Medical Cannabis for Non-Cancer Pain: A Systematic Review

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Executive Summary

This systematic review of medical cannabis use for treating chronic non-cancer pain was conducted to assist the Minnesota Department of Health (MDH) Intractable Pain Advisory Panel in its deliberations, to provide information to stakeholders, and to support MDH in its deliberations regarding extending the use of medical cannabis to chronic non-cancer pain patients. Main findings of the review are:

- The literature assessing the effects of medical cannabis treatments for non-cancer chronic pain is sparse and patchy.
    - Only 19 articles representing 21 studies were found.
    - No studies for pediatric populations were found.
    - With a few exceptions, studies usually used broad categories to recruit participants, making it difficult to group studies by type of pain or patient population.
- Essentially all studies treated medical cannabis as an adjunctive treatment for patients for whom current pain treatment was inadequate.
- The most commonly studied medical cannabis treatment was nabiximols, a botanical-based mouth spray, known by the brand-name Sativex.
- Low-strength evidence (likely to change with future research) suggested:
    - No difference between nabiximols and placebo for pain improvement among patients with MS and central neuropathic pain.
    - Improvement in neuropathic pain scale favors nabiximols over placebo among adults with peripheral neuropathic pain.
- All other evidence found was of insufficient strength to guide decisions. (Detailed study abstractions provide a minimum descriptive understanding of what has been studied.)
- When separated by specific treatments or patient populations, the evidence is generally insufficient to address whether a particular treatment works for a particular population. When the literature is examined as a whole, some patterns appear to signal that the hypothesis that medical cannabis could be beneficial to some patients is worth exploring. This position is consistent with the growing basic science around the pain mechanisms and treatment pathways.
- Cannabinoids are associated with greater risk of any Adverse Event (AE), serious AE, withdrawals due to AE, and other specified AEs, as compared to placebo. There was essentially no empirical literature, beyond one small study comparing nabilone to dihydrocodeine, comparing AEs between cannabinoids and opioids or other analgesics.
- The applicability of the review to chronic pain patients and the Minnesota program include:
    - It is difficult to judge whether the patient populations in the studies well-represent the patients who may sign up for the Minnesota program.
    - The botanical and synthetic treatments in this review provide indirect evidence regarding the benefits and harms of whole plant extract medical cannabis.
    - Treatment durations examined in the literature are too short to speak to long-term use for both benefits and harms. We do not know if or for whom any potential benefits may diminish over time. Duration and population sizes limit the ability to speak to the potential for more uncommon or difficult to detect harms.

Introduction

This systematic review of medical cannabis use for treating chronic non-cancer pain was conducted to assist the Minnesota Department of Health (MDH) Intractable Pain Advisory Panel in its deliberations, to provide information to stakeholders, and to support MDH in its deliberations regarding extending the use of medical cannabis to chronic non-cancer pain patients.

Review Scope

The review addresses the following key questions:

1) What are the benefits (short-term and long-term) of cannabis use for the treatment of non-cancer pain?
2) What are the harms (short-term and long-term) of cannabis use for the treatment of non-cancer pain?

We did not address patient populations or medical diagnoses for which medical cannabis is already approved in Minnesota. However, we did include studies if an eligible diagnosed condition is an underlying cause of chronic pain; thus, for example, studies with persons with MS are included.

Systematic review questions are commonly operationalized using the PICOTS format, which outlines the specific populations, interventions, comparators, outcomes, treatment and/or followup periods, and treatment settings. Table 1 outlines the PICOTS in terms of the criteria by which studies were assessed for inclusion or exclusion in the systematic review.

Table 1. Populations, interventions, comparators, outcomes, timing, and settings

PICOTS	Inclusion	Exclusion
Populations	Children or adults experiencing chronic non-cancer pain	Acute pain Animal studies
Interventions	Smokable marijuana Marijuana extraction products Dronabinol Nabilone Nabiximols	
Comparators	Placebo Active pain treatment	Studies were not excluded for type of comparator; however, a comparator arm must be present for benefits.
Outcomes	Pain measures (ex: visual analog scales)	Intermediate outcomes such as lab values
Timing	At least 2 weeks treatment (to match outcome timing to the anticipated extended treatment use for chronic pain)	
Settings	Outpatient	Inpatient (hospital treatment in response to acute episode)
Study Designs	Benefits: Randomized controlled trials, controlled trials, prospective or retrospective cohort with comparators Harms: case control, case series (at least 10 participants) for potential serious harms (hospitalizable events)	
Other limitations	No date limitations	

Cannabis and cannabis-related pharmaceuticals are available in several forms world-wide. The most common forms are provided in Table 2.

Table 2. Medical cannabis treatments

Generic	Manufacturer (Trade Name)	FDA Approval Date/ Indication	Delivery Form/ Source	Active Ingredients FDA Drug Classification
Dronabinol	Abbvie (marinol)	1985; anorexia associated with weight loss in patients with AIDS, nausea, and vomiting associated with cancer chemotherapy in patients who failed conventional antiemetic treatments	2.5mg, 5mg, or 10mg capsule; oral Synthetic	Delta-9-tetrahydrocannabinol Schedule III class substance
Nabilone	Meda Pharmaceuticals (cesamet)	1985; nausea and vomiting associated with cancer chemotherapy for patients who failed conventional antiemetic treatments	1 mg capsule; oral Synthetic	Mimics tetrahydrocannabinol Schedule II class substance – high potential for abuse.
Nabiximols	GWPharmaceuticals (sativex) developed in UK	Not approved (in trials in US)	Mouth spray Botanical	Tetrahydrocannabinol and cannabidiol in near 1:1 ratio
Whole plant extracts			Multiple – inhaled, ingested	Possibly multiple
Unmodified whole plant material			Smoked or ingested	Multiple

Source: FDA website and product labels.

Methods

We followed the methods suggested in the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews (available at http://www.effectivehealthcare.ahrq.gov/methodsguide.cfm); methods map to the PRISMA checklist.[1] All methods and analyses were determined *a priori*. This section summarizes the methods used.

Literature Search Strategy

We searched Ovid MEDLINE, EMBASE, AMED, and Cochrane Central Register of Controlled Trials (CENTRAL) from inception to July, 2015. The search algorithms are provided in Appendix A. We also hand searched reference lists of related prior published systematic reviews. Studies were included in the review based on the PICOTS framework outlined in Table 1 and the study-specific inclusion criteria described in Table 3.

Table 3. Study inclusion criteria

Category	Criteria for Inclusion
Study Enrollment	Studies that enroll adults with chronic pain
Study Design and Quality	Randomized controlled trials, nonrandomized controlled trials, and prospective cohort studies for each population and treatment option. Prospective studies must include a comparator and appropriate methods to correct for selection bias. Studies specifically addressing treatment harms may also include retrospective and case series designs.
Time of Publication	Start date for electronic database to current
Publication Type	Published in peer reviewed journals
Language of Publication	English language publications

Study Selection and Data Extraction

We reviewed bibliographic database search results for studies relevant to our PICOTS framework and study-specific criteria. All studies identified at title and abstract as relevant by either of two independent investigator underwent full-text screening. Two investigators independently performed full-text screening to determine if inclusion criteria were met. Differences in screening decisions were resolved by consultation between investigators, and, if necessary, consultation with a third investigator. Appendix B provides a list of articles excluded at full text. We abstracted data from eligible studies. One investigator abstracted the relevant information directly into evidence tables. A second investigator reviewed evidence tables and verified them for accuracy.

Risk of Bias Assessment of Individual Studies

Risk of bias of eligible studies was assessed by two independent investigators using instruments specific to each study design. For RCTs, questionnaires developed from the Cochrane Risk of Bias tool were used. We developed an instrument for assessing risk of bias for observational studies based on the RTI Observational Studies Risk of Bias and Precision Item Bank.[2] We selected items most relevant in assessing risk of bias for this topic, including participant selection, attrition, ascertainment, and appropriateness of analytic methods. Study power was assessed in studies with data that were not eligible for pooling. Overall summary risk of bias assessments for each study were classified as low, moderate, or high based upon the collective risk of bias inherent in each domain and confidence that the results were believable

given the study's limitations. When the two investigators disagreed, a third party was consulted to reconcile the summary judgment. (Table in Appendix C.)

Data Synthesis

We summarized included study characteristics and outcomes in evidence tables and conducted qualitative synthesis on all comparisons. We emphasized patient-centered outcomes in the evidence synthesis.

When comparisons could be pooled, we conducted meta-analyses using a random effects model. Data were analyzed in OpenMetaAnalyst. We calculated odds ratios (OR) with the corresponding 95% CI for binary primary outcomes. Weighted mean differences (WMD) with the corresponding 95% confidence intervals (CIs) were calculated for continuous outcomes. We assessed the clinical and methodological heterogeneity and variation in effect size to determine appropriateness of pooling data.[3] We assessed statistical heterogeneity with Cochran's Q test and measure magnitude with I^2 statistic.

Strength of Evidence for Major Comparisons and Outcomes

The overall strength of evidence for select outcomes within each comparison were evaluated based on four required domains: (1) study limitations (internal validity); (2) directness (single, direct link between intervention and outcome); (3) consistency (similarity of effect direction and size); and (4) precision (degree of certainty around an estimate).[4] A fifth domain, reporting bias, was assessed when strength of evidence based upon the first four domains was moderate or high.[4] Based on study design and conduct, risk of bias was rated as low, medium, or high. Consistency was rated as consistent, inconsistent, or unknown/not applicable (e.g., single study). Directness was rated as either direct or indirect. Precision was rated as precise or imprecise. Other factors that may be considered in assessing strength of evidence include dose-response relationship, the presence of confounders, and strength of association. Based on these factors, the overall evidence for each outcome was rated as:[4] (Appendix D)

- **High:** Very confident that estimate of effect lies close to true effect. Few or no deficiencies in body of evidence; findings believed to be stable.
- **Moderate:** Moderately confident that estimate of effect lies close to true effect. Some deficiencies in body of evidence; findings likely to be stable, but some doubt.
- **Low:** Limited confidence that estimate of effect lies close to true effect; major or numerous deficiencies in body of evidence. Additional evidence necessary before concluding that findings are stable or that estimate of effect is close to true effect.
- **Insufficient:** No evidence, unable to estimate an effect, or no confidence in estimate of effect. No evidence is available or the body of evidence precludes judgment.

