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The Effects of Cannabis Among Adults With Chronic Pain and an Overview of General Harms

A Systematic Review

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Background: Cannabis is increasingly available for the treatment of chronic pain, yet its efficacy remains uncertain.

Purpose: To review the benefits of plant-based cannabis preparations for treating chronic pain in adults and the harms of cannabis use in chronic pain and general adult populations.

Data Sources: MEDLINE, Cochrane Database of Systematic Reviews, and several other sources from database inception to March 2017.

Study Selection: Intervention trials and observational studies, published in English, involving adults using plant-based cannabis preparations that reported pain, quality of life, or adverse effect outcomes.

Data Extraction: Two investigators independently abstracted study characteristics and assessed study quality, and the investigator group graded the overall strength of evidence using standard criteria.

Data Synthesis: From 27 chronic pain trials, there is low-strength evidence that cannabis alleviates neuropathic pain but insufficient evidence in other pain populations. According to 11 systematic reviews and 32 primary studies, harms in general population studies include increased risk for motor vehicle accidents, psychotic symptoms, and short-term cognitive impairment. Although adverse pulmonary effects were not seen in younger populations, evidence on most other long-term physical harms, in heavy or long-term cannabis users, or in older populations is insufficient.

Limitation: Few methodologically rigorous trials; the cannabis formulations studied may not reflect commercially available products; and limited applicability to older, chronically ill populations and patients who use cannabis heavily.

Conclusion: Limited evidence suggests that cannabis may alleviate neuropathic pain in some patients, but insufficient evidence exists for other types of chronic pain. Among general populations, limited evidence suggests that cannabis is associated with an increased risk for adverse mental health effects.

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The use of medicinal cannabis has become increasingly accepted in the United States and globally (1, 2). Eight states and the District of Columbia have legalized cannabis for recreational purposes, and 28 states and the District of Columbia have legalized it for medical purposes (3). Between 45% and 80% of persons who seek medical cannabis do so for pain management (4, 5). Among patients who are prescribed long-term opioid therapy for pain, up to 39% are also using cannabis (6, 7). Physicians will increasingly need to engage in evidence-based discussions with their patients about the potential benefits and harms of cannabis use. However, little comprehensive and critically appraised information exists about the benefits and harms of using cannabis to treat chronic pain. The objectives of this systematic review were to assess the efficacy of cannabis for treating chronic pain and to provide a broad overview of the short- and long-term physical and mental health effects of cannabis use in chronic pain and general patient populations.

METHODS

Topic Development

This article is part of a larger report commissioned by the Veterans Health Administration (8). A protocol describing the review plan was posted to a publicly accessible Web site before the study began (9).

Data Sources and Searches

We searched MEDLINE, Embase, PubMed, PsycINFO, Evidence-Based Medicine Reviews (including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, Health Technology Assessments, and Cochrane Central Register of Controlled Trials), and gray literature sources from database inception through February 2016. We updated this search specifically for new randomized controlled trials (RCTs) and systematic reviews in March 2017. We obtained additional articles from systematic reviews, reference lists, and expert recommendations. We also searched for ongoing, unpublished, or re-

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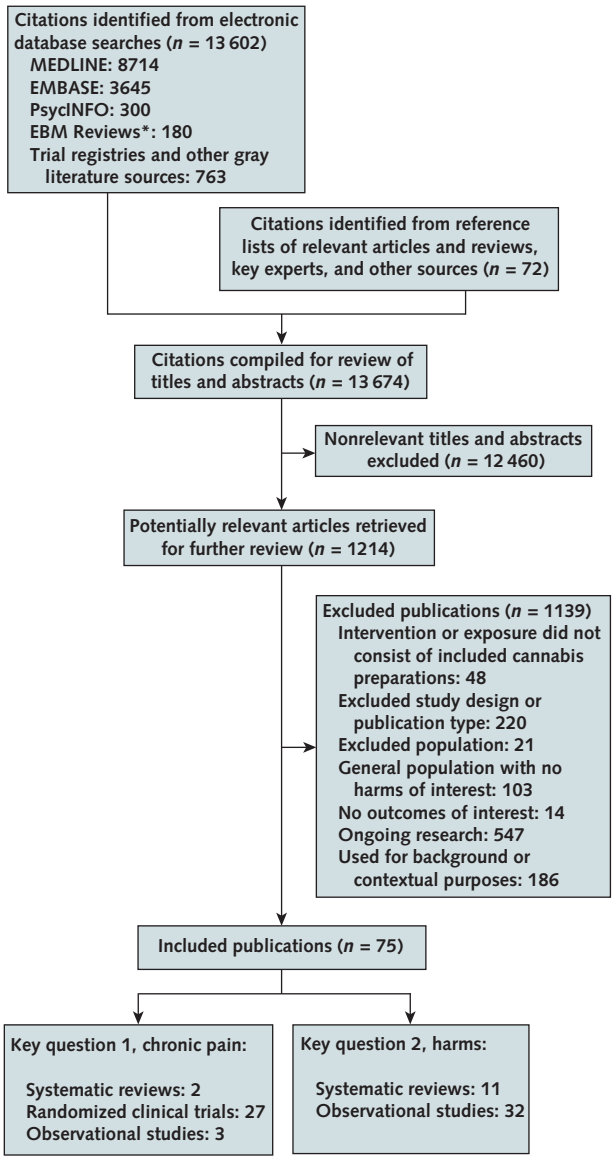
Figure. Literature flow diagram.



* Includes Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, Health Technology Assessments, and Cochrane Central Register of Controlled Trials.

cently completed studies on ClinicalTrials.gov, the International Clinical Trials Registry Platform, the ISRCTN Registry, National Institutes of Health RePORTER, and the Agency for Healthcare Research and Quality Grants On-Line Database. Supplement 1 (available at Annals .org) provides details on the search strategy, which we developed in consultation with a research librarian.

Study Selection

We included English-language studies assessing the effect on nonpregnant adults of plant-based cannabis preparations or whole-plant extracts, such as nabiximols, a nonsynthetic pharmaceutical product with a standard composition and dose (oromucosal spray delivering tetrahydrocannabinol [THC], 2.7 mg, and cannabidiol, 2.5 mg). We did not include synthesized, pharmaceutically prepared cannabinoids, such as dronabinol or nabilone, because they are not available in dispensaries, and the efficacy of synthetic cannabinoid preparations for chronic pain was examined in 2 recent reviews (10, 11). We broadly defined plant-based cannabis preparations to include any preparation of the cannabis plant itself (for example, cannabis cigarettes and oils) or cannabis plant extracts to capture the variety of products available in U.S. dispensaries (12).

To address the efficacy of cannabis for treating chronic pain, we included controlled clinical trials and cohort studies. This review focuses specifically on pain outcomes, although our larger report and search were designed to include other outcomes, such as sleep and quality of life (8). Because data about harms in the general population might be applicable to chronic pain populations, we examined harms broadly and reported whether the data were derived from studies of the general population or populations with chronic pain. To capture potential cannabis-related harms that may be of interest to clinicians and patients, but whose prevalence has not been well-characterized in larger-scale observational studies, we also included case series and descriptive studies of "emerging harms." Supplement 2 provides the criteria we used for study selection.

We searched for primary literature and systematic reviews; we dual-reviewed 5% of identified abstracts and all of the included full-text articles to ensure reliability. Disagreements were resolved by a third reviewer. Given the broad scope of this review, we summarized data from existing systematic reviews. We included only reviews that clearly reported their search strategy, reported inclusion and exclusion criteria, and appraised the internal validity of the included trials (13). We prioritized the most recent reviews and those with the broadest scope. In addition, we included individual studies that met inclusion criteria and either were published after the end search date of the included review or were not included in a prior systematic review.

Data Extraction and Quality Assessment

For all reports, 2 investigators abstracted details of study design, setting, patient population, intervention, and follow-up, as well as important co-interventions, health outcomes, health care use, and harms.

Two reviewers independently assessed each trial (including those that were identified from a prior systematic review) as having low, high, or unclear risk of bias (ROB) for the pain outcome using a tool developed by the Cochrane Collaboration (14). Disagreements were resolved by consensus. To assess the ROB of observational studies for the pain outcome, we considered potential sources of bias most relevant to this evidence base and adapted existing assessment tools (15, 16) (Supplement 3).

