (0.61-11.78)</td>
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<tr>
<td>Subtotal $i^2=0.0%$, ($P=0.36$)</td>
<td>55</td>
<td>71</td>
<td>33</td>
<td>72</td>
<td>4.84 (2.23-10.52)</td>
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<tr>
<td><strong>Ajulemic acid (CT3)</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Pain</td>
<td></td>
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<tr>
<td>Kasir et al,81 2003</td>
<td>12</td>
<td>19</td>
<td>5</td>
<td>19</td>
<td>4.80 (1.20-19.13)</td>
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<tr>
<td><strong>Tetrahydrocannabinol capsules</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Tourrette</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Müller-Vahl et al,160 2003</td>
<td>5</td>
<td>9</td>
<td>3</td>
<td>11</td>
<td>3.33 (0.51-21.58)</td>
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<tr>
<td>Müller-Vahl et al,162 2001</td>
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<td>12</td>
<td>2</td>
<td>12</td>
<td>3.57 (0.53-23.95)</td>
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<tr>
<td>Ungerleider et al,164 1982</td>
<td>136</td>
<td>172</td>
<td>99</td>
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<td>3.13 (1.96-5.00)</td>
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<tr>
<td>Subtotal $i^2=0.0%$, ($P=0.99$)</td>
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<td>193</td>
<td>104</td>
<td>204</td>
<td>3.16 (2.03-4.93)</td>
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<tr>
<td><strong>Tetrahydrocannabinol oromucosal spray</strong></td>
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<td></td>
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<tr>
<td>Tomida et al,159 2006</td>
<td>3</td>
<td>6</td>
<td>2</td>
<td>6</td>
<td>2.00 (0.19-20.61)</td>
<td></td>
</tr>
<tr>
<td><strong>Tetrahydrocannabinol/cannabidiol capsules</strong></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Zajicek et al,113 2012</td>
<td>133</td>
<td>143</td>
<td>100</td>
<td>134</td>
<td>4.52 (2.13-9.59)</td>
<td></td>
</tr>
<tr>
<td><strong>Overall</strong> $i^2=31.2%$, ($P=0.057$)</td>
<td>1438</td>
<td>1779</td>
<td>1058</td>
<td>1710</td>
<td>3.03 (2.42-3.80)</td>
<td></td>
</tr>
</tbody>
</table>

The square data markers indicate odds ratios (ORs) from primary studies, with sizes reflecting the statistical weight of the study using random-effects meta-analysis. The horizontal lines indicate 95% CIs. The blue diamond data markers represent the subtotal and overall OR and 95% CI. The vertical dashed line shows the summary effect estimate, the dotted line shows the line of no effect (OR = 1).
Table 3. Summary Estimates From Meta-analyses for Each AE Assessed: Odds of Participants Experiencing AE With Cannabinoid vs Placebo or Active Comparison

