Systematic reviews on therapeutic efficacy and safety of Cannabis (including extracts and tinctures) for patients with multiple sclerosis, chronic neuropathic pain, dementia and Tourette syndrome, HIV/AIDS, and cancer receiving chemotherapy

Laura Amato, Marina Davoli, Silvia Minozzi, Zuzana Mitrova, Elena Parmelli, Rosella Saulle, Simona Vecchi

DEPARTMENT OF EPIDEMIOLOGY LAZIO REGION, ASL ROMA 1 – ROME, ITALY

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Table of Abbreviations

5-HT_3	Serotonin
AIDS	Acquired Immunodeficiency Syndrome
BDI	Beck Depression Inventory
BPI-SF	Brief Pain Inventory (short form)
BRB-N	Brief Repeatable Battery of Neuropsychological tests
BSI	Brief Symptoms Inventory
CBD	Cannabidiol
CBM	Cannabis-Based Medicine
CI	Confidence Interval
CMT	Complex Motor Tics
CNS	Central Nervous System
CQ	Clinical Question
CRS	Category Rating Scale
EDSS	Expanded Disability Status Scale
FIS	Fatigue Impact Scale
GNDS	Guy's Neurological Disability scale
GRADE	Grading of Recommendation, Assessment, Development and Evaluation
GTS	Gilles de la Tourette Syndrome
HIV	Human Immunodeficiency Virus
ICTRP	International Clinical Trials Registry Platform
I-QoL	Incontinence Quality of Life
MD	Mean Difference
MS	Multiple sclerosis
MSSS-88	88-item Multiple Sclerosis Spasticity Scale
MT	Motor Tics
NEADL	Nottingham Extended Activities of Daily Living
NPS	Neuropathic Pain Scale
NRS	Numerical Rating Scale
NSAIDs	Nonsteroidal Anti-inflammatory Drugs
OCD	Obsessive–Compulsive Disorder
OIS	Optimal Information Size
PDQ	Perceived Deficit Questionnaire
PGIC	Patients Global Impression of Change
PICO	Patient, Intervention, Comparison, Outcomes
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QoL	Quality of Life
RA	Rheumatoid Arthritis
RCT	Randomised Controlled Trial
RR	Risk Ratio
SD	Standard Deviation
SF-MPQ	Short Form McGill Pain Questionnaire
SGIC	Subject Global Impression of Change
SMD	Standardised Mean Difference
SMT	Simple Motor Tics
STSSS	Shapiro Tourette Syndrome Severity Scale
TENS	Transcutaneous Electrical Nerve Stimulation
THC	Δ9- tetrahydrocannabinol

TPS	Total Pain Score
TSGS	Tourette Syndrome Global Scale
TSSL	Tourette's Syndrome Symptom List
VAS	Visual Analogue Scale
WHO	World Health Organization
YGTSS	Yale Global Tic Severity Scale

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Abstract

Cannabis is a generic term used for drugs produced from plants and tinctures belonging to the genus Cannabis and it is the most widely used recreational substance in Western countries including Europe, North America and Australia. Medical cannabis refers to the use of cannabis or cannabinoids as medical therapy to treat disease or alleviate symptoms. Canada and the Netherlands have government-run programs in which specialized companies supply quality-controlled herbal cannabis. In the United States, 23 states and Washington, DC (May 2015), have introduced laws to permit the medical use of cannabis[6]; other countries have similar laws.

Objectives

To provide evidence for benefits and harms of cannabis (including extracts and tinctures) treatment for adults in the following indications: multiple sclerosis, chronic pain, HIV/AIDS, Dementia or Tourette syndrome, and adults with cancer receiving chemotherapy.

Search methods

We searched the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews in the Cochrane Library, PubMed, and EMBASE from inception to September 2016. We also searched for on-going and unpublished studies via ClinicalTrials.gov (http://clinicaltrials.gov/) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (http://apps.who.int/trialsearch/). All searches included non-English language literature. We hand searched references of topic-related systematic reviews and the included studies.

Selection criteria

All relevant randomized controlled trials (RCTs) evaluating the safety and efficacy of cannabis (including extracts and tinctures) compared with placebo or other pharmacological agents were included.

Data collection and analysis

Three authors independently evaluated the titles and abstracts of studies identified in the literature searches for their eligibility. For studies considered eligible, we retrieved full texts. Three investigators independently extracted data. For the assessment of the quality of the evidence, we used the standard methodological procedures recommended by Cochrane and GRADE working Group.

Main results

Forty-three trials (4586 participants) were included. Fifteen studies considered efficacy and safety of cannabis for patients with multiple sclerosis, 12 for patients with chronic pain, two for patients with dementia/Tourette syndrome, and 14 for patients with cancer receiving chemotherapy. The included studies were published between 1975 and 2015, and the majority of them were conducted in Europe. We judged almost fifty percent of the studies to be at low risk of bias. Fourteen out of forty-four studies trials had an industrial sponsor or authors declared to be dependent upon the pharmaceutical industry producer of the drug object of the study

The large majority (81%) of the comparisons were with placebo; only eight studies included patients with cancer receiving chemotherapy comparing cannabis with other antiemetic drugs.

- ***Clinical effectiveness and safety of cannabis in patients with multiple sclerosis:*** For spasticity, different results were observed according to the scale utilized to assess the outcome. In the comparison with placebo, using the Ashworth scale (5 parallel trials, 1216 patients), no differences were observed: MD -0.1 (95%CI - 0.26 to 0.07); while, using NRS scale (three parallel trials, 860 patients), results were in favour of cannabis: MD -0.28 (95%CI -0.52 to -0.03). There was high confidence in the estimate for both comparisons. In the same comparison, cannabis does not improve sleep quality measured with the NRS scale (2 parallel trials, 676 patients): MD 0.40 (95% CI -0.30 to 1.09), with moderate confidence in the estimates.
- ***Clinical effectiveness and safety of cannabis in patients with chronic and neuropathic pain:*** mixed results were observed in the comparison with placebo. For pain intensity, the results of two crossover trials, 71 patients, were in favour of cannabis: MD -0.78 (95% CI -1.17 to -0.39), low confidence in estimates. For pain disability index the results coming from one crossover study (48 patients), showed no difference: MD -2.00 (95%CI -4.32 to 0.32), while results coming from one parallel trial (125 patients) were in favour of cannabis: MD -5.85 (95% CI -9.60 to -2.10), with low confidence in estimates for both comparisons.
- For minimum pain score, results of two crossover studies (39 patients), showed no difference between cannabis and placebo: SMD -0.36 (95% CI -0.80 to 0.09), low confidence in estimates. For the reduction of more than 30% in neuropathic pain, results showed no difference if we consider four parallel trials, (455 patients): MD 1.39 (95% CI 0.92 to 2.09); while results coming from three crossover studies, (93 patients), were in favour of cannabis: MD 1.65 (95% CI 1.01 to 2.70), moderate confidence in estimates for both comparisons.
- ***Clinical effectiveness and safety of cannabis for reducing tics and obsessive-compulsive symptoms in patients with dementia or Gilles de la Tourette syndrome***: Because there were only two studies, with

an overall 36 patients, it was impossible to draw reliable conclusions when comparing THC with placebo for treating the symptoms of Tourette's syndrome.

-***Clinical effectiveness and safety of cannabis for reducing morbidity and mortality in patients with HIV/AIDS:*** No evidence was available.

- ***Clinical effectiveness and safety of cannabis for reducing nausea and vomiting in adults with cancer receiving chemotherapy***: We had two comparisons, cannabis versus placebo and versus other antiemetic. In the comparison with placebo, for controlling nausea and vomiting considered together, cannabis performed better, with results from two parallel trials (91 patients): RR 2.33 (95% CI 1.20 to 4.55) and one crossover (22 patients): RR 3.17 (95% CI 1.57 to 6.39). No differences were found for control of vomiting, 3 crossover trials, 70 patients: RR 1.85 (95% CI 0.14 to 24.19; and repeated vomiting (one parallel trial, 75 patients). Very low confidence in estimates for all. For control of nausea alone, no difference was observed in one parallel trial, 143 patients: RR 1.06 (95% CI 0.56 to 1.98); while results from three crossover studies, (93 patients), were in favour of cannabis: RR 4.38 (95% CI 1.31 to 14.60). Very low confidence in estimates for all the comparisons.

In the comparison with other antiemetic drugs, if nausea and vomiting were considered together, the results of one parallel trial (79 patients) RR 0.95 (95% CI 0.56 to 1.63) and of two crossover studies (88 patients), RR 3.68 (95% CI 0.11 to 122.40), showed no difference between cannabis and other antiemetic drugs. There was a very low confidence in estimates for both comparisons. Considering control of vomiting, results from one parallel trial (30 patients), were in favour of metoclopramide, RR 0.36 (95% CI 0.15 to 0.89), low confidence in estimates. Considering control of nausea, results of one crossover trial (55 patients), were in favour of cannabis including extract and tinctures compared with cyclophosphamide, 5-fluorouracil, and doxorubicin: RR 5.00 (95% CI 2.58 to 9.68), very low confidence in estimates.

In regards ***to adverse events***, the included studies considered many adverse events, the majority of them were of low to moderate gravity. For the most serious adverse events (i.e. CNS side effects, depression and confusion) no differences were observed between cannabis and placebo. Incidence of general psychiatric disorders was higher in the cannabis groups but the results came only from two small studies (92 participants). In addition, frequency of dissociation was higher in the cannabis groups, and no studies considered the development of abuse or dependence.

Discussion

Concerning the efficacy of cannabis (compared with placebo) in patients with MS, confidence in the estimate was high in favour of cannabis for spasticity (NRS and VAS scales but not the Ashworth scale) and pain but not for sleep (confidence in estimate moderate). For chronic and neuropathic pain (compared

with placebo) there was some evidence of a small effect, however, confidence in the estimate is low and these results could not be considered conclusive. This absence of evidence and the absence of a particularly effective treatment for neuropathic pain, may force clinicians to balance the possible benefits against the potential adverse effects of the treatment. For tics and OCD symptoms in patients with Tourette's syndrome, there were only two studies, with an overall 36 patients and it was impossible to draw any reliable conclusion. Primary research needs to be improved to satisfy the demands of clinicians, patients and their caregivers,. There is uncertainty whether cannabis, including extracts and tinctures, compared with placebo or other antiemetic drugs, reduces nausea and vomiting in patients with cancer requiring chemotherapy, although the confidence in the estimate of the effect was low or very low.

Regarding adverse events, many adverse events were reported, the majority of them were of low or moderate gravity, but only a minority assessed the risk of serious adverse events such as dissociation, general psychiatric disorders, depression, and confusion. Most importantly, none of the included studies assessed the development of abuse or dependence.

Introduction

Cannabis is a generic term used for drugs produced from plants and tinctures belonging to the genus Cannabis[1]. The main psychoactive compound in all cannabis products is Δ9- tetrahydrocannabinol (THC). Cannabis is the most widely used recreational substance in Western countries including Europe (5.7% reporting past year use)[2], North America (7.5% reporting past month use)[3] and Australia (10.2% reporting past year use)[4].

Cannabis use causes significant adverse effects[5]. The acute effects of short-term cannabis use[6] include impaired memory[7]; impaired motor coordination with an associated increased risk of involvement in motor vehicle accidents[8]; altered judgment; and, in high doses, paranoia and psychosis. Long-term or heavy use of cannabis has been associated with the development of dependence[5], chronic bronchitis, and increased risk of chronic psychosis disorders in persons with a predisposition for development of such disorders[6].
Medical cannabis refers to the use of cannabis or cannabinoids as medical therapy to treat disease or alleviate symptoms[9]. Canada and the Netherlands have government-run programs in which specialized companies supply quality-controlled herbal cannabis[10]. In the United States, 23 states and Washington, DC (May 2015), have introduced laws to permit the medical use of cannabis[6]; other countries have similar laws[11].

Objective

This document provides an evaluation of the benefits and harms of cannabis treatment for adults in the following indications: multiple sclerosis, chronic pain, HIV/AIDS, Dementia or Tourette syndrome, and adults with cancer receiving chemotherapy. Throughout this review, when we refer to "cannabis" we include its extracts and tinctures. We conducted a systematic review for each Clinical Question (CQs) developed in consultation with the WHO Expert Committee on Drug Dependence Secretariat. Questions were as follows:

- **Clinical Question 1:** What is the clinical effectiveness and safety of cannabis for reducing pain, spasticity and insomnia in patients with Multiple Sclerosis?
- **Clinical Question 2:** What is the clinical effectiveness and safety of cannabis for reducing pain? (Neuropathic pain including diabetic neuropathy and HIV-associated sensory neuropathy, chronic pain, rheumatoid arthritis)
- **Clinical Question 3:** What is the clinical effectiveness and safety of cannabis for reducing tics and obsessive-compulsive symptoms in patients with Dementia or Gilles de la Tourette syndrome (GTS)?
- **Clinical Question 4:** What is the clinical effectiveness and safety of cannabis for reducing morbidity and mortality in patients with HIV/AIDS?

- **Clinical Question 5:** What is the clinical effectiveness and safety of cannabis for nausea and vomiting in adults with cancer receiving chemotherapy?

Methods

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 9) and the Cochrane Database of Systematic Reviews in the Cochrane Library (2016, Issue 9), PubMed (from 1948 to 10 September 2016), EMBASE (EMBASE.com) (from 1980 to 9 September 2016), with no limitations by date, language or publication type. For details of the electronic search strategies, see **Appendix 1**. We also searched ClinicalTrials.gov (http://clinicaltrials.gov/; the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (http://apps.who.int/trialsearch/). In addition, we scanned the reference lists of identified studies as well as systematic reviews to find additional trials not identified by the electronic searches.

Criteria for considering studies for this review

In collaboration with the WHO Expert Committee on Drug Dependence Secretariat, we developed inclusion and exclusion criteria (see PICOs (Patient, Intervention, Comparison, Outcomes) questions- Table 1 for each clinical question to guide the systematic reviews.

We aimed to identify all relevant randomized controlled trials (RCTs), parallel or crossover, published in peer-reviewed journals, evaluating the safety and efficacy of cannabis compared with placebo or other pharmacological agents. Crossover trials were included if an adequate washout period between treatment phases was considered. We also searched prospective observational studies that analysed the effects of cannabis on incidence of adverse effects. We extracted data from these studies only if no information was available from RCTs.

Table 1. PICOs questions

Elements of PICOs	Include	Exclude
Population and condition of interest	**CQ1** Patients, of any age and either sex, with Multiple sclerosis **CQ2** Patients, of any age and either sex, with neuropathic pain (including diabetic neuropathy, HIV-associated sensory neuropathy), chronic pain of a pathological or traumatic origin, (defined as constant or intermittent pain, for a minimum of 6 months); diagnosis of rheumatoid arthritis. **CQ3** People of any age and either sex diagnosed with Alzheimer's dementia, vascular dementia, mixed dementia or	

	unspecified dementia of any severity and from any setting or patients diagnosed clinically with Gilles de la Tourette Syndrome (GTS) **CQ4** Adults with HIV-1 or HIV-2 infection **CQ5** Adults with any type of cancer and receiving chemotherapeutic treatment	
Interventions	For **all CQ**: cannabis, in any dose, used either as monotherapy or adjunct to conventional drugs	Manufactured pharmacological interventions based on cannabinoids derived from cannabis such as nabilone and dronabinol
Comparators	**CQ1**:Placebo; Pharmacological agents (any) **CQ2**. Placebo; Other neuromodulators Analgesics (e.g. paracetamol, NSAIDs, opioids, tramadol, antidepressants etc.); non-pharmacological modalities (e.g. transcutaneous electrical nerve stimulation (TENS), acupuncture, etc.); **CQ3**. Placebo; any other drug(s) for tic reduction and/or reduction of obsessive-compulsive symptoms. **CQ4**. Placebo; No drug; Other form of cannabis **CQ5**. Placebo or conventional antiemetic agents	
Outcomes	**Primary outcomes** **CQ1 and CQ2**: pain relief measured with validated assessment tools **CQ1**:spasticity and insomnia, change in severity of ataxia as measured with validated measurement tools **CQ2**: Intensity of pain, as scored by VAS, categorical scales, or other validated assessment tools measuring pain intensity. **CQ3**. Tic frequency and severity, measured using standard rating scales such as the Yale Global Tic Severity Rating Scale, a video protocol, or a self-rating scale such as the Tourette Syndrome Symptom List). Obsessive compulsive symptoms measured using the Yale-Brown Obsessive Compulsive Scale; Clinical global impression of change; Cognitive function; Behavioural symptoms (i.e. agitation and night-time motor activity); Mood (e.g. sleep, appetite); Functional performance Activities of daily living; Caregiver burden and caregiver quality of life; Quality of life **CQ4.** Mortality (HIV-related; all-cause); Morbidity (frequency, type and duration of episodes of opportunistic infections; malignancies; incidence of AIDS (as defined by each study); hospital admissions; and other illness types as measured in the studies); Functional assessments of learning, memory, vigilance and psychomotor performance	
	CQ5. Complete control of nausea and vomiting (absence of episodes of nausea and vomiting without use of rescue medication) in the acute phase (within 24 hours of treatment with chemotherapy) and in the delayed phase (after 24 hours' treatment with chemotherapy. Complete control of vomiting (absence of episodes of vomiting without use of rescue medication) in the acute and delayed phases Complete control of nausea (absence of episodes of nausea without use of rescue medication) in the acute and delayed phases **Safety outcomes (secondary outcomes)** **For all CQ**: Number of participants with: any adverse event;	

	any serious adverse event (as reported in the study); withdrawal due to an adverse event; Occurrence of abuse and/or dependence **CQ3**. Mortality **CQ4.** Weight loss and anorexia	
Study design	**For all CQs**, randomized controlled trials either which were placebo-controlled or which compared two or more treatments For adverse effects: any prospective and retrospective cohort studies	Phase I, and II studies

Selection and Data collection

Three authors independently evaluated the titles and abstracts of studies identified in the literature searches for their eligibility. For studies considered eligible, we retrieved full texts. We extracted data from multiple publications of the same study considering as a single study. Three investigators independently extracted data. We extracted the following information: study design; characteristics of participants (total number at baseline, age range, gender, clinical features); description of the intervention and comparator (dosages and route of administration); outcomes reported, including methods of assessment; risk of bias. Differences in data extraction were resolved through consensus or in discussion with all the authors.

Assessment of Risk of Bias

Two investigators independently assessed the risk of bias for each study using the Cochrane 'Risk of bias tool"[12] for RCTs for the following criteria: adequate sequence generation; concealment of allocation; blinding of participants and providers, blinding of outcome assessor, and incomplete outcome data. Discrepancies were resolved through discussion and consensus. We provide in ***Appendix 2*** a detailed description of the criteria used to judge risk of bias for each domain. For each domain, risk of bias was classified as "high," "low," or "unclear". We used RevMan 2014[13] software to generate figures related to risk of bias.

Data analysis and synthesis

We grouped studies by condition, type of cannabinoid, and outcome. We attempted to measure the data from all randomised participants who received medication, and provided at least one post-baseline assessment (intention to-treat analysis). We analysed dichotomous outcomes by calculating the risk ratio (RR) for each trial with the uncertainty in each result being expressed with 95% confidence interval (CI). We analysed continuous outcomes by calculating the mean difference (MD) with 95% CI when the studies used the same instrument for assessing the outcome. We used the standardised mean difference (SMD) when

the studies used different instruments. We analysed heterogeneity by means of the I^2 statistic test[12]. The cut-off points to establish heterogeneity were I^2 values of more than 50%.

For each clinical condition, we conducted meta-analyses if sufficient data were available, using a random-effect model. If data available in the included studies were too heterogeneous to be pooled, we reported data narratively. Incorporating crossover trials in a meta-analysis as parallel trials, taking all measurements from experimental periods and all measurements from control periods, gives rise to a unit-of-analysis error. To avoid this risk, there are two possibilities: a) to include in the meta-analysis only results coming from the first period of the studies for both groups (i.e. before the cross over); b) to adjust the differences between the experimental and control periods of each study by the correlation coefficient and include the effect estimate in a meta-analysis using the generic inverse-variance method[12]. None of the included cross over studies reported separate results for the first period of the study and did not report data useful to adjust for unit of analysis error.

In this report, to avoid the unit of analysis error, we performed subgroup analyses according to the study design (parallel or crossover). This approach is conservative, although it may not be the most correct as it overestimates the variability between study periods [12]. We carried out statistical analyses using RevMan[13]. Key study characteristics, patient outcomes and study quality are summarized in tables and figures.
We assessed the overall quality of the evidence for the primary outcome using the GRADE system. The Grading of Recommendation, Assessment, Development and Evaluation (GRADE) Working Group developed a system for grading the certainty of evidence[14-17], which takes into account issues not only related to internal validity but also to external validity, such as directness of results. The 'Summary of findings' tables present the main findings of a review in a transparent and simple tabular format. In particular, they provide key information concerning the certainty of evidence, the magnitude of effect of the interventions examined for each outcome and the sum of available data on the main outcomes (number of studies and participants).

The GRADE approach uses five dimensions (study limitations risk of bias, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence is downgraded from 'high quality' by one level if serious, or by two levels for very serious limitations are found for each of the five dimensions, depending on assessments for risks of bias: indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias. See **Appendix 3 for** further explanation of the quality of the evidence.

Results

We identified 9953 records through database searching. After removing duplicates, we obtained 4514 unique references; we excluded 4385 based on title and abstract. We retrieved 129 articles in full text for more detailed evaluation, 85 of which we excluded for not meeting the inclusion criteria. **Appendix 4** provides information on the characteristics of excluded studies.

We included 43 RCTs that satisfied all criteria required for inclusion in the review. No other study designs with eligible intervention were identified. We included 29 studies in quantitative synthesis (meta-analyses). See Fig. 1 Prisma (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Flow Diagram for details on the selection procedure. Three studies are awaiting assessment[18-20]. We identified seven on-going trials related to the topics object of the reviews[21-27].

Table 2 provides aggregated information on the characteristics of all included studies. The 43 RCTs included 4586 participants, published between 1975 and 2015, with the majority conducted in Europe. Fifteen studies considered efficacy and safety of cannabis for patients with multiple sclerosis, 12 for patients with chronic pain, two for patients with dementia/Tourette syndrome, one for patients with HIV/AIDS, and 14 for patients with cancer receiving chemotherapy. For substantive descriptions of studies, see **Appendix 5** "Characteristics of the included studies".

Figure 1. PRISMA 2009 Flow Diagram for CQ1, CQ2, CQ3, CQ4, CQ5

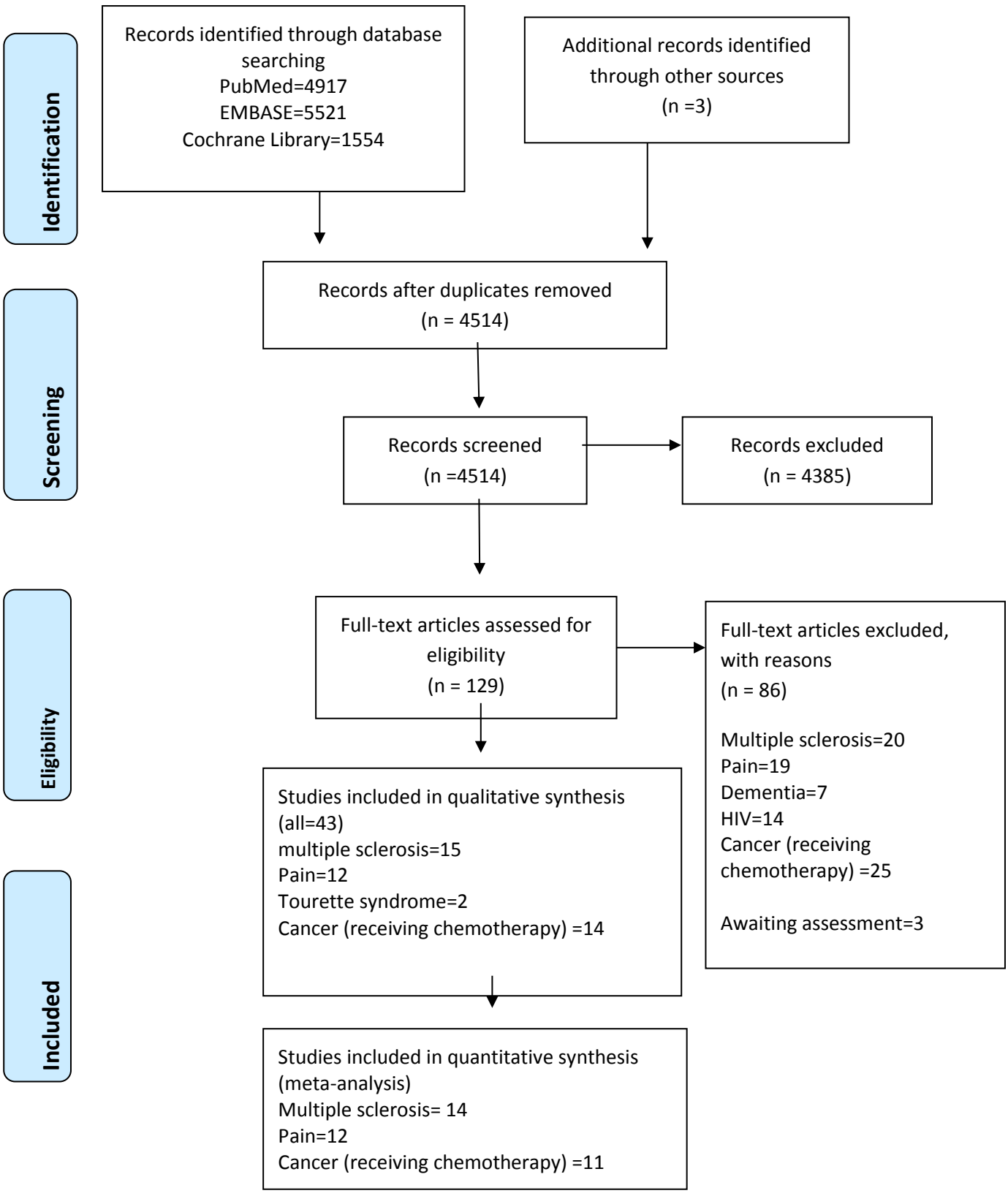


Table 2 - Synthesis of included studies characteristics

Condition	patients with multiple sclerosis		patients with chronic pain		patients with tourette sydrome		patients with CA receiving chemotherapy	
n° of studies	15		12		2		14	
	N	%	N	%	N	%	N	%
Average sample size (range)	162 (range 14-657)		89 (range 16-360)		18 (range 12-24)		68 (range 8-243)	
Age (mean)	46.7		52.5		33.5		44.7	
Sex , male		36.0**		58,0		85.6		54.3
Country								
USA	2	14,3	5	41,6	-		11	78.5
Canada	-		1	8,3	-		-	
Europe	13	85,7	6	50,0	2	100	3	21.4
years of publication								
before 2000			-				12	86,6
2001-2006	6	42,8	2	16,6	2	100	1	6,6
2007-2015	9	57,1	10	83,3			1	6,6
Duration (range)	2-48 weeks		1 day-15 weeks		4-6 weeks		24 hours-6 months*	
Design								
parallel	6	40	6	50	1	50	4	28,6
crossover	9	60	6	50	1	50	10	71,4

*7 studies

**14 studies

Clinical Question 1

Background

Multiple sclerosis (MS) is a progressive, chronic, immune-mediated disease of the central nervous system (CNS), diagnosed predominantly in young adults with approximately 500,000 patients in Europe and more than 2.3 million people worldwide[28, 29]. It is characterized by a broad range of signs and symptoms like restricted mobility, spasticity, fatigue, sensory deficits, palsy, pain, bladder dysfunction, cognitive dysfunction, depression and visual impairment[30, 31].

Spasticity is one of the most common symptoms of MS, affecting more than 80% of MS patients during the course of the disease [31]. It is defined from the pathophysiological perspective as a 'disordered sensorimotor control resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles[32]. Depending on the severity of spasticity, drug treatment varies widely. Commonly used medications like baclofen, tizanidine, gabapentin or dantrolene are administered orally. Their mode of action varies, but all cause muscle relaxation[33]. There is limited evidence of the effectiveness and efficacy of these drugs; in particular, a Cochrane systematic review of 2003 concluded that the absolute and comparative efficacy, as well as tolerability of classical antispasticity medication, is limited[34].

The search for alternative antispasticity drugshas raised interest in Cannabis sativa that has been used for medical purposes for a long time either to achieve or to investigate antispastic, muscle relaxant and analgesic effects[35, 36]. Since 2011, Δ-9-tetrahydrocannabinol-cannabidiol (THC-CBD) oromucosal spray (Sativex®) has been available as add-on therapy for patients with moderate to severe treatment-resistant spasticity in a growing number of European countries and Canada[33].

Another important symptom of MS is pain. The number of people with MS who suffer from pain is high, but the exact rate is unknown. Estimates vary widely from 10% to 80%, with an average of about 50%[37-40]. The incidence of pain has no apparent correlation to disease severity and, so far, no evidence has shown that pain occurs more frequently in any particular disease subtype[37]. Current pain treatments are unable to meet the objectives of pain management in MS[41]. Extracts of cannabis represent an option in treating pain[42, 43] and they could be a possibility for patients whose pain is not ameliorated by traditional drugs.

Results

For **patients with multiple sclerosis**, 35 articles were retrieved in full text for a more detailed evaluation, twenty of which were excluded for not meeting the inclusion criteria[28, 44-62]. For details on the reasons for exclusion, see **Appendix 4** "Characteristics of excluded studies".

We included 15 studies, with 2431 patients; nine were parallel trials[63-71] and six were crossover trials[72-77].

We included 14 studies in quantitative synthesis (meta-analyses).

