Original Investigation

Cannabinoids for Medical Use
A Systematic Review and Meta-analysis

Penny F. Whiting, PhD; Robert F. Wolff, MD; Sohan Deshpande, MSc; Marcello Di Nisio, PhD; Steven Duffy, PgD; Adrian V. Hernandez, MD, PhD; J. Christiaan Keurentjes, MD, PhD; Shona Lang, PhD; Kate Misso, MSc; Steve Ryder, MSc; Simone Schmidlkofer, MSc; Marie Westwood, PhD; Jos Kleijnen, MD, PhD

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.

Editorial page 2431

Related article page 2474

Supplemental content at jama.com

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Penny Whiting, PhD, NIHR CLAHRC West, University Hospitals Bristol NHS Foundation Trust, Ninth Floor, Whitefriars, Lewins Mead, Bristol BS1 2NT, United Kingdom (penny.whiting@bristol.ac.uk).

JAMA. 2015;313(24):2456-2473. doi:10.1001/jama.2015.6358
Last corrected on April 12, 2016.

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]

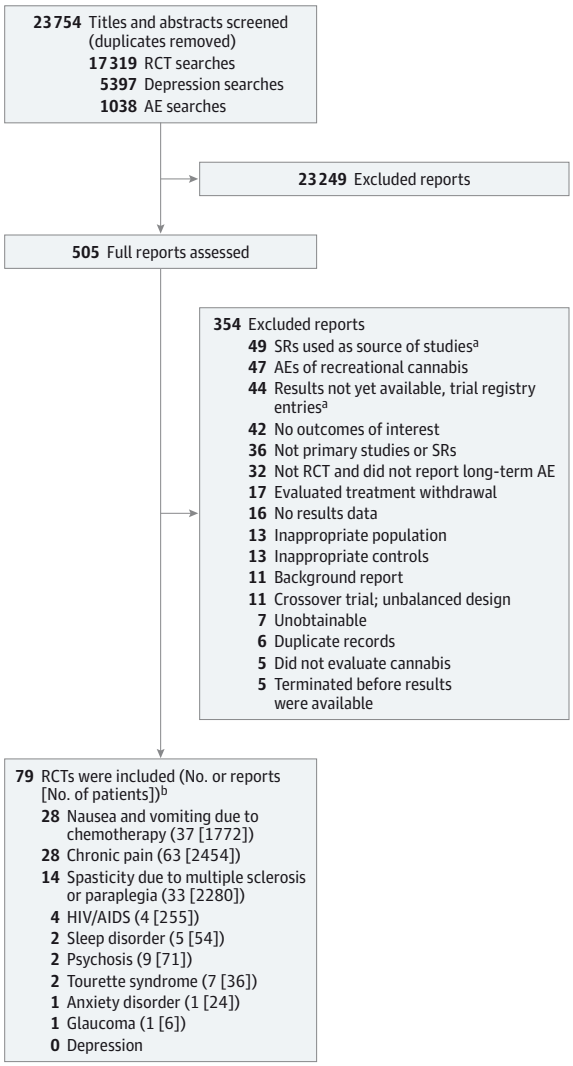
Results

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.

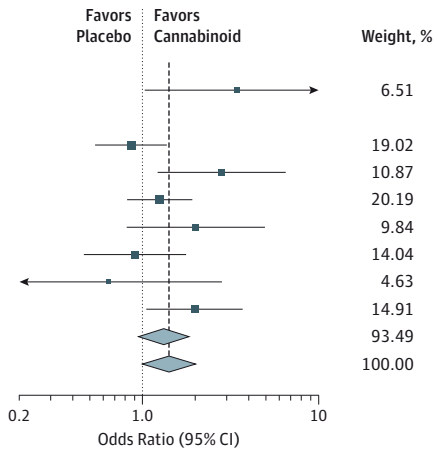
[a] No studies for glaucoma were included in the study estimate. The authors note that THC and cannabidiol were the interventions used in the reviewed glaucoma studies.

[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

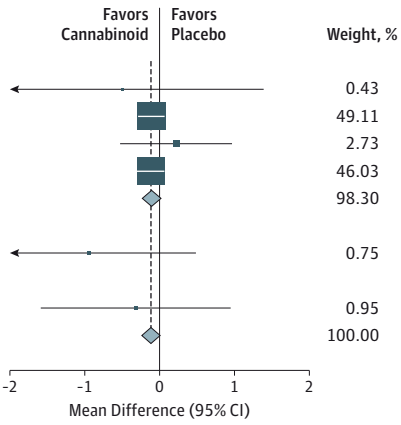
No studies evaluating cannabinoids for the treatment of depression fulfilled inclusion criteria. Five studies included for other indications reported depression as an outcome measure; 4 evaluated chronic pain and 1 evaluated spasticity in MS patients.[67,73,75,80,129] One trial assessed dronabinol (2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

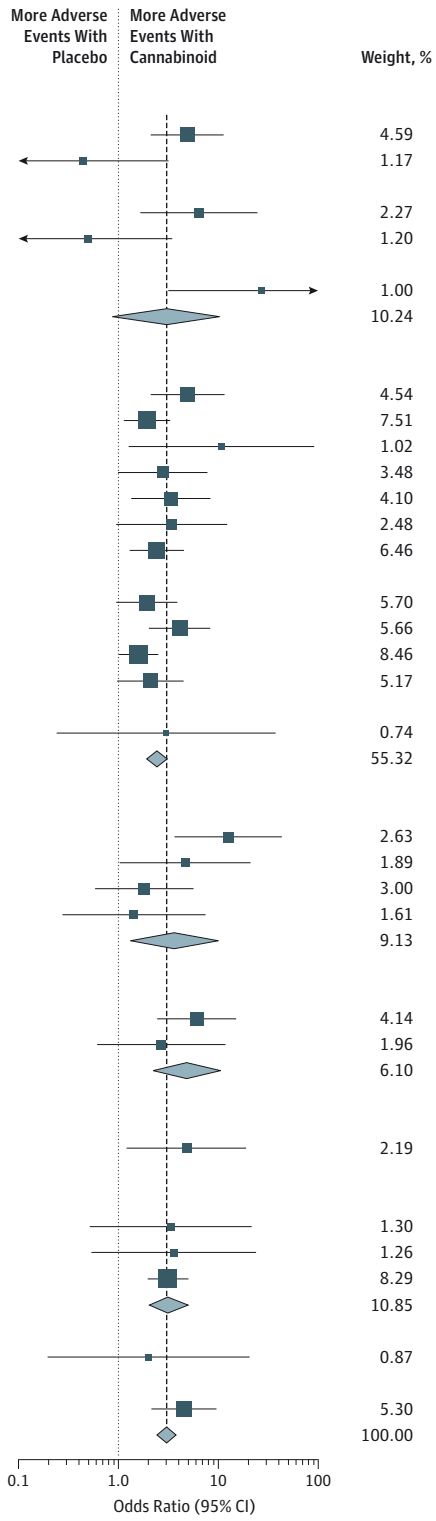
Data about AEs were reported in 62 studies (127 reports). Meta-regression and stratified analysis showed no evidence for a difference in the association of cannabinoids with the incidence of "any AE" based on type of cannabinoid, study design, indication, comparator, or duration of follow-up†; further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

