Systematic Review

Efficacy of Cannabis-Based Medicines for Pain Management: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

J. Aviram, RN, PhC[1] and G. Samuelly-Leichtag, PT, PhC[2]

From: [1]Faculty of Social Welfare and Health Sciences, University of Haifa, Israel and Rambam Health Care Campus, Haifa, Israel; [2]The Rappaport Faculty of Medicine, Technion - Israel Institute of Technology, Haifa, Israel

Address Correspondence:
Joshua Aviram, RN, PhC
Faculty of Social Welfare and Health Sciences
University of Haifa
Haifa 31905, Israel
E-mail: shukiaviram@gmail.com

Disclaimer: There was no external funding in the preparation of this manuscript. Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 09-12-2015
Revised manuscript received:01-18-2016, 02-22-2017
Accepted for publication: 04-12-2017

Free full manuscript: www.painphysicianjournal.com

Background: The management of chronic pain is a complex challenge worldwide. Cannabis-based medicines (CBMs) have proven to be efficient in reducing chronic pain, although the topic remains highly controversial in this field.

Objectives: This study's aim is to conduct a conclusive review and meta-analysis, which incorporates all randomized controlled trials (RCTs) in order to update clinicians' and researchers' knowledge regarding the efficacy and adverse events (AEs) of CBMs for chronic and postoperative pain treatment.

Study Design: A systematic review and meta-analysis.

Methods: An electronic search was conducted using Medline/Pubmed and Google Scholar with the use of Medical Subject Heading (MeSH) terms on all literature published up to July 2015. A follow-up manual search was conducted and included a complete cross-check of the relevant studies. The included studies were RCTs which compared the analgesic effects of CBMs to placebo. Hedges's g scores were calculated for each of the studies. A study quality assessment was performed utilizing the Jadad scale. A meta-analysis was performed utilizing random-effects models and heterogeneity between studies was statistically computed using I^2 statistic and tau^2 test.

Results: The results of 43 RCTs (a total of 2,437 patients) were included in this review, of which 24 RCTs (a total of 1,334 patients) were eligible for meta-analysis. This analysis showed limited evidence showing more pain reduction in chronic pain -0.61 (-0.78 to -0.43, $P < 0.0001$), especially by inhalation -0.93 (-1.51 to -0.35, $P = 0.001$) compared to placebo. Moreover, even though this review consisted of some RCTs that showed a clinically significant improvement with a decrease of pain scores of 2 points or more, 30% or 50% or more, the majority of the studies did not show an effect. Consequently, although the primary analysis showed that the results were favorable to CBMs over placebo, the clinical significance of these findings is uncertain. The most prominent AEs were related to the central nervous and the gastrointestinal (GI) systems.

Limitations: Publication limitation could have been present due to the inclusion of English-only published studies. Additionally, the included studies were extremely heterogeneous. Only 7 studies reported on the patients' history of prior consumption of CBMs. Furthermore, since cannabinoids are surrounded by considerable controversy in the media and society, cannabinoids have marked effects, so that inadequate blinding of the placebo could constitute an important source of limitation in these types of studies.

Conclusions: The current systematic review suggests that CBMs might be effective for chronic pain treatment, based on limited evidence, primarily for neuropathic pain (NP) patients. Additionally, GI AEs occurred more frequently when CBMs were administered via oral/oromucosal routes than by inhalation.

Key words: Cannabis, CBMs, chronic pain, postoperative pain, review, meta-analysis

Pain Physician 2017; 20:E755-E796

The treatment of chronic pain is based on a combination of pharmacotherapy and complementary non-pharmacotherapy treatment (1-3). The approach for pharmacological treatment for the relief of chronic pain is based primarily on pain intensity. This approach determines that mild pain should be treated with "simple" analgesics, whereas moderate to severe pain should be treated with opioids (4). However, the abundant use of opioids has become a highly controversial topic due to the wide range of problems it presents, such as the large potential for abuse, long-term safety, and difficulty to follow-up on.

Chronology of Cannabis

Cannabis sativa is thought to have been grown for at least 12,000 years, initially for fiber and grain. The earliest use of cannabis as a medicine is attributed to the Chinese emperor Shen Nung, around 2700 BC. The first evidence of the medical use of cannabis came from the fourth century burial in a cave west of Jerusalem; archeologists concluded that cannabis had been burnt in a vessel and was used by smoke inhalation to reduce pain during an unsuccessful child delivery (5). The Irish physician William Brooke O'Shaughnessy (6) first introduced the analgesic effect of cannabis to the Western world in a pioneer study in 1839. Today, the pain management field is largely leaning towards the research of cannabis-based medicines (CBMs) which have become some of the most debated medicines to-date. The paradigmatic change that accelerated the use of cannabinoids for pain treatment started in the 1960s. In 1964, Mechoulam and Gaoni (7) identified tetrahydrocannabinol (delta-9-THC) as the main psychoactive component of cannabis. Additionally, Lester Grinspoon (8) described the positive effect of cannabinoids for the treatment of intractable conditions. From a clinical standpoint, most physicians grasp CBMs as a palliative treatment or as a part of a multi-model pain treatment. On the other hand, the use of CBMs is poorly taught in the training of physicians due to the scarcity of quality randomized controlled trials (RCTs) in this field (9).

Cannabis Research Agendas

In pain clinics across Canada, the rate of the use of CBMs is estimated to be between 12–15% (10). Unlike opioids, there is a minority of cannaboid (CB) receptors in the brain stem in the areas that control breathing, which explains the low toxicity of cannabinoids (11). This is one of the main reasons that further research is needed on the use of CBMs for pain treatment. However, clinical research on CBMs is limited in quality and quantity (mainly when utilized by smoking and inhalation), due to the lack of research funding in this field. Furthermore, studying the positive effects of CBMs is in contrast to the global anti-smoking and anti-drugs strategies, and until those issues can be resolved, no large-scale phase III study can be made on the efficacy of herbal cannabinoids. In terms of drug trials, an overwhelming leap has been made from phase II trials directly to phase IV trials for the use of this complex botanical compound (9).

Clinically, the most common route of administration for CBMs is by inhalation, or smoking (12), followed only by ingestion. Other routes of administration include rectal, sublingual, transdermal, ocular, and intravenous (13). Despite the significant discoveries that support the therapeutic potential of CBMs, the health hazards of smoking (14) combined with the cognitive and emotional impacts that are related to cannabinoid use have generated regulatory obstacles worldwide (15). However, the use of cannabinoids as a medication is becoming more common (16), and there is ample development in the routes of administration. Specifically, new technologies are being implemented in order to simplify the medicinal use of cannabinoids, decrease side effects, and provide a constant level of cannabinoid in the blood stream (17).

Cannabinoids: Clinical Trials, Reviews, and Meta-Analyses Chronology

Thus far, 9 reviews of RCTs have been published regarding the effects of CBMs on pain. The earliest of them was published in 2001, by Campbell et al (18), which summarized studies that used single-dose CBM for the treatment of various types of chronic malignant and non-malignant pain in comparison to codeine or to codeine and placebo. The authors reported that, in general, no benefit was found for CBMs over codeine, but over placebo only. Two additional reviews reported conflicting results regarding the efficacy of CBM use for the treatment of various types of pain conditions including postoperative, visceral, cancer, and neuropathic pain (NP) (19,20). The effects of CBMs (e.g., nabilone, dronabinol, and THC analogue) and smoked cannabinoids were examined in several recent RCT studies; the appraising of those studies in 3 different reviews revealed overall evidence that cannabinoids are safe and moderately effective for the investigated diagnoses (21-23). Furthermore, the 3 most recent reviews of RCTs

showed that CBMs may provide effective analgesia for non-malignant NP (24) and for chronic non-malignant pain (25). One last review of 6 trials that included 325 chronic pain patients and 6 trials that included 396 NP patients suggested that cannabinoids may be efficacious for NP (26). Additionally, many more reviews were published regarding the effect of CBMs on pain, however, these studies were limited by case-based, anecdotal-based, or laboratory-based scientific research on headaches (27), NP (28-31), chemotherapy-induced pain (32), multiple sclerosis (MS) pain (33), HIV-associated sensory neuropathy (34), and rheumatoid arthritis pain (35). Finally, a few conference proceedings also investigated the effects of CBMs on pain (36), more specifically on musculoskeletal pain (37) and NP (38).

To this date, 4 meta-analyses summarized the efficacy and safety data of CBMs for chronic pain versus placebo; each has specific merits and faults (39-42). The first meta-analysis, by Iskedjian et al (39), investigated 7 (9 publications) randomized, double-blinded, placebo-controlled trials involving the use of CBMs in the treatment of pain associated with MS or other types of NP (43-51). All of these trials showed a significant decrease in pain intensity (ranging from 1.5–1.7 improvement, on a scale of 0–10) by CBMs, but also reported a significant decrease in pain intensity (a 0.8 improvement) by placebo. The authors explained this data by noting that 2 of the studies allowed patients to freely use rescue medications (48,50). Removing these studies lowered the placebo effect to 0.6-point improvement, which caused the effect to render non-significant. The second meta-analysis, by Martín–Sánchez et al (40), reviewed 18 double-blind RCTs having a crossover or parallel design (43,45-48,52-61) and included 7 of them in the meta-analysis (45,48,56,57,60,61) [one of the reviewed studies included 2 phases (60)], comparing any type of cannabinoid preparation to placebo in chronic pain patients. This meta-analysis presented an overall effect size of -0.61, favoring CBMs over placebo for pain reduction. The third meta-analysis, by Whiting et al (41), meta-analyzed many medicinal effects of CBMs including nausea and vomiting response, pain reduction, and spasticity reduction, as well as the assessment of AEs. Overall, this meta-analysis included in their primary analysis 8 double-blind RCTs having a parallel design (62-68), along with one that was not published (69) and showed a non-significant, higher incidence of pain reduction due to CBMs (n = 254, total = 685) compared to placebo (n = 215, total = 685). Further analyses showed a pain reduction effect size of -0.46 (95% CI, -0.80 to -0.11). Nonetheless, this study was later claimed to have some methodological weaknesses in the letter to the editor section of the same journal; one claim was regarding the lack of integration of some of the studies in the primary analysis and another claim which consisted of 2 issues: the lack of separation between chronic pain conditions and the shortage in the AEs' complete description (70). The fourth and most recent meta-analysis is by Andreae et al (42), meta-analyzed 5 RCTs (62,71-74), focusing only on the effect of inhalation of cannabinoids for chronic NP. This meta-analysis consisting of 178 patients with follow-up ranging from days to weeks, showed short term pain intensity reduction by 30% (75,76), with numbers needed to treat (NNT) (42) 5.6 for cannabis comparable to NNT of 5.9 for gabapentin (77). Their findings suggest that inhaled cannabinoids could potentially rival currently available therapeutics for chronic NP (78), whose NNT is comparable (42), but typically range above 8 (79-81). However, Deshpande et al (82) later concluded that the studies that Andreae et al (42) used in their analysis had challenges with masking. Data could not be pooled owing to heterogeneity in THC potency by dried weight, differing the frequency and duration of treatment, and variability in assessing the outcomes. Consequently, the clinical relevance of the findings from any of the 4 meta-analyses is unknown (39-42).

Taken together, the chronological changes in the aforementioned results show an interesting trend in the beneficial effect of cannabinoids on pain. These findings can be carefully explained by the pharmacological advancement in this field, but may also be due to society's favorable attitude toward the use of CBMs for pain treatment purposes. Furthermore, many of these studies included only a single selected dose and did not investigate the most commonly used route of CBMs, i.e., inhalation. Another explanation for the discrepancy in the reviews can be due to inter-individual variation in the analgesic response to CBMs, which is associated with the different routes of administration, bioavailability, or use of additional medications that can interact with CBMs.

Study Rationale

The conflicting results of the existing reviews and meta-analyses leave the question regarding the efficacy of CBMs in the treatment of postoperative and chronic pain unanswered. Moreover, the existing meta-analyses did not include all of the studies available at this time (5–8 trials), instead of the available 24 studies.

Study Objectives

Consequently, there is a need to conduct a new, conclusive review that will present all the specific information of the compatible trials, as well as to conduct meta-analyses, which will incorporate all of the comparable RCTs in order to update the knowledge of clinicians and researchers, regarding the efficacy and the entire range of expected adverse events (AEs) of CBMs for pain treatment.

Methods

Information Sources

The study was conducted according to the PRISMA statement (83). An electronic search was made in Medline/Pubmed and in Google Scholar by the use of Medical Subject Heading (MeSH) terms on all literature published until July 2015.

Search Strategy

We used the following search terms by the use of the Boolean combination of: "cannabis" OR "cannabinoids" OR "marijuana" OR "THC" OR "tetrahydrocannabinol" AND "pain", "chronic pain" AND "postoperative pain". This was followed by a manual search in all of the reviews regarding this topic. The search covered only full text manuscripts, published in English language.

Eligibility Criteria and Study Selection

The selected studies were double-blind, RCTs (most placebo-controlled, some included active drugs and placebo comparisons, and few included only active drugs comparisons) with a crossover or parallel design. In the intervention group, patients were to have received any type of cannabis preparation, by any route of administration. Synthetic derivates of THC, such as dronabinol, nabilone, sativex/nabiximol, cannabidiol, CT-3, ajulemic acid, synthetic nitrogen analog of tetrahydrocannabinol (NIB), cannabinoid cigarettes/vaporizer, cannabinoid extract, fatty acid amide hydrolase-1 (FAAH1) inhibitor (PF-04457845), levonantradol, and benzopyranoperidine (BPP), were included. In the control group, patients were to have received either placebo, whether "identical" or not, or an "active" (weak opioids or naproxen) treatment. The patients included were to have been suffering from either pre-existing chronic pain or postoperative pain. RCTs including healthy volunteers were excluded.

Data Collection Process and Quality Assessment

The 2 authors (Aviram and Samuelly) of this review assessed the studies' quality independently, and there were no disagreements in scoring that needed to be resolved. Even though the studies were not required to have a quality threshold level other than the pre-existing inclusion criteria, their validity was assessed by the Jadad scale (84). The majority of the included trials showed moderate to high quality of evidence (Tables 1–3). To conclude our findings, according to the Jadad scale (84), 10 studies received a "5" score, showing high quality evidence. Thirty-one studies received a "3–4" score, showing moderate quality evidence. Only 2 studies received a "1–2" score, showing low quality evidence (the assessment of each study and the total scores with component item scoring are provided in Table 4.

Outcome Measures (Data Items)

The efficacy measure that was chosen was the variable "pain intensity", as scored by the numerical rating scale (NRS-11) (85), numerical 11 point box (BS-11) (86), visual analog scale (VAS) (87), and the VAS section of the questionnaire short form McGill Pain Questionnaire (88). In all of the studies, the range of pain intensity was required to be from 0-10; the studies that used scales ranging from 0-100 were converted in order to evaluate all of the studies on the same range.

AEs were assessed by analyzing the number of AEs experienced in each sample (incidence). The AEs were categorized by the effected systems (Tables 5–7).

Risk of Limitations in Individual Items

Of the 24 studies included in the meta-analysis, 12 relied on 2 intervention arms/groups (CBMs vs. placebo) (45,46,48,59,61,64-66,89-92). While other studies used a placebo control group and various intervention arms, using diverse cannabinoid preparations (43,47,56,57,60,63,93,94) or increasing doses of the same preparation over long periods of time (45,47,48,59,90-92).

Furthermore, unlike former meta-analyses that evaluated the influence of CBMs on chronic pain (39-41), this meta-analysis included data from studies that examined the effects of CBMs on postoperative pain (89,93); these studies were included in the analysis for the examination of the influence of the overall effect size of CBMs on pain (Fig. 1). Consequently, they were redacted in the following analyses because of the weak

Table 1. *Cancer pain studies' characteristics.*

First author (year)	Design (duration)	N (Dropouts)	Pathology	Administration route	Intervention drug	Placebo/ active placebo	Baseline characteristics					WO	Pain reduction Mean±Sd	Pain scale	Quality*
							Age (M±SD, years)	Female (%)	Baseline pain intensity	Cannabis previous use	Current treatment				
Johnson 2010 (63)	randomized, double blind, placebo-controlled, parallel groups (2d+2w)	144 (33)	Cancer related pain	Oromucosal spray	1.THC-2.7mg 2.THC2.5mg/ CBD2.5mg,	3. placebo	1. 61.3±12.5 2. 59.4±12.1 3. 60.1±12.3	1. 48 2. 45 3. 46	1. 5.77 2. 5.68 3. 6.05	N/I	strong opioids for at least one week to relieve pain	N/I	1. -1.07 2. -1.37 3. -0.67	NRS Pain 0-10	4
Portenoy 2012 (67)**	randomized, double blind, placebo-controlled, graded dose, parallel groups (5w)	263 (37)	Poorly controlled opioid treated chronic cancer pain	Oromucosal spray	Nabiximol: 1. 1-4 sprays per d 2. 6-10 sprays per d 3. 11-16 sprays per d	4. placebo	1. 59±12.3 2. 59±13.1 3. 58±11.2 4. 56±12.2	1. 50.5 2. 44.3 3. 46.7 4. 51.6	1. 5.8±1.3 2. 5.8±1.2 3. 5.8±1.2 4. 5.7±1.2	1. 12.1% 2. 11% 3. 10% 4. 6%	Stable high dose opioids (120-180 morphine equivalent in mgs)	N/I	Primary analysis wasn't significant. Secondary analysis proportion of patients reporting 30% pain reduction in low and medium doses. 1. -1.5± N/I 2. -1.1± N/I 3. -1.0± N/I 4. -0.8± N/I	NRS 0-10	4
Noyes 1975a (57)	randomized, double-blind, placebo\ active controlled, crossover (6h)	34 (2)	Various cancer types	Oral (capsules)	1.THC 10mg 2.THC 20mg 3.Codeine 60mg 4.Codeine 120mg	5. Placebo	51±N/I	N/I	N/I	N/I	N/I	4 hr	1. -2.9±3.61 2. -4.7±3.79 3. -3.6±4.37 4. -4.3±4.54 5. -1.9±2.56	VAS 0-10	2
Noyes 1975b (56)	randomized, double-blind, placebo\ active controlled, crossover (6h)	10 (0)	Various cancer types	Oral (capsules)	1.THC 5mg 2.THC 10mg 3.THC 15mg 4.THC 20mg	5. Placebo	51±N/I	N/I	N/I	N/I	Maintained their usual analgesic regimen	4 hr	1. -2.6±1.67 2. -1.4±1.32 3. -3.6±2.05 4. -4.6±2.08 5. -0.9±0.94	VAS 0-10	2
Staquet 1978a (60)	Two consecutive, randomized, double-blind trials, placebo\ active controlled, crossover (1d+1d+1d)	26 (4)	Cancer pain (advanced stage)	Oral (capsules)	1.Synthetic nitrogen analog of tetrahydrocannabinol (NIB) 4 mg 2. Codeine 50 mg	3.Matching placebo	21-75	N/I	N/I	N/I	Not receiving large doses of narcotics	3hr for analgesics	1. -4.72±3.54 2. -4.79±3.19 3. -2.15±3.54	VAS 0-10	3

Table 1 (cont.). *Cancer pain studies' characteristics.*

First author (year)	Design (duration)	N (Dropouts)	Pathology	Administration route	Intervention drug	Placebo/ active placebo	Baseline characteristics					WO	Pain reduction Mean±Sd	Pain scale	Quality*
							Age (M±SD, years)	Female (%)	Baseline pain intensity	Cannabis previous use	Current treatment				
Staquet 1978b (60)	Two consecutive, randomized, double-blind trials, placebo\ active controlled, crossover (1d+1d+1d)	15 (0)	Cancer pain (advanced stage)	Oral (capsules)	1.Synthetic nitrogen analog of tetrahydrocannabinol (NIB) 4mg 2.Secobarbital 50mg	3.Matching placebo	21-75	N/I	N/I	N/I	Not receiving large doses of narcotics	3hr for analgesics	1. -4.40±2.08 2. -2.13±1.77 3. -1.87±2.08	VAS 0-10	3
Jochimsen 1987 (53)**	randomized, double blind, placebo\ active controlled, single dose, crossover (5d)**	35 (2)	Chronic cancer pain	Oral (capsules)	Benzopyranoperidine (BPP, THC): 1. 2mg 3. 4mg Codeine: 3. 60mg 4. 120mg	5. Matching placebo	57 (38-77)	82.8	N/I	N/I	N/I	N/I	Pain reduction in N%- 1. 76% 2. 57% 3. 71% 4. 89% 5. 71% Mean±Sd	VAS 0-10	4
Johnson 2010 (63)	randomized, double blind, placebo-controlled, parallel groups (2d+2w)	144 (33)	Cancer related pain	Oromucosal spray	1.THC-2.7mg 2.THC2.5mg/ CBD2.5mg,	3. placebo	1. 61.3±12.5 1. 48 2. 59.4±12.1 2. 45 3. 60.1±12.3 3. 46		1. 5.77 2. 5.68 3. 6.05	N/I	strong opioids for at least one week to relieve pain	N/I	1. -1.07 2. -1.37 3. -0.67	NRS Pain 0-10	4 (1+)
Portenoy 2012 (67)**	randomized, double blind, placebo-controlled, graded dose, parallel groups (5w)	263 (37)	Poorly controlled opioid treated chronic cancer pain	Oromucosal spray	Nabiximol: 1. 1-4 sprays per d 2. 6-10 sprays per d 3. 11-16 sprays per d	4. placebo	1. 59±12.3 2. 59±13.1 3. 58±11.2 4. 56±12.2	1. 50.5 2. 44.3 3. 46.7 4. 51.6	1. 5.8±1.3 2. 5.8±1.2 3. 5.8±1.2 4. 5.7±1.2	1. 12.1% 2. 11% 3. 10% 4. 6%	Stable high dose opioids (120-180 morphine equivalent in mgs)	N/I	Primary analysis wasn't significant. Secondary analysis proportion of patients reporting 30% pain reduction in low and medium doses. 1. -1.5± N/I 2. -1.1± N/I 3. -1.0± N/I 4. -0.8± N/I	NRS 0-10	4 (1++)
Noyes 1975a (57)	randomized, double-blind, placebo\ active controlled, crossover (6h)	34 (2)	Various cancer types	Oral (capsules)	1.THC 10mg 2.THC 20mg 3.Codeine 60mg 4.Codeine 120mg	5. Placebo	51±N/I	N/I	N/I	N/I	N/I	4 hr	1. -2.9±3.61 2. -4.7±3.79 3. -3.6±4.37 4. -4.3±4.54 5. -1.9±2.56	VAS 0-10	2 (1-)

Table 1 (cont.). *Cancer pain studies' characteristics.*

First author (year)	Design (duration)	N (Dropouts)	Pathology	Administration route	Intervention drug	Placebo/ active placebo	Baseline characteristics					WO	Pain reduction Mean±Sd	Pain scale	Quality*
							Age (M±SD, years)	Female (%)	Baseline pain intensity	Cannabis previous use	Current treatment				
Noyes 1975b (56)	randomized, double-blind, placebo\ active controlled, crossover (6h)	10 (0)	Various cancer types	Oral (capsules)	1.THC 5mg 2.THC 10mg 3.THC 15mg 4.THC 20mg	5. Placebo	51±N/I	N/I	N/I	N/I	Maintained their usual analgesic regimen	4 hr	1. -2.6±1.67 2. -1.4±1.32 3. -3.6±2.05 4. -4.6±2.08 5. -0.9±0.94	VAS 0-10	2 (1-)
Staquet 1978a (60)	Two consecutive, randomized, double-blind trials, placebo\ active controlled, crossover (1d+1d+1d)	26 (4)	Cancer pain (advanced stage)	Oral (capsules)	1.Synthetic nitrogen analog of tetrahydrocannabinol (NIB) 4mg 2.Codeine 50mg	3.Matching placebo	21-75	N/I	N/I	N/I	Not receiving large doses of narcotics	3hr for analgesics	1. -4.72±3.54 2. -4.79±3.19 3. -2.15±3.54	VAS 0-10	3 (1+)
Staquet 1978b (60)	Two consecutive, randomized, double-blind trials, placebo\ active controlled, crossover (1d+1d+1d)	15 (0)	Cancer pain (advanced stage)	Oral (capsules)	1.Synthetic nitrogen analog of tetrahydrocannabinol (NIB) 4mg 2.Secobarbital 50mg	3.Matching placebo	21-75	N/I	N/I	N/I	Not receiving large doses of narcotics	3hr for analgesics	1. -4.40±2.08 2. -2.13±1.77 3. -1.87±2.08	VAS 0-10	3 (1+)
Jochimsen 1987 (53)**	randomized, double blind, placebo\ active controlled, single dose, crossover (5d)**	35 (2)	Chronic cancer pain	Oral (capsules)	Benzopyranoperidine (BPP, THC): 1. 2mg 3. 4mg Codeine: 3. 60mg 4. 120mg	5. Matching placebo	57 (38-77)	82.8	N/I	N/I	N/I	N/I	Pain reduction in N%- 1. 76% 2. 57% 3. 71% 4. 89% 5. 71%	VAS 0-10	4 (1-)

*=Jadad scale (84); **=not introduced into the meta-analysis for pain reduction efficacy; NPS=numerical pain score; MS= multiple sclerosis; WO= wash out; VAS= visual analog scale; DMARDs= disease-modifying anti-rheumatic drugs; AUDC= areas under the difference curve; SF-McGill PQ= pain questionnaire; CRPS= chronic regional pain syndrome; DPN= diabetic painful neuropathy; NPS= neuropathic pain scale; N/I= no information; NP= neuropathic pain; DMT= disease-modifying therapy; NSAIDs= nonsteroidal anti-inflammatory drugs; SPID= Sum of Pain Intensity Difference; PCA= patient-controlled analgesia; NNT= number needed to treat; CNP= central neuropathic pain; TCA= tricyclic antidepressants; FMF= Familial Mediterranean fever; N/S= non-significant; PNP= peripheral neuropathic pain; MOH= medication-overuse headache; CM= combination medications; WOMAC= Western Ontario and McMaster Universities Osteoarthritis Index; d= days; w= weeks; m= months.