Results

Figure 1.provides the results of the search and selection process. Of 36 articles reviewed at full text, 19 were included, representing 14 randomized controlled trials and 7 observational studies. Open-label extensions of controlled trials were counted as a separate study. The most common reason for excluding an article was not meeting the inclusion criterion of treatment duration of at least 2 weeks. The 9 excluded articles' treatment duration ranged from 6 hours to 7 days. Appendix B provides a bibliography of excluded studies with detailed reasons for exclusions.

Figure 1. Literature flow diagram

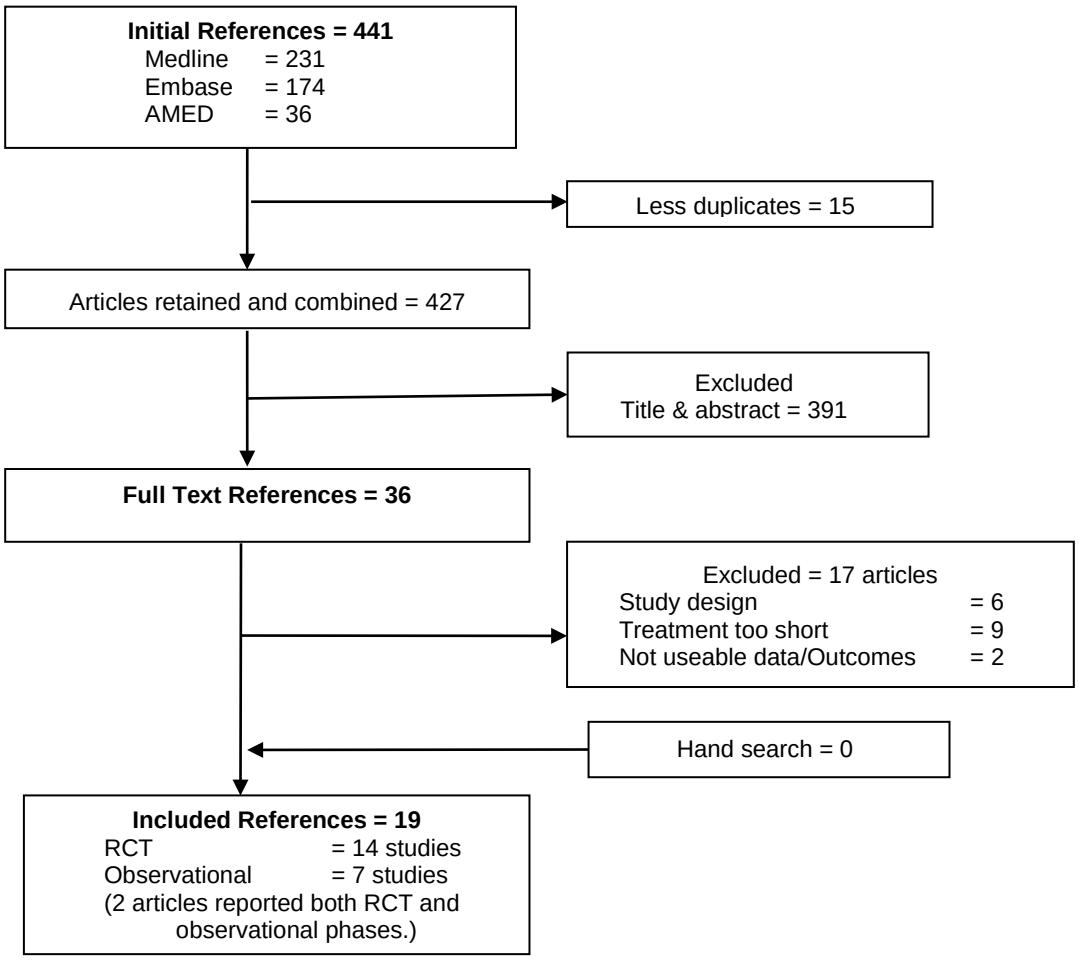

Table 4 provides a brief summary of the characteristics of the included studies. All were published after 2003. Only two studies used an active comparator, nabilone versus dihydrocodeine and nabilone versus amitriptyline; all others used a placebo control. All study populations were adults; no pediatric studies were located. Studies were largely funded by industry, and all but one were conducted outside the United States. Studies were of moderate (k=6) to high (k=14) risk of bias, with only one low risk of bias RCT. (Risk of bias table in Appendix C)

Table 4. Summary of study characteristics

Characteristic Category	Number of Studies (unless otherwise noted)
Countries in which studies were conducted	Austria (1) Belgium (4) Canada (7) Czech Republic (4) Denmark (1) France (2) Israel (1) Italy (1) Romania (2) Spain (1) UK (11) U.S. (1)
Study Design	Multisite parallel arm RCT (4) Single-site parallel arm RCT (4) Crossover RCT (6) Open-label extension of RCT (4) Open-label extension with randomized withdrawal (1) Case Series (2)
Number randomized (or enrolled for observational)	RCTs – median 42 (range 13-339) Open-label extensions – mean 104 (range 28-234) Case series – mean 17 range (13-21)
Populations	Pain related to MS (6) Fibromyalgia (2) Rheumatoid arthritis (1) Mixed populations with chronic pain (3) Unilateral peripheral neuropathic pain (2) Central neuropathic pain (2) Brachial plexus injury (1) Neuropathic pain (1) Diabetic neuropathic pain (1) Neuropathic pain due to conditions other than diabetes(1) Medication overuse headache (1) Chronic upper motor neuron syndrome (1)
Interventions	Nabiximols (11) Nabilone (7) Dronabinol (2) Delta-9-THC suspended in olive oil (1)
Treatment Duration	RCTs – 2 weeks to 14 weeks Open-label extensions – 4 weeks to 124 weeks (31 months) Case series – up to 36 months to up to over 48 months
Study Risk of Bias	RCT High risk of bias (7) RCT Moderate risk of bias (6) RCT Low risk of bias (1) Open-label and case series High risk of bias (7)
Funding Source	Industry (17) Non-governmental (2) Not reported (2) No funding (1)

Comparative Effectiveness Evidence

Table 5 lists two RCTs that were designed to test nabilone against an active control. The study of patients with fibromyalgia was intended to treat chronic insomnia but was included because fibromyalgia is a painful condition pain outcomes were reported as secondary outcomes.

- There is insufficient evidence for nabilone compared with dihydrocodeine largely due to high risk of bias and a single study. Study authors reported results favored

dihydrocodeine for treatment responders, but no difference in anxiety/depression and sleep.

- Despite a low risk of bias, there is insufficient evidence for nabilone compared with amitriptyline. The single study had too small a sample size to test for no difference between groups for pain (the test as run could not rule out the null hypothesis of no difference).

Table 5. Comparative effectiveness studies

Author, Year **Country** **Design** **Funding Source**	**Population** **Excluded** **Age, % Male, Race/ethnicity** **Setting**	**Sample Size** **Intervention(s)** **Control(s)** **Treatment** **Duration** **Followup**	**Outcomes (primary first)**	**Harms** **Side Effects**
Frank, 2008[5] UK Crossover RCT Industry	Adults with neuropathic pain >40mm of 100mm VAS (screened by single provider), receiving other analgesics except dihydrocodeine Severe mental illness, hepatic or renal disease, epilepsy, substance use, use of antipsychotics, monoamine oxidase inhibitors Mean age 48, 53% male, no race/ethnic data 3-site outpatient setting	N= 96 randomized (73 completed, 100 assessed) **Tr1**: 2.5 mg nabilone **Tr2**: 30 mg dihydrocodeine Duration: 6 weeks Followup: 2 week washout	Change in VAS (0-100): treatment effect 6.0 mm # of patients with clinically relevant response (>10mm improvement in VAS): Tr1 3, Tr2 12 (49 did not have a clinical response to either treatment) **Favors dihydrocodeine** Anxiety and depression: **no difference** Number hours of sleep: **no difference**	Withdrawals by group “equally well-tolerated” (no statistical analysis presented) No serious AEs reported Most common side effects: tiredness, sleeplessness, sickness, tingling, strangeness, nightmares, shortness of breath, headaches.

