Medical Marijuana Program

165 Capitol Avenue, Room 145, Hartford, CT 06106-1630 • (860) 713-6066
E-mail: dcp.mmp@ct.gov • Website: www.ct.gov/dcp/mmp

Petition to Add a Medical Condition, Medical Treatment or Disease to the List of Debilitating Conditions

INSTRUCTIONS: Please complete each section of this Petition and attach all supportive documents. All attachments must include a title referencing the Section letter to which it responds. Any Petition that is not fully or properly completed will not be submitted to the Board of Physicians.

Please Note: Any individually identifiable health information contained in a Petition shall be confidential and shall not be subject to disclosure under the Freedom of Information Act, as defined in section 1-200, Connecticut General Statutes.

Section A: Petitioner's Information

Name (First, Middle, Last): [redacted]		
Home Address (including Apartment or Suite #): [redacted]		
City: [redacted]	State: CT	Zip Code: [redacted]
Telephone Number: [redacted]	E-mail Address: [redacted]	

Section B: Medical Condition, Medical Treatment or Disease

Please specify the medical condition, medical treatment or disease that you are seeking to add to the list of debilitating medical conditions under the Act. Be as precise as possible in identifying the condition, treatment or disease.

Osteogenesis Imperfecta

Section C: Background

Provide information evidencing the extent to which the condition, treatment or disease is generally accepted by the medical community and other experts as a valid, existing medical condition, medical treatment or disease.

- Attach a comprehensive definition from a recognized medical source.
- Attach additional pages as needed.

Osteogenesis Imperfecta where children and adults have brittle bones and are at high risk for multiple fractures and long term chronic pain (see attached)

Section D: Negative Effects of Current Treatment

If you claim a treatment, that has been prescribed for your condition causes you to suffer (i.e. severe or chronic pain, spasticity, etc.), provide information regarding the extent to which such treatment is generally accepted by the medical community and other experts as a valid treatment for your debilitating condition.

- Attach additional pages as necessary.
- If not applicable, please indicate N/A.

Opioids and muscle relaxants can be helpful but have multiple side effects such as itching, constipation and the potential for overdose and addiction. (see attached)

Section E: Negative Effects of Condition or Treatment

Provide information regarding the extent to which the condition or the treatments thereof cause severe or chronic pain, severe nausea, spasticity or otherwise substantially limits one or more major life activities.

- Attach additional pages as necessary.

Many patients including myself are wheelchair bound, have severe chronic pain and spasm

Section F: Conventional Therapies

Provide information regarding the availability of conventional medical therapies, other than those that cause suffering, to alleviate suffering caused by the condition or the treatment thereof.

- Attach additional pages as necessary.

pamindronate (see attached)

Section G: General Evidence of Support for Medical Marijuana Treatment

Provide evidence, generally accepted among the medical community and other experts, that supports a finding that the use of marijuana alleviates suffering caused by the condition or the treatment thereof.

- Attach additional pages as necessary.

Medical Marijuana has been shown to treat pain and for a variety of conditions

Section H: Scientific Evidence of Support for Medical Marijuana Treatment

Provide any information or studies regarding any beneficial or adverse effects from the use of marijuana in patients with the condition, treatment or disease that is the subject of the petition.

- Supporting evidence needs to be from professionally recognized sources such as peer reviewed articles or professional journals.
- Attach complete copies of any article or reference, not abstracts.

see attached

Section I: Professional Recommendations for Medical Marijuana Treatment

Attach letters in support of your petition from physicians or other licensed health care professionals knowledgeable about the condition, treatment or disease at issue.

see attached

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Section J: Submission of Petition

In the event you are unable to answer or provide the required documentation to any of the Sections above (excluding Section D); provide a detailed explanation indicating what you believe is "good cause" for not doing so.

- Attach additional pages as necessary.

I hereby certify that the above information is correct and complete.

My signature below attests that the information provided in this petition is true and that the attached documents are authentic. I formally request that the commissioner present my petition and all supporting evidence to the Board of Physicians for consideration.

Signature: [redacted]	Date Signed: Aug 31, 2017

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

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Supplemental content at jama.com

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, −0.36 [95% CI, −0.69 to −0.05]; 7 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.

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).

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Cannabis is a generic term used for drugs produced from plants belonging to the genus *Cannabis*.[1] It is one of the most popular recreational drugs; worldwide, an estimated 178 million people aged 15 to 64 years used cannabis at least once in 2012.[2] Cannabis was included as a controlled drug in the United Nations' Single Convention on Narcotic Drugs, held in 1961,[3] and its use is illegal in most countries.

Medical cannabis refers to the use of cannabis or cannabinoids as medical therapy to treat disease or alleviate symptoms. Cannabinoids can be administered orally, sublingually,or topically; they can be smoked, inhaled, mixed with food, or made into tea. They can be taken in herbal form, extracted naturally from the plant, gained by isomerisation of cannabidiol, or manufactured synthetically.[4] Prescribed cannabinoids include dronabinol capsules, nabilone capsules, and the oromucosal spray nabiximols.[4] Some countries have legalized medicinal-grade cannabis for chronically ill patients. Canada and the Netherlands have government-run programs in which specialized companies supply quality-controlled herbal cannabis.[5] In the United States, 23 states and Washington, DC (May 2015), have introduced laws to permit the medical use of cannabis[6]; other countries have similar laws. The aim of this systematic review was to evaluate the evidence for the benefits and adverse events (AEs) of medical cannabinoids across a broad range of indications.

Methods

This review followed guidance published by the Centre for Reviews and Dissemination and the Cochrane Collaboration.[7,8] We established a protocol for the review (eAppendix 1 in Supplement 1).

Study Eligibility Criteria

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

Identification and Selection of Studies

Twenty-eight databases and gray literature sources were searched from inception to April 2015 without language restriction (Embase search strategy and details of databases searched available in eAppendix 2 in Supplement 2). The search strategy was peer reviewed[9] by a second information specialist. Reference lists of included studies were screened. Search results and full-text articles were independently assessed by 2 reviewers; disagreements were resolved through consensus or referral to a third reviewer.

Data Collection and Study Appraisal

We extracted data about baseline characteristics and outcomes (patient-relevant and disease-specific outcomes, activities of daily living, quality of life, global impression of change, and specified AEs). For dichotomous data such as number of patients with at least 30% improvement in pain, we calculated the odds ratio (OR) and 95% CI. For categorical data, we extracted details about each category assessed and the numbers of patients with an outcome in each category. Continuous data such as the Ashworth spasticity score[10] were extracted as means and SDs at baseline, follow-up, and the change from baseline and used to calculate mean differences with 95% CIs. Results (mean difference, 95% CIs, and *P* values) from the between-group statistical analyses reported by the study were also extracted. All relevant sources were used for data extraction including full-text journal articles, abstracts, and clinical trial registry entries. Where available, the journal article was used as the primary publication because it had been peer reviewed.

RCTs were assessed for methodological quality using the Cochrane Risk of Bias tool.[11] If at least one of the domains was rated as high, the trial was considered at high risk of bias. If all domains were judged as low, the trial was considered at low risk of bias. Otherwise, the trial was considered as having unclear risk of bias. Data extraction and risk-of-bias assessment were performed independently by 2 reviewers; disagreements were resolved by a third reviewer.

Synthesis

Clinical heterogeneity was assessed by grouping studies by indication, cannabinoid, and outcome. If there were 2 or more trials within a single grouping, data were pooled using random-effects meta-analysis.[12] For continuous outcomes, we analyzed the mean difference in change from baseline; if this was not reported and could not be calculated from other data, we used the mean difference at follow-up.[13] For dichotomous data, we used the OR. In order to avoid double counting, we selected a single data set from each study to contribute to the analysis. For studies evaluating multiple interventions, we selected the intervention or dose that was most similar to the other interventions being evaluated in the same analysis. Heterogeneity was investigated using forest plots and the I^2 statistic. Where data were considered too heterogeneous to pool or not reported in a format suitable for pooling (eg, data reported as medians), we used a narrative synthesis.