Types of interventions

The included studies considered Sativex (composed of whole cannabis plant extract containing Δ-9-tetrahydrocannabidiol - THC and cannabidiol - CBD), nine studies; Extract of Cannabis Sativa in gelatine capsule, five studies; and cannabis cigarettes, one study.

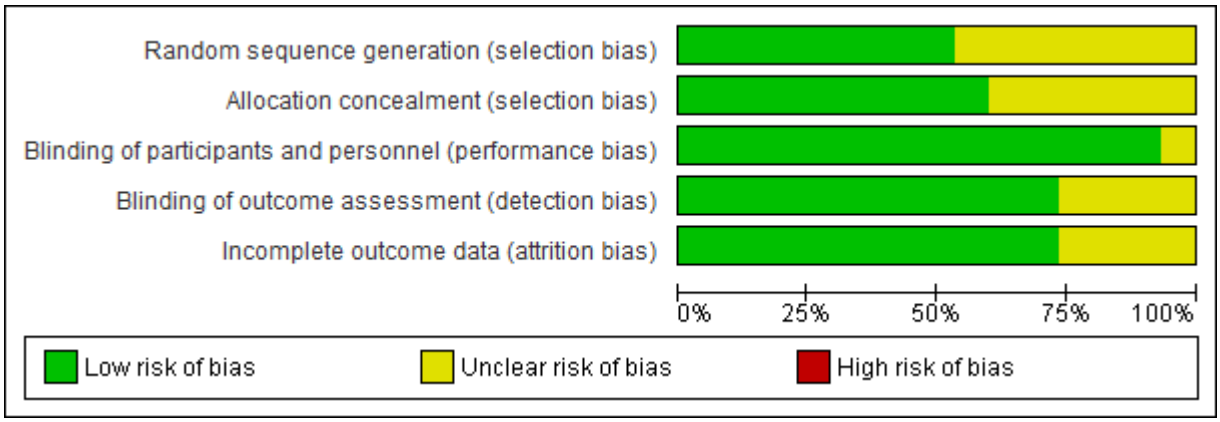
Type of comparisons

Cannabis versus placebo, all 15 studies.

Risk of bias in included studies

Review authors' judgements about each risk of bias item presented as percentages across all included studies are reported in figure 2. Details on review authors' judgements about each risk of bias item for each included study are reported Appendix 3 "Risk of bias summary".

Figure 2. Risk of bias graph for CQ1



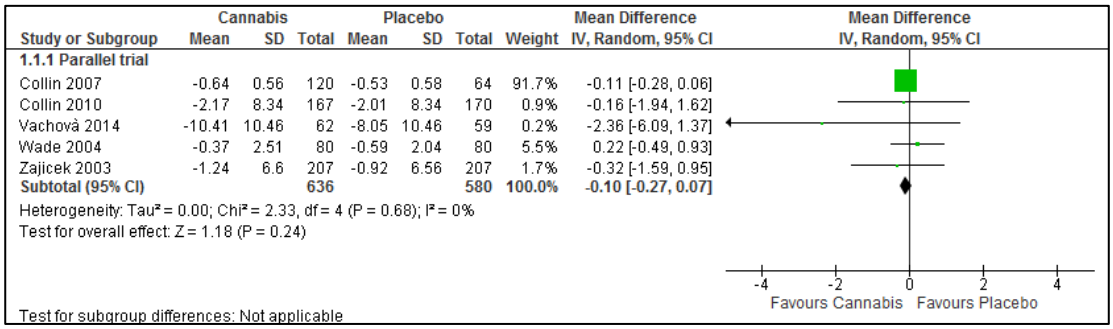
Effects of Intervention

Efficacy outcomes

Spasticity:

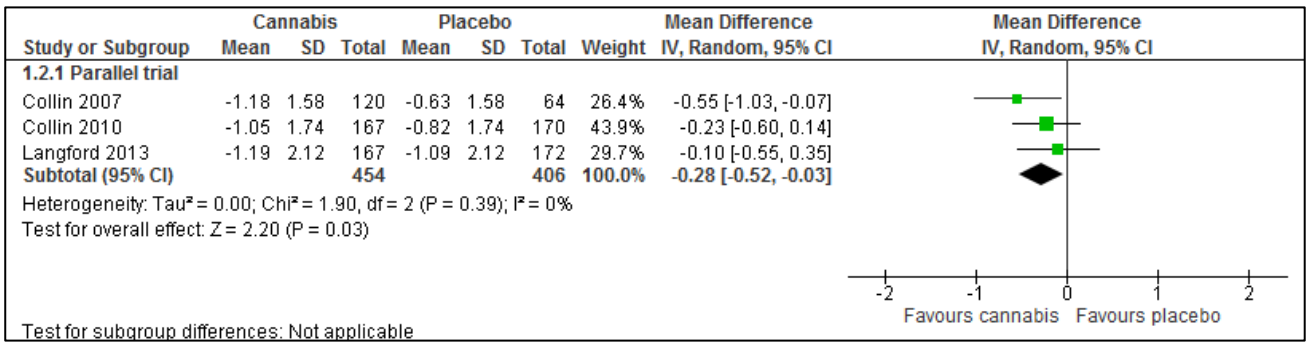
No significant difference was found in the reduction of spasticity from baseline using the Ashworth score. Based on data from five studies[63, 64, 68-70], 1216 patients, high confidence in estimates, MD -0.1 (95%CI - 0.26 to 0.07), see figure 3.

Figure 3. Cannabis vs placebo patients with MS, outcome: 1.1 Ashworth score.



Analysing an average reduction in NRS (Numerical Rating Scale) Spasticity Score results in a more favourable evaluation of cannabis, including its extracts and tinctures. Based on data from three studies[63, 64, 66], 860 patients, high confidence in estimates, MD -0.28 (95%CI -0.52 to -0.03), see figure 4.

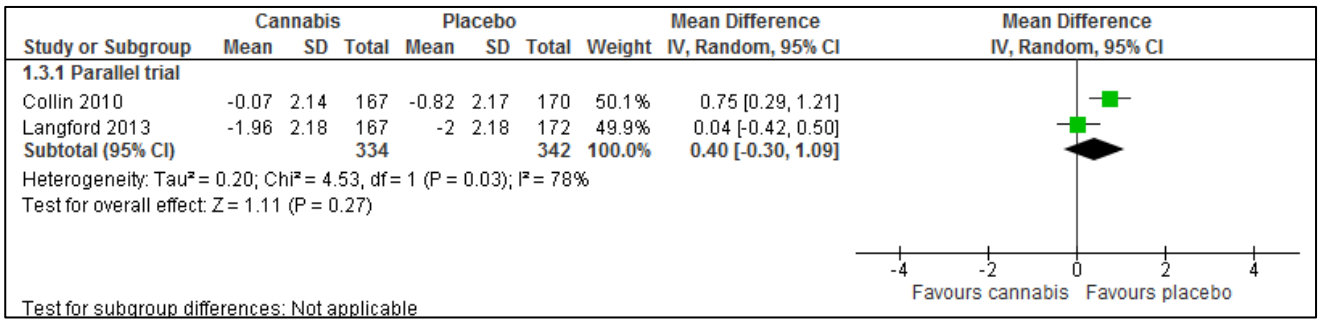
Figure 4. Cannabis vs placebo patients with MS, outcome: 1.2 NRS Spasticity score



Quality of sleep:

No difference in improvement of sleep quality measured with Sleep Quality NRS score. Data from two studies[64, 66], 676 patients, moderate confidence in estimates, MD 0.40 (95% CI -0.30 to 1.09), see figure 5.

Figure 5. Cannabis vs placebo patients with MS, outcome: 1.3 Sleep NRS.



For the overall certainty of evidence, see Summary of findings 1.

Summary of findings 1: Cannabis compared to placebo for patients with MS

Patient or population: Patients with MS
Setting: Outpatients
Intervention: Cannabis
Comparison: Placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with Cannabis**				
Ashworth score - Parallel trial Change from baseline (range 0-4). Better indicated by lower	The mean Ashworth score - Parallel trial was **0**	The mean Ashworth score - Parallel trial in the intervention group was 0,1 lower (0,27 lower to 0,07 higher)	-	1216 (5 RCTs)	⊕⊕⊕⊕ HIGH	Uncertain result
NRS Spasticity score - Parallel trial Change from baseline (range 0-10). Better indicated by lower	The mean NRS Spasticity score - Parallel trial was **-0.8**	The mean NRS Spasticity score - Parallel trial in the intervention group was 0,28 higher (0,52 higher to 0,03 higher)	-	860 (3 RCTs)	⊕⊕⊕⊕ HIGH	In favour of cannabis
Sleep NRS - Parallel trial Change from baseline (range 0-4). Better indicated by lower	The mean sleep NRS - Parallel trial was **-1.4**	The mean sleep NRS - Parallel trial in the intervention group was 0,4 higher (0,3 lower to 1,09 higher)	-	676 (2 RCTs)	⊕⊕⊕◯ MODERATE [1]	Uncertain result

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. high heterogeneity: I square 78%

Narrative results

The included studies also reported data about: Spasm Frequency and Pain measured with Visual Analog Scale (VAS) and Numerical Rating Scale (NRS), Neuropathic Pain Scale (NPS), Spasticity and Quality of Sleep measured with VAS, Quality of Sleep VAS, Muscle Stiffness and Spasm, Pain and Discomfort measured by the 88-item Multiple Sclerosis Spasticity Scale (MSSS-88), Tremor Index, Tremor Frequency, Ataxia Rating Score. These results were reported in ways that prevent the possibility to pool data. For these measures in all but four studies, no significant difference was found between cannabis including extract and tincture and placebo groups between cannabis and placebo groups.

One study[67] of 66 patients found a significant mean reduction of pain in favour of cannabis using NPS: MD -6.58 (95% CI -12.97 to -0.19) and using NRS: MD -1.25 (95% CI -2.11 to -0.39). Another study[73], (Corey-Bloom 2012), 30 patients, using VAS, found that cannabis reduced pain by 5.28 points (95% CI 2.48 to 10.01). In the study by Wade 2004 involving 160 patients, spasticity, measured by Spasticity VAS, was significantly reduced in the cannabis including extract and tincture group compared to placebo: MD -22.79 (CI 95% -35.52 to -10.07). In the same study, a significant difference in favour of cannabis including extract and tincture was also seen for Sleep Quality measured with VAS: MD-7.10 (95% CI -14.11 to -0.08). In a study by Zajicek 2012 involving 277 patients, the cannabis group showed a significant reduction in muscle stiffness and muscle spasms measured by MSSS-88 after 12 weeks. The differences were statistically significant in favour of cannabis for the section of the MSSS-88 Scale measuring muscle stiffness: MD -3.7 (95% CI -5.63 to -1.77) and muscle spasm: MD -3.1 (95% CI -5.35 to -0.85) respectively.

Clinical Question 2

Background

About 3% of the general population experiences chronic neuropathic pain, making it the most frequent condition affecting the peripheral nervous system[78]. Chronic neuropathic pain may result from diverse clinical diseases, including diabetes, HIV, trauma, and certain medications[79]. Regardless of aetiology, chronic neuropathic pain persists despite attempts at management with opioids, NSAIDs, anticonvulsants (gabapentin), anti-inflammatory agents, antidepressants and complementary medicine approaches[80].

Similarly, chronic pain associated with rheumatic diseases presents treatment challenges, with only a minority of individuals experiencing a clinically relevant benefit from any drug intervention. The proportion of patients who achieve clinically meaningful pain relief with nonsteroidal agents, antidepressants, and opioids is generally in the order of 10 to 25%[81].

Therefore, a need exists to identify new drug treatment options with different mechanisms of action. The endocannabinoid system can play a role in pain modulation and attenuation of inflammation. Cannabinoid receptors are widely distributed throughout the central and peripheral nervous system. The hypothesis is that cannabinoids can reduce sensitization of nociceptive sensory pathways and induce alterations in cognitive and autonomic processing in chronic pain states[82-83].

Results

Thirty-one articles were retrieved in full text involving **patients with chronic pain** for more detailed evaluation, nineteen of which were excluded for not meeting the inclusion criteria[84-102]. For details on the reasons for exclusion, see **Appendix 4** "Characteristics of excluded studies". We included 12 studies involving 1064 participants in which six were parallel[103-108] and six were crossover[109-114] trials. We included all the studies in a quantitative synthesis (meta-analyses).

Types of interventions

Seven studies used THC (oral, smoked, vaporized, and inhaled); five studies used a whole-plant cannabis-based medicine (Sativex) containing 2.7 mg THC and 2.5 mg CBD per 100 microliter spray. One study had three arms (Berman 2004) including both these interventions. Four studies[106, 110, 113, 114] had more than one arm that considered different dosages of THC ranging from: low-dose (1% THC) to (9.4% THC) high-dose. Furthermore, one study had three arms including both these interventions. Four studies had more than one arm that considered different dosages of THC ranging from: low-dose (1% THC) to (9.4% THC) high-dose.

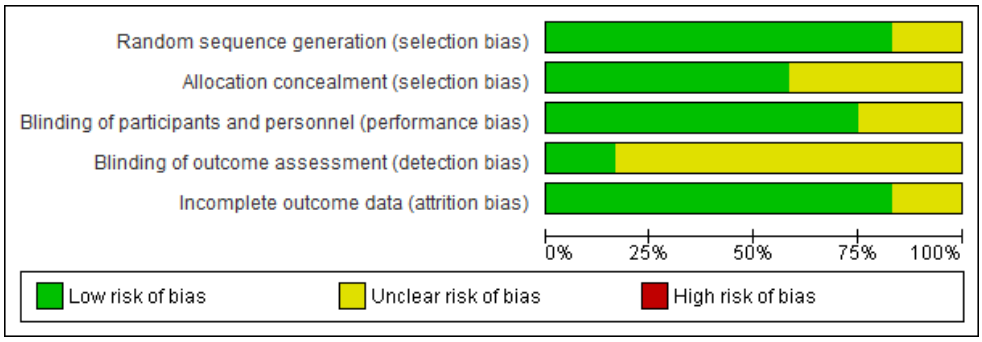
Type of comparisons

Cannabis versus placebo: all 12 studies

Risk of bias in included studies

Review authors' judgements about each risk of bias item presented as percentages across all included studies are reported in figure 6. Details on review authors' judgements about each risk of bias item for each included study are reported Appendix 3 "Risk of bias summary".

Figure 6. Risk of bias graph for CQ2



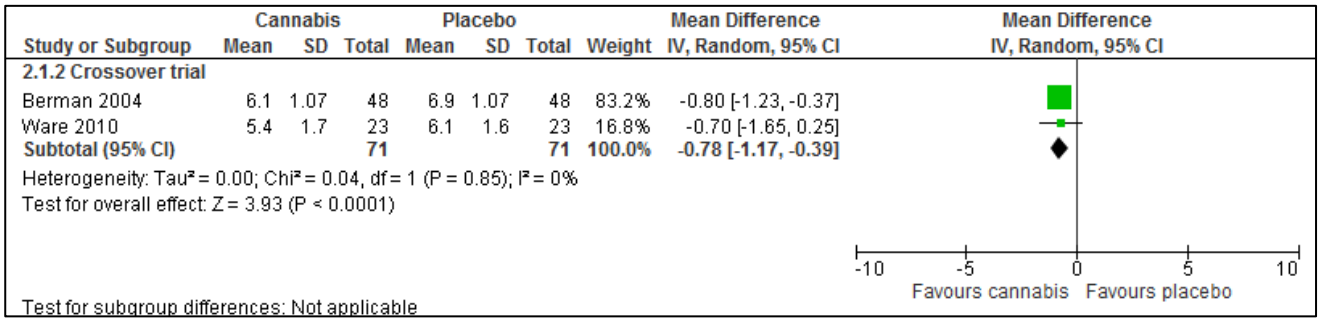
Effects of interventions

Efficacy outcomes

Intensity of pain

Cannabis performed better than placebo for controlling the intensity pain (two crossover studies[109, 111], 71 patients, MD -0.78 (95% CI -1.17 to -0.39), low confidence in estimates; see figure 7).

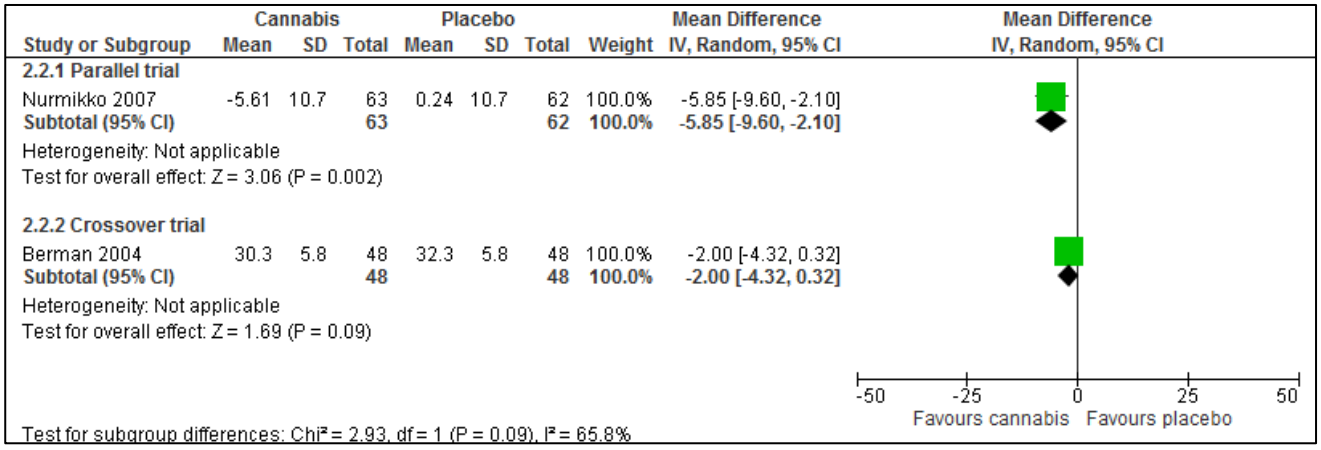
Figure 7. Cannabis vs placebo patients with chronic pain, outcome: 2.1 Pain intensity.



Pain disability index

Results of one parallel trial[105] containing 125 patients resulted in a positive outcome for cannabis, achieving a MD -5.85 (95% CI -9.60 to -2.10). On the other hand, results of one crossover trial (Berman 2004) involving 48 patients were unclear: MD -2.00 (95%CI -4.32 to 0.32). There was a low confidence in estimates for both comparisons, see figure 8.

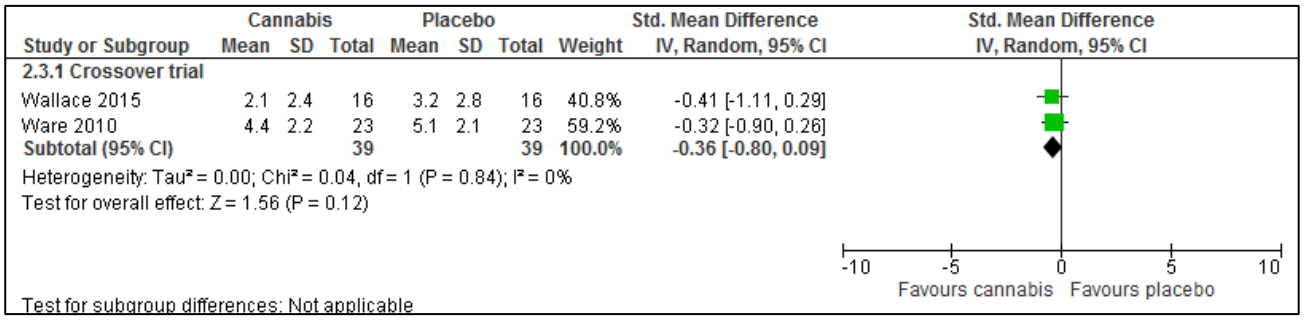
Figure 8. Cannabis vs placebo patients with chronic pain, outcome: 2.2 Pain disability index.



Minimum pain scores

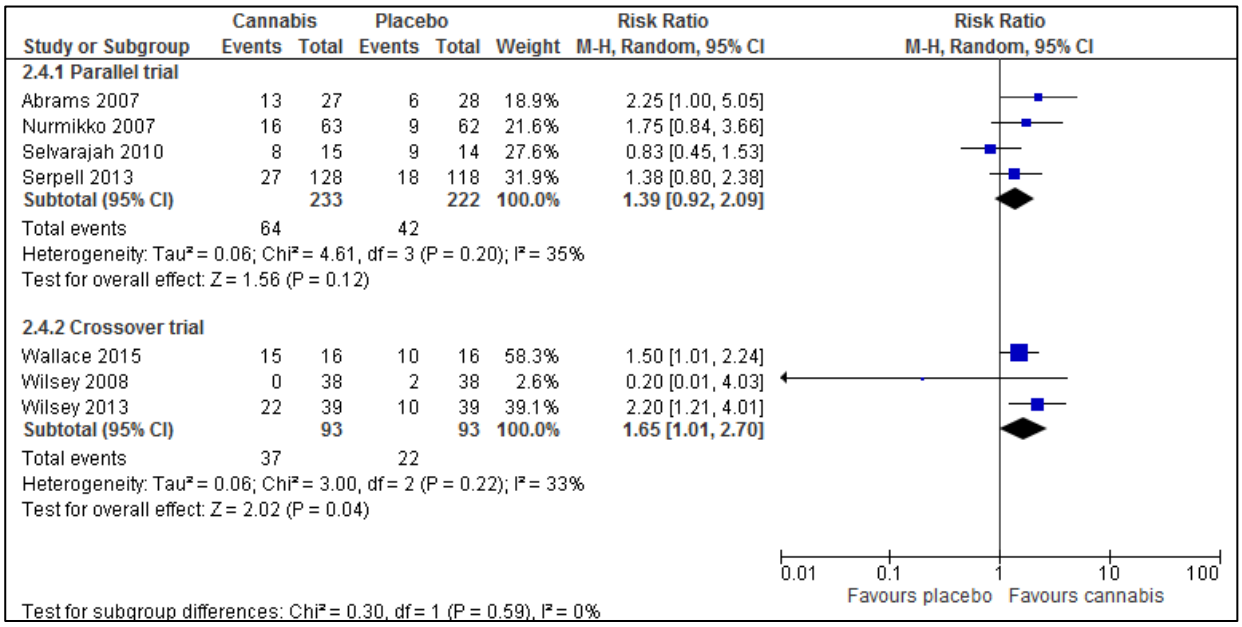
Results from two crossover studies[110-111] with 39 patients showed a trend in favour of cannabis, although the results did not reach statistical significance: SMD -0.36 (95% CI -0.80 to 0.09), and had a low confidence in estimates (see figure 9).

Figure 9. Cannabis vs placebo patients with chronic pain, outcome: 2.3 Minimum pain scores.



Outcomes with cannabis resulted in no differences in the reduction (> 30%) of neuropathic pain based on data from four parallel studies[103, 105, 107, 108] involving 455 patients: MD 1.39 (95% CI 0.92 to 2.09). Results coming from three crossover trials[110, 113, 114] involving 186 patients showed a better effect of cannabis: MD 1.65 (95% CI 1.01 to 2.70). There was a moderate confidence in estimates for both comparisons, see figure 10.

Figure 10. Cannabis vs placebo patients with chronic pain outcome: 2.4 Reduction >30% neuropathic pain.



For the overall certainty of evidence, see Summary of findings 2.

Summary of findings 2: Cannabis compared to placebo for patients with chronic pain

Patient or population: Patients with chronic pain
Setting: Outpatients
Intervention: Cannabis
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with Cannabis**				
Pain intensity - Crossover trial BS 11 scale (range 0-10) Better indicated by lower	The mean pain intensity - Crossover trial was **0**	The mean pain intensity - Crossover trial in the intervention group was 0,78 lower (1,17 lower to 0,39 lower)	-	71 (2 RCTs)	⨁⨁◯◯ LOW [1]	In favour of cannabis
Pain disability index - Parallel trial Pain disability index scale (range 0-70) Better indicated by lower	The mean pain disability index - Parallel trial was **0**	The mean pain disability index - Parallel trial in the intervention group was 5,85 lower (9,6 lower to 2,1 lower)	-	125 (1 RCT)	⨁⨁◯◯ LOW [1,2]	In favour of cannabis
Pain disability index - Crossover trial Pain disability index scale (range 0-70) Better indicated by lower	The mean pain disability index - Crossover trial was **0**	The mean pain disability index - Crossover trial in the intervention group was 2 lower (4,32 lower to 0,32 higher)	-	48 (1 RCT)	⨁⨁◯◯ LOW [1,2]	Uncertain result
Minimum pain scores at different scales - Crossover trial	-	-	-	39 (2 RCTs)	⨁⨁◯◯ LOW [3]	Uncertain result
Reduction >30% neuropathic pain - Parallel trial	189 per 1.000	**263 per 1.000** (174 to 395)	**RR 1.39** (0.92 to 2.09)	455 (4 RCTs)	⨁⨁⨁◯ MODERATE [1]	Uncertain result
Reduction >30% neuropathic pain - Crossover trial	237 per 1.000	**390 per 1.000** (239 to 639)	**RR 1.65** (1.01 to 2.70)	93 (3 RCTs)	⨁⨁⨁◯ MODERATE [1]	In favour of cannabis

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardised mean difference; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Optimal Information Size (OIS) not met
2. high heterogeneity: I square 66%
3. two studies with 39 patients

Narrative results

One study[104], 58 patients involved, reported efficacy outcomes in a way that prevented the possibility of pooling data. The study reports a significant improvement in favour of cannabis for pain on movement measured with the NRS scale: median difference - 0.95 (95% CI -1.83 to -0.02) and pain at rest measured with the NRS scale: median difference -1.04 (95% CI -1.90 to -0.18). No difference was observed with the Short-Form McGill Pain Questionnaire (SF-MPQ) for total intensity of pain: median difference 3.00 (95%CI -3.00 to 9.00).

Clinical Question 3

Background

Gilles de la Tourette syndrome (GTS) is a developmental neuropsychiatric disorder characterized by the presence of chronic motor and phonic tics. In many cases, tics are associated with behavioural difficulties, which can include attention problems, motor hyperactivity, obsessive-compulsive behaviours, lack of impulse control, anxiety, depression and self-injurious behaviour[115].

There are drugs currently used in the treatment of GTS but none has proven completely effective and free of side effects. Randomised controlled trials have shown that haloperidol and pimozide can be effective in reducing tics in many patients for much of the time[116-117]. However, only 20% to 30% of patients taking haloperidol or pimozide continue with the treatment due to adverse effects[118]. The atypical neuroleptics show fewer adverse effects and risperidone has been the most extensively studied[119-120].

There is some anecdotal and experimental evidence that cannabinoids might be useful in the treatment of the symptoms in patients with Tourette's syndrome

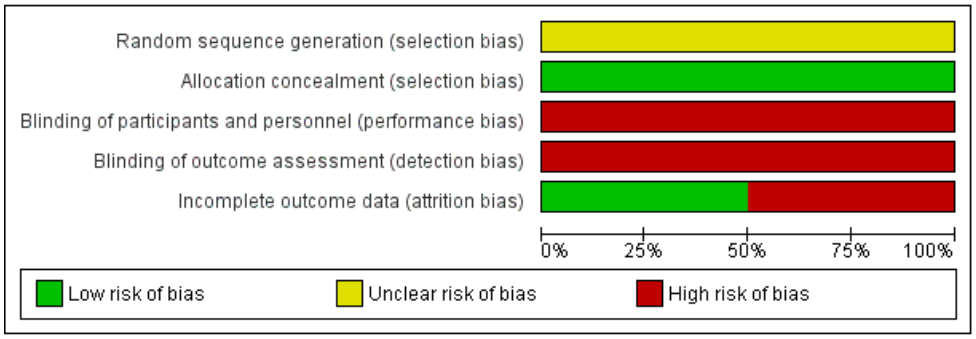
Results

For **patients with dementia/Tourette syndrome**, nine articles were retrieved in full text for more detailed evaluation, seven of which[121-127] were excluded for not meeting the inclusion criteria; for details on the reasons for exclusion see **Appendix 4** "Characteristics of excluded studies". Two RCTs, 36 participants, one crossover[128] and one parallel[129] trial, both comparing THC with placebo to treat the symptoms of Tourette's syndrome, were included.

Risk of bias in included studies

Review authors' judgements about each risk of bias item presented as percentages across all included studies are reported in figure 11. Details regarding the judgements about each risk of bias item for each included study are reported Appendix 3 “Risk of bias summary”.

Figure 11. Risk of bias graph for CQ3



Effects of interventions

Efficacy outcomes

It was not possible to pool data from these two studies because the outcomes results were reported in different ways. In the Muller-Vahl 2002 study involving 12 participants, the primary outcome was tic score measured by self-report and examiner scales (Tourette Syndrome Global Scale (TSGS); the Shapiro Tourette Syndrome Severity Scale (STSSS); the Yale Global Tic Severity Scale (YGTSS); the Tourette’s syndrome Symptom List (TSSL). No significant difference between the groups was found for Tic severity scores measured by the TSGS ($p = 0.132$). Using TSSL score, a self-rating scale, there was an improvement in patients treated with THC for complex motor tics (CMT) ($p=0.015$), simple motor tics (SMT) ($p=0.026$) and motor tics (MT= SMT+CMT) ($p=0.026$). In Muller-Vahl 2003, 24 participants, the primary outcome was tic reduction according to the TSGS, STSSS; YGTSS; video rating scale. Tic severity scores measured though examiner scales showed a significant differences reduction in THC group compared with placebo when the patients were taking the maximum dose ($p=0.030$)

Safety outcomes

Five patients in the THC group in the Muller-Vahl 2002 study reported mild adverse effects (i.e. headache, dizziness, tiredness) lasting between 1 to six hours after the treatment. In the placebo group, two patients reported headache. In Muller-Vahl 2003, no serious adverse effects were reported. Five patients from the THC group reported mild adverse effects such as tiredness, dry mouth, dizziness and muzziness. Three patients in the placebo group reported adverse effects like tiredness, dizziness, anxiety and depression.