Author, Year Country Design Funding Source	Population Excluded Age, % Male, Race/ethnicity Setting	Sample Size Intervention(s) Control(s) Treatment Duration Followup	Outcomes (primary first)	Harms Side Effects
Ware, 2010[6] Canada Crossover equivalency RCT Industry	Adults with fibromyalgia and self-reported chronic insomnia for past 6 months. Cancer pain, unstable cardiac disease, severe mental illness, seizure disorder, glaucoma, urinary retention, sensitivity to cannabinoids/ amitriptyline/ related tricyclic antidepressants, taking monoamine oxidase inhibitors. Mean age 49.5, 16% male, no race/ethnic data (78% >high school education) Single pain clinic.	N=32 randomized (39 enrolled, 29 completed) **Tr1:** nabilone oral capsule, .05 mg 1st week, 1 mg 2nd week if indicated **Tr2:** amitriptyline capsule, 10 mg 1st week, 20 mg 2nd week if indicated. Duration: 2 weeks plus 2 week washout	Insomnia Severity Index (ISI): adjusted difference (for period effect) -3.25 (95% CI -5.26, -1.24) **Favors nabilone** Leeds Sleep Evaluation Questionnaire (LSEQ): **no difference** McGill Pain Questionnaire: **no difference** FIQ: **no difference** Global Patient Satisfaction (wish to continue medication): **no difference** No evidence participants guessed assignment.	Withdrawals: 1 from side effects, 1 for lack of effect, 1 protocol violation. 2 severe AEs for amitriptyline: headache and insomnia 1 severe AE for nabilone: drowsiness. 91 AEs for nabilone; 53 for amitriptyline Most common AEs for nabilone: dizziness, nausea, dry mouth, drowsiness, constipation, insomnia, vomiting

Efficacy Studies by Patient Populations

As was seen in Table 4, the patient populations are varied in terms of pain etiology, mechanism, or disease condition. Because of this, we were unable in general to pool results. We therefore present the findings qualitatively by patient population and in brief statements of findings and specifics provided in table format.

Table 6 lists four RCTs, one RCT of treatment withdrawal, and one open-label extension among patients with pain related to MS. All pharmaceutical products, dronabinol, nabilone, and nabiximols, were tested as adjunctive treatments, with nabilone specifically adjunctive to gabapentin.

- There is insufficient evidence for dronabinol and nabilone due to the small study sizes and moderate to high risk of bias to allow for a definitive conclusion. Study authors reported mixed effects for pain measures for dronabinol. For nabilone pain intensity and impression of improvement favor treatment but there was no difference in pain impact.
- For nabiximols, two studies are inconsistent in finding a treatment effect. Based on the larger study of moderate risk of bias, low strength evidence suggests we cannot rule out the possibility of no difference between groups.
- The open-label extension found an adverse events pattern similar to the RCTs.

Table 6. Patients with pain related to MS

Author, Year Country Design Funding Source	Population Excluded Age, % Male, Race/Ethnicity Setting	Sample Size Intervention(s) Control(s) Treatment Duration Followup	Outcomes (primary first)	Harms Side Effects
Langford, 2013[7] UK, Czech Republic, Spain, France, Canada RCT – phase A Industry	MS patients with central neuropathic pain (CNP) with stable analgesic regimen and sum score of 24 from last 6 baseline days' numeric rating scale (NRS) (0-10) Comorbid pain of other origin, severe mental illness, renal, hepatic, cardiovascular, or convulsive disorders, sensitivity to cannabis. Mean age 49, 32% male, 98% white, mean 12 years with MS, 5.5 years with CNP, 6% used cannabis in last year. Multi-site outpatient	N=339 randomized, (297 completed, 393 screened) **Tr1:** nabiximols; maximum of 12 actuations every 24 hours. Patients self-titrated. (n=167) **C:** placebo spray (n=172) Duration: 14 weeks	Responder: 30% improvement in 7-day mean pain NRS: **No difference** (both groups improved) Also **no differences** in: Brief pain inventory-short form Patient Global Impression of Change Sleep quality NRS	Withdrawals by group not different. Treatment 15, Control 12. Severe AE withdrawals: Treatment 5, Control 3, no difference. Withdrawal for treatment related AEs: Treatment 12, Control 6 Severe emergent AE: Treatment 21, Control 14. Overall AEs: Treatment 120, Control 106.
Langford, 2013[7] France, Czech Republic RCT open label – phase B Industry	MS patients with central neuropathic pain (CNP) with stable analgesic regimen average ≥3 sprays per day last 7 days of RCT phase A. Comorbid pain of other origin, severe mental illness, renal, hepatic, cardiovascular, or convulsive disorders, sensitivity to cannabis, and no adverse events in RCT phase A Mean age 48, 40% male, 100% white, mean 12 years with MS, 5.5 years with CNP, 2% used cannabis in last year. Multi-site outpatient	N=42 randomized, (58 entered open label, 52 screened) Open label treatment for 12 week (plus 2 weeks to retitrate), and 4 week randomized withdrawal phase where again randomized to treatment or placebo **Tr1:** nabiximols; maximum 12 actuations every 24 hours. Patients self-titrated. **C:** placebo spray Duration: 18 weeks	Time to treatment failure: 24% treatment vs. 57% control, p=0.04. **Favors treatment** Sleep quality NRS: Difference -0.99, p=0.02 **Favors treatment** IVRS pain NRS: Difference -0.79, p=0.03 **Favors treatment** **No differences** in neuropathic pain scale or patient global impression of change	Serious AEs: Treatment 2 (disorientation, suicidal ideation) Control 1 (suicidal ideation) 6 patients stopped medication in open-label; all previously placebo group in RCT phase. Most common AEs: dizziness, fatigue, somnolence, vertigo, nausea.

Author, Year **Country** **Design** **Funding Source**	**Population** **Excluded** **Age, % Male, Race/Ethnicity** **Setting**	**Sample Size** **Intervention(s)** **Control(s)** **Treatment Duration** **Followup**	**Outcomes (primary first)**	**Harms** **Side Effects**
Rog, 2005[8] UK RCT Industry	Adult MS patients with central neuropathic pain syndromes ≥3 month duration on stable pain medication regimen. Severe mental illness, severe concomitant illness, seizures, substance abuse, concomitant non-neuropathic pain or diabetes neuropathic pain, pregnancy, levodopa therapy, hypersensitivity to cannabinoids. Mean age 49 years, 21% male, no race/ethnic data, mean 12 years with MS Single site outpatient	N=66 randomized (64 completed, 85 screened) **Tr1:** nabiximols; max 8 sprays per 3 hour period and 48 actuations every 24 hours. Patients self-titrated. (n=34) **C:** placebo spray (n=32) Duration: 4 weeks plus 1 week run-in	Change in Pain NRS (0-10): Mean difference -1.25 (95% CI -2.11, -0.39) **Favors treatment** Change in Neuropathic Pain Scale: Mean difference -6.58 (95% CI -12.97, -0.19) **Favors treatment** Change in sleep disturbance (0-10): Mean difference -1.39 (95% CI -2.27, -0.50) **Favors Treatment** Patient Global Impression of Change (PGIC): Treatment group 3.9 times more likely to rate themselves in any improved category vs control.	Withdrawals: 2 in treatment arm for serious AE, one for agitation with tachycardia and hypertension after 4 sprays, one for paranoid ideation. 88% Treatment group vs. 69% control group developed at least one AE. Dizziness more likely in treatment group. Other common AEs: dry mouth, somnolence, nausea, falls, weakness, dissociation
Rog, 2007[9] UK RCT open label extension Industry	95% of patients continued from Rog 2005 Mean age 49 years, 22% male, 100% white, mean12 years with MS	N=63 **Tr1**: nabiximols; max 8 sprays per 3 hour period and 48 actuations every 24 hours. Patients self-titrated. Duration: mean treatment duration 463 days; 44% completed with mean duration of 839 days.	*[Improvement in Pain score carried forward from RCT phase of study.]*	Withdrawals: 25% due to AEs. Mean treatment duration for withdrawals was 162 days. 95% experienced one or more AEs; 92% treatment-related; nausea, dizziness, intoxication. One patient hospitalized for ventricular bigeminy and circulatory collapse

Author, Year **Country** **Design** **Funding Source**	**Population** **Excluded** **Age, % Male, Race/Ethnicity** **Setting**	**Sample Size** **Intervention(s)** **Control(s)** **Treatment Duration** **Followup**	**Outcomes (primary first)**	**Harms** **Side Effects**
Svendsen, 2004[10] Denmark Crossover RCT Industry, Non-government	Adults ages 18-55 with MS and max pain intensity score ≥3 on 0-10 scale. Central lesion pain distinguishable from spastic pain. Musculoskeletal disorder or peripheral neuropathic pain, visceral pain at maximal pain site, sensitivity to cannabinoids, heart disease, severe mental illness, substance abuse, treatment with tricylic antidepressants, anticholinergic, antihistamine, or central nervous system depressant drugs, **other analgesics use except paracetamol**, pregnancy Mean age 50, 42% male, no race/ethnic data, mean 7 years with MS MS outpatient clinic	N=24 randomized (25 screened) **Tr1:** dronabinol oral capsule, maximum dosage 5 mg 2X daily **C:** placebo capsule Duration: 3 weeks with 3 week wash-out	Spontaneous pain intensity NRS (0-10): Mean difference (difference in change from baseline) -20.5% (95% CI -37.5, -4.5) **Favors treatment** Radiating pain intensity NRS (0-10): Mean difference(difference in change from baseline) -0.6 (95% CI -1.3, 0) **no difference** Pain relief NRS (0-10): Mean difference (difference in change from baseline) 2.5 (95% CI 0.5, 4.5) **Favors treatment** Patient preference: **no difference** Patients "unable to predict treatment assignment" (p=0.19)	Withdrawals: none AEs more common in treatment phase: Treatment 96% of patients, Control 46% of patients (p=0.001) 4 patients reduced treatment dosage due to intolerable AE. Most common AEs in treatment group: dizziness, headache, tiredness, myalgia,
Turcotte, 2015[11] Canada RCT Industry	Adults age 18-65 with relapsing-remitting MS with neuropathic pain on stable gabapentin regimen and VAS pain ≥50. Severe mental illness, renal, liver, cardiovascular disease, sensitivity to cannabinoids, concomitant diseases as cause for neuropathies, substance abuse, pregnancy or breastfeeding Mean age 46, 13% male, no race/ethnic data, mean 6.5 years with MS. MS outpatient clinic	N=15 randomized (14 completed, 22 screened) **Tr1:** nabilone oral capsule, adjunctive to gabapentin, titrated from 0.5 mg PO at bedtime to 1 mg 2X daily (n=8) **C:** placebo capsule (n=7) Duration: 9 weeks	VAS (0-100) pain intensity: average final 10 day significantly lower (p<0.001) **Favors treatment** VAS (0=100) pain impact: **no difference** Patient Global Impression of Change: improvement Treatment 100%, Control 43%(p<0.05) **Favors treatment**	Withdrawals: 1 from treatment group due to headache. Most common AEs in treatment group: dizziness, drowsiness, dry mouth.