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

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

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

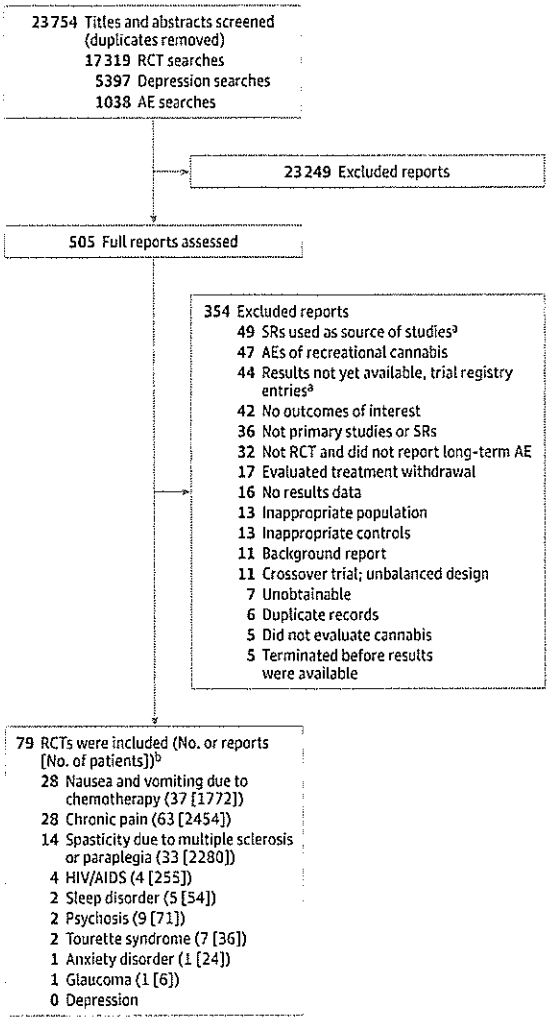
Results

The searches identified 23 754 hits (records) of which 505 were considered potentially relevant, based on title and abstract screening, and obtained as full-text studies. A total of 79 studies (6462 participants), available as 151 reports, were included; 3 studies (6 reports) were included in multiple indication categories (Figure 1). Thirty-four studies were parallel-group trials (4436 participants), and 45 were crossover trials (2026 participants). Four studies were available only as an abstract,[15-18] a further 3 were available only as abstracts[19-21] but with additional details available on trial registries including full results in one,[19] and details of 2 trials (including full trial results) were available only as trial registry entries[22,23]; all other trials were reported in full-length journal articles. Where reported, the proportion of participants who were men ranged from 0% to 100% (median, 50% [57 studies]), and the proportion of white participants ranged from 50% to 99% (median, 78% [18 studies]). Publication dates ranged from 1975 to 2015 (median, 2004 [with one-third of trials published before 1990]). Studies were conducted in a wide range of countries. A variety of cannabinoids were evaluated and compared with various different active comparators or placebos; most active comparators were included in the nausea and vomiting indication (Table 1). eAppendices 3 to 12 in Supplement 1 provide an overview of the included studies and their findings.

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

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

Figure 1. Flow of Studies Through the Review Process



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

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

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

Nausea and Vomiting Due to Chemotherapy

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

Table 1. Evaluation of Interventions by Included Studies

Intervention	US Legal Status and Approved Use	Cannabis-Related Properties	Administration Method	Dose Evaluated	Comparator	No. of Studies[a]	Indication
Ajulemic acid (CT3)	Available for licensing since February 10, 2015 Approved for treatment of inflammation in scleroderma in 2015	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) −0.32 (−1.59 to 0.95) −0.94 (−2.37 to 0.49)	CBM	0	Moderate
	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) 0.23 (−0.13 to 0.59) −0.03 (−0.39 to 0.33)	Placebo	0	Moderate
	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.

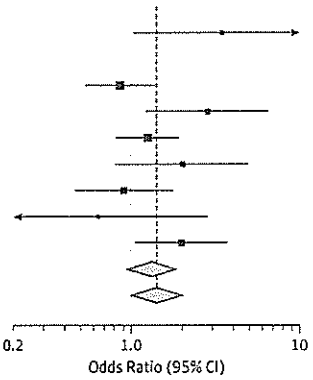
[a] No studies for glaucoma were included in the study estimate. The authors note that THC and cannabidiol were the interventions used in the reviewed glaucoma studies.

[b] Outcome includes the specific indication that was assessed, the means by which assessment was made, and follow-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)	Weight, %
Tetrahydrocannabinol (smoked)						
Abrams et al,[77] 2007	13	25	6	25	3.43 (1.03-11.48)	6.51
Nabiximols						
GW Pharmaceuticals,[22] 2005	54	149	59	148	0.86 (0.54-1.37)	19.02
Johnson et al,[69] 2010	23	53	12	56	2.81 (1.22-6.50)	10.87
Langford et al,[65] 2013	84	167	77	172	1.25 (0.81-1.91)	20.19
Nurmikko et al,[76] 2007	16	63	9	62	2.00 (0.81-4.96)	9.84
Portenoy et al,[67] 2012	22	90	24	91	0.90 (0.46-1.76)	14.04
Selvarajah et al,[70] 2010	8	15	9	14	0.63 (0.14-2.82)	4.63
Serpell et al,[88] 2014	34	123	19	117	1.97 (1.05-3.70)	14.91
Subtotal I^2=44.5%, (P=.0.94)	241	660	209	660	1.32 (0.94-1.86)	93.49
Overall I^2=47.6%, (P=.0.64)	254	685	215	685	1.41 (0.99-2.00)	100.00



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

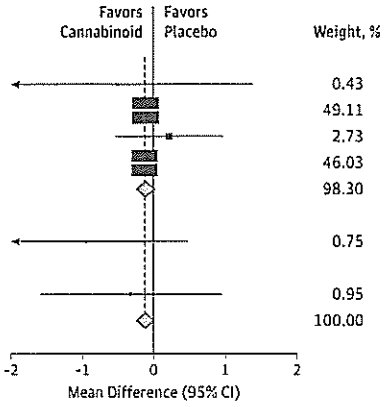
No studies evaluating cannabinoids for the treatment of depression fulfilled inclusion criteria. Five studies included for other indications reported depression as an outcome measure; 4 evaluated chronic pain and 1 evaluated spasticity in MS patients.[67,73,75,80,129] One trial assessed dronabinol (2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

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 = .0.82)	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).

lone, and nabiximols) than placebo but these studies were not restricted to patients with anxiety disorders.[73-75,80]

Sleep Disorder

Two studies (5 reports; 54 participants) evaluated cannabinoids (nabilone) specifically for the treatment of sleep problems. One was a parallel-group trial judged at high risk of bias. This reported a a greater benefit of nabilone compared with placebo on the sleep apnea/hypopnea index (mean difference from baseline, −19.64; *P* value = .02). The other was a crossover trial judged at low risk of bias in patients with fibromyalgia and compared nabilone with amitriptyline. This suggested that nabilone was associated with improvements in insomnia (mean difference from baseline, −3.25 [95% CI, −5.26 to −1.24]) but that amitriptyline was associated with greater sleep restfulness (mean difference from baseline, 0.48 [95% CI, 0.01 to 0.95]). Nineteen placebo-controlled studies included for other indications (chronic pain and MS) also evaluated sleep as an outcome.* Thirteen studies assessed nabiximols, 1 for nabilone, 1 for dronabinol, 2 for THC/CBD capsules, and two assessed smoked THC (one at various doses). Two of the studies that assessed nabiximols also assessed oral THC and the trial of dronabinol also assessed oral THC/CBD. There was some evidence that cannabinoids may improve sleep in these patient groups. Cannabinoids (mainly nabiximols) were associated with a greater average improvement in sleep quality (WMD, −0.58 [95% CI, −0.87 to −0.29]; 8 trials) and sleep disturbance (WMD, −0.26 [95% CI, −0.52 to 0.00]; 3 trials). One trial assessed THC/CBD, all others assessed nabiximols, results were similar for both cannabinoids.

