Original Investigation

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*.[1] 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.[2] Cannabis was included as a controlled drug in the United Nations' Single Convention on Narcotic Drugs, held in 1961,[3] 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.[4] Prescribed cannabinoids include dronabinol capsules, nabilone capsules, and the oromucosal spray nabiximols.[4] 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.[5] In the United States, 23 states and Washington, DC (May 2015), have introduced laws to permit the medical use of cannabis[6]; 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.[7,8] 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[9] 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[10] 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.[11] 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.[12] 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.[13] 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 I^2 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), compara-

tor (active vs placebo), and duration of follow-up (<24 hours, 24 hours-1 week, >1 week-4 weeks, >4 weeks) for the outcome of any AE. Statistical analyses were performed using Stata statistical software (version 10).

GRADE (Grading of Recommendations Assessment, Development and Evaluation) was used to rate the overall quality of the evidence for risk of bias, publication bias, imprecision, inconsistency, indirectness, and magnitude of effect. The GRADE ratings of very low-, low-, moderate-, or high-quality evidence reflect the extent to which we are confident that the effect estimates are correct.[14]

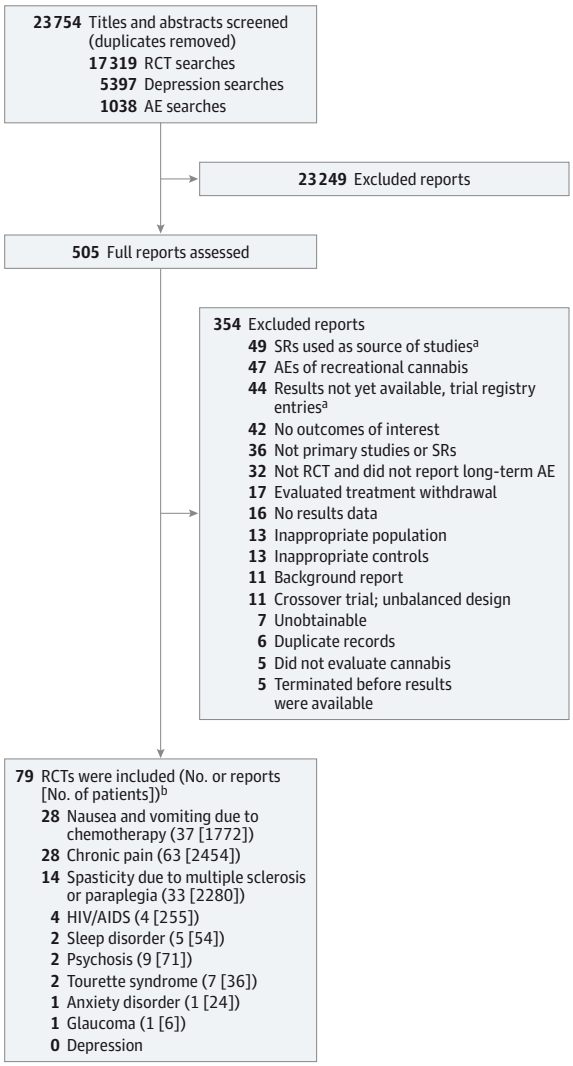
Results

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 abstracts[19-21] 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 entries[22,23]; 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 placebos; 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 blinding 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**.

Figure 1. Flow of Studies Through the Review Process



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

[a] These excluded reports were screened as full-text articles/reports.

[b] The number of included RCTS does not sum because some were included in more than 1 indication category.