<table>
<thead>
<tr>
<th>General AE categories</th>
<th>No. of Studies (No. of Patients)</th>
<th>Summary OR (95% CI)</th>
<th>( I^2 ), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>29 (3714)</td>
<td>3.03 (2.42-3.80)</td>
<td>31</td>
</tr>
<tr>
<td>Serious</td>
<td>34 (3248)</td>
<td>1.41 (1.04-1.92)</td>
<td>0</td>
</tr>
<tr>
<td>Withdrawal due to AE</td>
<td>23 (2755)</td>
<td>2.94 (2.18-3.96)</td>
<td>2</td>
</tr>
<tr>
<td>MedDRA high-level grouping164</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>10 (1960)</td>
<td>1.78 (1.43-2.22)</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>7 (1681)</td>
<td>1.13 (0.87-1.46)</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>8 (1672)</td>
<td>3.10 (1.81-5.29)</td>
<td>55</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>10 (1521)</td>
<td>3.17 (2.20-4.58)</td>
<td>46</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissues disorders</td>
<td>7 (1310)</td>
<td>1.32 (0.75-2.32)</td>
<td>34</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>6 (1208)</td>
<td>1.78 (1.34-2.36)</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>5 (929)</td>
<td>1.01 (0.51-2.00)</td>
<td>0</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>3 (922)</td>
<td>2.72 (1.55-4.75)</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>5 (851)</td>
<td>0.80 (0.46-1.39)</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>7 (833)</td>
<td>1.42 (0.58-3.48)</td>
<td>0</td>
</tr>
<tr>
<td>Blood disorders</td>
<td>3 (543)</td>
<td>1.42 (0.20-10.25)</td>
<td>18</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>3 (543)</td>
<td>1.18 (0.48-2.93)</td>
<td>0</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>3 (470)</td>
<td>2.45 (2.27-2.65)</td>
<td>0</td>
</tr>
<tr>
<td>Investigations</td>
<td>2 (427)</td>
<td>1.55 (0.36-6.71)</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition</td>
<td>2 (427)</td>
<td>2.37 (1.00-5.61)</td>
<td>0</td>
</tr>
<tr>
<td>Neoplasms, benign, malignant, and unspecified</td>
<td>2 (427)</td>
<td>0.99 (0.47-2.08)</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous</td>
<td>3 (405)</td>
<td>0.85 (0.34-2.13)</td>
<td>0</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>1 (339)</td>
<td>1.42 (0.46-4.33)</td>
<td>NA</td>
</tr>
<tr>
<td>Reproductive system</td>
<td>1 (246)</td>
<td>1.55 (0.20-11.92)</td>
<td>NA</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>1 (181)</td>
<td>3.07 (0.12-76.29)</td>
<td>NA</td>
</tr>
<tr>
<td>Mental status change</td>
<td>3 (106)</td>
<td>2.49 (0.49-12.64)</td>
<td>0</td>
</tr>
<tr>
<td>Other body systems</td>
<td>1 (42)</td>
<td>2.59 (0.34-19.47)</td>
<td>NA</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>1 (32)</td>
<td>2.49 (0.92-6.68)</td>
<td>NA</td>
</tr>
<tr>
<td>Individual AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>41 (4243)</td>
<td>5.09 (4.10-6.32)</td>
<td>18</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>36 (4181)</td>
<td>3.50 (2.58-4.75)</td>
<td>28</td>
</tr>
<tr>
<td>Nausea</td>
<td>30 (3579)</td>
<td>2.08 (1.63-2.65)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20 (2717)</td>
<td>2.00 (1.54-2.62)</td>
<td>0</td>
</tr>
<tr>
<td>Somnolence</td>
<td>26 (3168)</td>
<td>2.83 (2.05-3.91)</td>
<td>27</td>
</tr>
<tr>
<td>Euphoria</td>
<td>27 (2420)</td>
<td>4.08 (2.18-7.64)</td>
<td>49</td>
</tr>
<tr>
<td>Depression</td>
<td>15 (2353)</td>
<td>1.32 (0.87-2.01)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17 (2191)</td>
<td>1.67 (1.13-2.47)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17 (2077)</td>
<td>1.65 (1.04-2.62)</td>
<td>15</td>
</tr>
<tr>
<td>Disorientation</td>
<td>12 (1736)</td>
<td>5.41 (2.61-11.19)</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>15 (1717)</td>
<td>2.03 (1.35-3.06)</td>
<td>0</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>18 (1272)</td>
<td>3.68 (2.24-6.01)</td>
<td>44</td>
</tr>
<tr>
<td>Anxiety</td>
<td>12 (1242)</td>
<td>1.98 (0.73-5.35)</td>
<td>54</td>
</tr>
<tr>
<td>Confusion</td>
<td>13 (1160)</td>
<td>4.03 (2.05-7.97)</td>
<td>0</td>
</tr>
<tr>
<td>Balance</td>
<td>6 (920)</td>
<td>2.62 (1.12-6.13)</td>
<td>0</td>
</tr>
<tr>
<td>Hallucination</td>
<td>10 (898)</td>
<td>2.19 (1.02-4.68)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>4 (375)</td>
<td>0.83 (0.26-2.63)</td>
<td>0</td>
</tr>
<tr>
<td>Paranoia</td>
<td>4 (492)</td>
<td>2.05 (0.42-10.10)</td>
<td>0</td>
</tr>
<tr>
<td>Psychosis</td>
<td>2 (37)</td>
<td>1.09 (0.07-16.35)</td>
<td>25</td>
</tr>
<tr>
<td>Seizures</td>
<td>2 (42)</td>
<td>0.91 (0.05-15.66)</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event; \( I^2 \), measures of heterogeneity; NA, not applicable; OR, odds ratio; MedDRA, medical dictionary for regulatory activities.
Discussion