Table 2. *Chronic non-cancer studies' characteristics.*

First author (year)	Design (duration)	N (Dropouts)	Pathology	Administration route	Intervention drug	Placebo/active control	Baseline characteristics					WO	Pain reduction Mean ± Sd	Pain scale	Quality*
							Age (M ± SD, years)	Female (%)	Baseline pain intensity	Cannabis previous use	Current treatment				
Maurer 1990 (101) **	Open trial, randomized, double blind, placebo\active controlled (5m)	Case report 1 (0)	Spinal cord injury	Oral (capsules)	1.THC 5 mg 2.Codeine 50 mg	3.Matching placebo	28.0	0	N/I	N/I	Baclofen, Clonazepam	N/I	Not delta: 1. 25.6 ± 8.9 2. 19.7 ± 6.3 3. 34.3 ± 7.5	VAS 0-100	3
Holdcroft 1997 (102) **	double blind, placebo controlled, crossover study (6w)	Case report 1 (0)	FMF (abdominal pain)	Oral (capsules)	1. 50 mg tetrahydrocannabinol: THC5.75%, cannabidiol 2.42 %, cannabidiol 4.7.3%	2. placebo	22.0	0	(4.5) 4-5, breakthrough:10	N/I	Colchicine, CR Morphine, Temazepam	N/I	1. 0 2. + 2.5	VAS 0-10	3
Karst 2003 (44) **	Randomized, double blind, placebo controlled, crossover study (1w + WO + 1w)	19 (2)	Chronic NP	Oral (capsules)	1. CT-3: 20 mg X 2/d in the 1st 3 days and 40 mg X 2/d in the next 4 days.	2.Matching placebo	51 ± N/I	38.0	4 weeks AM- 1st sequence: 48.16 ± 11.15 2nd sequence: 70.66 ± 15.64	N/I	Stable for 2 mo, allowed: antipyretic, opioids, flupritine, anticonvulsants, antidepressants	Not allowed: NMDA receptor agonists and cannabinoids.	4 weeks AM- 1st sequence: -1.52 ± 12.98 2nd sequence: -13.0 ± 22.14	VAS 0-100	5
Wade 2003 (47)	double-blind, randomized, placebo-controlled single-patient cross-over trials (2w + 2w + 2w + 2w)	20 (1)	MS, various NP	Oromucosal spray	1.THC-rich CME2.5 mg 2.CBD-rich CME2.5 mg 3.THC2.5 mg/ CBD2.5 mg, maximum 120 mg per 24h	4.Matching placebo (spray)	N/I	N/I	69.9 ± 17.8	N/I	stable	cannabis use stopped for four weeks before entry	1. -2.1 ± 2.8 2. -1.8 ± 2.9 3. -1.7 ± 2.9 4. -1.2 ± 3.2	VAS 0-10	4
Notcutt 2004 (55) **	Randomized, double blind, placebo controlled, crossover study (1w + 1w)	Accumulated case reports 34 (12)	Chronic NP	Oromucosal spray	1.THC-2.5 mg 2.CBD-2.5 mg 3.THC2.5 mg/ CBD2.5 mg	4.Matching placebo (spray)	46.7 ± 10.0	67.7	N/I	64.7% medicinal	No change in the last 4 weeks	none	16\34 had 50% pain reduction for either 1 or 2	VAS 0-10	4
Berman 2004 (43)	double-blind, randomized, placebo-controlled crossover study (14d-20d)	46 (3)	central NP by brachial plexus root avulsion	Oromucosal spray	1.GW-1000-02 (Sativex) 2. GW-2000-02 (primarily THC)	3.placebo	39.0 ± N/I	4.1	7.5 ± N/I	N/I	stable in the last 4w	no cannabis 7d prior to entry	not delta: 1. 6.1 2. 6.3 3. 6.9 Difference in means: 1. -0.58 (-0.98 to -0.18) 2. -0.64 (-1.03 to -0.24)	Pain review BS-11 score	4
Wade 2004 (48)	randomized, placebo-controlled, double-blind parallel group (70d)	154 (6)	Stable MS	Oromucosal spray	1.CBME Sativex spray: THC2.7 mg/CBD2.5 mg, maximum of 120 mg THC and 120 mg CBD per day	2.Matching placebo	1. 51.0 ± 9.4 2. 50.4 ± 9.3	1. 58.7 2. 65.0	N/I	N/I	No change in the last 4 weeks	6w	not delta: 1. 11.4 2. 20.17	100mm VAS	3
Svendsen 2004 (46) **	Randomized, double blind, placebo controlled, crossover study (20d + 20d)	24 (1)	Central pain due to MS	Oral (capsules)	1. Dronabinol, initial dose 2.5 mg, increased by 2.5 mg every other day to a max dose of 5 mg X 2/d	2.Matching placebo	50 ± N/I	58.3	5.5 ± N/I	N/I	N/I	21.5d, analgesic drugs (except acetaminophen) stopped 1w before trial	1. -1.25 2. 0	NRS 0-10	5

Table 2 (cont.). Chronic non-cancer studies' characteristics.

First author (year)	Design (duration)	N (Dropouts)	Pathology	Administration route	Intervention drug	Placebo/active control	Baseline characteristics					WO	Pain reduction Mean ± Sd	Pain scale	Quality*
							Age (M ± SD, years)	Female (%)	Baseline pain intensity	Cannabis previous use	Current treatment				
Rog 2005 (45)	5-week, four-visit, randomized, double-blind, placebo-controlled, parallel-group (4w)	66 (2)	Multiple sclerosis (NP)	Oromucosal spray	1. CBM-Sativex, GW-1000-02 2.7 mg THC/2.5 mg CBD per spray, up to 48 sprays in 24 hours	2.Matching placebo (spray)	49.2 ± 8.3	78.8	6.5 ± 1.6	47% medicinal 16.7% recreational	Stable: NP meds, non-opioid analgesics, Benzodiazepine	none	1. -2.73 ± 2.6 2. -1.41 ± 2.7	BS11 (0-10)	5
Salim 2005 (103) **	randomized, double blind, placebo-controlled, crossover (7d + 7d)	19 (2)	NP	Oral (capsules)	1. ajulemic acid: 40 mg for 4d and 80 mg for 3 days	2. placebo	50.8	38	N/I	None	Stable analgesics for 2m, NSAIDs, opioids, anticonvulsants, TCA	7d	30% pain reduction in 50% for 1 compared to 20% for 2	VAS 0-100	4
Wissel 2006 (61)	double-blind, randomized, placebo-controlled crossover study (4w, WO, 4w)	11 (2)	Chronic upper motor neuron syndrome	Oral (capsules)	1. Nabilone 1 mg (THC)	2.Matching placebo	44.8 ± 14.3	69.2	6.0	none	Anti-neuropathic& anti-spacisity	four weeks	1. -1.6 ± 4.05 2. -0.3 ± 4.05	11-point-box test (0-10)	3
Blake 2006 (52)	randomized, placebo-controlled, double-blind parallel group (5w + follow up)	58 (4)	rheumatoid arthritis	Oromucosal spray	1. CBM Sativex THC2.7 mg/CBD2.5 mg	2.Matching placebo	62.8 ± 9.8	79	Median- 1. 48.0 2. 50.0	2% medicinal 3% recreational	Stable: Nsaids and prednisone (1m) , DMARDs (3m)	N/I	Not delta: Median- 1. 33.0 2. 50.0 Difference in means: -1.04 (-1.9 to -0.18)	SF-McGill PQ	3
Abrams 2007 (62) **	randomized, placebo-controlled parallel groups (7d + 2d + 5d + 7d)	50 (5)	HIV sensory neuropathy	Smoking (inhalation)	1. Cannabis 3.56%	2. placebo	1. 50 ± 6 2. 47 ± 7	26.0	1. 53 ± 20 2. 54 ± 23	Currently: Active: 78% Placebo: 68%	Gabapentin, opioids	Discontinue cannabis prior to admission	By graph Approx.- 1. 23 2. 48	VAS 0-100	5
Nurmikko 2007 (65)	randomized, placebo-controlled parallel groups (5w)	103 (22)	Unilateral NP and allodynia	Oromucosal spray	1. Sativex THC2.7 mg/CBD2.5 mg	2. Matching placebo	1. 52.4 ± 15.8 2. 54.3 ± 15.2	1. 55.6% 2. 62.9%	1. 7.3 ± 1.4 2. 7.2 ± 1.5	1. 21% 2. 19%	Stable: antiepileptic, opioids, TCA, Non-narcotic analgesics, NSAIDs	N/I	1. -1.48 2. -0.52 Difference in means: -0.96 (-1.59 to -0.32)	NRS Pain 0-10	5
Frank 2008 (90)	randomized, double blind, active-controlled, crossover (6w)	64 (32)	Chronic NP	Oral (capsules)	Maximum daily dose-1.Nabilone: 2 mg	Active control: 2. Dihydrocodeine 240 mg	1 vs 2: 49.7 ± 12.0 2 vs 1: 50.6 ± 15.2	1 vs 2: 32.8 2 v 1: 39.0	1 vs 2: 66.4 ± 14.9 2 vs 1: 68.0 ± 12.4	N/I	Stable analgesics, except Dihydrocodeine (washout 2w)	2w	Not delta: 1. 59.93 ± 24.42 2. 58.58 ± 24.08 Difference in means: 6.0 (1.4 to 10.5)	VAS 0-100	5
Skrabek 2008 (59) **	randomized, double blind, placebo-controlled, parallel group (1w + 1w + 4w)	40 (7)	Fibromyalgia	Oral (capsules)	1. Nabilone (THC) : 1w 0.5 mg and 1w 1.5-2 mg	2.Matching placebo	1. 47.6 ± 7.1 2. 50.1 ± 5.9	N/I	1. 6.86 ± 2.14 2. 6.2 ± 1.46	none	stable fibromyalgia medications	N/I	1. -2.04 2. -1.43	VAS 0-10	4
Wilsey 2008 (73)	randomized, double blind, placebo-controlled, crossover trial (6h)	38 (6)	CRPS type I, spinal cord injury, various NP	Smoking (inhalation)	Cannabis: 1. 3.5% 2. 7%	3. Matching placebo	Median (range) 46 (21-71)	47.3	5.6 ± 2.1	N/I	No change in the last 4 weeks	30d	1. -0.0085 2. -0.0085 3. -0.004 Difference in means: -0.004 (-0.006 to -0.001)	VAS 0-10	4

Table 2 (cont.). Chronic non-cancer studies' characteristics.

First author (year)	Design (duration)	N (Dropouts)	Pathology	Administration route	Intervention drug	Placebo/active control	Baseline characteristics					WO	Pain reduction Mean ± Sd	Pain scale	Quality*
							Age (M ± SD, years)	Female (%)	Baseline pain intensity	Cannabis previous use	Current treatment				
Narang 2008 (104) **	randomized, double blind, placebo-controlled, single-dose, crossover (phase I, 8hrs)	24 (6)	Chronic non-cancer pain	Oral (capsules)	Dronabinol: 1. 10 mg 2. 20 mg	3.Matching placebo	43.5 ± 11.8	53.3	6.9 ± 1.3	N/I	Stable opiods: 6m	3d	SPID: 1.-17.4 2.-19.7 3.-6.4	NRS 0-10	4
Ellis 2009 (71) **	randomized, double blind, placebo-controlled, crossover (5d)	28 (6)	HIV neuropathy	Smoking (inhalation)	1. Cannabis 1-8%, individual titration	2. placebo	48.8 ± 6.8	0	Median--17	96%	Non-narcotic analgesics Antidepressants Anticonvulsants opioids	none	Median- 1. -17 2. -4 NNT for 30% pain reduction was 3.5 for 1 vs 2	VAS 0-100	4
Ware 2010 (72)	Randomized, double-blind, placebo-controlled, four period. Crossover design (14d)	21 (2)	NP	Smoking pipe (inhalation)	Cannabis: 1. 2.5% 2. 6% 3. 9.4%	4. Matching placebo 0%	45.4 ± 12.3	52.2	6.89 ± 1.37	81%	NSAIDs, Antidepressants Anticonvulsants opioids	9d	Difference in means: 1. -0.13 (-0.83 to 0.56) 2. -0.09 (-0.78 to 0.6) 3. -0.71 (-1.4 to -0.02)	NRS Pain 0-10	4
Selvarajah 2010 (66)	randomized, double blind, placebo-controlled, parallel groups (2w + 10w)	29 (9)	chronic DPN	Oromucosal spray	1.Sativex (tetrahydrocannabinol: 27 mg/ml and cannabidiol: 25 mg/ml	2.Matching placebo	1. 58.2 ± 8.8 2. 54.4 ± 11.6	1. 10.5 2. 18.4	1. 7.6 ± 1.8 2. 6.9 ± 1.7	N/I	Continue anti-NP meds	N/I	1. -2.5 ± 2.2 2. -3.6 ± 2.6	VAS 0-10	3
Toth 2012 (92)	Enriched enrollement, randomized, flexible dose, double blind, parallel groups (28d)	26 (0)	DPN	Oral (capsules)	1. nabilone 1-4 mg	2. placebo	1. 60.8 ± 15.3 2. 61.6 ± 14.6	1. 62 2. 31	1. 6.54 ± 1.91 2. 6.59 ± 2.03	None	NP meds stable for 1m,	1w	1. -2.3 ± 1.3 2. -0.4 ± 1.7	VAS 0-100 transformed to 0-10	4
Corey-Bloom 2012 (96) **	randomized, double blind, placebo-controlled, crossover (3d + 3d)	30 (7)	MS	Smoking (inhalation)	1. 4% THC	2.Matching placebo	51 ± 8	63	N/I	80%	Spasticity meds: stable 3m, DMT: stable 6m	N/I	1. -5.28 ± N/I	VAS 0-100	4
Pini 2012 (95)	randomized, double blind, active-controlled, crossover (8w + 8w)	26 (4)	Chronic MOH	Oral (capsules)	1. 60 doses of nabilone 0.5 mg (total)	Active control: 2. 60 doses of ibuprufen 400 mg (total)	52.7 ± 9.6	33	7.9 ± 1.6	N/I	Meds overuse: triptans, CM and NSAIDs	N/I	1. -2.2 ± 1.9 2. -1.3 ± 2.2	VAS 0-10	4
Huggins 2012 (105) **	Multicenter, randomized, double blind, double dummy, placebo/active controlled, crossover (2w + 2w)	69 (5)	Knee osteoarthritis pain	Oral (capsules)	1. PF-04457845 4 mg (sequence 1 with placebo) 2. naproxen 500 mg (sequence 2 with placebo)	3. placebo	Differences between sequences	Differences between sequences	N/I	N/I	Stop al analgesic meds	2w	1st sequence: NS difference 0.04 (-0.63, 0.71)	WOMAC pain subscale 0-20	4
Zajicek 2012 (106) **	randomized, double blind, placebo-controlled, parallel groups (12w)	224 (55)	MS	Oral (ethanol extract)	1. cannabis extract (THC 2.5 mg/ CBD 0.8-1.8 mg)	2. placebo	1. 51.9 ± 7.7 2. 52.0 ± 7.9	1. 61.5 2. 64.9	N/I	N/I	Stable spasticity meds	Cannabis for 30d	Significant clinically relevant response: 1. 28% 2. 17.2%	11 point numerical likert scale 0-10	3

Table 2 (cont.). Chronic non-cancer studies' characteristics.

First author (year)	Design (duration)	N (Dropouts)	Pathology	Administration route	Intervention drug	Placebo/active control	Baseline characteristics					WO	Pain reduction Mean ± Sd	Pain scale	Quality*
							Age (M ± SD, years)	Female (%)	Baseline pain intensity	Cannabis previous use	Current treatment				
Wilsey 2013 (74) **	randomized, double blind, placebo-controlled, flexible dose, crossover (2h)	36 (2)	NP	Smoking (inhalation)	THC: 1. 3.53% 2. 7%	3. Matching placebo	50 ± 11	28.2	1. 53.4 ± 23.4 2. 57.3 ± 24.1 3. 57.5 ± 22.8	All patients	30d without THC, other meds stable for 3-4w	3-14d	NNT for 30% pain reduction: 3.2 for 1 vs 3, 2.9 for 2 vs 3 and 25 for 1 vs 2.	VAS 0-100	4
Langford 2013a (64)	randomized, double blind, placebo-controlled, parallel groups (phase A) (14w)	297 (42)	CNP in MS	spray	1. Sativex: THC 2.7 mg\CBD2.5 mg	2. placebo	1. 48.4 ± 10.4 2. 49.5 ± 10.5	1. 68 2. 68	1. 6.5 ± 1.3 2. 6.6 ± 1.2	N/I	Stable analgesics for 2w	N/I	1. -2.0 ± 2.2 2. -1.9 ± 2.2	NRS 0-10	5
Langford 2013b (64)	randomized, double blind, placebo-controlled, parallel groups (phase B) (28d)	41 (1)	CNP in MS	Oromucosal spray	1. Sativex: THC 2.7 mg\CBD2.5 mg	2. placebo	1. 46.2 ± 10.3 2. 49.8 ± 9.7	1. 52 2. 67	1. 6.2 ± 1.3 2. 6.4 ± 1.3	3 or more spray in the last week of phase A	Stable analgesics for 2w before phase A	N/I	24% treatment failure vs 57% for placebo Difference in means: -0.79 (-1.37 to -0.21)	NRS 0-10	5
Serpell 2014 (68) **	randomized, double blind, placebo-controlled, parallel groups (15w)	173 (73)	PNP	Oromucosal spray	1. Sativex: THC 2.7 mg\CBD2.5 mg	2. Matching placebo	1. 57.6 ± 14.4 2. 57.0 ± 14.1	1. 66 2. 55	N/I	10% in both groups	Paracetamol	1 year from cannabis	At the 30% responder level, there were statistically significant treatment differences in favor of 1 over 2	NRS 0-10	5
Lynch 2014 (107) **	randomized, double blind, placebo-controlled, crossover (4w + 4w)	16 (2)	Chemo-theraphy induced NP	Oromucosal spray	1. Sativex: THC 2.7 mg\CBD2.5 mg	2. placebo	S/P sequence: 58 ± 11.3 P/S sequence: 55 ± 10.6	S/P sequence: 70 P/S sequence: 80	S/P sequence: 6.56 ± 1.24 P/S sequence: 7.00 ± 1.12	N/I	2w stable analgesics	2w	1. -0.75 ± N/I 2. -0.37 ± N/I	NRS 0-10	3
Turcotte 2015 (108) **	randomized, double blind, placebo-controlled, parallel groups (5w)	14 (1)	MS induced NP	Oral (capsules)	1. nabilone 1 mg	2. Matching placebo	1. 42.1 ± 11.2 2. 50.0 ± 8.4	1. 88 2.86	1. 7.9 ± 1.3 2. 7.4 ± 1.3	N/I	gabapentin	N/I	Significant reduction in pain for 1 over 2, only after adjustments to covariates	VAS 0-100 transformed to 0-10	5
Wallace 2015 (94)	randomized, double blind, placebo-controlled, crossover (4h)	16 (14)	DPN	vaporizer (inhalation)	1. 1% THC 2. 4% THC 3. 7% THC	4. Matching placebo	56.9 ± 8.2	44	6.7 ± 1.6	N/I	Opioids, antidepressants, NSAIDs	2w	Mean of 11 time points during 4h: 1. -2.34 ± 0.38 2. -2.79 ± 0.39 3. -3.08 ± 0.36 4. -1.91 ± 0.38	VAS 0-10	4

*=Jadad scale (84); **=not introduced into the meta-analysis for pain reduction efficacy; NPS=numerical pain score; MS= multiple sclerosis; WO= wash out; VAS= visual analog scale; DMARDs= disease-modifying anti-rheumatic drugs; AUDC= areas under the difference curve; SF-McGill PQ= pain questionnaire; CRPS= chronic regional pain syndrome; DPN= diabetic painful neuropathy; NPS= neuropathic pain scale; N/I= no information; NP= neuropathic pain; DMT= disease-modifying therapy; NSAIDs= nonsteroidal anti-inflammatory drugs; SPID= Sum of Pain Intensity Difference; PCA= patient-controlled analgesia; NNT= number needed to treat; CNP= central neuropathic pain; TCA= tricyclic antidepressants; FMF= Familial Mediterranean fever; N/S= non-significant; PNP= peripheral neuropathic pain; MOH= medication-overuse headache; CM= combination medications; WOMAC= Western Ontario and McMaster Universities Osteoarthritis Index; d= days; w= weeks; m= months.

Table 3. *Acute post-operative pain studies' characteristics.*

						Baseline characteristics								
First author (year)	Design (duration)	N (Dropouts)	Pathology	Administration route	Intervention drug	Placebo/ active control	Age (M ± SD, years)	Female (%)	Baseline pain intensity	Cannabis previous use	Current treatment	WO	Pain reduction Mean ± Sd	Pain scale	Quality*
Jain 1981 (100)**	Five groups, randomized, double blind, placebo-controlled, crossover (6h)	56(0)	postoperative fracture or trauma pain	Intra-muscular	5. placebo	28.0 ± 7.6	2.24	Active groups:5 Placebo group: 8	N/I	N/I	N/I	N/I	AUDC- 1. 9.95 2. 9.84 3. 11.26 4. 9.1 5. 5.20	Pain intensity 0-3	3
Buggy 2003 (89)	randomized, double blind, placebo-controlled, single dose, parallel trial (6h)	40(0)	Postoperative pain: elective abdominal hysterectomy	Oral (capsules)	2.Matching placebo	1. 44.8 ± 8.5 2. 47.8 ± 10.2	100	Rest- 1. 3.3 ± 0.9 2. 3.2 ± 1.9	N/I	Rescue medication: codeine 50mg	N/I	N/I	Rest 2h: 1. -0.0 ± 1.7 2. -0.6 ± 1.5 Rest 4h: 1. -0.3 ± 1.4 2. -0.4 ± 1.4	VAS 0-100	4
Beaulieu 2006 (93)	randomized, double blind, placebo\ active controlled, parallel groups (24hrs)	102(61)	Post-operative gynecologic, ortophedic and other	Oral (capsules)	4.Matching placebo	1. 53 ± 2 2. 53 ± 4 3. 44 ± 3 4. 60 ± 4	1. 81.8 2. 88.8 3. 90.9 4. 60.0	N/I	N/I	PCA	N/I	N/I	Not delta: Rest: 1. 6.3 ± 0.5 2. 7.7 ± 0.5 3. 3.4 ± 0.3 4. 5.9 ± 0.5 Movement: 1. 4.4 ± 0.3 2. 5.9 ± 0.6 3. 5.6 ± 0.3 4. 3.8 ± 0.6	Vas 0-10	4

*=Jadad scale (84); **=not introduced into the meta-analysis for pain reduction efficacy; NPS=numerical pain score; MS= multiple sclerosis; WO= wash out; VAS= visual analog scale; DMARDs= disease-modifying anti-rheumatic drugs; AUDC= areas under the difference curve; SF-McGill PQ= pain questionnaire; CRPS= chronic regional pain syndrome; DPN= diabetic painful neuropathy; NPS= neuropathic pain scale; N/I= no information; NP= neuropathic pain; DMT= disease modifying therapy; NSAIDs= nonsteroidal anti-inflammatory drugs; SPID= Sum of Pain Intensity Difference; PCA= patient-controlled analgesia; NNT= number needed to treat; CNP= central neuropathic pain; TCA= tricyclic antidepressants; FMF= Familial Mediterranean fever; N/S= non-significant; PNP= peripheral neuropathic pain; MOH= medication-overuse headache; CM= combination medications; WOMAC= Western Ontario and McMaster Universities Osteoarthritis Index; d= days; w= weeks; m= months.

effects of CBMs vs. placebo in these trials and the small number of trials conducted on postoperative pain, which would not be comparable to the trials on chronic pain (Fig. 2). Furthermore, in 2 of the studies that were included in our meta-analysis (47,48), pain reduction was not the primary outcome for the study and was not measured for the entire sample.

In addition, 3 of the studies that were meta-analyzed in the primary analysis included only an intervention group of an active drug, utilizing analgesic medication (dihydrocodeine, ibuprufen, or diphenhydramine), as so, they were redacted in the following analysis because of their analgesic effect that may interfere with the comparisons between "real" placebo to CBMs (Fig. 3) (90, 91,95). Two other studies that were meta-analyzed had an analgesic medication (codeine or secobarbital) as one or more of the study arms as well as to placebo; however, these "comparator" arms were not included in any of the analyses (57,60).

Additionally, 5 studies that were reviewed included inhalation/vaporization of cannabinoids (72-74,94,96) with several concentration arms/groups compared to placebo, i.e., 0% THC, but only 3 of them (72,73,94), for reasons that will be explained in section 3.7, were meta-analyzed with the overall RCTs (Fig. 1) and separately (Fig. 4). In the past, this manner of administration has been either ignored or deliberately left out for various reasons (40), although evidence points to inhalation as the preferred route for rapid and effective cannabinoid use (12,14).

Summary of Measures and Synthesis of Results

All analyses were performed using the Comprehensive Meta-Analysis (CMA) Version 3 software (Biostat, Englewood, NJ) (97). For pain reduction efficacy, a few outcome measures were used in the current meta-analyses. Eighteen of the 24 included studies, which reported results by each intervention group's initial

Table 4. Jadad scale ratings.