Author Affiliations: School of Social and Community Medicine, University of Bristol, Bristol, United Kingdom (Whiting); The National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care West at University Hospitals, Bristol NHS Foundation Trust, Bristol, United Kingdom (Whiting); Kleijnen Systematic Reviews Ltd, Escrick, York, United Kingdom (Whiting, Wolff, Deshpande, Duffy, Lang, Misso, Ryder, Westwood, Kleijnen); Department of Medical, Oral, and Biotechnological Sciences, University "G. D'Annunzio" of Chieti-Pescara, Chieti, Italy (Di Nisio); Department of Vascular Medicine, Academic Medical Center, Amsterdam, the Netherlands (Di Nisio); Medical School, Universidad Peruana de Ciencias Aplicadas (UPC), Lima, Peru (Hernandez); Health Outcomes and Clinical Epidemiology Section, Department of Quantitative Health Sciences, Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio (Hernandez); Department of Pathology, Radboud University Medical Center, Nijmegen, the Netherlands (Keurentjes); Institut für Epidemiologie und kongenitale Erkrankungen, Cepicon GmbH, Hamburg, Germany (Schmidlkofer); School for Public Health and Primary Care (CAPHRI), Maastricht University, Maastricht, the Netherlands (Kleijnen).

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.
Study concept and design: Whiting, Wolff, Misso, Kleijnen.
Acquisition, analysis, or interpretation of data: Whiting, Wolff, Deshpande, Di Nisio, Duffy, Hernandez, Keurentjes, Lang, Misso, Ryder, Schmidlkofer, Westwood.
Drafting of the manuscript: Whiting, Keurentjes, Ryder.
Critical revision of the manuscript for important intellectual content: Whiting, Wolff, Deshpande, Di Nisio, Duffy, Hernandez, Keurentjes, Lang, Misso, Ryder, Schmidlkofer, Westwood, Kleijnen.
Statistical analysis: Whiting, Wolff, Di Nisio, Hernandez, Keurentjes, Schmidlkofer.
Obtained funding: Kleijnen.
Administrative, technical, or material support: Deshpande, Lang, Ryder.
Study supervision: Whiting, Kleijnen.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and declare support from the Swiss Federal Office of Public Health (FOPH) for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work. Dr Whiting reports that part of her time on this review was supported by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care West at University Hospitals Bristol NHS (National Health Service) Foundation Trust. No additional disclosures were reported.

Funding/Support: This funded by the Swiss Federal Office of Public Health (FOPH) under grant agreement 14.001443/204.0001/-1257.

Role of the Funder/Sponsor: The FOPH had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The decision to submit the article for publication was a condition of the funding and was made before any results were available.

Additional Author Contributions: Dr Whiting drafted the article, produced tables and figures and performed the analysis. Drs Whiting, Wolff, and Kleijnen and Ms Misso and Mr Duffy drafted the protocol. Mr Duffy and Ms Misso conducted the literature searches. Drs Whiting, Wolff, and Lang screened searched results and selected full-text studies for inclusion. Drs Whiting, Wolff, Lang, Westwood, Keurentjes, Di Nisio, Hernandez, and Messrs Deshpande and Ryder, and Ms Schmidlkofer performed data extraction and risk-of-bias assessment. Dr Wolff 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.

Disclaimer: The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

Additional Contributions: We would like to thank Julie Harker (MRes, Kleijnen Systematic Reviews at the time of this project) for help with inclusion screening and data extraction and Gillian Worthy (MSc, Kleijnen Systematic Reviews) for advice on data analysis. Neither of these individuals received additional compensation in association with their work on this article.

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.

REFERENCES

1. Small E, Cronquist A. A practical and natural taxonomy for cannabis. *Taxon*. 1976;25(4):405-435. doi:10.2307/1220524.

2. Poznyak V. SY14-1 global epidemiology of cannabis use and implications for public health. *Alcohol Alcohol*. 2014;49(suppl 1):i14. doi:10.1093/alcalc/agu052.58 i.

3. United Nations. *Single Convention on Narcotic Drugs, 1961*. New York, NY: United Nations; 1962.

4. Hazekamp A, Ware MA, Müller-Vahl KR, Abrams D, Grotenhermen F. The medicinal use of cannabis and cannabinoids—an international cross-sectional survey on administration forms. *J Psychoactive Drugs*. 2013;45(3):199-210.

5. Hazekamp A, Heerdink ER. The prevalence and incidence of medicinal cannabis on prescription in the Netherlands. *Eur J Clin Pharmacol*. 2013;69(8):1575-1580.

6. Office of National Drug Control Policy. Marijuana Resource Center: State Laws Related to Marijuana. https://www.whitehouse.gov/ondcp/state-laws-related-to-marijuana. Accessed May 18, 2015.

7. Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Version

5.1.0 (updated March 2011). The Cochrane Collaboration website. http://handbook.cochrane.org/. Accessed March 23, 2011.

8. Centre for Reviews and Dissemination. Systematic Reviews: CRD's Guidance for Undertaking Reviews in Health Care (Internet). York, England: University of York; 2009. https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf. Accessed March 23, 2011.

9. Canadian Agency for Drugs and Technologies in Health. CADTH Peer Review Checklist for Search Strategies (Internet). Ottawa, Canada: CADTH; 2013. https://www.cadth.ca/resources/finding-evidence/cadth-peer-review-checklist-search-strategies. Accessed March 17, 2014.

10. Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. *Phys Ther*. 1987;67(2):206-207.

11. Higgins JP, Altman DG, Gøtzsche PC, et al; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.

12. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188.

13. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-1558.

14. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. rating the quality of evidence—study limitations (risk of bias). *J Clin Epidemiol*. 2011;64(4):407-415.

15. Broder LE, Lean NL, Hilsenbeck SG. A randomized blinded clinical trial comparing delta-9-tetrahydrocannabinol (THC) and hydroxizine (HZ) as antiemetics (AE) for cancer chemotherapy (CT). *Proc Am Assoc Cancer Res*. 1982;23:514.

16. Long A, Mioduszewski J, Natale R. A randomized double-blind cross-over comparison of the antiemetic activity of levonantradol and prochlorperazine. *Proc Am Soc Clin Oncol*. 1982;1:C-220.

17. Hagenbach U, Luz S, Brenneisen R, Mäder M. The treatment of spasticity with D9-tetrahydrocannabinol (D9-THC) in patients with spinal cord injury. Paper presented at: IACM 2nd Conference on Cannabinoids in Medicine; September 12-13, 2003; Cologne, Germany.