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,

Table 1. Evaluation of Interventions by Included Studies

Intervention	US Legal Status and Approved Use	Cannabis-Related Properties	Administration Method	Dose Evaluated	Comparator	No. of Studies[a]	Indication
Ajulemic acid (JBT-101, CT3)	Not currently in clinical use	Synthetic nonpsychoactive cannabinoid Derivate of the THC metabolite 11-nor-9-carboxy-THC	Capsules (oral)	Maximum 40 mg 2 ×/d	Placebo	1	Pain
CBD	Use does not appear to be explicitly restricted	Active cannabinoid part of cannabis	Capsules (oral)	200-800mg/d	Placebo	2	Psychosis, anxiety
					Amisulpride	1	Psychosis
			Oromuscosal spray	20 mg 1 ×/d or 40 mg 1 ×/d (2 doses evaluated)	Placebo	1	Glaucoma
Cannabis (marijuana)	Regulated under Schedule I of the Controlled Substances Act 1970 Legal for medical use in 23 states	Numerous active cannabinoids that will vaporize at different temperatures	Vaporized	Two concentrations: 1.29% and 3.53% 4 puffs after 1 h then 4-8 puffs after 3 h	Placebo	1	Pain
			Smoked	Maximum 3 cigarettes/d	Placebo	1	HIV
Dronabinol	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)	Synthetic THC	Capsules (oral)	Maximum 5-30 mg/d 1-4 doses/d (most common, 2 doses)	Placebo	10	Nausea and vomiting, pain, spasticity, HIV, sleep
					Megestrol acetate	1	HIV
					Dronabinol + prochlorperazine or prochlorperazine	1	Nausea and vomiting
					Dronabinol + ondansetron, ondansetron, or placebo	1	
Levonantradol	Not currently in clinical use	Synthetic analogue of dronabinol	Capsules (oral)	Maximum 5 mg/d 1 mg 2 hours before chemotherapy then 1 mg every 4 hours	Prochlorperazine	1	Nausea and vomiting
			Intramuscular	Maximum 1.5 mg -4 mg 0.5 mg-1 mg, 1-2 h before chemotherapy then every 4 h	Prochlorperazine	1	
					Chlorpromazine	1	
					Metoclopramide	1	
Nabilone	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	Synthetic cannabinoid derivate mimicking THC	Capsules (oral)	Maximum 0.5 mg-8 mg Most common dose 2 mg 2 ×/d	Placebo	7[b]	Spasticity, pain, sleep, nausea and vomiting
					Dihydrocodeine	1	Pain
					Amitriptyline	1	Pain, sleep
					Chlorpromazine	1	Nausea and vomiting
					Alizapride	1	
					Domperidone	2	
					Prochlorperazine	7	
Nabiximols	Licensed for use in the United Kingdom, Spain, Czech Republic, Germany, Demark, 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	Each mL contains 27 mg THC and 25 mg CBD	Oromuscosal spray	Titrated to a maximum of 4-48 sprays/24 h Most common maximum was 8 sprays/3 h or 48 sprays/24 h	Placebo	19	Spasticity, pain, nausea and vomiting
ECP002A	No current marketing authorization	Pure (≥98%) Natural Δ^9-THC	Oral tablet	Individualized dose	Placebo	1	Spasticity

(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

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

Intervention	US Legal Status and Approved Use	Cannabis-Related Properties	Administration Method	Dose Evaluated	Comparator	No. of Studies[a]	Indication
THC	Same as cannabis	Active cannabinoid part of cannabis	Capsules (oral)	Maximum 5 mg-60 mg/d, given 1 ×/d or every 4-6 h in chemotherapy patients	Placebo	3	Pain, Tourette syndrome
					Placebo and codeine	1	Pain
					Placebo and prochloreperazine	2	Nausea and vomiting
					Prochlorperazine	3	
					Hydroxizine	1	
			Smoked	1-5 cigarettes/d Potency, where reported, ranged from 2.5%-9.4%	Placebo	5	Spasticity, pain
			Oromuscosal spray	Single daily dose to a maximum of 8 actuations/24 h Concentration 1%-7%	Placebo	4	Pain, glaucoma
THC/CBD	See individual components	Combination of CBD and THC	Capsules (oral)	Maximum 10 mg-60 mg/d, given as 2 doses	Placebo	4	Spasticity

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

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

[b] One trial evaluated nabilone as an adjunctive to gabapentin.

analysis (I^2 = 0%) and results were similar for both dronabinol and nabiximols.

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 dronabinol, 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 functional status. However, these outcomes were mostly assessed in single studies and associations failed to reach statistical significance. The trial that evaluated marijuana and dronabinol 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]

Chronic Pain

Chronic pain was assessed 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 ajuvenic acid capsules, and 1 for oral THC. One trial compared nabilone with amitriptyline[64]; all other studies were placebo controlled. One of these studies evaluated nabilone as an adjunctive treatment to gabapentin.[121] 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 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 noncancer 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 improvements 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 reduction 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 THC[77] 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 difference [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 status 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)

Table 2. Summary Estimates From Meta-analyses of Parallel-Group Studies and Results for Primary Outcomes With Associated GRADE Ratings