We conducted an extensive systematic review of the benefits and AEs associated with medical cannabinoids across a broad range of conditions. We included 79 RCTs (6462 participants), the majority of which evaluated nausea and vomiting due to chemotherapy or chronic pain and spasticity due to MS and paraplegia. Other patient categories were evaluated in fewer than 5 studies.

Most studies suggested that cannabinoids were associated with improvements in symptoms, but these associations did not reach statistical significance in all studies. Based on the GRADE approach, there was moderate-quality evidence to suggest that cannabinoids may be beneficial for the treatment of chronic neuropathic or cancer pain (smoked THC and nabiximols) and spasticity due to MS (nabiximols, nabilone, THC/CBD capsules, and dronabinol). There was low-quality evidence suggesting that cannabinoids were associated with improvements in nausea and vomiting due to chemotherapy (dronabinol and nabiximols), weight gain in HIV (dronabinol), sleep disorders (naboline, nabiximols), and Tourette syndrome (THC capsules); and very low-quality evidence for an improvement in anxiety as assessed by a public speaking test (cannabidiol). There was low-quality evidence for no effect on psychosis (cannabidiol) and very low-level evidence for no effect on depression (nabiximols). There was an increased risk of short-term AEs with cannabinoid use, including serious AEs. Common AEs included asthenia, balance problems, confusion, dizziness, disorientation, diarrhea, euphoria, drowsiness, dry mouth, fatigue, hallucination, nausea, somnolence, and vomiting. There was no clear evidence for a difference in association (either beneficial or harmful) based on type of cannabinoids or mode of administration. Only 2 studies evaluated cannabis. There was no evidence that the effects of cannabis differed from other cannabinoids.

Strengths and Weaknesses

This review followed recommendations for rigorous systematic reviews. In order to identify as many relevant studies as possible and reduce the risk of publication bias, a highly sensitive search strategy was used and an extensive range of resources were searched including electronic databases, guidelines, and systematic reviews. Both published and unpublished trials were eligible for inclusion. There were no date or language restrictions. In order to minimize bias and errors, the main Embase strategies were peer reviewed by a second independent information specialist and all stages of the review process were performed independently by 2 reviewers. We used the Cochrane risk of bias tool to assess the included RCTs. This highlighted a number of methodological weaknesses in the included trials including failure to appropriately handle withdrawals, selective outcome reporting, and inadequate description of methods of randomization, allocation concealment, and blinding. An additional limitation of many included studies was their very small sample sizes. This was particularly the case for the trial of glaucoma (N = 6), Tourette syndrome (average N = 18), sleep disorder (average N = 27), and anxiety disorder (N = 24), which means these studies may have lacked the power to detect differences between treatment groups.