Score criteria First author, year	Point for randomization	Point for double blind design	Point for dropouts description	Points for adequate randomization and/or appropriate blinding	Total score
Noyes, 1975a (57)	1	1	0	0	2
Noyes, 1975b (56)	1	1	0	0	2
Staquet, 1978a (60)	1	1	1	0	3
Staquet, 1978b (60)	1	1	1	0	3
Jochimsen, 1987 (53)*	1	1	1	1	4
Johnson, 2010 (63)	1	1	1	1	4
Portenoy, 2012 (67)*	1	1	1	1	4
Maurer, 1990 (101)*	1	1	0	1	3
Holdcroft, 1997 (102)*	1	1	1	0	3
Karst, 2003 (44)*	1	1	1	2	5
Wade, 2003 (47)	1	1	1	1	4
Notcutt, 2004 (55)*	1	1	1	1	4
Berman, 2004 (43)	1	1	1	1	4
Wade, 2004 (48)	1	1	1	0	3
Svendsen, 2004 (46)*	1	1	1	2	5
Rog, 2005 (45)	1	1	1	2	5
Salim, 2005 (103)*	1	1	1	1	4
Wissel, 2006 (61)	1	1	1	0	3
Blake, 2006 (52)	1	1	1	0	3
Abrams, 2007 (62)*	1	1	1	2	5
Nurmikko, 2007 (65)	1	1	1	2	5
Frank, 2008 (90)	1	1	1	2	5
Skrabek, 2008 (59)*	1	1	1	1	4
Wilsey, 2008 (73)	1	1	1	1	4
Narang, 2008 (104)*	1	1	1	1	4
Ellis 2009 (71)*	1	1	1	1	4
Ware, 2010 (72)	1	1	1	1	4
Selvarajah, 2010 (66)	1	1	1	0	3
Toth, 2012 (92)	1	1	1	1	4
Corey-Bloom, 2012 (96)*	1	1	1	1	4
Pini, 2012 (95)	1	1	1	1	4
Huggins, 2012 (105)*	1	1	1	1	4
Zajicek, 2012 (106)*	1	1	1	0	3
Wilsey, 2013 (74)*	1	1	1	1	4
Langford, 2013a (64)	1	1	1	2	5
Langford, 2013b (64)	1	1	1	2	5
Serpell, 2014 (68)*	1	1	1	2	5
Lynch, 2014 (107)*	1	1	1	0	3
Turcotte 2015(108)*	1	1	1	2	5
Wallace, 2015 (94)	1	1	1	1	4
Jain, 1981 (100)*	1	1	1	0	3
Buggy, 2003 (89)	1	1	1	1	4
Beaulieu, 2006 (93)	1	1	1	1	4

*=not introduced into the meta-analysis for pain reduction efficacy

Table 5. *Cancer pain studies' AE characteristics.*

First author (year)	Design (duration)	N (Dropouts)	Pathology	Administration route	Intervention drug	Placebo/active control	Adverse events: n\N	
Noyes 1975a (57)	randomized, double-blind, placebo\active controlled, crossover (6h)	34 (2)	Various cancer types	Oral (capsules)	1. THC 10 mg 2. THC 20 mg 3. Codeine 60 mg 4. Codeine 120 mg	5. Placebo	CNS: sedation: 1. 24/34 2. 32/34 3. 16/64 4. 17/34 5. 10/34 mental clouding: 1. 11/34 2. 18/34 3. 3/34 4. 2/34 5. 6/34 ataxia: 1. 10/34 2. 15/34 3. 4/34 4. 8/34 5. 3/34 numbness: 1. 4/34 2. 13/34 3. 5/34 4. 5/34 5. 3/34 disorientation: 1. 5/34 2. 12/34 3. 1/34 4. 1/34 5. 3/34 disconnected sought: 1. 10/34 2. 11/34 3. 3/34 4. 2/34 5. 3/34 slurred speech: 1. 6/34 2. 11/34 3. 4/34 4. 2/34 5. 3/34 impaired memory: 1. 2/34 2. 9/34 3. 1/34 4. 1/34 5. 2/34 dizziness: 1. 20/34 2. 33/34 3. 8/34 4. 20/34 5. 9/34 GI: increased appetite: 1. 9/34 2. 7/34 3. 5/34 4. 5/34 5. 3/34	nausea: 1. 7/34 2. 6/34 3. 11/34 4. 4/34 5. 5/34 diarrhea: 1. 1/34 2. 5/34 3. 0/34 4. 1/34 5. 2/34 epigastric distress: 1. 4/34 2. 4/34 3. 2/34 4. 7/34 5. 3/34 vomiting: 1. 1/34 2. 3/34 3. 1/34 4. 3/34 5. 1/34 dry mouth: 1. 25/34 2. 26/34 3. 20/34 4. 22/34 5. 12/34 musculoskeletal: muscle twitching: 1. 8/34 2. 10/34 3. 5/34 4. 3/4 5. 3/34 vision impairments: blurred vision: 1. 14/34 2. 22/34 3. 4/34 4. 8/34 5. 3/34 hearing impairments: tinnitus: 1. 4/34 2. 7/34 3. 3/34 4. 3/34 5. 3/34 others: itching: 1. 6/34 2. 5/34 3. 9/34 4. 8/34 5. 5/34 sweating: 1. 7/34 2. 3/34 3. 4/34 4. 7/34 5. 4/34
Noyes 1975b (56)	randomized, double-blind, placebo controlled, crossover (6h)	10 (0)	Various cancer types	Oral (capsules)	1. THC 5 mg 2. THC 10 mg 3. THC 15 mg 4. THC 20 mg	5. Placebo	CNS: drowsiness: 1. 7/10; 2. 5/10; 3. 7/10; 4. 10/10; 5. 3/10 slurred speech: 1. 4/10; 2. 4/10; 3. 8/10; 4. 8/10; 5. 2/10 mental clouding: 1. 5/10; 2. 4/10; 3. 7/10; 4. 6/10; 5. 2/10 dizziness: 1. 2/10; 2. 4/10; 3. 4/10; 4. 6/10; 5. 1/10 ataxia: 1. 3/10; 2. 3/10; 3. 7/10; 4. 5/10; 5. 3/10 dreaminess: 1. 4/10; 2. 3/10; 3. 6/10; 4. 3/10; 5. 3/10 disconnected sought: 1. 2/10; 2. 2/10; 3. 1/10; 4. 5/10; 5. 0/10 numbness: 1. 1/10; 2. 2/10; 3. 3/10; 4. 4/10; 5. 0/10	GI: increased appetite: 1. 2/10; 2. 5/10; 3. 5/10; 4. 4/10; 5. 0/10 psychological: euphoria: 1. 0/10; 2. 1/10; 3. 4/10; 4. 5/10; 5. 0/10 visual hallucinations: 1. 0/10; 2. 1/10; 3. 0/10; 4. 3/10; 5. 0/10 vision impairments: blurred vision: 1. 2/10; 2. 4/10; 3. 7/10; 4. 7/10; 5. 0/10 hearing impairments: tinnitus: 1. 0/10; 2. 4/10; 3. 2/10; 4. 0/10; 5. 0/10 other: headache: 1. 5/10; 2. 5/10; 3. 3/10; 4. 4/10; 5. 2/10
Staquet 1978a (60)	Two consecutive, randomized, double-blind trials, placebo\ active controlled, crossover (1d+1d+1d)	26 (4)	Cancer pain (advanced stage)	Oral (capsules)	1. Synthetic nitrogen analog of tetrahydrocannabinol (NIB) 4 mg 2. Codeine 50 mg	3. Matching placebo	N/I	
Staquet 1978b (60)	Two consecutive, randomized, double-blind trials, placebo\ active controlled, crossover (1d+1d+1d)	15 (0)	Cancer pain (advanced stage)	Oral (capsules)	1. Synthetic nitrogen analog of tetrahydrocannabinol (NIB) 4 mg 2. Secobarbital 50 mg	3. Matching placebo	N/I	

Table 5. *Cancer pain studies' AE characteristics.*

First author (year)	Design (duration)	N (Dropouts)	Pathology	Administration route	Intervention drug	Placebo/active control	Adverse events: n\N	
Jochimsen 1987 (53)**	randomized, double blind, placebo\active controlled, single dose, crossover (5d)**	35 (2)	Chronic cancer pain	Oral (capsules)	Benzopyranoperidine (BPP, THC): 1. 2 mg 3. 4 mg Codeine: 3. 60 mg 4. 120 mg	5. placebo	N/I	
Johnson 2010 (63)	randomized, double blind, placebo-controlled, parallel groups (2d+2w)	144 (33)	Cancer related pain	Oromucosal spray	1. THC-2. 7 mg 2. THC2. 5 mg/CBD2. 5 mg	3. placebo	Other: raised gamma GT: 1. 5/58 2. 2/60 3. 1/59 hypercalcemia: 1. 0/58 2. 0/60 3. 3/59 more adverse events are mentioned, but they were considered unrelated to study medications with exception of one incidence of syncope due to THC.	CNS: somnolence: 1. 8/58 2. 8/60 3. 6/59 dizziness: 1. 7/58 2. 7/60 3. 3/59 GI: nausea: 1. 4/58 2. 6/60 3. 4/59 vomiting: 1. 4/58 2. 3/60 3. 2/59 Cardiac: hypotension: 1. 0/58 2. 3/60 3. 0/59 Psychological: confusion: 1. 1/58 2. 4/60 3. 1/59
Portenoy 2012 (67)**	randomized, double blind, placebo-controlled, graded dose, parallel groups (5w)	263 (37)	Poorly controlled opioid treated chronic cancer pain	Oromucosal spray	Nabiximol: 1. 1-4 sprays per d 2. 6-10 sprays per d 3. 11-16 sprays per d	4. placebo	stomatitis: 1. 5/91 2. 2/87 3. 3/90 4. 0/91 weight decrease: 1. 5/91 2. 1/87 3. 2/90 4. 2/91 Psychological: hallucination: 1. 1/91 2. 1/87 3. 6/90 4. 5/91 Sleep related AEs: insomnia: 1. 2/91 2. 2/87 3. 4/90 4. 5/91 Other: headache: 1. 5/91 2. 6/87 3. 4/90 4. 1/91 fatigue: 1. 4/91 2. 4/87 3. 5/90 4. 4/91 pain: 1. 4/91 2. 2/87 3. 5/90 4. 2/91 neoplasm progression: 1. 24/91 2. 11/87 3. 12/90 4. 13/91 anemia: 1. 6/91 2. 5/87 3. 8/90 4. 4/91 asthenia: 1. 6/91 2. 7/87 3. 5/90 4. 6/91	CNS: dizziness: 1. 10/91 2. 21/87 3. 20/90 4. 12/91 disorientation: 1. 5/91 2. 5/87 3. 8/90 4. 1/91 somnolence: 1. 8/91 2. 16/87 3. 15/90 4. 4/91 GI: nausea: 1. 16/91 2. 18/87 3. 25/90 4. 12/91 vomiting: 1. 9/91 2. 14/87 3. 19/90 4. 7/91 anorexia: 1. 6/91 2. 5/87 3. 11/90 4. 10/91 constipation: 1. 4/91 2. 10/87 3. 6/90 4. 7/91 dry mouth: 1. 7/91 2. 8/87 3. 7/90 4. 7/91 diarrhea: 1. 5/91 2. 4/87 3. 8/90 4. 4/91 dysgeusia: 1. 1/91 2. 7/87 3. 3/90 4. 2/91 decreased appetite: 1. 4/91 2. 5/87 3. 2/90 4. 2/91

$=not introduced into the meta-analysis for adverse effects; **=not introduced into the meta-analysis for pain reduction efficacy; GI= gastro-intestinal; CNS= central nervous system; MS= multiple sclerosis; CRPS= chronic regional pain syndrome; DPN= diabetic painful neuropathy; NPS= neuropathic pain scale; N/I= no information; NP= neuropathic pain; CNP= central neuropathic pain; FMF= Familial Mediterranean fever; AEs= adverse events; URTI= upper respiratory tract infections; GT= glutamyl transferase; UTI= urinary tract infection; PN= peripheral neuropathy; d= days; w= weeks; m= months.

and final means and standard deviations (SD) difference from baseline separately for the intervention and for the placebo groups, measured on pain scales and quantified in the same direction. Based on these, the software consequently calculated the SD difference in means, standard error, and Hedges's g scores for each of these studies.

Some of the studies did not include in their report those raw results but rather reported their results as difference in means, confidence interval of 95% lower, and upper limits and the sample size; this was the case in 6 studies with a crossover design and 5 studies with a parallel design. For AEs, risk ratios with a 95% confidence interval were computed separately for each categorical system of AEs.

All the analyses performed are presented in the figures by fitting both fixed and random effects models. Heterogeneity between studies was statistically studied using the I^2 statistic and Tau^2 tests (98).

Due to insufficient reporting on raw data or due to inadaptable reporting of results, some of the studies that were reviewed were found as incompatible for the meta-analysis and therefore they were redacted from our study (as indicated in both Table 1-3 and Table 5-7). In the cases of the studies that investigated more than one cannabinoid preparation versus placebo, the comparisons were made separately and they were analyzed as separate studies; this should not have caused any

Table 6. *Chronic non-cancer pain studies' AE characteristics.*

First author (year)	Design (duration)	N (Dropouts)	Pathology	Administration route	Intervention drug	Placebo/active control	Adverse events: n\N	
Maurer 1990 (101)**	Open trial, randomized, double blind, placebo\ active controlled (5m)	Case report 1 (0)	Spinal cord injury	Oral (capsules)	1.THC 5 mg 2.Codeine 50 mg	3.Matching placebo	N/I	
Holdcroft 1997 (102)**	double blind, placebo controlled, crossover study (6w)	Case report 1 (0)	FMF (abdominal pain)	Oral (capsules)	1. 50 mg tetrahydrocannabinol: THC5.75%, cannabidiol 2.42 %, cannabidiol 4.7.3%	2. placebo	N/I	
Karst 2003 (44)**	Randomized, double blind, placebo controlled, crossover study (1w + WO + 1w)	19 (2)	Chronic NP	Oral (capsules)	1. CT-3: 20 mgX2/d in the 1st 3 days and 40 mgX2/d in the next 4 days.	2.Matching placebo	Tiredness, dry mouth, limited power of concentration, dizziness, sweating and more pain: 1st sequence: 1. 6/9 2. 0/9. 2nd sequence: 1. 6/10 2. 5/10	
Wade 2003 (47)	double-blind, randomized, placebo-controlled single-patient cross-over trials (2w + 2w + 2w + 2w)	20 (1)	MS, various NP	Oromucosal spray	1.THC-rich CME2.5 mg 2.CBD-rich CME2.5 mg 3.THC2.5 mg/CBD2.5 mg, maximum 120 mg per 24h	4.Matching placebo (spray)	sore mouth: 1. 1/20 2. 1/21 3. 0/20 4. 0/21 thirst: 1. 0/20 2. 1/21 3. 1/20 4. 0/21 Cardiac: hypotension: 1. 0/20 2. 0/21 3. 0/20 4. 1/21 Psychological: anxiety: 1. 0/20 2. 0/21 3. 0/20 4. 2/21 depressed mood: 1. 1/20 2. 1/21 3. 0/20 4. 0/21 Other: 'drug toxicity': 1. 1/20 2. 0/21 3. 1/20 4. 2/21 headache: 1. 3/20 2. 1/21 3. 1/20 4. 2/21 cough: 1. 1/20 2. 0/21 3. 1/20 4. 0/21 influenza-like symptoms: 1. 0/20 2. 0/21 3. 1/20 4. 1/21	CNS: sleepiness: 1. 1/20 2. 0/21 3. 2/20 4. 1/21 fall: 1. 1/20 2. 1/21 3. 1/20 4. 1/21 impaired balance: 1. 1/20 2. 0/21 3. 1/20 4. 0/21 fatigue: 1. 0/20 2. 0/21 3. 1/20 4. 1/21 disturbance in attention: 1. 1/20 2. 0/21 3. 0/20 4. 0/21 dizziness: 1. 0/20 2. 0/21 3. 0/20 4. 1/21 hypoesthesia: 1. 0/20 2. 1/21 3. 0/21 4. 0/21 GI: nausea: 1. 1/20 2. 1/21 3. 1/20 4. 3/21 vomiting: 1. 1/20 2. 0/21 3. 1/20 4. 2/21 diarrhea: 1. 2/20 2. 1/21 3. 1/20 4. 1/21
Notcutt 2004 (55)**	Randomized, double blind, placebo controlled, crossover study (1w + 1w)	Accumulated case reports 34 (12)	Chronic NP	Oromucosal spray	1.THC-2.5 mg 2.CBD-2.5 mg 3.THC2.5 mg/CBD2.5 mg	4.Matching placebo (spray)	dry mouth, drowsiness, dysphoria\euphoria: N/I	
Berman 2004 (43)	double-blind, randomized, placebo-controlled	46 (3)	central NP by brachial plexus root avulsion	Oromucosal spray	1.GW-1000-02 (Sativex) 2. GW-2000-02 (primarily THC)	3.placebo	GI: dysguesia (bad taste): 1. 10/46 2. 5/46 3. 1/46 nausea: 1. 1/46 2. 5/46 3. 3/46	CNS: dizziness: 1. 9/46 2. 11/46 3. 4/46 somnolence: 1. 7/46 2. 6/46 3. 5/46 feeling drunk: 1. 4/46 2. 4/46 3. 0/46
Wade 2004 (48)	single-patient cross-over trials (2w + 2w + 2w + 2w)	154 (6)	Stable MS	Oromucosal spray	1.CBME Sativex spray: THC2.7 mg/CBD2.5 mg, maximum of 120 mg THC and 120 mg CBD per day	2.Matching placebo	GI: nausea: 1. 7/80 2. 5/80 diarrhea: 1. 6/80 2. 2/80 mouth ulceration: 1. 4/80 2. 1/80 Other: headache: 1. 7/80 2. 13/80 application site discomfort: 1. 21/80 2. 18/80	CNS: dizziness: 1. 26/80 2. 10/80 disturbance in attention: 1. 7/80 2. 0/80 somnolence: 1. 7/80 2. 1/80 disorientation: 1. 6/80 2. 0/80 feeling drunk: 1. 4/80 2. 0/80 vertigo: 1. 5/80 2. 0/80 fatigue: 1. 12/80 2. 3/80

Table 6 (cont). *Chronic non-cancer pain studies' AE characteristics.*

First author (year)	Design (duration)	N (Dropouts)	Pathology	Administration route	Intervention drug	Placebo/active control	Adverse events: n\N	
Svendsen 2004 (46)**	Randomized, double blind, placebo controlled, crossover study (20d + 20d)	24 (1)	Central pain due to MS	Oral (capsules)	1. Dronabinol, initial dose 2.5 mg, increased by 2.5 mg every other day to a max dose of 5 mgX2/d	2.Matching placebo	hyperactivity: 1. 1/24 2. 0/24 nervousness: 1. 0/24 2. 1/24 Vision impairments: diplopia: 1. 0/24 2. 1/24 Cardiac: palpitations: 1. 4/24 2. 2/24 Other: headache: 1. 6/24 2. 1/24 migraine: 1. 1/24 2. 0/24 speech disorders: 1. 1/24 2. 0/24 MS aggravated: 1. 1/24 2. 2/24 hot flashes: 1. 1/24 2. 0/24 weight decrease: 1. 1/24 2. 0/24 fever: 1. 0/24 2. 1/24 chills: 1. 1/24 2. 0/24 URTI: 1. 1/24 2. 1/24 tenderness in nose: 1. 1/24 2. 0/24	CNS: dizziness\lightheadedness: 1. 14/24 2. 4/24 tiredness\drowsiness: 1. 10/24 2. 6/24 fatigue: 1. 1/24 2. 0/24 balance difficulty: 1. 2/24 2. 0/24 feeling of drunkenness: 1. 2/24 2. 0/24 GI: mouth dryness: 1. 3/24 2. 0/24 nausea: 1. 3/24 2. 4/24 abdominal pain: 1. 0/24 2. 1/24 anorexia: 1. 1/24 2. 0/24 Sleep related AEs: sleep difficulty: 1. 1/24 2. 2/24 Musculoskeletal: myalgia: 1. 6/24 2. 1/24 muscle weakness: 1. 3/24 2. 1/24 limb heaviness: 1. 1/24 2. 0/24 distortion of wrist: 1. 1/24 2. 0/24 Psychological: euphoria: 1. 3/24 2. 0/24
Rog 2005 (45)	5-week, four-visit, randomized, double-blind, placebo-controlled, parallel-group (4w)	66 (2)	Multiple sclerosis (NP)	Oromucosal spray	1. CBM-Sativex, GW-1000-02 2.7 mg THC/2.5 mg CBD per spray, up to 48 sprays in 24 hours	2.Matching placebo (spray)	oral pain: 1. 0/34 2. 3/32 thirst: 1. 1/34 2. 0/32 Psychological: dissociation: 1. 3/34 2. 0/32 euphoria: 1. 2/34 2. 0/32 feeling abnormal: 1. 1/34 2. 0/32 Other: headache: 1. 1/34 2. 3/32 weakness: 1. 3/34 2. 0/32 application site burning: 1. 0/34 2. 1/32 chest discomfort: 1. 0/34 2. 1/32 pharyngitis: 1. 2/34 2. 1/32 hoarseness (abnormal voice changes): 1. 1/34 2. 0/32 throat irritation: 1. 1/34 2. 0/32 dyspnea: 1. 0/34 2. 1/32	CNS: dizziness: 1. 18/34 2. 5/32 somnolence: 1. 3/34 2.0/32 disturbance in attention: 1. 2/34 2. 0/32 falls: 1. 3/34 2. 2/32 fatigue: 1. 2/34 2. 2/32 feeling drunk: 1. 1/34 2. 1/32 GI: dry mouth: 1. 4/34 2. 0/32 nausea: 1. 3/34 2. 2/32 diarrhea: 1. 2/34 2. 0/32 glossodynia (painful tongue): 1. 1/34 2. 3/32 mouth ulceration: 1. 1/34 2. 0/32 vomiting: 1. 1/34 2. 0/32 dyspepsia: 1. 0/34 2. 1/32
Salim 2005 (103)** $	randomized, double blind, placebo-controlled, crossover (7d + 7d)	19 (2)	NP	Oral (capsules)	1. ajulemic acid: 40 mg for 4d and 80 mg for 3 days	2. placebo	GI: dry mouth: 1. 8/19 2. N/I Other: sweating: 1. 1/19 2. N/I more pain: 1. 1/19 2. N/I	CNS: tiredness: 1. 3/19 2. N/I dizziness: 1. 2/19 2. N/I limited power of concentration: 1. 1/19 2. N/I
Wissel 2006 (61)	double-blind, randomized, placebo-controlled crossover study (4w,WO, 4w)	11 (2)	Chronic upper motor neuron syndrome	Oral (capsules)	1. Nabilone 1 mg (THC)	2.Matching placebo	Musculoskeletal: weakness of lower limbs (severe, drop out): 1. 1/13 2. 0/11 weakness of lower limbs (slight): 1. 1/11 2. 0/11 Other: relapse of MS (severe, drop out): 1. 1/13 2. 0/11	CNS: drowsiness: 1. 2/11 2. 1/11 GI: dysphagia (slight): 1. 0/11 2. 1/11
Blake 2006 (52)	randomized, placebo-controlled, double-blind parallel group (5w + follow up)	58 (4)	rheumatoid arthritis	Oromucosal spray	1. CBM Sativex THC2.7 mg/CBD2.5 mg	2.Matching placebo	vomiting: 1. 0/31 2. 2/27 dry mouth: 1. 4/31 2. 0/27 Cardiac: palpitations: 1. 0/31 2. 2/27 Musculoskeletal: arthritic pain: 1. 1/31 2. 1/27 Other: headache: 1. 1/31 2. 1/27	CNS: dizziness: 1. 8/31 2. 1/27 drowsiness: 1. 1/31 2. 1/27 fall: 1. 2/31 2. 0/27 light heedlessness: 1. 3/31 2. 1/27 GI: nausea: 1. 2/31 2. 1/27 constipation: 1. 1/31 2. 1/27

Table 6 (cont). *Chronic non-cancer pain studies' AE characteristics.*

First author (year)	Design (duration)	N (Dropouts)	Pathology	Administration route	Intervention drug	Placebo/active control	Adverse events: n\N	
Abrams 2007 (62)**	randomized, placebo-controlled parallel groups (7d + 2d + 5d + 7d)	50 (5)	HIV sensory neuropathy	Smoking (inhalation)	1. Cannabis 3.56%	2. placebo	nausea: N/I Psychological: anxiety: 1. 1/22 2. 1/28 paranoia: N/I confusion: N/I	CNS: sedation: N/I disorientation: N/I dizziness: 1. 1/22 2. 0/28 GI:
Nurmikko 2007 (65)	randomized, placebo-controlled parallel groups (5w)	103 (22)	Unilateral NP and allodynia	Oromucosal spray	1. Sativex THC2.7 mg/ CBD2.5 mg	2. Matching placebo	dry mouth: 1. 11/63 2. 3/62 vomiting: 1. 8/63 2. 3/62 diarrhea: 1. 4/63 2. 0/62 anorexia: 1. 4/63 2. 0/62 Other: headache: 1. 6/63 2. 9/62 naso-pharangythis: 1. 4/63 2. 2/62 abdominal pain upper: 1. 3/63 2. 1/62	CNS: dizziness: 1. 18/63 2. 9/62 fatigue: 1. 13/63 2. 5/62 feeling drunk: 1. 6/63 2. 1/62 somnolence: 1. 4/63 2. 1/62 disturbance in attention: 1. 3/63 2. 0/62 memory impairment: 1. 3/63 2. 0/62 GI: nausea: 1. 14/63 2. 7/62
Frank 2008 (90)	randomized, double blind, active-controlled, crossover (6w)	64 (32)	Chronic NP	Oral (capsules)	Maximum daily dose-1.Nabilone: 2 mg	Active control: 2. Dihydrocodeine 240mg	N/I	
Skrabek 2008 (59)	randomized, double blind, placebo-controlled, parallel group (1w + 1w + 4w)	40 (7)	Fibromyalgia	Oral (capsules)	1. Nabilone (THC): 1w 0.5 mg and 1w 1.5-2 mg	2.Matching placebo	dysphoria: 2w: 1. 2/18 2. 0/20 4w: 1. 1/15 2. 0/18 depression: 2w: 1. 0/18 2. 0/20 4w: 1. 0/15 2. 1/18 euphoria: 2w: 1. 0/18 2. 0/20 4w: 1. 1/15 2. 1/18 psychological high: 2w: 1. 1/18 2. 1/20 4w: 1. 0/15 2. 0/18 nightmares: 2w: 1. 1/18 2. 0/20 4w: 1. 0/15 2.1/18 hallucination: 2w: 1. 0/18 2. 0/20 4w: 1. 0/15 2. 0/18 Cardiac: orthostatic hypotension: 2w: 1. 1/18 2. 0/20 4w: 1. 2/15 2. 1/18 tachycardia: 2w: 1. 0/18 2. 0/20 4w: 1. 0/15 2.1/18 Vision impairments: blurred vision: 2w: 1. 1/18 2. 1/20 4w: 1. 0/15 2. 0/18 Other: headache: 2w: 1. 3/18 2. 2/20 4w: 1. 1/15 2. 3/18	CNS: drowsiness: 2w: 1. 7/18 2. 3/20 4w: 1. 7/15 2. 1/18 vertigo: 2w: 1. 2/18 2. 0/20 4w: 1. 4/15 2. 0/18 ataxia: 2w: 1. 3/18 2. 0/20 4w: 1. 3/15 2. 1/18 confusion: 2w: 1. 3/18 2. 0/20 4w: 1. 2/15 2. 1/18 decreased concentration: 2w: 1. 1/18 2. 0/20 4w: 1. 2/15 2. 1/18 disassociation: 2w: 1. 2/18 2. 0/20 4w: 1. 2/15 2. 0/18 lightheaded: 2w: 1. 1/18 2. 0/20 4w: 1. 0/15 2. 0/18 sensory disturbance: 2w: 1. 1/18 2. 0/20 4w: 1. 1/15 2. 0/18 GI: dry mouth: 2w: 1. 5/18 2. 5/20 4w: 1. 5/15 2. 1/18 anorexia: 2w: 1. 1/18 2. 0/20 4w: 1. 2/15 2. 1/18 Psychological:
Wilsey 2008 (73)	randomized, double blind, placebo-controlled, crossover trial (6h)	38 (6)	CRPS type I, spinal cord injury, various NP	Smoking (inhalation)	Cannabis: 1. 3.5% 2. 7%	3. placebo	N/I	
Narang 2008 (104)**	randomized, double blind, placebo-controlled, single-dose, crossover (phase I, 8hrs)	24 (6)	Chronic non-cancer pain	Oral (capsules)	Dronabinol: 1. 10 mg 2. 20 mg	3.Matching placebo	abnormal thinking: 1. 7/30 2. 11/30 3. 1/30 forgetfulness: 1. 12/30 2. 10/30 3. 1/30 depression: 1. 3/30 2. 4/30 3. 2/30 cardiac: fast heart beat: 1. 4/30 2. 7/30 3. 0/30 Vision impairments: change in vision: 1. 8/30 2. 12/30 3. 3/30 hearing impairments: ringing in the ears: 1. 4/30 2. 6/30 3. 0/30 Other:eye irritation: 1. 5/30 2. 8/30 3. 1/30 facial flushing: 1. 5/30 2. 8/30 3. 1/30 difficulty speaking: 1. 9/30 2. 7/30 3. 0/30 headache: 1. 6/30 2. 7/30 3. 0/30 weakness: 1. 6/30 2. 6/30 3. 3/30 itching: 1. 4/30 2. 6/30 3. 4/30 sweating: 1. 5/30 2. 3/30 3. 4/30	CNS:drowsiness: 1. 16/30 2. 20/30 3. 8/30 sleepiness: 1. 12/30 2. 16/30 3. 10/30 dizziness: 1. 14/30 2. 15/30 3.1/30 tiredness: 1. 13/30 2. 11/30 3. 7/30 difficulty balancing: 1. 6/30 2. 8/30 3. 2/30 GI:dry mouth: 1. 15/30 2. 14/30 3. 2/30 upset stomach: 1. 5/30 2. 6/30 3. 1/30 nausea: 1. 3/30 2. 6/30 3. 1/30 heartburn: 1. 1/30 2. 2/30 3. 0/30 abdominal pain: 1. 0/30 2. 2/30 3. 1/30 vomiting: 1. 1/30 2. 0/30 3. 0/30 Psychological: confusion: 1. 3/30 2. 12/30 3. 1/30 anxiety/nervousness: 1. 5/30 2. 12/30 3. 1/30 euphoria: 1. 14/30 2. 11/30 3. 1/30