Table 7 lists one RCT for nabiximols for fibromyalgia patients.

- The evidence is insufficient to draw a conclusion, due to the small sample size, moderate to high risk of bias, and unknown consistency due to a single study. Study authors report results favor nabilone

Table 7. Patients with fibromyalgia

Author, Year Country Design Funding Source	Population Excluded Age, % Male, Race/Ethnicity Setting	Sample Size Intervention(s) Control(s) Treatment Duration Followup	Outcomes (primary first)	Harms Side Effects
Skrabek, 2008[12] Canada RCT Industry	Adults 18-70 with fibromyalgia and continued pain despite other oral medications Concomitant pain from other diagnoses, severe mental illness, history of untreated emotional disorder, abnormal routine bloodwork, heart disease, major illness of other organ system, sensitivity to cannabis, pregnancy, substance use Mean age 49, no sex or race/ethnic data. Outpatient pain clinic	N=40 randomized (33 completed, 44 screened) **Tr1:** nabilone oral capsule at bedtime and morning, titrated from 0.5 mg at bedtime to 1 mg 2X daily (n=20) **C:** placebo capsule (n=20) Duration: 4 weeks Followup: 4 weeks after treatment stopped	VAS (10 cm): Mean difference (difference in change from baseline) -1.43 (no CI, p<0.05) **Favors treatment** Fibromyalgia Impact Questionnaire (FIQ): Mean difference (difference in change from baseline) -10.76 (no CI, p<.01) **Favors treatment** FIQ anxiety scale: Mean difference (difference in change from baseline) -2.20 (no CI, p<.01) **Favors treatment** No differences noted at 4 weeks following treatment end.	Withdrawals: 17.5% (Treatment 5, Control 2) No serious adverse events reported. Side effects more common in treatment group at 4 weeks (p<.05) Most common AEs in treatment group: drowsiness, dry mouth, vertigo, ataxia.

Table 8 lists the RCT for nabilone for patients with rheumatoid arthritis.

- The evidence is insufficient to draw a conclusion, due to the small sample size, moderate risk of bias, and unknown consistency due to a single study.

Table 8. Patients with rheumatoid arthritis

Author, Year Country Design Funding Source	Population Excluded Age, % Male, Race/Ethnicity Setting	Sample Size Intervention(s) Control(s) Treatment Duration Followup	Outcomes (primary first)	Harms Side Effects
Blake, 2006[13] UK RCT Industry	Adult patients with rheumatoid arthritis (meet ACR criteria) with active arthritis not controlled by current stable medication regime Serious mental illness or substance use, severe cardiovascular, renal, or hepatic disorder, epilepsy. Mean age 62.8, 21% male, no race/ethnicity data Multi-site Outpatient setting	N=58 randomized (75 assessed) **Tr1**: nabiximols (n=31) before bedtime Max 6 actuations per day **C**: placebo nasal spray (n=27) Duration: 5 weeks Followup: 7-10 days after 5 week period	Change in morning pain on movement (0-10 rating scales): Difference -0.95 (CI -1.83, -0.02) **Favors treatment** Change in morning pain at rest (0-10 rating scale): Difference -1.04 (CI -1.90, -0.18) **Favors treatment** Change in sleep quality: Difference -1.17 (CI -2.20, -0.14) **Favors treatment** SF-MPQ pain rating: **No difference** SF-MPQ VAS: **No difference**	Withdrawals: 1 treatment (unrelated surgery), 3 placebo (adverse events) No serious AEs leading to withdrawal reported in treatment group (3 in placebo) Most common side effects: Dizziness, light-headedness, dry mouth

Table 9 lists three RCTs, two of which followed with open label extensions for nabiximols for patients with peripheral neuropathic pain. The Hoggart open label study is an extension of two similar RCTs by the same sponsor; one RCT of patients with peripheral neuropathic pain not due to diabetes (Serpell) and one of patients with diabetic neuropathic pain. The second study (of diabetic neuropathic pain) was never published; according to the posting on ClinicalTrials.gov, there were no differences between nabiximols and placebo on any outcome.

- There is low-strength evidence from 3 studies that nabiximols reduces neuropathic pain better than placebo for patients with peripheral neuropathic pain. (Figure 2) The rating signifies low confidence in the stability of the finding in the face of new research.

Table 9. Patients with peripheral neuropathic pain

Author, Year Country Design Funding Source	Population Excluded Age, % Male, Race/Ethnicity Setting	Sample Size Intervention(s) Control(s) Treatment Duration Followup	Outcomes (primary first)	Harms Side Effects
Serpell, 2014[14] UK, Czech Republic, Romania, Belgium, Canada RCT Industry	Adults 18+ with peripheral neuropathic pain, ≥6 months, on stable analgesic regimen, diagnosed with post-herpetic neuralgia, peripheral neuropathy, focal nerve lesion, radiculopathy, or Complex Regional Pain Syndrome type 2. Sum score of 24 on 0-10 NRS pain scale over 6 days	N=246 randomized (173 completed, 303 screened) **Tr1:** nabiximols; max 8 sprays per 3 hour period and 24 actuations every 24 hours. Patients self-titrated. (n=128) **C:** placebo spray (n=118)	30% reduction in Pain NRS (0-10): Treatment 28%, Control 16%, OR 1.97 (95% CI 1.05, 3.70) **Favors treatment** Change in Pain NRS: **no difference** Neuropathic Pain Scale: **no difference** Sleep quality NRS (0-10): **Favors treatment** Patient Global Impression of Change: **no difference**	Withdrawal:13% (another 9% stopped treatment but remained in study) 10 patients in treatment arm "experienced [serious AEs], none of which was considered to be treatment-related." AEs were experienced more frequently by treatment arm: most

Author, Year Country Design Funding Source	Population Excluded Age, % Male, Race/Ethnicity Setting	Sample Size Intervention(s) Control(s) Treatment Duration Followup	Outcomes (primary first)	Harms Side Effects
	Peripheral neuropathic pain due to diabetes, cancer, or CRPS type 1, severe mental illness, concomitant pain, renal, hepatic, cardiovascular, or convulsive disorders, sensitivity to cannabis, pregnancy Mean age 57, 39% male, 99% white, mean 6 years duration of neuropathic condition. Multisite – 21 centers	Duration: 14 weeks plus 1 week run-in Followup: 28 days after study end	Brief Pain Inventory: **no difference**	common AEs: dizziness, dysgeusia, nausea, fatigue
Hoggart, 2015[15] UK, Czech Republic, Romania, Belgium, Canada Open label extension of 2 similar trials (Serpell and unpublished study of diabetic neuropathic pain) Industry	Adult patients with peripheral neuropathic pain who completed either of two original studies, tolerated the study medication, and were expected to gain clinical benefit. Allowed to receive other analgesics. Severe mental illness, concomitant pain, renal, hepatic, cardiovascular, or convulsive disorders, sensitivity to cannabis, substance abuse, pregnancy or breastfeeding Mean age 57.8, 53% male, 98% white, 84% taking at least 1 other analgesic, 25% taking at least 4 Multi-site outpatient	N=380 enrolled, 230 completed **Tr1:** nabiximols, max 8 sprays per 3 hour period and 24 actuations every 24 hours. Patients self-titrated. Duration: 38 weeks	*[Of completers, 70% reported improvement in nerve pain and 8% reported worsening. 22% no change.]*	11% (n=40) patients had serious AEs, 1% (n=4) treatment related; amnesia (n=2), paranoia (n=1), suicide attempt (n=1) 23% patients dropped due to AEs: 7% severe, 18% treatment related. 78% (n=295) experienced at least one AE, 59% (n=224) treatment related. Mean intoxication score (0-10 numerical rating scale) 1.5 (±2.3)