Clinical Question 4

Background

Acquired immunodeficiency syndrome (AIDS) is a disease caused by the human immunodeficiency virus (HIV) that has a complex life cycle in the human body. The virus is spread by sexual contact, sharing of other body fluids, particularly blood (for example during the birth process, through blood transfusions and through the sharing of needles for injection drug use), and breastfeeding. The HIV virus infects CD4 lymphocytes, resulting in significant losses of these cells. During the (often long) latent phase of the disease, the immune system remains functional, but during the end stages of the disease (classified as AIDS), the infected individual is vulnerable to developing various opportunistic infections as well as certain types of cancers[130].

The use of cannabis has been advocated in patients with HIV/AIDS, in order to improve appetite, promote weight gain and ameliorate mood disturbance.

Some of the effects of cannabis seem to directly address the symptoms of HIV disease, such as loss of appetite, loss of weight and peripheral neuropathy. However, cannabis may also affect psychomotor performance, which may exacerbate the neuropsychiatric symptoms of HIV. It is therefore important to assess evidence for the benefits of cannabis in HIV/AIDS, compared to its adverse effects.

Results

For **patients with HIV/AIDS**, 15 articles were retrieved in full text for more detailed evaulation, all[131- 144] were excluded for not meeting the inclusion criteria (for details on the reasons for exclusion see **Appendix 4** "Characteristics of excluded studies"

Clinical Question 5

Background

Nausea and vomiting are considered the most stressful adverse effects of chemotherapy by people with cancer[145]. Up to 75% of all people with cancer experience chemotherapy-related nausea and vomiting[146], which can lead to depression, anxiety and a feeling of helplessness, lower quality of life and may affect chemotherapy adherence[147]. Guidelines recommending standard protocols ensure best practice in managing chemotherapy-induced nausea and vomiting[148-149].

During the 1990s, serotonin (5-HT_3) receptor antagonists, combined with dexamethasone, became the gold standard in the prevention of vomiting caused by chemotherapy[150]. Currently, the anti-emetics indicated for chemotherapy with high emesis-inducing potential are 5-HT_3 receptor antagonists, dexamethasone and aprepitant given during the acute emetic phase[148, 151, 152]. For people who experience refractory nausea and vomiting (i.e. people who do not respond to first line prophylactic anti-emetics) many additional anti-emetics can be added to the prophylactic anti-emetic regimen: phenothiazines, antihistamines, butyrophenones (haloperidol), other dopamine antagonists and benzodiazepines (lorazepam)[150, 152]. Other drugs that can be effective are dexamethasone, olanzapine and the second-generation $5HT_3$ receptor antagonist, palonosetron[153].

Cannabinoids may be considered for controlling nausea and vomiting as fourth-line agents. The blockade of CB1 cannabinoid receptors induces vomiting, suggesting the existence of cannabinoid receptors within the areas of the brain related to nausea and vomiting[154, 155].

Results

For **patients with cancer receiving chemotherapy**, 41 articles were retrieved in full text for more detailed evaluation, twenty-seven of which were excluded for not meeting the inclusion criteria[156-181] and 14 were included. For details on the reasons for exclusion, see **Appendix 4** "Characteristics of excluded studies".
A total of 960 participants comprised the 14 included studies, four of which were parallel trials[182-185] and 10 crossover trials[186-195]. We included 11 studies in a quantitative synthesis (meta-analyses). All trials enrolled patients with cancer who were receiving chemotherapy. The chemotherapy regimens varied across the studies and for detailed description see **Appendix 5** "Characteristics of included studies".

Types of interventions

Thirteen of the included studies involved oral and smoked THC, and one study involved a whole-plant cannabis-based medicine (CBM) containing THC and cannabidiol.

Type of comparisons

We grouped the studies into two comparisons.

1. Cannabis versus placebo: three parallel trials[182, 183, 185] and five crossover trials[186, 187, 189, 192, 193].

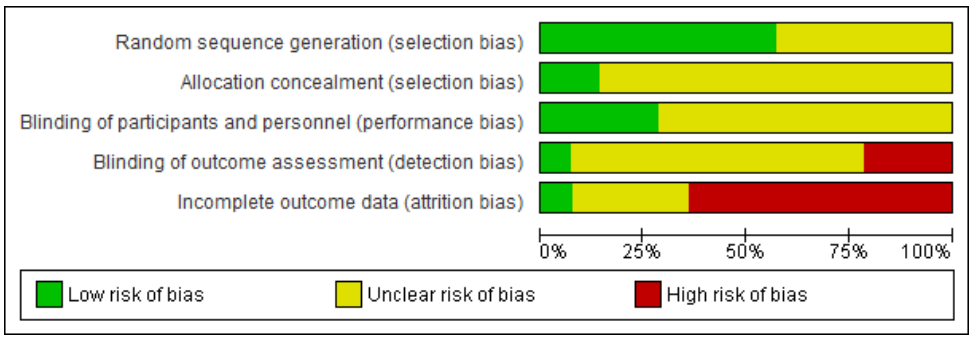
2. Cannabis versus other antiemetic drugs: two parallel trials[183-184] and six crossover trials[188, 190, 191, 192, 194, 195].

Two studies had more three arms[183,192].

Risk of bias in included studies

Review authors' judgements about each risk of bias item presented as percentages across all included studies are reported in figure 12. Details on review authors' judgements about each risk of bias item for each included study are reported Appendix 3 “Risk of bias summary”.

Figure 12. Risk of bias graph for CQ5



Effects of interventions

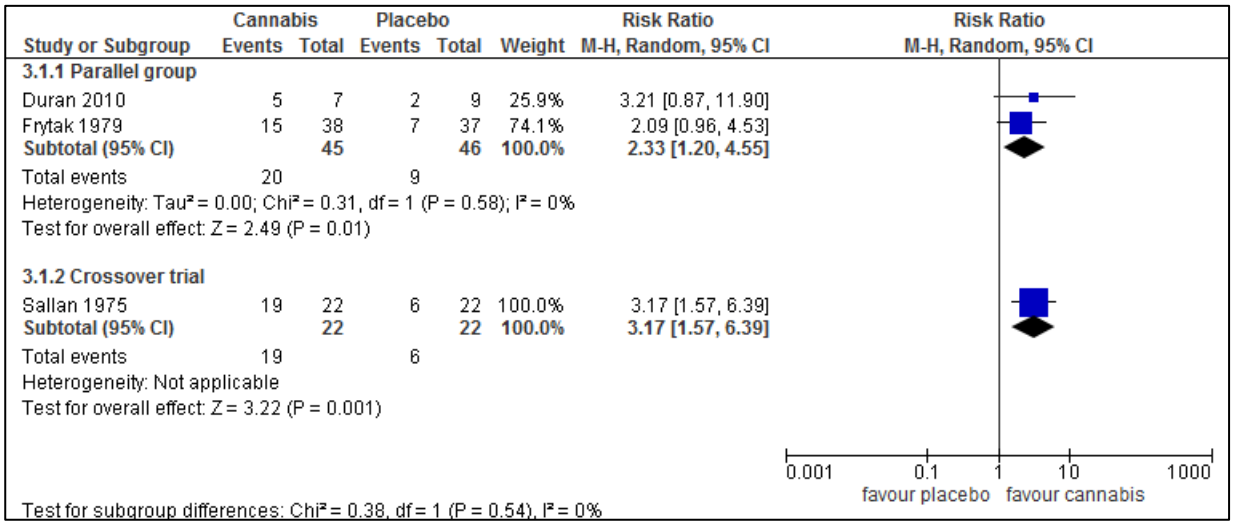
Efficacy outcomes

Comparison 1. Cannabis versus placebo in patients receiving chemotherapy

Control of nausea and vomiting

Cannabis is more effective in controlling nausea and vomiting based on data from two parallel trials[182, 183] involving 91 patients, RR 2.33 (95% CI 1.20 to 4.55) and one crossover study[193], 22 patients, RR 3.17 (95% CI 1.57 to 6.39). There was a very low confidence in estimates for both studies, see figure 13.

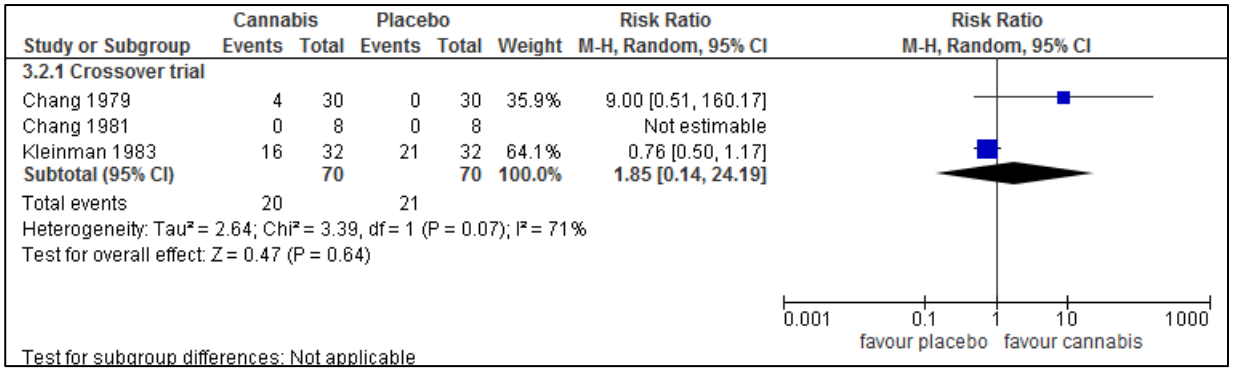
Figure 13. Cannabis vs placebo patients receiving chemotherapy, outcome: 3.1 Control of nausea and vomiting



Control of vomiting

The effects were uncertain. Three crossover studies[186-188] involving 70 patients, RR 1.85 (95% CI 0.14 to 24.19) had very low confidence in estimates, see figure 14.

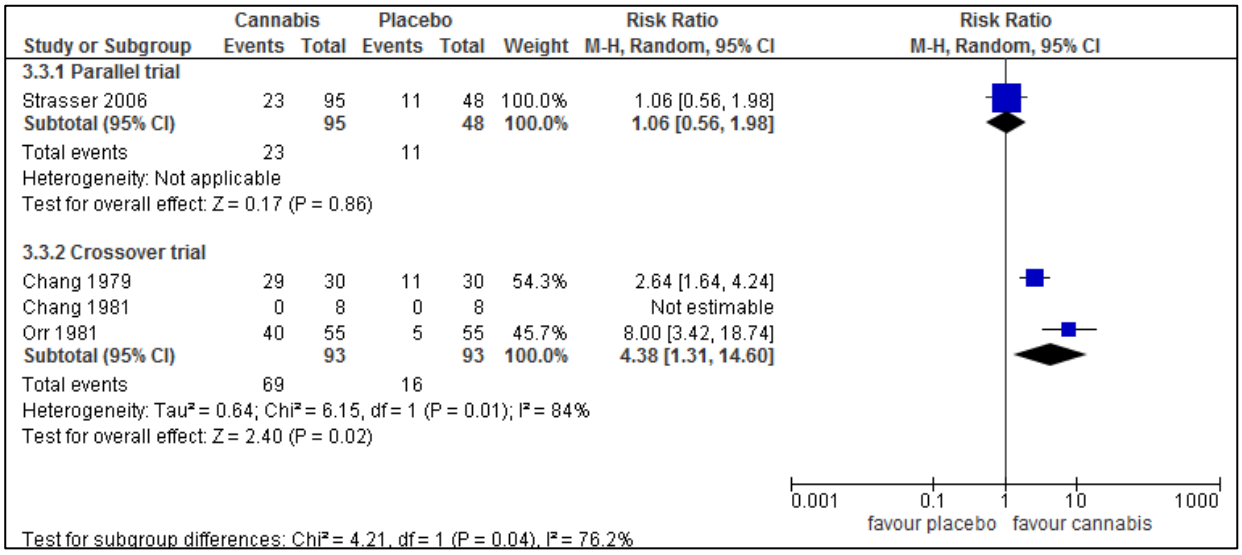
Figure 14. Cannabis vs placebo patients receiving chemotherapy, outcome: 3.2 Control of vomiting.



Control of nausea

Results for control of nausea were uncertain in one parallel trial[185], 23 patients RR 1.06 (95% CI 0.56 to 1.98) and in favour of cannabis in three crossover trials[186,187, 192], 93 patients, RR 4.38 (95% CI 1.31 to 14.60). There was a very low confidence in estimates for both studies, see figure 15.

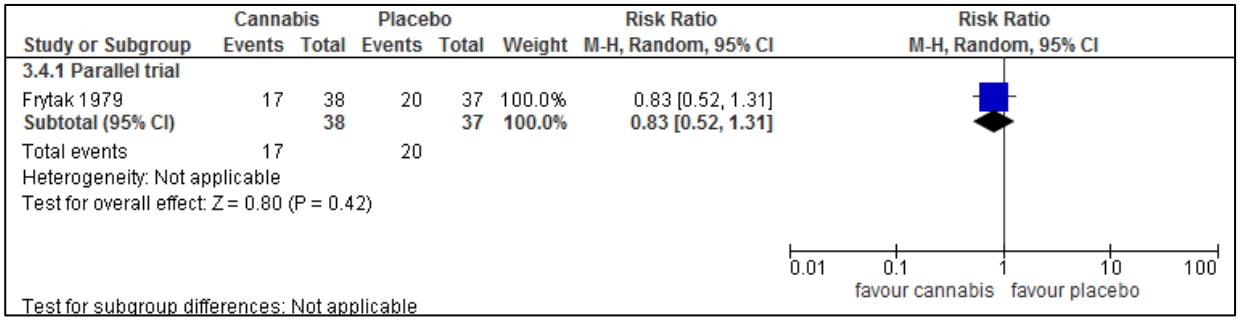
Figure 15. Cannabis vs placebo patients receiving chemotherapy, outcome: 3.3 Control of nausea.



Repeated vomiting

Only a single study[183] comprised of 75 patients considered this outcome: RR 0.83 (95% CI 0.52 to 1.31), and had a very low confidence in estimates, see figure 16.

Figure 16. Cannabis vs placebo patients receiving chemotherapy, outcome: 3.4 Repeated vomiting



For the overall certainty of evidence, see Summary of findings table 3.

Summary of findings 3: Cannabis compared to placebo for patients receiving chemotherapy, efficacy outcomes

Patient or population: Patients with cancer receiving chemotherapy
Setting: Inpatient and outpatient
Intervention: Cannabis
Comparison: Placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	**Risk with Cannabis**				
Control of nausea and vomiting - Parallel group	196 per 1.000	456 per 1.000 (235 to 890)	RR 2.33 (1.20 to 4.55)	91 (2 RCTs)	⨁◯◯◯ VERY LOW [1,2]	In favour of cannabis
Control of nausea and vomiting - Crossover trial	273 per 1.000	865 per 1.000 (428 to 1.000)	RR 3.17 (1.57 to 6.39)	22 (1 RCT)	⨁◯◯◯ VERY LOW [2,3]	In favour of cannabis
Control of vomiting - Crossover trial	300 per 1.000	555 per 1.000 (42 to 1.000)	RR 1.85 (0.14 to 24.19)	70 (3 RCTs)	⨁◯◯◯ VERY LOW [2,4,5]	uncertain result
Control of nausea - Parallel trial	229 per 1.000	243 per 1.000 (128 to 454)	RR 1.06 (0.56 to 1.98)	143 (1 RCT)	⨁◯◯◯ VERY LOW [2,3]	uncertain result
Control of nausea - Crossover trial	172 per 1.000	754 per 1.000 (225 to 1.000)	RR 4.38 (1.31 to 14.60)	93 (3 RCTs)	⨁◯◯◯ VERY LOW [2,4,6]	In favour of cannabis
Repeated vomiting - Parallel trial	541 per 1.000	449 per 1.000 (281 to 708)	RR 0.83 (0.52 to 1.31)	75 (1 RCT)	⨁◯◯◯ VERY LOW [2,7]	uncertain result

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

1. high risk of detection bias in two studies
2. Optimal Information Size (OIS) not met
3. high risk of attrition bias
4. high risk of detection bias in one study and of attrition bias in another study
5. high heterogeneity: I square 71%
6. high heterogeneity: I square 84%
7. high risk of detection bias

Narrative results

In a crossover placebo trial[189] of 11 patients, the authors investigated whether THC orally administered could be useful and acceptable to patients receiving chemotherapy. The authors reported that two patients dropped out, but did not report to which treatment group they were assigned. A five-point scale,

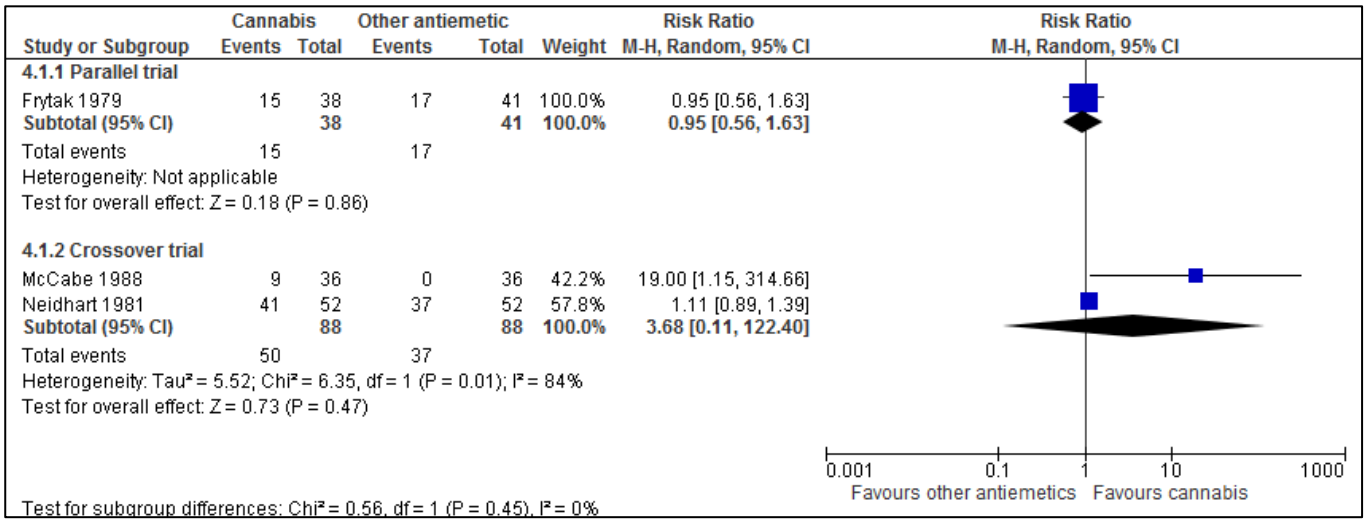
ranging from one (no improvement) to five (complete improvement) expressed the intensity of vomiting and nausea. The mean score of placebo on day one and day eight was 1.09 and 1.67 respectively. On the same days, the mean scores for THC were 2.27 and 3.93. The differences were both significant (p<0.01). The authors reported that most patients in the THC group complained of dizziness, somnolence, concentration weakness, feeling of depersonalization and derealisation.

Comparison 2. Cannabis vs antiemetic drugs in patients receiving chemotherapy

Control of nausea and vomiting

Comparing cannabis with other antiemetic drugs, no evidence of a difference was found in one parallel trial[183] , 79 patients, RR 0.95 (95% CI 0.56 to 1.63) and two crossover studies[190,191], 88 patients, RR 3.68 (95% CI 0.11 to 122.40), and had a very low confidence in estimates for both comparisons, see figure 17.

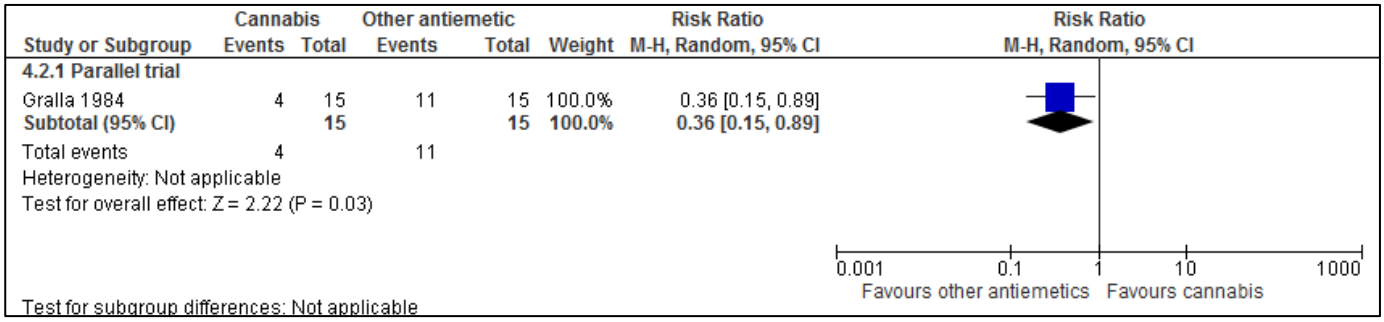
Figure 17. Cannabis vs antiemetic drugs patients receiving chemotherapy, outcome: 4.1



Control of vomiting

Results from one parallel trial[184] of 30 participants were in favour of metoclopramide RR 0.36 (95% CI 0.15 to 0.89), but with a low confidence in estimates, see figure 18.

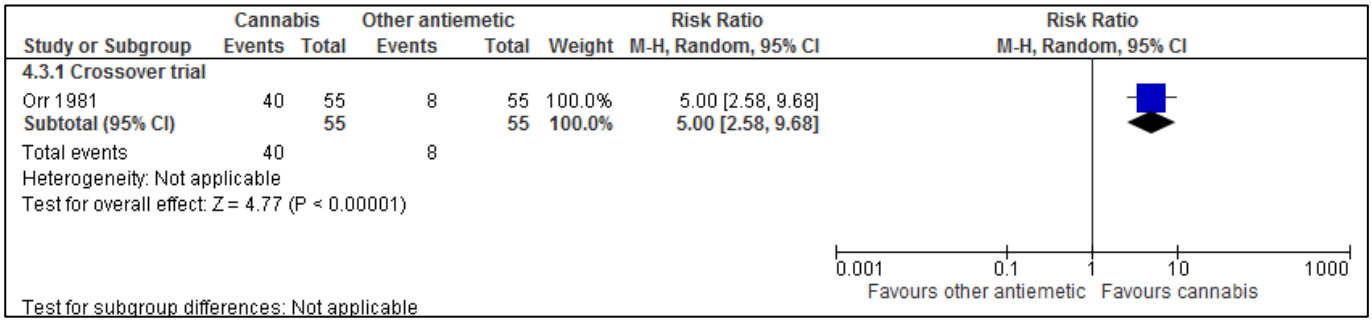
Figure 18. Cannabis vs antiemetic drugs patients receiving chemotherapy, outcome: 4.2 Control of vomiting.



Control of nausea

Results from a single crossover study[192] with 55 participants showed a better effect of cannabis compared to prochlorperazine, RR 5.00 (95% CI 2.58 to 9.68), but with a very low confidence in estimates, see figure 19.

Figure 19. Cannabis vs antiemetic drugs patients receiving chemotherapy, outcome: 4.3 Control of nausea.



For the overall certainty of evidence, see Summary of findings 4.

Summary of findings 4: Cannabis compared to antiemetic drugs for patients receiving chemotherapy

Patient or population: Patients with cancer receiving chemotherapy
Setting: Inpatient and outpatient
Intervention: Cannabis
Comparison: Antiemetic drugs

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with antiemetic drugs	**Risk with Cannabis**				
Control of nausea and vomiting - Parallel trial	415 per 1.000	394 per 1.000 (232 to 676)	RR 0.95 (0.56 to 1.63)	79 (1 RCT)	⊕◯◯◯ VERY LOW [1,2]	uncertain result
Control of nausea and vomiting - Crossover trial	420 per 1.000	1000 per 1.000 (46 to 1.000)	RR 3.68 (0.11 to 122.40)	176 (2 RCTs)	⊕◯◯◯ VERY LOW [2,4]	uncertain result
Control of vomiting - Parallel trial	733 per 1.000	264 per 1.000 (110 to 653)	RR 0.36 (0.15 to 0.89)	30 (1 RCT)	⊕⊕◯◯ LOW [2,3]	
Control of nausea - Crossover trial	145 per 1.000	727 per 1.000 (375 to 1.000)	RR 5.00 (2.58 to 9.68)	110 (1 RCT)	⊕◯◯◯ VERY LOW [2,4]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

1. one study at high risk of detection bias
2. Optimal Information Size (OIS) not met
3. high heterogeneity: I square 84%
4. high risk of attrition bias

Narrative results

It was not possible to pool data from the other two crossover studies[194, 195] that compared cannabis with prochlorperazine.

Sallan 1980, in a randomized, double blind, crossover trial (included 84 patients) investigated if THC is an effective antiemetic as compared with prochlorperazine. Only 38 of the 84 patients randomized completed the three assigned courses of treatment. The authors reported that there were more complete responses (defined as no nausea or vomiting after chemotherapy) to the THC treatment course than to prochlorperazine (in 16/78 courses). Increased food intake occurred more frequently with THC (p = 0.008) and it was associated with the presence of a "high".

Ungerleider 1982, in a randomized, double blind, crossover trial (included 214 patients) aimed to assess the relative efficacy of THC and prochlorperazine in alleviating nausea and vomiting associated with cancer

chemotherapy. Additional parameters evaluated were effects on appetite, food intake, mood, activity, relaxation, interaction, and concentration. Results showed that THC was associated with significant nausea reduction ($P < 0.05$), while no significant differences between the two drugs were found in the level of food intake or appetite. There were significant drug effects with THC that included less ability to concentrate ($P < 0.01$), less social interaction ($P < 0.05$), and less activity ($P < 0.05$). These drug-related effects associated with THC did not reduce the patients' preference for the drug.

Safety outcomes parallel trials all patients

Considering the parallel trials, adverse effects were obtained with cannabis for the following effects: Dizziness, 14 trials, 2712 patients, high confidence in estimate of evidence; Somnolence, 10 studies, 2178 patients, high confidence in estimate of evidence; Gastrointestinal disorders, 10 studies, 1909 patients, moderate confidence in estimate of evidence; Dry mouth, 9 studies, 1982 patients, and moderate confidence in estimate of evidence; Fatigue, 7 studies, 1489 patients, moderate confidence in estimate of evidence; Disorientation, 5 studies, 942 patients, moderate confidence in estimate of evidence; Disturbance in attention, 4 studies, 754 patients, low confidence in estimate of evidence; Vision blurred, 4 studies, 1063 patients, moderate confidence in estimate of evidence; Vertigo, 4 studies, 957 patients, moderate confidence in estimate of evidence; Dysgeusia, 3 studies, 774 patients, low confidence in estimate of evidence; General psychiatric disorder, 3 studies, 764 patients, moderate confidence in estimate of evidence; Asthenia, 3 studies, 735 patients, low confidence in estimate of evidence; Dissociation, 2 studies, 499 patients, low confidence in estimate of evidence. Furthermore, studies considering the safety of cannabis for patients with multiple sclerosis and chronic neuropathic pain, found results that are more favourable with vehicle for nausea involving 11 studies and 1928 patients, and with a high confidence in estimate of evidence.

There were no significant differences between cannabis and placebo for the other adverse events reported including headache, feeling high, renal and urinary disorders, CNS side effects, weakness, musculoskeletal and connective disorders, withdrawal for any reason, depression, respiratory disorders, mouth ulceration, application site discomfort, confusion, and vomiting in patients with MS or chronic pain (see Figures 20-46 in Appendix 6). For the overall confidence in estimates, see Summary of findings 5.