18. Prasad B, Radulovacki MG, Carley DW. Randomized placebo controlled trial of dronabinol in obstructive sleep apnea. Paper presented at: American Thoracic Society International Conference, ATS 2011; May 13-18, 2011; Denver, CO. *Am J Respir Crit Care Med*. 2011;183(1):A2720.

19. GW Pharmaceuticals Ltd. A study of cannabis based medicine extracts and placebo in patients with pain due to spinal cord injury. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT01606202. Accessed April 7, 2014.

20. Center for Medicinal Cannabis Research. Efficacy of inhaled cannabis in diabetic painful peripheral neuropathy. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00781001. Accessed April 7, 2014.

21. Stanley Medical Research Institute, Coordinating Centre for Clinical Trials Cologne. University of Cologne. A clinical trial on the antipsychotic properties of cannabidiol. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00309413. Accessed April 7, 2014.

22. GW Pharma Ltd. A double blind, randomised, placebo controlled, parallel group study of Sativex in the treatment of subjects with pain due to diabetic neuropathy. EU Clinical Trials Register. https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2004-002530-20. Accessed August 4, 2014.

23. GW Pharmaceuticals Ltd. A study to evaluate the effects of cannabis based medicine in patients with pain of neurological origin. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT01606176 Accessed April 7, 2014.

24. Duran M, Pérez E, Abanades S, et al. Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting. *Br J Clin Pharmacol*. 2010;70(5):656-663.

25. Meiri E, Jhangiani H, Vredenburgh JJ, et al. Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. *Curr Med Res Opin*. 2007;23(3):533-543.

26. Lane M, Vogel CL, Ferguson J, et al. Dronabinol and prochlorperazine in combination for treatment of cancer chemotherapy-induced nausea and vomiting. *J Pain Symptom Manage*. 1991;6(6):352-359.

27. McCabe M, Smith FP, Macdonald JS, Woolley PV, Goldberg D, Schein PS. Efficacy of tetrahydrocannabinol in patients refractory to standard antiemetic therapy. *Invest New Drugs*. 1988;6(3):243-246.

28. Chan HS, Correia JA, MacLeod SM. Nabilone versus prochlorperazine for control of cancer chemotherapy-induced emesis in children: a double-blind, crossover trial. *Pediatrics*. 1987;79(6):946-952.

29. Pomeroy M, Fennelly JJ, Towers M. Prospective randomized double-blind trial of nabilone versus domperidone in the treatment of cytotoxic-induced emesis. *Cancer Chemother Pharmacol*. 1986;17(3):285-288.

30. Dalzell AM, Bartlett H, Lilleyman JS. Nabilone: an alternative antiemetic for cancer chemotherapy. *Arch Dis Child*. 1986;61(5):502-505.

31. Niederle N, Schütte J, Schmidt CG. Crossover comparison of the antiemetic efficacy of nabilone and alizapride in patients with nonseminomatous testicular cancer receiving cisplatin therapy. *Klin Wochenschr*. 1986;64(8):362-365.

32. Niiranen A, Mattson K. A cross-over comparison of nabilone and prochlorperazine for emesis induced by cancer chemotherapy. *Am J Clin Oncol*. 1985;8(4):336-340.

33. Heim ME, Queisser W, Altenburg HP. Randomized crossover study of the antiemetic activity of levonantradol and metoclopramide in cancer patients receiving chemotherapy. *Cancer Chemother Pharmacol*. 1984;13(2):123-125.

34. Hutcheon AW, Palmer JB, Soukop M, et al. A randomised multicentre single blind comparison of a cannabinoid anti-emetic (levonantradol) with chlorpromazine in patients receiving their first cytotoxic chemotherapy. *Eur J Cancer Clin Oncol*. 1983;19(8):1087-1090.

35. George M, Pejovic MH, Thuaire M, Kramar A, Wolff JP. [Randomized comparative trial of a new anti-emetic: nabilone, in cancer patients treated with cisplatin]. *Biomed Pharmacother*. 1983;37(1):24-27.

36. Jones SE, Durant JR, Greco FA, Robertone A. A multi-institutional phase III study of nabilone vs placebo in chemotherapy-induced nausea and vomiting. *Cancer Treat Rev*. 1982;9(suppl B):45-48.

37. Wada JK, Bogdon DL, Gunnell JC, Hum GJ, Gota CH, Rieth TE. Double-blind, randomized, crossover trial of nabilone vs placebo in cancer chemotherapy. *Cancer Treat Rev*. 1982;9(suppl B):39-44.

38. Johansson R, Kilkku P, Groenroos M. A double-blind, controlled trial of nabilone vs. prochlorperazine for refractory emesis induced by cancer chemotherapy. *Cancer Treat Rev*. 1982;9(suppl B):25-33.

39. Orr LE, McKernan JF. Antiemetic effect of delta 9-tetrahydrocannabinol in chemotherapy-associated nausea and emesis as compared to placebo and compazine. *J Clin Pharmacol*. 1981;21(8-9 suppl):76S-80S.

40. Einhorn LH, Nagy C, Furnas B, Williams SD. Nabilone: an effective antiemetic in patients receiving cancer chemotherapy. *J Clin Pharmacol*. 1981;21(8-9 suppl):64S-69S.

41. Orr LE, McKernan JF, Bloome B. Antiemetic effect of tetrahydrocannabinol: compared with placebo and prochlorperazine in chemotherapy-associated nausea and emesis. *Arch Intern Med*. 1980;140(11):1431-1433.

42. Steele N, Gralla RJ, Braun DW Jr, Young CW. Double-blind comparison of the antiemetic effects of nabilone and prochlorperazine on chemotherapy-induced emesis. *Cancer Treat Rep*. 1980;64(2-3):219-224.

43. Sallan SE, Cronin C, Zelen M, Zinberg NE. Antiemetics in patients receiving chemotherapy for cancer: a randomized comparison of delta-9-tetrahydrocannabinol and prochlorperazine. *N Engl J Med*. 1980;302(3):135-138.

44. Frytak S, Moertel CG, O'Fallon JR, et al. Delta-9-tetrahydrocannabinol as an antiemetic for patients receiving cancer chemotherapy: a comparison with prochlorperazine and a placebo. *Ann Intern Med*. 1979;91(6):825-830.

45. Ahmedzai S, Carlyle DL, Calder IT, Moran F. Anti-emetic efficacy and toxicity of nabilone, a synthetic cannabinoid, in lung cancer chemotherapy. *Br J Cancer*. 1983;48(5):657-663.

46. Ungerleider JT, Andrysiak T, Fairbanks L, Goodnight J, Sarna G, Jamison K. Cannabis and cancer chemotherapy: a comparison of oral delta-9-THC and prochlorperazine. *Cancer*. 1982;50(4):636-645.