Data Synthesis and Analysis

For the subgroup of neuropathic pain studies, we did a study-level meta-analysis of the proportion of

patients experiencing clinically significant (≥30%) pain relief (Supplement 4), and we used the profile-likelihood random-effects model (17) to combine risk ratios. We assessed the magnitude of statistical heterogeneity among the studies using the standard Cochran chi-square test, the I^2 statistic (18). All analyses were done using Stata/IC, version 13.1 (StataCorp). Clinical heterogeneity, variation in outcomes reported, and the small number of trials precluded meta-analysis for other subgroups and outcomes, so we reported these qualitatively. After group discussion, we classified the overall strength of evidence for each outcome as high, moderate, low, or insufficient on the basis of the consistency, coherence, and applicability of the body of evidence as well as the internal validity of individual studies (19, 20).

Role of the Funding Source

The U.S. Department of Veterans Affairs Quality Enhancement Research Initiative supported the review but had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review, and approval of the manuscript; or decision to submit the manuscript for publication.

RESULTS

After reviewing 13 674 titles and abstracts, we included 13 systematic reviews and 62 primary studies (Figure). Table 1 provides study-level details and the ROB rating for each of the chronic pain trials. Table 2 summarizes findings, including the ROB rating, by pain subgroup. Table 3 summarizes the harms in both pain and general populations. Supplement 5 provides additional study-level data from pain studies not included in prior reviews and from studies on general harms.

Effects of Cannabis in Treating Chronic Pain

We identified 22 RCTs (21–42) from 2 recently published systematic reviews (10, 11) and an additional 8 studies (5 RCTs [43–47] and 3 cohort studies [48–50]) that met our inclusion criteria and were not included in prior reviews. The primary methods of continuous pain assessment were a visual analogue scale from 0 to 100 mm and a numerical rating scale (NRS) from 0 to 10 (where 0 indicated no pain and 10 indicated the worst possible pain). Some of the studies identified the proportion of participants who had clinically significant improvements in pain intensity (defined as ≥30% reduction, or approximately 2 points on the NRS and 20 mm on the visual analogue scale).

Neuropathic Pain

Thirteen trials examined the effects of cannabis-based preparations on neuropathic pain (Table 1). Participants had central or peripheral neuropathic pain related to various health conditions. Of these studies, 11 were rated as having low ROB (24, 27, 28, 30, 31, 33, 36, 39, 40, 43, 47), 1 as having unclear ROB (26), and 1 as having high ROB (35). Overall, we found low-strength evidence that cannabis may alleviate neuropathic pain in some patients (Table 2). Studies generally did not find clinically significant between-group differences on continuous pain scales, but a higher proportion of intervention patients had clinically significant pain relief up to several months later. Across 9 studies, intervention patients were more likely to report at least 30% improvement in pain (risk ratio, 1.43 [95% CI, 1.16 to 1.88]; I^2 = 38.6%; P = 0.111) (Supplement 4). Most studies were small, few reported outcomes beyond 2 to 3 weeks, and none reported long-term outcomes.

In the largest RCT, 246 patients with peripheral neuropathic pain self-titrated nabiximols up to a maximum dosage of 24 sprays per day or received a placebo (27). Those who completed the study (79 in the nabiximols group and 94 in the placebo group) and responded positively to the intervention had a significant decrease in pain (odds ratio, 1.97 [CI, 1.05 to 3.70]). However, among all participants, including those who did not have an intervention response, the reduction in the NRS pain score did not reach clinical or statistical significance. The second-largest RCT with low ROB included 55 patients with HIV-associated sensory neuropathy who were randomly assigned to smoke either 3.56% THC cigarettes or a placebo 3 times per day for 5 days. Among those who completed the study, 52% (n = 13) of the treatment group had a clinically significant reduction in pain compared with 24% (n = 6) of the placebo group (33).

A 1-year prospective cohort study (n = 431) of patients with nociceptive and neuropathic chronic noncancer pain provides information about long-term treatment effects (50). Cannabis users had a reduction in average pain intensity (using a visual analogue scale from 0 to 10) that was stable across 4 time points over 1 year, but the change was small and not clinically significant (0.92 [CI, 0.62 to 1.23]).

Multiple Sclerosis

Nine trials examined the effects of cannabis-based preparations on pain among patients with multiple sclerosis (MS) (Table 1). Participants generally had intractable body pain or neuropathic pain related to a clinically confirmed diagnosis of MS. Three of these trials were rated as having low ROB (29, 42, 44), 5 as having unclear ROB (22, 37, 38, 41, 45), and 1 as having high ROB (32). Overall, we found insufficient evidence to characterize the effects of cannabis on pain in patients with MS (Table 2) because of the small number of methodologically rigorous studies, inconsistent findings across studies, lack of long-term outcomes, and small number of patients included in the trials.

Of the 3 low-ROB trials, 1 found small but clinically nonsignificant alleviation of pain at 5 weeks, 1 found

Table 1. Characteristics and Findings of RCTs on Cannabis Extracts for Treating Chronic Pain*

Trial	Pain Type	*N*	Intervention Formulation; Dosage; Study Design	Duration
Abrams et al, 2007 (33)	Neuropathic sensory, HIV-associated	55	Smoked THC, 4%; 1 cigarette/d (0.9 g)	12 d
Berman et al, 2004 (30)	Neuropathic brachial plexus avulsion	48	Nabiximols (THC oromucosal spray); ≤48 sprays/d; crossover	2 wk (no washout)
Ellis et al, 2009 (31)	Neuropathic sensory, HIV-associated	34	Smoked THC, started at 4% and adjusted as necessary; 4 smoking sessions/d; crossover	5 d (2-wk washout)
Lynch et al, 2014 (24)	Neuropathic chemotherapy-induced	18	Nabiximols; ≤12 sprays/d	4 wk (2-wk washout)
Notcutt et al, 2004 (43)	Mostly neuropathic; 47% MS	34	Sublingual spray delivering 2.5-mg THC, 2.5-mg CBD, or 2.5 mg each; 1 to 8 sprays/d	8 wk
Nurmikko et al, 2007 (35)	Neuropathic pain with allodynia	125	Nabiximols; ≤48 sprays/d	5 wk
Selvarajah et al, 2010 (26)	Neuropathic diabetic peripheral	30	Nabiximols; maximum unclear	12 wk
Serpell et al, 2014 (27)	Neuropathic peripheral with allodynia	246	Nabiximols; ≤24 sprays/d	15 wk
Wallace et al, 2015 (36)	Neuropathic diabetic peripheral	16	Vaporized THC, 7%, 4%, or 1%; 4 h observation at each dose; crossover	4 h (2-wk washout)
Ware et al, 2010 (39)	Neuropathic, postsurgical or posttraumatic	23	Smoked THC, 2.5%, 6%, or 9.4%; crossover	5 d (9-d washout)
Wilsey et al, 2008 (28)	Neuropathic	38	Smoked THC, 3.5% or 7%; 9 puffs; crossover	6 h (3- to 21-d washout)
Wilsey et al, 2013 (40)	Neuropathic, peripheral	39	Vaporized THC, 1.29% or 3.53%; 4 puffs at 1 h after baseline, 4 to 8 puffs at 3 h; crossover	6 h (3- to 7-d washout)
Wilsey et al, 2016 (47)	Neuropathic, spinal cord injury	42	Vaporized THC, 2.9% or 6.7%; 400 mg using Foltin Puff Procedure at 8 to 12 puffs over 240 min, adaptable dose design	8 h
Collin et al, 2010 (22)	MS	337	Nabiximols; ≤24 sprays/d	14 wk
Corey-Bloom et al, 2012 (37)	MS	37	Smoked THC, 4%; one 800-mg cigarette	3 d (11-d washout)
Langford et al, 2013 (41)	MS	339	Nabiximols; ≤12 sprays/d	14 wk
Rog et al, 2005 (42)	MS	66	Nabiximols; ≤48 sprays/d	5 wk
Van Amerongen et al, 2017 (45)	MS	24	Orally ingested THC, 99% (EPC002A, Namisol); 1.5 or 5 mg 3 times/d	2 wk
Wade et al, 2003 (44)	MS (67%)	24	Pump-action sublingual spray delivering 2.5-mg THC, 2.5-mg CBD, or 2.5 mg each; ≤120 mg/d; crossover	2 wk (no washout)
Wade et al, 2004 (38)	MS	160	Nabiximols; ≤48 sprays/d	6 wk
Zajicek et al, 2003 (32)	MS	657	THC/CBD capsules; ≤25 mg/d	15 wk
Zajicek et al, 2012 (29)	MS	279	THC/CBD capsules; ≤25 mg/d	12 wk
Johnson et al, 2010 (23)	Cancer	60 58	Nabiximols; ≤48 sprays/d 2.7 mg THC oromucosal spray; ≤48 sprays/d	2 wk 2 wk
Noyes et al, 1975 (34)	Cancer	10	THC capsules; 5, 10, or 15 mg; crossover	1 d (no washout)
Portenoy et al, 2012 (25)	Cancer	360	Nabiximols; 1 to 4, 6 to 10, or 11 to 16 sprays/d	9 wk
de Vries et al, 2016 (46)	Abdominal pain (includes chronic pancreatitis, postsurgical pain)	65	Orally ingested THC, 99% (EPC002A, Namisol); step-up phase: days 1 to 5, 3 mg 3 times/d; days 6 to 10, 5 mg 3 times/d; stable dose phase: days 11 to 52, 8 mg 3 times/d	7 wk
Blake et al, 2006 (21)	Rheumatoid arthritis	58	Nabiximols; ≤48 sprays/d	5 wk