Summary of findings 5: Cannabis parallel trial compared to placebo parallel trial for MS, Chronic pain, cancer receiving chemotherapy

Patient or population: MS, Chronic pain, cancer receiving chemotherapy
Setting: outpatient
Intervention: Cannabis including extracts and tinctures parallel trial
Comparison: placebo parallel trial

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo parallel trial	**Risk with Cannabis parallel trial**				
Dizziness	114 per 1.000	**375 per 1.000** (292 to 482)	**RR 3.28** (2.55 to 4.21)	2712 (14 RCTs)	⊕⊕⊕⊕ HIGH	In favour of placebo
Somnolence	107 per 1.000	**305 per 1.000** (164 to 566)	**RR 2.85** (1.53 to 5.29)	2178 (10 RCTs)	⊕⊕⊕⊕ HIGH	In favour of placebo
Headache	80 per 1.000	**78 per 1.000** (57 to 107)	**RR 0.97** (0.71 to 1.34)	1776 (10 RCTs)	⊕⊕⊕◯ MODERATE [1]	Uncertain results
Gastrointestinal disorders	65 per 1.000	**87 per 1.000** (67 to 115)	**RR 1.34** (1.03 to 1.76)	1909 (10 RCTs)	⊕⊕⊕◯ MODERATE [1]	In favour of placebo
Dry mouth	60 per 1.000	**127 per 1.000** (86 to 189)	**RR 2.13** (1.44 to 3.17)	1982 (9 RCTs)	⊕⊕⊕◯ MODERATE [1]	In favour of placebo
Feeling high	13 per 1.000	**36 per 1.000** (13 to 100)	**RR 2.65** (0.94 to 7.45)	1252 (7 RCTs)	⊕⊕⊕◯ MODERATE [1]	Uncertain results
Renal and urinary disorders	67 per 1.000	**77 per 1.000** (48 to 123)	**RR 1.15** (0.72 to 1.84)	1779 (7 RCTs)	⊕⊕⊕◯ MODERATE [1]	Uncertain results
Fatigue	84 per 1.000	**145 per 1.000** (108 to 194)	**RR 1.72** (1.28 to 2.30)	1489 (7 RCTs)	⊕⊕⊕◯ MODERATE [1]	In favour of placebo
CNS side effects	191 per 1.000	**329 per 1.000** (184 to 590)	**RR 1.72** (0.96 to 3.08)	661 (5 RCTs)	⊕◯◯◯ VERY LOW [1,2,3]	Uncertain results
Disorientation	5 per 1.000	**19 per 1.000** (6 to 60)	**RR 4.25** (1.36 to 13.34)	942 (5 RCTs)	⊕⊕⊕◯ MODERATE [1]	In favour of placebo
Disturbance in attention	3 per 1.000	**19 per 1.000** (5 to 72)	**RR 6.72** (1.80 to 25.02)	754 (4 RCTs)	⊕⊕◯◯ LOW [1]	In favour of placebo
Weakness	148 per 1.000	**192 per 1.000** (142 to 259)	**RR 1.30** (0.96 to 1.75)	804 (4 RCTs)	⊕⊕⊕◯ MODERATE [1]	Uncertain results
Vision blurred	20 per 1.000	**45 per 1.000** (22 to 93)	**RR 2.28** (1.11 to 4.66)	1063 (4 RCTs)	⊕⊕⊕◯ MODERATE [1]	In favour of placebo
Musculoskeletal and connective disorders	80 per 1.000	**95 per 1.000** (65 to 139)	**RR 1.19** (0.81 to 1.74)	1103 (4 RCTs)	⊕⊕⊕◯ MODERATE [1]	Uncertain results
Vertigo	27 per 1.000	**82 per 1.000** (45 to 149)	**RR 3.04** (1.68 to 5.50)	957 (4 RCTs)	⊕⊕⊕◯ MODERATE [1]	In favour of placebo
Withdrawal for any reason	55 per 1.000	**110 per 1.000** (7 to 1.000)	**RR 2.01** (0.13 to 30.45)	149 (3 RCTs)	⊕◯◯◯ VERY LOW [1,2,4]	Uncertain results
Dysgeusia (bad taste)	11 per 1.000	**58 per 1.000** (20 to 165)	**RR 5.14** (1.81 to 14.60)	774 (3 RCTs)	⊕⊕◯◯ LOW [1]	In favour of placebo

Summary of findings 5: *continued*

Patient or population: MS, Chronic pain, cancer receiving chemotherapy
Setting: outpatient
Intervention: Cannabis including extracts and tinctures parallel trial
Comparison: placebo parallel trial

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo parallel trial	**Risk with Cannabis parallel trial**				
Depression	5 per 1.000	**15 per 1.000** (4 to 57)	**RR 3.12** (0.84 to 11.56)	865 (3 RCTs)	⊕⊕◯◯ LOW [1]	Uncertain results
Respiratory disorders	75 per 1.000	**63 per 1.000** (34 to 117)	**RR 0.84** (0.45 to 1.57)	493 (3 RCTs)	⊕⊕◯◯ LOW [1]	Uncertain results
General psychiatric disorders	32 per 1.000	**95 per 1.000** (53 to 173)	**RR 3.00** (1.66 to 5.45)	764 (3 RCTs)	⊕⊕⊕◯ MODERATE [1]	In favour of placebo
Mouth ulceration	12 per 1.000	**23 per 1.000** (5 to 111)	**RR 2.00** (0.42 to 9.51)	347 (3 RCTs)	⊕⊕◯◯ LOW [1]	Uncertain results
Application site discomfort	111 per 1.000	**128 per 1.000** (76 to 218)	**RR 1.15** (0.68 to 1.96)	347 (3 RCTs)	⊕⊕◯◯ LOW [1]	Uncertain results
Asthenia	66 per 1.000	**140 per 1.000** (89 to 221)	**RR 2.12** (1.35 to 3.34)	735 (3 RCTs)	⊕⊕◯◯ LOW [1]	In favour of placebo
Dissociation	24 per 1.000	**70 per 1.000** (29 to 169)	**RR 2.95** (1.22 to 7.10)	499 (2 RCTs)	⊕⊕◯◯ LOW [1]	In favour of placebo
Confusion	9 per 1.000	**19 per 1.000** (5 to 75)	**RR 2.19** (0.55 to 8.79)	526 (2 RCTs)	⊕⊕◯◯ LOW [1]	Uncertain results
Nausea in patients with MS and chronic pain	73 per 1.000	**144 per 1.000** (109 to 189)	**RR 1.97** (1.49 to 2.59)	1928 (11 RCTs)	⊕⊕⊕⊕ HIGH	In favour of placebo
Vomiting in patients with MS or chronic pain	51 per 1.000	**74 per 1.000** (34 to 162)	**RR 1.45** (0.66 to 3.18)	1156 (8 RCTs)	⊕⊕⊕⊕ HIGH	Uncertain results

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Optimal Information Size (OIS) not met
2. two studies at high risk of detection and one at high risk of attrition bias
3. high heterogeneity; I square 72%
4. No explanation was provided

Safety outcomes crossover trials all patients

Adverse events were reported for cannabis for the following effects: Feeling high, seven trials, 173 patients, and moderate certainty of evidence; Dizziness, five studies, 160 patients, low certainty of evidence; General psychiatric disorder, two studies, 46 patients, with a low certainty of evidence; Cannabis improved disgeusia, two studies involving 71 patients, but with a low certainty of evidence. Furthermore, studies considering the safety of cannabis for patients with multiple sclerosis and chronic neuropathic pain found results in favour of placebo for nausea, 11 studies, 1903 patients, and high certainty of evidence.

There were no significant differences between cannabis and placebo for the other adverse events reported including headache, somnolence, withdrawal for any reason, depression, gastrointestinal disorders, dry mouth, dysphoria, fatigue, and nausea, in those patients with multiple sclerosis and with chronic pain. See Figures 47-59 in **Appendix 6**. For the overall certainty of evidence, see Summary of findings 6.

Summary of findings 6: Cannabis including extracts and tinctures crossover trial compared to placebo crossover trials for MS, chronic pain, cancer receiving chemotherapy

Patient or population: MS, chronic pain, cancer receiving chemotherapy
Setting: outpatient
Intervention: Cannabis including extracts and tinctures crossover trials
Comparison: placebo crossover trials

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo crossover trials	**Risk with Cannabis crossover trials**				
Feeling high	81 per 1.000	**208 per 1.000** (95 to 454)	**RR 2.55** (1.17 to 5.58)	442 (8 RCTs)	⊕⊕⊕◯ MODERATE [1]	In favour of cannabis
Dizziness	106 per 1.000	**207 per 1.000** (127 to 338)	**RR 1.96** (1.20 to 3.20)	416 (6 RCTs)	⊕⊕◯◯ LOW [1]	In favour of placebo
Headache	112 per 1.000	**135 per 1.000** (75 to 246)	**RR 1.21** (0.67 to 2.20)	286 (5 RCTs)	⊕⊕◯◯ LOW [1]	Uncertain results
Somnolence	94 per 1.000	**148 per 1.000** (89 to 245)	**RR 1.58** (0.95 to 2.62)	342 (5 RCTs)	⊕⊕◯◯ LOW [1]	Uncertain results
Withdrawal for any reason	80 per 1.000	**23 per 1.000** (5 to 110)	**RR 0.29** (0.06 to 1.38)	176 (3 RCTs)	⊕◯◯◯ VERY LOW [1,2]	Uncertain results
Depression	21 per 1.000	**34 per 1.000** (4 to 262)	**RR 1.59** (0.20 to 12.30)	94 (2 RCTs)	⊕⊕◯◯ LOW [1]	Uncertain results
Gastrointestinal disorders	63 per 1.000	**74 per 1.000** (2 to 1.000)	**RR 1.18** (0.03 to 50.96)	160 (2 RCTs)	⊕◯◯◯ VERY LOW [1,3]	Uncertain results
Dry mouth	0 per 1.000	**0 per 1.000** (0 to 0)	**RR 7.61** (0.97 to 59.70)	148 (2 RCTs)	⊕⊕◯◯ LOW [1]	Uncertain results
Dysgeusia (bad taste)	28 per 1.000	**64 per 1.000** (2 to 1.000)	**RR 2.28** (0.08 to 62.76)	142 (2 RCTs)	⊕⊕◯◯ LOW [1]	Uncertain results
General psychiatric disorders	43 per 1.000	**345 per 1.000** (83 to 1.000)	**RR 7.94** (1.92 to 32.87)	92 (2 RCTs)	⊕⊕◯◯ LOW [1]	In favour of placebo
Dysphoria	0 per 1.000	**0 per 1.000** (0 to 0)	**RR 9.00** (0.51 to 160.17)	76 (2 RCTs)	⊕◯◯◯ VERY LOW [1,4]	Uncertain results
Fatigue	106 per 1.000	**266 per 1.000** (104 to 681)	**RR 2.50** (0.98 to 6.40)	94 (2 RCTs)	⊕⊕◯◯ LOW [1]	Uncertain results
Nausea for patients with MS or chronic pain	38 per 1.000	**84 per 1.000** (32 to 218)	**RR 2.21** (0.85 to 5.74)	316 (4 RCTs)	⊕⊕⊕⊕ HIGH	Uncertain results

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. Optimal Information Size (OIS) not met
2. high risk of attrition in one study and of detection bias in another study
3. high heterogeneity; I square 78%
4. one study at high risk of detection bias

Safety outcomes cannabis versus other antiemetic drugs in patients with cancer receiving chemotherapy

For this comparison, it was possible to pool data only for withdrawal, two parallel trials involving 110 patients, and that had a very low certainty of evidence and with no differences between the two treatments. For feeling high there were two parallel trials, 110 patients, and a low certainty of evidence and results in favour of placebo.

See Figures 60-61 in Appendix 6. For the overall confidence in estimates, see Summary of findings 7.

Summary of findings 7: Side effects Cannabis including extracts and tinctures compared to other antiemetic drugs for patients with cancer receiving chemotherapy

Patient or population: patients with cancer receiving chemotherapy
Setting: inpatient and outpatient
Intervention: Cannabis including extracts and tinctures
Comparison: other antiemetic drugs

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with other antiemetic drugs	Risk with Side effects Cannabis				
Feeling high	229 per 1.000	**612 per 1.000** (170 to 1.000)	**RR 2.67** (0.74 to 9.65)	214 (3 RCTs)	⨁⨁◯◯ LOW [1,3]	Uncertain results
Withdrawal for any reason - Parallel trial	35 per 1.000	**93 per 1.000** (3 to 1.000)	**RR 2.64** (0.08 to 89.05)	110 (2 RCTs)	⨁◯◯◯ VERY LOW [1,2,3]	Uncertain results

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1. one study at high risk of detection bias
2. high heterogeneity: I square 73%
3. Optimal Information Size (OIS) not met

Synthesis of the main results

In regards to the clinical effectiveness and safety of cannabis in patients with multiple sclerosis: For spasticity, different results were observed according to the scale utilized to assess the outcome. In comparison with placebo using the Ashworth scale (five parallel trials, 1216 patients), no differences were observed: MD -0.1 (95%CI - 0.26 to 0.07); while, using the NRS scale (three parallel trials, 860 patients), results were in favour of cannabis: MD -0.28 (95%CI -0.52 to -0.03). There was a high confidence in estimate of evidence for both comparisons. In the same comparison, cannabis does not improve sleep quality measured with the NRS scale (2 parallel trials, 676 patients): MD 0.40 (95% CI -0.30 to 1.09), moderate confidence in estimate of evidence.

In regards to the clinical effectiveness and safety of cannabis in patients with chronic and neuropathic pain: We found mixed results in the comparison with placebo. For pain intensity, results of two crossover trials, 71 patients, were in favour of cannabis: MD -0.78 (95% CI -1.17 to -0.39), low confidence in estimate of evidence. For pain disability index results coming from one crossover study (48 patients), showed no difference: MD -2.00 (95%CI -4.32 to 0.32) while results coming from one parallel trial (125 patients) were in favour of cannabis: MD -5.85 (95% CI -9.60 to -2.10), low confidence in estimate of evidence for both comparisons. For minimum pain score, results of two crossover studies (39 patients), showed no difference between cannabis and placebo: SMD -0.36 (95% CI -0.80 to 0.09), low confidence in estimate of evidence. For the reduction of more than 30% in neuropathic pain, results showed no difference if we consider four parallel trials, (455 patients): MD 1.39 (95% CI 0.92 to 2.09); while results coming from three crossover studies, (93 patients), were in favour of cannabis: MD 1.65 (95% CI 1.01 to 2.70), moderate confidence in estimate of evidence for both comparisons.

In regards to clinical effectiveness and safety of cannabis for reducing tics and obsessive-compulsive symptoms in patients with dementia or Gilles de la Tourette syndrome: Based on only two studies, with overall 36 patients, comparing THC with placebo to treat the symptoms of Tourette's syndrome, it is impossible to draw any reliable conclusion.

In regards to clinical effectiveness and safety of cannabis for reducing morbidity and mortality in patients with HIV/AIDS: No evidence was available from studies fulfilling the criteria for selection.

In regards to clinical effectiveness and safety of cannabis for reducing nausea and vomiting in adults with cancer receiving chemotherapy: We had two comparisons, cannabis versus placebo and cannabis versus other antiemetics. In the comparison with placebo, for controlling nausea and vomiting considered

together, cannabis performed better, results from two parallel trials (91 patients): RR 2.33 (95% CI 1.20 to 4.55) and one crossover (22 patients): RR 3.17 (95% CI 1.57 to 6.39). No differences were found for control of vomiting, 3 crossover trials, 70 patients: RR 1.85 (95% CI 0.14 to 24.19; and repeated vomiting (one parallel trial, 75 patients). Very low confidence in estimate of evidence for all. For control of nausea alone, no difference was observed in one parallel trial, 143 patients: RR 1.06 (95% CI 0.56 to 1.98); while results from three crossover studies, (93 patients), were in favour of cannabis: RR 4.38 (95% CI 1.31 to 14.60). Very low confidence in estimate of evidence for all the comparisons. In the comparison with other antiemetic drugs, if nausea and vomiting were considered together, results of one parallel trial (79 patients) RR 0.95 (95% CI 0.56 to 1.63) and of two crossover studies (88 patients), RR 3.68 (95% CI 0.11 to 122.40), showed no difference between cannabis including extract and tinctures and other antiemetic drugs. There was a very low confidence in the estimate of evidence for both comparisons. Considering control of vomiting, results from one parallel trial (30 patients) were in favour of metoclopramide, RR 0.36 (95% CI 0.15 to 0.89), low confidence in estimate of evidence. Considering control of nausea, results of one crossover trial (55 patients), were in favour of cannabis including extract and tinctures compared with cyclophosphamide, 5-fluorouracil, and doxorubicin: RR 5.00 (95% CI 2.58 to 9.68), very low confidence in estimate of evidence.

In regards to adverse events, the included studies considered many adverse events, the majority of them were of low to moderate gravity. For the most serious adverse events (i.e. CNS side effects, depression and confusion) no differences were observed between cannabis and placebo. Incidence of general psychiatric disorders was higher in the cannabis groups but results came only from two small studies (92 participants). In addition, frequency of dissociation was higher in the cannabis groups, and no studies considered the development of abuse or dependence. The included studies considered many adverse events; the majority of them were of low to moderate gravity. For the most serious adverse events (i.e. CNS side effects, depression and confusion), no differences were observed between cannabis and placebo. Incidence of general psychiatric disorders was higher in the cannabis groups, but results came only from two small studies (92 participants). In addition, frequency of dissociation was higher in the cannabis groups. No studies considered the development of abuse or dependence.

Discussion

The extent to which a review can draw conclusions about the effects of an intervention depends on whether the data and results from the included studies are valid. Systematic reviews should evaluate and take into account not only the internal validity (i.e. the extent to which systematic errors or bias are

avoided) of each trial, but also their applicability and generalizability, or external validity (i.e. whether the results of a trial can be reasonably applied to a definable group of people in a particular setting in routine practice)[196] . The main challenge to external validity comes from the clinical setting, and the social and cultural context in which the studies were conducted.

Results considered for this review came from 43 RCTs (parallel and crossover) involving 4586 patients whose studies were published between 1975 and 2015. Regarding internal validity, the proportion of trials included in our reviews having a documented low risk of bias was around 50%. Regarding external validity, the majority of studies were conducted in Europe. Fifteen studies considered efficacy and safety of cannabis for patients with multiple sclerosis, 12 for patients with chronic pain, two for patients with Tourette syndrome, and 14 for patients with cancer receiving chemotherapy.

The large majority (81%) of the comparisons were with placebo, only eight studies included patients with cancer receiving chemotherapy that compared cannabis with other antiemetic drugs. The number of included participants varied among the studies, but in general, sample sizes did not meet the Optimal Information Size (OIS). This means that the total number of patients included in the comparisons were less than the number of patients generated by a conventional sample size calculation for a single adequately powered trial. Finally, 14/44 trials had an industrial sponsor or authors declared to be dependent upon the pharmaceutical producer of the study drug. This possible source of bias must be considered.

Concerning the efficacy of cannabis (compared with placebo) in patients with MS, confidence in the estimate was high in favour of cannabis for spasticity (NRS scale and VAS but not the Ashworth scale) and pain (albeit with only two studies with results reported in a way that allowed statistical synthesis), but not for sleep, confidence in estimate moderate.

In the comparison with placebo for chronic and neuropathic pain, there was some evidence of effect, but the effect size was small and confidence in the estimate was low, and these results could not be considered conclusive. This absence of evidence and the absence of particularly effective treatment for neuropathic pain, may leave clinicians the alternative of balancing the possible benefits against the potential adverse effects of cannabis treatment.

For tics and obsessive–compulsive disorder (OCD) symptoms in patients with Tourette's syndrome, there were only two studies, with overall 36 patients and it is impossible to draw any reliable conclusion. More primary research is needed to satisfy the demands of clinicians, patients and their caregivers.

There is uncertainty whether cannabis, including extracts and tinctures, compared with placebo or other antiemetic drugs, reduces nausea and vomiting in patients with cancer requiring chemotherapy, and the confidence in estimate of the effect was low or very low.

Epidemiological studies show that cannabis use may cause significant adverse events such as impairments in memory[7], impairments of motor co-ordination with an associated increased risk of involvements in motor vehicle accidents[8], alterations of judgment, and at high doses, significant psychiatric distress including somatisation, depression, anxiety, irritability, phobic anxiety, paranoid ideation, and psychoticism[5, 197]. Moreover, long-term or heavy use of cannabis has been associated with the development of dependence[5], chronic bronchitis and increased risk of chronic psychosis disorders in persons with a predisposition for development of such disorders[6, 197]. The most frequent psychiatric pathologies associated with cannabis use are bipolar disorder, substance use disorders and specific (antisocial, dependant and histrionic) personality disorders[198]. Furthermore, it has been estimated that some 10% of those who have used cannabis at least once will develop cannabis dependence[198]. Based on a large epidemiological survey in the USA, it has been estimated that among those exposed once to cannabis, 7.0% of males and 5.3% of females will develop cannabis dependence at some point in their life, while 47.4% of males and 32.5% of females will develop cannabis use disorders (abuse or dependence) at some point in their life[199].

In the studies included in our reviews, many adverse events were reported, the majority of them were of low or moderate gravity, but only a minority assessed the risk of serious adverse events such as dissociation, general psychiatric disorders, depression, and confusion. Most importantly, none of the included studies assessed the development of abuse or dependence.

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Appendix 1. Search Strategies

CQ 1: Patient with Multiple sclerosis

The Cochrane Central Register of Controlled Trials (CENTRAL) "The Cochrane Library" (8, 2016);

1. multiple next/2 sclerosis:ti,ab
2. MeSH descriptor: [Multiple Sclerosis] explode all trees
3. "secondary progressive":ti,ab
4. MS:ti,ab
5. #1 OR #2 OR #3 OR #4
6. MeSH descriptor: [Cannabis] explode all trees
7. MeSH descriptor: [Cannabidiol] explode all trees
8. MeSH descriptor: [Cannabinol] explode all trees
9. cannabis:ti,ab OR THC:ti,ab OR CBD:ti,ab OR CBN:ti,ab OR cannabinoid*:ti,ab OR endocannabinoid*:ti,ab cannabidiol :ti,ab OR delta-9-tetrahydrocannabinol:ti,ab OR marihuana:ti,ab OR Marijuana:ti,ab OR hashish:ti,ab OR CBN:ti,ab OR cannabinoid*:ti,ab OR sativex:ti,ab OR nabiximols:ti,ab
10. #6 OR #7 OR #8 OR #9
11. #5 AND #8

Hits:45

Pubmed (25 August 2016)

1. "Multiple Sclerosis+" [mesh]
2. "multiple sclerosis" [title/abstract]
3. "secondary progressive" [title/abstract]
4. MS [title abstract]
5. #1 OR #2 OR #3 OR #4
6. "Cannabis" [mesh]
7. "Cannabidiol"[Mesh]
8. "Cannabinol"[Mesh]
9. cannabis[title/abstract] OR THC[title/abstract] OR CBD [title/abstract] CBN [title/abstract] OR cannabinoid*[Title/Abstract] OR sativex[title/abstract] OR nabiximols [title/abstract] OR endocannabinoid* [title/abstract] OR cannabidiol[title/abstract] OR delta-9-tetrahydrocannabinol[title/abstract] OR marihuana [title/abstract] OR Marijuana [title/abstract] OR hashish [title/abstract]
10. #6 or #7 or #8 or #9
11. (animals[MeSH Terms]) NOT humans[MeSH Terms]
12. #5 AND #8
12. #10 NOT #9

Hits:737

Embase.com (8th September 2016)

'cannabis'/exp/mj OR cannabinoid*:ab,ti OR endocannabinoid*:ab,ti OR cannabidiol:ab,ti OR sativex:ti,ab OR nabiximols:ti,ab OR 'delta-9-tetrahydrocannabinol':ab,ti OR marihuana:ab,ti OR marijuana:ab,ti OR hashish:ab,ti AND ('multiple sclerosis'/exp OR 'multiple sclerosis':ab,ti) AND [humans]/lim

Hits: 828

CQ 2. Patients with chronic pain

The Cochrane Central Register of Controlled Trials (CENTRAL) "The Cochrane Library" (8, 2016);

1. MESH descriptor PAIN explode all trees
2. (pain* or discomfort* or analgesi*):ti,ab,kw
3. #1 OR #2 OR #3 OR #4
4. MeSH descriptor: [Cannabis] explode all trees
5. MeSH descriptor: [Cannabidiol] explode all trees
6. MeSH descriptor: [Cannabinol] explode all trees
7. cannabis:ti,ab OR THC:ti,ab OR CBD:ti,ab OR CBN:ti,ab OR cannabinoid*:ti,ab OR endocannabinoid*:ti,ab cannabidiol :ti,ab OR delta-9-tetrahydrocannabinol:ti,ab OR marihuana:ti,ab OR Marijuana:ti,ab OR hashish:ti,ab OR CBN:ti,ab OR cannabinoid*:ti,ab OR sativex:ti,ab OR nabiximols:ti,ab
8. #4 OR #5 OR #6 OR #7
9. #4 OR #5
10. #3 AND #6

Hits: 1340

Pubmed (25 August 2016)

1. PAIN [mesh]
2. (pain*[Text Word] or discomfort*[Text Word] or analgesi*[Text Word])
3. #1 OR #2
4. "Cannabis" [mesh]
5. "Cannabidiol"[Mesh]
6. "Cannabinol"[Mesh]
7. cannabis[title/abstract] OR THC[title/abstract] OR CBD [title/abstract] CBN [title/abstract] OR cannabinoid*[Title/Abstract] OR sativex[title/abstract] OR nabiximols [title/abstract] OR endocannabinoid* [title/abstract] OR cannabidiol[title/abstract] OR delta-9-tetrahydrocannabinol[title/abstract] OR marihuana [title/abstract] OR Marijuana [title/abstract] OR hashish [title/abstract]
8. #4 OR #5 OR #6 OR #7
9. #3 AND #8
10. (animals[MeSH Terms]) NOT humans[MeSH Terms]
11. #9 NOT #10

Hits: 2353

Embase.com (8th September 2016)

pain*:ab,ti OR discomfort*:ab,ti OR analgesi*:ab,ti OR 'pain'/exp/mj AND ('cannabis'/exp/mj OR cannabinoid*:ab,ti OR endocannabinoid*:ab,ti OR cannabidiol:ab,ti OR sativex:ti,ab OR nabiximols:ti,ab OR 'delta-9-tetrahydrocannabinol':ab,ti OR marihuana:ab,ti OR marijuana:ab,ti OR hashish:ab,ti) AND [humans]/lim

Hits: 2278

CQ 3. Patients with Dementia and Tourette syndrome

The Cochrane Central Register of Controlled Trials (CENTRAL) "The Cochrane Library" (8, 2016);

1. (dement* OR Alzheimer* OR vascular dementia OR "vascular cognitive impairment" OR multi-infarct*):ti,ab,kw
2. (lewy* AND bod*): :ti,ab,kw
3. delir*

4. MeSH descriptor: [Alzheimer Disease] explode all trees
5. MeSH descriptor: [Dementia, Vascular] explode all trees
6. MeSH descriptor: [Dementia] this term only
7. #1 or #2 or #3 or #4 or #5 or #6
8. MeSH descriptor: [Cannabis] explode all trees
9. MeSH descriptor: [Cannabidiol] explode all trees
10. MeSH descriptor: [Cannabinol] explode all trees
11. cannabis:ti,ab OR THC:ti,ab OR CBD:ti,ab OR CBN:ti,ab OR cannabinoid*:ti,ab OR endocannabinoid*:ti,ab cannabidiol :ti,ab OR delta-9-tetrahydrocannabinol:ti,ab OR marihuana:ti,ab OR Marijuana:ti,ab OR hashish:ti,ab OR CBN:ti,ab OR cannabinoid*:ti,ab OR sativex:ti,ab OR nabiximols:ti,ab
12. #8 OR #9 OR #10 OR #11
13. #7 AND #12

Hits: 18

Pubmed (25 August 2016)

1. dement*[title/abstract]
2. “vascular cognitive impairment” [Title/Abstract]
3. “multi-infarct*” [Title/Abstract]
4. dementia[mesh]
5. "Tourette Syndrome"[Mesh]
6. tourette[Title/Abstract]
7. (Gilles[Title/Abstract]) AND Tourette[Title/Abstract]
8. #1 OR #2 OR #3 OR #4 OR #5 OR #6 or 7
9. "Cannabis" [mesh]
10. "Cannabidiol"[Mesh]
11. "Cannabinol"[Mesh]
12. cannabis[title/abstract] OR THC[title/abstract] OR CBD [title/abstract] CBN [title/abstract] OR cannabinoid*[Title/Abstract] OR sativex[title/abstract] OR nabiximols [title/abstract] OR endocannabinoid* [title/abstract] OR cannabidiol[title/abstract] OR delta-9-tetrahydrocannabinol[title/abstract] OR marihuana [title/abstract] OR Marijuana [title/abstract] OR hashish [title/abstract]
13. #9 OR #10 OR #11 OR #12
14. #8 and #13
15. (animals[MeSH Terms]) NOT humans[MeSH Terms]
16. #14 NOT #15

Hits: 512

Embase.com (8th September 2016)

'cannabis'/exp/mj OR thc:ab,ti OR cbd:ab,ti OR cannabinoid*:ab,ti OR endocannabinoid*:ab,ti OR cannabidiol:ab,ti OR sativex:ti,ab OR nabiximols:ti,ab OR 'delta-9-tetrahydrocannabinol':ab,ti OR marihuana:ab,ti OR marijuana:ab,ti OR hashish:ab,ti AND ('dementia'/exp/mj OR dement*:ab,ti OR 'gilles de la Tourette syndrome'/exp OR 'vascular cognitive impairment') AND [humans]/lim

Hits: 745

CQ 4: patients with HIV/AIDS

The Cochrane Central Register of Controlled Trials (CENTRAL) “The Cochrane Library” (8, 2016);

1. MeSH descriptor: [HIV Infections] explode all trees
2. MeSH descriptor: [HIV] explode all trees
3. hiv-1*:ti,ab
4. hiv*:ti,ab

5. HIV INFECT*:ti,ab
6. HUMAN NEAR/3 VIRUS:ti,ab
7. ACQUIRED NEAR/3 SYNDROME:ti,ab
8. MeSH descriptor Lymphoma, AIDS-Related, this term only
9. MeSH descriptor Sexually Transmitted Diseases, Viral, this term only
10. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
11. MeSH descriptor: [Cannabis] explode all trees
12. MeSH descriptor: [Cannabidiol] explode all trees
13. MeSH descriptor: [Cannabinol] explode all trees
14. cannabis:ti,ab OR THC:ti,ab OR CBD:ti,ab OR CBN:ti,ab OR cannabinoid*:ti,ab OR endocannabinoid*:ti,ab cannabidiol :ti,ab OR delta-9-tetrahydrocannabinol:ti,ab OR marihuana:ti,ab OR Marijuana:ti,ab OR hashish:ti,ab OR cannabinoid*:ti,ab OR sativex:ti,ab OR nabiximols:ti,ab
15. #7 OR #8 OR #9 OR #10
16. #6 AND #9

Hits:70

Pubmed (25 August 2016)

1. HIV Infections[MeSH]
2. HIV[MeSH]
3. hiv[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw]
4. "sexually transmitted diseases, viral"[MESH:NoExp]
5. #1 OR #2 OR #3 OR #4
6. "Cannabis" [mesh]
7. "Cannabidiol"[Mesh]
8. "Cannabinol"[Mesh]
9. cannabis[title/abstract] OR THC[title/abstract] OR CBD [title/abstract] CBN [title/abstract] OR cannabinoid*[Title/Abstract] OR sativex[title/abstract] OR nabiximols [title/abstract] OR endocannabinoid* [title/abstract] OR cannabidiol[title/abstract] OR delta-9-tetrahydrocannabinol[title/abstract] OR marihuana [title/abstract] OR Marijuana [title/abstract] OR hashish [title/abstract]
10. #5 OR #6 OR #7 OR #8
11. #4 AND #9
12. (animals[MeSH Terms]) NOT humans[MeSH Terms]
13. #10 NOT #11