Indication[a]	No. of Studies (No. of Patients)	Cannabinoid (No. of Studies)	Comparator	Outcome[b]	Summary Estimate	Favors	I^2, %	GRADE Rating[c]
Nausea and vomiting due to chemotherapy	3 (102)	Dronabinol (2), Nabiximols (1)	Placebo	Nausea and vomiting Complete response	OR (95% CI), 3.82 (1.55 to 9.42)	CBM	0	Low
HIV/AIDS	1 (88)	Dronabinol	Placebo	Weight gain No. of patients who gained ≥2 kg within 6 weeks	OR (95% CI), 2.2 (0.68 to 7.27)	CBM	NA	Low
Chronic pain (neuropathic and cancer pain)	8 (1370)	Smoked THC (1), Nabiximols (7)	Placebo	Pain reduction ≥30% NRS or VAS scores Follow-up 2-15 weeks	OR (95% CI), 1.41 (0.99 to 2.00)	CBM	48	Moderate
	6 (948)	Nabiximols (6)	Placebo	Pain NRS scores (0-10) Follow-up 2-14 weeks	WMD (95% CI), −0.46 (−0.80 to −0.11)	CBM	59	Moderate
	3 (613)	Nabiximols (3)	Placebo	Pain Brief Pain Inventory-Short Form scale (0 to 10) Follow-up 3-15 weeks	WMD (95% CI), −0.17 (−0.50 to 0.16)	CBM	0	Moderate
	6 (267)	Nabiximols (5), Nabilone (1)	Placebo	Patient global impression of change Follow-up 3-14 weeks	OR (95% CI), 2.08 (1.21 to 3.59)	CBM	68	Low
	5 (764)	Nabiximols (5)	Placebo	Neuropathic pain Neuropathic Pain Scale (0-100) Follow-up 5-15 weeks	WMD (95% CI), −3.89(−7.32 to −0.47)	CBM	41	Moderate
	3 (573)	Nabiximols (3)	Placebo	Quality of life EQ-5D scale (0 to 100) Follow-up 12-15 weeks	WMD (95% CI), −0.01 (−0.05 to 0.02)	Placebo	0	Moderate
Spasticity due to multiple sclerosis or paraplegia	2 (519)	Nabiximols (2)	Placebo	50% Reduction in spasticity symptoms NRS (0-10) Follow-up 6-14 weeks	OR (95% CI), 1.40 (0.81 to 2.41)	CBM	0	Low
	2 (519)	Nabiximols (2)	Placebo	30% Reduction in spasticity symptoms NRS Follow-up 6-14 weeks	OR (95% CI), 1.64 (0.95 to 2.83)	CBM	44	Low
	5 (1244)	Nabiximols (4), THC/CBD (1), Dronabinol (1)	Placebo	Spasticity Ashworth Spasticity Scale Follow-up 3-15 weeks	WMD (95% CI), −0.11 (−0.23 to 0.02)	CBM	0	Moderate
					−0.32 (−1.59 to 0.95)			
					−0.94 (−2.37 to 0.49)			
	3 (698)	Nabiximols (2), Nabilone (1)	Placebo	Spasticity NRS or VAS scores	WMD (95% CI), −0.76 (−1.38 to −0.14)	CBM	73	Low
	4 (1433)	Nabilone (2), Dronabinol (1), THC/CBD (1)	Placebo	ADLs Barthel Index of ADL	WMD (95% CI), −0.58 (−1.73 to 0.56)	Placebo	0	Moderate
					0.23 (−0.13 to 0.59)			
					−0.03 (−0.39 to 0.33)			
	2 (497)	Nabiximols (2)	Placebo	Walking speed as assessed by timing	WMD (95% CI), −0.86 (−3.08 to 1.36)	CBM	24	Moderate
	3 (461)	Nabiximols	Placebo	Global Impression Patient global impression of change	OR (95% CI), 1.44 (1.07 to 1.94)	CBM	0	Low

(continued)

Table 2. Summary Estimates From Meta-analyses of Parallel-Group Studies and Results for Primary Outcomes With Associated GRADE Ratings (continued)