Table 6 (cont). *Chronic non-cancer pain studies' AE characteristics.*

First author (year)	Design (duration)	N (Dropouts)	Pathology	Administration route	Intervention drug	Placebo/active control	Adverse events: n\N	
Ellis 2009 (71)**	randomized, double blind, placebo-controlled, crossover (5d)	28 (6)	HIV neuropathy	Smoking (inhalation)	1. Cannabis 1-8%, individual titration	2. placebo	concentration difficulties, fatigue, sleepiness\sedation, increased duration of sleep, reduced salivation, thirst: greater with cannabis than placebo, N/I.	
Ware 2010 (72)	Randomized, double-blind, placebo-controlled, four period. Crossover design (14d)	21 (2)	NP	Smoking pipe (inhalation)	Cannabis: 1. 2.5% 2. 6% 3. 9.4%	4. Matching placebo 0%	decreased motor skill: 1. 0/22 2. 0/21 3. 2/22 4. 0/21 heaviness in leg: 1. 0/22 2. 1/21 3. 1/22 4. 0/21 injury to right knee: 1. 0/22 2. 0/21 3. 4. 0/21 contracted jaw muscles: 1. 0/22 2. 1/21 3. 1/22 4. 0/21 musculoskeletal pain: 1. 0/22 2. 0/21 3. 0/22 4. 1/21 weakness of right leg: 1. 0/22 2. 0/21 3. 0/22 4. 1/21 achy bones: 1. 1/22 2. 0/21 3. 0/22 4. 0/21 bruise on left back shoulder: 1. 0/22 2. 0/21 3. 0/22 4. 1/21 Sleep related AEs: insomnia: 1. 1/22 2. 1/21 3. 0/22 4. 1/21 nightmares: 1. 0/22 2. 0/21 3. 0/22 4. 1/21 not sleeping well: 1. 0/22 2. 0/21 3. 0/22 4. 1/21 vision impairments: blurry vision: 1. 1/22 2. 0/21 3. 0/22 4. 1/21 hearing impairments: ear buzzing: 1. 0/22 2. 1/21 3. 0/22 4. 0/21 Other: headache: 1. 3/22 2. 7/21 3. 4/22 4. 3/21 migraine: 1. 1/22 2. 0/21 3. 0/22 4. 0/21 tiredness: 1. 1/22 2. 1/21 3. 0/22 4. 1/21 unbalanced: 1. 1/22 2. 0/21 3. 1/22 4. 0/21 burning sensation: 1. 2/22 2. 3/21 3. 3/22 4. 3/21 cheeks flushed: 1. 0/22 2. 1/21 3. 0/22 4. 0/21 chills: 1. 2/22 2. 1/21 3. 0/22 4. 1/21 diaphoresis (excessive sweating): 1. 0/22 2. 0/21 3. 0/22 4. 1/21 heaviness: 1. 2/22 2. 0/21 3. 1/22 4. 0/21 hematoma: 1. 0/22 2. 0/21 3. 1/22 4. 0/21 itchiness: 1. 0/22 2. 0/21 3. 1/22 4. 0/21 face itchiness: 1. 0/22 2. 0/21 3. 1/22 4. 0/21 nose itchiness: 1. 0/22 2. 2/21 3. 1/22 4. 0/21 pain: 1. 0/22 2. 3/21 3. 2/22 4. 2/21 tingling nose: 1. 0/22 2. 1/21 3. 1/22 4. 0/21 cough: 1. 0/22 2. 3/21 3. 3/22 4. 1/21 pneumonia: 1. 1/22 2. 0/21 3. 0/22 4. 1/21 short of breath: 1. 1/22 2. 1/21 3. 1/22 4. 0/21 throat irritation: 1. 0/22 2. 3/21 3. 3/22 4. 3/21 dry eyes: 1. 0/22 2. 0/21 3. 1/22 4. 0/21 eyes red: 1. 0/22 2. 1/21 3. 0/22 4. 0/21 itchiness of eyes: 1. 0/22 2. 2/21 3. 1/22 4. 0/21 edema: 1. 0/22 2. 0/21 3. 0/22 4. 1/21	CNS: dizziness: 1. 3/22 2. 4/21 3. 4/22 4. 2/21 drowsiness: 1. 2/22 2. 2/21 3. 0/22 4. 1/21 heavy headed: 1. 0/22 2. 0/21 3. 1/22 4. 0/21 lethargic: 1. 0/22 2. 1/21 3. 0/22 4. 0/21 lightheaded: 1. 1/22 2. 0/21 3. 1/22 4. 1/21 numbness: 1. 2/22 2. 1/21 3. 2/22 4. 1/21 sleepiness: 1. 0/22 2. 1/21 3. 2/22 4. 0/21 spasm: 1. 0/22 2. 0/21 3. 0/22 4. 1/21 fall: 1. 1/22 2. 0/21 3. 0/22 4. 2/21 fatigue: 1. 3/22 2. 3/21 3. 2/22 4. 2/21 lack of concentration: 1. 0/22 2. 2/21 3. 2/22 4. 1/21 less alert: 1. 0/22 2. 0/21 3. 1/22 4. 0/21 GI: bad taste: 1. 1/22 2. 0/21 3. 0/22 4. 1/21 oral irritation: 1. 0/22 2. 0/21 3. 1/22 4. 0/21 dry mouth: 1. 4/22 2. 0/21 3. 1/22 4. 0/21 gastric acid: 1. 0/22 2. 1/21 3. 0/22 4. 0/21 increased appetite: 1. 0/22 2. 1/21 3. 2/22 4. 0/21 loss of appetite: 1. 0/22 2. 0/21 3. 0/22 4. 0/21 nausea: 1. 1/22 2. 2/21 3. 1/22 4. 1/21 thirst: 1. 1/22 2. 1/21 3. 0/22 4. 0/21 vomiting: 1. 2/22 2. 0/21 3. 0/22 4. 0/21 decreased appetite: 1. 0/22 2. 1/21 3. 0/22 4. 1/21 Psychological: anxiety: 1. 0/22 2. 1/21 3. 0/22 4. 0/21 craving for sweets: 1. 0/22 2. 0/21 3. 1/22 4. 0/21 disinterest in surroundings: 1. 1/22 2. 0/21 3. 1/22 4. 0/21 dysphoria: 1. 0/22 2. 0/21 3. 2/22 4. 0/21 euphoria: 1. 0/22 2. 0/21 3. 1/22 4. 0/21 feel high: 1. 0/22 2. 1/21 3. 0/22 4. 0/21 fidgety fingers: 1. 1/22 2. 0/21 3. 1/22 4. 0/21 foggy mental state: 1. 0/22 2. 1/21 3. 1/22 4. 0/21 lost in time: 1. 2/22 2. 0/21 3. 0/22 4. 0/21 paranoia: 1. 0/22 2. 0/21 3. 1/22 4. 0/21 racing thoughts: 1. 1/22 2. 0/21 3. 1/22 4. 0/21 stressful: 1. 0/22 2. 0/21 3. 0/22 4. 0/21 Musculoskeletal: Asthenia (loss/lack of strength): 1. 3/22 2. 0/21 3. 2/22 4. 1/21
Selvarajah 2010 (66)	randomized, double blind, placebo-controlled, parallel groups (2w + 10w)	29 (9)	chronic DPN	Oromucosal spray	1. Sativex (tetrahydrocannabinol: 27 mg/ml and cannabidiol: 25 mg/ml	2.Matching placebo	N/I	

Table 6 (cont). *Chronic non-cancer pain studies' AE characteristics.*

First author (year)	Design (duration)	N (Dropouts)	Pathology	Administration route	Intervention drug	Placebo/active control	Adverse events: n\N	
Rintala 2010 (91)	randomized, double blind, active-controlled, crossover (56d + 56d)	5 (2)	Spinal cord injury NP	Oral (capsules)	1. Dronabinol 5 mg per d (max 20 mg per d)	Active control: 2. diphen-hydramine 25 mg (max 75 mg per d)	Psychological: feeling high: 1. 2/7 2. 0/5 confusion: 1. 1/7 2. 0/5 cardiac: abnormal heart rate: 1. 0/7 2. 0/5 Other: itchiness: 1. 3/7 2. 1/5 weakness: 1. 1/7 2. 2/5 rash: 1. 1/7 2. 1/5 weight gain: 1. 0/7 2. 0/5	CNS: fatigue: 1. 4/7 2. 5/5 drowsiness: 1. 4/7 2. 3/5 dizziness: 1. 1/7 2. 0/5 incoordination: 1. 1/7 2. 0/5 GI: dry mouth: 1. 5/7 2. 3/5 constipation: 1. 5/7 2. 3/5 abdominal discomfort: 1. 2/7 2. 0/5 nausea: 1. 0/7 2. 0/5 vomiting: 1. 0/7 2. 0/5
Toth 2012 (92)	Enriched enrollment, randomized, flexible dose, double blind, parallel groups (28d)	26 (0)	DPN	Oral (capsules)	1. nabilone 1-4 mg	2. placebo	treatment-emergent AEs: 1. 6/13 2. 6/13 no specific data	
Corey-Bloom 2012 (96)**	randomized, double blind, placebo-controlled, crossover (3d + 3d)	30 (7)	MS	Smoking (inhalation)	1. 4% THC	2.Matching placebo	Psychological: feeling too high: 1. 2/30 2. 0/30 Other: headache: 1. 7/30 2. 6/30 throat irritation: 1. 1/30 2. 1/30	CNS: dizziness: 1. 8/30 2. 1/30 fatigue: 1. 7/30 2. 2/30 GI: nausea: 1.4/30 2. 1/30
Pini 2012 (95)	randomized, double blind, active-controlled, crossover (8w + 8w)	26 (4)	Chronic MOH	Oral (capsules)	1. 60 doses of nabilone 0.5 mg (total)	Active control: 2. 60 doses of ibuprufen 400 mg (total)	nausea: 1. 1/26 2. 2/26 epigastric discomfort: 1. 1/26 2. 2/26 dry mouth: 1. 2/26 2. 0/26 Sleep related AEs: sleep disorders: 1. 0/26 2. 1/26 Other: asthenia: 1. 2/26 2. 0/26	CNS: dizziness: 1. 2/26 2. 0/26 drowsiness: 1. 0/26 2. 0/26 loss of attention: 1. 0/26 2. 1/26 GI: decreased appetite: 1. 1/26 2. 2/26 vomiting: 1. 2/26 2. 0/26
Huggins 2012 (105)**	Multicenter, randomized, double blind, double dummy, placebo/active-controlled, crossover (2w + 2w)	69 (5)	Knee osteoarthritis pain	Oral (capsules)	1. PF-04457845 4 mg (sequence 1 with placebo) 2. naproxen 500 mg (sequence 2 with placebo)	3. placebo	Other: URTI: 1. 6/37 2. 3/36 3. 6/70 headache: 1. 1/37 2. 2/36 3. 10/70 back pain: 1. 2/37 2. 2/36 3. 2/70	CNS: dizziness: 1. 2/37 2. 2/36 3. 1/70 fatigue: 1. 0/37 2. 1/36 3.4/70 GI: diarrhea: 1. 1/37 2. 2/36 3. 3/70 constipation: 1. 1/37 2. 3/36 3. 0/70 dyspepsia: 1. 0/37 2. 3/36 3. 0/70
Zajicek 2012 (106)**	randomized, double blind, placebo-controlled, parallel groups (12w)	224 (55)	MS	Oral (ethanol extract)	1. cannabis extract (THC 2.5 mg/ CBD 0.8-1.8 mg)	2. placebo	Other: headache: 1. 22/143 2. 20/134 asthenia: 1. 25/143 2. 11/134 UTI: 1. 34/143 2. 19/134	CNS: dizziness: 1. 89/143 2. 10/134 fatigue: 1. 25/143 2. 9/134 GI: dry mouth: 1. 34/143 2. 10/134
Wilsey 2013 (74)**	randomized, double blind, placebo-controlled, flexible dose, crossover (2h)	36 (2)	NP	Smoking (inhalation)	THC: 1. 3.53% 2. 7%	3. placebo	N/I	

Table 6 (cont). *Chronic non-cancer pain studies' AE characteristics.*

First author (year)	Design (duration)	N (Dropouts)	Pathology	Administration route	Intervention drug	Placebo/active control	Adverse events: n\N	
Langford 2013a (64)	randomized, double blind, placebo-controlled, parallel groups (phase A) (14w)	297 (42)	CNP in MS	spray	1. Sativex: THC 2.7 mg\ CBD2.5 mg	2. placebo	Musculoskeletal: pain in extremity: 1. 0/167 2. 1/172 muscular weakness: 1. 1/167 2. 1/172 Psychological: depression: 1. 2/167 2. 0/172 feeling abnormal: 1. 5/167 2. 2/172 Vision impairments: vision blurred: 1. 4/167 2. 1/172 Other: pain: 1. 0/167 2. 1/172 infections and infestations: 1. 34/167 2. 27/172 headache: 1. 7/167 2. 6/172 neuralgia: 1. 1/167 2. 1/172 pharyngo-laryngeal pain: 1. 2/167 2. 1/172	CNS: vertigo: 1. 15/167 2. 6/172 dizziness: 1. 34/167 2. 7/172 somnolence: 1. 16/167 2. 3/172 disturbance in attention: 1. 6/167 2. 1/172 memory impairment: 1. 6/167 2. 1/172 balance disorder: 1. 5/167 2. 2/172 psychomotor skills impaired: 1. 5/167 2. 0/172 fatigue: 1. 16/167 2. 9/172 GI: nausea: 1. 13/167 2. 7/172 dry mouth: 1. 12/167 2. 10/172 diarrhea: 1. 7/167 2. 5/172 vomiting: 1. 5/167 2. 5/172 bad taste: 1. 6/167 2. 1/172
Langford 2013b (64)	randomized, double blind, placebo-controlled, parallel groups (phase B) (28d)	41 (1)	CNP in MS	Oromucosal spray	1. Sativex: THC 2.7 mg\ CBD2.5 mg	2. placebo	Sleep related AEs: hypersomnia: 1. 0/21 2. 0/21 insomnia: 1. 0/21 2. 1/21 Cardiac: cardiac disorders: 1. 0/21 2. 0/21 Other: hepatobiliary disorders: 1. 0/21 2. 0/21 infections and infestations: 1. 0/21 2. 1/21 hepatic enzyme increased: 1. 0/21 2. 0/21 cognitive disorder: 1. 0/21 2. 0/21 dysarthria: 1. 0/21 2. 0/21 headache: 1. 0/21 2. 0/21 monoparesis: 1. 0/21 2. 0/21 quadriparesis: 1. 0/21 2. 0/21 tremor: 1. 0/21 2. 0/21 reproductive system and stress disorders: 1. 0/21 2. 0/21 dry skin: 1. 0/21 2. 1/21	CNS: vertigo: 1. 0/21 2. 0/21 fatigue: 1. 0/21 2. 0/21 feeling drunk: 1. 0/21 2. 0/21 somnolence: 1. 0/21 2. 0/21 GI: paresthesia oral: 1. 0/21 2. 0/21 diarrhea: 1. 0/21 2. 0/21 dry mouth: 1. 0/21 2. 0/21 hypoesthesia oral: 1. 0/21 2. 0/21 nausea: 1. 0/21 2. 0/21 vomiting: 1. 0/21 2. 0/21 mucosal erosion: 1. 1/21 2. 0/21 bad taste: 1. 0/21 2. 0/21 Psychological: depression: 1. 1/21 2. 0/21 Musculoskeletal: pain in extremity: 1. 0/21 2. 0/21
Serpell 2014 ((68)**	randomized, double blind, placebo-controlled, parallel groups (15w)	173 (73)	PNP	Oromucosal spray	1. Sativex: THC 2.7 mg\ CBD2.5 mg	2. placebo	anorexia: 1. 1/128 2. 1/118 Psychological: dissociation: 1. 9/128 2. 0/118 disorientation: 1. 8/128 2. 0/118 depression: 1. 3/128 2. 0/118 anxiety: 1. 3/128 2. 1/118 panic attack: 1. 3/128 2. 0/118 vision impairments: eye disorders: 1. 5/128 2. 3/118 hearing impairments: vertigo: 1. 5/128 2. 0/118 cardiac: cardiac disorders: 1. 1/128 2. 0/118 Other: headache: 1. 8/128 2. 7/118 application site pain: 1. 7/128 2. 0/118 nasophryngitis: 1. 1/128 2. 1/118 pharyngolaryngial pain: 1. 2/128 2. 1/118 dyspnea: 1. 1/128 2. 0/118 vascular disorders: 1. 3/128 2. 2/118 renal disorders: 1. 0/128 2. 1/118 rash: 1. 1/128 2. 0/118 PN: 1. 3/128 2. 0/118	CNS: dizziness: 1. 50/128 2. 11/118 disturbance in attention: 1. 8/128 2. 1/118 tremor: 1. 4/128 2. 0/118 somnolence: 1. 5/128 2. 2/118 balance disorder: 1. 4/128 2. 2/118 memory impairment: 1. 4/128 2. 2/118 sedation: 1. 4/128 2. 0/118 fatigue: 1. 19/128 2. 3/118 feeling drunk: 1. 8/128 2. 2/118 GI: nausea: 1. 22/128 2. 9/118 vomiting: 1. 6/128 2. 3/118 diarrhea: 1. 8/128 2. 2/118 dry mouth: 1. 11/128 2. 4/118 abdominal pain: 1. 4/128 2. 0/118 dyspepsia: 1. 1/128 2. 3/118 constipation: 1. 2/128 2. 6/118 mouth ulceration: 1. 4/128 2. 3/118 oral pain: 1. 4/128 2. 5/118 dysguesia: 1. 14/128 2. 2/118 increased appetite: 1. 6/128 2. 0/118

Table 6 (cont). *Chronic non-cancer pain studies' AE characteristics.*

First author (year)	Design (duration)	N (Dropouts)	Pathology	Administration route	Intervention drug	Placebo/active control	Adverse events: n\N	
Lynch 2014 (107)**	randomized, double blind, placebo-controlled, crossover (4w + 4w)	16 (2)	Chemo-theraphy induced NP	Oromucosal spray	1. Sativex: THC 2.7 mg\ CBD2.5 mg	2. placebo	decreased appetite: 1. 1/9 2. 0/9 Psychological: feeling "stoned": 1. 1/9 2. 0/9 anxiety: 1. 1/9 2. 0/9 panic attack: 1. 1/9 2. 0/9 foggy brain: 1. 2/9 2. 0/9 Other: headache: 1. 2/9 2. 0/9	CNS: fatigue: 1. 7/9 2. 0/9 dizziness: 1. 6/9 2. 0/9 confusion: 1. 1/9 2. 0/9 GI: dry mouth: 1. 5/9 2. 1/9 nausea: 1. 6/9 2. 1/9 increased appetite: 1. 2/9 2. 0/9 diarrhea: 1. 2/9 2. 0/9
Turcotte 2015 (108)**	randomized, double blind, placebo-controlled, parallel groups (5w)	14 (1)	MS induced NP	Oral (capsules)	1. nabilone 1 mg	2. placebo	nabilone: 62.5% dizziness, 50% drowsiness and dry mouth. One withdrawal due to headache	
Wallace 2015 (94)	randomized, double blind, placebo-controlled, crossover (4h)	16 (14)	DPN	vaporizer (inhalation)	1. 1% THC 2. 4% THC 3. 7% THC	4. placebo	euphoria: N/I somnolence: N/I	

$=not introduced into the meta-analysis for adverse effects; **=not introduced into the meta-analysis for pain reduction efficacy; GI= gastro-intestinal; CNS= central nervous system; MS= multiple sclerosis; CRPS= chronic regional pain syndrome; DPN= diabetic painful neuropathy; NPS= neuropathic pain scale; N/I= no information; NP= neuropathic pain; CNP= central neuropathic pain; FMF= Familial Mediterranean fever; AEs= adverse events; URTI= upper respiratory tract infections; GT= glutamyl transferase; UTI= urinary tract infection; PN= peripheral neuropathy; d= days; w= weeks; m= months.

limitations to the overall results due to the double-blinding procedure of these trials. No additional analyses were made.

Risk of Limitations across Studies

An important consideration for limitation across the studies is publication. Unpublished studies could have given our study more evidence for either direction, but this would have come on the expense of our study's reliability. Furthermore, the decision to include only studies that were published in English may have caused publication limitation as well. Specifically, 2 studies that were included in the former review/meta-analysis were not published in English, thereby, they could not be included (58,99).

Furthermore, from the studies included in the efficacy meta-analysis, only 2 did not report any information regarding the analgesic treatments permitted during the intervention period (57,89). Moreover, only 7 studies reported on the patients' history of prior consumption of CBMs (Tables 1–3) (45,52,59,65,67,72,92).

Results

Study Selection

The flow chart of studies through selection process is presented in Fig. 5. The electronic and manual search yielded 1,126 titles of studies that examined the effects of CBMs on pain from 1975 to July of 2015. Inspection of the abstracts led to 972 of these studies to be discarded. As a result, 154 full text studies were reviewed. Unpublished or poster-based data were not included or analyzed in this review due to the need for valid, peer-reviewed data. An additional 111 studies were excluded for various reasons: 78 studies failed to meet the requirement of RCT standards, 15 studies were conducted on healthy volunteers, and 18 studies had an open-label design.

We ended up including the 42 studies which fulfilled our inclusion criteria for this review (43-48,52,53,55-57,59-68,71-74,89-96,100-108) (Tables 1–3 and 5-7). However, the meta-analysis section of this study had much more specific requirements. Of the 42 studies that were reviewed for the efficacy evaluation of CBMs, 19 had been redacted. Fifteen studies used outcome measures that did not fit to any form of analysis in the CMA software (44,46,53, 62,67,68,71,74,96,100,103-108). An additional 2 studies were case reports of RCTs (101,102), one reported on the results of accumulated case reports

of RCTs (55), and one study was redacted because the different intervention groups did not report similar baseline pain intensity scores, which may have led to a limitation in the results (44). Consequently, 24 studies were included in the meta-analyses for the examination of the efficacy of CBMs for pain reduction. Of these, 5 studies (43,60,89,93,109) had more than one arm of intervention that was included in the meta-analysis. Study characteristics are presented in Tables 1–3.

Study Quality and Risk of Limitations within Studies

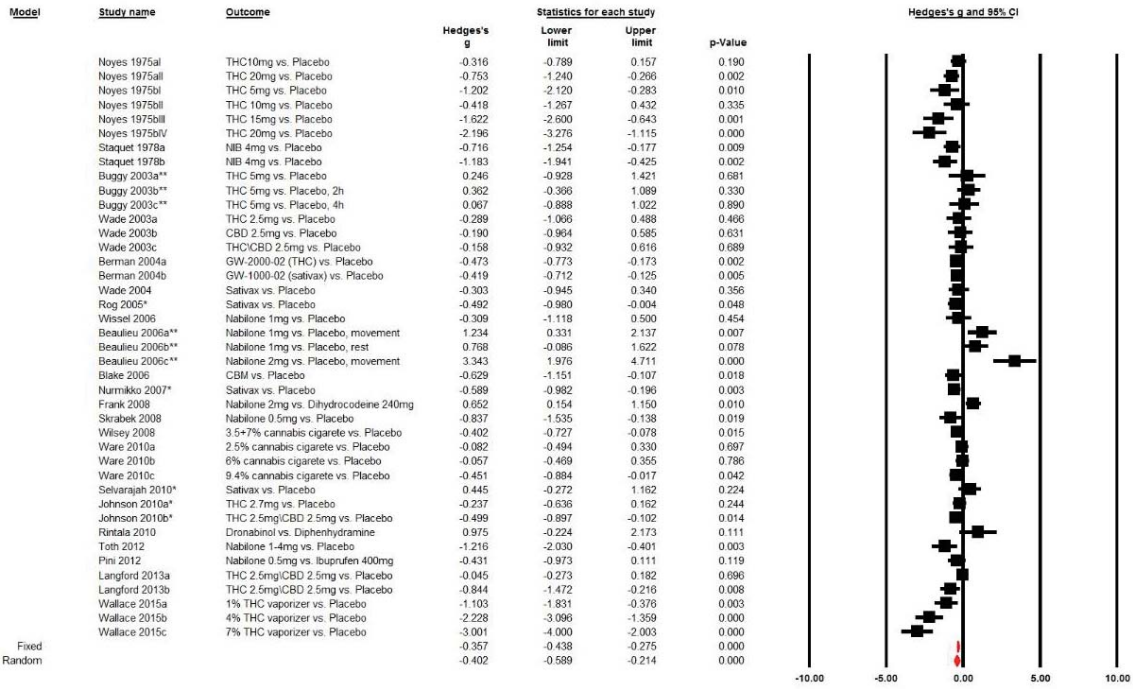
A summary of the methodological quality and level of evidence for each study is shown in tables 1–3. Some studies displayed flaws with respect to control of selection limitation. In most cases, no information was provided regarding the concealment allocation process or the method of randomization (43,44,46-48,52,53,55-57,59-61,66,74,89,91,93,100-102). This phenomenon, which is usual in small trials, increases the risk of possible selection limitation (110). All of the studies were conducted on a double-blind basis; however, the adequacy of blinding was not tested in any of the trials.