HITS:994

Embase.com (8th September 2016)

'cannabis'/exp/mj OR thc:ab,ti OR cbd:ab,ti OR cannabinoid*:ab,ti OR endocannabinoid*:ab,ti OR cannabidiol:ab,ti OR sativex:ti,ab OR nabiximols:ti,ab OR 'delta-9-tetrahydrocannabinol':ab,ti OR marihuana:ab,ti OR marijuana:ab,ti OR hashish:ab,ti AND ('human immunodeficiency virus'/exp/mj OR hiv:ab,ti OR 'human immunodeficiency virus':ab,ti OR 'human immunedeficiency virus':ab,ti OR 'human immuno-deficiency virus':ab,ti OR 'human immune-deficiency virus':ab,ti OR 'acquired immunodeficiency syndrome':ab,ti OR 'acquired immunedeficiency syndrome':ab,ti OR 'acquired immuno-deficiency syndrome':ab,ti OR 'acquired immune-deficiency syndrome':ab,ti) AND [humans]/lim

Hits: 879

CQ5: adults with cancer receiving chemotherapy

The Cochrane Central Register of Controlled Trials (CENTRAL) "The Cochrane Library" (8, 2016);

1. MeSH descriptor: [Antineoplastic Agents] explode all trees
2. MeSH descriptor: [Antineoplastic Combined Chemotherapy Protocols] explode all trees
3. chemotherap*
4. #1 or #2 or #3
5. MeSH descriptor: [Nausea] explode all trees
6. MeSH descriptor: [Vomiting] explode all trees
7. nause*:ti,ab or vomit*:ti,ab
8. emesis*:ti,ab or emetic*:ti,ab or antiemetic*:ti,ab or emetogenic*:ti,ab
9. #5 or #6 or #7 or #8
10. MeSH descriptor: [Cannabis] explode all trees
11. MeSH descriptor: [Cannabidiol] explode all trees
12. MeSH descriptor: [Cannabinol] explode all trees
13. cannabis:ti,ab OR THC:ti,ab OR CBD:ti,ab OR CBN:ti,ab OR cannabinoid*:ti,ab OR endocannabinoid*:ti,ab cannabidiol :ti,ab OR delta-9-tetrahydrocannabinol:ti,ab OR marihuana:ti,ab OR Marijuana:ti,ab OR hashish:ti,ab OR cannabinoid*:ti,ab OR sativex:ti,ab OR nabiximols:ti,ab
14. #10 OR #11 OR #12 OR #13
15. #4 AND #9 AND #14

Hits:81

Pubmed (25 August 2016)

1. "Drug Therapy"[Mesh]
2. "Antineoplastic Agents"[Mesh]
3. chemotherap*[text word]
4. #1 or #2 or #3
5. nause*[title/abstract] OR vomit* [title/abstract]
6. "Vomiting"[Mesh]
7. "Nausea"[Mesh]
8. emesis*[title/abstract] or emetic*[title/abstract] or antiemetic*[title/abstract] or emetogenic*[title/abstract]
9. #5 OR #6 OR#7 OR #8
10. "Cannabis" [mesh]
11. "Cannabidiol"[Mesh]
12. "Cannabinol"[Mesh]
13. cannabis[title/abstract] OR THC[title/abstract] OR CBD [title/abstract] CBN [title/abstract] OR cannabinoid*[Title/Abstract] OR sativex[title/abstract] OR nabiximols [title/abstract] OR endocannabinoid* [title/abstract] OR cannabidiol[title/abstract] OR delta-9-tetrahydrocannabinol[title/abstract] OR marihuana [title/abstract] OR Marijuana [title/abstract] OR hashish [title/abstract]
14. #10 OR #11 OR #12 OR #13
15. #4 AND #9 AND #14
16. (animals[MeSH Terms]) NOT humans[MeSH Terms]
17. #15 NOT #16

Hits :321

Embase.com (8th September 2016)

'cannabis'/exp/mj OR thc:ab,ti OR cbd:ab,ti OR cannabinoid*:ab,ti OR endocannabinoid*:ab,ti OR cannabidiol:ab,ti OR sativex:ti,ab OR nabiximols:ti,ab OR 'delta-9-tetrahydrocannabinol':ab,ti OR marihuana:ab,ti OR marijuana:ab,ti OR hashish:ab,ti AND ('chemotherapy'/exp OR 'antineoplastic agent'/exp OR chemotherap*:ab,ti) AND (nause* OR vomit* OR emesis* OR emetic* OR antiemetic* OR emetogenic*) AND [humans]/lim

Hits: 491

Appendix 2. Criteria for judging risk of bias

Item	Judgment	Description
1. random sequence generation (selection bias)	low risk	The investigators describe a random component in the sequence generation process such as: random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization
	high risk	The investigators describe a non-random component in the sequence generation process such as: odd or even date of birth; date (or day) of admission; hospital or clinic record number; alternation; judgement of the clinician; results of a laboratory test or a series of tests; availability of the intervention
	Unclear risk	Insufficient information about the sequence generation process to permit judgement of low or high risk
2. allocation concealment (selection bias)	low risk	Investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based, and pharmacy-controlled, randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.
	high risk	Investigators enrolling participants could possibly foresee assignments because one of the following method was used: open random allocation schedule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards (e.g. if envelopes were unsealed or non opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear risk	Insufficient information to permit judgement of low or high risk This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement
3. blinding of participants and providers (performance bias)	low risk	No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	high risk	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear risk	Insufficient information to permit judgement of low or high risk;
5. blinding of outcome assessor (detection bias)	low risk	No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
	high risk	No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding

	Unclear risk	Insufficient information to permit judgement of low or high risk;
7. incomplete outcome data (attrition bias)	low risk	No missing outcome data; Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; Missing data have been imputed using appropriate methods All randomised patients are reported/analysed in the group they were allocated to by randomisation irrespective of non-compliance and co-interventions (intention to treat)
	high risk	Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation;
	Unclear risk	Insufficient information to permit judgement of low or high risk (e.g. number randomised not stated, no reasons for missing data provided; number of drop out not reported for each group);

Appendix 3. GRADE criteria for assessing grades of evidence

The GRADE system uses the following criteria for assigning grades of evidence.

High: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Grading is decreased for the following reasons.

Serious (−1) or very serious (−2) study limitation for risk of bias.

Serious (−1) or very serious (−2) inconsistency between study results.

Some (−1) or major (−2) uncertainty about directness (the correspondence between the population, the intervention, or the outcomes measured in the studies actually found and those under consideration in our systematic review).

Serious (−1) or very serious (−2) Imprecision of the pooled estimate.

Strong suspicion of publication bias (−1).

Appendix 4. Characteristics of excluded studies

CQ1. Patients with Multiple Sclerosis (MS)

Study	Reason for exclusion
De Ridder 2006[44]	Conference proceeding, no sufficient data available
Ferrè 2016[45]	Type of intervention: No control group
Flachenecker 2014[28]	Type of intervention: No control group
Freeman 2006[46]	Type of outcome: Report of data on incontinence of Zajicek 2003
Grotenhermen 2004[47]	Summary of Zajicek 2003
Hobart 2012[48]	Conference proceeding, no sufficient data available
Kavia 2006[49]	Conference proceeding, no sufficient data available
Killestein 2000[50]	Conference proceeding, no sufficient data available
Leocani 2014[51]	Conference proceeding, no sufficient data available
Notcutt 2012[52]	Type of participants: Selected population of respondent patients
Novotna 2011[53]	Type of participants: Selected population of respondent patients
Petro 1981[54]	Type of intervention: synthetic THC
Riva 2016[55]	Conference proceeding, no sufficient data available
Rog 2007[56]	Type of study: Long-term outcomes of Rog 2005. No control group
Serpell 2013[57]	Type of study: Extension of Collin 2007. No control group
Svendsen 2004[58]	Type of intervention: Dronabinol (synthetic)
Ungerleider 1987[59]	Type of intervention: two different doses of cannabinoids
Wade 2003[60]	Type of participants: Not only patients with MS
Wade 2006[61]	Type of study: Extension of Wade 2004. No control group
Zajicek 2005[62]	Follow up of Zajicek 2003, no useful data available

CQ2. Patients with chronic pain

Study	Reason for exclusion
Abrams 2011[84]	Type of intervention: describe the disposition kinetics of sustained-release morphine and oxycodone.
Buggy 2003[85]	Type of intervention: analgesic efficacy of orald-9-tetrahydrocannabinol in postoperative pain
Cudmore 2015[86]	Type of study: A retrospective chart review of cancer patients, aim of the study is to determine if the addition of cannabinoids (medical cannabis) resulted in the reduction of the average opioid dose required for pain control
de Vries 2016[87]	Type of participants: do not respect the PICO criteria (duration of chronic pain under 6 months)
Eisenberg 2014[88]	Type of study: PHASE I STUDY
Ellis 2009[89]	Type of study: PHASE I and II STUDY
Johnson 2010[90]	Type of participants: duration of chronic pain < 6 months
Johnson 2013[91]	Type of participants: duration of chronic pain < 6 months. Follow up di Johnson 2010
Karst 2003[92]	Type of intervention: synthetic:1',1'dimethylheptyl-Delta8-tetrahydrocannabinol-11-oic acid (CT-3)
Lynch 2014[93]	Type of participants: (duration of chronic pain < 6 months)
Malik 2016[94]	Type of intervention: dronabinol (synthetic)
Naef 2003[95]	Type of participants: healthy subjects under experimental pain conditions
Narang 2008[96]	Type of study: PHASE I and II study crossover
Notcutt 2004[97]	Type of intervention: no wash out period ('N of 1' methodology)
Noyes 1975[98]	Type of intervention not in the inclusion criteria: to evaluate the dose effect and for the duration of pain (information not reported as required in PICO that duration must be >6 months) and because only 1 day of wash out duration
Nurmikko 2005[99]	Conference proceeding, no sufficient data available
Savage 2016[100]	Type of study: consensus document
Staud 2008[101]	Type of intervention: nabilone
Wallace 2013[102]	Conference proceeding, no sufficient data available

CQ3. Patients with Dementia and Tourette syndrome

Ahmed 2015[121]	Type of study: phase II study
Müller-Vahl 1999[122]	Type of study: Case report
Müller-Vahl 2001[123]	Type of study and intervention: This is not a trial of the efficacy and safety of D9-THC. Instead it presents data to support the view that D9-THC does not have a negative impact on neuropsychological performance, when given as a single dose to 12 patients
Müller-Vahl 2003[124]	Type of study and intervention: This study presents evidence that there were neither acute nor long term cognitive deficits in patients given 6 weeks treatment with D9-THC
Shelef 2016[125]	Type of study: not control group
van de Elsen 2015[126]	Type of study: Poster Presentations
van de Elsen 2015a[127]	Type of intervention: dronabinol (synthetic)

CQ4. Patients with HIV/AIDS

Study	**Reason for exclusion**
Abrams 2003	**Type of outcome measures: primary outcomes were HIV RNA levels, CD4 and CD8 cell counts, or protease inhibitor levels over a 21-day treatment. Secondary outcomes were appetite and weight gain.**
Allshouse 2015[131]	Type of intervention: self-reported marijuana use
Badowski 2016[132]	Type of intervention: dronabinol (synthetic)
Beal 1995[133]	Type of intervention: dronabinol (synthetic)
Beal 1997[134]	Type of intervention: dronabinol (synthetic)
Bedi 2010[135]	Type of participants and intervention: dronabinol
Bredt 2002[136]	Duplicate publication: Abrams 2003
Haney 2002[137]	Type of intervention and comparison: Effects of Smoked Marijuana in Healthy and HIV+ Marijuana Smokers
Haney 2005[138]	Type of participants and comparison: to compare dronabinol and marijuana in HIV+ marijuana smokers; outcome: caloric intake and mood
Haney 2007[139]	Type of participants and comparison: to compare dronabinol and marijuana in HIV+ marijuana smokers
Kosel 2002[140]	Type of intervention: The effect of cannabinoids on the pharmacokinetic of indinavir and nelfinavir
Struwe 1993[141]	Type of intervention: dronabinol (synthetic)
Timpone 1997[142]	Type of intervention: dronabinol (Marinol)+ megestrol acetate (Megace)
Williams 2014[143]	Type of study and intervention: to investigate the effects of THC ex vivo on macrophage susceptibility to HIV-1 infection.

CQ5. Patients with cancer receiving chemotherapy

Study	**Reason for exclusion**
Abrams 2016[156]	Type of intervention: Dronabinol (synthetic)
Brisbois 2011[157]	Type of intervention: Dronabinol (synthetic)
Broder 1982[158]	Conference proceeding, no sufficient data available
Cerny 2003[159]	Type of study: conference proceedings data available in Strasser 2006
Citron 1985[160]	Type of comparison: cannabis versus synthetic cannabis
Davies 1974[161]	Type of intervention not in the inclusion criteria: synthetic A1-THC
Dow 1984[162]	Type of study: letter no sufficient data available
Elliott 2016[163]	Type of study: no RCT, questionnaire
Gralla 1982[164]	Conference proceeding, no sufficient data available
Hernandez 2015[165]	Type of intervention: Dronabinol (synthetic)
Jatoi 2002[166]	Type of intervention: Dronabinol (synthetic)
Johnson 2005[167]	Conference proceeding, no sufficient data available
Kinzbrunner 2002[168]	Type of study: review of studies including only synthetic cannabis
Lane 1990[169]	Type of intervention: Dronabinol (synthetic)
Lane 1991[170]	Type of intervention: Dronabinol (synthetic)
Levitt 1982[171]	Type of intervention: Nabilone (synthetic)
Levitt 1984[172]	Conference proceeding, no sufficient data available
Liu 2010[173]	Type of study: review on the relationship between cannabinoids and cancer
Manzo 1988[174]	Type of intervention: Dronabinol (synthetic)
May 2016[175]	Type of intervention not in the inclusion criteria: Dronabinol (synthetic)
Martellucci 2015[176]	Conference proceeding, no sufficient data available
Meiri 2007[177]	Type of intervention not in the inclusion criteria: Dronabinol (synthetic)
Noyes 1975[178]	Type of study: non RCT effect on pain in 5 subjects
Rock 2016[179]	Type of study: study using rodent models
Sweet 1981[180]	Type of study: no RCT, pilot study without control group
Todaro 2012[181]	Type of study: editorial

Appendix 5. Characteristics of Included Studies

CLINICAL CONDITION: MULTIPLE SCLEROSIS

Study	Methods	Objective	Patients	Interventions	Outcome
Aragona 2009[72]	Randomised, double-blind, 2-period cross-over Country of origin: Italy Duration of study: 8 weeks	To study possible psychopathological symptoms and cognitive deficits, abuse induction, as well as general tolerability and effect on QoL, fatigue and motor function in cannabis naïve patients with multiple sclerosis treated with a free-dose cannabis plant extract (Sativex)	N=17 people, all participants were cannabis naive. (6/17 (35%) men; 11/17 (65%) women), mean age 49.8 years (SD +/-6.64), All the patients had secondary progressive multiple sclerosis with a mean duration of disease of 20.76 years (SD +/-8.42). EDSS mean score 6.1 (SD 0.3).	– Sativex composed of whole cannabis plant extract containing THC 27 mg/ml and CBD 25 mg/ml in ethanol/propylene glycol (50:50) excipient, presented in a pump action sublingual spay. Each actuation delivers 100 µL of spray containing THC 2.7 mg and CBD 2.5 mg. – Placebo had the appearance, smell and taste of the active formulation in ethanol/propylene glycol (50:50) excipient but contained no active components.	Rating scales were used to assess fatigue, disability, psychopathology, cognitive functioning and physical and psychological impact of MS on QoL and AE.
Collin 2007[63]	Randomised, double-blind, multicentre, parallel group, placebo-controlled trial Country of origin: 8 centres in UK, 4 in Romania Duration of study: 6 weeks	To investigate efficacy, safety and tolerability of a standardized oro-mucosal whole plant cannabis-based medicine.	N=189 people (75/189 (39.7%) men; 114/189 (60.3%) women), mean age 49.1 years. Mean duration of disease 12.6 years.	– Sativex (N=124), highly standardise oromucosal spray: each 100-µL actuation yields 2.7 mg of THC and 2.5 mg of CBD in a solution of 50:50 ethanol: propylene glycol. – Placebo preparation (N=65) was identically flavoured incipient.	NRS (0-10 NRS) for spasticity, Ashworth score, Motricity Index, daily spasm score, PGIC, AE.
Collin 2010[64]	Randomised, double blind, parallel group, placebo-controlled trial. Multicentre study Country of origin: 15 centres in UK, 8 in Czech Republic Duration of study: 15 weeks	To compare Sativex to placebo in relieving symptoms of spasticity due to MS	N=337 people (130/337 (39%) men; 207/337 (61%) women), mean age 47.5 years. Mean duration of disease 15.2 years. Previous cannabis use 81/337 (24%). EDSS mean score 6.0 (SD 1.53).	– Sativex (N=167), pump action oromucosal spray: each 100-µL actuation delivered 2.7 mg of THC and 2.5 mg of CBD. – Placebo preparation (N=170), each actuation delivered 100 µL of vehicle containing excipients plus colourants.	NRS (0-10 NRS) for spasticity, timed 10-meter walk test, the Barthel activity of daily living index, caregiver's global impression of change (CGIC), 0-10 NRS for spasm, tremor, pain, fatigue, bladder symptoms and sleep quality, the modified Ashworth score, quality of life scales (EQ-5D and MSQoL-54), AE.

Study	Methods	Objective	Patients	Interventions	Outcome
Corey-Bloom 2012[73]	Randomised, double-blind, placebo-controlled, 2-period cross-over trial Country of origin: USA Duration of study: 2 weeks	To determine the short-term effect of smoked cannabis on spasticity	N=30 people (11/30 (37%) men; 19/30 (63%) women), mean age 51 years. Mean duration of disease 8.5 years. Any previous cannabis use 24/30 (80%). EDSS mean score 5.3 (SD 1.5).	– Cannabis cigarettes contained about 4% of THC by weight. – Placebo cigarettes had the same base materials with THC removed. The pre-rolled cigarettes were identical in appearance and weight. Participants smoked either placebo or cannabis cigarettes using the Foltin uniform puff procedure (inhalation for 5 s followed by a 10-s breath-hold and exhalation with a 45-s wait between puffs) under supervision in a ventilated room. Participants completed an average of 4 puffs per cigarettes.	Ashworth score, Pain VAS, Physical performance (timed walk), Cognitive function (PASAT), BSI, PDQ, FIS, feeling of "highness", AE.
Fox 2004[74]	Randomised, double-blind, placebo-controlled, 2-period cross-over trial Country of origin: UK Duration of study: 6 weeks	To examine the effect of oral cannador (cannabis extract) on tremors	N=14 people (6/14 (43%) men; 8/14 (57%) women), mean age 45 years. Previous cannabis use 1/14 (7%). EDSS mean score 6.25 (3.5 to 7.5).	– Cannador, an ethanolic extract of cannabis sativa, was standardised to 2.5 mg of THC capsule. – Placebo consisted of identical capsules.	Severity of tremors, tremor index, accelerometry, ataxia scale, spiral drawing, finger tapping, and nine-hole pegboard test performance, AE
Kavia 2010[65]	Randomised, double-blind, multicentre, parallel group, placebo-controlled trial Country of origin: 9 centres in UK, 3 in Belgium and 3 in Romania. Duration of study: 8 weeks	To assess the efficacy, tolerability and safety of Sativex as an add-on therapy in alleviating bladder symptoms in pts with MS	N=135 people (37/135 (27%) men; 98/135 (73%) women), mean age 47.7 years. Any previous cannabis use 48/135 (36%).	– Sativex (N=67), pump action oromucosal spray: each 100 µL actuation delivered 2.7 mg of THC and 2.5 mg of CBD – Placebo preparation (N=68), each actuation delivered 100 µL of vehicle containing excipients plus colourants and flavouring.	Reduction in daily n° of urinary incontinence episodes, void urgency and nocturne episodes, n° of incontinence pads used per day, change in symptoms (0-10 NRS) of overall bladder condition (OBC), daytime frequency, I-QoL, PGIC, volume voided, AE.

Study	Methods	Objective	Patients	Interventions	Outcome
Killenstein 2002[75]	Randomised, double-blind, placebo-controlled, twofold cross-over trial Country of origin: Netherlands Duration of study: 20 weeks	To investigate safety, tolerability and efficacy of synthetic oral THC and Cannabis sativa plant extract in pts with MS and severe spasticity.	N=16 people, mean age 46 years. Mean duration of disease 15 years. 10 patients had secondary progressive and 6 patients had primary progressive MS. EDSS mean score 6.2 (SD 1.2).	– Patients received identical-appearing capsules for 4 weeks each containing: – Dronabinol (synthetic THC) – Cannabis Sativa plant extract (standardise THC content=20 to 30% CBD and <5% other cannabinoids) – -Placebo	Aschworth scale, EDSS, MS-specific Fatigue Severity Scale, composite MSFC score Medical Outcomes Study Short Form 36, QoL questionnaire, VAS, AE.
Langford 2013[66]	A double-blind, randomized, multicentre, placebo-controlled, parallel-group study Multicentre study Country of origin: 12 centres in UK, 7 in Czech Republic, 5 in Canada, 5 in Spain and 4 in France. Duration of study: 14 weeks	To investigate the efficacy of THC/CBD oromucosal spray to alleviate central neuropathic pain (CNP).	N=339 people, (109/339 (32%) men; 230/339 (68%) women), mean age 48.97 years. Mean duration of disease 11.99 years. 136 patients had Secondary Progressive, 40 patients had primary progressive, 157 had relapsing/remitting and 6 had progressive relapsing MS.	– THC/CBD (N=167), pump action oromucosal spray: each 100-µL actuation delivered 2.7 mg of THC and 2.5 mg of CBD. – Placebo preparation (N=172), each actuation delivered 100 µL of vehicle containing excipients plus colourants.	Improvement in patient's mean pain NRS score, Brief Pain Inventory- Short Form, Subject Global Impression Change, sleep quality assessment, AE.
Leocani 2015[76]	Randomised, double-blind, placebo-controlled, cross-over trial Country of origin: Italy Duration of study: 4 weeks	To investigate Sativex-induced changes in neurophysiological measures of spasticity in patients with progressive MS.	N=43 people, (23/43 (53%) men; 20/43 (47%) women), mean age 48 years. Mean duration of disease 17 years. EDSS mean score 5.5 (SD 1.0).	– Sativex oromucosal spray is an endocannabinoid system modulator containing THC and CBD in a near 1:1 ratio – Placebo preparation	The modified Ashworth score, 0-10 NRS, timed 10-meter walk, 9-hole peg test, sleep quality NRS, pain NRS, spasm frequency score, fatigue severity scale, AE.
Rog 2005[67]	A double-blind, randomized, placebo-controlled, parallel-group study Country of origin: UK Duration of study: 5 weeks	To compare efficacy, safety and tolerability of THC+CBD with placebo in relieving central neuropathic pain in pts with MS.	N=66 people, (14/66 (21%) men; 52/66 (79%) women), mean age 49.2 years. Mean duration of disease 11.6 years. EDSS mean score 5.9 (SD 1.3).	– Sativex (N=34), pump action oromucosal spray: each spray delivered 2.7 mg of THC and 2.5 mg of CBD. – Placebo preparation (N=32), matched appearance, smell and taste, but contained no active components.	NRS-11 scale, NPS total pain score, Pain-related sleep disturbance, PGIC, cognitive function, mood, MS-related disability, AE.

Study	Methods	Objective	Patients	Interventions	Outcome
Vachovà 2014[68]	A double-blind, randomized, multicentre, placebo-controlled, parallel-group study Country of origin: 6 centres in Czech Republic.	To assess the long term impact of Sativex on cognitive function and mood in MS patients with spasticity.	121 people, (45/121 (37%) men; 76/121 (63%) women), mean age 48.6 years. Mean duration of disease 13.9 years. 43 patients had Secondary Progressive, 16 patients had Primary Progressive, 59 had Relapsing/Remitting MS, 3 had Progressive Relapsing.	– Sativex (N=62), pump action oromucosal spray: each spray delivered 2.7 mg of THC and 2.5 mg of CBD. – Placebo preparation (N=59), delivered excipients plus colourants.	Paced Auditory Serial Addition Test (PASAT) I&II, Modified Ashworth Scale, 10-meter walk time, n° of visits to healthcare professional, Subject-, Physician- and Caregiver Global Impression of Change (GIC), AE.
Vaney 2004[77]	Randomised, double-blind, placebo-controlled, cross-over trial Country of origin: Switzerland Duration of study: 4 weeks	To investigate the effect of orally administered THC+CBD in MS pts with poorly controlled spasticity.	N=57 people, (28/57 (49%) men; 29/57 (51%) women), mean age 50.7 years. EDSS mean score 7.0 (SD 6.0).	– Whole-plant cannabis extract containing 2.5 mg THC and 0.9 mg CBD in a gelatine capsule to be taken orally. – Placebo capsules were identical in shape, taste and colour	The modified Ashworth scale, Rivermead Mobility Index, 10-minute timed walk, 9-hole peg test, NEADL, EDSS, PASAT, WAIS R intelligence scale, AE.
Wade 2004[69]	A double-blind, randomized, placebo-controlled, parallel-group study Country of origin: UK Duration of study: 6 weeks	To determine whether a cannabis-based medicine extract benefits a range of symptoms du to MS	N=160 people, (61/160 (38%) men; 99/160 (62%) women), mean age 54.9 years. Mean duration of disease 17 years.	– Sativex (N=80), pump action oromucosal spray: each spray delivered 2.7 mg of THC and 2.5 mg of CBD. – Placebo preparation (N=80), contained excipient only. Both preparation incorporated a peppermint flavour and colouring to disguise the taste and appearance of Sativex.	VAS for major symptoms, Barthel Activity Daily Living index, Rivermead Mobility Index, short Orientation-Memory-Concentration Test, Adult Memory and Information Processing Battery test for attention adapted to MS, General Health Questionnaire 28, GNDS, BDI, Fatigue Severity scale, VAS for sleep, the modified Ashworth scale, tremor ADL questionnaire, nine-hole peg test, time in seconds to walk 10 meters, urinary incontinence questionnaire, AE.

Study	Methods	Objective	Patients	Interventions	Outcome
Zajicek 2003[70]	A double-blind, randomized, multicentre, placebo-controlled, parallel-group study Country of origin: 33 centres in UK. Duration of study: 15 weeks	To test beneficial effects of cannabinoids on spasticity and other symptoms of MS.	N=640 people, (217/640 (34%) men; 413/640 (65%) women), mean age 50.5 years. 452 patients had Secondary Progressive, 145 patients had primary progressive, 33 had relapsing/remitting MS. EDSS score: 0-3.5 n=3; 4-5.5 n=23; 6-6.5 n=299; 7-9 n=299; missing n=6.	– Synthetic THC capsules (N=216). – Cannabis extract capsules (N=219) containing 2.5 THC equivalent, 1.25 cannabidiol and less than 5% of other cannabinoids. – Placebo capsules (N=222) containing vegetable oil vehicle.	Ashworth score, Rivermead Mobility Index, timed 10-minute walk, United Kingdom Neurological Disability score, Barthel Index, General Health Questionnaire, nine category-rating scales, EDSS, AE.
Zajicek 2012[71]	A double-blind, randomized, multicentre, placebo-controlled study Country of origin: 22 centres in UK. Duration of study: 12 weeks	To investigate the effect of a standardised oral cannabis extract for the symptomatic relief of muscle stiffness and pain in adult pts with MS.	N=277 people, (102/277 (37%) men; 175/277 (63%) women), mean age 52 years.	– Extract of Cannabis Sativa in gelatine capsule (N=144), standardised on cannabidiol and containing 2.5 mg of THC. – Placebo gelatine capsule (N=135).	11-point category rating scale (CRS) for: perceived change in muscle stiffness, relief from body pain, spasm and sleep disturbance; absolute amount of muscle stiffness, body pain, spasm and sleep disturbance. MS Spasticity scale, MS Walking scale, MS Impact scale, EDSS, AE.