Indication[a]	No. of Studies (No. of Patients)	Cannabinoid (No. of Studies)	Comparator	Outcome[b]	Summary Estimate	Favors	I^2, %	GRADE Rating[c]
Depression	1 (66)	Nabiximols	Placebo	Depression Hospital Anxiety and Depression Scale (0-52) Follow-up 5 weeks	Mean difference (95% CI), 0.15 (−1.0 to 1.31)	Placebo	NA	Very low
	1 (182)	Nabiximols	Placebo	Depression assessed using the Montgomery-Åsberg Depression Scale (0-54) Follow-up 9 weeks	Mean difference (95% CI), 1.90 (−0.22 to 4.02)	Placebo	NA	Very low
	1 (160)	Nabiximols	Placebo	Depression Beck Depression Inventory Scale (0-63) Follow-up 6 weeks	Mean difference (95% CI), 0.69 (−0.76 to 2.14)	Placebo	NA	Very low
Anxiety disorder	1 (24)	Cannabidiol	Placebo	Anxiety Visual Analogue Mood Scale (anxiety factor scale; 0-100) Follow-up 107 minutes	Mean difference, −16.52 *P* value = .01	CBM	NA	Very low
Sleep disorder	1 (22)	Nabilone	Placebo	Sleep apnea/hypopnea Apnea Hypopnea Index Follow-up 3 weeks	Mean difference, −19.64 *P* value = .02	CBM	NA	Low
	8 (539) In other indications	Nabiximols (7), THC/CBD (1)	Placebo	Sleep quality NRS (0-10) Follow-up 2-15 weeks	WMD (95% CI), −0.58 (−0.87 to −0.29)	CBM	33	Very low
	3 (1637) In other indications	Nabiximols (3)	Placebo	Sleep disturbance NRS (0-10) Follow-up 2-15 weeks	WMD (95% CI), −0.26 (−0.52 to 0.00)	CBM	64	Very low
Psychosis	1 (35)	Cannabidiol	Amisulpride	Mental health Brief Psychiatric Rating Scale Follow-up 4 weeks	Mean difference (95% CI), −0.10 (−9.20 to 8.90)	CBM	NA	Low
	1 (35)	Cannabidiol	Amisulpride	Mood Positive and Negative Syndrome Scale (30-210) Follow-up 4 weeks	Mean difference (95% CI), 1 (−12.60 to 14.60)	Amisulpride	NA	Low
Tourette syndrome	1 (17)	THC capsules	Placebo	Tic severity Shapiro Tourette Syndrome Severity Scale (0-6) Follow-up 6 weeks	Mean difference, −0.70 *P* value = .03	THC	NA	Low
	1 (17)	THC capsules	Placebo	Tic severity Tourette syndrome symptom list (tic rating) Follow-up 6 weeks	Mean difference, −16.2 *P* value < .05	THC	NA	Low
	1 (18)	THC capsules	Placebo	Tic severity Yale Global Tic Severity Scale (0-100) Follow-up 6 weeks	Mean difference, −12.03 *P* value = .061	THC	NA	Low
	1 (17)	THC capsules	Placebo	Tic severity Tourette Syndrome Clinical Global Impression Scale (0-6) Follow-up 6 weeks	Mean difference, −0.57 *P* value = .008	THC	NA	Low

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.

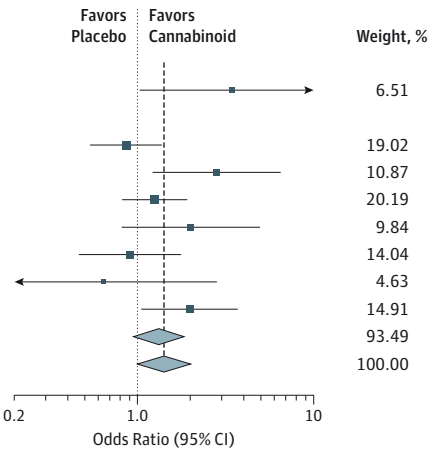
[a] No studies for glaucoma were included in the study estimate. The authors note that THC and cannabidiol were the interventions used in the reviewed glaucoma studies.

[b] Outcome includes the specific indication that was assessed, the means by which assessment was made, and folow-up (not shown for all studies).

[c] GRADE Working Group grades of evidence: (1) high quality, further research is very unlikely to change the group's confidence in the estimate of effect; (2) moderate quality, further research is likely to have an important impact on the group's confidence in the estimate of effect and may change the estimate; (3) low quality, further research is very likely to have an important impact on the group's confidence in the estimate of effect and is likely to change the estimate; (4) very low quality, the group is very uncertain about the estimate.