Since cannabis is a substance surrounded by considerable controversy in

Table 7. *Acute post-operative pain studies' AE characteristics.*

First author (year)	Design (duration)	N (Dropouts)	Pathology	Administration route	Intervention drug	Placebo/ active placebo	Adverse events: n\N	
Jain 1981 (100)**	Five groups, randomized, double blind, placebo-controlled, crossover (6h)	56(0)	postoperative fracture or trauma pain	Intra-muscular	Levonantradol 1. 1.5mg 2. 2mg 3. 2.5mg 4. 3mg	5. placebo	dysphoria: 1. 0/56 2. 0/56 3. 1/56 4. 1/56 5. 0/56 anxiety: 1. 0/56 2. 0/56 3. 1/56 4. 1/56 5. 0/56 confusion: 1. 1/56 2. 0/56 3. 0/56 4. 0/56 5. 0/56 depression: 1. 0/56 2. 0/56 3. 0/56 4. 1/56 5. 0/56 uncooperative: 1. 0/56 2. 0/56 3. 1/56 4. 0/56 5. 0/56 hearing impairments: loud noise: 1. 2/56 2. 0/56 3. 0/56 4. 0/56 5. 0/56 other: headache: 1. 0/56 2. 1/56 3. 0/56 4. 1/56 5. 0/56 weakness: 1. 0/56 2. 1/56 3. 0/56 4. 0/56 5. 1/56 red eyes: 1. 0/56 2. 0/56 3. 0/56 4. 1/56 5. 0/56	CNS: dizziness: 1. 1/56 2. 0/56 3. 2/56 4. 1/56 5. 0/56 drowsiness\sedation: 1. 4/56 2. 3/56 3. 5/56 4. 6/56 5. 1/56 apprehension: 1. 0/56 2. 0/56 3. 1/56 4. 0/56 5. 0/56 lack of concentration: 1. 0/56 2. 1/56 3. 0/56 4. 0/56 5. 0/56 GI: dry mouth: 1. 2/56 2. 2/56 3. 1/56 4. 0/56 5. 0/56 nausea: 1. 1/56 2. 0/56 3. 0/56 4. 0/56 5. 0/56 psychological: weird dreams: 1. 1/56 2. 0/56 3. 2/56 4. 0/56 5. 0/56 nervousness: 1. 0/56 2. 0/56 3. 1/56 4. 1/56 5. 0/56 hallucination: 1. 1/56 2. 1/56 3. 1/56 4. 0/56 5. 0/56
Buggy 2003 (89)	randomized, double blind, placebo-controlled, single dose, parallel trial (6h)	40(0)	Postoperative pain: elective abdominal hysterectomy	Oral (capsules)	1. THC 5mg	2.Matching placebo	hallucinations: 1. 0/40 2. 1/40 cardiac: palpitations: 1. 8/40 2. 5/40 musculoskeletal: involuntary muscle twitching: 1. 3/40 2. 3/40 tremor: 1. 1/40 2. 2/40 vision impairments: blurred vision: 1. 2/40 2. 3/40 other: headache: 1. 8/40 2. 10/40	CNS: increased awareness of surroundings: 1. 8/40 2. 1/40 drowsiness: 1. 18/40 2. 19/40 impaired memory: 1. 2/40 2. 3/40 slurred speech: 1. 3/40 2. 2/40 dizziness: 1. 5/40 2. 6/40 GI: dry mouth: 1. 16/40 2. 15/40 Psychological: change of mood: 1. 8/40 2. 6/40
Beaulieu 2006 (93)	randomized, double blind, placebo\ active controlled, parallel groups (24hrs)	41(0)	Post-operative gynecologic, orthopedic and others	Oral (capsules)	1. Nabilone 1mg 2. Nabilone 2mg 3. ketoprofen 50mg	4.Matching placebo	GI: some nausea: 1. 3/11 2. 2/9 3. 2/11 4. 4/10 severe nausea: 1. 1/11 2. 1/9 3. 5/11 4. 2/10 vomiting: 1. 3/11 2. 3/9 3. 2/11 4. 1/10	

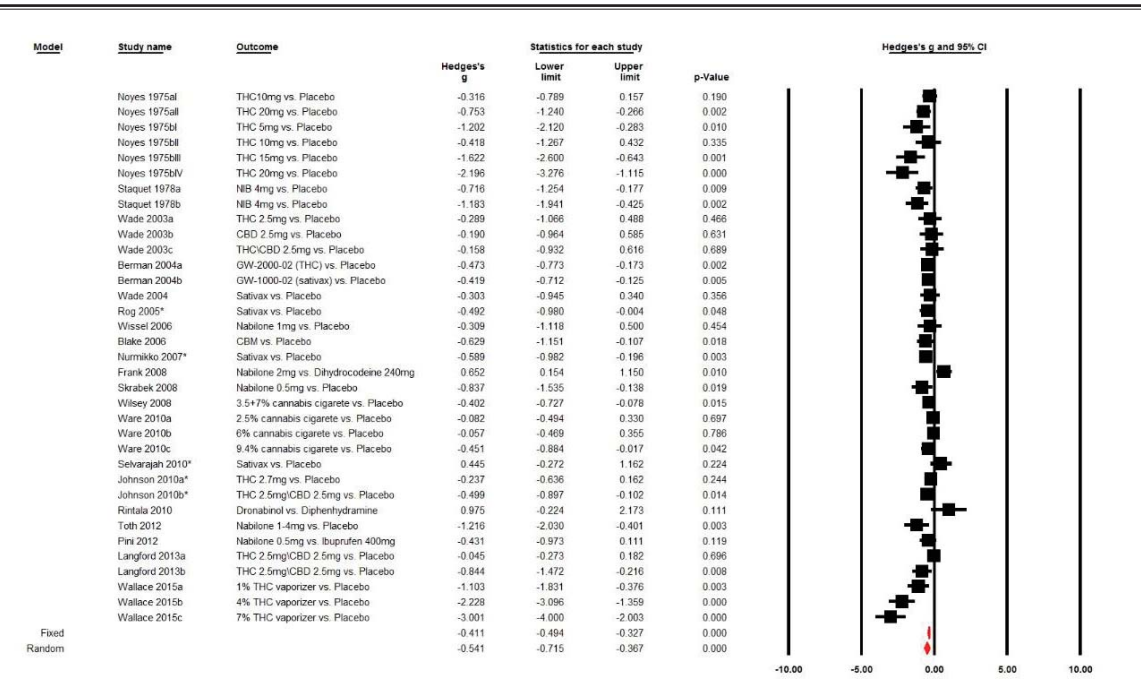
$=not introduced into the meta-analysis for adverse effects; **=not introduced into the meta-analysis for pain reduction efficacy; GI= gastro-intestinal; CNS= central nervous system; MS= multiple sclerosis; CRPS= chronic regional pain syndrome; DPN= diabetic painful neuropathy; NPS= neuropathic pain scale; N/I= no information; NP= neuropathic pain; CNP= central neuropathic pain; FMF= Familial Mediterranean fever; AEs= adverse events; URTI= upper respiratory tract infections; GT= glutamyl transferase; UTI= urinary tract infection; PN= peripheral neuropathy; d= days; w= weeks; m= months.



Model	Study name	Outcome	Hedges's g	Lower limit	Upper limit	p-Value
	Noyes 1975al	THC10mg vs. Placebo	-0.316	-0.789	0.157	0.190
	Noyes 1975all	THC 20mg vs. Placebo	-0.753	-1.240	-0.266	0.002
	Noyes 1975bl	THC 5mg vs. Placebo	-1.202	-2.120	-0.283	0.010
	Noyes 1975bll	THC 10mg vs. Placebo	-0.418	-1.267	0.432	0.335
	Noyes 1975blll	THC 15mg vs. Placebo	-1.622	-2.600	-0.643	0.001
	Noyes 1975blV	THC 20mg vs. Placebo	-2.196	-3.276	-1.115	0.000
	Staquet 1978a	NIB 4mg vs. Placebo	-0.716	-1.254	-0.177	0.009
	Staquet 1978b	NIB 4mg vs. Placebo	-1.183	-1.941	-0.425	0.002
	Buggy 2003a**	THC 5mg vs. Placebo	0.246	-0.928	1.421	0.681
	Buggy 2003b**	THC 5mg vs. Placebo, 2h	0.362	-0.386	1.089	0.330
	Buggy 2003c**	THC 5mg vs. Placebo, 4h	0.067	-0.888	1.022	0.890
	Wade 2003a	THC 2.5mg vs. Placebo	-0.289	-1.066	0.488	0.466
	Wade 2003b	CBD 2.5mg vs. Placebo	-0.190	-0.964	0.585	0.631
	Wade 2003c	THC\CBD 2.5mg vs. Placebo	-0.158	-0.932	0.616	0.689
	Berman 2004a	GW-2000-02 (THC) vs. Placebo	-0.473	-0.773	-0.173	0.002
	Berman 2004b	GW-1000-02 (sativax) vs. Placebo	-0.419	-0.712	-0.125	0.005
	Wade 2004	Sativax vs. Placebo	-0.303	-0.945	0.340	0.356
	Rog 2005*	Sativax vs. Placebo	-0.492	-0.980	-0.004	0.048
	Wissel 2006	Nabilone 1mg vs. Placebo	-0.309	-1.118	0.500	0.454
	Beaulieu 2006a**	Nabilone 1mg vs. Placebo, movement	1.234	0.331	2.137	0.007
	Beaulieu 2006b**	Nabilone 1mg vs. Placebo, rest	0.768	-0.086	1.622	0.078
	Beaulieu 2006c**	Nabilone 2mg vs. Placebo, movement	3.343	1.976	4.711	0.000
	Blake 2006	CBM vs. Placebo	-0.629	-1.151	-0.107	0.018
	Nurmikko 2007*	Sativax vs. Placebo	-0.589	-0.982	-0.196	0.003
	Frank 2008	Nabilone 2mg vs. Dihydrocodeine 240mg	0.652	0.154	1.150	0.010
	Skrabek 2008	Nabilone 0.5mg vs. Placebo	-0.837	-1.535	-0.138	0.019
	Wilsey 2008	3.5+7% cannabis cigarete vs. Placebo	-0.402	-0.727	-0.078	0.015
	Ware 2010a	2.5% cannabis cigarete vs. Placebo	-0.082	-0.494	0.330	0.697
	Ware 2010b	6% cannabis cigarete vs. Placebo	-0.057	-0.469	0.355	0.786
	Ware 2010c	9.4% cannabis cigarete vs. Placebo	-0.451	-0.884	-0.017	0.042
	Selvarajah 2010*	Sativax vs. Placebo	0.445	-0.272	1.162	0.224
	Johnson 2010a*	THC 2.7mg vs. Placebo	-0.237	-0.636	0.162	0.244
	Johnson 2010b*	THC 2.5mg\CBD 2.5mg vs. Placebo	-0.499	-0.897	-0.102	0.014
	Rintala 2010	Dronabinol vs. Diphenhydramine	0.975	-0.224	2.173	0.111
	Toth 2012	Nabilone 1-4mg vs. Placebo	-1.216	-2.030	-0.401	0.003
	Pini 2012	Nabilone 0.5mg vs. Ibuprufen 400mg	-0.431	-0.973	0.111	0.119
	Langford 2013a	THC 2.5mg\CBD 2.5mg vs. Placebo	-0.045	-0.273	0.182	0.696
	Langford 2013b	THC 2.5mg\CBD 2.5mg vs. Placebo	-0.844	-1.472	-0.216	0.008
	Wallace 2015a	1% THC vaporizer vs. Placebo	-1.103	-1.831	-0.376	0.003
	Wallace 2015b	4% THC vaporizer vs. Placebo	-2.228	-3.096	-1.359	0.000
	Wallace 2015c	7% THC vaporizer vs. Placebo	-3.001	-4.000	-2.003	0.000
Fixed			-0.357	-0.438	-0.275	0.000
Random			-0.402	-0.589	-0.214	0.000

*= Parallel design; **= Postoperative pain

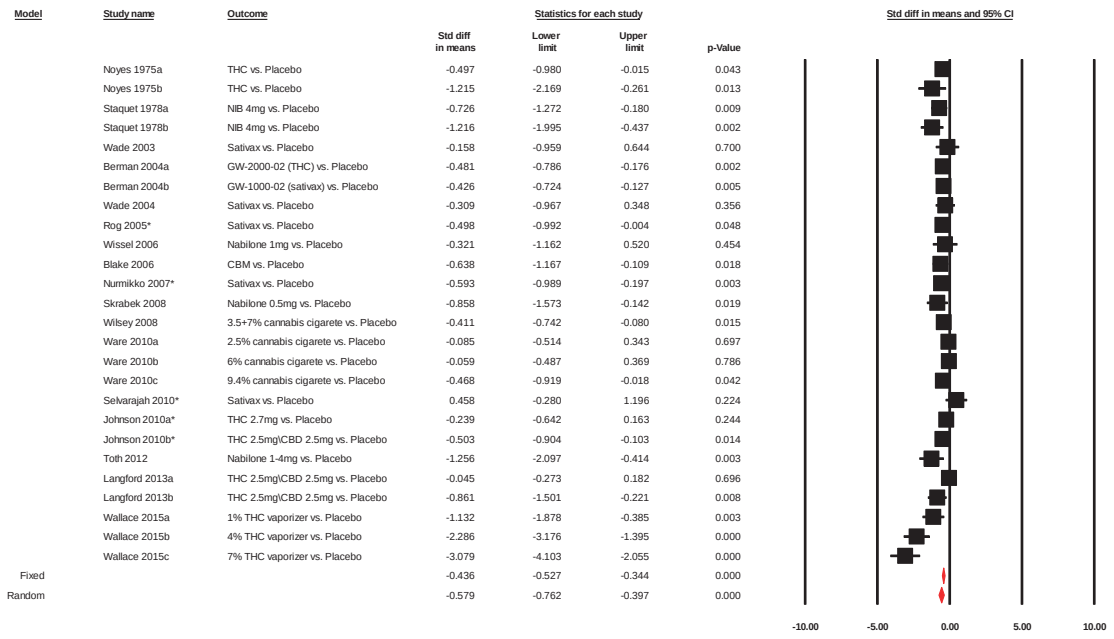
Fig. 1. *A meta-analysis of all of the RCTs.*



Model	Study name	Outcome	Hedges's g	Lower limit	Upper limit	p-Value
	Noyes 1975al	THC10mg vs. Placebo	-0.316	-0.789	0.157	0.190
	Noyes 1975all	THC 20mg vs. Placebo	-0.753	-1.240	-0.266	0.002
	Noyes 1975bl	THC 5mg vs. Placebo	-1.202	-2.120	-0.283	0.010
	Noyes 1975bll	THC 10mg vs. Placebo	-0.418	-1.267	0.432	0.335
	Noyes 1975blll	THC 15mg vs. Placebo	-1.622	-2.600	-0.643	0.001
	Noyes 1975blV	THC 20mg vs. Placebo	-2.196	-3.276	-1.115	0.000
	Staquet 1978a	NIB 4mg vs. Placebo	-0.716	-1.254	-0.177	0.009
	Staquet 1978b	NIB 4mg vs. Placebo	-1.183	-1.941	-0.425	0.002
	Wade 2003a	THC 2.5mg vs. Placebo	-0.289	-1.066	0.488	0.466
	Wade 2003b	CBD 2.5mg vs. Placebo	-0.190	-0.964	0.585	0.631
	Wade 2003c	THC\CBD 2.5mg vs. Placebo	-0.158	-0.932	0.616	0.689
	Berman 2004a	GW-2000-02 (THC) vs. Placebo	-0.473	-0.773	-0.173	0.002
	Berman 2004b	GW-1000-02 (sativax) vs. Placebo	-0.419	-0.712	-0.125	0.005
	Wade 2004	Sativax vs. Placebo	-0.303	-0.945	0.340	0.356
	Rog 2005*	Sativax vs. Placebo	-0.492	-0.980	-0.004	0.048
	Wissel 2006	Nabilone 1mg vs. Placebo	-0.309	-1.118	0.500	0.454
	Blake 2006	CBM vs. Placebo	-0.629	-1.151	-0.107	0.018
	Nurmikko 2007*	Sativax vs. Placebo	-0.589	-0.982	-0.196	0.003
	Frank 2008	Nabilone 2mg vs. Dihydrocodeine 240mg	0.652	0.154	1.150	0.010
	Skrabek 2008	Nabilone 0.5mg vs. Placebo	-0.837	-1.535	-0.138	0.019
	Wilsey 2008	3.5+7% cannabis cigarete vs. Placebo	-0.402	-0.727	-0.078	0.015
	Ware 2010a	2.5% cannabis cigarete vs. Placebo	-0.082	-0.494	0.330	0.697
	Ware 2010b	6% cannabis cigarete vs. Placebo	-0.057	-0.469	0.355	0.786
	Ware 2010c	9.4% cannabis cigarete vs. Placebo	-0.451	-0.884	-0.017	0.042
	Selvarajah 2010*	Sativax vs. Placebo	0.445	-0.272	1.162	0.224
	Johnson 2010a*	THC 2.7mg vs. Placebo	-0.237	-0.636	0.162	0.244
	Johnson 2010b*	THC 2.5mg\CBD 2.5mg vs. Placebo	-0.499	-0.897	-0.102	0.014
	Rintala 2010	Dronabinol vs. Diphenhydramine	0.975	-0.224	2.173	0.111
	Toth 2012	Nabilone 1-4mg vs. Placebo	-1.216	-2.030	-0.401	0.003
	Pini 2012	Nabilone 0.5mg vs. Ibuprufen 400mg	-0.431	-0.973	0.111	0.119
	Langford 2013a	THC 2.5mg\CBD 2.5mg vs. Placebo	-0.045	-0.273	0.182	0.696
	Langford 2013b	THC 2.5mg\CBD 2.5mg vs. Placebo	-0.844	-1.472	-0.216	0.008
	Wallace 2015a	1% THC vaporizer vs. Placebo	-1.103	-1.831	-0.376	0.003
	Wallace 2015b	4% THC vaporizer vs. Placebo	-2.228	-3.096	-1.359	0.000
	Wallace 2015c	7% THC vaporizer vs. Placebo	-3.001	-4.000	-2.003	0.000
Fixed			-0.411	-0.494	-0.327	0.000
Random			-0.541	-0.715	-0.367	0.000

x*= Parallel design.

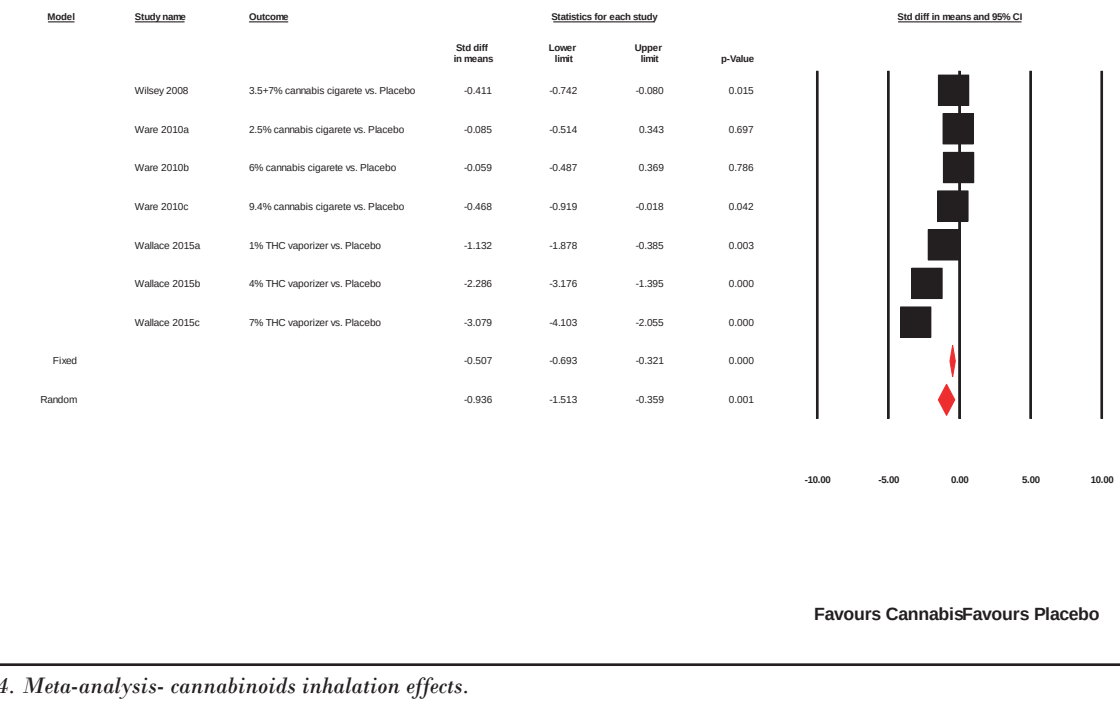
Fig. 2. Meta-analysis- without acute postoperative pain.



Model	Study name	Outcome	Std diff in means	Lower limit	Upper limit	p-Value
	Noyes 1975a	THC vs. Placebo	-0.497	-0.980	-0.015	0.043
	Noyes 1975b	THC vs. Placebo	-1.215	-2.169	-0.261	0.013
	Staquet 1978a	NIB 4mg vs. Placebo	-0.726	-1.272	-0.180	0.009
	Staquet 1978b	NIB 4mg vs. Placebo	-1.216	-1.995	-0.437	0.002
	Wade 2003	Sativax vs. Placebo	-0.158	-0.959	0.644	0.700
	Berman 2004a	GW-2000-02 (THC) vs. Placebo	-0.481	-0.786	-0.176	0.002
	Berman 2004b	GW-1000-02 (sativax) vs. Placebo	-0.426	-0.724	-0.127	0.005
	Wade 2004	Sativax vs. Placebo	-0.309	-0.967	0.348	0.356
	Rog 2005*	Sativax vs. Placebo	-0.498	-0.992	-0.004	0.048
	Wissel 2006	Nabilone 1mg vs. Placebo	-0.321	-1.162	0.520	0.454
	Blake 2006	CBM vs. Placebo	-0.638	-1.167	-0.109	0.018
	Nurmikko 2007*	Sativax vs. Placebo	-0.593	-0.989	-0.197	0.003
	Skrabek 2008	Nabilone 0.5mg vs. Placebo	-0.858	-1.573	-0.142	0.019
	Wilsey 2008	3.5+7% cannabis cigarete vs. Placebo	-0.411	-0.742	-0.080	0.015
	Ware 2010a	2.5% cannabis cigarete vs. Placebo	-0.085	-0.514	0.343	0.697
	Ware 2010b	6% cannabis cigarete vs. Placebo	-0.059	-0.487	0.369	0.786
	Ware 2010c	9.4% cannabis cigarete vs. Placebo	-0.468	-0.919	-0.018	0.042
	Selvarajah 2010*	Sativax vs. Placebo	0.458	-0.280	1.196	0.224
	Johnson 2010a*	THC 2.7mg vs. Placebo	-0.239	-0.642	0.163	0.244
	Johnson 2010b*	THC 2.5mg\CBD 2.5mg vs. Placebo	-0.503	-0.904	-0.103	0.014
	Toth 2012	Nabilone 1-4mg vs. Placebo	-1.256	-2.097	-0.414	0.003
	Langford 2013a	THC 2.5mg\CBD 2.5mg vs. Placebo	-0.045	-0.273	0.182	0.696
	Langford 2013b	THC 2.5mg\CBD 2.5mg vs. Placebo	-0.861	-1.501	-0.221	0.008
	Wallace 2015a	1% THC vaporizer vs. Placebo	-1.132	-1.878	-0.385	0.003
	Wallace 2015b	4% THC vaporizer vs. Placebo	-2.286	-3.176	-1.395	0.000
	Wallace 2015c	7% THC vaporizer vs. Placebo	-3.079	-4.103	-2.055	0.000
Fixed			-0.436	-0.527	-0.344	0.000
Random			-0.579	-0.762	-0.397	0.000

x*= Parallel design.

Fig. 3. Meta-analysis- without active-controlled trials.



Model	Study name	Outcome	Std diff in means	Lower limit	Upper limit	p-Value
	Wilsey 2008	3.5+7% cannabis cigarete vs. Placebo	-0.411	-0.742	-0.080	0.015
	Ware 2010a	2.5% cannabis cigarete vs. Placebo	-0.085	-0.514	0.343	0.697
	Ware 2010b	6% cannabis cigarete vs. Placebo	-0.059	-0.487	0.369	0.786
	Ware 2010c	9.4% cannabis cigarete vs. Placebo	-0.468	-0.919	-0.018	0.042
	Wallace 2015a	1% THC vaporizer vs. Placebo	-1.132	-1.878	-0.385	0.003
	Wallace 2015b	4% THC vaporizer vs. Placebo	-2.286	-3.176	-1.395	0.000
	Wallace 2015c	7% THC vaporizer vs. Placebo	-3.079	-4.103	-2.055	0.000
Fixed			-0.507	-0.693	-0.321	0.000
Random			-0.936	-1.513	-0.359	0.001

Fig. 4. Meta-analysis- cannabinoids inhalation effects.

the media and in society, cannabinoids have a marked placebo effect; therefore, inadequate blinding would constitute an important source of limitation in these types of studies. Additionally, the characteristic side effects caused by these substances render perfect masking extremely difficult. Moreover, some of the studies did not note that they used matching placebo (same appearance), but rather plain placebo (43,56,57,63,73,92), which can misattribute to the masking procedure considerably, especially due to the unusual taste and smell of cannabinoids. Some studies even used an active drug as an active control (90,91,95).

Another important flaw in terms of study quality lay in the control of attrition limitation. In only 8 of the studies there were no losses or withdrawals of subjects (56,60,89,92,93,100-102), while only 6 studies specified that results had been analyzed on an intention to treat basis (43,45,52,64,65,109).

Lastly, studies varied considerably in outcome assessment and reporting approaches. Specifically, several studies expressed data as median values (46,52,55,71), with only reporting means without standard deviations (43,46,48,59,65,71,73,96,100,102,109), as areas under the difference curve (AUDC) (100), as sum of pain intensity difference (SPID) (104), as pain reduction in N% (percentage of subjects that reported pain reduction) (53), as the number of the subjects with 30% and/or 50% pain reduction (55,64,71,74,103), or as non-quantitative data where pain reduction is shown only on a graph, with no raw data (62).

Results of Individual Studies

The results of individual studies are presented in particulars in Tables 1–3.

Synthesis of Results

Meta-Analysis of All Included RCTs

In measures of change from baseline pain intensity, the overall effect size of the included 24 crossover and parallel design RCTs (and some of their intervention arms) that examined the effect of CBMs on pain registered standardized mean differences (SMD). For a fixed-effect model of -0.35 Hedge's g (-0.43 to -0.27, $P < 0.0001$) and for a random-effect model of -0.40 Hedge's g (-0.58 to -0.21, $P < 0.0001$), both were found favorable towards CBMs over placebo. Not all of the studies yielded results in the same direction, and a statistical heterogeneity was in evidence (I2 = 77.83%, $P < 0.0001$), which represents that the dispersion is due to real dispersion in the effect sizes of the studies (Tau2 = 0.25, Tau = 0.50) (Fig. 1).

Meta-Analysis- Without Active-Controlled Trials

Because active control can be regarded as a more efficient analgesic than real placebo, a further reduction of those 3 studies (90,91,95) was made from the meta-analysis in order to get more precise results regarding the analgesic effects of CBMs. This analysis produced more benefit for CBMs over placebo: SMD for a fixed-effect model of -0.45 Hedge's g (-0.54 to -0.36, $P < 0.0001$) and for a random-effect model of -0.61 Hedge's g (-0.78 to -0.43, $P < 0.0001$). Again, not all of the studies yielded results in the same direction, and statistical heterogeneity was in evidence (I2 = 70.12%, $P < 0.0001$), which represents that the dispersion is due to real dispersion in the effect sizes of the studies (Tau2 = 0.15, Tau = 0.39) (Fig. 3).