THC= Δ9-tetrahydrocannabinol; AE = adverse events; CBD =Cannabidiol; MS= Multiple sclerosis; EDSS=Expanded Disability Status Scale; NRS= Numerical rating scale; PGIC=Patients Global Impression of Change; BSI=Brief Symptoms Inventory; PDQ=Perceived Deficit Questionnaire; NEADL=Nottingham Extended ADL index; FIS=Fatigue Impact Scale; I-QoL= Incontinence Quality of Life; VAS=Visual Analogue Scale; GNDS=Guy's Neurological Disability scale; BDI=Beck Depression Inventory

CONDITION: CHRONIC PAIN

Study	Methods	Objective	Patients	Interventions	Outcome
Abrams 2007[103]	Randomized, double blind, parallel, placebo-controlled trial. Country of origin: USA Duration of study: 3 weeks	To determine the effect of smoked cannabis on the neuropathic pain of HIV-associated sensory neuropathy and an experimental pain model	N=55 Patients were adults with HIV infection and symptomatic HIV-SN with an average daily pain score of sensation (such as burning, tenderness, or more intense pricking).	– Cigarettes containing 3.56% THC and weighing an average of 0.9 g; smoked 3 times per die (n=27); – Placebo cigarettes containing 0% THC identical to the cannabis cigarettes (n=28) Setting: inpatient	Daily diary of pain ratings on a VAS (0-100 mm); Total mood disturbance; Profile of Mood States, AE
Berman 2004[109]	Randomized, double blind, placebo-controlled, three period crossover study (2w + 2w + 2w; no washout period). Single centre Country of origin: UK Duration of study: 3 weeks	To investigate the effectiveness of cannabis-based medicines for treatment of chronic pain associated with brachial plexus root avulsion.	N=48, mean age= 39 years (range 23–63 years). Inclusion criteria: >18 years with Central neuropathic pain (brachial plexus avulsion); with the injury occurring >18 months previously were included and baseline pain score of four or more on an 11-point ordinate scale. No analgesics were prohibited. Average daily pain score ≥4 on NRS. Patients were required to stop any cannabis or cannabinoid use at least 7 days prior to entry into the study.	– whole plant extracts of Cannabis sativa L.: GW-1000-02 (Sativex), containing THC: (CBD) in an approximate 1:1 ratio (2.7 mg THC/2.5 mg CBD) – GW-2000-02, containing primarily THC. (2.7 mg THC); – Placebo	mean pain severity score during the last 7 days of treatment; quality of life
Blake 2006[104]	Randomized double-blind, parallel-group multicentre Country of origin: UK Duration of study: 5 weeks	To assess the efficacy of a CBM in the treatment of pain due RA.	N=58 mean age=62.8 (SD 9.8), male=12 (21%) Inclusion criteria: diagnosis of RA meeting ACR criteria, with active arthritis not adequately controlled by standard medication. NSAID and prednisolone regimes had to have been stabilized for 1 month and DMARDs for 3 months prior to enrolment, and were maintained constant throughout the study.	– Sativex administered by oromucosal spray. Each activation delivering 2.7 mg THC and 2.5 mg CBD; – Placebo	Pain on movement (0-10 NRS) Pain at rest (0-10 NRS); SF-MPQ; Sleep quality (0-10 NRS); Morning stiffness; 28-joint disease activity score (DAS28)

Study	Methods	Objective	Patients	Interventions	Outcome
Nurmikko 2007[105]	Randomised, double blind, placebo-controlled parallel group study. Multicentre Country of origin: 5 centres in UK, 1 in Belgium Duration of study: 5-week	To evaluate the effect of oro-mucosal sativex, (THC: CBD), an endocannabinoid system modulator, on pain and allodynia in patients with neuropathic pain of peripheral origin	N=125 patients aged 18 or over, male or female, with a current history of unilateral peripheral neuropathic pain and allodynia; a history of at least 6 months duration of pain due to a clinically identifiable nerve lesion	– Oro-mucosal Sativex administration (n=63); – Placebo medication (n=62)	intensity of global neuropathic pain: (0-10 NRS) ; mechanical allodynia (NPS), sleep disturbance (four-step verbal rating scale for sleep disturbance the Pain Disability Index (PDI), PGIC of both pain and allodynia, and the General Health Questionnaire (GHQ-12). Cognitive decline (BRB-N)
Portenoy 2012[106]	Randomized, double-blind, placebo-controlled, graded-dose study Multicentre Country of origin: Belgium, Canada, Chile, Czech Republic, Finland, France, Germany, India, Italy, Mexico, Poland, Romania, South Africa, Spain, UK, USA Duration of study: 9 weeks	To explore the analgesic efficacy and safety of nabiximols in 3 dose ranges in a population with medical illness and pain that is not adequately controlled with an opioid.	N=360 Adult patients with active cancer and chronic pain; Score 4-8 on NRS pain scale, not changed by ≥2 points over 3 consecutive days in 14 days	– NABIXIMOLS at a low dose 1–4 SPRAYS (n=71); – NABIXIMOLS medium dose 6–10 SPRAY (n=67); – NABIXIMOLS high dose 11–16 SPRAYS (n=59); – PLACEBO (n=66);	Average pain, worst pain and sleep disruption; quality of life; mood
Selvarajah 2010[107]	Randomized controlled trial, double blind, parallel. Country of origin: UK Duration of study: 10 weeks	To assess the efficacy of Sativex, a cannabis-based medicinal extract, as adjuvant treatment in painful diabetic peripheral neuropathy (DPN)	N= 30 patients with chronic painful DPN (Neuropathy Total Symptom Score 6 4 and 16) for at least 6 months with stable glycaemic control (A1C 11%) were assessed. Those with persistent pain, despite an adequate trial of tricyclic antidepressants, were recruited.	– Sativex (tetrahydrocannabinol [27 mg/ml] and cannabidiol [25 mg/ml]); – Placebo presented as a pump-action spray. Doses were administered sublingually in divided doses up to four times a day.	Pain assessed by the pain diary, NPS, and total pain score (TPS); Quality of life (QOL), assessed by McGill Pain and QOL (5), SF-36 Health Survey (6), and Euro QOL (7) questionnaires; AE

Study	Methods	Objective	Patients	Interventions	Outcome
Serpell 2014[108]	Randomized, double blind, placebo-controlled, parallel group study. Multicentre Country of origin: UK, Czech Republic, Romania, Belgium and Canada Duration of study: 15 weeks	To investigate the therapeutic benefits of 15-week THC/CBD spray treatment on PNP associated with allodynia, as well as associated sleep disturbance and patient quality of life.	N=246 patients were aged 18 or older with peripheral neuropathic pain (PNP) associated with allodynia; Patients also had a sum score of at least 24 on a pain 0–10 NRS for more than 6 days (baseline days 2–7)and pain that was not wholly relieved by their current therapy.	– THC/CBD administered by oromucosal spray (100 µL spray of THC/CBD delivered 2.7 mg of THC and 2.5 mg of CBD) – Placebo. Both THC/CBD spray and placebo contained peppermint oil to blind the smell and taste.	Pain severity measures as improvement in PNP (0–10 NRS); improvement in NPS, sleep quality 0–10 NRS, SGIC, BPI-SF; dynamic and punctate allodynia tests, quality of life (EQ-5D) health questionnaire, 50% or more improvement in PNP 0–10 NRS score, and the use of rescue analgesia
Wallace 2015[110]	Randomized, double-blind, placebo controlled crossover study Country of origin: USA Duration of study: 4 sessions	To assess the short-term efficacy and tolerability of inhaled cannabis.	N=16 Painful diabetic peripheral neuropathy; > 4 on 11 point NPS	– Low dose (1% THC) – medium dose (4% THC) – high (7% THC) dose of cannabis; – Placebo Subjects participated in four sessions, separated by 2 weeks, where they were exposed to placebo	spontaneous and evoked pain scores; subjective "highness" scores, euphoria and somnolence; cognitive testing
Ware 2010[111]	Randomized, double blind, placebo-controlled, four period crossover design. Country of origin: Canada Duration of study: 14 days	The purpose of the present study was to compare medium- (3.53% THC) to low-dose (1.29% THC) cannabis.	N=23 patients with neuropathic pain of at least three months in duration caused by trauma or surgery, with allodynia or hyperalgesia, and with an average weekly pain intensity score greater than 4 on a 10-cm visual analogue scale. Participants had a stable analgesic regimen and reported not having used cannabis during the year before the study.	– THC (0%, 2.5%, 6% and 9.4% tetrahydrocannabinol) over four 14-day periods Participants inhaled a single 25-mg dose through a pipe three times daily for the first five days in each cycle, followed by a nine-day washout period; – Placebo	Pain intensity, Pain quality, Quality of life
Weber 2010[112]	Randomised, double-blind, placebo-controlled crossover Country of origin: Switzerland Duration of study: 2 weeks	To determine the effect of orally administered tetrahydrocannabinol (THC) on cramps in ALS patients.	N=27 Patients with amyotrophic lateral sclerosis suffering from moderate to severe (VAS) daily cramps	– 5 mg THC twice daily – placebo Each treatment period lasted for 2 weeks and was preceded by a 2-week drug-free observation period (run-in, washout period respectively).	Cramp intensity (VAS); number of cramps per day, number of cramps during daytime and bedtime, intensity of fasciculation (VAS); quality of life (ALSAQ-40); quality of sleep (SDQ); appetite (FAACT); depression (HADS).

Study	Methods	Objective	Patients	Interventions	Outcome
Wilsey 2008[113]	Randomized, double-blinded, placebo-controlled, crossover design. Country of origin: California Duration of study: unclear	To evaluate the analgesic efficacy of smoking cannabis for neuropathic pain.	N=38 patients with central and peripheral neuropathic pain Mean age= 46 years (21–71 years)	– Smoking THC high-dose (7%) – Smoking THC low-dose; (3.5%) – Placebo cannabis. Duration of study: 3, 6-h experimental sessions; there were 3- to 14-d intervals between sessions. Duration of wash out ranged from 3 to 21 days, with a mean (SD) of 7.8 (3.4) days.	Pain intensity (VAS) (0-100 mm) and the NP scale Evoked pain using heat-pain threshold, sensitivity to light touch, psychoactive side effects, and neuropsychological performance
Wilsey 2013[114]	Randomized, double-blind, placebo controlled, crossover design Country of origin: USA Duration of study: 18 hours	To evaluate the analgesic efficacy of vaporized cannabis in subjects, the majority of whom were experiencing neuropathic pain despite traditional treatment.	N=38 Adults with neuropathic pain disorder (CRPS [type I, formerly known as reflex sympathetic dystrophy], thalamic pain, spinal cord injury, peripheral neuropathy, radiculopathy, or nerve injury). Mean age= 50 years	– Vaporised Cannabis (3.53%); – vaporised Cannabis (1.29%) 4 puffs 1 hour from baseline, 4-8 puffs 3 hours; – Placebo Study duration was 3, 6-h experimental sessions; there were 3- to 14-d intervals between sessions.	Spontaneous pain relief was assessed by asking participants to indicate the intensity of their current pain on a 100-mm visual analog scale (VAS) between 0 (no pain) and 100 (worst possible pain). pain relief measured through PGIC and NPS

Legend: QoL = Quality of Life; THC= Δ9-tetrahydrocannabinol; RA= rheumatoid arthritis; SF-MPQ =Short Form McGill Pain Questionnaire; NPS=Neuropathic Pain Scale; BRB-N=Brief Repeatable Battery of Neuropsychological tests; PGIC=Patient Global Impression of Change; TPS=total pain score; SGIC =Subject Global Impression of Change; BPI-SF= Brief Pain Inventory (short form)

CONDITION: patients with Tourette syndrome

Study	Methods	Objective	Patients	Interventions	Outcome
Muller-Vahl 2002[128]	Double blind, placebo controlled crossover trial. Country: Germany Duration of study: 4 weeks	To evaluate the efficacy and safety of cannabinoids compared with placebo or other drugs in treating tics and obsessive compulsive symptoms in patients with TS	12 adult patients, 11 male 1 female. Mean age 34 years (Range 18-66 years), DSM-III; Exclusion criteria: < 18, history of psychosis and schizophrenia, significant concomitant illness, or pregnant placebo	– THC (gelatine capsules of either 2.5 mg or 5.0 mg) – placebo Patients received different doses based on weight, gender, age and prior cannabis use	1. Tic severity patient rated using TSSL. 2. Tic examiner rated using STSS, YGTSS, TSGS, 3. video-based rating scale
Muller-Vahl 2003[129]	Randomized, double blind, placebo controlled trial parallel group Country: Germany Duration of study: 6 week	To evaluate if THC is effective and safe in reducing tics in TS	Adult=24 patients with a TS (DSM-III); 19 male 5 female. Mean age =33	– THC (n=12) (gelatine capsules of 2.5 mg and 5.0 mg) – Placebo (n=12). Dose titrated to target dose of 10mg/day	Tic severity using examiner rating scales TSGS, STSSS; YGTSS; a video protocol for assessment of tic intensity and frequency; and patient self-rating scale (TSSL)

TS= Tourette syndrome; TSGS =Tourette syndrome Clinical Global Impressions scale; STSSS= the Shapiro Tourette-syndrome Severity Scale; YGTSS= the Yale Global Tic Severity Scale; TSSL= Tourette Syndrome Symptom List

CONDITION: CANCER RECEIVING CHEMOTHERAPY

Study	Methods	Objective	Patients	Interventions	Outcome
Chang 1979[186]	Randomized, double-blind, 3-period cross-over, placebo-controlled trial Country of origin: USA Duration of study: 6 months	To study the efficacy of oral and smoked THC as an antiemetic.	N=15 people (10/15 (67%) men; 5/15 (33%) women) aged 15-49 years (median = 24 years). 4/15 (27%) participants were cannabis naive. Tumour type: osteogenic sarcoma. Chemotherapy regimens: methotrexate 250 mg/kg with leucovorin calcium rescue every 3 weeks for 18 months. Chemotherapy ematogenicity: low	– THC 10 mg/m2 orally every 3 hours for total 5 doses. If participant vomited during this period, oral dose was replaced with THC cigarette for remaining doses; – Placebo	Episodes of nausea and vomiting on day of therapy; frequency and severity of nausea; episodes of sedation, euphoria, dizziness, depression, paranoia
Chang 1981[187]	Randomised, double-blind, 2-period cross-over trial Country of origin: USA Duration of study: 5 months	To define the clinical utility of THC as antiemetic in patients receiving a variety of chemotherapy regimens	N=8 people (6/8 (75%) men; 2/8 (25%) women) aged 17-58 years (median = 41 years), 7/8 (88%) participants were cannabis naive. Tumour types: resected soft tissue sarcoma. Chemotherapy regimen: adjuvant doxorubicin and cyclophosphamide every 4 weeks until a total cumulative doxorubicin dose of 500-550 mg/m2 Doxorubicin (70 mg/m2) and cyclophosphamide (700 mg/m2) were given at constant doses for all participants. Chemotherapy ematogenicity: high	– THC, 10 mg/m2 orally every 3 hours for total 5 doses, if vomited then participant given marijuana cigarettes 900 mg, containing THC 1.93% (approximately 17.4 mg), n = 8 – Placebo Setting: inpatient	Episodes of nausea and vomiting on day of therapy
Duran 2010[182]	Randomized, double-blind, placebo-controlled trial Country of origin: Spain Duration of study: 10 days inpatient	To evaluate the tolerability, preliminary efficacy, and pharmacokinetics of an acute dose titration of a whole-plant cannabis-based medicine (CBM) containing delta-9-tetrahydrocannabinol and cannabidiol, taken in conjunction with standard therapies in the control of chemotherapy Induced Nausea and Vomiting (CINV).	N=16 , median age =50 years; range 34-76 Chemotherapy regimen: 1-day MEC [carboplatin, cisplatin (50 mgm-2), cyclophosphamide (1500 mgm-2), doxorubicin (60 mgm-2), idarubicin ifosfamide, irinotecan, mitoxantrone (15 mgm-2) for epirubicin (90 mgm-2)]. Standard anti-emetic treatment included corticosteroids as well as 5-HT3R antagonists or metoclopramide.	– CBM (n= 6). Each spray push delivered 2.7 mg of THC – Placebo (n= 9)	Number of withdrawals from the study for AE, proportion of patients showing complete or partial response.

Study	Methods	Objective	Patients	Interventions	Outcome
Frytak 1979[183]	Randomized, double-blind, parallel trial Country of origin: USA Duration of study: 4 days	To evaluate the efficacy of THC as an antiemetic agent using a larger population of patients within the more typical cancer age groups and to compare the antiemetic effects and side-effects of THC with those of prochlorperazine, and placebo	N=116 people, median age = 61 years. All cannabis naive. THC (22men/16 women), prochlorperazine (21 men/20 women), placebo (27 men/10 women) Tumour types: colorectal cancer (28 people), gastric cancer (7 people), liver cancer (2 people), miscellaneous (1 person), gastric surgery (5 people), hepatic metastasis (20 people). Chemotherapy regimens: 5-fluorouracil and semustine or 5-fluorouracil and semustine plus triazinate, razoxane, doxorubicin or vincristine. 5-fluorouracil 300-350 mg/m2 IV for 5 days. Semustine 110-175 mg/m2 day 1 only. Chemotherapy ematogenicity: moderate	– THC(n = 38), 15 mg on day 1, 2 hours prior to chemotherapy, then 2 and 8 hours after initiation of chemotherapy. Then 3 times daily x 3 days orally – Prochlorperazine (n = 41), 10 mg on day 1, 2 hours prior to chemotherapy, then 2 and 8 hours after initiation of chemotherapy. Then 3 times daily x 3 days orally, – Placebo (n=37) Setting: inpatient	Episodes of nausea and vomiting during 24 hours, sedation, feeling high; withdrawal due to intolerable central nervous system toxicity or excessive vomiting
Gralla 1984[184]	Randomised, double-blind, parallel trial Country of origin: USA Duration of study: unclear	To evaluate the antiemetic effect of THC versus Metoclopramide	N=31 people (23 men/ 5 women). THC (13 men/2 women), aged 39-72 years (median = 58 years); metoclopramide (11 men/5 women), aged 45-70 years (median = 58 years). Tumour types: bronchogenic carcinoma (12 people), oesophageal carcinoma (2 people) , head and neck carcinoma head and neck carcinoma (1 person) Chemotherapy regimens: all receiving first course of cisplatin 120 mg/m2 IV. Chemotherapy emetogenicity: high	– THC (n=15) 10 mg/m2 1.5 hours prior to chemotherapy, then at 1.5, 4.5, 7.5 and 10.5 hours after chemotherapy orally – Metoclopramide (n = 16), 2 mg/kg 30 minutes prior to chemotherapy, then 1.5, 3.5, 5.5 and 8.5 hours after chemotherapy IV Setting: inpatient	Episodes of nausea and vomiting during 24 hours, sedation, dizziness, orthostatic hypotension, feeling high
Kleinman 1983[188]	Randomised, double-blind, 4-period cross-over study Country of origin: USA Duration of study: unclear	To evaluate the efficacy of Prochlorperazine + THC versus prochlorperazine + placebo	N=16 people (9 men/7 women) aged 18-53 years (median = 38 years). Tumour types: not reported Chemotherapy regimens: "Cancer chemotherapy known to cause acute gastrointestinal toxicity" Chemotherapy emetogenicity: unable to classify. Results on 14 patients who completed the study.	– Prochlorperazine, 10 mg + THC 15 mg x 2 courses orally, – Prochlorperazine + placebo orally Setting: inpatient	Episodes of nausea and vomiting 24 hours after chemotherapy, euphoria, sedation
Kluin-Neleman 1979[189]	Randomised, double-blind, 2-period cross-over study Country of origin: Netherlands Duration of study: 5 months	To evaluate efficacy and safety of THC for nausea in patients receiving chemotherapy	N=11 patients with lymphoma. Chemotherapy regimens: day 1 and 8 chlormetine 6mg/m^2 vincristine 1.4mg/m^2. From day 1 to 14 antiemetic therapy with procarbazine 100mg/m^2 and prednisone 40/mg/m^2. 6 cycles of therapy	– THC 10 mg/m2 orally – Placebo Setting: inpatient	Episodes of nausea and vomiting at end of day of therapy, feeling high, dizziness, hallucinations

Study	Methods	Objective	Patients	Interventions	Outcome
McCabe 1988[190]	Randomised, 2-period cross-over trial Country of origin: USA Duration of study: 3 months	To evaluate the efficacy of oral THC compared to PCZ, for the control of cancer chemotherapy-related emesis	N=36 (9 men/27 women) aged 18-69 years (median = 48 years). Tumour types: breast cancer (11 people), haematological malignancies (9 people), sarcomas (6 people), gastrointestinal malignancies (5 people), melanoma (2 people), ovarian cancer (2 people), testicular cancer (1 person). Chemotherapy regimens: doxorubicin (13 people), cyclophosphamide, methotrexate and 5-fluorouracil (7 people), nitrogen mustard, vincristine, procarbazine and prednisone (7 people), platinum combinations (4 people), DTIC (2 people), 5-fluorouracil combinations (2 people), 5-azacytadine (1 person). No information on doses reported Chemotherapy emetogenicity: moderate to high	– THC 15 mg/m2 1 hour prior to chemotherapy, then every 4 hours for 24 hours after chemotherapy orally – PCZ 10 mg 1 hour prior to chemotherapy, then every 4 hours for 24 hours after chemotherapy orally Setting: inpatient	Episodes of nausea and vomiting during 24 hours, feeling high, dizziness, dysphoria, hallucination, paranoia
Neidhart 1981[191]	Double-blind, randomized study with a 2 period crossover design Country of origin: USA Duration of study: 3 months	To determine the relative efficacy of THC and haloperidol in patients receiving those cancer chemotherapeutic agents known to induce severe nausea and vomiting.	N=77 THC (21 men/16 women), mean age=41; haloperidol (21 men/15 women), mean age= 44.8. Chemotherapy regimens: Cisplatin (22 people), Doxorubicin (16 people), Nitrogen mustard (9 people), Cisplatin and doxorubicin (16 people), Other (10 people)	– THC 10 mg THC in 0.12 ml sesame oil. N= 52 – Haloperidol 2 mg tablet was placed in an opaque capsule filled with powdered lactose N = 52 Antiemetic was administered at 2 hours and at 30 minutes prior to chemotherapy. Subsequent dosing started 1 hour after chemotherapy and was then given at 3-to 4-hour intervals for a maximum of eight doses.	Number of episodes, severity, and duration of vomiting and nausea; patient estimates of the ability of the antiemetic to prevent vomiting or to treat vomiting; overall estimate of efficacy; time interval until the patient was able to eat or drink; and toxicity.

Study	Methods	Objective	Patients	Interventions	Outcome
Orr 1981[192]	Double-blind, randomized study with a 2 period crossover design Country of origin: USA Duration of study: 4 months	To evaluate the antiemetic effect of THC in chemotherapy-associate nausea and emesis as compared to placebo and PCZ	N=79 people (51 women/28 men) aged 22-71 years, mean = 46 years. Tumour type: variety of neoplasms Chemotherapy regimen: doxorubicin, cyclophosphamide, 5-fluorouracil (with methotrexate), nitrogen mustard, imidazole carboxamide, nitrosaurea and cytosine arabinoside. No information on doses reported. Chemotherapy emetogenicity: high	– THC, 7 mg/m2 every 4 hours x 4 doses orally – PCZ, 7 mg every 4 hours x 4 doses orally – Placebo Setting: inpatient	Nausea 24 hours post treatment and adverse events
Sallan 1975[193]	Double-blind, randomized study with a 2 period crossover design Country of origin: USA Duration of study: 5 months	To determine the effect of oral THC on nausea and vomiting in patients receiving cancer chemotherapy	N=22 people (10 men/12 women) aged 18-76 years (median = 29.5 years). Tumour types: variety of neoplasms Chemotherapy regimen: adriamycin, 5-azacytidine, nitrogen mustard, imidazole carboxamide, procarbazine, high-dose cyclophosphamide or high-dose methotrexate or combinations. No information on doses reported Chemotherapy emetogenicity: unable to classify	– THC, 7 mg/m2 every 4 hours x 4 doses orally – PCZ, 7 mg every 4 hours x 4 doses orally – Placebo Setting: inpatient	Nausea, vomiting, food intake, side effects
Sallan 1980[194]	Double-blind, randomized study with a 2 period crossover design Country of origin: USA Duration of study: 5 months	To evaluate the efficacy of THC compared with PCZ in patients who had failed to benefit from standard antiemetic therapy	N=84 patients with neoplasms. 55 male, age range from 9 to 70 years (average 32, 5 years). Chemotherapy regimen: doxorubicin, cyclophosphamide, high dose methotrexate, cisplatin, bleomycin, vinblastine	– THC 10 mg/m2 suspended in 0, 12 of sesame oil and supplied in gelatine capsules with 15 mg the amount most commonly administered. – PCZ, 10 mg Setting: inpatient	Nausea and vomiting, food intake, development of a "high"
Strasser 2006[185]	Multicentre, Phase III, Randomized, Double-Blind, Placebo-Controlled Clinical Trial Country of origin: Switzerland Duration of study: 6 weeks	To compare the effects of cannabis extract (CE) THC on appetite and quality of life in patients with cancer-related anorexia-cachexia syndrome (CACS).	N=243 patients with incurable cancer, ECOG performance status (PS)≤ 2 Mean age= 61 years, sex=54% men, weight loss>5% over 6 months	– cannabis extract (n = 95) – THC (n= 100); – Placebo (n= 48) Setting: inpatient	Appetite change from baseline to week 6, change in QOL from baseline to week 6, feeling of nausea and mood.

Study	Methods	Objective	Patients	Interventions	Outcome
Ungerleider 1982[195]	Double-blind, randomized study with a 2 period crossover design Country of origin: USA Duration of study: unclear	To assess the relative efficacy of THC and PCZ in alleviating nausea and vomiting associated with cancer chemotherapy.	N=214 people (107 men/107 women) aged 18-82 years (median = 47 years). Tumour types: "wide variety of neoplasms" Chemotherapy regimens: antibiotics (70 people), nitrosoureas (21 people), alkylating agents (119 people), antimetabolites (82 people), vinca-alkaloids (60 people), hormones (13 people), miscellaneous (33 people) and combinations. Chemotherapy emetogenicity: unable to classify - unknown combinations	– THC, 7.5 mg for < 1.4/m2, 10 mg for 1.4-1.8 m2 or 12.5 mg for > 1.8 m2 orally – PCZ, 10 mg 1 hour prior to chemotherapy, then every 4 hours x 4 doses per day x all chemotherapy days orally Setting: inpatient	Nausea and vomiting, Appetite and Food Intake, Mood/Behaviour scales, Side Effects