Author, Year Country Design Funding Source	Population Excluded Age, % Male, Race/Ethnicity Setting	Sample Size Intervention(s) Control(s) Treatment Duration Followup	Outcomes (primary first)	Harms Side Effects
Nurmikko 2007[16] UK, Belgium RCT Industry	Adult patients with at least 6 months unilateral peripheral neuropathic pain and allodynia on stable medication regimen. Baseline severity score at least 4 (on NRS) at least 4 of 7 previous days. (Recruited from chart review) Severe mental illness, severe non-neuropathic pain or pain from cancer or diabetes, sensitive to cannabinoids, renal, hepatic, or cardiovascular conditions, substance use, pregnancy/lactating, epilepsy Mean age 53, 60% male, 97% white. Etiologies: post-infection, traumatic, vascular, idiopathic Multi-center outpatient	N=125 randomized , (103 completed, 141 screened) **Tr1:** nabiximols; max 8 sprays per 3 hour period and 24 actuations every 24 hours. Patients self-titrated. (n=63) **C:** placebo spray (n=62) Duration: 5 weeks Followup: unclear	Change in Global pain intensity NRS (0-10) from baseline. Mean difference 0.96 (95% CI -1.59,-0.32) **Favors treatment** >30% reduction in pain NRS: Treatment 16/63, Control 9/62, OR 1.9(95% CI 0.80, 4.75) **Favors treatmen**t Neuropathic Pain Scale(NPS): Mean difference: **Favors treatment** Sleep disturbance NRS: **Favors treatment** Pain Disability Index (PDI): **Favors treatment** Patient Global Impression of Change (PGIC): **Favors treatment** Allodynia: **Favors treatment**	Withdrawals: Treatment 13 (11 side effects, 1 lack of effect), Control 7 (2 side effects, 5 lack of effect) Protocol violators: Treatment 15, Control 5 Gastrointestinal AEs more common (p=0.003) in treatment Most common AEs (higher in treatment group): dizziness, nausea, fatigue, dry mouth, vomiting, feeling drunk, diarrhea, nasopharyngitis, anorexia, somnolence Intoxication reported to remain low, marginally higher in treatment group.
Nurmikko 2007[16] UK, Belgium RCT Open label extension Industry	71% of patients continued.	N= 89 patients continued on nabiximols. Duration: 1 to 871 days	*For 76 patients analyzed at 52 weeks, mean change in pain decreased from 7.3 to 5.9, similar to RCT phase.*	56 (63%) patients withdrew; 18 side effects, 16 lack of efficacy, 15 withdrew consent, 7 other reasons 2 serious AE
Selvarajah, 2010[17] UK RCT Industry	Adults with diabetic neuropathy of ≥6 months and stable glycemic control, failed tricyclic antidepressants for pain, on stable pain regimen. No exclusion rules provided. Mean age 56, 63% male, no race/ethnic data provided No setting information	N=30 randomized (38 assessed) **Tr1:** nabiximols; (n=unclear) **C:** placebo spray (n=unclear) Duration: 10 weeks plus 2 week run-in	Neuropathic Pain Scale: no difference by group McGill Pain and QOL: no differences by group Post-hoc analysis of depression subgroup analysis: Patients with depression were more likely to respond to intervention.	Withdrawals: 6 (20%) NOTE: Primary study article (that would have reported no differences) cannot be located.

Figure 2. Change in neuropathic pain scale

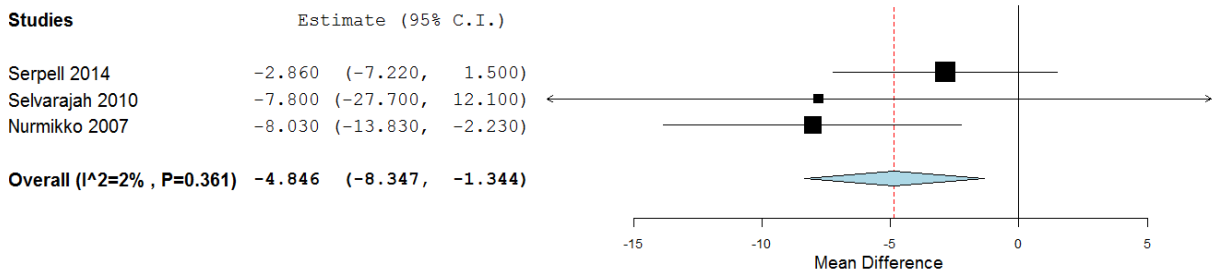

Table 10 lists 3 RCTs for other painful conditions. All studies are of relatively small size and moderate to high risk of bias. The outcomes come in various forms of pain, disability, and global improvements. The positive findings are generally borderline statistically significant, would disappear if corrections were made for multiple outcome assessment, and small enough that they may not be clinically important. On the other hand, studies with findings of no difference were likely not powered to detect a difference, despite attempts to recruit patients to meet power calculations.

- As single studies, all would be insufficient evidence for the indicated patient populations.
- Taken as a whole body of evidence, along with the studies examined in Tables 6-9, there appear to be some suggestion that the hypothesis that medical cannabis could be beneficial to some patients is worth exploring. This position is consistent with the growing basic science around the pain mechanisms and treatment pathways.
    - In the Berman study, for example, there are statistically significant benefits, but the size of these effects is less than what has been judged to be a minimum important difference, and a responder analysis was not presented.

Table 10. Patients representing other chronic pain patient populations

Author, Year **Country** **Design** **Funding Source**	**Population** **Excluded** **Age, % Male, Race/Ethnicity** **Setting**	**Sample Size** **Intervention(s)** **Control(s)** **Treatment Duration** **Followup**	**Outcomes (primary first)**	**Harms** **Side Effects**
Berman, 2004[18] UK Crossover RCT Industry	Adult patients with brachial plexus (spinal cord near neck and shoulder) injury with stable pain pattern. Receiving other analgesics. Serious mental illness other than depression due to chronic illness, serious cardiovascular disease, renal, or hepatic disorder; epilepsy or convulsions, substance use history,	N=48 randomized (50 screened 45 completed all arms) **Tr1**: nabiximols **Tr2**: whole plant THC extract, 27mg/ml in an oromucosal spray Max 48 sprays per day	11 point pain scale: Tr1 (6.1) or TR2 (6.3) vs. placebo (6.9): **statistically significant** but less than 2 point change considered to be clinically important change. 11 point sleep quality scale: TR1 (5.9) or Tr2 (6.0) vs. placebo (5.3): **statistically significant**	Withdrawals: 1 treatment (feeling faint), 2 placebo (nausea and vomiting, anxiety and paranoia) No serious AEs reported Most common side effects: dizziness, somnolence, bad taste, nausea, feeling drunk

Author, Year Country Design Funding Source	Population Excluded Age, % Male, Race/Ethnicity Setting	Sample Size Intervention(s) Control(s) Treatment Duration Followup	Outcomes (primary first)	Harms Side Effects
	general surgery within 2 months, nerve surgery within 6 months, pregnancy/lactating, known adverse reaction to cannabis. Mean age 39, 96% male, no race/ethnicity data Outpatient setting	**C**: placebo nasal spray Duration: 13 days No wash-out period between crossover arms.	difference but less than 2 point clinically important change. McGill questionnaire (SF-MPQ pain rating index): **Favors treatment** SF-MPQ VAS: **Favors treatment** Pain disability index (PDI): **No difference** General health questionnaire-12 (GHQ-12): **Favors treatment**	Intoxication VAS (100 mm): placebo-1 mm, nabiximols – 5.9 mm, THC – 9.7 mm
Pini 2012[19] Italy Crossover RCT No funding	Adult patients 35-65 with at least 5 years medication overuse headache, failed detoxification $\geq$3 times Severe mental illness, previous continuous ibuprofen use, previous anticoagulant or antiplatelet agents, sensitive to cannabinoids, renal, hepatic, cardiovascular conditions, pregnancy/lactation, epilepsy Mean age 53, 33% male, mean chronic headache 12 years	N=30 **Tr1**: nabilone (0.5 mg) oral capsules **C:** ibuprofen (400 mg) identical oral capsules Duration:8 weeks with 1 week washout Followup: 2 weeks after stopping treatment	6 primary outcomes: Reduction in headache frequency (# headache days/month); Duration of headache pain; Intensity of headache pain; Daily analgesic intake Both arms showed improvement in all primary outcomes. Statistically different between arms for daily analgesic intake, duration of pain. **Favors Treatment** Headache Impact Test: Both arms improved, **no difference** Zung Depression and Anxiety Scales: Both arms improved, **Favors Treatment** *Patients taking nabilone during 2nd phase showed some continuation of benefit at 2 weeks after stopping treatment.*	Withdrawals: 2 per arm. 1 per arm for AE Most common AE: Dizziness, sleep disorders, decreased appetite, vomiting, nausea, asthenia, gastric discomfort, dry mouth, loss of attention

Author, Year Country Design Funding Source	Population Excluded Age, % Male, Race/Ethnicity Setting	Sample Size Intervention(s) Control(s) Treatment Duration Followup	Outcomes (primary first)	Harms Side Effects
Wissel, 2006[20] Austria Crossover RCT Not Reported	Adults with chronic upper motor neuron syndrome with spasticity-related pain refractory to treatment. No exclusion criteria reported Mean age 45 years, 31% males, no race/ethnic data	N=13 randomized (11 completers) **Tr1:** Nabilone oral capsule, titrated from 0.5 mg to 1 mg per day **C:** placebo capsule Duration: 4 weeks plus 1 week washout	11 point box test pain intensity rating: 2 point decrease in pain for nabilone vs placebo (p=0.05, no other data provided)	Withdrawals: 2 MS patients from nabilone for acute relapse and exacerbation of lower limb weakness. No other severe side effects reported. Other AEs reported: drowsiness, weakness in lower limbs

Other Contributing Studies

Table 11 lists two case series and an open label extension of an RCT that was excluded at the RCT phase due to treatment duration. Along with the other open-label studies (listed in Tables 6-10 to keep the studies together with the parent RCT), Patients were observed for much longer periods in the open-label and case series studies, generally between 6 months and 4 years. The longer durations were off-set by the relatively small study numbers, limiting the ability of these observational designs to add to our understanding of potential harms. Too small patient numbers make it difficult to capture relatively rare serious adverse events, if they exist. Otherwise, the harms profiles in the observational studies paralleled those seen in shorter-term trials.