Meta-Analysis- Cannabinoids Inhalation Effects

Although the most clinically common route of administration is by smoking/inhalation, only 3 studies that used this route of administration were meta-analyzed (72,73,94). This analysis produced more benefit for CBMs over placebo: SMD for a fixed-effect model of -0.50 Hedge's g (-0.69 to -0.32, $P < 0.0001$) and for a random-effect model of -0.93 Hedge's g (-1.51 to -0.35, $P = 0.001$). However, in this analysis, all of the studies yielded results in the same direction, but a statistical heterogeneity was in evidence (I2 = 88.11%, $P < 0.0001$), and a dispersion of Tau2 = 0.50, Tau = 0.71 (Fig. 4).

Meta-Analysis- Cannabinoids Effects on Chronic NP

In order to examine the effectiveness of CBMs for NP, a separate meta-analysis was made to the RCTs that examined NP directly. The studies that did examine NP, but used an active control (90,91), were excluded in order to make a more precise comparison. Eleven RCTs qualified for this analysis. This analysis produced more benefit for CBMs over placebo: SMD for a fixed-effect model of -0.38 Hedge's g (-0.48 to -0.27, $P < 0.0001$) and for a random-effect model of -0.52 Hedge's g (-0.75 to -0.30, $P < 0.0001$). However, in this analysis, all of the studies yielded results in the same direction, but there was a statistical heterogeneity in evidence (I2 = 75.70%, $P < 0.0001$), and a dispersion of Tau2 = 0.16, Tau = 0.41 (Fig. 6).

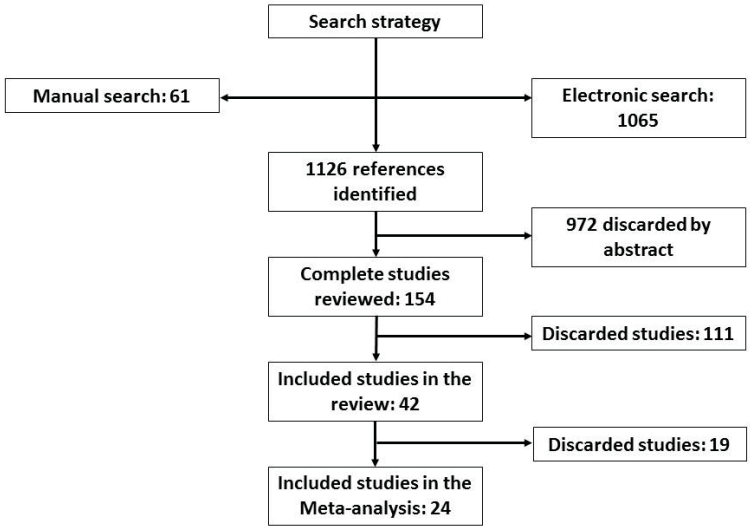


Fig. 5. A flow chart of the studies throughout the selection process.

Meta-Analysis- Cannabinoids Effects on Cancer Pain

In order to examine the effects of CBMs on cancer pain, a separate meta-analysis was made to the RCTs that examined cancer pain directly. The 2 studies that did examine cancer pain but could not be used in the meta-analysis, for previously mentioned reasons in section 3.7, were excluded (Table 1). Three RCTs (10 arms) qualified for this analysis. This analysis produced more benefit for CBMs over placebo: SMD for a fixed-effect model of -0.62 Hedge's g (-0.80 to -0.44, $P < 0.0001$) and for a random-effect model of -0.76 Hedge's g (-1.06 to -0.45, $P < 0.0001$). In this analysis, all of the studies yielded results in the same direction, but a statistical heterogeneity was in evidence (I2 = 59.0%, $P < 0.01$), and a dispersion of Tau2 = 0.12, Tau = 0.35 (Fig. 7).

Meta-Analysis- Cannabinoids Effects on Chronic Non-Cancer Pain

In order to examine the effects of CBMs on chronic non-cancer pain, a separate meta-analysis was made for the RCTs that examined chronic non-cancer pain directly. The 17 studies that did examine chronic non-cancer pain, but could not be used in the meta-analysis for previously mentioned reasons in section 3.7, were excluded (Table 2). Fourteen RCTs (22 arms) qualified for this analysis. This analysis produced more benefit for CBMs over placebo: SMD for a fixed-effect model of -0.39 Hedge's g (-0.49 to -0.29, $P < 0.0001$) and for a random-effect model of -0.53 Hedge's g (-0.75 to -0.32, $P < 0.0001$). However, in this analysis, all of the studies yielded results in the same direction, but there was a statistical heterogeneity in evidence (I2 = 72.56%, $P < 0.0001$), and a dispersion of Tau2 = 0.15, Tau = 0.39 (Fig. 8).

Meta-Analysis- Cannabinoids Effects on Acute Postoperative Pain

In order to examine the effects of CBMs on acute postoperative pain, a separate meta-analysis was made for the RCTs that examined acute postoperative pain directly. The one study that examined acute postoperative pain, but could not be used in the meta-analysis for previously mentioned reasons in section 3.7, was excluded (Table 3). Three RCTs (7 arms) were qualified for this analysis, which produced opposite direction results, where placebo produced a higher benefit over CBMs. The analysis produced a SMD for a fixed-effect model of 0.81 Hedge's g (0.41 to 1.21, $P < 0.0001$) and for a random-effect model of 0.96 Hedge's g (0.16 to 1.76, $P < 0.05$). In this analysis, all of the studies yielded results in the same direction, but there was a statistical homogeneity in evidence (I2 = 72.99%, $P < 0.05$), and a dispersion of Tau2 = 0.70, Tau = 0.84 (Fig. 9).

Review

In reviewing the 43 RCTs that were included in the

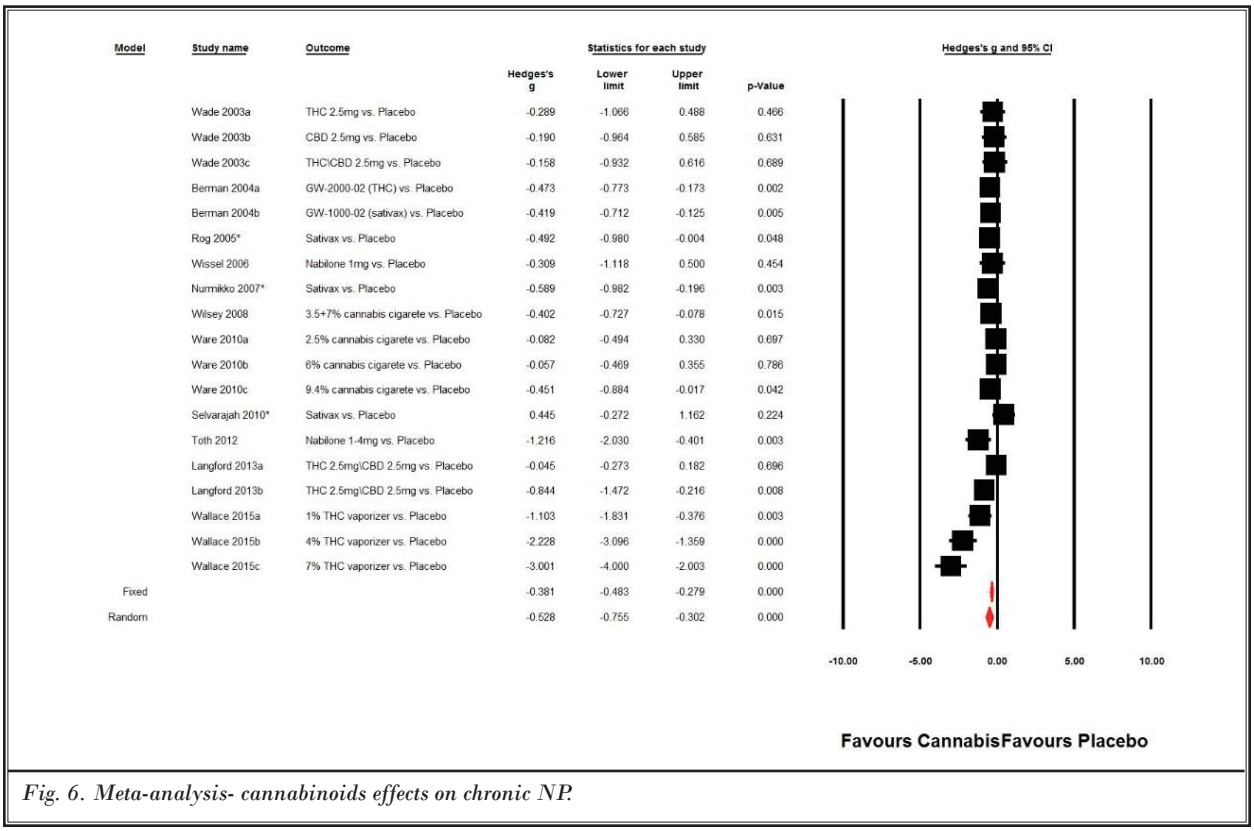


Fig. 6. Meta-analysis- cannabinoids effects on chronic NP.

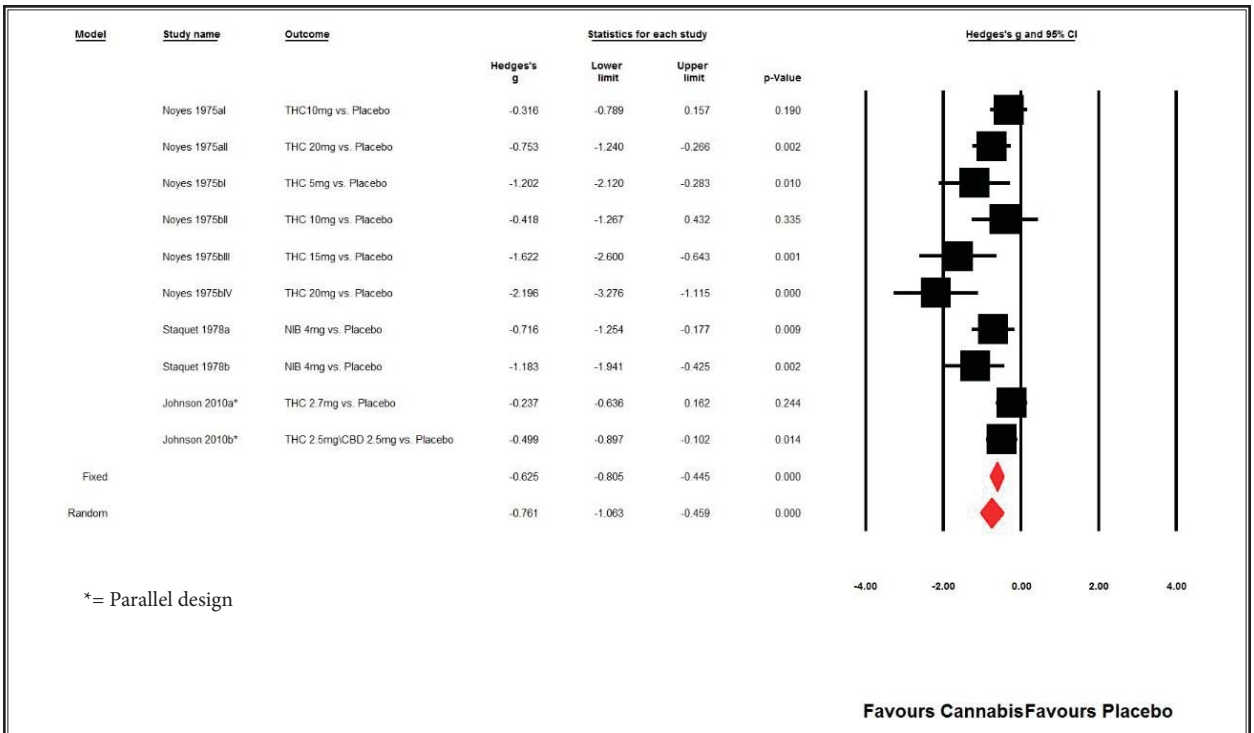
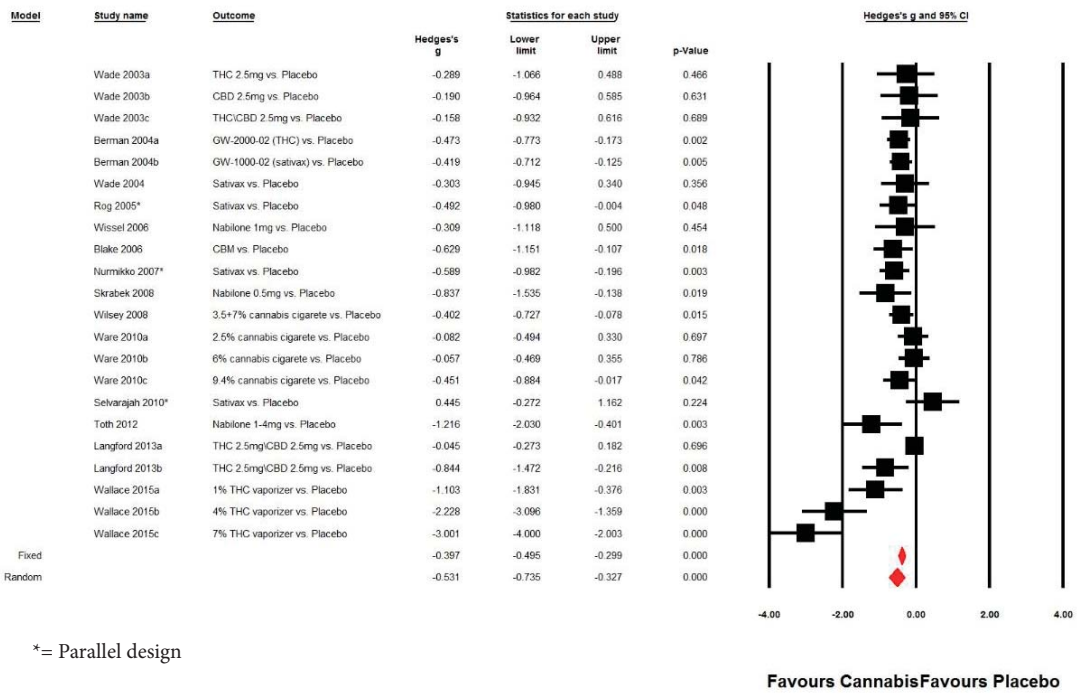


Fig. 7. Meta-analysis- cannabinoids effects on cancer pain.



Model	Study name	Outcome	Hedges's g	Lower limit	Upper limit	p-Value
	Wade 2003a	THC 2.5mg vs. Placebo	-0.289	-1.066	0.488	0.466
	Wade 2003b	CBD 2.5mg vs. Placebo	-0.190	-0.964	0.585	0.631
	Wade 2003c	THC\CBD 2.5mg vs. Placebo	-0.158	-0.932	0.616	0.689
	Berman 2004a	GW-2000-02 (THC) vs. Placebo	-0.473	-0.773	-0.173	0.002
	Berman 2004b	GW-1000-02 (sativax) vs. Placebo	-0.419	-0.712	-0.125	0.005
	Wade 2004	Sativax vs. Placebo	-0.303	-0.945	0.340	0.356
	Rog 2005*	Sativax vs. Placebo	-0.492	-0.980	-0.004	0.048
	Wissel 2006	Nabilone 1mg vs. Placebo	-0.309	-1.118	0.500	0.454
	Blake 2006	CBM vs. Placebo	-0.629	-1.151	-0.107	0.018
	Nurmikko 2007*	Sativax vs. Placebo	-0.589	-0.982	-0.196	0.003
	Skrabek 2008	Nabilone 0.5mg vs. Placebo	-0.837	-1.535	-0.138	0.019
	Wilsey 2008	3.5+7% cannabis cigarete vs. Placebo	-0.402	-0.727	-0.078	0.015
	Ware 2010a	2.5% cannabis cigarete vs. Placebo	-0.082	-0.494	0.330	0.697
	Ware 2010b	6% cannabis cigarete vs. Placebo	-0.057	-0.469	0.355	0.786
	Ware 2010c	9.4% cannabis cigarete vs. Placebo	-0.451	-0.884	-0.017	0.042
	Selvarajah 2010*	Sativax vs. Placebo	0.445	-0.272	1.162	0.224
	Toth 2012	Nabilone 1-4mg vs. Placebo	-1.216	-2.030	-0.401	0.003
	Langford 2013a	THC 2.5mg\CBD 2.5mg vs. Placebo	-0.045	-0.273	0.182	0.696
	Langford 2013b	THC 2.5mg\CBD 2.5mg vs. Placebo	-0.844	-1.472	-0.216	0.008
	Wallace 2015a	1% THC vaporizer vs. Placebo	-1.103	-1.831	-0.376	0.003
	Wallace 2015b	4% THC vaporizer vs. Placebo	-2.228	-3.096	-1.359	0.000
	Wallace 2015c	7% THC vaporizer vs. Placebo	-3.001	-4.000	-2.003	0.000
Fixed			-0.397	-0.495	-0.299	0.000
Random			-0.531	-0.735	-0.327	0.000

Fig. 8. Meta-analysis- cannabinoids effects on chronic non-cancer pain.

current manuscript, we found that there is evidence for limited effectiveness of CBMs for pain treatment. Additionally, in most cases, the patients used additional medications (even, tough, stable dosage) for their diagnoses (Tables 1–3).

Diagnoses

The majority of the moderate to high quality studies were conducted on chronic pain, particularly on NP, due to various conditions (N = 27). Few of the studies investigated cancer pain (N = 7), however most of these studies were published few decades ago and exhibited low quality methodology. Nonetheless, several recent studies on cancer pain from 2010 to 2014 showed higher quality. Additionally, it should be mentioned that cancer pain could also have NP attributes (111).

In addition, chronic non-cancer pain was also investigated in one study of abdominal pain due to Familial Mediterranean fever (FMF), one study investigated rheumatoid arthritis, one study investigated knee osteoarthritis pain, one study investigated medication-overuse headaches (MOH), and one study investigated fibromyalgia. Three studies investigated postoperative pain (Tables 1–3).

Notably, although 19 of the 43 reviewed studies were not included in the meta-analyses, they showed moderate quality methodology, indicating that CBMs induced pain reduction, either by N% of patients or by demonstrating significant pain reduction visually by a graph.

Furthermore, 7 studies included in this review reported significant (30–50%) pain reduction in a substantial part of their patients. Specifically, Portenoy et al (67) showed that chronic cancer pain patients with poorly controlled opioid treatment consistently showed that low doses of nabiximols yielded significant analgesic effects. Notcutt et al (55) showed, by accumulated case reports of RCTs, that administration of oromucosal spray of THC and CBD separately, yielded 50% pain reduction in 16 of 34 chronic NP patients. Salim et al (103) showed that NP patients treated with ajulemic acid yielded 30% pain reduction in 50% of the sample compared to 20% of the sample by placebo. Ellis et al (71) showed that HIV NP patients yielded NNT of 3.5 for 30% pain reduction by cannabinoids inhalation over placebo. Zajicek et al (106) showed that MS patients reported significant clinical pain reduction by orally administered cannabis extract in 28% of the sample, compared to 17.2% in placebo. Wilsey et al (74) showed

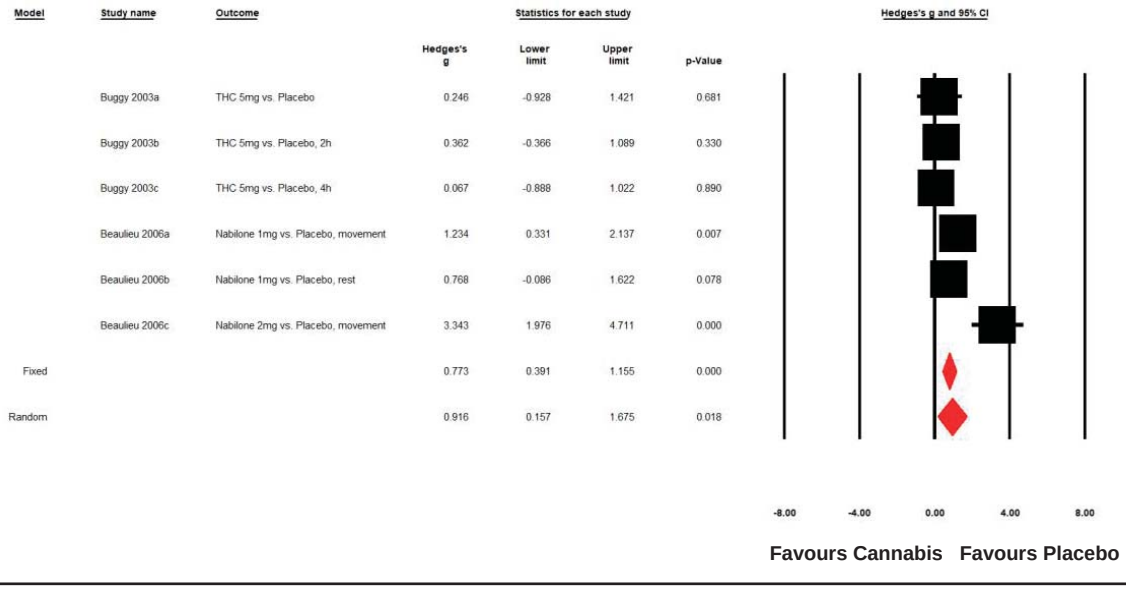


Fig. 9. Meta-analysis- cannabinoids effects on acute postoperative pain.

that NP patients showed NNT of 3.2 and 2.9 for 30% pain reduction by low/high THC content cannabinoids inhalation over placebo, respectively. Serpell et al (68) showed that peripheral NP patients reported significant treatment outcomes for sativex over placebo at 30% responder level (Tables 1-3).

Adverse Events (AEs) Meta-Analysis

More than half of the studies (28 of 43 RCTs) included in this review reported on AEs that were experienced by the patients in their studies (Tables 5–7). The most commonly reported AEs were for the central nervous system (CNS) and the gastro-intestinal system (GI). Other AEs were divided into groups by psychological, musculoskeletal, cardiac, vision, and hearing AEs. No separate analyses were performed for each particular AE because of the large variety of AEs; furthermore, some of the AEs were similar, but were referred to with different definitions between studies. Thus, a combined analysis was performed for each affected group. The results showed a significantly higher harm by CBMs over placebo for all the above-mentioned systems, except for the musculoskeletal and cardiac systems.

Nonetheless, the participating patients in the included trials had preexisting diagnoses and in many of the trials, they used concomitant medications. For these reasons, the following AEs could not be attributed entirely to CBMs administration.

Overall, unlike the comparisons for CBMs efficacy, all of the results in the AEs analyses showed significant homogeneity. Results are demonstrated by risk ratio and 95% confidence interval form.

Central Nervous System (CNS) AEs

The combined risk ratio for all CNS-related AEs, which was reported in 26 RCTs (including apprehension, ataxia, confusion, disassociation, disconnected thought, disorientation, disturbance in attention, dizziness, dreaminess, drowsiness, falling, fatigue, feeling drunk, heavy headed, hypoesthesia, impaired balance, impaired memory, impaired psychomotor skill, incoordination, disorientation, increased awareness, lack of concentration, less alert, lethargic, lightheaded, mental clouding, numbness, slurred speech, somnolence, spasm, tiredness, and vertigo), was significantly more harmful from CBMs than by placebo, for both fixed-effect and random-effect risk ratio models 2.84 (2.16 to 3.73, $P < 0.0001$) (Fig. 10). Homogeneity was in evidence ($I2 = 0\%$, $P = 1.0$) and a dispersion of Tau2 = 0, Tau = 0.

Some of the most prevalent CNS-related AEs were dizziness and drowsiness. Dizziness was presented in 18 studies (43,45-48,52,56,62,64,65,72,89,91,96,100,104,109) and drowsi-

ness was presented in 10 studies (43,46,48,52,56,65,72 ,91,100,104), both showing more harm by CBMs over placebo.

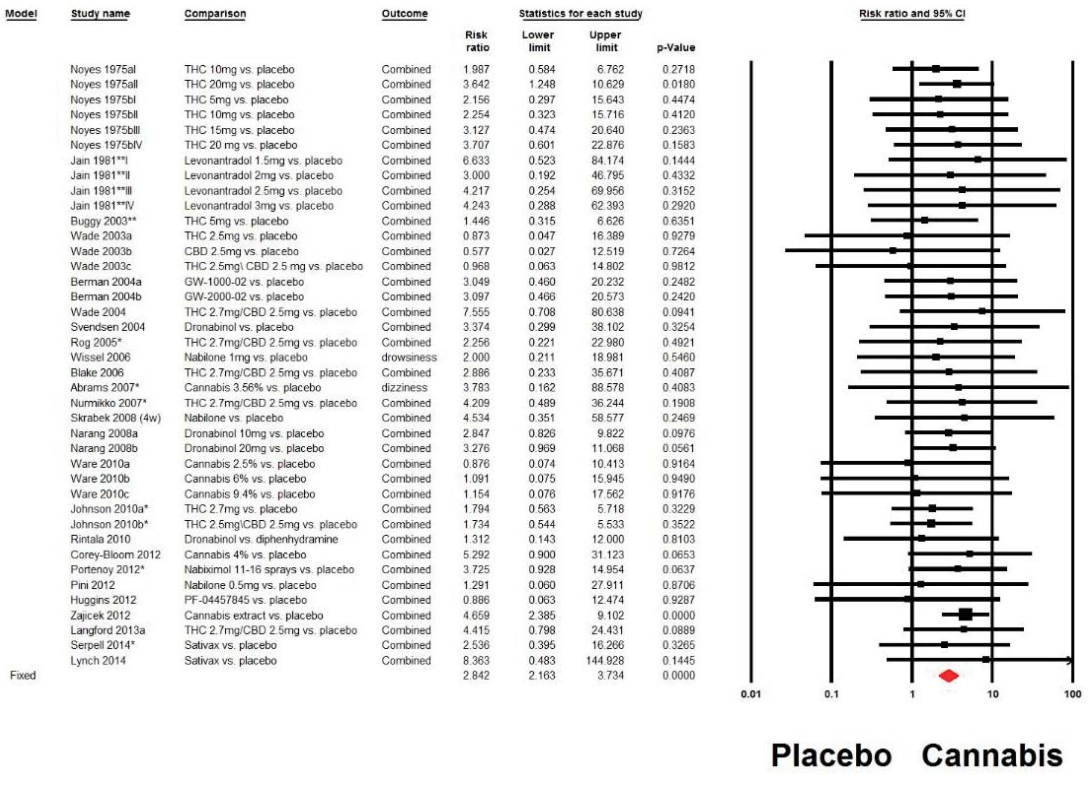
Gastrointestinal (GI) AEs

The combined risk ratio for all GI-related AEs, which was reported in 20 RCTs (including abdominal discomfort, abdominal pain, anorexia, bad taste, constipation, decreased appetite, loss of appetite, increased appetite, diarrhea, dry mouth, dyspepsia, epigastric distress, gastric acid, glossodynia, heartburn, hypoesthesia oral, mouth dryness, mouth ulceration, mucosal erosion, nausea, oral irritation, oral pain, paresthesia oral, sore mouth, thirst, upset stomach, and vomiting), was significantly more harmful from CBMs than from placebo; for both fixed-effect and random-effect, the risk ratio models were 1.86 (1.43 to 2.43, $P = 0.001$) (Fig. 11). Homogeneity was in evidence (I2 = 0%, $P = 0.99$) and a dispersion of Tau2 = 0, Tau = 0.