PCZ=prochlorperazine; ECOG=Eastern Cooperative Oncology Group

Appendix 6. Forest Plots for Side effects

Figures 20-46. Comparison: 5 Side effects Cannabis vs placebo parallel trial

Figure 20. Outcome 5.1: Dizziness

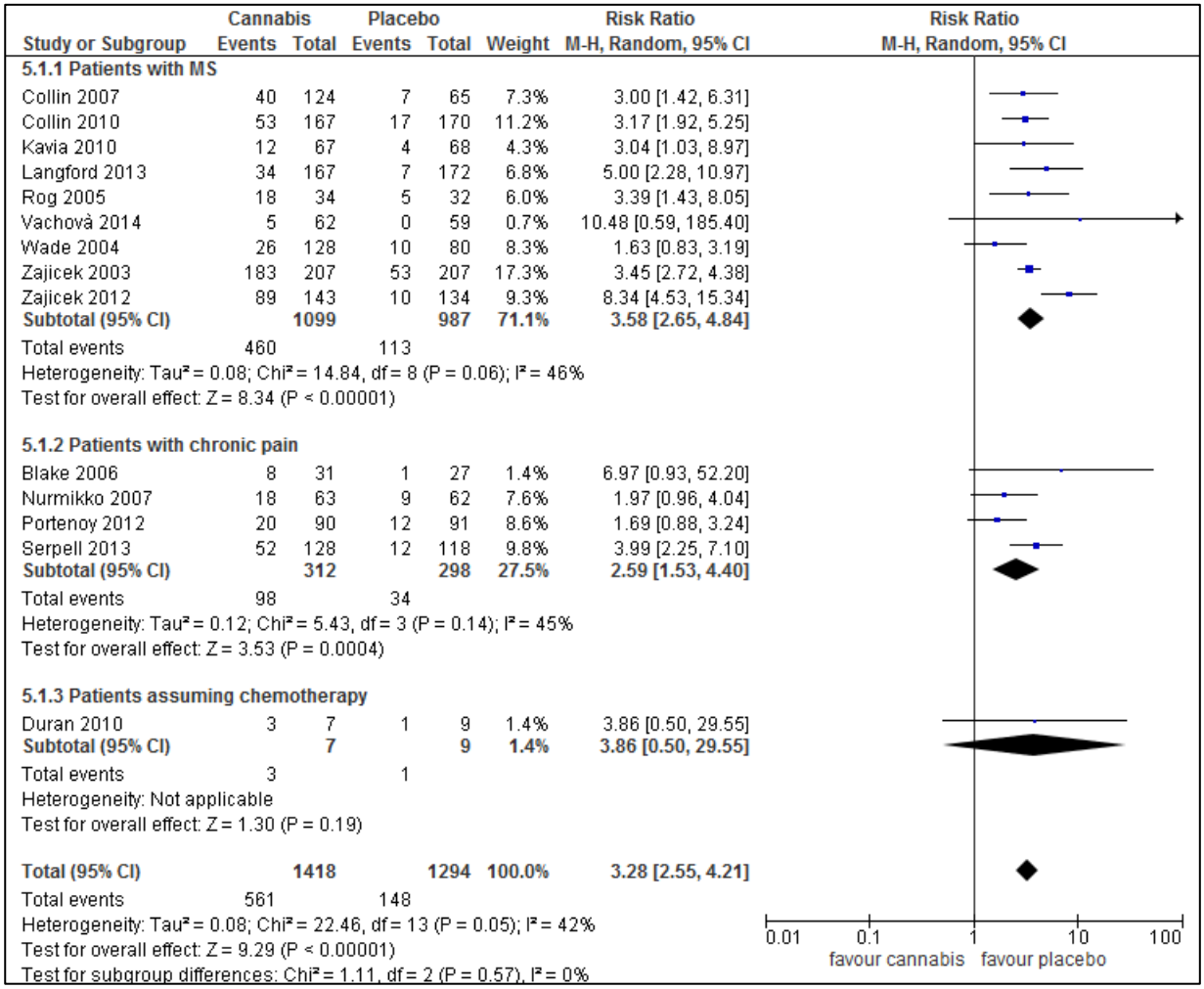


Figure 21. Outcome 5.2: Somnolence

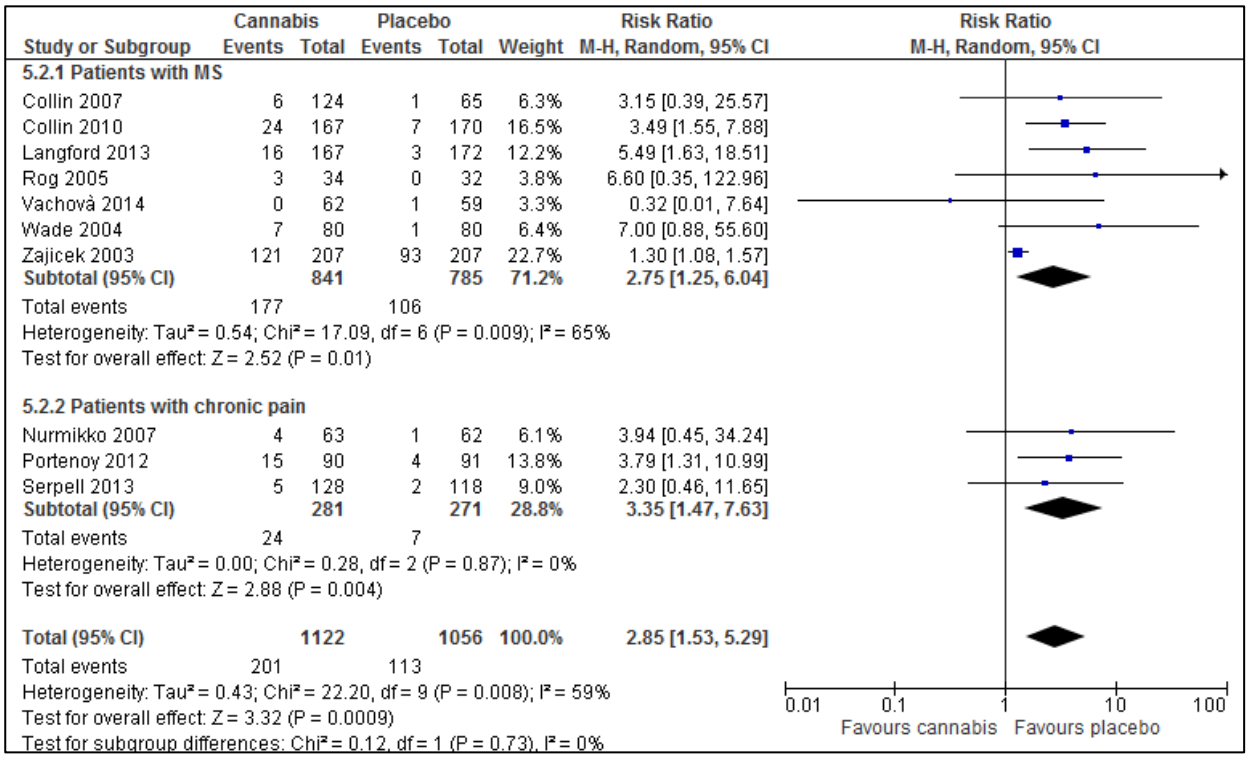


Figure 22. Outcome 5.3: Headache

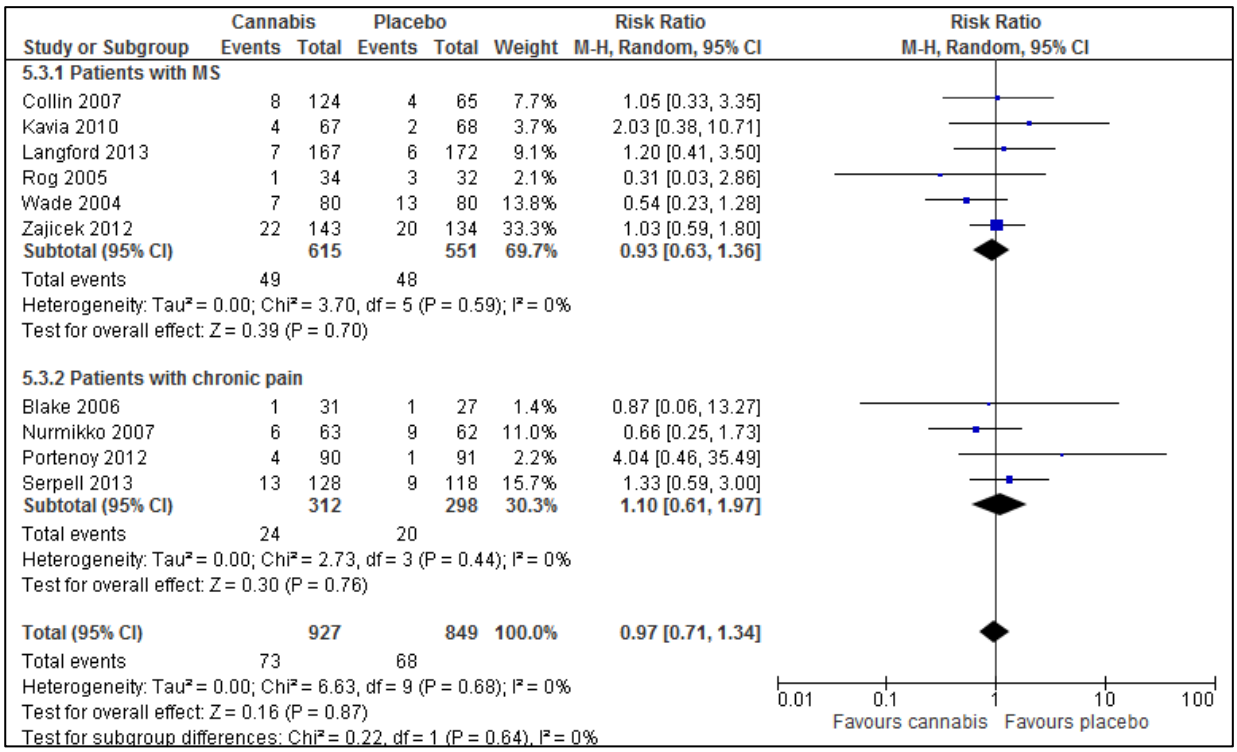


Figure 23. Outcome 5.4: Gastrointestinal disorders

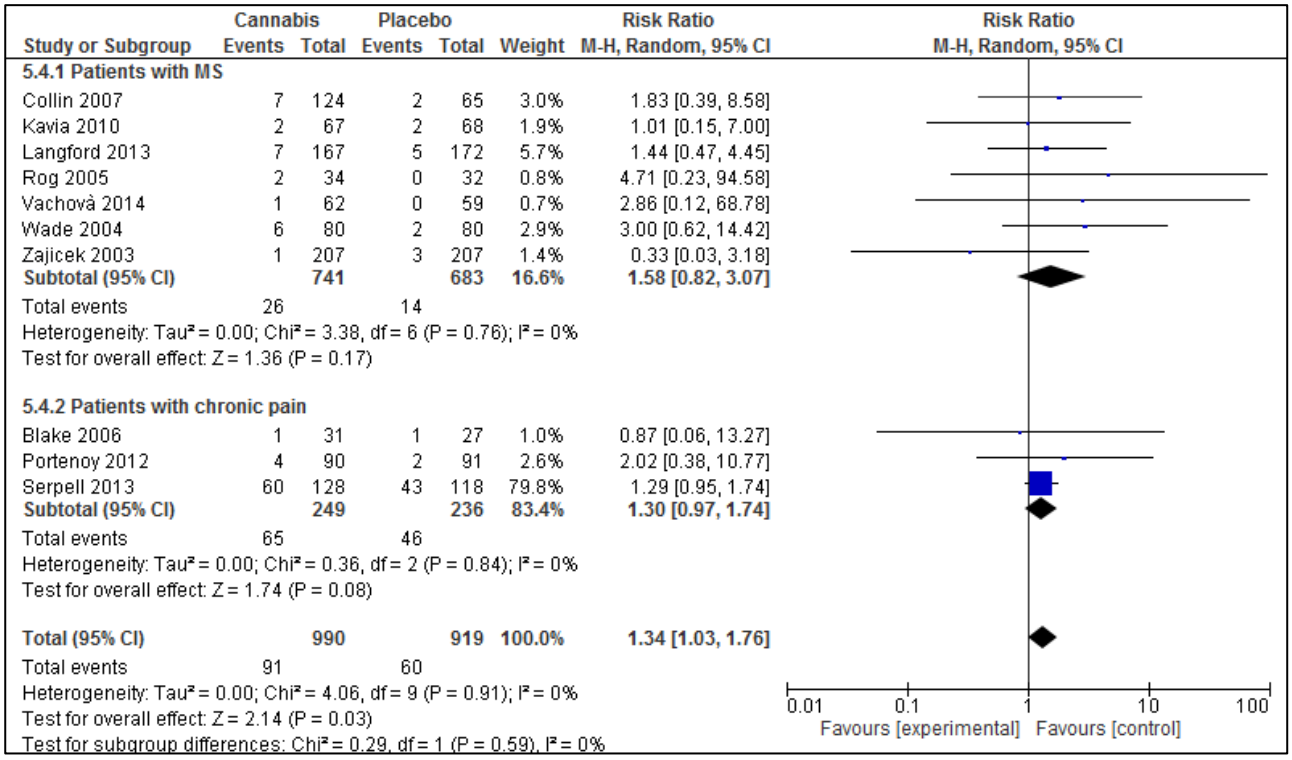


Figure 24. Outcome 5.5: Dry mouth

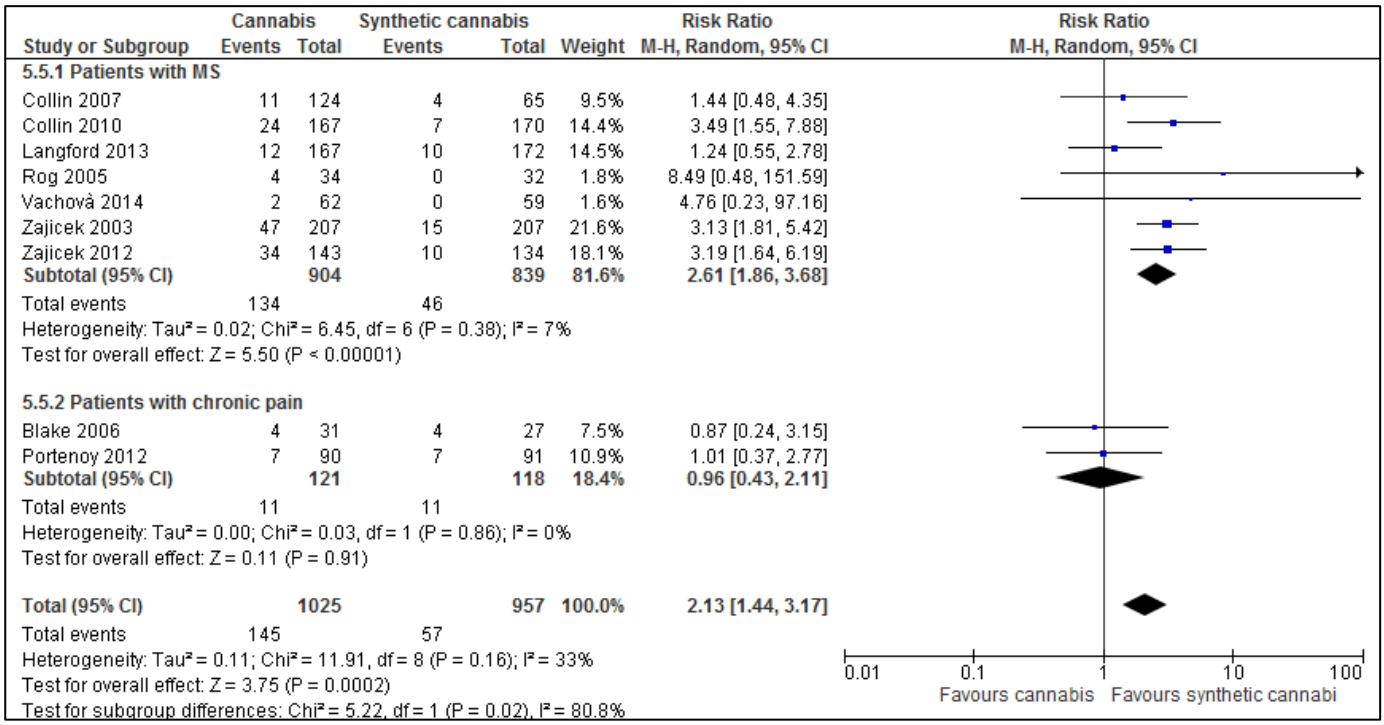


Figure 25. Outcome 5.6: Feeling high

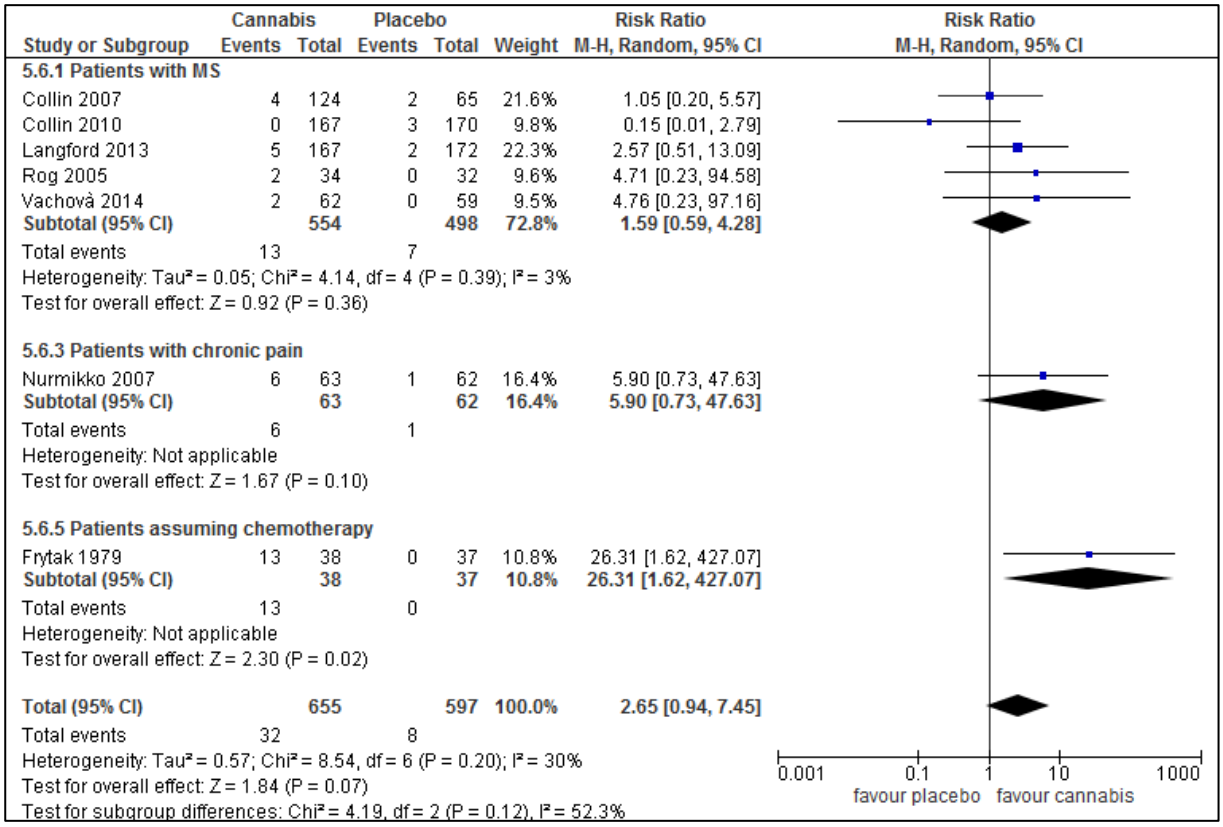


Figure 26. Outcome 5.7: Renal and urinary disorders.

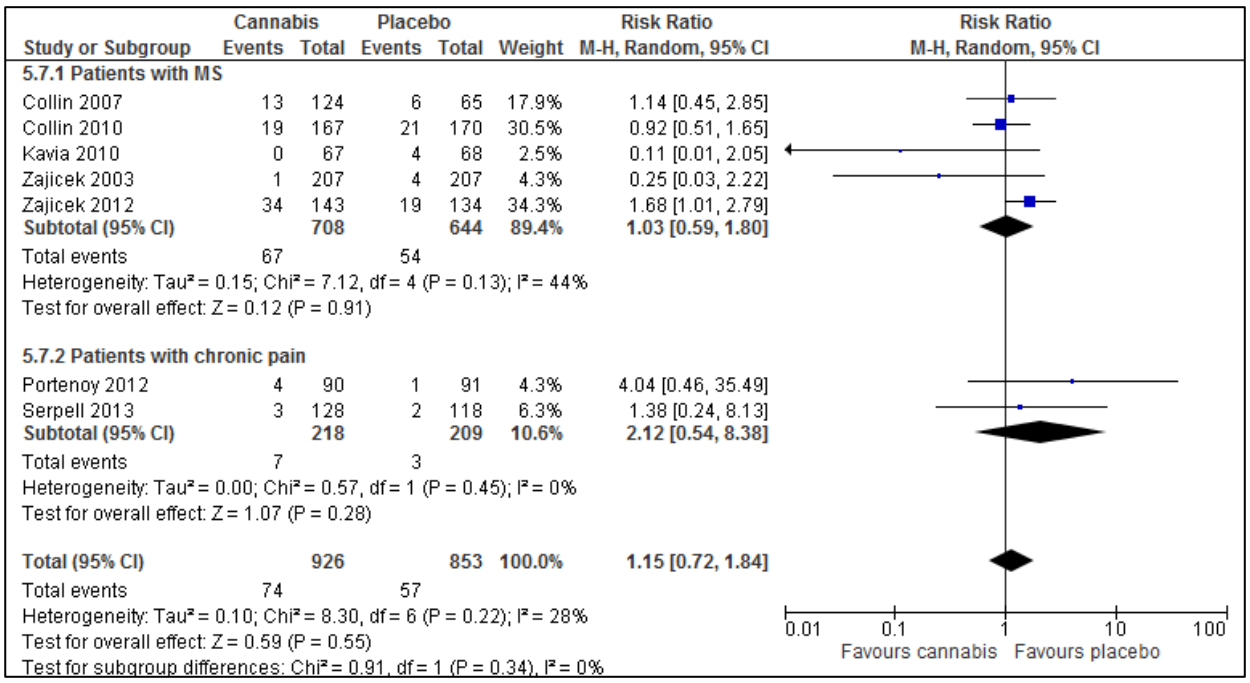


Figure 27. Outcome 5.8: Fatigue

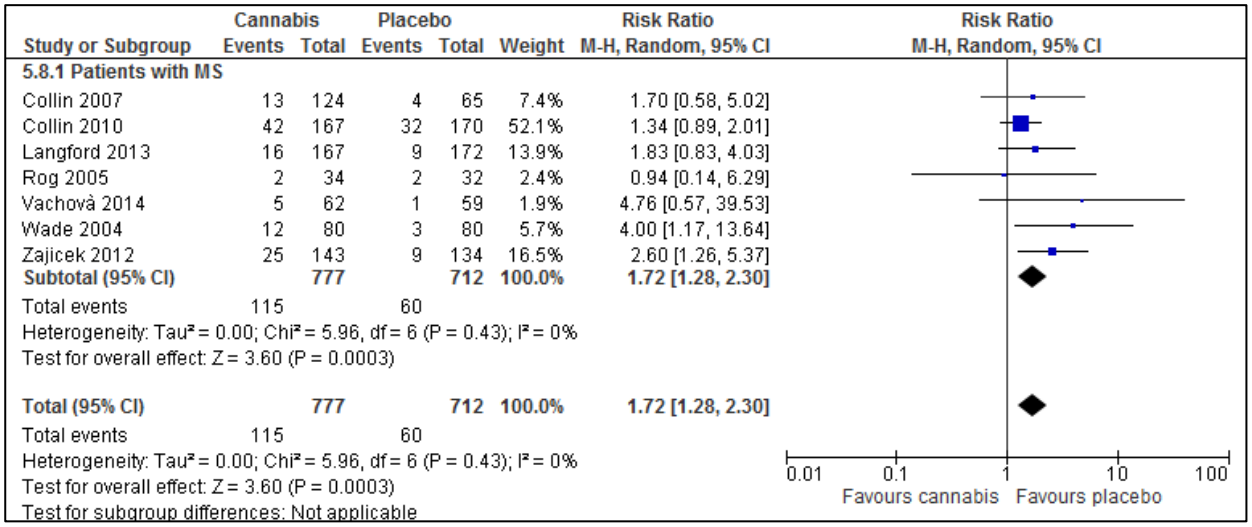


Figure 28. Outcome 5.9: CNS side effects

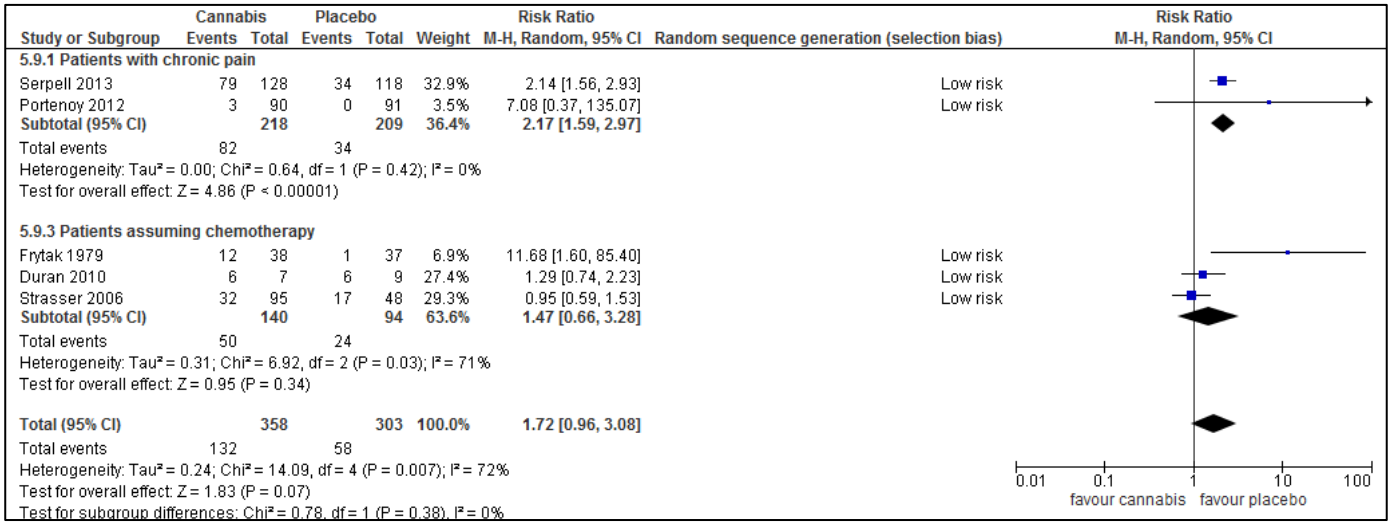


Figure 29. Outcome 5.10: Disorientation

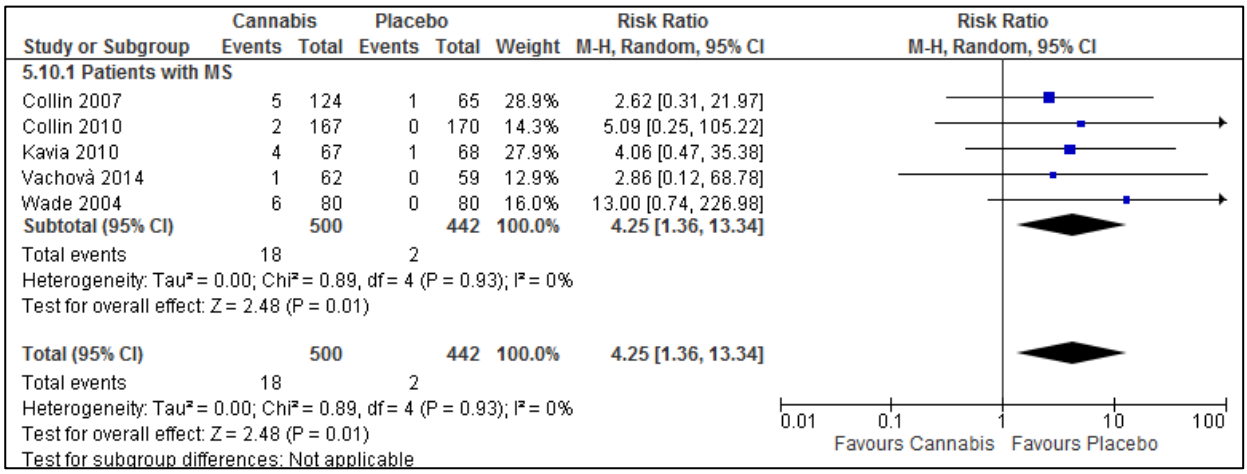


Figure 30. Outcome 5.11: Disturbance in attention.

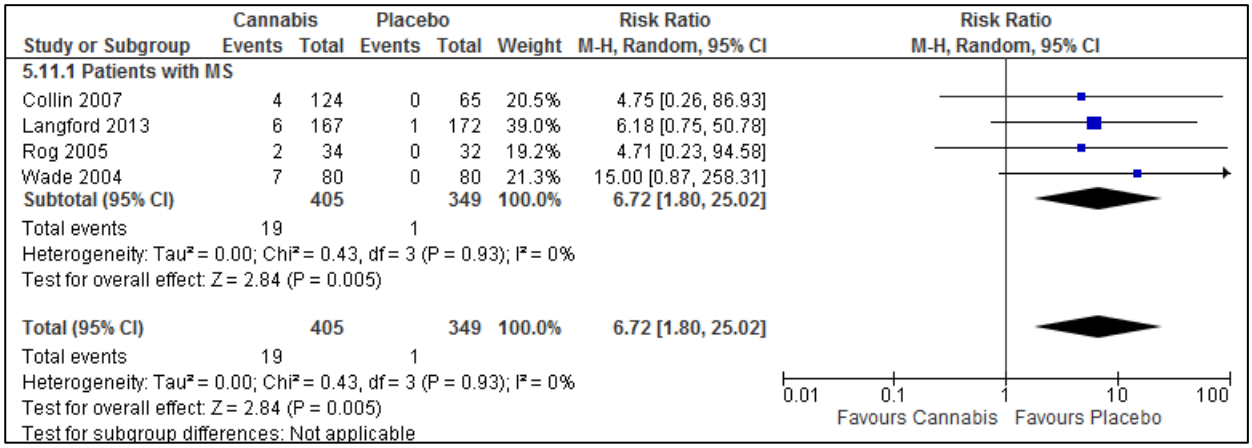


Figure 31. Outcome 5.12: Weakness

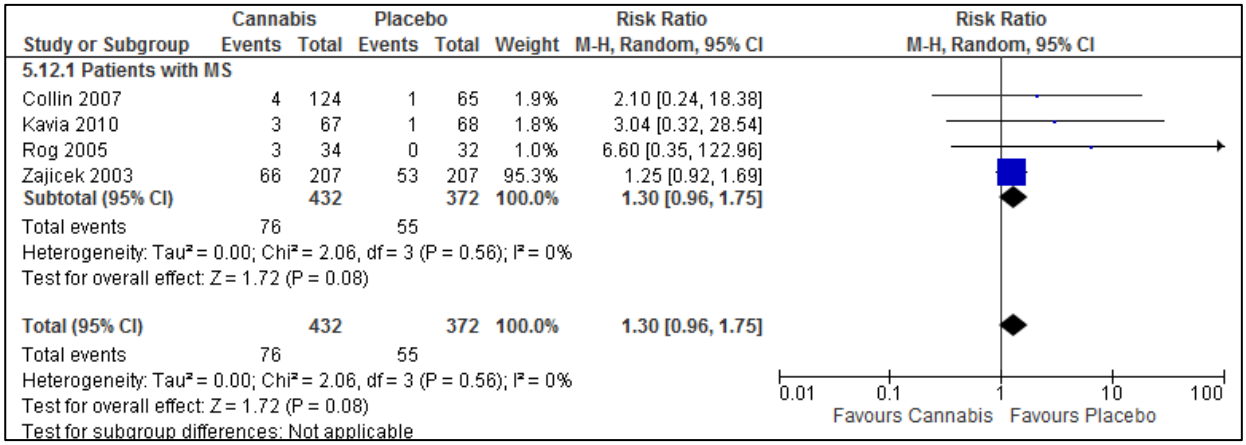


Figure 32. Outcome 5.13: Vision blurred

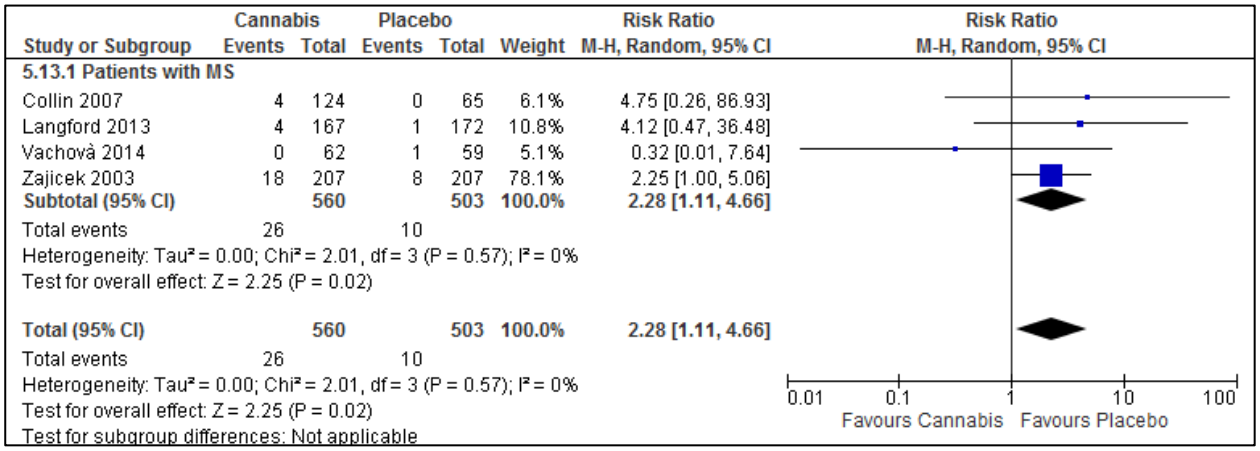


Figure 33. Outcome 5.14: Muskoskeletal and connective disorders.