47. Sheidler VR, Ettinger DS, Diasio RB, Enterline JP, Brown MD. Double-blind multiple-dose crossover study of the antiemetic effect of intramuscular levonantradol compared to prochlorperazine. *J Clin Pharmacol*. 1984;24(4):155-159.

48. Harden-Harrison MM, Munsell MF, Fisch MJ, et al. Dronabinol for the prevention of nausea from cyclophosphamide and/or adriamycin. Paper presented at: International MASCC/ISOO Symposium: Supportive Care in Cancer; June 28-30, 2012; New York, NY. *Support Care Cancer*. 2012;20:S209-S210.

49. Grunberg SM, Munsell MF, Morrow PKH, et al. Randomized double-blind evaluation of dronabinol for the prevention of chemotherapy-induced nausea. Paper presented at: Annual Meeting of the American Society of Clinical Oncology (ASCO); 1-5 Jun 2012; Chicago, IL. *J Clin Oncol*. 2012;30(15)(suppl 1):9061.

50. Lane M, Vogel CL, Ferguson J, et al. Dronabinol and prochlorperazine in combination are better than either single agent alone for treatment of chemotherapy-induced nausea and vomiting. *Proc Am Soc Clin Oncol*. 1989;8:326.

51. Levitt M. Nabilone vs placebo in the treatment of chemotherapy-induced nausea and vomiting in cancer patients. *Cancer Treat Rev*. 1982;9(suppl B):49-53.

52. Chan HS, MacLeod SM, Correia JA. Nabilone vs prochlorperazine for control of cancer chemotherapy-induced emesis in children. *Proc Am Soc Clin Oncol*. 1984;3:108.

53. Solvay Pharmaceuticals. Dronabinol versus standard ondansetron antiemetic therapy in preventing delayed-onset chemotherapy-induced nausea and vomiting. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00642512 Accessed April 7, 2014.

54. Frytak S, Moertel CG, Ofallon JR. Comparison of delta-9-tetrahydrocannabinol (THC), prochlorperazine (PCP) and placebo as anti-emetics for cancer-chemotherapy. *Proc Am Assoc Cancer Res*. 1979;20:391.

55. Jhangiani H, Vredenburgh JJ, Barbato L, et al. Dronabinol or ondansetron alone and combined for delayed chemotherapy-induced nausea and vomiting (CINV). *Blood*. 2005;106(11, part 2):477B.

56. McCabe M, Smith FP, Goldberg D, et al. Comparative trial of oral 9 tetrahydrocannabinol and prochlorperazine for cancer chemotherapy related nausea and vomiting. *Proc Am Assoc Cancer Res and Am Soc Clin Oncol*. 1981;22:416.

57. Herman TS, Einhorn LH, Jones SE, et al. Superiority of nabilone over prochlorperazine as an antiemetic in patients receiving cancer chemotherapy. *N Engl J Med*. 1979;300(23):1295-1297.

58. Melhem-Bertrandt AI, Munsell MF, Fisch MJ, et al. A randomized, double-blind, placebo-controlled trial of palonosetron plus dexamethasone with or without dronabinol for the prevention of chemotherapy-induced nausea and vomiting after moderately emetogenic chemotherapy [Unpublished manuscript]. 2014:1-23.

59. Abrams DI, Hilton JF, Leiser RJ, et al. Short-term effects of cannabinoids in patients with HIV-1 infection: a randomized, placebo-controlled clinical trial. *Ann Intern Med*. 2003;139(4):258-266.

60. Timpone JG, Wright DJ, Li N, et al; Division of AIDS Treatment Research Initiative. The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome: the DATRI 004 Study Group. *AIDS Res Hum Retroviruses*. 1997;13(4):305-315.

61. Struwe M, Kaempfer SH, Geiger CJ, et al. Effect of dronabinol on nutritional status in HIV infection. *Ann Pharmacother*. 1993;27(7-8):827-831.

62. Beal JE, Olson R, Laubenstein L, et al. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *J Pain Symptom Manage*. 1995;10(2):89-97.

63. Ware M, Fitzcharles MA, Joseph L, Shir Y. The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. Paper presented at: Canadian Rheumatology Association Meeting; February 18-21, 2009; Kananaskis, AB: Canada. Abstract 149 *J Rheumatol*. 2009;36(11):2607.

64. Ware MA, Fitzcharles M-A, Joseph L, Shir Y. The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. *Anesth Analg*. 2010;110(2):604-610.

65. Langford RM, Mares J, Novotna A, et al. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. *J Neurol*. 2013;260(4):984-997.

66. Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H. Low-dose vaporized cannabis significantly improves neuropathic pain. *J Pain*. 2013;14(2):136-148.

67. Portenoy RK, Ganae-Motan ED, Allende S, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. *J Pain*. 2012;13(5):438-449.

68. Ware MA, Wang T, Shapiro S, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. *CMAJ*. 2010;182(14):E694-E701.

69. Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, Fallon MT. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. *J Pain Symptom Manage*. 2010;39(2):167-179.

70. Selvarajah D, Gandhi R, Emery CJ, Tesfaye S. Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor. *Diabetes Care*. 2010;33(1):128-130.

71. Ellis RJ, Toperoff W, Vaida F, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. *Neuropsychopharmacology*. 2009;34(3):672-680.

72. Wilsey B, Marcotte T, Tsodikov A, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *J Pain*. 2008;9(6):506-521.

73. Narang S, Gibson D, Wasan AD, et al. Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. *J Pain*. 2008;9(3):254-264.

74. Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. *J Pain*. 2008;9(2):164-173.

75. Frank B, Serpell MG, Hughes J, Matthews JNS, Kapur D. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. *BMJ*. 2008;336(7637):199-201.

76. Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. *Pain*. 2007;133(1-3):210-220.

77. Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology*. 2007;68(7):515-521.

78. Pinsger M, Schimetta W, Volc D, Hiermann E, Riederer F, Pölz W. [Benefits of an add-on treatment with the synthetic cannabinomimetic nabilone on patients with chronic pain—a randomized controlled trial]. *Wien Klin Wochenschr*. 2006;118(11-12):327-335.

79. Blake DR, Robson P, Ho M, Jubb RW, McCabe CS. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology (Oxford)*. 2006;45(1):50-52.

80. Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology*. 2005;65(6):812-819.

81. Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. *Pain*. 2004;112(3):299-306.

82. Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? randomised double blind placebo controlled crossover trial. *BMJ*. 2004;329(7460):253.

83. Karst M, Salim K, Burstein S, Conrad I, Hoy L, Schneider U. Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial. *JAMA*. 2003;290(13):1757-1762.

84. Noyes R Jr, Brunk SF, Baram DA, Canter A. Analgesic effect of delta-9-tetrahydrocannabinol. *J Clin Pharmacol*. 1975;15(2-3):139-143.