Some of the most prevalent GI-related AEs were nausea and vomiting. Nausea was reported in 15 studies (43,45-48,52,56,63-65,72,96,100,104,112) and vomiting was reported in 10 studies (45,47,52,56,63-65,72,104,112). Both were more prevalent in oromucosal and oral administration than in inhalation.

Psychological AEs

The combined risk ratio for all psychological AEs that appeared in 13 RCTs (including abnormal thinking, anxiety, confusion, craving for sweets, depressed mood, depression, disinterest in surroundings, dissociation, dysphoria, euphoria, feeling high, feeling abnormal, fidgety fingers, foggy mental state, forgetfulness, hallucinations, hyperactivity, lost in time, nervousness, nightmares, paranoia, psychological high, racing thoughts, stressful, uncooperativeness, and weird dreams) was significantly more harmful from CBMs than from placebo; for both fixed-effect and random-effect, the risk ratio models were 3.07 (1.79 to 5.26, $P < 0.0001$) (Fig. 12). Homogeneity was in evidence (I2



*= Parallel design; **= Postoperative pain.

Fig. 10. Meta-analysis for CNS-related AEs.

= 0%, *P* = 0.99) and a dispersion of Tau2 = 0, Tau = 0.

Musculoskeletal AEs

The combined risk ratio for all musculoskeletal AEs, which were reported in only 6 RCTs (including achy bones, arthritic pain, contracted jaw muscles, decreased motor skill, distortion of wrist, left back shoulder bruise, limb heaviness, limb weakness, muscle weakness, muscle twitching, musculoskeletal pain, myalgia, pain in extremity, right knee injury, and tremor), was insignificant for more harm from CBMs than from placebo; for both fixed-effect and random-effect, the risk ratio models were 1.89 (0.92 to 3.86, *P* = 0.07) (Fig. 13). Homogeneity was in evidence (I2 = 0%, *P* = 0.93) and a dispersion of Tau^2 = 0, Tau = 0.

Cardiac AEs

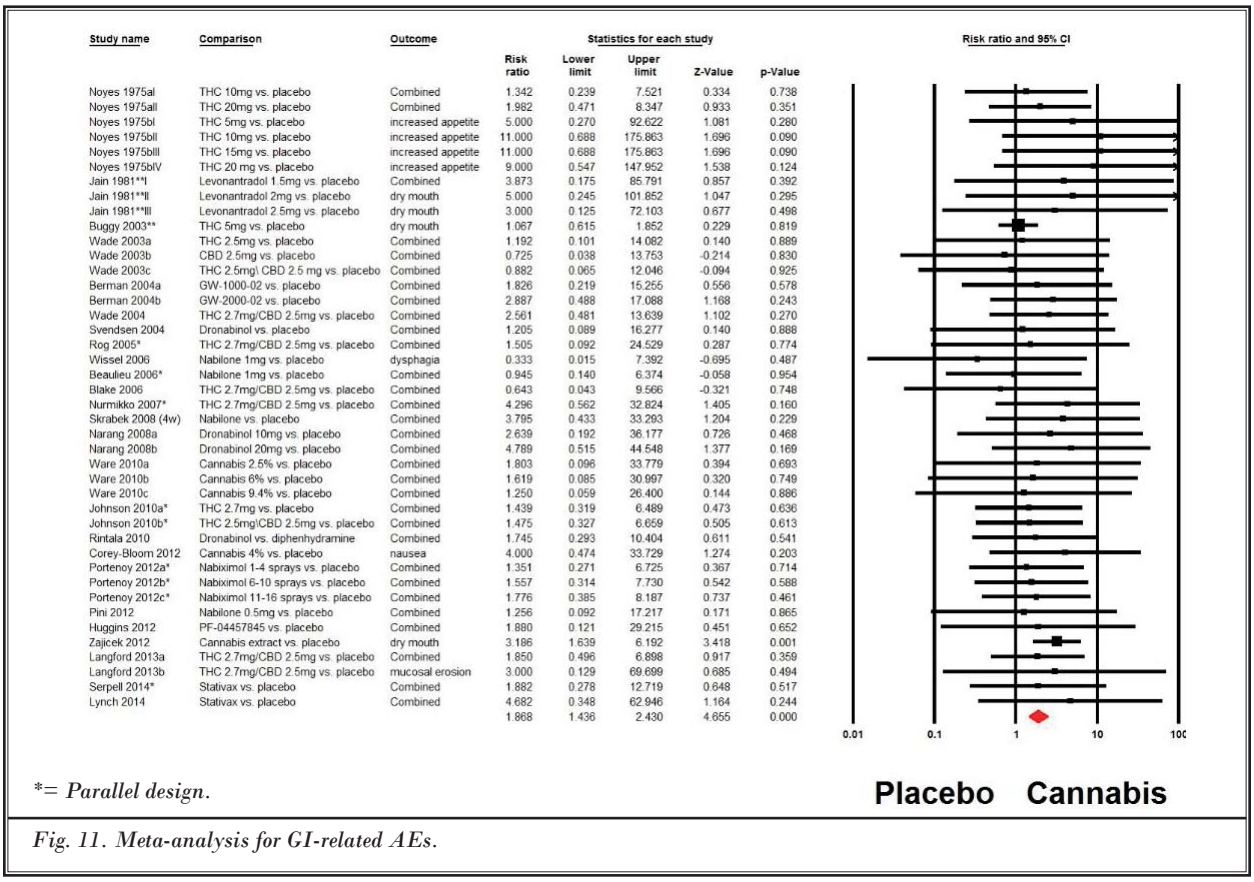
The combined risk ratio for all cardiac-related AEs, which were reported in 6 RCTs (including abnormal heart rate, cardiac disorders, hypotension, orthostatic hypotension, palpitations, and tachycardia), was insignificant for more harm from CBMs than from placebo; for both fixed-effect and random effect, the risk ratio models were 1.49 (0.76 to 2.92, *P* = 0.23) (Fig. 14). Homogeneity was in evidence (I2 = 0.0%, *P* = 0.44) and a dispersion of Tau2 = 0.0, Tau = 0.0. The most common cardiac-related AE was palpitations.

Vision-Related AEs

The combined risk ratio for all visual AEs, which were reported in 7 RCTs (including blurred vision, diplopia, and change in vision), was significantly more harmful from CBMs than from placebo; for fixed-effect, the risk ratio model was 3.14 (2.00 to 4.91, *P* < 0.0001), and for random-effect, the risk ratio model was 2.99 (1.78 to 5.02, *P* < 0.0001) (Fig. 15). Homogeneity was in evidence (I2 = 17.00%, *P* = 0.26) and a dispersion of Tau2 = 0.1, Tau = 0.41. The most common vision-related AE was blurred vision.

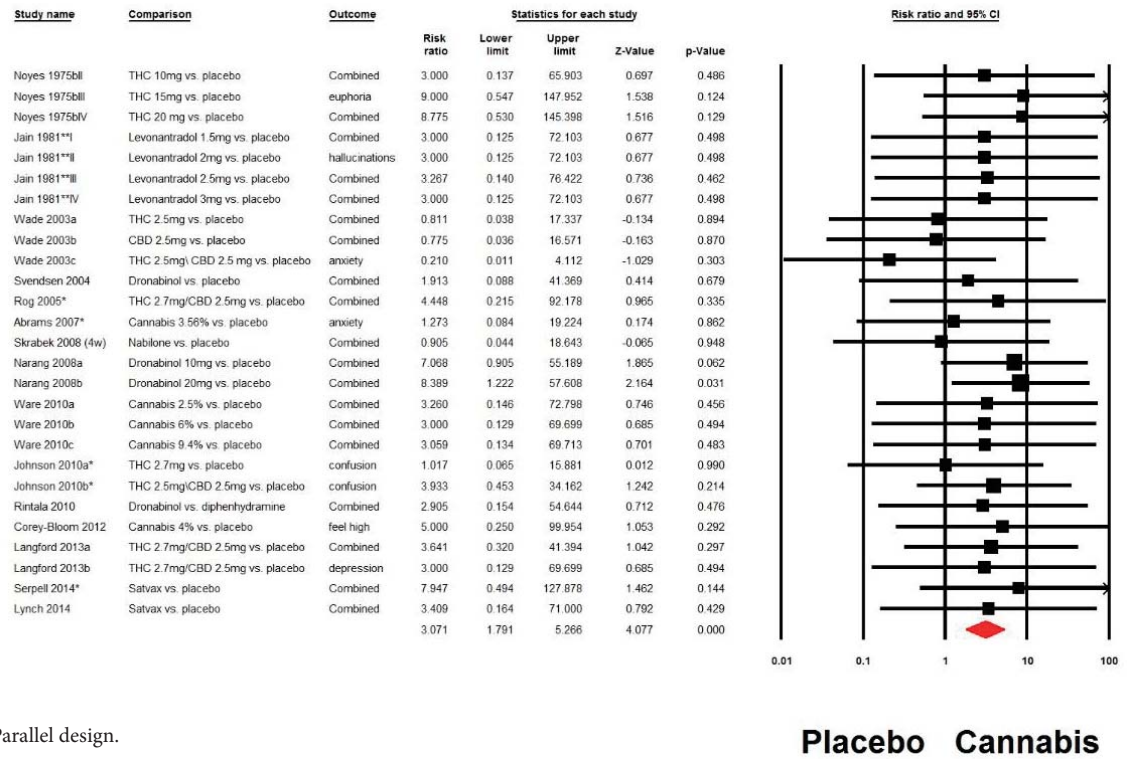
Hearing-Related AEs

The combined risk ratio for all hearing-related AEs,



*= *Parallel design.*

Fig. 11. Meta-analysis for GI-related AEs.



Study name	Comparison	Outcome	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
Noyes 1975bII	THC 10mg vs. placebo	Combined	3.000	0.137	65.903	0.697	0.486
Noyes 1975bIII	THC 15mg vs. placebo	euphoria	9.000	0.547	147.952	1.538	0.124
Noyes 1975bIV	THC 20 mg vs. placebo	Combined	8.775	0.530	145.398	1.516	0.129
Jain 1981**I	Levonantradol 1.5mg vs. placebo	Combined	3.000	0.125	72.103	0.677	0.498
Jain 1981**II	Levonantradol 2mg vs. placebo	hallucinations	3.000	0.125	72.103	0.677	0.498
Jain 1981**III	Levonantradol 2.5mg vs. placebo	Combined	3.267	0.140	76.422	0.736	0.462
Jain 1981**IV	Levonantradol 3mg vs. placebo	Combined	3.000	0.125	72.103	0.677	0.498
Wade 2003a	THC 2.5mg vs. placebo	Combined	0.811	0.038	17.337	-0.134	0.894
Wade 2003b	CBD 2.5mg vs. placebo	Combined	0.775	0.036	16.571	-0.163	0.870
Wade 2003c	THC 2.5mg\ CBD 2.5 mg vs. placebo	anxiety	0.210	0.011	4.112	-1.029	0.303
Svendsen 2004	Dronabinol vs. placebo	Combined	1.913	0.088	41.369	0.414	0.679
Rog 2005*	THC 2.7mg/CBD 2.5mg vs. placebo	Combined	4.448	0.215	92.178	0.965	0.335
Abrams 2007*	Cannabis 3.56% vs. placebo	anxiety	1.273	0.084	19.224	0.174	0.862
Skrabek 2008 (4w)	Nabilone vs. placebo	Combined	0.905	0.044	18.643	-0.065	0.948
Narang 2008a	Dronabinol 10mg vs. placebo	Combined	7.068	0.905	55.189	1.865	0.062
Narang 2008b	Dronabinol 20mg vs. placebo	Combined	8.389	1.222	57.608	2.164	0.031
Ware 2010a	Cannabis 2.5% vs. placebo	Combined	3.260	0.146	72.798	0.746	0.456
Ware 2010b	Cannabis 6% vs. placebo	Combined	3.000	0.129	69.699	0.685	0.494
Ware 2010c	Cannabis 9.4% vs. placebo	Combined	3.059	0.134	69.713	0.701	0.483
Johnson 2010a*	THC 2.7mg vs. placebo	confusion	1.017	0.065	15.881	0.012	0.990
Johnson 2010b*	THC 2.5mg\CBD 2.5mg vs. placebo	confusion	3.933	0.453	34.162	1.242	0.214
Rintala 2010	Dronabinol vs. diphenhydramine	Combined	2.905	0.154	54.644	0.712	0.476
Corey-Bloom 2012	Cannabis 4% vs. placebo	feel high	5.000	0.250	99.954	1.053	0.292
Langford 2013a	THC 2.7mg/CBD 2.5mg vs. placebo	Combined	3.641	0.320	41.394	1.042	0.297
Langford 2013b	THC 2.7mg/CBD 2.5mg vs. placebo	depression	3.000	0.129	69.699	0.685	0.494
Serpell 2014*	Satvax vs. placebo	Combined	7.947	0.494	127.878	1.462	0.144
Lynch 2014	Satvax vs. placebo	Combined	3.409	0.164	71.000	0.792	0.429
			3.071	1.791	5.266	4.077	0.000

*= Parallel design.

Fig. 12. Meta-analysis for psychological AEs.

which were reported in 7 RCTs (including tinnitus, loud noise, ringing in the ears, vertigo, and ear buzzing), was significant for establishing more harm from CBMs than by placebo; for both fixed-effect and random-effect, the risk ratio models were 3.25 (1.58 to 6.67, $P = 0.001$) (Fig. 16). Homogeneity was in evidence ($I2 = 0\%$, $P = 0.81$) and a dispersion of Tau2 = 0, Tau = 0. Notably, the most common hearing-related AE was tinnitus, and the other terms (e.g., ringing in the ears and ear buzzing) were used in different studies to address the same AE.

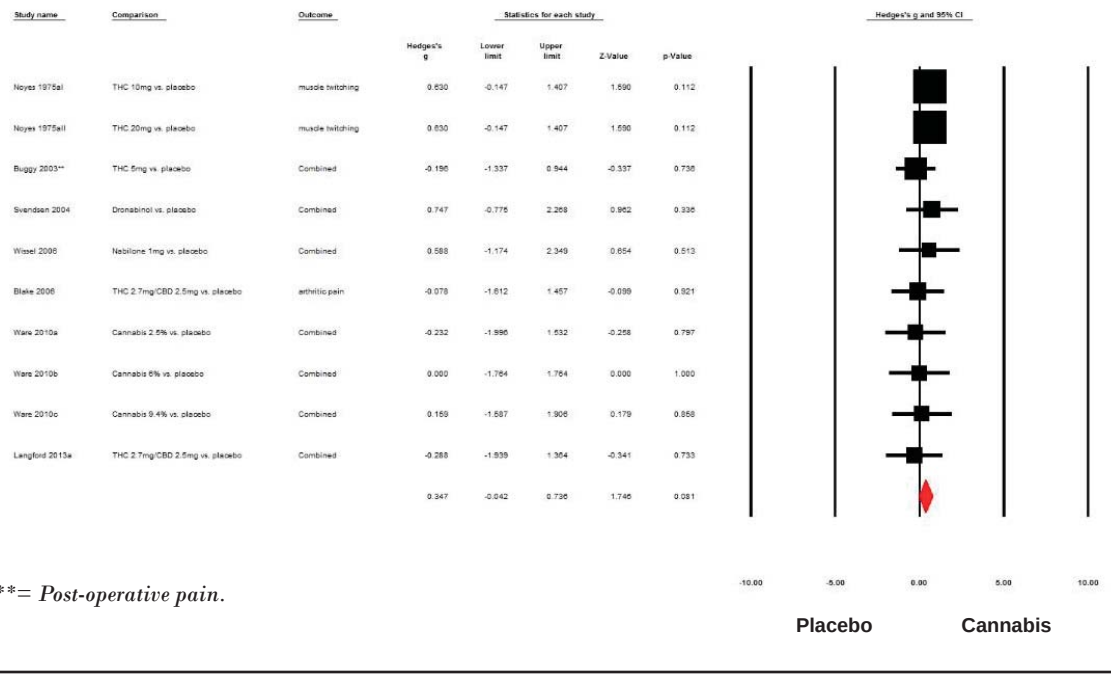
Miscellaneous AEs

Many of the AEs that could not be attributed to a specific system, but were reported in the included studies are presented here: itching, sweating, headache, weakness, red eyes, drug toxicity, cough, influenza-like symptoms, application site discomfort, migraine, speech disorders, aggravation of MS symptoms, relapse of MS, hot flashes, weight decrease, fever, chills, upper respiratory tract infection, tenderness in the nose, application site burning, chest discomfort, pharyngitis, hoarseness, throat irritation, dyspnea, pain increase, nasopharyngitis, upper abdominal pain, eye irritation, facial flushing, difficulty speaking, unbalanced feeling, burning sensation, cheeks flushed, diaphoresis, heaviness, pneumonia, shortness of breath, dry eyes, raised gamma GT, hypercalcemia, rash, infections and infestations, neuralgia, pharyngolaryngeal pain, hepatobiliary disorders, hepatic enzyme increase, cognitive disorders, dysarthria, monoparesis, quadriparesis, reproductive system disorders, stress disorders, and dry skin. Due to the variability of these symptoms, they were not analyzed. Their incidence is presented in Tables 5–7. Notably, the most common AE from the above list was headache.

Discussion

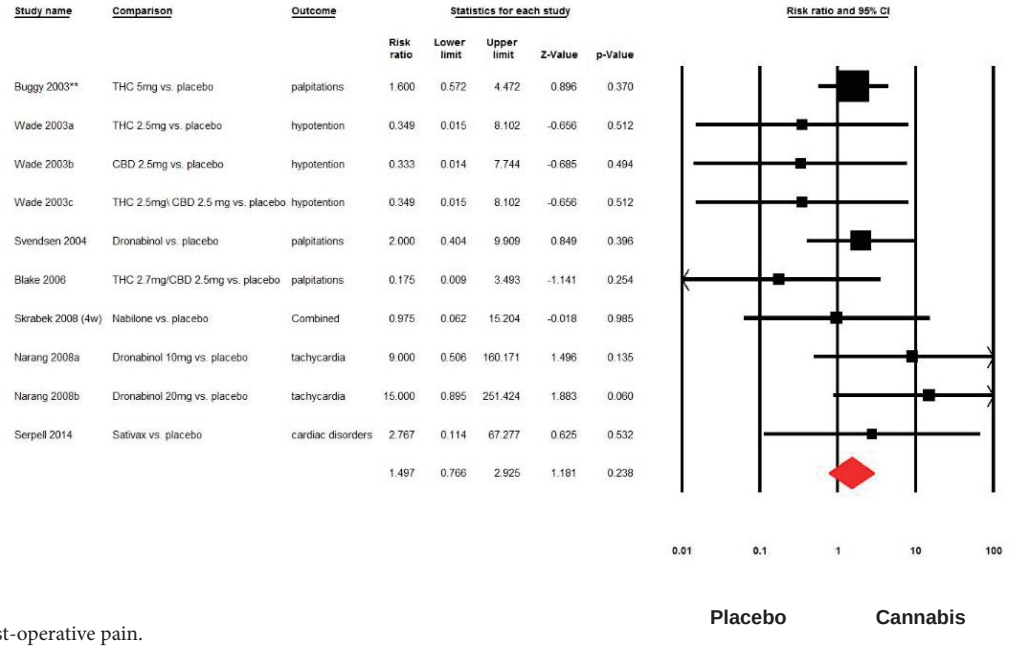
Summary of Evidence

This review of 42 studies and meta-analysis of 24 RCTs is perhaps one of the most comprehensive analyses of studies that focused on the effects of cannabinoids on pain reduction and AEs to be published in recent years. This analysis found moderate to high quality of evidence for the efficacy of CBMs for treatment of chronic pain patients, especially for cancer



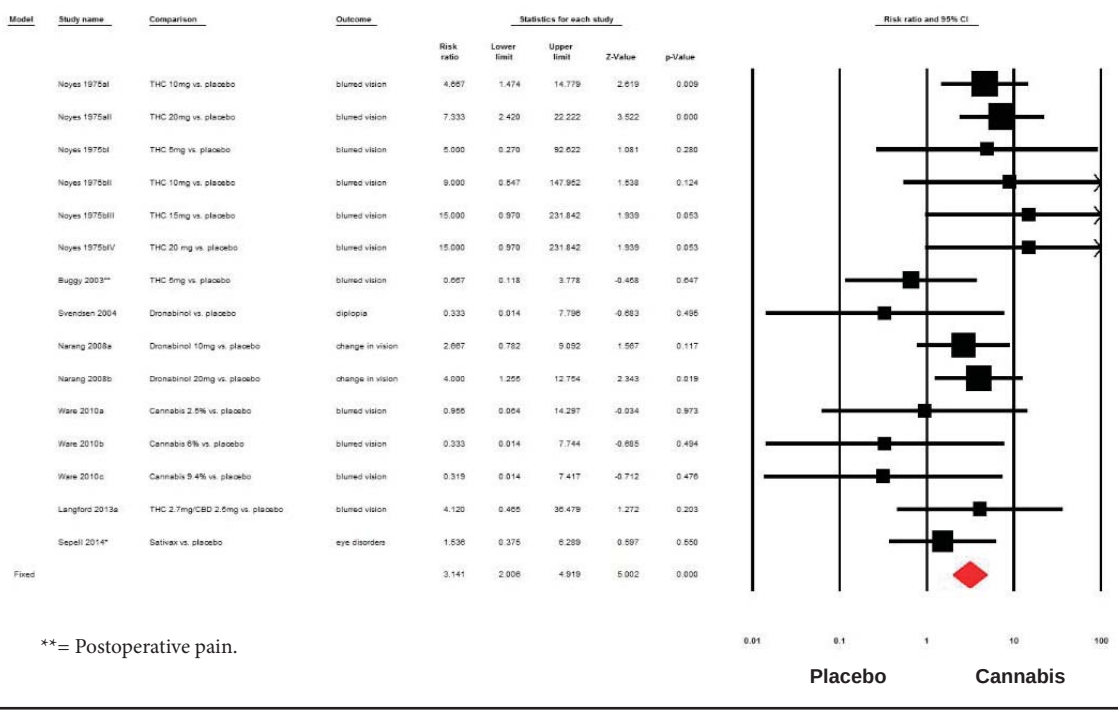
**= *Post-operative pain.*

Fig. 13. Meta-analysis for musculoskeletal AEs.



**= Post-operative pain.

Fig. 14. Meta-analysis for cardiac AEs.



**= Postoperative pain.

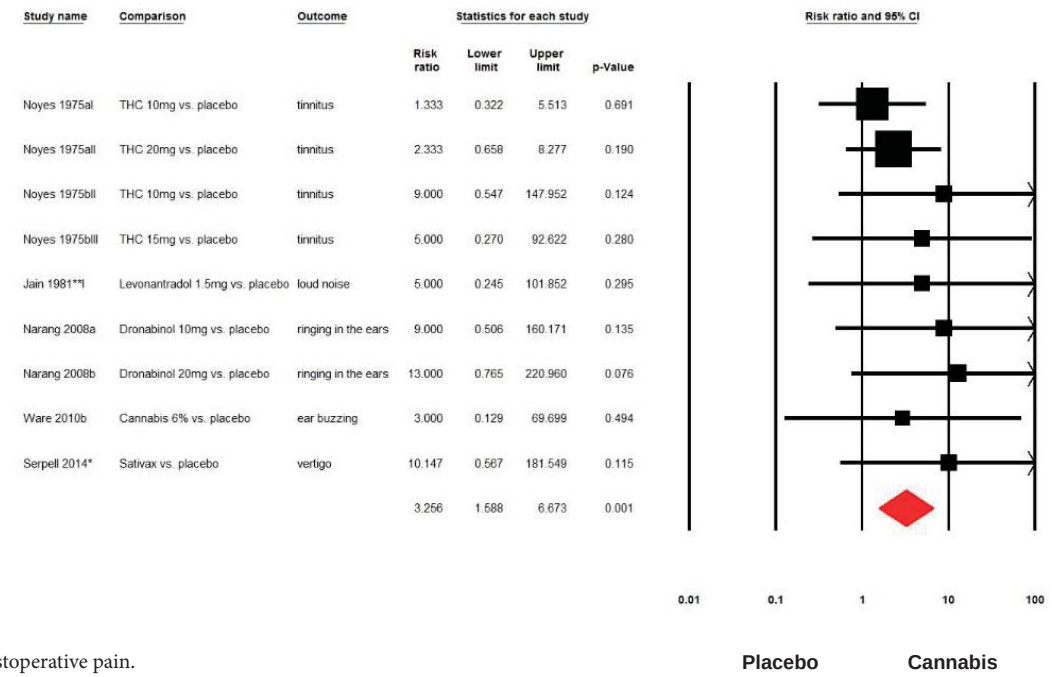
Fig. 15. Meta-analysis for vision-related AEs.

pain. However, the studies on cancer pain were scarce and mostly not from recent years, leaving chronic, non-cancer pain and especially NP as the most investigated and substantiated diagnoses suitable for CBMs treatment. Conversely, postoperative pain studies showed an inverse result, where not only was there no pain reduction, in some cases, placebo was more effective than CBMs treatment.

The mode of administration in most of the studies was either oral or oromucosal, while the most rapid method of cannabinoid delivery seems to be by inhalation (13). It has been shown that when inhaling cannabinoids, plasma levels increase more rapidly and peak concentrations occur at one to 3 minutes, resulting in an analgesic effect after approximately 7 minutes (13). Furthermore, a recent international survey of 31 countries showed in approximately 1,000 patients that inhalation of cannabinoids might be the preferred route of administration, in 86.6% (62.9% for smoking and 23.7% for vaporizing) of the patients (12). In addition, a minority of the patients used other routes, i.e., oral and oromucosal. This preference can possibly be partially related to the slow and erratic pharmacokinetics of cannabinoids when orally administrated (112). Moreover, there was no significant difference in pharmacokinetics of CBMs between oral and oromucosal routes of administration (113). Additionally, although consisting of only 3 of the RCTs, the current study showed that the largest effect size for CBMs' beneficial effect on pain was found when only studies that used inhalation of cannabinoids were included in the analysis and the most promising results were shown by the most recent RCT that used a vaporizer (94). Furthermore, the results of Andreae et al's 2015 study (42), which consisted of 5 RCTs (62,71-74) and analyzed 30% reduction in pain intensity as opposed to raw pain reduction, coincides with the current study's findings.

The first meta-analysis showed the same direction of results (39), but the authors did not show any use of a funnel plot analysis and, furthermore, used unpublished studies that have not made it to publication up to now, 10 years later. This renders that meta-analysis as impossible for comparison.

Surprisingly, the second meta-analysis on the analgesic value of CBMs did not use all of the available studies to perform their analysis (40), but only 7 of them (consisting of 6 publications), which were mostly recent studies (43-51). Their meta-analysis showed an overall fixed-model effect size of -0.61 (-0.84 to -0.37) for CBMs over placebo, and showed no heterogeneity (I2 = 0%,



**= Postoperative pain.

Fig. 16. Meta-analysis for hearing-related AEs.