Psychosis

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

Glaucoma

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

Movement Disorders Due to Tourette Syndrome

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

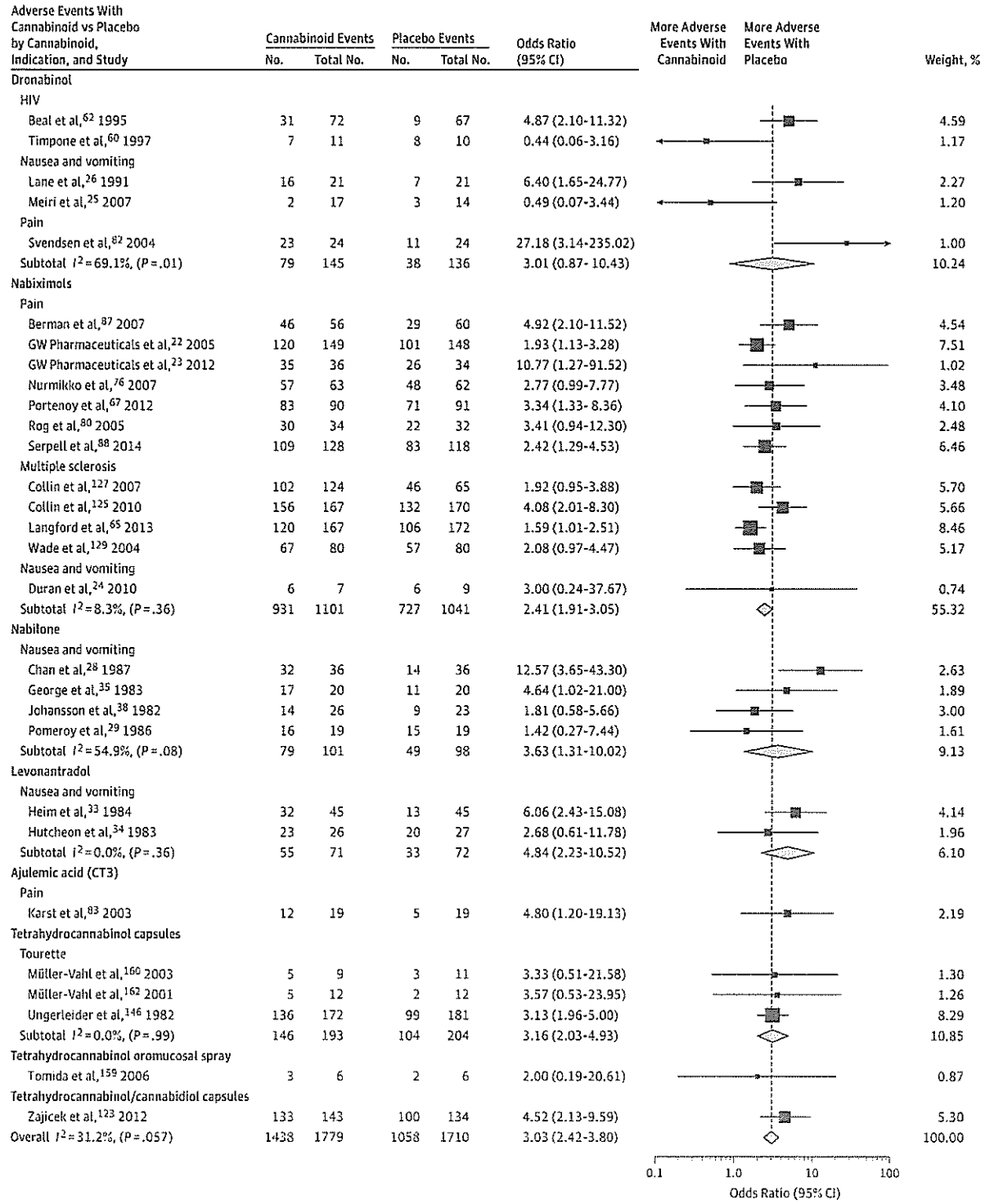
Adverse Events

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

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

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

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



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)[198] 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.
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Clinical Crossroads

Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems
A Clinical Review

Kevin P. Hill, MD, MHS

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IMPORTANCE As of March 2015, 23 states and the District of Columbia had medical marijuana laws in place. Physicians should know both the scientific rationale and the practical implications for medical marijuana laws.

OBJECTIVE To review the pharmacology, indications, and laws related to medical marijuana use.

EVIDENCE REVIEW The medical literature on medical marijuana was reviewed from 1948 to March 2015 via MEDLINE with an emphasis on 28 randomized clinical trials of cannabinoids as pharmacotherapy for indications other than those for which there are 2 US Food and Drug Administration–approved cannabinoids (dronabinol and nabilone), which include nausea and vomiting associated with chemotherapy and appetite stimulation in wasting illnesses.

FINDINGS Use of marijuana for chronic pain, neuropathic pain, and spasticity due to multiple sclerosis is supported by high-quality evidence. Six trials that included 325 patients examined chronic pain, 6 trials that included 396 patients investigated neuropathic pain, and 12 trials that included 1600 patients focused on multiple sclerosis. Several of these trials had positive results, suggesting that marijuana or cannabinoids may be efficacious for these indications.

CONCLUSIONS AND RELEVANCE Medical marijuana is used to treat a host of indications, a few of which have evidence to support treatment with marijuana and many that do not. Physicians should educate patients about medical marijuana to ensure that it is used appropriately and that patients will benefit from its use.

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Author Affiliations: Substance Abuse Consultation Service, McLean Hospital, Belmont, Massachusetts; Harvard Medical School, Boston, Massachusetts.

Corresponding Author: Kevin P. Hill, MD, MHS, McLean Hospital, Division of Alcohol and Drug Abuse, 115 Mill St, Belmont, MA 02478 (khill@mclean.harvard.edu).

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This article is based on a conference that took place at the Medicine Grand Rounds at Beth Israel Deaconess Medical Center, Boston, Massachusetts, on May 16, 2014.

Dr Burns Mr Z is a 60-year-old man who fell at work 19 years ago and has had chronic low back pain and left leg radicular symptoms since that time. None of the numerous interventions performed in an effort to treat this pain were effective. These include an L2-3 laminectomy in 1996, multiple lumbar epidural steroid injections, selective nerve root blocks, lidocaine infusions, and a trial of a spinal cord stimulator. He has been to a pain psychologist and received physical therapy. Several medications have helped, such as gabapentin, sertraline, and nortriptyline.

His most recent magnetic resonance imaging scan showed posterior disk bulges at L2-3, L3-4, L4-5, and L5-S1, with the largest bulge at L2-3. Mild effacement of the thecal sac and narrowing of the left-sided neural foramina were seen. Mr Z was diagnosed as having failed back syndrome (chronic back pain following a laminectomy) and treated with long-term narcotics. He signed a narcotics contract with his primary care physician and has never violated the contract. Since signing his narcotics contract, Mr Z has decreased his narcotic requirements and is now taking oxycodone, 10 mg, along with ibuprofen, 600 mg, every 6 hours.

Because his overall goal remains pain relief, he has recently begun using marijuana. He received a recommendation from a cannabis clinic, a clinic whose primary function is to certify patients for the use of medical marijuana, but is now wondering if this is something his primary care physician could also agree with and therefore be responsible for the recommendation of in the future. He uses marijuana at home in the evening after returning from work. He has found marijuana to have a sedative effect, enabling him to get a good night's sleep and to have less pain the next day.

Mr Z's medical history is notable for hyperlipidemia, prediabetes, basal cell carcinoma, and anxiety. His other medications include bupropion, 150-mg sustained-release tablet twice daily; clonazepam, 0.5 mg twice daily as needed; and simvastatin, 20 mg once daily. Previously he was received disability benefits but currently works as an arborist. He drinks alcohol socially and continues to smoke cigarettes, although he has been able to cut down from 1½

packs to a half pack daily since starting bupropion. He lives at home with his adult son.

Mr Z: His View

My first experience with what would later blossom into chronic pain was about 3 weeks postsurgically after I had the L2-3 and L4-5 levels of my back worked on. Since then, I went through everything from cortisone shots to lidocaine infusions. I actually had a test for the spinal cord stimulator and there was even talk about an intrathecal morphine pump. I totally exhausted every option that was there, and my final procedure was going to be a lysis of spinal adhesions.

When I first went through my medical requirements and was screened by the doctor, I told her that it really was not a matter of needing a lot of it, as I was going to use it at home after work. So there was no question of still being under its influence at any point in time where I would be going to work or driving. I felt that my medical history alone warranted at least my looking at it as an alternative medication. The [Massachusetts 2012 medical marijuana] ballot initiative made me more comfortable with my decision.

Search Methods and Results

Dr Hill Mr Z is a 60-year-old man with a long history of chronic low back pain refractory to multiple procedures and medications. In an effort to obtain better control of his chronic pain, he began using medical marijuana after receiving a certification from a local specialty medical marijuana clinic. He thought that medical marijuana improved his pain control and approached his primary care physician about continued use of medical marijuana.

The medical literature on medical marijuana was searched from 1948 to March 2015 using MEDLINE. The search terms used included *cannabis*, *cannabinoids*, and *tetrahydrocannabinol*. The limits used were "administration and dosage" "adverse effects" "therapeutic use," or "clinical trial." The MEDLINE search resulted in 562 articles. Articles that discussed cannabinoids as pharmacotherapy in a clinical trial were selected for an initial brief review. After additional citations were obtained from references, a total of 74 articles were reviewed. There are no meta-analyses on the topic of medical marijuana; there are 3 systematic reviews.[1-3] Similarly, there is only 1 set of guidelines that addresses the use of medical marijuana as a treatment.[4] As a result, the main emphasis was on randomized clinical trials.

Medical Marijuana: Scientific Rationale and Practical Implications

As of March 2015, 23 states and the District of Columbia have enacted medical marijuana laws to facilitate access to marijuana as a treatment for a variety of medical conditions (Table 1). This is concerning to some because marijuana is the most commonly used illicit drug in the United States: approximately 12% of people aged 12 years or older reported use in the past year, and use among teens has drifted upward in recent years while their perception of its risk has declined.[6,7] With decriminalization of medical marijuana and Washington, Colorado, Alaska, Oregon, and the District of Columbia legalizing the recreational use of marijuana, there has been an increase in marijuana use. As a result, physicians are increasingly faced with questions from patients about marijuana and its medical applications.[8]

Pharmacology of Marijuana

Marijuana comprises more than 60 pharmacologically active cannabinoids.[9] Both exogenous ligands, such as the cannabinoids from marijuana, and endogenous ligands or endocannabinoids, such as anandamide and 2-arachidonylglycerol, act on cannabinoid receptors located throughout the body but mostly in the brain and spinal cord.[10] Activation of 2 types of G protein–coupled receptors, CB1 and CB2, exerts multiple actions by directly inhibiting the release of multiple neurotransmitters including acetylcholine, dopamine, and glutamate while indirectly affecting γ-aminobutyric acid, *N*-methyl-D-aspartate, opioid, and serotonin receptors.[11] CB1 receptors are concentrated primarily in the basal ganglia, cerebellum, hippocampus, association cortices, spinal cord, and peripheral nerves and CB2 receptors are found mainly on cells in the immune system, which may in part explain cannabinoids' effects on pain and inflammation. The physiological responses that result from cannabinoid receptor activation are euphoria, psychosis, impaired memory and cognition, reduced locomotor function, increased appetite, and antiemetic, pain-relieving, antispasticity, and sleep-promoting effects.[3]

The primary cannabinoids contained in marijuana are Δ^9-tetrahydrocannabinol (THC) and cannabidiol. THC produces the euphoria that comes from using marijuana, but it also can produce psychosis. Cannabidiol is not psychoactive and is thought to have antianxiety and possibly antipsychotic effects as well.[12,13] Marijuana's therapeutic effects depend on the concentration of THC in a given formulation as well as the ratio of THC to cannabidiol because of cannabidiol's ability to mitigate the psychoactive effects of THC. As a result, the THC-cannabidiol ratio for many strains of marijuana has been engineered to achieve desired effects.