85. Lynch ME, Cesar-Rittenberg P, Hohmann AG. A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. *J Pain Symptom Manage*. 2014;47(1):166-173.

86. Wallace M, Atkinson J, Gouaux B, Marcotte T, Umlauf A. Effect of smoked cannabis on painful diabetic peripheral neuropathy. Paper presented at: 32nd Annual Scientific Meeting of the American Pain Society; May 9-11, 2013; New Orleans: LA. *J Pain*. 2013;14(4)(suppl 1):S62 doi:10.1016/j.jpain.2013.01.587.

87. Berman J, Bosworth T, Guy G, Stott C; Sativex Spinal Cord Injury Study Group. Sativex in the treatment of central neuropathic pain due to spinal cord injury: a randomised controlled study. Paper presented at: British Pain Society Annual Scientific Meeting; April 2007; Glasgow: United Kingdom.

88. Serpell M, Ratcliffe S, Hovorka J, et al. A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. *Eur J Pain*. 2014;18(7):999-1012.

89. Fitzcharles MA, Shir Y, Joseph L, Ware MA. The effects of nabilone on insomnia in fibromyalgia: results of a randomized controlled trial. Paper presented at: American College of Rheumatology/Association of Rheumatology

Health Professionals Annual Scientific Meeting (ACR/ARHP 09); November 6-11, 2009; Atlanta: GA. *Arthritis Rheum*. 2009;60:1429.

90. McGill University Health Center. Nabilone versus amitriptyline in improving quality of sleep in patients with fibromyalgia. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00381199 Accessed April 7, 2014.

91. GW Pharmaceuticals Ltd. Sativex versus placebo when added to existing treatment for central neuropathic pain in MS. http://ClinicalTrials.gov/show/NCT00391079 Accessed April 7, 2014.

92. Svendsen KB, Jensen TS, Bach FW. [Effect of the synthetic cannabinoid dronabinol on central pain in patients with multiple sclerosis–secondary publication]. *Ugeskr Laeger*. 2005;167(25-31):2772-2774.

93. Salim K, Schneider U, Burstein S, Hoy L, Karst M. Pain measurements and side effect profile of the novel cannabinoid ajulemic acid. *Neuropharmacology*. 2005;48(8):1164-1171.

94. Pinsger M. Benefit of an add-on-treatment with a synthetic cannabinomimeticum on patients with chronic back pain-a randomized controlled trial. Paper presented at 8th International Conference on Early Psychosis: From Neurobiology to Public Policy; October 11-13, 2012; San Francisco: CA. *Eur Spine J*. 2012;21(11):2366 doi:10.1007/s00586-012-2522-6.

95. Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ. A multi-centre, double-blind, randomized, controlled trial of oro-mucosal cannabis based medicine in the treatment of neuropathic pain characterized by allodynia. *Neurology*. 2005;64(suppl 1):A374.

96. Issa MA, Narang S, Jamison RN, et al. The subjective psychoactive effects of oral dronabinol studied in a randomized, controlled crossover clinical trial for pain. *Clin J Pain*. 2014;30(6):472-478.

97. Abrams DI, Jay CA, Vizoso H, et al. Smoked cannabis therapy for HIV-related painful peripheral neuropathy: results of a randomized, placebo-controlled clinical trial. Paper presented at: IACM 3rd Conference on Cannabinoids in Medicine; September 9-10, 2005; Leiden, the Netherlands.

98. Young CA, Rog DJ. Randomised controlled trial of cannabis based medicinal extracts (CBME) in central neuropathic pain due to multiple sclerosis. Paper presented at: IV Congress of the European Federation of IASP Chapters (EFIC); September 2-6, 2003; Prague, Czech Republic.

99. Berman J, Lee J, Cooper M, et al. Efficacy of two cannabis-based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. Paper presented at: Pain Society Annual Meeting; April 1-4, 2003; Glasgow, United Kingdom. *Anaesthesia*. 2003;58(9):938 doi:10.1046/j.1365-2044.2003.03408_3.x.

100. Center for Medicinal Cannabis Research. Effects of smoked marijuana on neuropathic pain. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00254761. Accessed April 7, 2014.

101. Center for Medicinal Cannabis Research. Medicinal cannabis for painful HIV neuropathy. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00255580. Accessed April 7, 2014.

102. University of California Davis. Center for Medicinal Cannabis Research, VA Northern California Health Care System. Effects of vaporized marijuana on neuropathic pain. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT01037088. Accessed April 7, 2014.

103. Center for Medicinal Cannabis Research. Marijuana for HIV-related peripheral neuropathy. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00046722. Accessed April 7, 2014.

104. GW Pharmaceuticals Ltd. A study of Sativex® for pain relief in patients with advanced malignancy. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00530764. Accessed April 7, 2014.

105. GW Pharmaceuticals Ltd. A study of sativex® for pain relief in patients with advanced malignancy. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00674609. Accessed April 7, 2014.

106. GW Pharmaceuticals Ltd. A study of sativex® for relief of peripheral neuropathic pain associated with allodynia. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00711880. Accessed April 7, 2014.

107. GW Pharmaceuticals Ltd. A study of sativex in the treatment of central neuropathic pain due to multiple sclerosis. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT01604265. Accessed April 7, 2014.

108. GW Pharmaceuticals Ltd. A study of sativex® for pain relief due to diabetic neuropathy. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00710424. Accessed April 7, 2014.

109. GW Pharmaceuticals Ltd. A study of Sativex® for pain relief of peripheral neuropathic pain, associated with allodynia. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00710554. Accessed April 7, 2014.

110. Mary Lynch, Capital District Health Authority Canada. Sativex for treatment of chemotherapy induced neuropathic pain. .ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00872144. Accessed April 7, 2014.

111. Brigham and Women's Hospital; Solvay Pharmaceuticals. Study to evaluate the efficacy of dronabinol (Marinol) as add-on therapy for patients on opioids for chronic pain. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00153192. Accessed April 7, 2014.

112. Winnipeg Regional Health Authority; Valeant Canada Limited. A trial assessing the effect of nabilone on pain and quality of life in patients with fibromyalgia. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00272207. Accessed April 7, 2014.

113. GW Pharma Ltd. A double blind, randomised, placebo controlled parallel group study of cannabis based medicine extract (CBME), in the treatment of peripheral neuropathic pain characterised by allodynia. metaRegister of Controlled Trials. http://www.controlled-trials.com/ISRCTN38250575. Accessed April 7, 2014.

114. Montreal General Hospital. Pilot study of smoked cannabis for chronic neuropathic pain. metaRegister of Controlled Trials (mRCT), http://www.controlled-trials.com/ISRCTN68314063. Accessed April 7, 2014.

115. GW Pharma Ltd. A double blind, randomised, placebo controlled, parallel group study of Sativex, in the treatment of subjects with peripheral neuropathic pain associated with allodynia. EU Clinical Trials Register. https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2004-002531-32. Accessed April 8, 2014.