C = control; CBD = cannabidiol; MS = multiple sclerosis; NRS = numerical rating scale; NS = not significant; RCT = randomized controlled trial; T = treatment; THC = tetrahydrocannabinol; VAS = visual analogue scale.
* Study findings other than those specified (proportion of patients with ≥30% pain reduction and mean between-group difference in change from baseline in pain score) are not shown.
† NRS score range, 0–10 points
‡ VAS score range, 0–100 mm.

no difference in outcome, and a larger trial found that more intervention patients reported relief from body pain at 12 weeks (28.0% vs. 18.7%; $P = 0.028$) (29).

Cancer Pain

Three trials ($n = 547$) examined the effects of cannabis-based preparations on pain among patients with cancer-related pain (Table 1). Participants had

Table 1–Continued

Patients Achieving ≥30% Pain Reduction, T vs. C, *n/N (%)*	Mean Difference (T − C) in Change From Baseline		Overall Risk of Bias
	NRS Pain Scale, *points†*	VAS Pain Scale, *mm‡*	
13/25 vs. 6/25 (52.0 vs. 24.0)	–	–	Low
–	–	–	Low
–	–	–	Low
–	–	–	Low
THC: 9/24 vs. NR (37.5 vs. NR) CBD: 3/24 vs. NR (12.5 vs. NR) THC+CBD: 9/24 vs. NR (37.5 vs. NR)	–	–	Low
16/63 vs. 9/62 (25.4 vs. 14.5)	–	−8.03 (−13.83 to −2.23)	High
8/15 vs. 9/14 (53.3 vs. 64.3)	–	9.50 (−11.30 to 27.80)	Unclear
34/123 vs. 19/117 (27.6 vs. 16.2)	−0.34 (−0.79 to 0.11)	−2.86 (−7.22 to 1.50)	Low
1% THC: 10/16 vs. 10/16 (62.5 vs. 62.5) 4% THC: 12/16 vs. 10/16 (75.0 vs. 62.5) 7% THC: 13/16 vs. 10/16 (81.3 vs. 62.5)	–	–	Low
–	–	–	Low
3.5% THC: 4/36 vs. 2/33 (11.1 vs. 6.1) 7% THC: 0/34 vs. 2/33 (0.0 vs. 6.1)	–	–	Low
1.29% THC: 21/37 vs. 10/38 (56.8 vs. 26.3) 3.53% THC: 22/36 vs. 10/38 (61.1 vs. 26.3)	–	1.29% THC: −11 3.53% THC: −10	Low
2.9% THC: 18/26 vs. 8/18 (69.2 vs. 44.4) 6.7% THC: 31/35 vs. 8/18 (88.6 vs. 44.4)	–	–	Low
–	–	–	Unclear
–	–	–	Unclear
84/167 vs. 77/172 (50.3 vs. 44.8)	0.17 (−0.62 to 0.29)	–	Unclear
–	−1.25 (−2.11 to −0.39)	−6.58 (−12.97 to −0.19)	Low
–	Week 2: −1.09 (−1.98 to −0.20) (P = 0.018) Week 4: −0.85 (−1.74 to −0.04) (P = 0.061)	–	Unclear
–	–	Baseline: 30.1 (SD, 17.8) 2nd week of each group: CBD: 54.8 (SD, 22.6; P < 0.05) THC: 54.6 (SD, 27.4; P < 0.05) THC+CBD: 51.3 (SD, 27.0; P = NS) Placebo: 44.5 (SD, 22.7)	Low
–	–	–	Unclear
–	–	–	High
–	–	–	Low
23/53 vs. 12/56 (43.4 vs. 21.4) 12/52 vs. 12/56 (23.1 vs. 21.4)	−0.32 (−0.86 to 0.22) −0.67 (−1.21 to −0.14)	–	Unclear
–	–	–	High
1 to 4 sprays: 30/91 vs. 24/91 (33.0 vs. 26.4) 6 to 10 sprays: 26/87 vs. 24/91 (29.9 vs. 26.4) 11 to 16 sprays: 22/90 vs. 24/91 (24.4 vs. 26.4)	1 to 4 sprays: −0.75 (−1.28 to −0.22) 6 to 10 sprays: −0.36 (−0.89 to 0.18) 11 to 16 sprays: −0.09 (−0.62 to 0.44)	–	Unclear
–	−1.6 (SD, 1.78) vs. −1.9 (SD, 2.18) (P = 0.92)	–	High
–	–	−3 (−18 to 9)	Unclear

moderate to severe intractable pain related to a clinically confirmed diagnosis of cancer, although the exact cause of pain was unspecified. Two studies were rated as having unclear ROB (23, 25), and 1 study was rated as having high ROB (34). Overall, these trials provide insufficient evidence because of the small number of studies and their methodological limitations, including high attrition, exclusion of patients with variable pain

scores, use of some nonvalidated measures, and lack of clarity about randomization and blinding procedures (Table 2).

Other or Mixed Pain Conditions

Two trials (21, 46) and 3 cohort studies (48–50) examined the effects of cannabis-based preparations on pain among patients with other or mixed pain conditions, including fibromyalgia, rheumatoid arthritis, and inflammatory abdominal pain (Table 1). One trial was rated as having unclear ROB (21), and 1 was rated as having high ROB (46). One observational study was rated as having low ROB (50), and the other 2 were at high ROB (48, 49). Overall, evidence was insufficient because of the inconsistent results and the paucity of methodologically rigorous studies (Table 2). Limitations of individual studies include lack of follow-up, inadequate allocation concealment, selection bias, high attrition, and lack of inclusion of nonnaive cannabis users.

Harms of Cannabis Use

General Adverse Events Among Patients With Chronic Pain

Data from 2 systematic reviews examining cannabis for chronic pain suggest that cannabis use may be associated with a higher risk for short-term adverse effects (10, 11). However, the rates of adverse events did not significantly differ between groups in the additional pain trials we reviewed. Although most reported adverse events were mild, such as dizziness and lightheadedness, some were serious, such as suicide attempts, paranoia, and agitation (Table 3). An additional prospective observational study did not detect a difference in serious adverse events between a cannabis group (12.5% ± 1.5% THC, 2.5 g/d) and control group (adjusted incidence rate ratio for event, 1.08 [CI, 0.57 to 2.04]) (50).

Medical Harms in the General Population

Moderate-strength evidence from 2 well-designed cohort studies (52, 53) suggests that low levels of cannabis smoking do not adversely affect lung function over about 20 years in young adults, but some evidence suggests that daily use may cause adverse pulmonary effects over an extended period (Table 3). Because of methodological limitations, including a lack of longitudinal exposure measurement and potential recall bias, 2 studies (55, 56) give insufficient evidence about the effect of cannabis use on the risk for cardiovascular events. A meta-analysis (59) of 9 case–control studies provides low-strength evidence that cannabis use is not associated with an increased risk for head and neck cancer (odds ratio, 1.02 [CI, 0.91 to 1.14]). Another meta-analysis (57) of 6 case–control studies provides low-strength evidence of no elevated risk for lung cancer with cannabis use (odds ratio, 0.96 [CI, 0.66 to 1.38]). Insufficient evidence exists about the effects of cannabis on testicular (60) or transitional cell cancer (61) (Table 3).

Mental Health and Cognitive Harms in the General Population

One systematic review (64) and 8 studies (65–71, 74) consistently found an association between cannabis use (specifically related to THC content) and the development of psychotic symptoms (low strength of evidence) (Table 3). The association was seen both in populations at risk for psychotic spectrum disorders and in average-risk populations. The possibility that cannabis contributes directly to the development of psychotic symptoms is supported but not proved by biological plausibility, evidence of a dose–response relationship, prospective cohort studies, and small experimental studies.