Medical Indications for Cannabinoids

There are currently 2 US Food and Drug Administration (FDA)–approved cannabinoids available in the United States: dronabinol and nabilone.[14,15] Both are available in pill form and are FDA approved for nausea and vomiting associated with cancer chemotherapy as well as for appetite stimulation in wasting illnesses such as human immunodeficiency virus infection or cancer. Medical marijuana, which may be identical in form to recreational marijuana, is dried material from the *Cannabis* plant consisting of THC, cannabidiol, and other cannabinoids. Medical marijuana is purchased from dispensaries in a variety of preparations (Table 2) or grown by patients for the treatment of myriad illnesses. It is not available from pharmacies because of its status as federally illegal.

Table 1. Medical Marijuana Laws by State[a]

State	Approved Conditions	Legal Limit
Alaska, 1998	Cachexia, cancer, chronic pain, epilepsy and other disorders characterized by seizures, glaucoma, HIV/AIDS, MS and other disorders characterized by muscle spasticity, and nausea; other conditions are subject to approval by the Alaska Department of Health and Social Services	1 oz usable; 6 plants (3 mature, 3 immature)
Arizona, 2010	Cancer, glaucoma, HIV/AIDS, hepatitis C, ALS, Crohn disease, Alzheimer disease, cachexia, severe and chronic pain, severe nausea, seizures (including epilepsy), severe or persistent muscle spasms	2.5 oz usable; 0-12 plants
California, 1996	AIDS, anorexia, arthritis, cachexia, cancer, chronic pain, glaucoma, migraine, persistent muscle spasms (including spasms associated with MS), seizures (including seizures associated with epilepsy), severe nausea, other chronic or persistent medical symptoms	8 oz usable; 6 mature or 12 immature plants
Colorado, 2000	Cancer, glaucoma, HIV/AIDS, cachexia, severe pain, severe nausea, seizures (including those characteristic of epilepsy), persistent muscle spasms (including those characteristic of MS); other conditions are subject to approval by the Colorado Board of Health	2 oz usable; 6 plants (3 mature, 3 immature)
Connecticut, 2012	Cancer, glaucoma, HIV/AIDS, Parkinson disease, MS, damage to the nervous tissue of the spinal cord with objective neurological indication of intractable spasticity, epilepsy, cachexia, Crohn disease, PTSD, or any medical condition, medical treatment, or disease approved by the Department of Consumer Protection	1-mo supply (exact amount to be determined)
Washington, DC, 2010	HIV/AIDS, cancer, glaucoma, conditions characterized by severe and persistent muscle spasms such as MS, patients undergoing chemotherapy or radiotherapy or using azidothymidine or protease inhibitors	2 oz dried; limits on other forms to be determined
Delaware, 2011	Cancer, HIV/AIDS, decompensated cirrhosis (hepatitis C), ALS, Alzheimer disease A chronic or debilitating disease or medical condition or its treatment that produces ≥1 of the following: cachexia; severe, debilitating pain that has not responded to previously prescribed medication or surgical measures for more than 3 mo or for which other treatment options produced serious adverse effects; intractable nausea; seizures; severe and persistent muscle spasms including but not limited to those characteristic of MS	6 oz usable
Hawaii, 2000	Cancer, glaucoma, HIV/AIDS, a chronic or debilitating disease or medical condition or its treatment that produces cachexia, severe pain, severe nausea, seizures including those characteristic of epilepsy, or severe and persistent muscle spasms including those characteristic of MS or Crohn disease; other conditions are subject to approval by the Hawaii Department of Health	3 oz usable; 7 plants (3 mature, 4 immature)
Illinois, 2013	Cancer, glaucoma, HIV/AIDS, hepatitis C, ALS, Crohn disease, agitation related to Alzheimer disease, cachexia/wasting syndrome, muscular dystrophy, severe fibromyalgia, spinal cord disease (including but not limited to arachnoiditis), Tarlov cysts, hydromyelia syringomyelia, rheumatoid arthritis, fibrous dysplasia, spinal cord injury, traumatic brain injury and postconcussion syndrome, MS, Arnold-Chiari malformation and syringomelia, spinocerebellar ataxia, Parkinson disease, Tourette syndrome, myoclonus, dystonia, reflex sympathetic dystrophy (complex regional pain syndromes type 1), causalgia, complex regional pain syndrome type 2, neurofibromatosis, chronic inflammatory demyelinating polyneuropathy, Sjogren syndrome, lupus, interstitial cystitis, myasthenia gravis, hydrocephalus, nail patella syndrome or residual limb pain, or treatment of these conditions	2.5 ounces usable cannabis during 14-d period
Maine, 1999	Epilepsy and other disorders characterized by seizures, glaucoma, MS and other disorders characterized by muscle spasticity, and nausea or vomiting as a result of AIDS or cancer chemotherapy	2.5 oz usable; 6 plants
Maryland, 2014	Cachexia, anorexia, or wasting syndrome, severe or chronic pain, severe nausea, seizures, severe or persistent muscle spasms, or other conditions approved by the commission	30-d supply, amount to be determined
Massachusetts, 2012	Cancer, glaucoma, HIV/AIDS, hepatitis C, ALS, Crohn disease, Parkinson disease, MS, and other conditions as determined in writing by a qualifying patient's physician	60-d supply (10 oz) for personal medical use
Michigan, 2008	Cancer, glaucoma, HIV/AIDS, hepatitis C, ALS, Crohn disease, agitation of Alzheimer disease, nail patella syndrome, cachexia or wasting syndrome, severe and chronic pain, severe nausea, seizures, epilepsy, muscle spasms, MS, PTSD	2.5 oz usable; 12 plants
Minnesota, 2014	Cancer (if the underlying condition or treatment produces severe or chronic pain, nausea, severe vomiting, or cachexia or severe wasting), glaucoma, HIV/AIDS, Tourette syndrome, ALS, seizures/epilepsy, severe and persistent muscle spasms/MS, Crohn disease, terminal illness with a life expectancy of <1 y	30-d supply of nonsmokable marijuana
Montana, 2004	Cancer, glaucoma, HIV/AIDS, or the treatment of these conditions; cachexia or wasting syndrome, severe or chronic pain, severe nausea, seizures including those caused by epilepsy, severe or persistent muscle spasms including those caused by MS or Crohn disease, or any other medical condition or treatment for a medical condition adopted by the department by rule	1 oz usable; 4 plants (mature); 12 seedlings
Nevada, 2000	AIDS, cancer, glaucoma, and any medical condition or treatment for a medical condition that produces cachexia, persistent muscle spasms or seizures, severe nausea or pain, PTSD; other conditions are subject to approval by the health division of the state department of human resources	1 oz usable; 7 plants (3 mature, 4 immature)
New Hampshire, 2013	Cancer, glaucoma, HIV/AIDS, hepatitis C, ALS, muscular dystrophy, Crohn disease, agitation of Alzheimer disease, MS, chronic pancreatitis, spinal cord injury or disease, traumatic brain injury, or ≥1 injuries that significantly interferes with daily activities as documented by the patient's clinician; a severely debilitating or terminal medical condition or its treatment that has produced ≥1 of the following: elevated intraocular pressure, cachexia, chemotherapy induced anorexia, wasting syndrome, severe pain not responding to previously prescribed medication or surgical measures or for which other treatment options produced serious adverse effects, constant or severe nausea, moderate to severe vomiting, seizures, or severe, persistent muscle spasms	Two oz of usable cannabis during a 10-d period
New Jersey, 2010	Seizure disorder including epilepsy, intractable skeletal muscular spasticity, glaucoma, severe or chronic pain, severe nausea or vomiting, cachexia or wasting syndrome resulting from HIV/AIDS or cancer, ALS, MS, terminal cancer, muscular dystrophy, IBD including Crohn disease, terminal illness (physician-determined prognosis of <12 mo of life), or any other medical condition or its treatment approved by the Department of Health and Senior Services	2 oz usable
New Mexico, 2007	Severe chronic pain, painful peripheral neuropathy, intractable nausea/vomiting, severe anorexia/cachexia, hepatitis C, Crohn disease, PTSD, ALS, cancer, glaucoma, MS, damage to the nervous tissue of the spinal cord with intractable spasticity, epilepsy, HIV/AIDS, hospice care, cervical dystonia, inflammatory autoimmune-mediated arthritis, Parkinson disease, Huntington disease	6 oz usable; 16 plants (4 mature, 12 immature)

(continued)

Table 1. Medical Marijuana Laws by State[a] (continued)