Figure 2. Improvement in Pain

Improvement in Pain With Cannabinoid vs Placebo by Study	Cannabinoid Events No.	Cannabinoid Events Total No.	Placebo Events No.	Placebo Events Total No.	Odds Ratio (95% CI)
Tetrahydrocannabinol (smoked)					
Abrams et al,[77] 2007	13	25	6	25	3.43 (1.03-11.48)
Nabiximols					
GW Pharmaceuticals,[22] 2005	54	149	59	148	0.86 (0.54-1.37)
Johnson et al,[69] 2010	23	53	12	56	2.81 (1.22-6.50)
Langford et al,[65] 2013	84	167	77	172	1.25 (0.81-1.91)
Nurmikko et al,[76] 2007	16	63	9	62	2.00 (0.81-4.96)
Portenoy et al,[67] 2012	22	90	24	91	0.90 (0.46-1.76)
Selvarajah et al,[70] 2010	8	15	9	14	0.63 (0.14-2.82)
Serpell et al,[88] 2014	34	123	19	117	1.97 (1.05-3.70)
Subtotal I^2 = 44.5%, (P = .0.94)	241	660	209	660	1.32 (0.94-1.86)
Overall I^2 = 47.6%, (P = .0.64)	254	685	215	685	1.41 (0.99-2.00)



Odds indicate 30% or greater improvement in pain with cannabinoid compared with placebo, stratified according to cannabinoid. 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 shows the line of no effect (OR = 1).

assessed patients with cancer pain, all other studies assessed patients with neuropathic pain. There were no clear differences based oncause 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

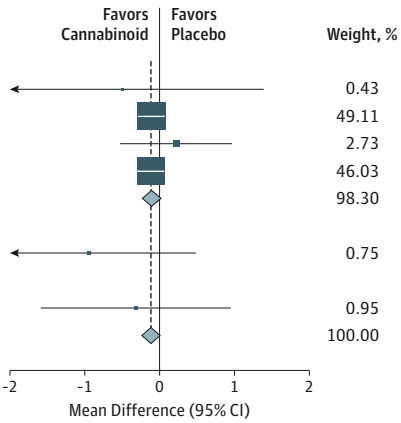
No studies evaluating cannabinoids for the treatment of depression fulfilled inclusion criteria. Five studies included for other indications reported depression as an outcome measure; 4 evaluated chronic pain and 1 evaluated spasticity in MS patients.[67,73,75,80,129] One trial assessed dronabinol (2 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 nabiximols 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-

Figure 3. Change in Ashworth Score for Cannabinoid Compared With Placebo, Stratified According to Cannabinoid

Score Change With Cannabinoid vs Placebo by Study	Cannabinoid No. of Patients	Cannabinoid Mean (SD) Score Change	Placebo No. of Patients	Placebo Mean (SD) Score Change	Mean Difference (95% CI)	Weight, %
Nabiximols						
Collin,[125] 2010	156	-3.3 (9.25)	160	-2.8 (7.81)	-0.50 (-2.39 to 1.39)	0.43
Collin,[127] 2007	114	-.64 (.56)	63	-.53 (.58)	-0.11 (-0.29 to 0.07)	49.11
Wade,[129] 2004	73	-.37 (2.51)	70	-.59 (2.04)	0.22 (-0.53 to 0.97)	2.73
Berman,[87] 2007	40	-.13 (.43)	44	-.01 (.42)	-0.12 (-0.30 to 0.06)	46.03
Subtotal I^2 = 0.0%, (*P* = .82)	383		337		-0.11 (-0.23 to 0.02)	98.30
Dronabinol						
Zajicek,[131] 2003	197	-1.86 (7.95)	207	-.92 (6.56)	-0.94 (-2.37 to 0.49)	0.75
Tetrahydrocannabinol/cannabidiol						
Zajicek,[131] 2003	207	-1.24 (6.6)	207	-.92 (6.56)	-0.32 (-1.59 to 0.95)	0.95
Overall I^2 = 0.0%, (*P* = .80)	590		544		-0.12 (-0.24 to 0.01)	100.00



The square data markers indicate mean differences from primary studies, with sizes reflecting the statistical weight of the study using random-effects meta-analysis. The horizontal line indicate, 95% CIs. The blue diamond data markers represent the subtotal and overall weighted mean difference and 95% CI. The vertical dashed line shows the summary effect estimate, the solid vertical line shows the line of no effect (mean difference = 0).