A systematic review of 6 longitudinal studies provides low-strength evidence of an association between cannabis use and exacerbation of manic symptoms in patients with known bipolar disorder. The review found higher incidence of new-onset mania symptoms among populations without a diagnosis of bipolar disorder (pooled odds ratio, 2.97 [CI, 1.80 to 4.90]) (63).

Two systematic reviews of studies in general populations provide moderate-strength evidence that active, long-term cannabis use is associated with small to moderate negative effects on many domains of cognitive function, but evidence on cognitive effects in past users is insufficient (72, 73).

A meta-analysis of 4 epidemiologic studies found significantly increased odds of suicide death (pooled odds ratio, 2.56 [CI, 1.25 to 5.27]) with any cannabis use. However, our confidence in the findings is limited by inconsistent findings among included studies, inadequate assessment of exposure, and inadequate adjustment for confounding among the studies (insufficient strength of evidence) (62, 64).

Motor Vehicle Accidents in the General Population

Moderate-strength evidence from a recent meta-analysis of 21 multinational observational studies suggests that acute cannabis intoxication is associated with a moderate increase in collision risk (odds ratio, 1.35 [CI, 1.15 to 1.61]) (51).

Other Harms in the General Population

Long-term cannabis use has been associated with a severe form of cyclic vomiting called cannabinoid hyperemesis syndrome (75–82). Serious infectious diseases, including aspergillosis (83–86) and tuberculosis, have also been associated with smoking cannabis (87, 88). Evidence of the effects of cannabis on violent behavior is mixed (89, 90). Cannabis use was associated with incident cannabis use disorder (adjusted odds ratio, 9.5 [CI, 6.4 to 14.1]) in a large (N = 34 653) prospective cohort study (91). In a cross-sectional study of patients receiving daily opioid therapy for chronic pain, the prevalence of cannabis use disorder was 2.4%, and 13.2% reported having used cannabis in the past 30 days. The prevalence of cannabis use disorder among the subgroup of current users, however, was not reported (92).

DISCUSSION

In our systematic review, we found limited evidence on the potential benefits and harms of cannabis use in chronic pain populations (Tables 2 and 3). We found low-strength evidence that cannabis preparations with precisely defined THC–cannabidiol content (most in a 1:1 to 2:1 ratio) may alleviate neuropathic pain but insufficient evidence in populations with other types of pain. Most studies are small, many have methodological flaws, and the long-term effects are unclear given the brief follow-up of most studies.

Among neuropathic pain studies, we found a discrepancy between continuous and dichotomous pain outcomes. Possible interpretations are that cannabis is simply not consistently effective or that, although cannabis may not have clinically important effects on average, subgroups of patients may experience large effects. We did not find data to clarify which subgroups of patients are more or less likely to benefit.

Our findings complement several recent reviews. In 1 review, the authors concluded that low- to moderate-strength evidence supports the efficacy of cannabis in chronic pain populations, limited mainly to those with MS or neuropathic pain. However, a separate group reviewed and reanalyzed a similar set of published articles and determined that insufficient to low-strength evidence supports the use of cannabis to treat chronic noncancer pain (11). A recent report from the National Academies of Sciences, Engineering, and Medicine examined the biological and clinical effects of cannabis across a broad range of indications and concluded that there is substantial evidence of benefit for patients with

Table 2. Summary of Evidence of the Benefits of Cannabis in Populations With Chronic Pain

Pain Type	Studies	Findings	Strength of Evidence*	Comments
Neuropathic	11 low-ROB studies; combined $N = 593$: 4 of smoked THC (28, 31, 33, 39); combined $N = 150$ 3 of vaporized THC (36, 40, 47); combined $N = 97$ 3 of nabiximols (24, 27, 42); combined $N = 312$ 1 of oromucosal spray delivering THC or THC+CBD (43); $N = 34$ 1 unclear-ROB study of nabiximols (26); $N = 30$ 1 high-ROB trial (35); $N = 125$	Studies did not find a clinically significant between-group difference on continuous pain scales, but a higher proportion of intervention patients had clinically significant pain relief up to several months later In a meta-analysis of 9 studies, intervention patients were more likely to report ≥30% improvement in pain (combined RR, 1.43 [95% CI, 1.16–1.88]; $I^2 = 38.6\%$; $P = 0.111$)	Low	Few patients enrolled in most low-ROB studies; inconsistent results; marked differences among studies in dosing and delivery mechanism; brevity of study duration; low applicability to formulations available in dispensaries
MS	3 low-ROB trials; combined $N = 369$; 24–279 per study: 1 of THC/CBD capsules (29) 1 of nabiximols (42) 1 of sublingual spray delivering THC, CBD, or THC+CBD (44) 5 unclear-ROB trials; combined $N = 897$; 24–339 per study: 3 of nabiximols (22, 38, 41) 1 of smoked THC (37) 1 of orally ingested THC (EPC002A) (45) 1 high-ROB trial of THC/CBD capsules (32), $N = 657$	No consistent clinically significant effects on pain	Insufficient	Few methodologically rigorous studies; inconsistent results; little long-term data; inclusion of pain as a secondary outcome; low applicability to formulations available in dispensaries
Cancer	2 unclear-ROB trials; combined $N = 596$; 177–360 per study: 1 of nabiximols (25) 1 of nabiximols and THC oromucosal spray in separate groups (23) 1 high-ROB trial of THC capsules (34), $N = 10$	No consistent clinically significant effects on pain	Insufficient	Small number of studies; methodological flaws, including high attrition, lack of clarity about randomization and blinding procedures, and use of nonstandard outcome measures
Other/mixed	1 unclear-ROB trial of nabiximols for rheumatoid arthritis (21); $N = 58$ 1 high-ROB trial of EPC002A (orally ingested 99% THC) for abdominal pain (46); $N = 65$ 3 cohort studies of mixed forms of cannabis (smoked, orally ingested, vaporized) for fibromyalgia (48), inflammatory bowel disease/Crohn disease (49), and nociceptive and/or neuropathic pain (50)	Small improvements in pain	Insufficient	Larger observational study had high attrition

CBD = cannabidiol; MS = multiple sclerosis; ROB = risk of bias; RR = risk ratio; THC = tetrahydrocannabinol.
* Based on the consistency, coherence, and applicability of the body of evidence, as well as the internal validity of individual studies. The strength of evidence is classified as follows: high = further research is very unlikely to change our confidence in the estimate of effect; moderate = further research is likely to have an important effect on our confidence in the estimate of effect and may change the estimate; low = further research is very likely to have an important effect on our confidence in the estimate of effect and is likely to change the estimate; insufficient = any estimate of effect is very uncertain.

chronic pain. Although the overall conclusions seem to differ from our findings, the authors stipulated that the clinical improvements were modest and limited to neuropathic pain (93), and they underscored the urgent need for better research clarifying the effects of cannabis. Our review augments this report by using a systematic approach on a more focused topic (chronic pain and harms) as well as standard terminology for describing the strength of the body of evidence (19).

Even though we did not find strong, consistent evidence of benefit, clinicians will still need to engage in evidence-based discussions with patients managing chronic pain who are using or requesting to use cannabis. Therefore, clinicians must understand what is known and unknown about its potential harms.

We found moderate-strength evidence that light to moderate cannabis smoking does not adversely affect lung function over about 20 years. However, the limited data on the effects of heavy use suggest a possible deleterious effect on lung function over time (52, 53). We found low-strength evidence that light to moderate cannabis use is not associated with lung cancer or head and neck cancer diagnoses independent of tobacco use, but the data are limited to case–control studies and do not address heavy use. We found insufficient evidence examining whether cannabis use is associated with cardiovascular events over the long term.

Cannabis use has potentially serious mental health and adverse cognitive effects, although data are insufficient to characterize the magnitude of risk or in whom the risk is highest. Cannabis seems to be associated with at least small, short-term deleterious effects on cognition in active users, but long-term effects in past users are uncertain. We found a consistent association between cannabis use and the development of psychotic symptoms over the short and long term. A large prospective cohort study in the United States found that cannabis use was associated with a substantial risk for incident cannabis use disorder and a smaller risk for incident alcohol and other substance use disorders (91). Finally, we found some adverse effects that seem to be related to cannabis use and are important for clinicians to know (for example, infectious disease complications, cannabis hyperemesis syndrome, and violent behavior), but the incidence of these effects has not been well-characterized.