State	Approved Conditions	Legal Limit
New York, 2014	Cancer, HIV/AIDS, ALS, Parkinson disease, MS, spinal cord damage causing spasticity, epilepsy, IBD, neuropathies, Huntington disease The Department of Health commissioner has the discretion to add or delete conditions and must decide whether to add Alzheimer disease, muscular dystrophy, dystonia, PTSD, and rheumatoid arthritis within 18 mo of the law becoming effective	30-d supply nonsmokable marijuana
Oregon, 1998	Cancer, glaucoma, HIV/AIDS, or treatment of these conditions; a medical condition or treatment for a medical condition that produces cachexia, severe pain, severe nausea, seizures including those caused by epilepsy, or persistent muscle spasms including those caused by MS; other conditions are subject to approval by the Health Division of the Oregon Department of Human Resources	24 oz usable; 24 plants (6 mature, 18 immature)
Rhode Island, 2006	Cancer, glaucoma, HIV/AIDS, hepatitis C, or treatment of these conditions; a chronic or debilitating disease or medical condition or its treatment that produces cachexia or wasting syndrome, severe debilitating chronic pain, severe nausea, seizures including but not limited to those characteristic of epilepsy, or severe and persistent muscle spasms including but not limited to those characteristic of MS or Crohn disease, agitation of Alzheimer disease, or any other medical condition or its treatment approved by the state department of health	2.5 oz usable; 12 plants
Vermont, 2004	Cancer, HIV/AIDS, MS, or the treatment of these conditions if the disease or the treatment results in severe, persistent, and intractable symptoms; a disease, medical condition, or its treatment that is chronic, debilitating, and produces ≥1 severe, persistent, intractable symptoms of cachexia or wasting syndrome, severe pain or nausea, or seizures	2 oz usable; 9 plants (2 mature, 7 immature)
Washington, 1998	Cachexia, cancer, HIV/AIDS, epilepsy, glaucoma, intractable pain (defined as pain unrelieved by standard treatment or medications), chronic renal failure, MS Crohn disease, hepatitis C with debilitating nausea or intractable pain, or diseases including anorexia that result in nausea, vomiting, wasting, appetite loss, cramping, seizures, muscle spasms, or spasticity when those conditions are unrelieved by standard treatments or medications	24 oz usable; 15 plants

Abbreviations: ALS, amyotrophic lateral sclerosis; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; MS, multiple sclerosis; PTSD, posttraumatic stress disorder.

[a] For up to date medical marijuana regulations, see http://medicalmarijuana.procon.org/view.resource.php?resourceID=000881.[5]

Aside from the 2 FDA-approved indications for cannabinoids, the scientific evidence supporting the medical use of marijuana and cannabinoids varies widely by disease entity from high-quality evidence to poor-quality evidence. High-quality evidence is defined herein as multiple randomized clinical trials with positive results (Table 3). Despite the variability in evidence supporting various uses for medical marijuana, state policies suggest the use of medical marijuana for many medical problems beyond nausea, vomiting, and anorexia. For some of the medical conditions approved for use in some states (eg, glaucoma), there are only preliminary data supporting the use of medical marijuana as pharmacotherapy.

Data from more than 40 clinical trials of marijuana and cannabinoids have been published; beyond the 2 indications for which dronabinol and nabilone are already approved by the FDA, the strongest evidence exists for the use of marijuana and cannabinoids as pharmacotherapies for chronic pain, neuropathic pain, and spasticity associated with multiple sclerosis. As of March 2015, there were 6 trials (n=325 patients) examining chronic pain, 6 trials (n=396 patients) that investigated neuropathic pain, and 12 trials (n=1600 patients) that focused on multiple sclerosis. Several of these trials had positive results, suggesting that marijuana or cannabinoids may be efficacious for these indications. The American Academy of Neurology (AAN) recently published evidence-based guidelines that recommended an oral cannabis extract containing both THC and cannabidiol (not available in the United States as an FDA-approved medication) as having the highest level of empirical support as a treatment for spasticity and pain associated with multiple sclerosis.[4] The AAN also published a systematic review of medical marijuana as a treatment for neurological disorders, suggesting nabiximols, a spray containing both THC and cannabidiol, as probably effective in treating spasticity, central pain, and urinary dysfunction associated with multiple sclerosis, and dronabinol as probably effective as a treatment for spasticity and central pain associated with multiple sclerosis.[6] Thus, while medical marijuana is not a first-line treatment for Mr Z's chronic pain, it is reasonable to consider medical marijuana as a treatment after other treatments have failed. In general, the evidence supporting the use of marijuana and cannabinoids for other conditions aside from the FDA indications and chronic pain, neuropathic pain, and spasticity resulting from multiple sclerosis is either equivocal or weak.

Marijuana contains numerous cannabinoids. It is not known how individual cannabinoids affect the various diseases currently treated by marijuana. Two of the cannabinoids, dronabinol and nabilone, are available in the United States and can be prescribed. When treating patients for conditions that would otherwise be treated by marijuana itself, it is reasonable to initiate therapy with dronabinol or nabilone. If these are not successful, treatment can be escalated to marijuana itself because it contains numerous pharmacologically active cannabinoids.

Some conditions might respond to cannabinoids not yet available in the United States such as cannabidiol. Under these circumstances, it is reasonable to treat with marijuana itself. A variety of cannabinoids are in development, so new cannabinoids, likely with new FDA indications, should reach the market in the future.

Risks and Benefits of Cannabinoids

Medical marijuana and cannabinoids have health risks and benefits. Mr Z and the physician recommending medical marijuana for him should discuss these risks and benefits thoroughly prior to starting treatment with medical marijuana because many adverse effects may result from either short-term (single-use or sporadic) or long-term use.[45] The acute effects of marijuana include impaired short-

Table 2. Common Cannabis Preparations

Preparations	Description
Marijuana[a]	Dried plant product consisting of leaves, stems, and flowers; typically smoked or vaporized
Hashish	Concentrated resin cake that can be ingested or smoked
Tincture[a]	Cannabinoid liquid extracted from plant; consumed sublingually
Hashish oil	Oil obtained from cannabis plant by solvent extraction; usually smoked or inhaled; butane hash oil (sometimes referred to as "dabs"), for example
Infusion[a]	Plant material mixed with nonvolatile solvents such as butter or cooking oil and ingested

[a] These preparations are available from state-approved medical marijuana dispensaries.

term memory, motor coordination, and judgment. This is especially relevant for driving; short-term use of marijuana doubles the risk of involvement in a motor vehicle crash.[46] Paranoid ideation and psychotic symptoms, albeit rare, may occur in response to high doses of THC. Long-term regular (daily or nearly every day) marijuana use is especially problematic for young people, whose brains continue to develop into their mid-20s.[47] A recent study showed structural brain changes in the nucleus accumbens and the amygdala in occasional marijuana users compared with controls, underscoring the need for additional research into the effects of nonregular marijuana use on the developing brain.[48] Impaired brain development as measured by functional connectivity may contribute to the association between early, regular marijuana use and decline in IQ.[45,49]

Marijuana is potentially addictive, causing significant problems for work, school, and relationships in about 9% of adult and 17% of adolescent users.[50,51] Regular marijuana use is associated with an increased risk of anxiety, depression, and psychotic illness, and marijuana use can worsen the courses of these disorders as well.[52-57] Mr Z has an anxiety disorder for which he takes multiple medications; this anxiety must be monitored closely if medical marijuana pharmacotherapy is used. Functional outcomes are also affected, with regular marijuana use leading to poor school performance, lower income, increased likelihood of requiring socioeconomic assistance, unemployment, criminal behavior, and decreased satisfaction with life.[58-60] The cessation of regular marijuana use is associated with a withdrawal syndrome marked by anxiety, irritability, craving, dysphoria, and insomnia.[61]

Regular marijuana use results in physical problems as well. It is associated with increased incidence of symptoms of chronic bronchitis and increased rates of respiratory tract infections and pneumonia. Preliminary research points to an association between marijuana use and myocardial infarction, stroke, and peripheral vascular disease.[62]

Evaluation of a Patient for Medical Marijuana Certification

Patient requests for medical marijuana are now common in clinical practice. Determining which patients may be appropriate for a medical marijuana certificate (eAppendix in the Supplement) is complicated (Box). Patients administered marijuana should have a condition known to be responsive to marijuana or cannabinoids based on high-quality evidence such as randomized clinical trials. Before receiving marijuana, patients should have undergone adequate trials of other evidence-based treatments. Medical conditions such as major depressive disorder, anxiety disorders, and viral upper respiratory tract infections that may be exacerbated by marijuana should not be present. Patients present to their primary care physicians seeking medical marijuana certification or they may be already using marijuana. Mr Z's case was the latter—he raised the issue with his primary care physician after initiating medical marijuana pharmacotherapy outside of his usual medical care with the assistance of a medical marijuana clinic.

Medical marijuana evaluations should be comprehensive assessments that include risk-benefit discussions. Certifications should only be written by physicians who have thoroughly assessed a patient, know him or her well, and have a full understanding of the patient's debilitating condition requiring treatment. If the certification does not come from the patient's primary care physician or the specialist treating the debilitating condition, it is essential for the certifying physician to communicate with the patient's other health care clinicians in the same manner as any other specialists would be expected to.

The clinical evaluation should start with the patient expressing how they think medical marijuana will be helpful to treat their medical condition. The physician should take a careful history with special focus on previous treatments for the debilitating condition and possible contraindications for medical marijuana such as anxiety disorders, mood disorders, psychotic disorders, and substance use disorders. A thorough risk-benefit discussion should follow, covering both the adverse health effects of marijuana along with the scientific evidence from studies investigating marijuana or cannabinoids as pharmacotherapy for the debilitating condition being treated. It may be useful to provide a context for medical consensus by informing the patient that there currently is little support from major medical organizations for the use of medical marijuana.[63]

If the physician decides to write the certification for medical marijuana, a discussion of marijuana's federal legal status and that state's regulations must follow. According to the US government, marijuana is an illegal drug that is classified as Schedule I under the Controlled Substances Act, meaning that it has no currently accepted medical use and a high potential for abuse.[64] Marijuana's status as a Schedule I substance that is illegal according to the federal government is the reason that physicians cannot prescribe medical marijuana and can only certify its use. Although the US Department of Justice has stated that it plans to leave the issue of medical marijuana to the states and not enforce the federal statute, the federal stance on marijuana still is a cause for concern for some physicians who are considering recommending medical marijuana as a treatment or aligning with medical marijuana dispensaries or treatment centers.