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 a greater benefit of nabilone compared with placebo on the sleep apnea/hypopnea index (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, −3.25 [95% CI, −5.26 to −1.24]) but that amitriptyline was associated with greater sleep restfulness (mean difference from baseline, 0.48 [95% CI, 0.01 to 0.95]). Nineteen placebo-controlled studies included for other indications (chronic pain and MS) also evaluated sleep as an outcome.* Thirteen studies assessed nabiximols, 1 for nabilone, 1 for dronabinol, 2 for THC/CBD capsules, and two assessed smoked THC (one at various doses). Two of the studies that assessed nabiximols also assessed oral THC and the trial of dronabinol also assessed oral THC/CBD. There was some evidence that cannabinoids may improve sleep in these patient groups. Cannabinoids (mainly nabiximols) were associated with a greater average improvement in sleep quality (WMD, −0.58 [95% CI, −0.87 to −0.29]; 8 trials) and sleep disturbance (WMD, −0.26 [95% CI, −0.52 to 0.00]; 3 trials). One trial assessed THC/CBD, all others assessed nabiximols, results were similar for both cannabinoids.

Psychosis

Psychosis was assessed in 2 studies (9 reports; 71 participants) judged at high risk of bias, which evaluated cannabidiol compared with amisulpride or placebo.[21,151-158] The trials found no difference in mental health outcomes between treatment groups.

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

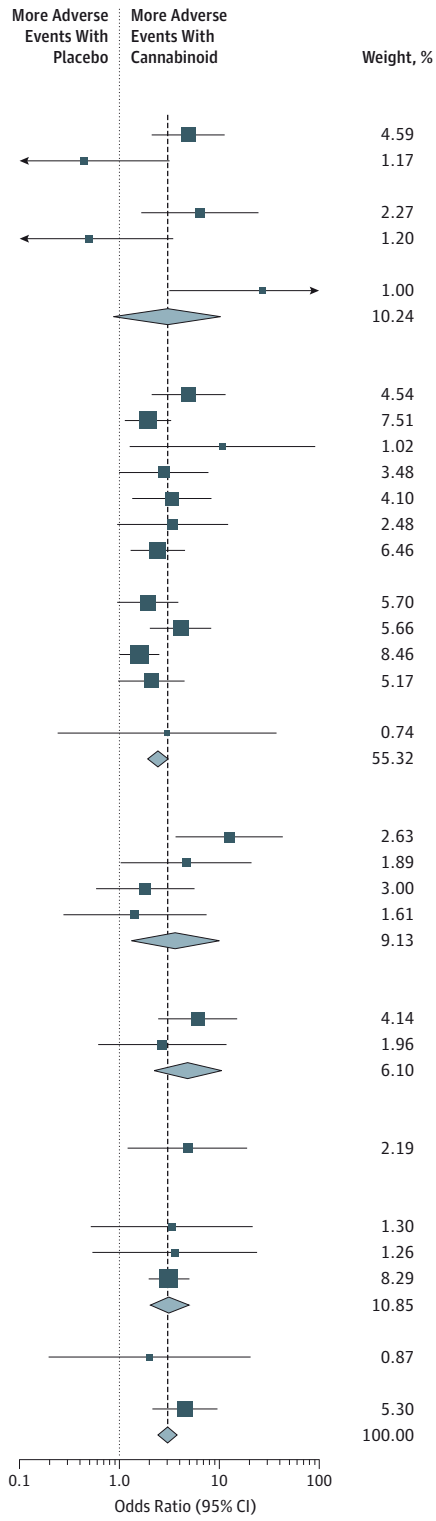
Data about AEs were reported in 62 studies (127 reports). Meta-regression and stratified analysis showed no evidence for a difference in the association of cannabinoids with the incidence of "any AE" based on type of cannabinoid, study design, indication, comparator, or duration of follow-up†; further 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.

*References 22, 23, 65, 67-69, 75, 76, 79-81, 87, 88, 123-125, 129-131

†References 15, 16, 18, 22-26, 28-31, 33-38, 41, 42, 44-47, 51, 57, 58, 60, 62, 64-69, 72-85, 87, 88, 123-127, 129-131, 159, 160, 162

Figure 4. Odds of Having Any Adverse Event With Cannabinoids Compared With Placebo, Stratified According to Cannabinoid