Table 11. Other contributing observational studies

Author, Year Country Design Funding Source	Population Excluded Age, % Male, Race/Ethnicity Setting	Sample Size Intervention(s) Control(s) Treatment Duration Followup	Outcomes (primary first)	Harms Side Effects
Berlach, 2006[21] Canada Case Series University	Adult chronic pain patients receiving nabilone off-label as adjunctive treatment. Pain etiologies: posttraumatic (n=7), reflex sympathetic dystrophy (n=3), arthritis (n=2), Crohn's disease (n=2), other (n=6) No exclusion criteria reported. Mean age 48, 52% male, no race data Single site	N=20 1 mg at night, increased to 1 mg bid if tolerated, up to 2 mg bid Duration: for 9 patients who remained on nabilone, average use 1.5 years; longest over 4 years Followup: unclear	*[Pain intensity 0-10 scale standard clinic practice. No difference in pain scores from baseline to final for change in highest pain level for week, average level for week, lowest level for week, and current level. Patients who remained on stayed on for reported improvements in quality or duration of sleep, decrease in nausea or vomiting, and helped to reduce (smoked) cannabis intake.]*	Withdrawals: 3 for palpitations, dry mouth, urinary retention Side effects: decreased: clarity, concentration, focus (3); dry mouth (2), headaches (2), nausea/vomiting (2), 1 each: apathy, puffy lips, red cheeks, fatigue, palpitations, dizziness; drowsiness; transient deformity of left side of face; depression; forgetfulness

Author, Year Country Design Funding Source	Population Excluded Age, % Male, Race/Ethnicity Setting	Sample Size Intervention(s) Control(s) Treatment Duration Followup	Outcomes (primary first)	Harms Side Effects
Haroutiunian, 2008[22] Israel Case series Not reported	Adult patients with chronic nonmalignant pain not adequately responding to other medications. Mean age 46, 54% male, no race/ethnic data Single site outpatient	N=13 5 mg in 0.2 mL of olive oil delta-9-THC, liquid oral dose under tongue 2 times per day, max 3 times per day for inadequate responders Duration: 5 days to 36 months (responders 1 month to 26 months)	*[Single items from categories from TOPS quality of life instrument. 5 of 13 were treatment responders (diffuse bone pain, fibromyalgia, low back pain, trigeminal neuralgia, combination fibromyalgia and migraine and vestibulitis) and chose to continue.]*	Sleepiness (n=2), heaviness (n=2), 1 each sedation, dizziness, abdominal discomfort, nausea, nervousness, difficulty concentrating, weight gain
Narang, 2008[23] US RCT open label extension Industry	Adults with chronic non-cancer pain on stable opioid regimen (>6 months) and pain ≥4 on 0-10 scale. Cancer pain, using transdermal fentanyl patch or intrathecal opioid, severe mental illness, substance abuse, pregnant Mean age 43, 47% male, 97% white Pain classifications: neuropathic (7), nociceptive (7), mixed neuropathic and nociceptive (11), uncategorized (5). 57% had had spine surgery.	N=28 (24 completed) **Tr1**: dronabinol capsule, from 5 mg 1X per day to 20 mg 3X per day, self-titrated Duration: 4 weeks	*[Average pain decreased each week over the 4 week period, using 0-10 scale. Patient satisfaction and pain relief increased by 1.7 and 1.8 respectively from 0-10 scale, pain bothersomeness decreased 0.74 from 0-10 scale. Also improvements from baseline in Brief Pain Inventory sleep, RAND-36 Energy/Fatigue, Pain, and social Functioning scores, and MOS Sleep Scale for sleep disturbance, sleep problems, and sleep adequacy. No difference in Hamilton Depression Scale.]*	4 of 28 withdrew – 1 believed dronabinol precipitated migraines; 1 due to side effects, 1 "pain unrelated to study," 1 lost to followup. Most common AE: dry mouth, tiredness, sleepiness, drowsiness, anxiety/nervousness, headache, dizziness, abdominal pain, nausea, forgetfulness

Addressing the JAMA 2015 Summary of Cannabinoids for Medical Use Systematic Review

We did not use the recently published JAMA 2015 review to replace any systematic review process for benefits. The JAMA 2015 review included patient populations (cancer pain), and study designs (data from studies that did not undergo peer vetting through publication processes) outside the scope of this review. While the decision about whether or how to include unpublished data (generally industry-funded) remains under discussion, we prefer the conservative approach of using unpublished studies to assess whether a bias in the types of studies published may exist, but otherwise not use unpublished data in meta-analyses. We were also unable to verify the risk of bias assessments employed by the JAMA 2015 team for those studies. Some studies were excluded for too short treatment durations. However, this set of excluded studies was not used in the JAMA 2015 pooled analyses, so this loss of studies does not affect the review findings.

After removing the excluded studies, we re-analyzed the relevant outcomes assessed in the JAMA 2015 review following the same broad pooling of studies across all chronic pain patients and medical cannabis treatments. The Brief Pain Inventory outcome was not re-analyzed as the number of included studies dropped too low. (We also did not re-analyze the EQ-5D because it is not a pain-specific outcome.) Removing excluded studies also narrowed the poolable studies to tests of nabiximols (Table 12).

Table 12. Comparison of JAMA review to re-analyses

Outcome	JAMA 2015 Review		Re-analysis	
Pain reduction ≥30% (NRS or VAS)	8 studies (N=1370)	OR 1.41 (95% CI 0.99, 2.00) No difference Moderate strength	3 studies (N=493)	OR 1.30 (95% CI 0.89, 1.89) No difference Low strength
NRS score (1-10)	6 studies (N=948)	WMD -0.46 (95% CI -0.80, -0.11) Favors treatment Moderate strength	3 studies (N=530)	WMD -0.62 (95% CI -1.63, 0.40) No difference Low strength
Neuropathic pain scale (0-100)	5 studies (N=764)	WMD -3.89 (95% CI -7.32, -0.47) Favors treatment Moderate strength	4 studies (N=467)	WMD -5.18 (95% CI -8.24, -2.12) Favors treatment Low strength
Patient global impression of change	6 studies (N=267)	OR 2.08 (95% CI 1.21, 3.59) Favors treatment Low strength	2 studies (N=81)	OR 6.07 (95% CI 2.24, 16.47) Favors treatment Insufficient strength

Of the four outcomes re-analyzed, pain reduction by 30% remained non-significant, pain numerical rating scale became non-significant between groups, change in neuropathic pain remained significant in favor of nabiximols, as did patient global impressions of change. (Forest plots are available in Appendix E.) However, given the increase in the width of the confidence intervals, if one continues to be satisfied with the pooling strategy, the strength of evidence for 30% responders, the neuropathic pain scale, and the numerical rating scale would drop to low, and patient global impressions would become insufficient.

This re-analysis illuminated that the reported quantitative findings of benefit generally hinged on a smaller subset of studies. After dropping studies that did not meet our inclusion criteria, only six studies reported similar outcomes with enough detail to allow for pooling. This subset of studies did not necessarily represent the best evidence available in terms of risk of bias or chosen outcomes. They merely represented what was quantitatively poolable. The results are, however, consistent with the earlier qualitative analysis by patient populations.

The JAMA 2015 results for adverse events, or harms, are representative of the literature examined in this review, therefore we let stand the JAMA 2015 findings that cannabinoids are associated with greater risk of any AE, serious AE, withdrawals due to AE, and other specified AEs as compared with placebo. Neither the JAMA 2015 review nor our review can speak to comparing AEs between cannabinoids and opioids or other analgesics, since there was no literature beyond the one small study on nabilone versus dihydrocodeine to support any statements.

Discussion

Overall, the literature for medical cannabis for chronic non-cancer pain is sparse, patchy, of low quality, and leads to generally insufficient evidence for most patient populations and treatments. We found only two populations for which low-strength evidence exists for nabiximols as an adjunctive treatment to improve pain outcomes relative to placebo. One population was for pain related to MS, and the other peripheral neuropathic pain with allodynia. The small study sizes and difficulty designing and conducting a study for treatments prone to placebo effects and patients discerning which arm they were assigned to contribute to the lack of evidence.

There are also challenges with the applicability of the findings to the Minnesota Medical Cannabis program. First, it is difficult to judge whether the patient populations in the studies well represent the patients who may sign up for the program. The RCTs certainly suffer from the well-known problem of highly-selected patients who frequently lack the comorbidities and other complexities of the general population of patients. On the other hand, the study investigators generally attempted to identify patients with enough pain chronicity and pain severity that they may compare well. The literature is also silent on large swaths of patients, such as those with chronic and severe low back pain and other musculoskeletal pain conditions.

The applicability of the treatments is also a challenge. Nabiximols was the most commonly studied treatment, and is relevant to the extent that the botanical source and combination THC/CBD of the product compares better than synthetic products with a single active ingredient to the whole-plant extracts available through the Minnesota program. However, all the treatments examined in this review remain at best indirect evidence.

The other major problem with the literature is the treatment duration. The studies are too short to speak to the long-term use that could be expected for people with chronic pain. We do not know much about how treatment effects may change over time, including the possibility of diminishing benefits, nor enough about the long-term harms. We included in the review what longer-term studies we could identify, but they lacked comparison arms to understand what benefits were attributable to the treatment, and the studies were often too small to adequately capture long-term harms if they are more rare and if not yet identified.