Evidence-based nonpharmacologic and nonopioid pharmacologic therapies are the preferred initial methods for treating chronic pain (94). Clinicians may struggle with treating chronic pain in patients who have not responded to first-line treatment, and cannabis may be perceived as a safer strategy in these patients (95). The scale and severity of adverse events, including death, seen with opioids have not been described with cannabis in the literature (although less research is available on cannabis than on opioids) (95). However, no studies have directly compared cannabis with opioids, and no good-quality data exist on how cannabis use affects opioid use and opioid-related adverse effects. Cross-sectional studies suggest an association between co-occurring cannabis use and adverse opioid-related events (that is, misuse or more refills) among patients prescribed opioids (6, 7, 96–98). By contrast, an open-label study found that pain scores and opioid use decreased over 6 months in participants with chronic pain who initiated cannabis treatment, although confidence in the findings is limited by the large number of participants lost to follow-up (99).

The applicability of study data to current practice is limited in several ways. The patient populations in many studies were highly selected, and some studies included a run-in period after which patients who did not respond were excluded from further study. The data on effectiveness largely come from trials examining formulations with precisely defined THC and cannabidiol content, which differs from the reality of clinical practice. Even though dispensaries are increasingly labeling products' content, discrepancies often exist between labeled and measured content (100). Moreover, the dose of THC assessed in many of the studies is substantially lower than that in products commonly available in dispensaries (for example, 2.5 mg of THC vs. a range of 15 to 200 mg) (100).

Finally, the evidence base on harms is limited because studies include relatively few patients who are older, are chronically ill, or have a history of heavy and prolonged cannabis use. In observational studies, the exact dose of exposure to cannabis was rarely known because of recall bias, and the potency (that is, in estimates of cannabis cigarettes smoked per day) was impossible to assess. On the other hand, this imprecision probably mirrors the uncertainty clinicians will face in discussing benefits and harms with their patients.

Our approach to synthesizing the literature also has limitations. Given the broad scope of our review, we relied on existing systematic reviews to identify the best available evidence. However, we also comprehensively searched for and included newer primary studies, included only good-quality systematic reviews, and reassessed the quality of primary pain studies included in prior reviews. We excluded studies of synthetic prescription cannabinoids, in part because these were included in recent reviews and are not available in cannabis dispensaries. Regardless, inclusion of these studies would not have changed our overall findings because so few studies were available, they were methodologically flawed, and they had very small sample sizes. We examined harms in both chronic pain and general populations, although the degree to which harms data in general populations apply to patients with chronic pain is uncertain. Finally, we focused specifically on pain outcomes in patients with chronic pain, but we acknowledge that other outcomes are also important in the treatment of chronic pain. In our larger report, we describe low-strength evidence that cannabis may reduce spasticity and improve sleep in patients with MS. We found insufficient evidence regarding the effects of cannabis on these outcomes in other patient populations and regarding effects on quality of life and functional status in any population (8).

Virtually no conclusive information exists about the benefits of cannabis in chronic pain populations, and

limited information is available on harms, so methodologically strong research in almost any area is likely to add to the strength of evidence (see **Table 8** of **Supplement 5** for a list of important research gaps and **Table 9** of **Supplement 5** for a list of ongoing studies). Of note, many of the studies we found were done in European countries, suggesting that there may be fewer barriers to conducting cannabis-related research there than in the United States, where barriers are substantial.

Although cannabis is increasingly available for medical and recreational use, little methodologically rigorous evidence examines its effects in patients with chronic pain. Limited evidence suggests that it may alleviate neuropathic pain, but evidence in other pain

Table 3. Summary of Evidence for the Harms of Cannabis in Chronic Pain and General Adult Populations

Outcome	Studies	Findings	Strength of Evidence*	Comments
General AEs	2 systematic reviews (10, 11) and 1 observational study of chronic pain (50)	Cannabis-based treatments associated with higher overall risk for short-term, nonserious AEs.	–	Consistent findings except for serious AE
Motor vehicle accidents	Meta-analysis (51) of 21 observational studies; combined *N* = 239 739	Increase in collision risk (OR, 1.35 [95% CI, 1.15–1.61]).	Moderate	Small but significant increase in risk seen consistently across numerous sensitivity analyses and after adjustment in meta-regression analyses
Medical AEs				
Pulmonary function	2 low-ROB prospective cohort studies (52, 53) with 20–32 y follow-up; combined *N* = 6053 1 systematic review (54) of 5 observational studies (3 cohort, 2 cross-sectional); combined *N* = 851	In young adults, low levels of cannabis smoking did not adversely affect lung function over about 20 y A previous meta-analysis of 5 studies found no increased risk for pulmonary adverse effects (OR, 0.80 [95% CI, 0.46–1.39])	Young adults: moderate Older adults: no evidence	2 well-done prospective cohort studies, but limited information about effects of heavy use and no information in older or multimorbid populations
Cardiovascular effects	2 high-ROB observational studies: 1 case–crossover (55), *N* = 3882; 1 cohort (56), *N* = 2097	Cannabis use at time of MI not associated with mortality after mean 12.7-y follow-up, but longitudinal use not assessed Risk of MI within 1 h of cannabis use significantly elevated compared with periods of nonuse, but finding may be inflated by recall bias (OR, 4.8 [95% CI, 2.9–9.5])	Insufficient	Recall bias; inadequate controlling for confounders; lack of longitudinal exposure data
Lung cancer	1 patient-level meta-analysis (57) of 6 case–control studies; combined *N* = 2150 1 high-ROB cohort study (58); *N* = 49 231	Meta-analysis found no association between light cannabis use and lung cancer	Low	Recall bias; mostly light users, few heavy users; large cohort study had no information about exposure over time
Head/neck/oral cancer	Meta-analysis (59) of 9 case–control studies; combined *N* = 5732	No association between cannabis use and cancer (OR, 1.02 [95% CI, 0.91–1.14]); generally consistent across studies and no evidence of dose-response	Low	Imprecise exposure measurement with potential recall bias; ever-use among studies ranged from 1%–83%
Testicular cancer	Meta-analysis (60) of 3 high-ROB case–control studies; combined *N* = 719	Increased cancer risk for weekly users compared with never-users seen with nonseminoma cancer but not seminoma cancer (OR, 1.92 [95% CI, 1.35–2.72])	Insufficient	Potential confounding from recall bias and tobacco use
Transitional cell cancer	1 high-ROB VA case–control study (61); *N* = 52	Risk of cancer with >40 joint-years cannabis use vs. none (OR, 3.4; unadjusted *P* = 0.012).	Insufficient	1 very small case–control study with several methodological flaws
Mental health AEs				
Suicidal behaviors	1 meta-analysis (62) of 4 observational studies	Significantly increased odds of suicide with any cannabis use (OR, 2.56 [95% CI, 1.25–5.27])	Insufficient	Inconsistent results; inadequate exposure ascertainment and adjustment for confounding
Mania	1 meta-analysis (63) of 2 prospective studies	Increased incidence of new-onset mania symptoms among populations without diagnosis of bipolar disorder (OR, 2.97 [95% CI, 1.80–4.90])	Low	Small number of studies; exposure not well-characterized in 1 study, but other was large community-based cohort study also showing dose–response effect
Psychosis	1 systematic review (64) 8 studies (65-71, 74) including patients without psychotic symptoms at baseline: 3 low ROB, 3 medium ROB, 2 high ROB	History of cannabis use associated with increased risk for psychotic symptoms	Low	Consistent evidence from large observational studies and some evidence of increased risk with higher levels of use; consistent with data from small experimental studies suggesting risk of acute psychosis in some patients; magnitude of risk unclear and not specifically studied in chronic pain populations
Cognitive effects	2 systematic reviews (72, 73)	Active long-term cannabis use associated with small negative effects on all aspects of cognition Mixed, inconsistent findings on long-term effects in past users.	Moderate Insufficient (past use)	Consistent data from large number of studies on effects on active long-term use, but inconsistent findings from smaller number of studies regarding effects in those who abstained and no data available specifically in chronic pain populations

AE = adverse effect; MI = myocardial infarction; OR = odds ratio; ROB = risk of bias; VA = U.S. Department of Veterans Affairs.
* Based on the consistency, coherence, and applicability of the body of evidence, as well as the internal validity of individual studies. The strength of evidence is classified as follows: high = further research is very unlikely to change our confidence in the estimate of effect; moderate = further research is likely to have an important effect on our confidence in the estimate of effect and may change the estimate; low = further research is very likely to have an important effect on our confidence in the estimate of effect and is likely to change the estimate; insufficient = any estimate of effect is very uncertain.

populations is insufficient. Evidence is also limited on its association with an increased risk for nonserious short-term adverse effects and potentially serious mental health adverse effects, such as psychosis.