Adverse Events With Cannabinoid vs Placebo by Cannabinoid, Indication, and Study	Cannabinoid Events No.	Cannabinoid Events Total No.	Placebo Events No.	Placebo Events Total No.	Odds Ratio (95% CI)	Weight, %
Dronabinol						
HIV						
Beal et al,[62] 1995	31	72	9	67	4.87 (2.10-11.32)	4.59
Timpone et al,[60] 1997	7	11	8	10	0.44 (0.06-3.16)	1.17
Nausea and vomiting						
Lane et al,[26] 1991	16	21	7	21	6.40 (1.65-24.77)	2.27
Meiri et al,[25] 2007	2	17	3	14	0.49 (0.07-3.44)	1.20
Pain						
Svendsen et al,[82] 2004	23	24	11	24	27.18 (3.14-235.02)	1.00
Subtotal I^2 = 69.1%, (P = .01)	79	145	38	136	3.01 (0.87- 10.43)	10.24
Nabiximols						
Pain						
Berman et al,[87] 2007	46	56	29	60	4.92 (2.10-11.52)	4.54
GW Pharmaceuticals et al,[22] 2005	120	149	101	148	1.93 (1.13-3.28)	7.51
GW Pharmaceuticals et al,[23] 2012	35	36	26	34	10.77 (1.27-91.52)	1.02
Nurmikko et al,[76] 2007	57	63	48	62	2.77 (0.99-7.77)	3.48
Portenoy et al,[67] 2012	83	90	71	91	3.34 (1.33- 8.36)	4.10
Rog et al,[80] 2005	30	34	22	32	3.41 (0.94-12.30)	2.48
Serpell et al,[88] 2014	109	128	83	118	2.42 (1.29-4.53)	6.46
Multiple sclerosis						
Collin et al,[127] 2007	102	124	46	65	1.92 (0.95-3.88)	5.70
Collin et al,[125] 2010	156	167	132	170	4.08 (2.01-8.30)	5.66
Langford et al,[65] 2013	120	167	106	172	1.59 (1.01-2.51)	8.46
Wade et al,[129] 2004	67	80	57	80	2.08 (0.97-4.47)	5.17
Nausea and vomiting						
Duran et al,[24] 2010	6	7	6	9	3.00 (0.24-37.67)	0.74
Subtotal I^2 = 8.3%, (P = .36)	931	1101	727	1041	2.41 (1.91-3.05)	55.32
Nabilone						
Nausea and vomiting						
Chan et al,[28] 1987	32	36	14	36	12.57 (3.65-43.30)	2.63
George et al,[35] 1983	17	20	11	20	4.64 (1.02-21.00)	1.89
Johansson et al,[38] 1982	14	26	9	23	1.81 (0.58-5.66)	3.00
Pomeroy et al,[29] 1986	16	19	15	19	1.42 (0.27-7.44)	1.61
Subtotal I^2 = 54.9%, (P = .08)	79	101	49	98	3.63 (1.31-10.02)	9.13
Levonantradol						
Nausea and vomiting						
Heim et al,[33] 1984	32	45	13	45	6.06 (2.43-15.08)	4.14
Hutcheon et al,[34] 1983	23	26	20	27	2.68 (0.61-11.78)	1.96
Subtotal I^2 = 0.0%, (P = .36)	55	71	33	72	4.84 (2.23-10.52)	6.10
Ajulemic acid (CT3)						
Pain						
Karst et al,[83] 2003	12	19	5	19	4.80 (1.20-19.13)	2.19
Tetrahydrocannabinol capsules						
Tourette						
Müller-Vahl et al,[160] 2003	5	9	3	11	3.33 (0.51-21.58)	1.30
Müller-Vahl et al,[162] 2001	5	12	2	12	3.57 (0.53-23.95)	1.26
Ungerleider et al,[146] 1982	136	172	99	181	3.13 (1.96-5.00)	8.29
Subtotal I^2 = 0.0%, (P = .99)	146	193	104	204	3.16 (2.03-4.93)	10.85
Tetrahydrocannabinol oromucosal spray						
Tomida et al,[159] 2006	3	6	2	6	2.00 (0.19-20.61)	0.87
Tetrahydrocannabinol/cannabidiol capsules						
Zajicek et al,[123] 2012	133	143	100	134	4.52 (2.13-9.59)	5.30
Overall I^2 = 31.2%, (P = .057)	1438	1779	1058	1710	3.03 (2.42-3.80)	100.00