116. Cambridge Laboratories Ltd. A randomised, crossover, double blind comparison of the analgesic effect and patient tolerability of nabilone and dihydrocodeine in chronic neuropathic pain. metaRegister of Controlled Trials. http://isrctn.org/ISRCTN15330757. Accessed April 7, 2014.

117. Selvarajah D, Gandhi RA, Witte D, Bowler H, Emery C, Tesfaye S. Treatment of painful diabetic neuropathy with Sativex (a cannabis based medicinal product)—results of a randomised placebo controlled trial. *Diabetologia*. 2006;49 (suppl 1):671-672 doi:10.1007/s00125-006-0358-5.

118. Rog DJ, Nurmikko T, Young C, Sarantis NS. Randomized controlled trial of sativex, a cannabis based medicine (CBM), in central neuropathic pain due to multiple sclerosis, followed by an open-label extension. *Neurology*. 2006;66(5):A31.

119. Ventegodt S, Merrick J. Psychoactive drugs and quality of life. *ScientificWorldJournal*. 2003;3:694-706.

120. Wallace MS, Marcotte TD, Umlauf A, Gouaux B, Atkinson JH. Efficacy of inhaled cannabis on painful diabetic neuropathy. *J Pain*. 2015;pii:S1526-5900(1515)00601-X.

121. Turcotte D, Doupe M, Torabi M, et al. Nabilone as an adjunctive to gabapentin for multiple sclerosis-induced neuropathic pain: a randomized controlled trial. *Pain Med*. 2015;16(1):149-159.

122. Zajicek JP, Sanders HP, Wright DE, et al. Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. *J Neurol Neurosurg Psychiatry*. 2005;76(12):1664-1669.

123. Zajicek JP, Hobart JC, Slade A, Barnes D, Mattison PG; MUSEC Research Group. Multiple sclerosis and extract of cannabis: results of the MUSEC trial. *J Neurol Neurosurg Psychiatry*. 2012;83(11):1125-1132.

124. Corey-Bloom J, Wolfson T, Gamst A, et al. Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. *CMAJ*. 2012;184(10):1143-1150.

125. Collin C, Ehler E, Waberzinek G, et al. A double-blind, randomized, placebo-controlled, parallel-group study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis. *Neurol Res*. 2010;32(5):451-459.

126. Pooyania S, Ethans K, Szturm T, Casey A, Perry D. A randomized, double-blinded, crossover pilot study assessing the effect of nabilone on spasticity in persons with spinal cord injury. *Arch Phys Med Rehabil*. 2010;91(5):703-707.

127. Collin C, Davies P, Mutiboko IK, Ratcliffe S; Sativex Spasticity in MS Study Group. Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. *Eur J Neurol*. 2007;14(3):290-296.

128. Freeman RM, Adekanmi O, Waterfield MR, Waterfield AE, Wright D, Zajicek J. The effect of cannabis on urge incontinence in patients with multiple sclerosis: a multicentre, randomised placebo-controlled trial (CAMS-LUTS). *Int Urogynecol J Pelvic Floor Dysfunct*. 2006;17(6):636-641.

129. Wade DT, Makela P, Robson P, House H, Bateman C. Do cannabis-based medicinal extracts

have general or specific effects on symptoms in multiple sclerosis? a double-blind, randomized, placebo-controlled study on 160 patients. *Mult Scler*. 2004;10(4):434-441.

130. Vaney C, Heinzel-Gutenbrunner M, Jobin P, et al. Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled, crossover study. *Mult Scler*. 2004;10(4):417-424.

131. Zajicek J, Fox P, Sanders H, et al; UK MS Research Group. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet*. 2003;362(9395):1517-1526.

132. Killestein J, Hoogervorst ELJ, Reif M, et al. Safety, tolerability, and efficacy of orally administered cannabinoids in MS. *Neurology*. 2002;58(9):1404-1407.

133. Hobart JC, Zajicek JP. Cannabis as a symptomatic treatment for MS: Clinically meaningful MUSEC to the stiffness and walking problems of people with MS. Paper presented at: 28th Congress of the European Committee for Treatment and Research in Multiple Sclerosis; October 10-13, 2012; Lyon: France. *Mult Scler*. 2012;18(4 suppl 1):247.

134. Zajicek J, Reif M, Schnelle M. Cannabis extract in the treatment of muscle stiffness and other symptoms in multiple sclerosis—Results of the MUSEC study. Paper presented at: 25th Congress of the European Committee for Treatment and Research in Multiple Sclerosis; September 9-12, 2009; Dusseldorf: Germany. *Mult Scler*. 2009;15(9)(suppl S):S274 doi:10.1177/1352458509107025.

135. Killestein J, Hoogervorst ELJ, Kalkers NF, et al. The effects of orally administered cannabinoids in multiple sclerosis patients: a pilot study. *Mult Scler*. 2000;6(1 suppl 1):S28 doi:10.1177/135245850000600101.

136. Zajicek J, Reif M, Schnelle M; UK MUSEC Study Investigators. Cannabis extract in the treatment of muscle stiffness and other symptoms in multiple sclerosis – results of the MUSEC study. Paper presented at: IACM 5th Conference on Cannabinoids in Medicine; October 2-3, 2009; Cologne, Germany.

137. Collin C, Ambler Z, Kent R, McCalla R. A randomised controlled study of Sativex® in patients with symptoms of spasticity due to multiple sclerosis. Paper presented at: 22nd Congress of the ECTRIMS; September 27-30, 2006; Madrid, Spain.

138. Robson P, Wade D, Makela P, House H, Bateman C. Cannabis-based medicinal extract (Sativex) produced significant improvements in a subjective measure of spasticity which were maintained on long-term treatment with no evidence of tolerance. Paper presented at: IACM 3rd Conference on Cannabinoids in Medicine; September 9-10, 2005; Leiden, the Netherlands.

139. Center for Medicinal Cannabis Research. Short-term effects of medicinal cannabis therapy on spasticity in multiple sclerosis. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00248378. Accessed April 7, 2014.

140. Institut fur Klinische Forschung Germany; Weleda AG. Multiple Sclerosis and Extract of Cannabis (MUSEC) study. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00552604. Accessed April 7, 2014.

141. GW Pharmaceuticals Ltd. A study of Sativex® for relief of spasticity in subjects with multiple sclerosis. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00711646. Accessed April 7, 2014.

142. GW Pharmaceuticals Ltd. A study to evaluate the efficacy of Sativex in relieving symptoms of spasticity due to multiple sclerosis. ClinicalTrials.gov.http://ClinicalTrials.gov/show/NCT01599234. Accessed April 7, 2014.

143. GW Pharmaceuticals Ltd. An investigation of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in multiple sclerosis patients. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT01610700. Accessed April 7, 2014.