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References

1. **Ryan-Ibarra S, Induni M, Ewing D.** Prevalence of medical marijuana use in California, 2012. Drug Alcohol Rev. 2015;34:141-6. [PMID: 25255903] doi:10.1111/dar.12207
2. **Adler JN, Colbert JA.** Clinical decisions. Medicinal use of marijuana–polling results. N Engl J Med. 2013;368:e30. [PMID: 23718175] doi:10.1056/NEJMclde1305159
3. **National Conference of State Legislatures.** Marijuana Overview. Accessed at www.ncsl.org/research/civil-and-criminal-justice/marijuana-overview.aspx on 19 May 2017.
4. **Bonn-Miller MO, Boden MT, Bucossi MM, Babson KA.** Self-reported cannabis use characteristics, patterns and helpfulness among medical cannabis users. Am J Drug Alcohol Abuse. 2014;40:23-30. [PMID: 24205805] doi:10.3109/00952990.2013.821477
5. **Ilgen MA, Bohnert K, Kleinberg F, Jannausch M, Bohnert AS, Walton M, et al.** Characteristics of adults seeking medical marijuana certification. Drug Alcohol Depend. 2013;132:654-9. [PMID: 23683791] doi:10.1016/j.drugalcdep.2013.04.019
6. **Degenhardt L, Lintzeris N, Campbell G, Bruno R, Cohen M, Farrell M, et al.** Experience of adjunctive cannabis use for chronic non-cancer pain: findings from the Pain and Opioids IN Treatment (POINT) study. Drug Alcohol Depend. 2015;147:144-50. [PMID: 25533893] doi:10.1016/j.drugalcdep.2014.11.031
7. **Reisfield GM, Wasan AD, Jamison RN.** The prevalence and significance of cannabis use in patients prescribed chronic opioid therapy: a review of the extant literature. Pain Med. 2009;10:1434-41. [PMID: 19793342] doi:10.1111/j.1526-4637.2009.00726.x
8. **Kansagara D, O'Neil M, Nugent S, Freeman M, Low A, Kondo K, et al.** Benefits and harms of cannabis in chronic pain or post-traumatic stress disorder: a systematic review. Washington, DC: U.S. Department of Veterans Affairs; 2016. VA ESP project no. 05-225.
9. **Kansagara D, O'Neil ME, Morasco B, Madore S, Elven C, Freeman M, et al.** Cannabis for the management of symptoms of chronic pain and/or PTSD. Accessed at www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42016033623 on 19 May 2017.
10. **Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, et al.** Cannabinoids for medical use: a systematic review and meta-analysis. JAMA. 2015;313:2456-73. [PMID: 26103030] doi:10.1001/jama.2015.6358
11. **Butler M, Krebs E, Sunderlin B, Kane R.** Medical cannabis for non-cancer pain: a systematic review. Accessed at www.health.state.mn.us/topics/cannabis/intractable/medicalcannabisreport.pdf on 19 May 2017.
12. **Oregon Health Authority.** Medical Marijuana Rules and Statutes. Accessed at https://public.health.oregon.gov/DiseasesConditions/ChronicDisease/MedicalMarijuanaProgram/Pages/legal.aspx on 19 May 2017.
13. **Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al.** Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007;7:10. [PMID: 17302989]
14. **Higgins JPT, Altman DG, Sterne JAC, on behalf of the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group.** Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0. The Cochrane Collaboration; 2011. Accessed at www.handbook.cochrane.org on 19 May 2017.
15. **Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al.** The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Accessed at www.ohri.ca/programs/clinical_epidemiology/oxford.asp on 19 May 2017.
16. **Viswanathan M, Ansari M, Berkman N, Chang S, Hartling L, McPheeters L, et al.** Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. Rockville: Agency for Healthcare Research and Quality; 2012. AHRQ publication no. 12-EHC047-EF. (Methods Guide for Comparative Effectiveness Reviews). Accessed at www.effectivehealthcare.ahrq.gov/ehc/products/322/998/MethodsGuideforCERs_Viswanathan_IndividualStudies.pdf on 19 May 2017.
17. **Hardy RJ, Thompson SG.** A likelihood approach to meta-analysis with random effects. Stat Med. 1996;15:619-29. [PMID: 8731004]
18. **Higgins JP, Thompson SG, Deeks JJ, Altman DG.** Measuring inconsistency in meta-analyses. BMJ. 2003;327:557-60. [PMID: 12958120]
19. **Berkman N, Lohr K, Ansari M, McDonagh M, Balk E, Whitlock E, et al.** Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update. Rockville: Agency for Healthcare Research and Quality; 2013. AHRQ publication no. 13(14)-EHC130-EF. (Methods Guide for Comparative Effectiveness Reviews). Accessed at www.effectivehealthcare.ahrq.gov/ehc/products/457/1752/methods-guidance-grading-evidence-131118.pdf on 19 May 2017.
20. **Atkins D, Chang S, Gartlehner G, Buckley D, Whitlock E, Berliner E, et al.** Assessing the Applicability of Studies When Comparing Medical Interventions. Rockville: Agency for Healthcare Research and Quality; 2013. AHRQ publication no. 11-EHC019-EF. (Methods Guide for Comparative Effectiveness Reviews). Accessed at www.effectivehealthcare.ahrq.gov/ehc/products/272/603/Methods%20Guide--Atkins--01-03-2011KM.pdf on 19 May 2017.
21. **Blake DR, Robson P, Ho M, Jubb RW, McCabe CS.** Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. Rheumatology (Oxford). 2006;45:50-2. [PMID: 16282192]
22. **Collin C, Ehler E, Waberzinek G, Alsindi Z, Davies P, Powell K, et al.** A double-blind, randomized, placebo-controlled, parallel-group study of Sativex, in subjects with symptoms of spasticity due to