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Appendix A: Search Algorithms

MEDLINE Search Strategy

1. exp *Pain/
2. pain.ti.
3. exp Terminal Care/
4. exp Respite Care/
5. exp Medical Marijuana/
6. exp Cannabis/
7. cannabi*.tw.
8. dronabinol.tw.
9. exp Dronabinol/
10. tetrahydrocanni*.tw.
11. nabilone*.tw.
12. tetranabin*.tw.
13. benzopyranoperidine.tw.
14. sativex.tw.
15. idrasil.tw.
16. exp Cannabinoids/
17. exp Cannabidiol/
18. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 1 or 2 or 3 or 4
20. 18 and 19
21. limit 20 to "therapy (maximizes sensitivity)"
22. Case-Control Studies/ or Control Groups/ or Matched-Pair Analysis/ or retrospective studies/ or ((case* adj5 control*) or (case adj3 comparison*) or control group*).ti,ab.
23. Cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/ or cohort.ti,ab. or longitudinal.ti,ab. or prospective.ti,ab. or retrospective.ti,ab.
24. Cross-Sectional Studies/ or cross-sectional.ti,ab. or ("prevalence study" or "incidence study" or "prevalence studies" or "incidence studies" or "transversal studies" or "transversal study").ti,ab.
25. ("clinical trial" or "clinical trial, phase i" or "clinical trial, phase ii" or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or "multicenter study" or "randomized controlled trial").pt. or double-blind method/ or clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or early termination of clinical trials as topic/ or multicenter studies as topic/ or ((randomi?ed adj7 trial*) or (controlled adj3 trial*) or (clinical adj2 trial*) or ((single or doubl* or tripl* or treb*) and (blind* or mask*))).ti,ab.
26. Epidemiologic Studies/
27. ((("semi-structured" or semistructured or unstructured or informal or "in-depth" or indepth or "face-to-face" or structured or guide) adj3 (interview* or discussion* or questionnaire*)) or (focus group* or qualitative or ethnograph* or fieldwork or "field work" or "key informant")).ti,ab. or interviews as topic/ or focus groups/ or narration/ or qualitative research/

28. (((comprehensive* or integrative or systematic*) adj3 (bibliographic* or review* or literature)) or (meta-analy* or metaanaly* or "research synthesis" or ((information or data) adj3 synthesis) or (data adj2 extract*))).ti,ab. or (cinahl or (cochrane adj3 trial*) or embase or medline or psyclit or (psycinfo not "psycinfo database") or pubmed or scopus or "sociological abstracts" or "web of science").ab. or ("cochrane database of systematic reviews" or evidence report technology assessment or evidence report technology assessment summary).jn. or Evidence Report: Technology Assessment*.jn. or ((review adj5 (rationale or evidence)).ti,ab. and review.pt.) or meta-analysis as topic/ or Meta-Analysis.pt.
29. (case$ and series).tw. or case reports.pt. or (case$ adj2 report$).tw. or (case$ adj2 stud$).tw.
30. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31. 20 and 30
32. 21 or 31
33. limit 32 to humans
34. limit 33 to (addresses or autobiography or bibliography or biography or comment or congresses or dataset or dictionary or directory or duplicate publication or editorial or festschrift or in vitro or interactive tutorial or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index or portraits)
35. 33 not 34

<u>EMBASE Search Strategy</u>

1. exp *Pain/
2. pain.ti.
3. exp Terminal Care/
4. exp Respite Care/
5. exp Medical Marijuana/
6. exp Cannabis/
7. cannabi*.tw.
8. dronabinol.tw.
9. exp Dronabinol/
10. tetrahydrocanni*.tw.
11. nabilone*.tw.
12. tetranabin*.tw.
13. benzopyranoperidine.tw.
14. sativex.tw.
15. idrasil.tw.
16. exp Cannabinoids/
17. exp Cannabidiol/
18. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 1 or 2 or 3 or 4
20. 18 and 19
21. limit 20 to "therapy (maximizes sensitivity)"
22. limit 21 to human

23. limit 22 to (book or book series or conference abstract or conference paper or conference proceeding or "conference review" or editorial or erratum or letter or note or "review" or short survey or trade journal)
24. 22 not 23

AMED [OVID] Search Strategy

1. exp Pain/
2. pain.ti.
3. exp Terminal Care/
4. exp suicide, assisted
5. exp Respite Care/
6. exp Cannabis/
7. cannabi*.tw.
8. dronabinol.tw.
9. tetrahydrocanni*.tw.
10. nabilone*.tw.
11. tetranabin*.tw.
12. benzopyranoperidine.tw.
13. sativex.tw.
14. idrasil.tw.
15. exp Cannabinoids/
16. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. 1 or 2 or 3 or 4 or 5
18. 16 and 17

Appendix B: Excluded Studies

1. Abrams DI, Couey P, Shade SB, Kelly ME, Benowitz NL. Cannabinoid-opioid interaction in chronic pain. Clin Pharmacol Ther. 2011 Dec;90(6):844-51. PubMed PMID: 22048225. English. Treatment less than 2 weeks
2. 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 February;68(7):515-21. PubMed PMID: 2007090773. English. Treatment less than 2 weeks
3. Eisenberg E, Ogintz M, Almog S. The pharmacokinetics, efficacy, safety, and ease of use of a novel portable metered-dose cannabis inhaler in patients with chronic neuropathic pain: A phase 1a study. Journal of Pain and Palliative Care Pharmacotherapy. 2014 September;28(3):216-25. PubMed PMID: 2014576008. English. Treatment less than 2 weeks
4. 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 Feb;34(3):672-80. PubMed PMID: 18688212. Pubmed Central PMCID: NIHMS277052 PMC3066045. English. Treatment less than 2 weeks
5. Issa MA, Narang S, Jamison RN, Michna E, Edwards RR, Penetar DM, et al. The subjective psychoactive effects of oral dronabinol studied in a randomized, controlled crossover clinical trial for pain. Clin J Pain. 2014 Jun;30(6):472-8. PubMed PMID: 24281276. Pubmed Central PMCID: NIHMS541723 [Available on 06/01/15] PMC4013220 [Available on 06/01/15]. English. Treatment less than 2 weeks
6. Karst M, Salim K, Burstein S, Conrad I, Hoy L, Schneider U. Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial. Jama. 2003 Oct 1;290(13):1757-62. PubMed PMID: 14519710. English. Treatment less than 2 weeks
7. Lynch ME, Young J, Clark AJ. A case series of patients using medicinal marihuana for management of chronic pain under the Canadian Marihuana Medical Access Regulations. J Pain Symptom Manage. 2006 Nov;32(5):497-501. PubMed PMID: 17085276. English. Questioinnaire without chart verification
8. Maurer M, Henn V, Dittrich A, Hofmann A. Delta-9-tetrahydrocannabinol shows antispastic and analgesic effects in a single case double-blind trial. European Archives of Psychiatry and Neurological Sciences. 1990;240(1):1-4. PubMed PMID: 1990329799. English. N of 1 study
9. 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 May;59(5):440-52. PubMed PMID: 15096238. English. N of 1 study
10. Rintala DH, Fiess RN, Tan G, Holmes SA, Bruel BM. Effect of dronabinol on central neuropathic pain after spinal cord injury: a pilot study. Am J Phys Med Rehabil. 2010 Oct;89(10):840-8. PubMed PMID: 20855984. English. RCT of only 5 patients
11. Salim K, Schneider U, Burstein S, Hoy L, Karst M. Pain measurements and side effect profile of the novel cannabinoid ajulemic acid. Neuropharmacology. 2005 Jun;48(8):1164-71. PubMed PMID: 15910892. English. Treatment shorter than 2 weeks
12. Schley M, Legler A, Skopp G, Schmelz M, Konrad C, Rukwied R. Delta-9-THC based monotherapy in fibromyalgia patients on experimentally induced pain, axon reflex flare, and pain relief. Curr Med Res Opin. 2006 Jul;22(7):1269-76. PubMed PMID: 16834825. English. Case series less than 10
13. Toth C, Mawani S, Brady S, Chan C, Liu C, Mehina E, et al. An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. Pain. 2012 Oct;153(10):2073-82. PubMed PMID: 22921260. English. Case series less than 10
14. 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 Aug;10(4):434-41. PubMed PMID: 15327042. English. Data not specific to patients identifying pain as primary symptom

15. 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 Feb;17(1):21-9. PubMed PMID: 12617376. English. Data not usable – not specific to pain patients
16. Wallace M, Marcotte T, Umlauf A, Gouaux B. Efficacy of inhaledcannabis on painful diabetic neuropathy. The Journal of Pain. 2015;16(7):616-27. Treatment shorter than 2 weeks
17. 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 Oct 5;182(14):E694-701. PubMed PMID: 20805210. Pubmed Central PMCID: PMC2950205. English. Treatment shorter than 2 weeks
18. 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 Jun;9(6):506-21. PubMed PMID: 18403272. English. Treatment shorter than 2 weeks
19. Zajicek J, Hobart J, Slade A, Barnes D, Mattison P, on behalf of the MUSEC Research Group. MUltiple Scelrosis and Extract of Cannabis: results of the MUSEC trial. J Neurol Neurosurg Psychiatry. 2012;83:1125-32. Unclear patient population

Appendix C: Risk of Bias

Author, Year Country	Study Design	Overall Summary Score	Comments
Berlach, 2006[21] Canada University	Case Series	High	Selection issues, no controls, data imputation used, but unknown amount.
Berman, 2004[18] UK Industry	Crossover RCT	Moderate (high per JAMA)	No information on allocation concealment. Did not check for patient guessing assignment. Patients completed daily diary of pain outcomes. All patients retained, missing data from 2 in one arm, 1 in one arm, 0 in one arm.
Blake, 2006[13] UK Industry	RCT	High (unknown per JAMA)	No information on blinding process. No information on allocation concealment. Patients completed daily diary of pain outcomes. N not provided for outcome table (unknown incomplete data issues)
Frank, 2008[5] UK Industry	Crossover RCT	High (high per JAMA)	No information on randomization process. No information on blinding. No information on allocation concealment. Patients completed pain diary and other outcome forms. Incomplete outcome data.
Haroutiunian, 2008[22] Israel Not reported	Case series	High	Selection issues, no controls
Hoggart, 2015[15] UK, Czech Republic, Belgium, Canada Industry	Open label extension (Serpell study extension)	High	No controls. Patients completed daily and weekly diary of pain outcomes.
Langford, 2013[7] UK, Czech Republic, Spain, France, Canada Industry	RCT	Moderate (unclear per JAMA)	No information on allocation concealment. Did not check for patient guessing assignment.
Langford, 2013[7] France, Czech Republic Industry	Open-label with blinded randomized withdrawal	High	No information on allocation concealment. Did not check for patient guessing assignment – placebo effect could again be in direction of favoring treatment.
Narang, 2008[23] US Industry	RCT open label extension	High	No controls
Nurmikko 2007[16] UK, Belgium Industry	RCT	Moderate (high per JAMA)	Both arms used peppermint oil to mask treatment. Patients completed daily diary for pain and sleep quality and adverse events.17.6% noncompleters but ITT. Did not check for patient guessing assignment.
Nurmikko 2007[16,19] UK, Belgium Industry	RCT Open label extension	High	No controls
Pini 2012[19] Italy No funding	Crossover RCT	High	No information on recruitment, screening. Oral capsules provided by independent pharmacy. No information on allocation concealment. Patients completed daily diary for pain. Outcome assessor blinded. 13% drop-out, no ITT
Rog, 2005[8] UK Industry	RCT	Moderate (unclear per JAMA)	No information on allocation concealment. Did not check for patient guessing assignment.