144. University of Manitoba, Valeant Canada Limited. Randomized double blind cross over study for nabilone in spasticity in spinal cord injury persons. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00623376. Accessed April 7, 2014.

145. Medical Research Council (MRC). A multiple randomised controlled trial of cannabinoids on spasticity in multiple sclerosis (MS). metaRegister of Controlled Trials. http://www.controlled-trials.com/ISRCTN39371386. Accessed April 7, 2014.

146. Gesellschaft fuer klinische Forschung e.V. Multiple Sclerosis and Extract of Cannabis (MUSEC): a randomised, double-blind, placebo-controlled phase III trial to determine the efficacy and safety of a standardised oral extract of cannabis sativa for the symptomatic relief of muscle stiffness and pain in multiple sclerosis. EU Clinical Trials Register. https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2005-005263-29. Accessed April 8, 2014.

147. Corey-Bloom J, Wolfson TJ, Anthony GC, Bentley H, Gouaux B. Short-term effects off medicinal cannabis on spasticity in multiple sclerosis. *Neurology*. 2008;70(11)(suppl 1):A86-A87.

148. Leocani L, Nuara A, Houdayer E, et al. Effect of THC-CBD oromucosal spray (Sativex) on measures of spasticity in multiple sclerosis: a double-blind, placebo-controlled, crossover study. Paper presented at: Joint Americas Committee for Treatment and Research in Multiple Sclerosis ACTRIMS—European Committee for Treatment and Research in Multiple Sclerosis ECTRIMS Meeting; September 10-13, 2014; Boston, MA. *Mult Scler*. 2014;20(1 suppl 1):498 doi:10.1177/1352458514547846.

149. Van Amerongen G, Beumer T, Killestein J, Groeneveld GJ. Individualized dosing of a novel oral DELTA9-THC formulation improves subjective spasticity and pain in patients with progressive multiple sclerosis. Paper presented at Joint Americas Committee for Treatment and Research in Multiple Sclerosis ACTRIMS—European Committee for Treatment and Research in Multiple Sclerosis ECTRIMS Meeting; September 10-13, 2014; Boston,MA. *Mult Scler*. 2014;20(1)(suppl 1):478-479 doi:10.1177/1352458514547846.

150. Bergamaschi MM, Queiroz RH, Chagas MH, et al. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients. *Neuropsychopharmacology*. 2011;36(6):1219-1226.

151. Leweke FM, Piomelli D, Pahlisch F, et al. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Transl Psychiatry*. 2012;2:e94.

152. Leweke FM, Gerth CW, Nolden BM, et al. Cannabidiol as antipsychotic. Paper presented at: 21st ECNP Congress; August 30, 2008; Barcelona, Spain. *Eur Neuropsychopharmacol*. 2008;18(S4):S171 doi:10.1016/S0924-977X(08)70156-1.

153. Leweke FM, Koethe D, Pahlisch F, et al. Antipsychotic effects of cannabidiol. Paper presented at: 17th European Psychiatric Association, EPA Congress; January 24-28, 2009; Lisbon, Portugal. *Eur Psychiatry*. 2009;24(supp 1):S207 doi:10.1016/S0924-9338(09)70440-7.

154. University of Cologne. Evaluation of the antipsychotic efficacy of cannabidiol in acute schizophrenic psychosis. ClinicalTrials.gov. http://ClinicalTrials.gov/show/NCT00628290. Accessed April 7, 2014.

155. Rohleder C, Pahlisch F, Schaefer C, et al. The endocannabinoid system as a pharmacological target for antipsychotic treatment and more? Paper presented at: 8th International Conference on Early Psychosis: From Neurobiology to Public Policy; October 11-13, 2012; San Francisco, CA. *Early Interv Psychiatry*. 2012;6(suppl 1):7 doi:10.1111/j.1751-7893.2012.00392.x.

156. Markus F, Leweke M, Kranaster L, et al. The efficacy of cannabidiol in the treatment of schizophrenia—A translational approach. Paper presented at: 13th International Congress on Schizophrenia Research, ICOSR; April 2-6, 2011; Colorado Springs, CO. *Schizophr Bull*. 2011;37(suppl 1):313 doi:10.1093/schbul/sbq173.

157. Leweke FM, Kranaster L, Hellmich M, Koethe D. Cannabidiol as a new type of an antipsychotic: results from a placebo-controlled clinical trial. Paper presented at: 49th Annual Conference of the American College of Neuropsychopharmacology, ACNP 2010; December 5-9, 2010; Miami Beach, FL. *Neuropsychopharmacology*. 2010;35(suppl 1):S280 doi:10.1038/npp.2010.217.

158. Leweke FM, Hellmich M, Kranaster L, Koethe D. Cannabidiol as a new type of an antipsychotic: results from a placebo-controlled clinical trial. Paper presented at: 67th Annual Scientific Convention and Meeting of the Society of Biological Psychiatry; May 3-5, 2012; Philadelphia, PA. *Biol Psychiatry*. 2012;78(8)(suppl 1):63S.

159. Tomida I, Azuara-Blanco A, House H, Flint M, Pertwee RG, Robson PJ. Effect of sublingual application of cannabinoids on intraocular pressure: a pilot study. *J Glaucoma*. 2006;15(5):349-353.

160. Müller-Vahl KR, Prevedel H, Theloe K, Kolbe H, Emrich HM, Schneider U. Treatment of Tourette syndrome with delta-9-tetrahydrocannabinol (delta 9-THC): no influence on neuropsychological performance. *Neuropsychopharmacology*. 2003;28(2):384-388.

161. Müller-Vahl KR, Schneider U, Prevedel H, et al. Delta 9-tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: a 6-week randomized trial. *J Clin Psychiatry*. 2003;64(4):459-465.

162. Müller-Vahl KR, Koblenz A, Jöbges M, Kolbe H, Emrich HM, Schneider U. Influence of treatment of Tourette syndrome with delta9-tetrahydrocannabinol (delta9-THC) on neuropsychological performance. *Pharmacopsychiatry*. 2001;34(1):19-24.

163. Müller-Vahl KR, Schneider U, Koblenz A, et al. Treatment of Tourette's syndrome with Delta 9-tetrahydrocannabinol (THC): a randomized crossover trial. *Pharmacopsychiatry*. 2002;35(2):57-61.

164. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. MeDRA (Medical Dictionary for Regulatory Activities). http://www.meddra.org/. Accessed September 2, 2014.

165. McGowan J, Sampson M, Lefebvre C. An evidence based checklist for the peer review of electronic search strategies (PRESS EBC). Evid Based Libr Inf Pract. 2010;5(1):1-6. http://ejournals.library.ualberta.ca/index.php/EBLIP/article/view/7402. Accessed Month, date, year.

166. Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. *Int J Epidemiol*. 2002;31(1):140-149.