multiple sclerosis. Neurol Res. 2010;32:451-9. [PMID: 20307378] doi: 10.1179/016164109X12590518685660
23. **Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, Fallon MT.** Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. J Pain Symptom Manage. 2010;39:167-79. [PMID: 19896326] doi:10.1016/j.jpainsymman.2009.06.008
24. **Lynch ME, Cesar-Rittenberg P, Hohmann AG.** A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. J Pain Symptom Manage. 2014;47:166-73. [PMID: 23742737] doi:10.1016/j.jpainsymman.2013.02.018
25. **Portenoy RK, Ganae-Motan ED, Allende S, Yanagihara R, Shaiova L, Weinstein S, et al.** Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. J Pain. 2012;13:438-49. [PMID: 22483680] doi:10.1016/j.jpain.2012.01.003
26. **Selvarajah D, Gandhi R, Emery CJ, Tesfaye S.** Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor. Diabetes Care. 2010;33:128-30. [PMID: 19808912] doi:10.2337/dc09-1029
27. **Serpell M, Ratcliffe S, Hovorka J, Schofield M, Taylor L, Lauder H, et al.** A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. Eur J Pain. 2014;18:999-1012. [PMID: 24420962] doi:10.1002/j.1532-2149.2013.00445.x
28. **Wilsey B, Marcotte T, Tsodikov A, Millman J, Bentley H, Gouaux B, et al.** A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. J Pain. 2008;9:506-21. [PMID: 18403272] doi:10.1016/j.jpain.2007.12.010
29. **Zajicek JP, Hobart JC, Slade A, Barnes D, Mattison PG; MUSEC Research Group.** Multiple sclerosis and extract of cannabis: results of the MUSEC trial. J Neurol Neurosurg Psychiatry. 2012;83:1125-32. [PMID: 22791906] doi:10.1136/jnnp-2012-302468
30. **Berman JS, Symonds C, Birch R.** Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. Pain. 2004;112:299-306. [PMID: 15561385]
31. **Ellis RJ, Toperoff W, Vaida F, van den Brande G, Gonzales J, Gouaux B, et al.** Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacology. 2009;34:672-80. [PMID: 18688212] doi:10.1038/npp.2008.120
32. **Zajicek J, Fox P, Sanders H, Wright D, Vickery J, Nunn A, et al; UK MS Research Group.** Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. Lancet. 2003;362:1517-26. [PMID: 14615106]
33. **Abrams DI, Jay CA, Shade SB, Vizoso H, Reda H, Press S, et al.** Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology. 2007;68:515-21. [PMID: 17296917]
34. **Noyes R Jr, Brunk SF, Avery DA, Canter AC.** The analgesic properties of delta-9-tetrahydrocannabinol and codeine. Clin Pharmacol Ther. 1975;18:84-9. [PMID: 50159]
35. **Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D.** Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. Pain. 2007;133:210-20. [PMID: 17997224]
36. **Wallace MS, Marcotte TD, Umlauf A, Gouaux B, Atkinson JH.** Efficacy of Inhaled Cannabis on Painful Diabetic Neuropathy. J Pain. 2015;16:616-27. [PMID: 25843054] doi:10.1016/j.jpain.2015.03.008
37. **Corey-Bloom J, Wolfson T, Gamst A, Jin S, Marcotte TD, Bentley H, et al.** Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. CMAJ. 2012;184:1143-50. [PMID: 22586334] doi:10.1503/cmaj.110837
38. **Wade DT, Makela P, Robson P, House H, Bateman C.** Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. Mult Scler. 2004;10:434-41. [PMID: 15327042]
39. **Ware MA, Wang T, Shapiro S, Robinson A, Ducruet T, Huynh T, et al.** Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ. 2010;182:E694-701. [PMID: 20805210] doi: 10.1503/cmaj.091414
40. **Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H.** Low-dose vaporized cannabis significantly improves neuropathic pain. J Pain. 2013;14:136-48. [PMID: 23237736] doi:10.1016/j.jpain.2012.10.009
41. **Langford RM, Mares J, Novotna A, Vachova M, Novakova I, Notcutt W, et al.** A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. J Neurol. 2013;260:984-97. [PMID: 23180178] doi:10.1007/s00415-012-6739-4
42. **Rog DJ, Nurmikko TJ, Friede T, Young CA.** Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology. 2005;65:812-9. [PMID: 16186518]
43. **Notcutt W, Price M, Miller R, Newport S, Phillips C, Simmons S, et al.** Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 'N of 1' studies. Anaesthesia. 2004;59:440-52. [PMID: 15096238]
44. **Wade DT, Robson P, House H, Makela P, Aram J.** A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. Clin Rehabil. 2003;17:21-9. [PMID: 12617376]
45. **van Amerongen G, Kanhai K, Baakman AC, Heuberger J, Klaassen E, Beumer TL, et al.** Effects on spasticity and neuropathic pain of an oral formulation of Δ9-tetrahydrocannabinol in patients with progressive multiple sclerosis. Clin Ther. 2017. [PMID: 28189366] doi: 10.1016/j.clinthera.2017.01.016
46. **de Vries M, van Rijckevorsel DC, Vissers KC, Wilder-Smith OH, van Goor H; Pain and Nociception Neuroscience Research Group.** Tetrahydrocannabinol does not reduce pain in patients with chronic abdominal pain in a phase 2 placebo-controlled study. Clin Gastroenterol Hepatol. 2016. [PMID: 27720917] doi:10.1016/j.cgh.2016.09.147
47. **Wilsey B, Marcotte TD, Deutsch R, Zhao H, Prasad H, Phan A.** An exploratory human laboratory experiment evaluating vaporized cannabis in the treatment of neuropathic pain from spinal cord injury and disease. J Pain. 2016;17:982-1000. [PMID: 27286745] doi:10.1016/j.jpain.2016.05.010
48. **Fiz J, Durán M, Capellà D, Carbonell J, Farré M.** Cannabis use in patients with fibromyalgia: effect on symptoms relief and health-related quality of life. PLoS One. 2011;6:e18440. [PMID: 21533029] doi:10.1371/journal.pone.0018440
49. **Storr M, Devlin S, Kaplan GG, Panaccione R, Andrews CN.** Cannabis use provides symptom relief in patients with inflammatory bowel disease but is associated with worse disease prognosis in patients with Crohn's disease. Inflamm Bowel Dis. 2014;20:472-80. [PMID: 24407485] doi:10.1097/01.MIB.0000440982.79036.d6
50. **Ware MA, Wang T, Shapiro S, Collet JP; COMPASS study team.** Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS). J Pain. 2015;16:1233-42. [PMID: 26385201] doi:10.1016/j.jpain.2015.07.014
51. **Rogeberg O, Elvik R.** The effects of cannabis intoxication on motor vehicle collision revisited and revised. Addiction. 2016;111:1348-59. [PMID: 26878835] doi:10.1111/add.13347
52. **Hancox RJ, Poulton R, Ely M, Welch D, Taylor DR, McLachlan CR, et al.** Effects of cannabis on lung function: a population-based cohort study. Eur Respir J. 2010;35:42-7. [PMID: 19679602] doi:10.1183/09031936.00065009
53. **Pletcher MJ, Vittinghoff E, Kalhan R, Richman J, Safford M, Sidney S, et al.** Association between marijuana exposure and pulmonary function over 20 years. JAMA. 2012;307:173-81. [PMID: 22235088] doi:10.1001/jama.2011.1961
54. **Tetrault JM, Crothers K, Moore BA, Mehra R, Concato J, Fiellin DA.** Effects of marijuana smoking on pulmonary function and respi-