P = 0.50). Similarly, the current meta-analysis presented lesser values in the same direction. For comparison, the analysis, which consisted of 26 chronic pain studies (18 publications) without an active control (Fig. 4), showed a fixed-effect model of -0.45 Hedge's g (-0.54 to -0.36, *P* < 0.0001) and a random-effect model of -0.61 Hedge's g (-0.78 to -0.43, *P* < 0.0001); a statistical heterogeneity was in evidence (I2 = 70.12%, *P* < 0.0001). When comparing our results, no improvement was found for the efficacy of CBMs over placebo after the addition of the studies that were missing from the former meta-analysis.

The third meta-analysis of CBMs effects on pain (41) would have been the best source of comparison to the current study, but it analyzed the overall results (8 trials) based on the average number of patients who reported at least 30% reduction in pain, rather than the actual average reduction (δ) comparison between treatment and placebo (114). However, they also analyzed some of these trials similarly to the current study, by weighted mean differences (WMDs). Based on 6 trials, they presented a similar outcome -0.46 (95% CI, -0.80 to -0.11) to the current study's results. Their analysis of NP scale reduction in 5 trials showed a WMD of -3.89 (95% CI, -7.32 to -0.47). Additionally, a similar understanding between our study and theirs was found regarding the NP indication as the most studied indication for CBMs administration.

Limitations and Methodological Considerations

There is a substantial limitation in our study, since not all of the appropriate RCTs that were used for the review section met the inclusion criteria of the meta-analysis. If these studies could have been included, they could have altered the result of the overall effect size.

Another methodological consideration is heterogeneity. All the analyses for pain reduction efficacy showed a significant heterogeneity between the results of the studies; this could have been affected by the different cannabinoid derivates, different treatment indications between the studies and sometimes, within the studies themselves, the inclusion of both parallel and crossover designs, different trial durations, different administration routes, differences in doses, the continuation of other analgesic medication throughout

some of the trials, the differences between the trials where the patients had prior recreational experience of cannabinoids, and the studies where the patients were naïve. The latter could have been a major limitation, since a patient who had felt the analgesic effects as well as the AEs of cannabinoids before, would have known for a high degree of certainty if they had been given the intervention/placebo arm, which in turn, could have debilitated the blinding procedure, no matter how matched/ identical the placebo was. Additionally, there was heterogeneity between the studies' washout periods. In the studies that had short washout periods, the placebo arm could have been affected by the analgesic effects of the intervention arm that was prior to it, therefore, it needs to be taken into account as a limitation. These methodological considerations should be considered in future RCTs.

In conclusion, first, based on the 3 RCTs included in this meta-analysis, CBMs were not effective for postoperative pain. Further investigation is advised. Second, there is a need for larger sample size studies of homogenous treatment indications. Third, as it can be seen in the results of the current study, inhalation is perhaps the preferred route of administration for pain relief. Future RCTs on this route of administration, with the addition of the new technologies that can produce a measured amount of inhaled THC and prevent the potential harm from noxious pyrolytic byproducts (17), may potentially turn the table and transform CBMs into a legitimate medication that can be added to the arsenal of chronic pain treatments.

Clinical Implications

Concurrently with the first meta-analysis (39), this current study needs a clinical interpretation. There is a need for a cut-point that indicates what a clinical significant reduction of pain intensity is. Farrar et al (115) stated that a reduction of 2 points on a 0-10 numeric pain scale would be the optimal cut-off point for a clinically relevant response. Although this review consisted of some RCTs that showed a clinical response, i.e., a 2 or more point decrease (45,56,57,60,64,92,94), most of the studies did not. Although, our primary analysis showed significant results favorable to CBMs over placebo. Yet, it is unclear whether our results represent any clinical significance (Fig. 2).

Notably, in most of the RCTs that were included in this review, there was a considerable incidence of AEs. However, some of these AEs can be attributed to the treated indication [i.e., arthritic pain AE was found only in the study that examined rheumatoid arthritis pain (52)] or due to the rescue medication that was permitted during some studies [i.e., similar or more AEs to placebo over CBMs in postoperative pain (89)]. Furthermore, fewer overall AEs were reported when CBMs were utilized for postoperative pain, where no preexisting conditions were reported (100). Unambiguously, less GI-related AEs were reported when CBMs were administered intra muscular (100) or by smoking (62,71,72,94,96) compared to oral or oromucosal administration. Furthermore, more psychological AEs were reported with administration of oral dronabinol (104).

Notably, the longest list of AEs appeared when CBMs were administered by pipe smoke inhalation (72). However, these AEs appeared in a very small portion of the sample (most commonly in one of 21–22 patients). Irrefutably, the total amount of AEs that were accumulated in our meta-analysis indicates that CBMs cannot be taken lightly, and the physician should consider CBMs treatment after a complete discussion about the possible AEs that can appear. Additionally, due to the high rates of CNS-related AEs, specifically dizziness, drowsiness, and cannabinoid-related vision impairments, the patient needs to be warned not to drive a vehicle or operate heavy machinery (41).

Conclusions

The current study's results suggest that medicinal use of cannabinoids should be further investigated for chronic pain treatment, either as a single treatment, or as a combination treatment with the more conventional treatments, such as opioids and anti-NP medications, as we are not aware of the possible AEs of combination treatments with CBMs.

In comparison to other indications, CBMs have most extensively been investigated on NP (42) and evidence suggests a moderate to good treatment effect. Furthermore, NP patients should be advised that the inhalation of cannabinoids showed relatively better pain reduction effects than other routes of administration. However, the inhalation route of administration for cannabinoids for medical treatment is not followed universally (i.e., in some countries inhalation of cannabinoids is not permitted).

Acknowledgments

I would like to thank Rohtem Aviram, M.Sc and Ofrit Bar-Bachar, M.Sc for their help in English language editing. Rohtem Aviram and Ofrit Bar-Bachar have no conflict of interest or commercial association to declare.

References

1. Cherkin DC, Sherman KJ, Balderson BH, Turner JA, Cook AJ, Stoelb B, Herman PM, Deyo RA, Hawkes RJ. Comparison of complementary and alternative medicine with conventional mind-body therapies for chronic back pain: Protocol for the Mind-body Approaches to Pain (MAP) randomized controlled trial. *Trials* 2014; 15:211-215.
2. Lee C, Crawford C, Buckenmaier C, Schoomaker E, Delgado R, York A. Active, self-care complementary and integrative medicine therapies for the management of chronic pain symptoms: A rapid evidence assessment of the literature. *J Altern Complement Med* 2014; 20:A137-A138.
3. Breen J. Transitions in the concept of chronic pain. *ANS Adv Nurs Sci* 2002; 24:48-59.
4. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment. *Eur J Pain* 2006; 10:287-287.
5. Pain S. A potted history. *Nature* 2015; 525:S10-S11.
6. O'Shaughnessy W. Case of tetanus, cured by a preparation of hemp (the cannabis indica). In: O'Shaughnessy W (ed). *Transactions of the Medical and Physical Society of Bengal, On the preparations of Indian hemp*. Calcutta Bishops Cotton Press 1839, pp 1838-1840.
7. Mechoulam R, Gaoni Y. A total synthesis of dl-Δ1-tetrahydrocannabinol, the active constituent of hashish1. *J Am Chem Soc* 1965; 87:3273-3275.
8. Grinspoon L. *Marijuana Reconsidered. 1st ed*. Harvard University Press, Cambridge, 1971.
9. Ware M, Desroches J. Pain: Clinical updates. Medical cannabis and pain. *IASP* 2014; 22:1-5.
10. Ware MA, Doyle CR, Woods R, Lynch ME, Clark AJ. Cannabis use for chronic non-cancer pain: Results of a prospective survey. *Pain* 2003; 102:211-216.
11. Hall W, Degenhardt L. Adverse health effects of non-medical cannabis use. *Lancet* 2009; 374:1383-1391.
12. Hazekamp A, Ware MA, Muller-Vahl KR, Abrams D, Grotenhermen F. The medicinal use of cannabis and cannabinoids—an international cross-sectional survey on administration forms. *J Psychoactive Drugs* 2013; 45:199-210.
13. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. *Clin Pharmacokinet* 2003; 42:327-360.
14. Loflin M, Earleywine M. No smoke, no fire: What the initial literature suggests regarding vapourized cannabis and respiratory risk. *Can J Respir Ther* 2015; 51:7-9.
15. Eisenstein M. Medical marijuana: Showdown at the cannabis corral. *Nature* 2015; 525:S15-S17.
16. Mechoulam R. *Cannabinoids as Therapeutics*. Birkhäuser, Springer Science & Business Media, Boston, 2005.
17. 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. *J Pain Palliat Care Pharmacother* 2014; 28:216-225.
18. Campbell FA, Tramèr MR, Carroll D, Reynolds DJM, Moore RA, McQuay HJ. Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. *BMJ* 2001; 323:13.
19. Hazekamp A, Grotenhermen F. Review on clinical studies with cannabis and cannabinoids 2005-2009. *Cannabinoids* 2010; 5:1-21.
20. Amar MB. Cannabinoids in medicine: A review of their therapeutic potential. *J Ethnopharmacol* 2006; 105:1-25.
21. Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain: A systematic review of randomized trials. *Br J Clin Pharmacol* 2011; 72:735-744.
22. Fine PG, Rosenfeld MJ. The endocannabinoid system, cannabinoids, and pain. *Rambam Maimonides Med J* 2013; 4:1-15.
23. Aggarwal SK. Cannabinergic pain medicine: A concise clinical primer and survey of randomized-controlled trial results. *Clin J Pain* 2013; 29:162-171.
24. Boychuk DG, Goddard G, Mauro G, Orellana MF. The effectiveness of cannabinoids in the management of chronic nonmalignant neuropathic pain: A systematic review. *J Oral Facial Pain Headache* 2015; 29:7-14.
25. Lynch ME, Ware MA. Cannabinoids for the treatment of chronic non-cancer pain: An updated systematic review of randomized controlled trials. *J Neuroimmune Pharmacol* 2015; 10:293-301.
26. Hill KP. Medical marijuana for treatment of chronic pain and other medical and psychiatric problems: A clinical review. *JAMA* 2015; 313:2474-2483.
27. Baron EP. Comprehensive review of medicinal marijuana, cannabinoids, and therapeutic implications in medicine and headache: What a long strange trip it's been…. *Headache* 2015; 55(6):885-916.
28. Ashton JC, Milligan ED. Cannabinoids for the treatment of neuropathic pain: Clinical evidence. *Curr Opin Investig Drugs* 2008; 9:65-75.
29. Fontelles MIM, García CG. Role of cannabinoids in the management of neuropathic pain. *CNS Drugs* 2008; 22:645-653.
30. Burns TL, Ineck JR. Cannabinoid analgesia as a potential new therapeutic option in the treatment of chronic pain. *Ann Pharmacother* 2006; 40:251-260.
31. Pittler MH, Ernst E. Complementary therapies for neuropathic and neuralgic pain: Systematic review. *Clin J Pain* 2008; 24:731-733.
32. Davis MP. Oral nabilone capsules in the treatment of chemotherapy-induced nausea and vomiting and pain. *Expert Opin Investig Drugs* 2008; 17(1):85-95.
33. Jawahar R, Oh U, Yang S, Lapane KL. A systematic review of pharmacological pain management in multiple sclerosis. *Drugs* 2013; 73:1711-1722.
34. Phillips TJ, Cherry CL, Cox S, Marshall SJ, Rice AS. Pharmacological treatment of painful HIV-associated sensory neuropathy: A systematic review and meta-analysis of randomised controlled trials. *PLoS One* 2010; 5:e14433.
35. Richards BL, Whittle SL, Buchbinder R. Neuromodulators for pain management in rheumatoid arthritis. *Cochrane Database Syst Rev* 2012; 1:CD008921. doi:10.1002/14651858.CD008921.pub2.
36. Parsai S, Herman R, Johnson S. Systematic literature review of randomized controlled trials to evaluate the efficacy of medical marijuana for analgesia. *Pharmacotherapy* 2014; 34:287.
37. Kung T, Hochman J, Sun Y, Bessette L, Haraoui B, Pope J, Bykerk V. Efficacy and safety of cannabinoids for pain in musculoskeletal diseases: A systematic review and meta-analysis. *J Rheumatol* 2011; 38:1171-1171.
38. Canadian Agency for Drugs and Technologies in Health (CADTH). Cannabinoids for the management of neuropathic pain: review of clinical effectiveness. 2010; Ottawa, Canada. {HOLLY: Unsure about this one}
39. Iskedjian M, Bereza B, Gordon A, Piwko C, Einarson TR. Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain. *Curr Med Res Opin* 2006; 23:17-24.
40. Martín-Sánchez E, Furukawa TA, Tay-

lor J, Martin JLR. Systematic review and meta-analysis of cannabis treatment for chronic pain. *Pain Med* 2009; 10:1353-1368.

41. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, Keurentjes JC, Lang S, Misso K, Ryder S, Schmidlkofer S, Westwood M, Kleijnen J. Cannabinoids for medical use: A systematic review and meta-analysis. *JAMA* 2015; 313:2456-2473.
42. Andreae MH, Carter GM, Shaparin N, Suslov K, Ellis RJ, Ware MA, Abrams DI, Prasad H, Wilsey B, Indyk D, Johnson M, Sacks HS. Inhaled cannabis for chronic neuropathic pain: A meta-analysis of individual patient data. *J Pain* 2015; 16(12):1221-1232.
43. 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.
44. Karst M, Salim K, Burstein S, Conrad I, Hoy L, Schneider U. Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: A randomized controlled trial. *JAMA* 2003; 290:1757-1762.
45. Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology* 2005; 65:812-819.
46. Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. *BMJ* 2004; 329:253.
47. 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; 17:21-29.
48. 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; 10:434-441.
49. Bosworth T. Clinical study report: a double blind, randomised, parallel group, placebo-controlled trial of a combination of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in patients with multiple sclerosis, followed by an open label assessment and study extension [Study Code: GWMS0001, GW Pharma Ltd]. 2003; 1-228.
50. Dempster B. Clinical study report: a multi centre randomised, double blind, placebo controlled, parallel group comparison of the effects of cannabis based medicine standardised extracts over 4 weeks, in patients with chronic refractory pain due to multiple sclerosis or other defects of neurological function [Study Code: GWPS0105, GW Pharma Ltd]. 2003; 1-259.
51. Davidson A. Clinical study report: a double blind, randomised, parallel group placebo controlled study of cannabis based medicine extract (CBME) to validate the neuropathic pain scale (NPS) compared with a single pain severity score, in central neuropathic pain in multiple sclerosis [Study Code:GWMS0107, GW Pharma Ltd]. 2003; 1-237.
52. 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; 45:50-52.
53. Jochimsen PR, Lawton RL, VerSteeg K, Noyes R Jr. Effect of benzopyranoperidine, a delta-9-THC congener, on pain. *Clin Pharmacol Ther* 1978; 24:223-227.
54. Killestein J, Hoogervorst EL, Reif M, Kalkers NF, Van Loenen AC, Staats PG, Gorter RW, Uitdehaag BM, Polman CH. Safety, tolerability, and efficacy of orally administered cannabinoids in MS. *Neurology* 2002; 58:1404-1407.
55. Notcutt W, Price M, Miller R, Newport S, Phillips C, Simmons S, Sansom C. Initial experiences with medicinal extracts of cannabis for chronic pain: Results from 34 'N of 1'studies. *Anaesthesia* 2004; 59:440-452.
56. Noyes R Jr, Brunk SF, Baram DA, Canter A. Analgesic effect of delta-9-tetrahydrocannabinol. *J Clin Pharmacol* 1975; 15:139-143.
57. Noyes R Jr, Brunk SF, Avery DA, Canter AC. The analgesic properties of delta-9-tetrahydrocannabinol and codeine. *J Clin Pharmacol* 1975; 18:84-89.
58. Pinsger M, Schimetta W, Volc D, Hiermann E, Riederer F, Pölz W. Benefits of an add-on treatment with the synthetic cannabinomimetic nabilone on patients with chronic pain--a randomized controlled trial. *Wien Klin Wochenschr* 2006; 118:327-335.
59. Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. *J Pain* 2008; 9:164-173.
60. Staquet M, Gantt C, Machin D. Effect of a nitrogen analog of tetrahydrocannabinol on cancer pain. *Clin Pharmacol Ther* 1978; 23:397-401.
61. Wissel J, Haydn T, Müller J, Brenneis C, Berger T, Poewe W, Schelosky LD. Low dose treatment with the synthetic cannabinoid Nabilone significantly reduces spasticity-related pain. *J Neurol* 2006; 253:1337-1341.
62. Abrams DI, Jay CA, Shade SB, Vizoso H, Reda H, Press S, Kelly ME, Rowbotham MC, Petersen KL. Cannabis in painful HIV-associated sensory neuropathy: A randomized placebo-controlled trial. *Neurology* 2007; 68:515-521.
63. 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; 39:167-179.
64. Langford R, Mares J, Novotna A, Vachova M, Novakova I, Notcutt W, Ratcliffe S. 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; 260:984-997.
65. 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; 133:210-220.
66. 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; 33:128-130.
67. Portenoy RK, Ganae-Motan ED, Allende S, Yanagihara R, Shaiova L, Weinstein S, McQuade R, Wright S, Fallon MT. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: A randomized, placebo-controlled, graded-dose trial. *J Pain* 2012; 13:438-449.
68. Serpell M, Ratcliffe S, Hovorka J, Schofield M, Taylor L, Lauder H, Ehler E. 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.

69. GW Pharma Ltd. A double blind, randomised, placebo controlled parallel group study of sativax in the treatment of subjects with pain due to diabetic neuropathy. EU Clinical Trials Register. *EU Clinical Trials Register* 2004; 2014:http://clinicaltrialsregister.eu//ctr-search?query=eudract_number:2004-002530-20.
70. Whiting P, Wolff R. Medical Use of Cannabinoids-Reply. *JAMA* 2015; 314:1751-1752.
71. Ellis RJ, Toperoff W, Vaida F, van den Brande G, Gonzales J, Gouaux B, Bentley H, Atkinson JH. Smoked medicinal cannabis for neuropathic pain in HIV: A randomized, crossover clinical trial. *Neuropsychopharmacology* 2009; 34:672-680.
72. Ware MA, Wang T, Shapiro S, Robinson A, Ducruet T, Huynh T, Gamsa A, Bennett GJ, Collet JP. Smoked cannabis for chronic neuropathic pain: A randomized controlled trial. *CMAJ* 2010; 182:694-701.
73. Wilsey B, Marcotte T, Tsodikov A, Millman J, Bentley H, Gouaux B, Fishman S. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *J Pain* 2008; 9:506-521.
74. Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H. Low-dose vaporized cannabis significantly improves neuropathic pain. *J Pain* 2013; 14:136-148.
75. Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, Kalso EA, Loeser JD, Miaskowski C, Nurmikko TJ, Portenoy RK, Rice AS, Stacey BR, Treede RD, Turk DC, Wallace MS. Pharmacologic management of neuropathic pain: Evidence-based recommendations. *Pain* 2007; 132:237-251.
76. Farrar JT, Troxel AB, Stott C, Duncombe P, Jensen MP. Validity, reliability, and clinical importance of change in a 0-10 numeric rating scale measure of spasticity: A post hoc analysis of a randomized, double-blind, placebo-controlled trial. *Clin Ther* 2008; 30:974-985.
77. Moore RA, Wiffen PJ, Derry S, Toelle T, Rice AS. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev* 2014; 4:CD007938. doi: 10.1002/14651858.CD007938.pub3.
78. Wiffen PJ, Derry S, Moore RA, Aldington D, Cole P, Rice AS, Lunn MP, Hamunen K, Haanpaa M, Kalso EA. Antiepileptic drugs for neuropathic pain and fibromyalgia an overview of Cochrane reviews. *Cochrane Database Syst Rev* 2013; 11:CD010567. doi: 10.1002/14651858.CD10567.pub2.
79. Birse F, Derry S, Moore RA. Phenytoin for neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev* 2012; 5:CD009485. doi: 10.1002/14651858.CD009485.pub2.
80. Chaparro LE, Wiffen PJ, Moore RA, Gilron I. Combination pharmacotherapy for the treatment of neuropathic pain in adults. *Cochrane Database Syst Rev* 2012; 7:CD008943. doi: 10.1002/14651858.CD008943.pub2.
81. Corrigan R, Derry S, Wiffen PJ, Moore RA. Clonazepam for neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev* 2012; 5:CD009486. doi: 10.1002/14651858.CD009486.pub2.
82. Deshpande A, Mailis-Gagnon A, Zoheiry N, Lakha SF. Efficacy and adverse effects of medical marijuana for chronic noncancer pain: Systematic review of randomized controlled trials. *Can Fam Physician* 2015; 61:372-81.
83. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Ann Intern Med* 2009; 151:264-269.
84. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Control Clin Trials* 1996; 17:1-12.
85. Hartrick CT, Kovan JP, Shapiro S. The numeric rating scale for clinical pain measurement: A ratio measure? *Pain Pract* 2003; 3:310-316.
86. Jensen MP, Karoly P, O'Riordan EF, Bland F Jr, Burns RS. The subjective experience of acute pain. An assessment of the utility of 10 indices. *Clin J Pain* 1989; 5:153-159.
87. Huskisson EC. Measurement of pain. *J Rheumatol* 1982; 9:768-769.
88. Melzack R. The short-form McGill Pain Questionnaire. *Pain* 1987; 30:191-197.
89. Buggy DJ, Toogood L, Maric S, Sharpe P, Lambert DG, Rowbotham DJ. Lack of analgesic efficacy of oral delta-9-tetrahydrocannabinol in postoperative pain. *Pain* 2003; 106:169-172.
90. Frank B, Serpell MG, Hughes J, Matthews JN, Kapur D. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: Randomised, crossover, double blind study. *BMJ* 2008; 336:199-201.
91. 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; 89:840-848.
92. Toth C, Mawani S, Brady S, Chan C, Liu C, Mehina E, Garven A, Bestard J, Korngut L. 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; 153:2073-2082.
93. Beaulieu P. Effects of nabilone, a synthetic cannabinoid, on postoperative pain. *Can J Anaesth* 2006; 53:769-775.
94. Wallace MS, Marcotte TD, Umlauf A, Gouaux B, Atkinson JH. Efficacy of inhaled cannabis on painful diabetic neuropathy. *J Pain* 2015; 16(7):616-627.
95. Pini LA, Guerzoni S, Cainazzo MM, Ferrari A, Sarchielli P, Tiraferri I, Ciccarese M, Zappaterra M. Nabilone for the treatment of medication overuse headache: Results of a preliminary double-blind, active-controlled, randomized trial. *J Headache Pain* 2012; 13:677-684.
96. Corey-Bloom J, Wolfson T, Gamst A, Jin S, Marcotte TD, Bentley H, Gouaux B. Smoked cannabis for spasticity in multiple sclerosis: A randomized, placebo-controlled trial. *CMAJ* 2012; 184:1143-1150.
97. Borenstein M, Hedges L, Higgins J, Rothstein H. Comprehensive meta-analysis version 2. *Englewood, NJ: Biostat* 2005; 104. {HOLLY: Unsure about this one}
98. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; 327:557-560.
99. Seeling W, Kneer L, Büchele B, Gschwend JE, Maier L, Nett C, Simmet T, Steffen P, Schneider M, Rockemann M. [Delta(9)-tetrahydrocannabinol and the opioid receptor agonist piritramide do not act synergistically in postoperative pain]. *Anaesthesist* 2006; 55:391-400.
100. Jain AK, Ryan JR, McMahon FG, Smith G. Evaluation of intramuscular levonantradol and placebo in acute postoperative pain. *J Clin Pharmacol* 1981; 21:320S-326S.
101. Maurer M, Henn V, Dittrich A, Hofmann

A. Delta-9-tetrahydrocannabinol shows antispastic and analgesic effects in a single case double-blind trial. *Eur Arch Psychiatry Clin Neurosci* 1990; 240:1-4.

102. Holdcroft A, Smith M, Jacklin A, Hodgson H, Smith B, Newton M, Evans F. Pain relief with oral cannabinoids in familial Mediterranean fever. *Anaesthesia* 1997; 52:483-486.
103. Salim K, Schneider U, Burstein S, Hoy L, Karst M. Pain measurements and side effect profile of the novel cannabinoid ajulemic acid. *Neuropharmacology* 2005; 48:1164-1171.
104. Narang S, Gibson D, Wasan AD, Ross EL, Michna E, Nedeljkovic SS, Jamison RN. Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. *J Pain* 2008; 9:254-264.
105. Huggins JP, Smart TS, Langman S, Taylor L, Young T. An efficient randomised, placebo-controlled clinical trial with the irreversible fatty acid amide hydrolase-1 inhibitor PF-04457845, which modulates endocannabinoids but fails to induce effective analgesia in patients with pain due to osteoarthritis of the knee. *Pain* 2012; 153:1837-1846.
106. 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; 83:1125-1132.
107. 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; 47:166-173.
108. Turcotte D, Doupe M, Torabi M, Gomori A, Ethans K, Esfahani F, Galloway K, Namaka M. Nabilone as an adjunctive to gabapentin for multiple sclerosis-induced neuropathic pain: A randomized controlled trial. *Pain Med* 2015; 16:149-159.
109. Johnson J, Potts R. Cannabis-based medicines in the treatment of cancer pain: A randomised, double-blind, parallel group, placebo controlled, comparative study of the efficacy, safety and tolerability of Sativex and Tetranabinex in patients with cancer-related pain. *British Pain Society. Edinburgh, Scotland* 2005:8-11.
110. Higgins T, Green S. *Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006].* John Wiley & Sons, Ltd., Chichester, 2006.
111. Boland EG, Mulvey MR, Bennett MI. Classification of neuropathic pain in cancer patients. *Curr Opin Support Palliat Care* 2015; 9:112-115.
112. Ohlsson A, Lindgren J, Wahlen A, Agurell S, Hollister LE, Gillespie HK. Plasma delta-9-tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. *Clin Pharmacol Ther* 1980; 28:409-416.
113. Karschner EL, Darwin WD, Goodwin RS, Wright S, Huestis MA. Plasma cannabinoid pharmacokinetics following controlled oral delta9-tetrahydrocannabinol and oromucosal cannabis extract administration. *Clin Chem* 2011; 57:66-75.
114. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, Haythornthwaite JA, Jensen MP, Kerns RD, Ader DN, Brandenburg N, Burke LB, Cella D, Chandler J, Cowan P, Dimitrova R, Dionne R, Hertz S, Jadad AR, Katz NP, Kehlet H, Kramer LD, Manning DC, McCormick C, McDermott MP, McQuay HJ, Patel S, Porter L, Quessy S, Rappaport BA, Raushkolb C, Revicki DA, Rothman M, Schmader KE, Stacey BR, Stauffer JW, von Stein T, White RE, Witter J, Zavisic S. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain* 2008; 9:105-121.
115. Farrar JT, Portenoy RK, Berlin JA, Kinman JL, Strom BL. Defining the clinically important difference in pain outcome measures. *Pain* 2000; 88:287-294.