167. Lakhan SE, Rowland M. Whole plant cannabis extracts in the treatment of spasticity in multiple sclerosis: a systematic review. *BMC Neurol*. 2009;9:59.

168. Sevilla Guerra S. Are cannabinoids more effective than placebo in decreasing MS-related bladder dysfunction? *Br J Neurosci Nurs*. 2012;8(2):71-78 doi:10.12968/bjnn.2012.8.2.71.

169. Shakespeare D, Boggild M, Young CA. Anti-spasticity agents for multiple sclerosis. *Cochrane Database Syst Rev*. 2003;(4):CD001332.

170. Wade DT, Collin C, Stott C, Duncombe P. Meta-analysis of the efficacy and safety of Sativex (nabiximols), on spasticity in people with multiple sclerosis. *Mult Scler*. 2010;16(6):707-714.

171. Brook JS, Lee JY, Finch SJ, Brown EN. Course of comorbidity of tobacco and marijuana use: psychosocial risk factors. *Nicotine Tob Res*. 2010;12(5):474-482.

172. Machado Rocha FC, Stéfano SC, De Cássia Haiek R, Rosa Oliveira LM, Da Silveira DX. Therapeutic use of *Cannabis sativa* on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. *Eur J Cancer Care (Engl)*. 2008;17(5):431-443.

173. Phillips RS, Gopaul S, Gibson F, et al Antiemetic medication for prevention and treatment of chemotherapy induced nausea and vomiting in childhood. *Cochrane Database Syst Rev*. 2010;(9):CD007786.

174. Tramèr MR, Carroll D, Campbell FA, Reynolds DJ, Moore RA, McQuay HJ. Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. *BMJ*. 2001;323(7303):16-21.

175. van den Elsen GAH, Ahmed AIA, Lammers M, et al. Efficacy and safety of medical cannabinoids in older subjects: a systematic review. *Ageing Res Rev*. 2014;14(1):56-64.

176. Burns TL, Ineck JR. Cannabinoid analgesia as a potential new therapeutic option in the treatment of chronic pain. *Ann Pharmacother*. 2006;40(2):251-260.

177. Campbell FA, Tramèr MR, Carroll D, Reynolds DJ, Moore RA, McQuay HJ. Are cannabinoids an effective and safe treatment option in the management of pain? a qualitative systematic review. *BMJ*. 2001;323(7303):13-16.

178. Canadian Agency for Drugs and Technologies in Health (CADTH). *Cannabinoids as Co-Analgesics: Review of Clinical Effectiveness*. Ottawa, Canada: Canadian Agency for Drugs and Technologies in Health;2010.

179. Canadian Agency for Drugs and Technologies in Health (CADTH). *Cannabinoids for the Management of Neuropathic Pain: Review of Clinical Effectiveness*. Ottawa, Canada: Canadian Agency for Drugs and Technologies in Health);2010.

180. Davis MP. Oral nabilone capsules in the treatment of chemotherapy-induced nausea and vomiting and pain. *Expert Opin Investig Drugs*. 2008;17(1):85-95.

181. Iskedjian M, Bereza B, Gordon A, Piwko C, Einarson TR. Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain. *Curr Med Res Opin*. 2007;23(1):17-24.

182. Jawahar R, Oh U, Yang S, Lapane KL. A systematic review of pharmacological pain management in multiple sclerosis. *Drugs*. 2013;73(15):1711-1722.

183. Kung T, Hochman J, Sun Y, et al. Efficacy and safety of cannabinoids for pain in musculoskeletal diseases: a systematic review and meta-analysis. Paper presented at: 2nd Mexican-Canadian Congress of Rheumatology; February 10-15, 2011; Cancun, Mexico. *J Rheumatol*. 2011;38(6):1171 doi:10.3899/jrheum.110506.

184. Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. *Br J Clin Pharmacol*. 2011;72(5):735-744.

185. Martín-Sánchez E, Furukawa TA, Taylor J, Martin JL. Systematic review and meta-analysis of cannabis treatment for chronic pain. *Pain Med*. 2009;10(8):1353-1368.

186. Phillips TJ, Cherry CL, Cox S, Marshall SJ, Rice AS. Pharmacological treatment of painful HIV-associated sensory neuropathy: a systematic review and meta-analysis of randomised controlled trials. *PLoS One*. 2010;5(12):e14433.

187. Pittler MH, Ernst E. Complementary therapies for neuropathic and neuralgic pain: systematic review. *Clin J Pain*. 2008;24(8):731-733.

188. Richards BL, Whittle SL, Buchbinder R. Neuromodulators for pain management in rheumatoid arthritis. *Cochrane Database Syst Rev*. 2012;(1):CD008921.

189. Boychuk DG, Goddard G, Mauro G, Orellana MF. The effectiveness of cannabinoids in the management of chronic nonmalignant neuropathic pain: a systematic review. *J Oral Facial Pain Headache*. 2015;29(1):7-14.

190. Parsai S, Herman R, Johnson S. Systematic literature review of randomized controlled trials to evaluate the efficacy of medical marijuana for analgesia. Paper presented at: Annual Meeting of the American College of Clinical Pharmacy; October 12-15, 2014; Austin, TX. *Pharmacotherapy*. 2014;34(10):e287 doi:10.1002/phar.1497.

191. Lynch ME, Ware MA. Cannabinoids for the treatment of chronic non-cancer pain: an updated systematic review of randomized controlled trials [published online March 22, 2015]. *J Neuroimmune Pharmacol* doi.org/10.1007/s11481-015-9600-6.

192. Rathbone J, Variend H, Mehta H. Cannabis and schizophrenia. *Cochrane Database Syst Rev*. 2008;(3):CD004837.

193. Schoeler T, Kambeitz J, Bhattacharyya S. The effect of cannabis on memory function in users with and without a psychotic disorder: a meta-analysis. Paper presented at: 26th European College of Neuropsychopharmacology, ECNP Congress; October 5-9, 2013; Barcelona, Spain. *Eur Neuropsychopharmacol*. 2013;23:S216-S217 doi:10.1016/S0924-977X(13)70334-1.

194. Zammit S, Moore THM, Lingford-Hughes A, et al. Effects of cannabis use on outcomes of psychotic disorders: systematic review. *Br J Psychiatry*. 2008;193(5):357-363.

195. Curtis A, Clarke CE, Rickards HE. Cannabinoids for Tourette's syndrome. *Cochrane Database Syst Rev*. 2009;CD00656520090(4):CD006565.

196. Waldon K, Hill J, Termine C, Balottin U, Cavanna AE. Trials of pharmacological interventions for Tourette syndrome: a systematic review. *Behav Neurol*. 2013;26(4):265-273.

197. Boers M. Updated Consolidated Standards of Reporting Trials (CONSORT): it just gets better. *J Clin Epidemiol*. 2010;63(8):813-814.