ratory complications: a systematic review. Arch Intern Med. 2007; 167:221-8. [PMID: 17296876]
55. **Mittleman MA, Lewis RA, Maclure M, Sherwood JB, Muller JE.** Triggering myocardial infarction by marijuana. Circulation. 2001; 103:2805-9. [PMID: 11401936]
56. **Frost L, Mostofsky E, Rosenbloom JI, Mukamal KJ, Mittleman MA.** Marijuana use and long-term mortality among survivors of acute myocardial infarction. Am Heart J. 2013;165:170-5. [PMID: 23351819] doi:10.1016/j.ahj.2012.11.00757.
57. **Zhang LR, Morgenstern H, Greenland S, Chang SC, Lazarus P, Teare MD, et al; Cannabis and Respiratory Disease Research Group of New Zealand.** Cannabis smoking and lung cancer risk: pooled analysis in the International Lung Cancer Consortium. Int J Cancer. 2015;136:894-903. [PMID: 24947688] doi:10.1002/ijc.29036
58. **Callaghan RC, Allebeck P, Sidorchuk A.** Marijuana use and risk of lung cancer: a 40-year cohort study. Cancer Causes Control. 2013; 24:1811-20. [PMID: 23846283] doi:10.1007/s10552-013-0259-0
59. **de Carvalho MF, Dourado MR, Fernandes IB, Araújo CT, Mesquita AT, Ramos-Jorge ML.** Head and neck cancer among marijuana users: a meta-analysis of matched case-control studies. Arch Oral Biol. 2015;60:1750-5. [PMID: 26433192] doi:10.1016/j.archoralbio.2015.09.009
60. **Gurney J, Shaw C, Stanley J, Signal V, Sarfati D.** Cannabis exposure and risk of testicular cancer: a systematic review and meta-analysis. BMC Cancer. 2015;15:897. [PMID: 26560314] doi:10.1186/s12885-015-1905-6
61. **Chacko JA, Heiner JG, Siu W, Macy M, Terris MK.** Association between marijuana use and transitional cell carcinoma. Urology. 2006;67:100-4. [PMID: 16413342]
62. **Borges G, Bagge CL, Orozco R.** A literature review and meta-analyses of cannabis use and suicidality. J Affect Disord. 2016;195: 63-74. [PMID: 26872332] doi:10.1016/j.jad.2016.02.007
63. **Gibbs M, Winsper C, Marwaha S, Gilbert E, Broome M, Singh SP.** Cannabis use and mania symptoms: a systematic review and meta-analysis. J Affect Disord. 2015;171:39-47. [PMID: 25285897] doi:10.1016/j.jad.2014.09.016
64. **Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, et al.** Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet. 2007;370:319-28. [PMID: 17662880]
65. **Kuepper R, van Os J, Lieb R, Wittchen HU, Höfler M, Henquet C.** Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study. BMJ. 2011; 342:d738. [PMID: 21363868] doi:10.1136/bmj.d738
66. **Dominguez MD, Saka MC, can Saka M, Lieb R, Wittchen HU, van Os J.** Early expression of negative/disorganized symptoms predicting psychotic experiences and subsequent clinical psychosis: a 10-year study. Am J Psychiatry. 2010;167:1075-82. [PMID: 20634371] doi:10.1176/appi.ajp.2010.09060883
67. **Rössler W, Hengartner MP, Angst J, Ajdacic-Gross V.** Linking substance use with symptoms of subclinical psychosis in a community cohort over 30 years. Addiction. 2012;107:1174-84. [PMID: 22151745] doi:10.1111/j.1360-0443.2011.03760.x
68. **Kaufmann RM, Kraft B, Frey R, Winkler D, Weiszenbichler S, Bäcker C, et al.** Acute psychotropic effects of oral cannabis extract with a defined content of Delta9-tetrahydrocannabinol (THC) in healthy volunteers. Pharmacopsychiatry. 2010;43:24-32. [PMID: 20178093] doi:10.1055/s-0029-1237397
69. **Englund A, Morrison PD, Nottage J, Hague D, Kane F, Bonaccorso S, et al.** Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. J Psychopharmacol. 2013;27:19-27. [PMID: 23042808] doi:10.1177/0269881112460109
70. **Di Forti M, Morgan C, Dazzan P, Pariante C, Mondelli V, Marques TR, et al.** High-potency cannabis and the risk of psychosis. Br J Psychiatry. 2009;195:488-91. [PMID: 19949195] doi:10.1192/bjp.bp.109.064220
71. **van Nierop M, Janssens M, Bruggeman R, Cahn W, de Haan L, Kahn RS, et al; Genetic Risk OUtcome of Psychosis Investigators.** Evidence that transition from health to psychotic disorder can be traced to semi-ubiquitous environmental effects operating against background genetic risk. PLoS One. 2013;8:e76690. [PMID: 24223116] doi:10.1371/journal.pone.0076690
72. **Schreiner AM, Dunn ME.** Residual effects of cannabis use on neurocognitive performance after prolonged abstinence: a meta-analysis. Exp Clin Psychopharmacol. 2012;20:420-9. [PMID: 22731735] doi:10.1037/a0029117
73. **Ganzer F, Bröning S, Kraft S, Sack PM, Thomasius R.** Weighing the evidence: a systematic review on long-term neurocognitive effects of cannabis use in abstinent adolescents and adults. Neuropsychol Rev. 2016;26:186-222. [PMID: 27125202] doi:10.1007/s11065-016-9316-2
74. **Mason O, Morgan CJ, Dhiman SK, Patel A, Parti N, Patel A, et al.** Acute cannabis use causes increased psychotomimetic experiences in individuals prone to psychosis. Psychol Med. 2009;39:951-6. [PMID: 19017430] doi:10.1017/S0033291708004741
75. **Ramos S, Rodrigues R, Almeida N, Sá JM, Fonseca L.** Cannabinoid hyperemesis syndrome [Abstract]. Psychother Psychosom. 2013;82(Suppl 1):90. Abstract no. 357.
76. **Sadiq M.** Cannabis hyperemesis syndrome [Abstract]. J Addict Med. 2013;7(Suppl):E3. doi:10.1097/ADM.0b013e3182a3b16f
77. **Soriano-Co M, Batke M, Cappell MS.** The cannabis hyperemesis syndrome characterized by persistent nausea and vomiting, abdominal pain, and compulsive bathing associated with chronic marijuana use: a report of eight cases in the United States. Dig Dis Sci. 2010; 55:3113-9. [PMID: 20130993] doi:10.1007/s10620-010-1131-7
78. **Velasco A, Pentecost P.** An unexpected etiology of cyclical vomiting [Abstract]. J Hosp Med. 2012;7(suppl2). Abstract no. 97987.
79. **Vujasinović M, Ivartnik M, Tretjak M.** Cannabinoid hyperemesis syndrome - case report. Zdravniški vestnik. 2012;81:159-62. doi:10.6016/722
80. **Welder JD.** Some like it hot: a case of cannabinoid hyperemesis syndrome [Abstract]. J Gen Intern Med. 2012;27:S480-1.
81. **Woods JA, Wright NJ, Gee J, Scobey MW.** Cannabinoid hyperemesis syndrome: an emerging drug-induced disease. Am J Ther. 2016;23:e601-5. [PMID: 24413371] doi:10.1097/MJT.0000000000000034
82. **Sorensen CJ, DeSanto K, Borgelt L, Phillips KT, Monte AA.** Cannabinoid hyperemesis syndrome: diagnosis, pathophysiology, and treatment–a systematic review. J Med Toxicol. 2017;13:71-87. [PMID: 28000146] doi:10.1007/s13181-016-0595-z
83. **Cescon DW, Page AV, Richardson S, Moore MJ, Boerner S, Gold WL.** Invasive pulmonary aspergillosis associated with marijuana use in a man with colorectal cancer. J Clin Oncol. 2008;26:2214-5. [PMID: 18445848] doi:10.1200/JCO.2007.15.2777
84. **Chusid MJ, Gelfand JA, Nutter C, Fauci AS.** Letter: Pulmonary aspergillosis, inhalation of contaminated marijuana smoke, chronic granulomatous disease. Ann Intern Med. 1975;82:682-3. [PMID: 1094876]
85. **Marks WH, Florence L, Lieberman J, Chapman P, Howard D, Roberts P, et al.** Successfully treated invasive pulmonary aspergillosis associated with smoking marijuana in a renal transplant recipient. Transplantation. 1996;61:1771-4. [PMID: 8685958]
86. **Institute of Medicine Committee on Advancing Pain Research, Care, and Education.** Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington, DC: National Academies Pr; 2011.
87. **Munckhof WJ, Konstantinos A, Wamsley M, Mortlock M, Gilpin C.** A cluster of tuberculosis associated with use of a marijuana water pipe. Int J Tuberc Lung Dis. 2003;7:860-5. [PMID: 12971670]
88. **Oeltmann JE, Oren E, Haddad MB, Lake Lk, Harrington TA, Ijaz K, et al.** Tuberculosis outbreak in marijuana users, Seattle, Washington, 2004. Emerg Infect Dis. 2006;12:1156-9. [PMID: 16836841]
89. **Carabellese F, Candelli C, Martinelli D, La Tegola D, Catanesi R.** Cannabis use and violent behaviour: a psychiatric patients cohort study in Southern Italy. Riv Psichiatr. 2013;48:43-50. [PMID: 23438700] doi:10.1708/1228.13614
90. **Myerscough R, Taylor S.** The effects of marijuana on human physical aggression. J Pers Soc Psychol. 1985;49:1541-6. [PMID: 3003332]

91. **Blanco C, Hasin DS, Wall MM, Flórez-Salamanca L, Hoertel N, Wang S, et al.** Cannabis use and risk of psychiatric disorders: prospective evidence from a US national longitudinal study. JAMA Psychiatry. 2016;73:388-95. [PMID: 26886046] doi:10.1001/jamapsychiatry.2015.3229
92. **Fleming MF, Balousek SL, Klessig CL, Mundt MP, Brown DD.** Substance use disorders in a primary care sample receiving daily opioid therapy. J Pain. 2007;8:573-82. [PMID: 17499555]
93. **National Academies of Sciences, Engineering, and Medicine**. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. Washington, DC: National Academies Pr; 2017. doi:10.17226/24625
94. **Dowell D, Haegerich TM, Chou R.** CDC guideline for prescribing opioids for chronic pain–United States, 2016. MMWR Recomm Rep. 2016;65:1-49. [PMID: 26987082] doi:10.15585/mmwr.rr6501e1
95. **Abrams DI, Couey P, Shade SB, Kelly ME, Benowitz NL.** Cannabinoid-opioid interaction in chronic pain. Clin Pharmacol Ther. 2011;90:844-51. [PMID: 22048225] doi:10.1038/clpt.2011.188
96. **DeGeorge M, Dawson E, Woster P, Ko M, Burke L, Bronstein K.** An analysis of the association between marijuana use and potential nonadherence in patients prescribed hydrocodone. Proceedings of the 2013 annual meeting of the American Academy of Pain Medicine. Fort Lauderdale, FL: 2013, April. Poster Abstract 114. Accessed at www.painmed.org/2013posters/poster114.pdf on 19 May 2017.
97. **Hefner K, Sofuoglu M, Rosenheck R.** Concomitant cannabis abuse/dependence in patients treated with opioids for non-cancer pain. Am J Addict. 2015;24:538-45. [PMID: 26246069] doi:10.1111/ajad.12260
98. **Ashrafioun L, Bohnert KM, Jannausch M, Ilgen MA.** Characteristics of substance use disorder treatment patients using medical cannabis for pain. Addict Behav. 2015;42:185-8. [PMID: 25481452] doi:10.1016/j.addbeh.2014.11.024
99. **Haroutounian S, Ratz Y, Ginosar Y, Furmanov K, Saifi F, Meidan R, et al.** The effect of medicinal cannabis on pain and quality-of-life outcomes in chronic pain: a prospective open-label study. Clin J Pain. 2016;32:1036-1043. [PMID: 26889611]
100. **Vandrey R, Raber JC, Raber ME, Douglass B, Miller C, Bonn-Miller MO.** Cannabinoid dose and label accuracy in edible medical cannabis products. JAMA. 2015;313:2491-3. [PMID: 26103034] doi:10.1001/jama.2015.6613

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