The medical marijuana certification must state the medical condition that the physician believes would be treated effectively with medical marijuana and, in some states, the recommended amount of marijuana needed to treat the condition. For example, a physician in Massachusetts must state the medical condition for

Table 3. Randomized Clinical Trials Beyond Current FDA Indications for Cannabinoids[a]

Source	Drug (Maximum Dose), Route	Control	Sample Size, Experimental Condition/Control	Primary Outcome	Results
Chronic pain					
Skrabek et al,[16] 2008	Nabilone (2 mg) orally	Placebo	n=20 Nabilone; n=20 placebo (fibromyalgia)	VAS	Significant decrease in VAS (−2.04; $P < .02$)
Narang et al,[17] 2008	Dronabinol (20 mg) orally	Placebo	n = 29 Placebo; n = 30 dronabinol, 10 mg; n = 29 dronabinol, 20 mg	Total pain relief at 8 h	Significant increase in Total pain relief, dronabinol conditions (20 mg vs placebo at $P < .01$; 10 mg vs placebo at $P < .05$)
Frank et al,[18] 2008	Dihydrocodeine (240 mg), nabilone (2 mg) orally	Crossover	n=48 Dihydrocodeine followed by nabilone; n=48 nabilone followed by dihydrocodeine (chronic neuropathic pain)	VAS	Dihydrocodeine provided better pain relief than nabilone (6.0; 95% CI, 1.4-10.5; $P=.01$)
Pinsger et al,[19] 2006	Nabilone (1 mg) add-on orally	Placebo	n=30 Crossover	VAS	Significant decrease in VAS ($P < .006$)
Wissel et al,[20] 2006	Nabilone (1 mg) orally	Placebo	n=13 Crossover	11-Point box test (pain rating)	Significant decrease in pain rating ($P < .05$)
Blake et al,[21] 2006	Nabiximols: THC (15 mg)/ cannabidiol (13.5 mg) oromucosal spray	Placebo	n=31 Nabiximols; n=27 placebo	Pain on movement	Significant decrease in pain (−0.95; 95% CI, −1.85 to −0.02, $P=.04$)
Neuropathic pain					
Ellis et al,[22] 2009	Cannabis (1%-8% THC) smoked	Placebo	n=34 Crossover	Change in pain intensity	Significant decrease in pain ($P=.02$)
Abrams et al,[23] 2007	Cannabis (3.56% THC) smoked	Placebo	n=27 Cannabis; n=28 placebo	VAS, percent achieving >30% pain reduction	Significant decrease in pain ($P=.03$); 52% cannabis group vs 24% placebo reported >30% pain reduction ($P=.04$)
Wilsey et al,[24] 2008	Cannabis (7%, THC) smoked	Placebo	n=38 Crossover	VAS	Significant decrease in pain (−0.0035; 95% CI, −0.0063 to −0.0007 ($P=.02$)
Nurmikko et al,[25] 2007	Nabiximols: THC (30 mg)/ cannabidiol (27.5 mg) oromucosal spray	Placebo	n=63 Nabiximols; n=62 placebo	Change in pain intensity (NRS)	Significant decrease in pain ($P=.004$; 95% CI, −1.59 to −0.32)
Berman et al,[26] 2004	Nabiximols: THC (129.6 mg)/ cannabidiol (120 mg) oromucosal spray	Placebo	n=48 Crossover	Mean pain severity	Significant decrease in pain (THC/cannabidiol, −0.58, 95% CI, −0.98 to −0.18, $P=.005$; THC, −0.64, 95% CI, −1.05 to −0.24, $P=.002$)
Multiple sclerosis					
Zajicek et al,[27] 2003, and Freeman et al,[28] 2006	OCE: THC (25 mg), cannabidiol (12.5 mg); THC (25 mg) orally	Placebo	n=211 OCE; n=206 THC; n=213 placebo	Change in spasticity (Ashworth scale)[27]; incontinence episodes[28]	No effect ($P=.40$) on spasticity; decrease in episodes for both OCE and THC ($P=.005$ OCE; $P=.04$ THC)
Zajicek et al,[29] 2012	OCE (THC, 25 mg) orally	Placebo	n=144 OCE; n=135 placebo	Change in muscle stiffness	Significant decrease in muscle stiffness (odds ratio, 2.26; 95% CI, 1.24-4.13; $P=.004$)
Aragona et al,[30] 2009	Nabiximols: THC (27 mg)/ cannabidiol (25 mg) oromucosal spray	Placebo	n=17 Crossover	Psychopathology, cognition (Paced Auditory Serial Addition Test, Symptom Checklist 90-Revised)	No effect (Symptom Checklist 90-Revised, $P=.36$-$.91$; Paced Auditory Serial Addition Test, $P=.39$)
Collin et al,[31] 2007	Nabiximols: THC (129 mg)/ cannabidiol (120 mg) oromucosal spray	Placebo	n=124 nabiximols; n=65 placebo	Change in spasticity (NRS)	Significant decrease in spasticity (−0.52, 95% CI, −1.029 to −0.004, $P=.048$)
Kavia et al,[32] 2010	Nabiximols: THC (129 mg)/ cannabidiol (120 mg) oromucosal spray	Placebo	n=67 Nabiximols; n=68 placebo (overactive bladder)	Incontinence episodes	No difference ($P=.57$)
Vaney et al,[33] 2004	OCE: THC (30 mg) orally	Placebo	n=57 Crossover	Change in spasticity (self-report, frequency of symptoms)	No difference (frequency, $P=.01$; 95% CI, 1.76-4.63)
Ungerleider et al,[34] 1987	THC (7.5 mg) orally	Placebo	n=13 Crossover	Change in spasticity (self-report)	Significant decrease in spasticity ($P < .03$)
Svendsen et al,[35]2004	Dronabinol (10 mg) orally	Placebo	n=24 Crossover (central pain)	Median spontaneous pain intensity (NRS) in last week of treatment	Significant decrease in median spontaneous pain intensity ($P=.02$)
Rog et al,[36] 2005	Nabiximols: THC (129.6 mg)/ cannabidiol (120 mg) oromucosal spray	Placebo	n=34 Nabiximols; n=32 placebo (central pain)	Pain, sleep disturbance (NRS)	Significant decrease in pain ($P=.005$), significant decrease in sleep disturbance ($P=.003$)
Fox et al,[37] 2004	OCE: THC (10 mg) orally	Placebo	n=14 Crossover (upper limb tremors)	Change in tremor index	No significant improvements ($P=.55$)

(continued)

Table 3. Randomized Clinical Trials Beyond Current FDA Indications for Cannabinoids[a] (continued)

Source	Drug (Maximum Dose), Route	Control	Sample Size, Experimental Condition/Control	Primary Outcome	Results
Wade et al,[38] 2004	Nabiximols: THC (129.6 mg)/cannabidiol (120 mg) oromucosal spray	Placebo	n=80 Nabiximols; n=80 placebo	VAS, most troublesome symptom	No significant improvements (*P*=.12); significant decrease in spasticity (−22.79; 95% CI, −35.52 to −10.07; *P*=.001)
Killestein et al,[39] 2002	Dronabinol (5 mg); OCE: THC (5 mg) orally	Placebo	n=16 Crossover (spasticity)	Change in spasticity (Ashworth scale)	No significant improvements
Parkinson disease					
Carroll et al,[40] 2004	OCE: THC (10 mg) orally	Placebo	n=19 Crossover (levodopa-induced dyskinesia)	Change in Unified Parkinson Disease Rating Scale dyskinesia score	No significant improvements (*P*=.09)
Crohn disease					
Naftali et al,[41] 2013	Cannabis: THC (115 mg) smoked	Placebo	n=11 Cannabis; n=10 placebo	Induction of remission (Crohn's Disease Activity Index score <150 after 8 wk)	No significant difference (*P*=.43)
Amyotrophic lateral sclerosis					
Weber et al,[42] 2010	Sesame oil: THC (10 mg) orally	Placebo	n=27 Crossover (cramps)	VAS, cramp intensity	No significant difference (0.24; 95% CI, −0.32 to 0.81; *P*=.38)
Neurogenic symptoms					
Wade et al,[43] 2003	Nabiximols: THC (120 mg)/cannabidiol (120 mg); THC (120 mg); cannabidiol (120 mg) oromucosal spray	Placebo	n=24 Crossover (n=18 multiple sclerosis, n=4 spinal cord injury, n=1 brachial plexus damage, n=1 limb amputation due to neurofibromatosis)	VAS	Significant decrease in pain with cannabidiol, THC; significant decrease in spasm with THC, cannabidiol, THC; significant decrease in spasticity with THC (*P* < .05)

Abbreviations: NRS, numerical rating scale; OCE, oral cannabis extract; THC, δ-9-tetrahydrocannabinol; VAS, visual analog scale.