Author, Year Country	Study Design	Overall Summary Score	Comments
Rog, 2007[9] UK Industry	RCT open label extension	High	No controls.
Selvarajah, 2010[17] UK Industry	RCT	High (unclear per JAMA)	Short report – no information provided on randomization, blinding, allocation concealment, outcome assessing. 20% withdrawal rate (ITT used)
Serpell, 2014[14] UK, Czech Republic, Romania, Belgium, Canada Industry	RCT	High (unclear per JAMA)	Both arms used peppermint oil to mask treatment. Patients completed daily diary for pain and adverse events.>25% noncompleters but ITT. Did not check for patient guessing assignment.
Skrabek, 2008[12] Canada Industry	RCT	Moderate (unclear per JAMA)	No information on allocation concealment. Attrition rate 17.5%, no ITT analysis, no data for baseline comparison for completers.
Svendsen, 2004[10] Denmark Industry, Private Grant	Crossover RCT	Moderate (unclear per JAMA)	Masked treatment with sesame oil. Patient completed daily diary for pain and adverse events. Asked patients for assignment guess.
Turcotte, 2015[11] Canada Industry	RCT	High (high per JAMA)	No information on allocation concealment. Patient completed daily diary for pain and adverse events. Missing data imputation for 16%, differences by groups.
Ware, 2010[6] Canada Industry	Crossover equivalency RCT	Low (low per JAMA)	Asked patients for assignment guess. Daily diaries used but supplemented with telephone-administered questionnaires by outcome assessor.
Wissel, 2006[20] Austria Not Reported	Crossover RCT	High	No information on randomization, allocation, blinding, including outcome assessor.

Appendix D. Strength of Evidence

Comparison	Sample	Finding	Study Limitations	Directness (for cannabis studied)	Precision	Consistency	Evidence Rating
Comparative effectiveness							
Nabilone vs. dihydrocodeine	N=96 (Frank[5]) neuropathic pain	Pain outcomes	High	Direct	Imprecise	Single study	Insufficient
Nabilone vs. amitriptyline	N=32 (Ware[6]) fibromyalgia	Pain outcomes	Moderate	Direct	Imprecise (small n)	Single study	Insufficient
Pain related to MS							
Dronabinol vs. placebo	N=24 (Svendsen[10])	Pain outcomes	Moderate	Direct	Imprecise (small n)	Single study	Insufficient
Nabilone vs. placebo	N=15 (Turcotte[11])	Pain outcomes	High	Direct	Imprecise (small n)	Single study	Insufficient
Sativex vs. placebo	N=405 (Langford,[7] Rog[8])	No difference between nabiximols and placebo for pain for patients with MS and central neuropathic pain.	Moderate	Direct	Imprecise (across outcomes)	Inconsistent	Low (based on moderate RoB Langford with n=339)
Fibromyalgia							
Sativex vs. placebo	N= 58 (Blake[13])	Pain outcomes	High	Direct	Imprecise (small n)	Single study	Insufficient
Rheumatoid Arthritis							
Sativex vs. placebo	N=246 (Serpell[14])	% responders (>30% improvement in pain) larger for nabiximols group for adults with peripheral neuropathic pain/allodynia	High	Direct		Single study	Low (based on relatively large multi-site N)

Appendix E: Forest Plots of Re-analyzed JAMA review

Figure E1. Percent of patients with 30% improvement in pain

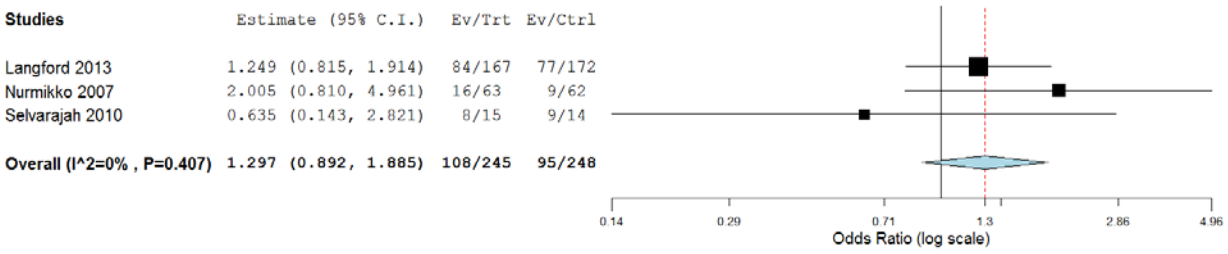

Figure F1 pools MS patients with central neuropathic pain (Langford[7]), adults with unilateral peripheral neuopathic pain (Nurmikko[16]), and adults with diabetic neuropathy (Selvarajah[17]). All for nabiximols.

Figure E2. Change in neuropathic pain scale

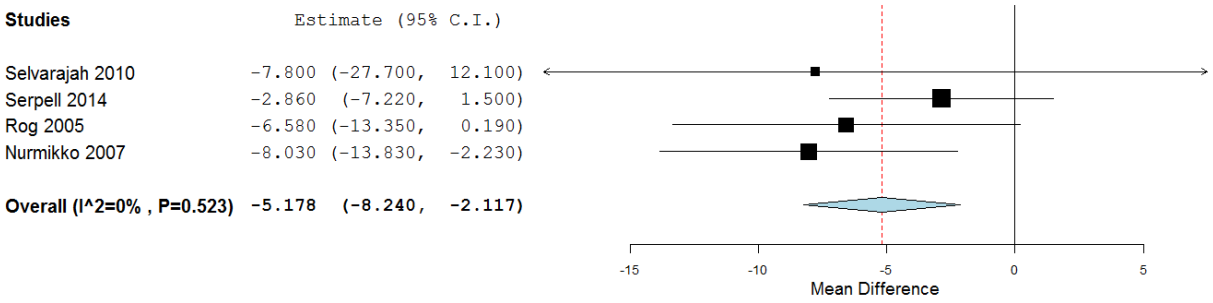

Figure F2 pools adults with unilateral peripheral neuopathic pain (n=125) (Nurmikko[16]), adults with diabetic neuropathy (n=30) (Selvarajah[17]), adults with peripheral neuropathic pain (n=246) (Serpell[14]), and adults with MS with central neuropathic pain symptoms (n=66)(Rog[8]). All for nabiximols. If reduced to only Serpell and Nurmikko, the estimate changes to -5.077 (-10.091, -0.062)

Figure E3. Change in numerical rating scale for pain

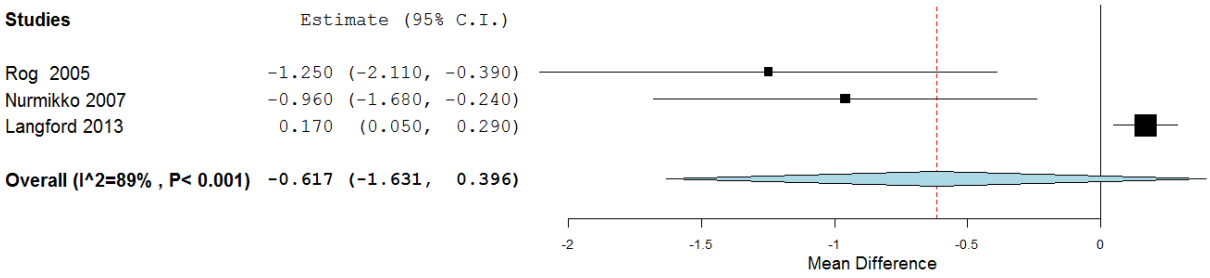

Figure F3 pools adults with unilateral peripheral neuropathic pain (n=125) (Nurmikko[16]), and adults with MS with central neuropathic pain symptoms (n=66) (Rog[8]), and MS patients with central neuropathic pain (Langford). All for nabiximols.

Figure E4. Change in patient global impression of change

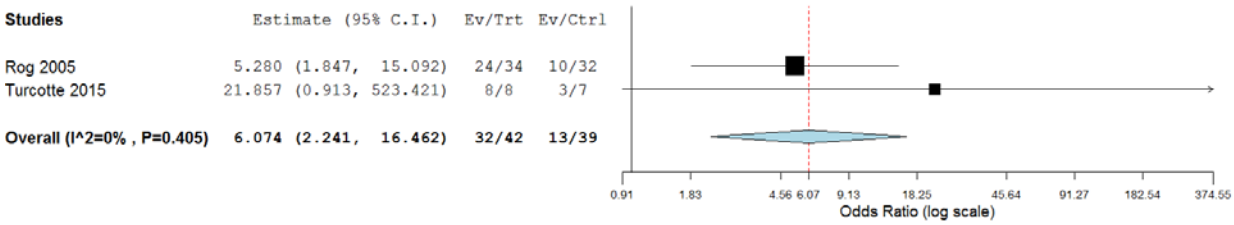

Figure F4 pools adults with MS with central neuropathic pain symptoms (n=66)(Rog[8]), and relapse-remitting MS patients with neuropathic pain on gabapentin (n=15) (Turcotte[11]). All for nabiximols