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

	No. of Studies (No. of Patients)	Summary OR (95% CI)	I^2, %
General AE categories			
Any	29 (3714)	3.03 (2.42-3.80)	31
Serious	34 (3248)	1.41 (1.04-1.92)	0
Withdrawal due to AE	23 (2755)	2.94 (2.18-3.96)	2
MedDRA high-level grouping[164]			
Gastrointestinal disorders	10 (1960)	1.78 (1.43-2.22)	0
Infections and infestations	7 (1681)	1.13 (0.87-1.46)	0
Psychiatric disorders	8 (1672)	3.10 (1.81-5.29)	55
Nervous system disorders	10 (1521)	3.17 (2.20-4.58)	46
Musculoskeletal and connective tissues disorders	7 (1310)	1.32 (0.75-2.32)	34
General disorders and administration site conditions	6 (1208)	1.78 (1.34-2.36)	0
Death	5 (929)	1.01 (0.51-2.00)	0
Ear and labyrinth disorders	3 (922)	2.72 (1.55-4.75)	0
Respiratory, thoracic, and mediastinal disorders	5 (851)	0.80 (0.46-1.39)	0
Cardiac disorders	7 (833)	1.42 (0.58-3.48)	0
Blood disorders	3 (543)	1.42 (0.20-10.25)	18
Injury, poisoning and procedural complications	3 (543)	1.18 (0.48-2.93)	0
Renal and urinary disorders	3 (470)	2.45 (2.27-2.65)	0
Investigations	2 (427)	1.55 (0.36-6.71)	0
Metabolism and nutrition	2 (427)	2.37 (1.00-5.61)	0
Neoplasms, benign, malignant, and unspecified	2 (427)	0.99 (0.47-2.08)	0
Skin and subcutaneous	3 (405)	0.85 (0.34-2.13)	0
Eye disorders	1 (339)	1.42 (0.46-4.33)	NA
Reproductive system	1 (246)	1.55 (0.20-11.92)	NA
Hepatobiliary disorders	1 (181)	3.07 (0.12-76.29)	NA
Mental status change	3 (106)	2.49 (0.49-12.64)	0
Other body systems	1 (42)	2.59 (0.34-19.47)	NA
Injection site pain	1 (32)	2.49 (0.92-6.68)	NA
Individual AEs			
Dizziness	41 (4243)	5.09 (4.10-6.32)	18
Dry mouth	36 (4181)	3.50 (2.58-4.75)	28
Nausea	30 (3579)	2.08 (1.63-2.65)	0
Fatigue	20 (2717)	2.00 (1.54-2.62)	0
Somnolence	26 (3168)	2.83 (2.05-3.91)	27
Euphoria	27 (2420)	4.08 (2.18-7.64)	49
Depression	15 (2353)	1.32 (0.87-2.01)	0
Vomiting	17 (2191)	1.67 (1.13-2.47)	0
Diarrhea	17 (2077)	1.65 (1.04-2.62)	15
Disorientation	12 (1736)	5.41 (2.61-11.19)	0
Asthenia	15 (1717)	2.03 (1.35-3.06)	0
Drowsiness	18 (1272)	3.68 (2.24-6.01)	44
Anxiety	12 (1242)	1.98 (0.73-5.35)	54
Confusion	13 (1160)	4.03 (2.05-7.97)	0
Balance	6 (920)	2.62 (1.12-6.13)	0
Hallucination	10 (898)	2.19 (1.02-4.68)	0
Dyspnea	4 (375)	0.83 (0.26-2.63)	0
Paranoia	4 (492)	2.05 (0.42-10.10)	0
Psychosis	2 (37)	1.09 (0.07-16.35)	25
Seizures	2 (42)	0.91 (0.05-15.66)	0

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 (nabilone, 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.[59,77] There was no evidence that the effects of cannabis differed from other cannabinoids.

Strengths and Weaknesses

This review followed recommendations for rigorous systematic reviews.[7,8] 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[165] and all stages of the review process were performed independently by 2 reviewers. We used the Cochrane risk of bias tool[11] 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).[14] 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.[7] 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.[166] 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,[167-170] nau-

sea and vomiting due to chemotherapy,[171-175] pain,[176-191] psychosis,[192-194] and Tourette syndrome.[195,196] Almost all previous reviews focused on single indications and all but one (which evaluated cannabinoids in 4 trials in patients with pain due to rheumatoid arthritis)[188] did not use the GRADE approach to rating the quality of the evidence. As far as we are aware, our review is the first comprehensive review to evaluate the safety and efficacy of cannabinoids across a broad range of indications. A key strength of review was that it allowed us to conduct pooled analysis for the AEs associated with medicinal cannabinoids, adding considerable power to this analysis.

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[197] 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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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.

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