[a] Randomized clinical trials are graded as level 2 evidence (level 1 includes systematic reviews of randomized clinical trials) according to the Oxford Centre for Evidence-Based Medicine 2011 levels of evidence.[44]

Box. Practical Considerations for Medical Marijuana

An appropriate medical marijuana candidate should have

1. A debilitating medical condition that data from randomized clinical trials suggest would respond to medical marijuana pharmacotherapy, such as nausea and vomiting associated with cancer chemotherapy, anorexia from wasting illnesses like AIDS, chronic pain, neuropathic pain, or spasticity associated with multiple sclerosis
2. Multiple failed trials of first- and second-line pharmacotherapies for these conditions
3. A failed trial of an US Food and Drug Administration–approved cannabinoid (dronabinol or nabilone)
4. No active substance use disorder or psychotic disorder or no unstable mood disorder or anxiety disorder
5. Residence in a state with medical marijuana laws and meets requirements of these laws

which medical marijuana is the treatment and a recommended amount per 60-day period. The amount should be estimated from the route of administration and the anticipated number of treatments per day. Patients receive advice on which marijuana species or strain to purchase and dosing and administration from the dispensary, which differs from the manner in which prescriptions of FDA-approved medications are specified. Once the patient begins medical marijuana pharmacotherapy, close follow-up with the physician is imperative, as it would be with any medications having significant adverse effects and abuse potential. The patient should be seen in follow-up within a month's time with additional telephone contact as necessary. Patients may be followed up monthly for 3 months, with further follow-up determined by the patient's clinical situation.

Patients requesting medical marijuana may already be taking opioids for chronic pain. In these instances, narcotics contracts may be in effect as an additional safeguard to mitigate the potential for abuse. Physicians recommending medical marijuana to these patients can use the narcotics contract to their advantage because in addition to the patient specifying where her or she will fill narcotics prescriptions, the patient can be asked to specify where he or she will obtain marijuana. The contract may also stipulate that random urine drug screening results positive for substances other than the prescribed opioids and recommended medical marijuana may be grounds for discharge.

Recommendations for Mr Z

Mr Z has had extensive treatment for his chronic pain over an extended period. He was referred to a variety of health care practitioners from multiple disciplines for his chronic pain. His clinicians used multiple modalities including multiple medications resulting in limited pain control before Mr Z considered medical marijuana as a treatment for his chronic pain. Overall, it appears that his treatment course was reasonable and likely a result of thoughtful collaboration between Mr Z and his primary care physician.

Mr Z appears to meet all but 1 of the criteria listed in the Box: he has a debilitating condition that data suggest may respond to marijuana, he has had multiple failed treatment trials of first- and second-line medications, his anxiety disorder appears to be clinically stable, and he resides in Massachusetts, a state with an active medical marijuana law. Only a previous trial of an FDA-approved synthetic cannabinoid was not done.

The course of treatment may have been altered if Mr Z had a discussion with his primary care physician prior to obtaining a medical marijuana certification. Mr Z and his primary care physician may have opted for a trial of one of the FDA-approved cannabinoids dronabinol or nabilone, despite Mr Z's medical history of anxiety. This anxiety, which appears to be clinically stable now, should have been monitored closely and medications adjusted accordingly. A trial of dronabinol still makes sense at this time because it would allow for the use of an FDA-approved (and thus likely safer in terms of composition and quality control) medication under the close supervision of Mr Z's primary care physician. He went to a specialty medical marijuana clinic, however, and 4 to 6 weeks elapsed without follow-up prior to Mr Z notifying his primary care physician that he was taking a medication with potentially significant adverse effects. This lack of follow-up is one of the major concerns about specialty medical marijuana clinics that often certify large numbers of new patients for medical marijuana each day. Regardless of where patients receives certification, they must be followed up closely by the certifying physician because of the potential for significant adverse effects, and the certifying physician should communicate with all other health care professionals delivering care that may be affected by a patient's use of medical marijuana.

Initiation of medical marijuana pharmacotherapy by patients before consulting their physician is becoming more common as additional states enact medical marijuana laws. These patients, along with others contemplating medical marijuana pharmacotherapy for their own medical problems, will likely continue to comprise a growing proportion of physicians' patients. Although the medical marijuana landscape will change as novel cannabinoids are approved for additional medical indications, the question of the role of medical marijuana as a pharmacotherapy in medicine persists. Physicians must educate patients about proper use of medical marijuana to ensure that only appropriate patients use it and limit the numbers of patients inappropriately using this treatment.

Questions and Discussion

QUESTION One of my patients said that he found one strain that worked better than others for chronic pain. Do different strains of marijuana that are available at the dispensaries have different effects?

DR HILL Different strains may have different effects because of their THC and cannabidiol content and differing ratios of THC to cannabidiol in the strain.[65] Just as different people may respond differently to the same drug, some may report better results from a particular strain than other people might. Medical marijuana dispensaries may make claims about certain strains being useful for particular illnesses, but those claims are theoretical or anecdotal in nature and may be made with marketing in mind.

QUESTION As it stands right now in Massachusetts, can any physician write a medical marijuana certification? What if a physician wants to write a certification for a patient to use medical marijuana for a medical condition that is not specified by the laws?

DR HILL Yes, in Massachusetts and in every other state with medical marijuana laws, any physician can write a medical marijuana certification for any medical indication they choose, provided the physician has completed the requisite training.[66] This training usually consists of a few hours of continuing medical education activities related to the risks and benefits of marijuana.

QUESTION In Massachusetts, the state allows the certifying physician to stipulate how much medical marijuana a patient may possess in a 60-day period, and the recommended 60-day supply of marijuana is 10 oz. Is that an unnecessarily high amount? How does one determine the correct dose of marijuana to use?

DR HILL The 60-day supply of 10 oz is a recommended amount, but this may be exceeded if a physician provides a rationale for it in writing. According to the World Health Organization, a standard marijuana cigarette contains as little as 0.5 g of marijuana, so a 60-day supply of 10 oz is up to 560 marijuana cigarettes or almost 10 per day.[67] Thus, based on the estimate of 0.5 g per marijuana cigarette, a patient requiring the marijuana equivalent of 1 to 2 marijuana cigarettes per day would need 0.5 to 1 oz of marijuana per month. Although no one wants to keep a medication away from someone who might benefit from it, this 60-day supply estimate appears to be another example in which marijuana policy is ahead of the science. Circumstances in which people need 10 oz per 60 days to make tinctures or other forms of marijuana-based medicines should be rare. There are little data available for optimal dosing of marijuana for particular medical conditions.[68] Dosing differs based on the route of administration, which determines the pharmacology of the various cannabinoids in marijuana as well as the processes of absorption and metabolism.[69] Dosing is determined for an individual patient using a titration process. The marijuana dose is increased until the desired clinical effect—pain relief in Mr Z's case—is achieved. The necessary dose is highly dependent on the THC concentration of the marijuana being used. If using a vaporizer to heat the plant material into a vapor for inhalation, a patient should start with a single inhalation of marijuana vapor and monitor for effect. If 20 minutes pass with no effect, the patient may take 2 inhalations consecutively, then monitor for another 20 minutes. Inhalations are spaced out because numerous consecutive inhalations may result in missing the window of optimal treatment effect. This titration process must be repeated if a different strain of marijuana is used.

QUESTION What is the state of insurance coverage on some of these FDA-approved cannabinoid medications and medical marijuana?

DR HILL No insurance companies cover medical marijuana, and there has not been any movement toward increased coverage by insurance companies. The cannabinoids dronabinol and nabilone are expensive medications that are covered by insurance companies for their FDA indications as well as for other indications on a case-by-case basis.

Conclusions

Medical marijuana use is now common in clinical practice, and it is critical for physicians to understand both the scientific rationale and the practical implications of medical marijuana laws. Medical marijuana and cannabinoids have significant health risks as well as many potential medical benefits. While medical marijuana has been at times a controversial and contentious issue, physicians have a responsibility to provide evidence-based guidance on this important issue.

- With more states enacting medical marijuana laws, it is imperative for physicians to understand both the scientific rationale and the practical implications of medical marijuana laws.
- Aside from nausea and appetite stimulation, indications for which there are 2 FDA-approved cannabinoids (dronabinol and nabilone), chronic pain, neuropathic pain, and spasticity associated with multiple sclerosis are the indications for medical marijuana supported by high-quality evidence.
- Medical marijuana and cannabinoids have significant potential health risks, such as addiction and worsening of psychiatric illnesses such as some anxiety disorders, mood disorders, psychotic disorders, and substance use disorders, as well as many potential medical benefits.
- Evaluations to determine the appropriateness of medical marijuana for a patient should be comprehensive assessments that revolve around risk-benefit discussions.

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Fast Facts on Osteogenesis Imperfecta

Definition
Osteogenesis imperfecta (OI) is a genetic disorder characterized by bones that break easily, often from little or no apparent cause. A classification system of different types of OI is commonly used to help describe how severely a person with OI is affected. For example, a person may have just a few or as many as several hundred fractures in a lifetime.

Prevalence
While the number of people affected with OI in the United States is unknown, the best estimate suggests a minimum of 20,000 and possibly as many as 50,000.