The synthesis combined a narrative discussion of individual study results with meta-analysis (for studies in which suitable data were available), supplemented by interpretation (following guidance of the GRADE Working Group). The data analysis was complicated by a number of issues. The included studies used a large variety of measures to evaluate outcomes, and even very similar outcomes were often assessed using different measures. Furthermore, a wide range of time points were reported in the included trials, which limited the applicability of the findings of these studies. Multiple different cannabinoids were evaluated in the included studies. We stratified analyses based on type of cannabinoid to investigate whether there were differences in associations based on type of cannabinoid. The majority of the studies were 2-group trials with a placebo control group; however, some studies included active comparisons and multiple groups comparing more than 1 form of cannabinoid, different doses of cannabinoids, or active and placebo comparator groups. This necessitated selecting a single result from each trial to contribute to the meta-analysis to avoid double counting of studies. Where possible, we selected the result for the treatment or dose most similar to the other studies contributing to that meta-analysis and for placebo-controlled comparisons rather than active comparisons. For the short-term AE analysis, we selected the highest-reported cannabinoids dose because we hypothesized that this would be most likely to be associated with AEs—additionally, this analysis would present a worst-case scenario. Studies evaluated various forms of cannabis administered via various routes (oral capsules, smoked, vaporized, oromucosal spray, intramuscular injection) and active comparators differed across trials. These differences in form, combined with the variety of outcome measures and the broad indication groupings considered by this review, resulted in a very heterogeneous set of included studies, which meant that meta-analysis was not always possible or appropriate. Many studies reported insufficient information to allow meta-analysis (eg, reporting only P values for group differences) or no information on the analysis performed. A further difficulty with the continuous data were that even for the same outcomes, some studies reported results as difference between groups at follow-up and others reported results for difference in change from baseline. As advised by the Cochrane Handbook for Systematic Reviews of Interventions, we combined both types of data when estimating summary mean differences. A potential problem with RCTs using crossover designs is the possible unblinding due to strong treatment or AEs. Additionally, studies of this design were rarely analyzed appropriately and none reported the required data accounting for their crossover design to permit appropriate inclusion in meta-analyses. Primary analyses were therefore based on parallel-group studies, with crossover trials included as sensitivity analyses.

Our search identified a number of existing reviews that assessed the use of medical cannabinoids for MS, and nuisance disorders.
Unanswered Questions and Future Research

Further large, robust, RCTs are needed to confirm the effects of cannabinoids, particularly on weight gain in patients with HIV/AIDS, depression, sleep disorders, anxiety disorders, psychosis, glaucoma, and Tourette syndrome are required. Further studies evaluating cannabis itself are also required because there is very little evidence on the effects and AEs of cannabis. Future trials should adhere to the CONSORT (Consolidated Standards of Reporting Trials) reporting standards and ensure that appropriate methods are used for randomization, allocation concealment, patient and outcome assessor blinding, handling of withdrawals, and avoiding selective outcome reporting. Future studies should assess patient-relevant outcomes (including disease-specific end points, quality of life, and AEs) using standardized outcome measures at similar time points to ensure inclusion in future meta-analyses.

Conclusions

There was moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity. There was low-quality evidence suggesting that cannabinoids were associated with improvements in nausea and vomiting due to chemotherapy, weight gain in HIV, sleep disorders, and Tourette syndrome. Cannabinoids were associated with an increased risk of short-term AEs.

ARTICLE INFORMATION

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Author Contributions: Dr Whiting had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Drafting of the manuscript: Whiting, Keurentjes, Ryder. Critical revision of the manuscript for important intellectual content: Wolf, Whiting, Di Nisio, Duffy, Hernandez, Keurentjes, Lang, Misso, Ryder, Schmidkofler.


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Additional Author Contributions: Dr Whiting drafted the article, produced tables and figures and performed the analysis. Drs Whiting, Wolf, and Kleijnen and Ms Misso and Mr Duffy drafted the protocol. Mr Duffy and Ms Misso conducted the literature searches. Drs Whiting, Wolf, and Lang screened searched results and selected full text studies for inclusion. Drs Whiting, Wolf, Lang, Westwood, Keurentjes, Di Nisio, Henderson, and Messrs Deshpande and Ryder, and Ms Schmidkofler performed data extraction and risk-of-bias assessment. Dr Wolf performed the GRADE assessments. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Correction: This article was corrected online July 13, 2015, for incorrect axis labeling in Figure 4 and for a corrected average reduction to the Ashworth spasticity scale (as reported in the Abstract); and on November 5, 2015, for an incorrect nonproprietary name and approved use for a drug in Table 1, and on April 12, 2016, for an incorrect effect estimate.

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