Diagnosis
OI is caused by genetic defects that affect the body's ability to make strong bones. In dominant (classical) OI, a person has too little type I collagen or a poor quality of type I collagen due to a mutation in one of the type I collagen genes. Collagen is the major protein of the body's connective tissue. It is part of the framework that bones are formed around. In recessive OI, mutations in other genes interfere with collagen production. The result in all cases is fragile bones that break easily.

It is often, though not always, possible to diagnose OI based solely on clinical features. Clinical geneticists can also perform biochemical (collagen) or molecular (DNA) tests that can help confirm a diagnosis of OI in some situations. These tests generally require several weeks before results are known. Both the collagen biopsy test and DNA test are thought to detect almost 90% of all type I collagen mutations.

A positive type I collagen study confirms the diagnosis of dominant OI, but a negative result could mean that either a collagen type I mutation is present but was not detected or the patient has a form of the disorder that is not associated with type 1 collagen mutations or the patient has a recessive form of OI. Therefore, a negative type I collagen study does not rule out OI. When a type I collagen mutation is not found, other DNA tests to check for recessive forms are available.

Clinical Features
The characteristic features of OI vary greatly from person to person, even among people with the same type of OI, and even within the same family. Not all characteristics are evident in each case. The majority of cases of OI (possibly 85-90 %) are caused by a dominant mutation in a gene coding for type I collagen (Types I, II, III, and IV in the following list). Types VII and VIII are newly identified forms that are inherited in a

recessive manner. The genes causing these two types have been identified. Types V and VI do not have a type 1 collagen mutation, but the genes causing them have not yet been identified. The general features of each known type of OI are as follows:

Type I

- Most common and mildest type of OI.
- Bones fracture easily. Most fractures occur before puberty.
- Normal or near-normal stature.
- Loose joints and muscle weakness.
- Sclera (whites of the eyes) usually have a blue, purple, or gray tint.
- Triangular face.
- Tendency toward spinal curvature.
- Bone deformity absent or minimal.
- Brittle teeth possible.
- Hearing loss possible, often beginning in early 20s or 30s.
- Collagen structure is normal, but the amount is less than normal.

Type II

- Most severe form.
- Frequently lethal at or shortly after birth, often due to respiratory problems.
- Numerous fractures and severe bone deformity.
- Small stature with underdeveloped lungs.
- Tinted sclera.
- Collagen improperly formed.

Type III

- Bones fracture easily. Fractures often present at birth, and x-rays may reveal healed fractures that occurred before birth.
- Short stature.
- Sclera have a blue, purple, or gray tint.
- Loose joints and poor muscle development in arms and legs.
- Barrel-shaped rib cage.
- Triangular face.
- Spinal curvature.
- Respiratory problems possible.
- Bone deformity, often severe.
- Brittle teeth possible.
- Hearing loss possible.
- Collagen improperly formed.

Type IV

- Between Type I and Type III in severity.
- Bones fracture easily. Most fractures occur before puberty.
- Shorter than average stature.
- Sclera are white or near-white (i.e. normal in color).
- Mild to moderate bone deformity.
- Tendency toward spinal curvature.
- Barrel-shaped rib cage.
- Triangular face.
- Brittle teeth possible.
- Hearing loss possible.
- Collagen improperly formed.

By studying the appearance of OI bone under the microscope, investigators noticed that some people who are clinically within the Type IV group had a distinct pattern to their bone. When they reviewed the full medical history of these people, they found that groups had other features in common. They named these groups Types V and VI OI. **The mutations causing these forms of OI have not been identified, but people in these two groups do not have mutations in the type I collagen genes.**

Type V

- Clinically similar to Type IV in appearance and symptoms of OI.
- A dense band seen on x-rays adjacent to the growth plate of the long bones.
- Unusually large calluses (hypertrophic calluses) at the sites of fractures or surgical procedures. (A callus is an area of new bone that is laid down at the fracture site as part of the healing process.)
- Calcification of the membrane between the radius and ulna (the bones of the forearm). This leads to restriction of forearm rotation.
- White sclera.
- Normal teeth.
- Bone has a "mesh-like" appearance when viewed under the microscope.
- Dominant inheritance pattern

Type VI

- Clinically similar to Type IV in appearance and symptoms of OI.
- The alkaline phosphatase (an enzyme linked to bone formation) activity level is slightly elevated in OI Type VI. This can be determined by a blood test.
- Bone has a distinctive "fish-scale" appearance when viewed under the microscope.
- Diagnosed by bone biopsy.
- Whether this form is inherited in a dominant or recessive manner is unknown, but researchers believe the mode of inheritance is most likely recessive.
- Eight people with this type of OI have been identified.

Recessive Forms of OI

After years of research, two forms of OI that are inherited in a recessive manner were discovered in 2006. Both types are caused by genes that affect collagen formation. These forms provide information for people who have severe or moderately severe OI but who do not have a primary collagen mutation.

Type VII

- The first described cases resemble Type IV OI in many aspects of appearance and symptoms.
- In other instances the appearance and symptoms are similar to Type II lethal OI, except infants had white sclera, a small head and a round face.
- Short stature.
- Short humerus (arm bone) and short femur (upper leg bone)
- Coxa vera is common (the acutely angled femur head affects the hip socket).
- Results from recessive inheritance of a mutation to the CRTAP (cartilage-associated protein) gene. Partial function of CRTAP leads to moderate symptoms while total absence of CRTAP was lethal in all 4 identified cases.

Type VIII

- Resembles lethal Type II or Type III OI in appearance and symptoms except that infants have white sclera.
- Severe growth deficiency.
- Extreme skeletal under mineralization.
- Caused by a deficiency of P3H1 (Prolyl 3-hydroxylase 1) due to a mutation to the LEPRE1 gene

Inheritance Factors
Most cases of OI (85-90%) are caused by a dominant genetic defect. This means that only one copy of the mutation carrying gene is necessary for the child to have OI. Children who have the dominant form of OI have either inherited it from a parent or, when the parent does not have OI, as a spontaneous mutation.

Approximately 10-15 percent of cases of OI are the result of a recessive mutation. In this situation, the parents do not have OI, but both carry the mutation in their genes. To inherit recessive OI the child must receive a copy of the mutation from both parents.

When a child has recessive OI, there is a 25 percent chance per pregnancy that the parents will have another child with OI. Siblings of a person with a recessive form of OI have a 50 percent chance of being a carrier of the recessive gene. DNA testing is available to help parents and siblings determine if they are carriers of this type of gene mutation.

A person with a form of OI caused by a dominant mutation has a 50 percent chance of passing on the disorder to each of his or her children. If one parent has OI because of a recessive mutation, 100 percent of their children will be carriers of the recessive OI mutation. Whether any of these children will have OI will depend on their inheritance from the other parent. Genetic counselors can help people with OI and their family members further understand OI genetics and the possibility of recurrence, and assist in prenatal diagnosis for those who wish to exercise that option. For more information on OI inheritance, see the OI Foundation fact sheet titled "Genetics."

Treatment
There is not yet a cure for OI. Treatment is directed toward preventing or controlling the symptoms, maximizing independent mobility, and developing optimal bone mass and muscle strength. Care of fractures, extensive surgical and dental procedures, and physical therapy are often recommended for people with OI. Use of wheelchairs, braces, and other mobility aids is common, particularly (although not exclusively) among people with more severe types of OI.

People with OI are encouraged to exercise as much as possible to promote muscle and bone strength, which can help prevent fractures. Swimming and water therapy are common exercise choices for people with OI, as water allows independent movement with little risk of fracture. For those who are able, walking (with or without mobility aids) is excellent exercise. People with OI should consult their physician and/or physical therapist to discuss appropriate and safe exercise.

Children and adults with OI will also benefit from maintaining a healthy weight, eating a nutritious diet, and avoiding activities such as smoking, excessive alcohol and caffeine consumption, and taking steroid medications — all of which may deplete bone and make bones more fragile. For more information on nutrition, see the OI Foundation fact sheet titled "Nutrition."

A surgical procedure called "rodding" is frequently considered for people with OI. This treatment involves inserting metal rods through the length of the long bones to strengthen them and prevent and/or correct deformities. For more information, see the OI Foundation's fact sheet on "Rodding Surgery."

Several medications and other treatments are being explored for their potential use to treat OI. These include growth hormone treatment, treatment with intravenous and oral drugs called bisphosphonates, an injected drug called teriparatide (for adults only) and gene therapies. It is not clear if people with recessive OI will respond in the same manner as people with dominant OI to these treatments. The OI Foundation provides current information on research studies, as well as information about participating in clinical trials.

Prognosis
The prognosis for a person with OI varies greatly depending on the number and severity of symptoms. Respiratory failure is the most frequent cause of death for people with OI, followed by accidental trauma. Despite numerous fractures, restricted physical activity, and short stature, most adults and children with OI lead productive and successful lives.

They attend school, develop friendships and other relationships, have careers, raise families, participate in sports and other recreational activities and are active members of their communities.

For more information about osteogenesis imperfecta contact:

Osteogenesis Imperfecta Foundation
804 W. Diamond Avenue, Suite 210, Gaithersburg, MD 20878
Tel: 844-889-9579 or 301-947-0083
Fax: 301-947-0456
Internet: www.oif.org
E-mail: bonelink@oif.org

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Osteoporosis and Related Bone Diseases ~ National Resource Center
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