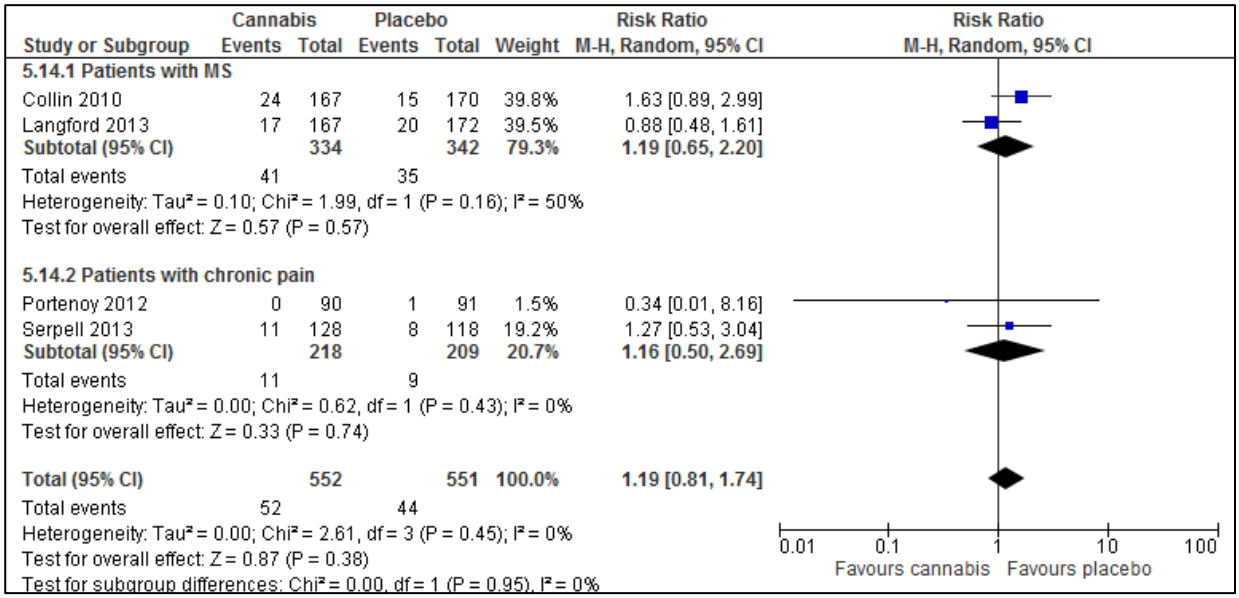


Figure 34. Outcome 5.15: Vertigo.

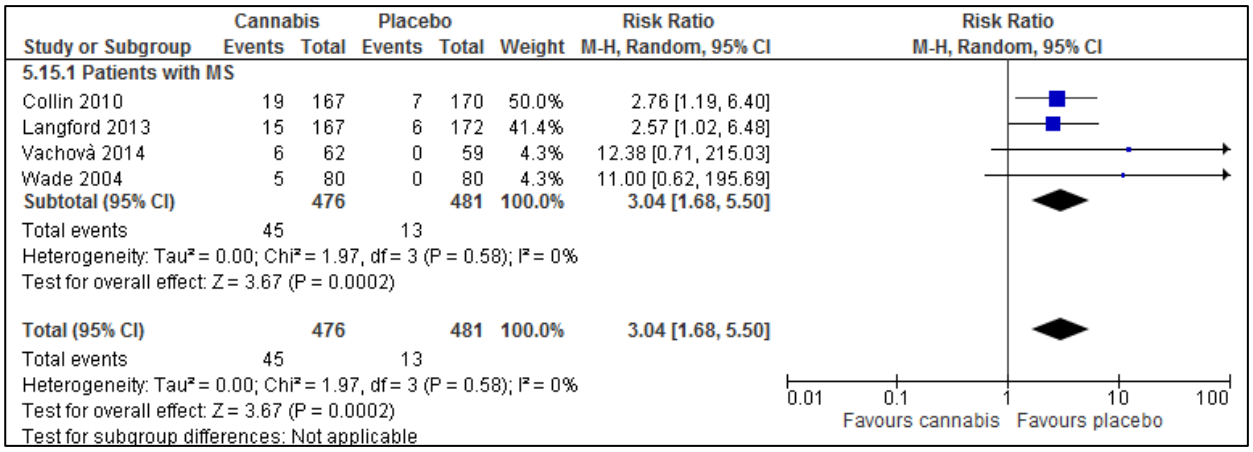


Figure 35. Outcome 5.16: Withdrawal for any reason

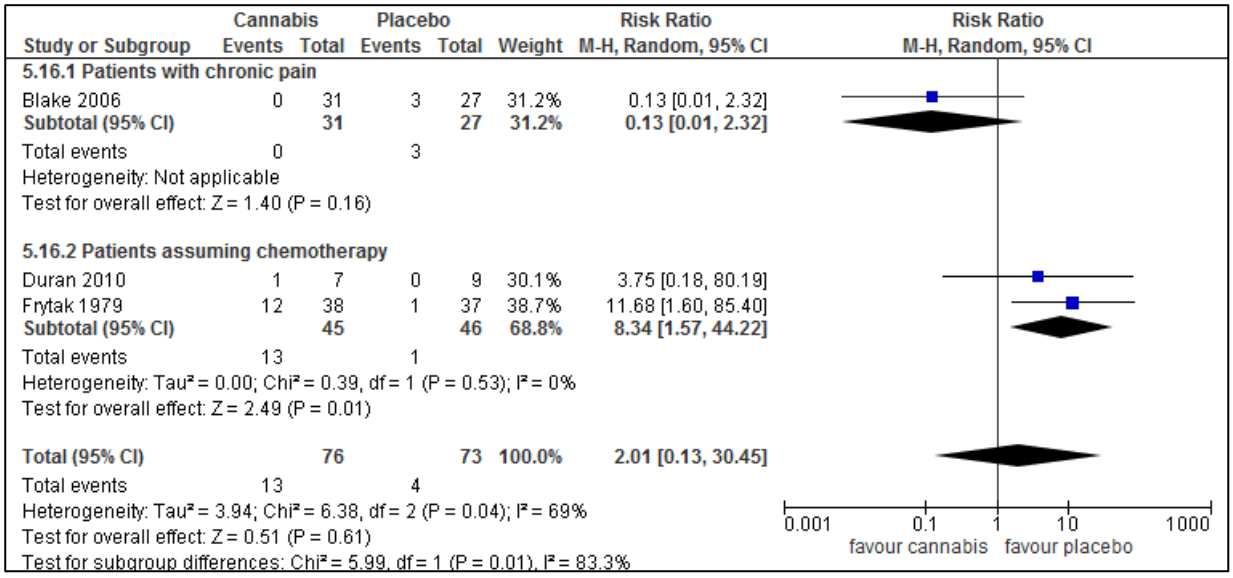


Figure 36. Outcome 5.17: Dysgeusia (bad taste)

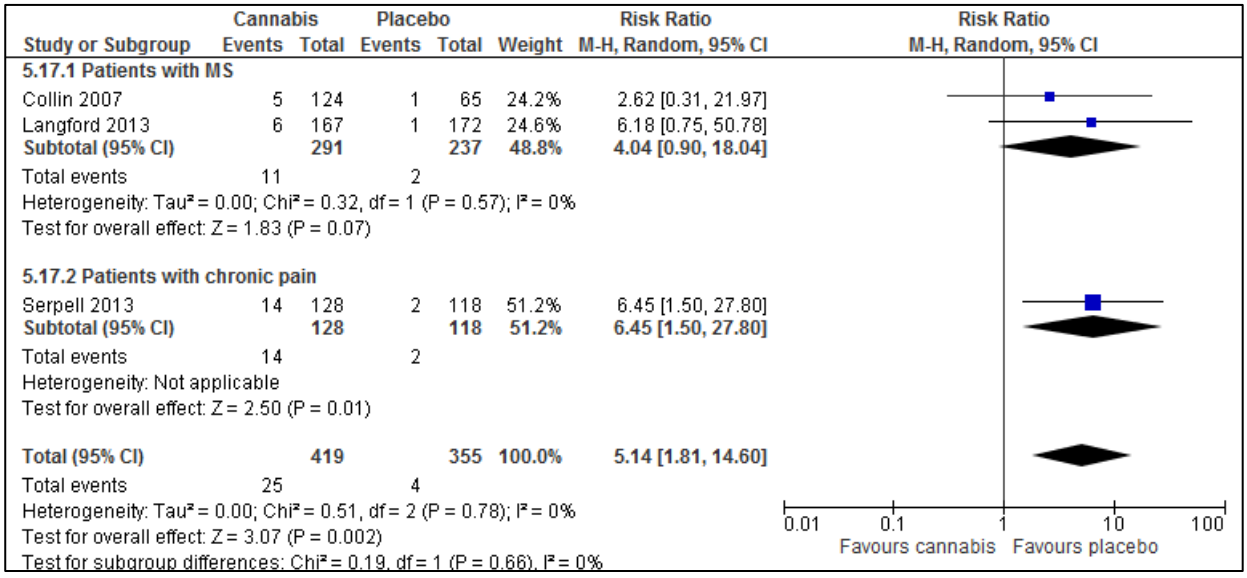


Figure 37. Outcome 5.18: Depression

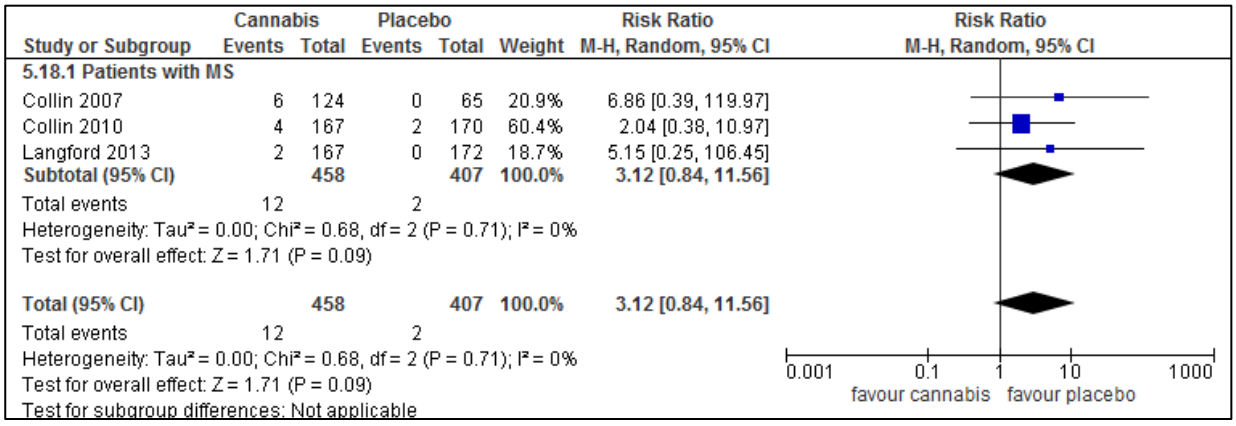


Figure 38. Outcome 5.19: Respiratory disorders

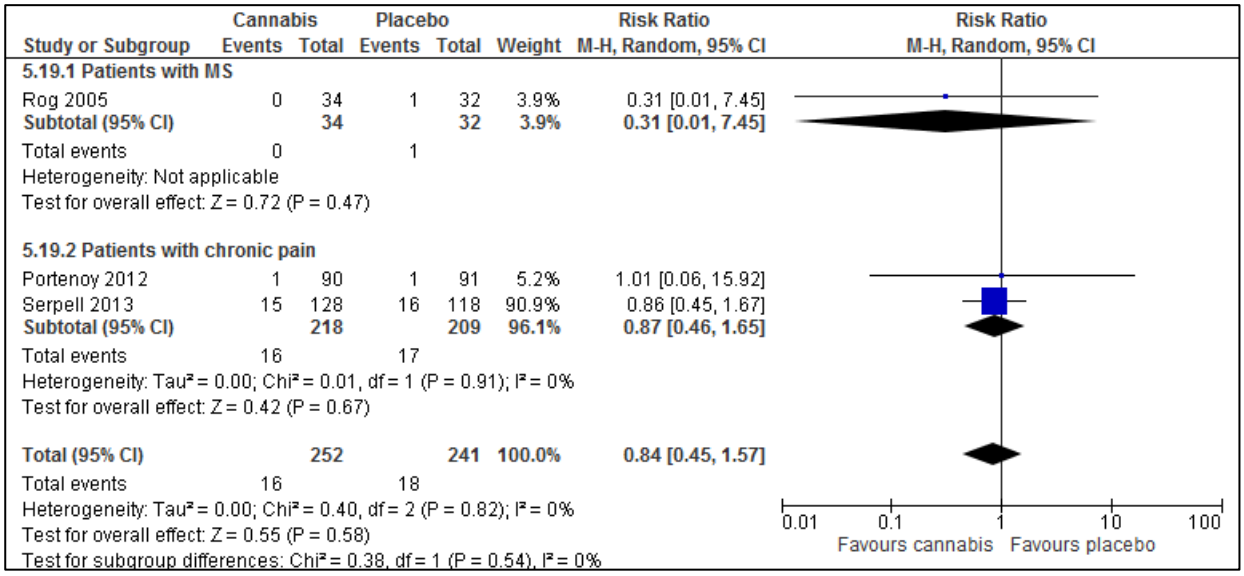


Figure 39. Outcome 5.20: General psychiatric disorders

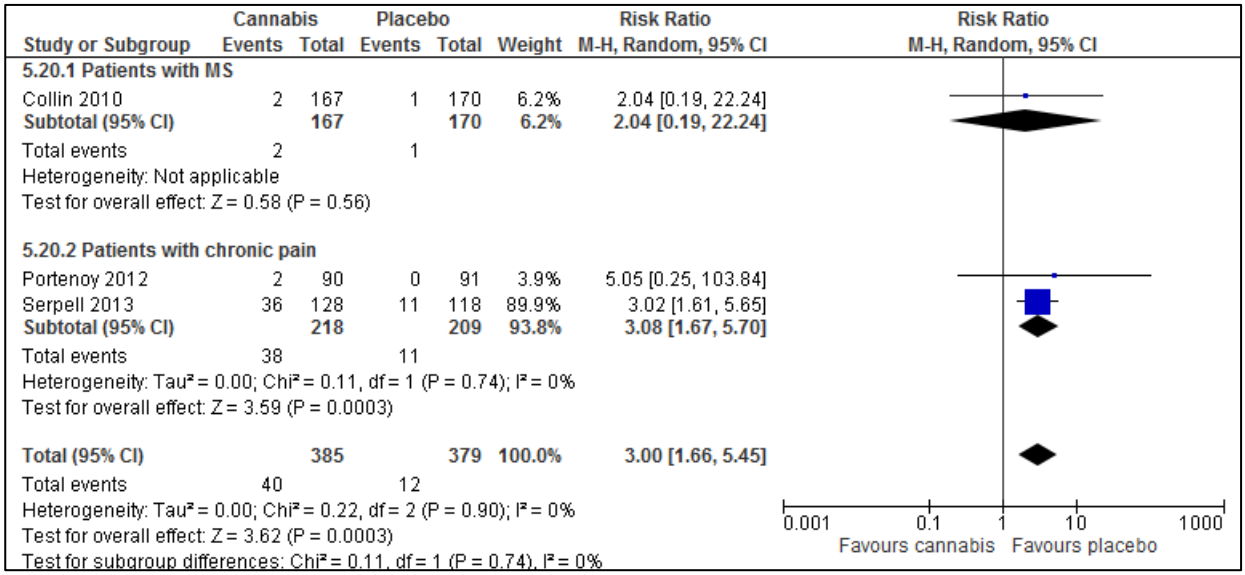


Figure 40. Outcome 5.21: Mouth ulceration

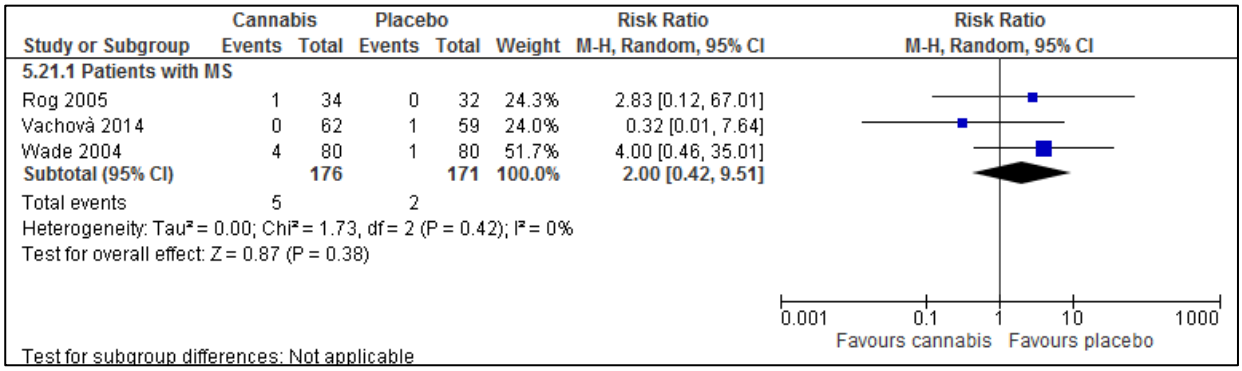


Figure 41. Outcome 5.22: Application site discomfort

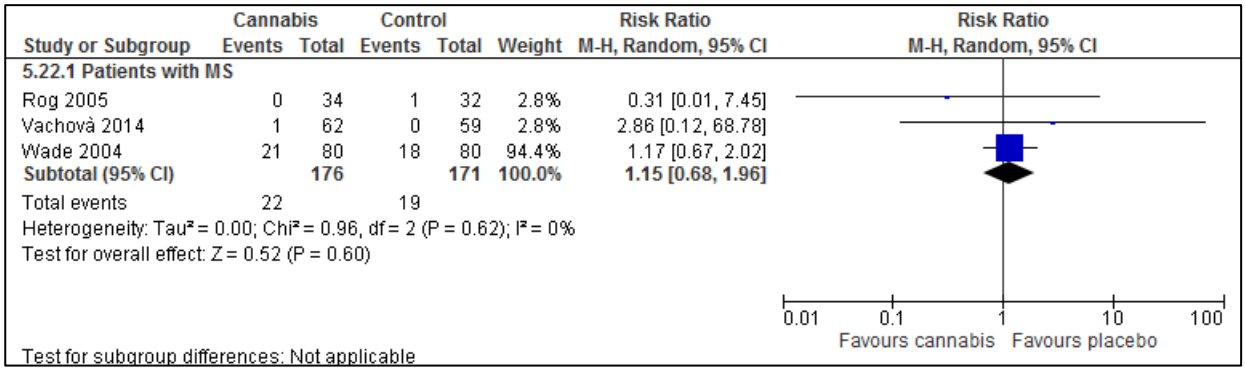


Figure 42. Outcome 5.23: Asthenia

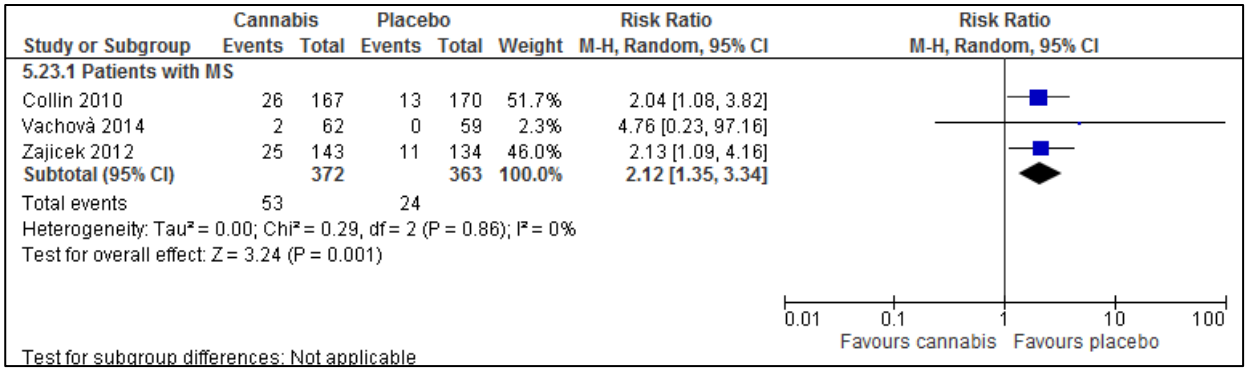


Figure 43. Outcome 5.24: Dissociation

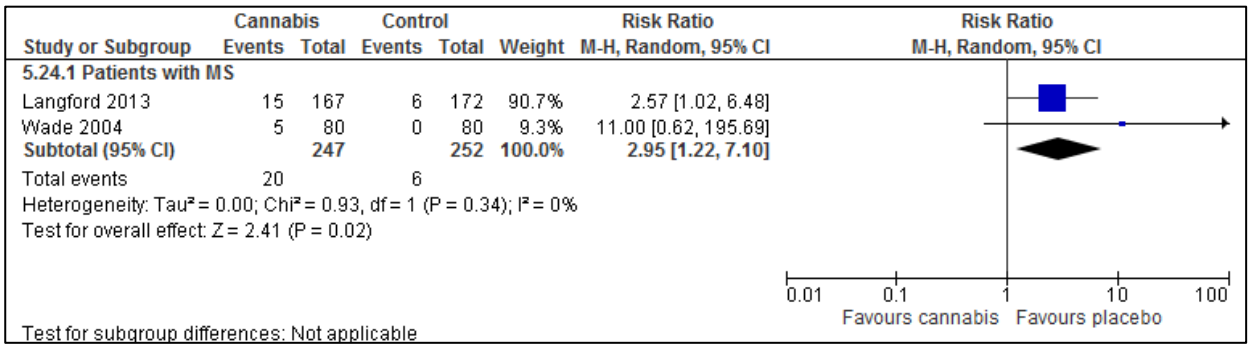


Figure 44. Outcome 5.25: Confusion

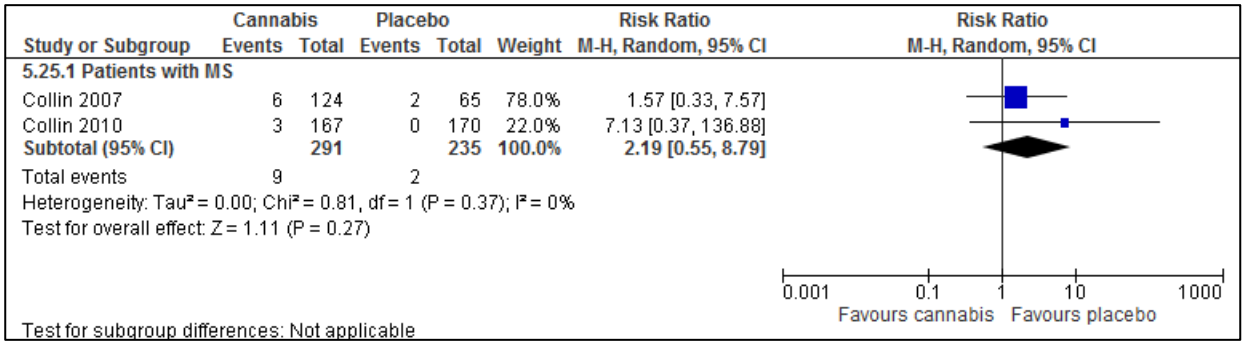


Figure 45. Outcome 5.26: Nausea in patients with MS and chronic pain.

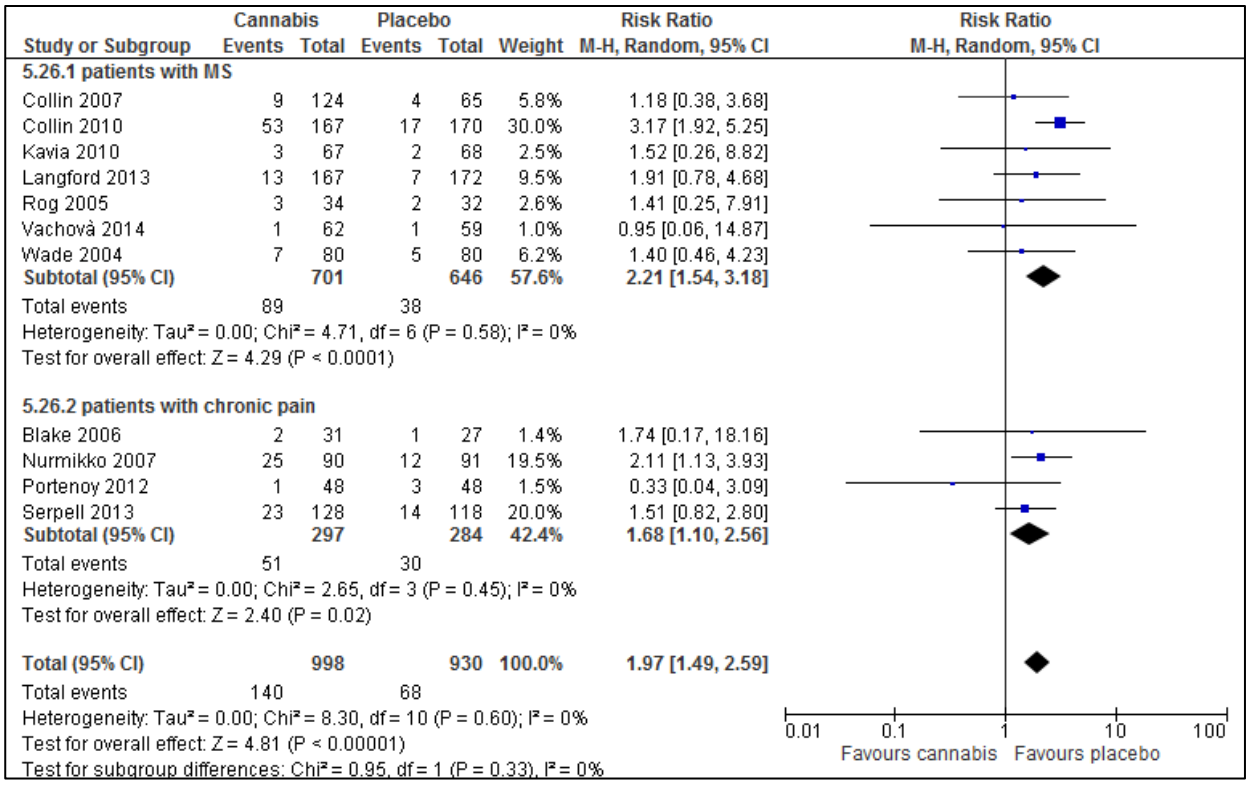
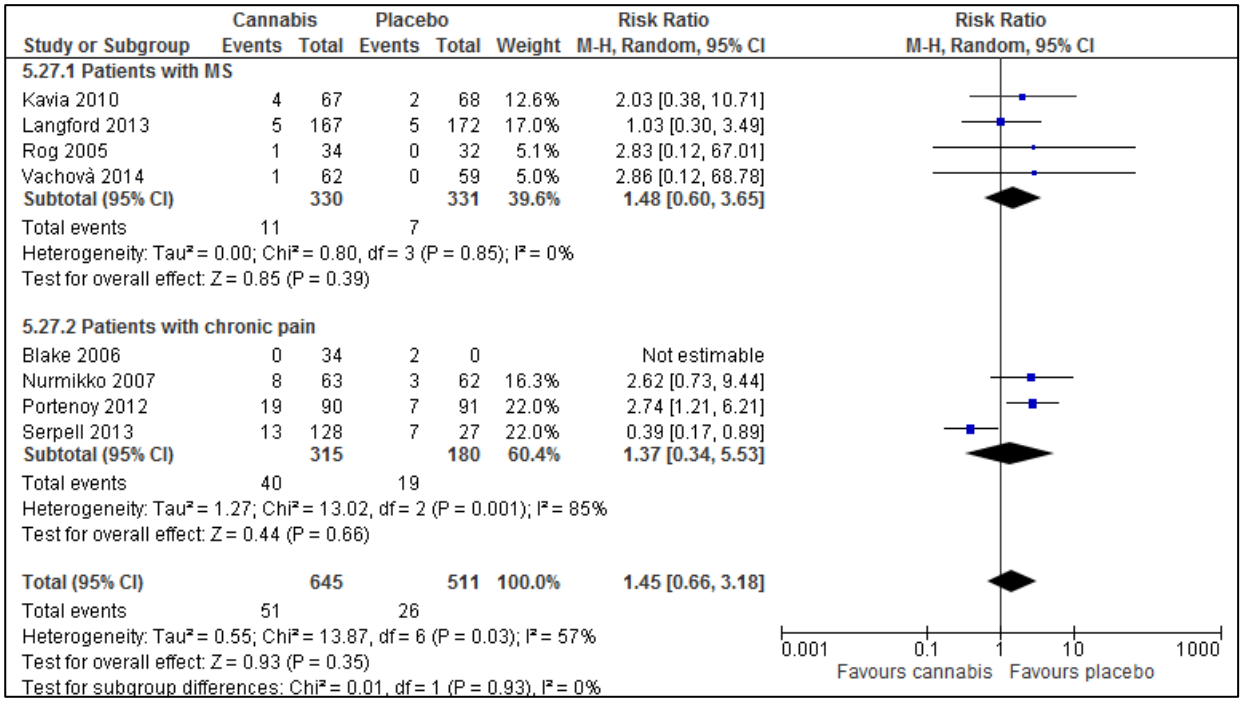


Figure 46. Outcome 5.27: Vomiting in patients with MS or chronic pain



Figures 47- 59. Comparison 6: Side effects Cannabis versus placebo crossover trials

Figure 47. Outcome 6.1: Feeling high.

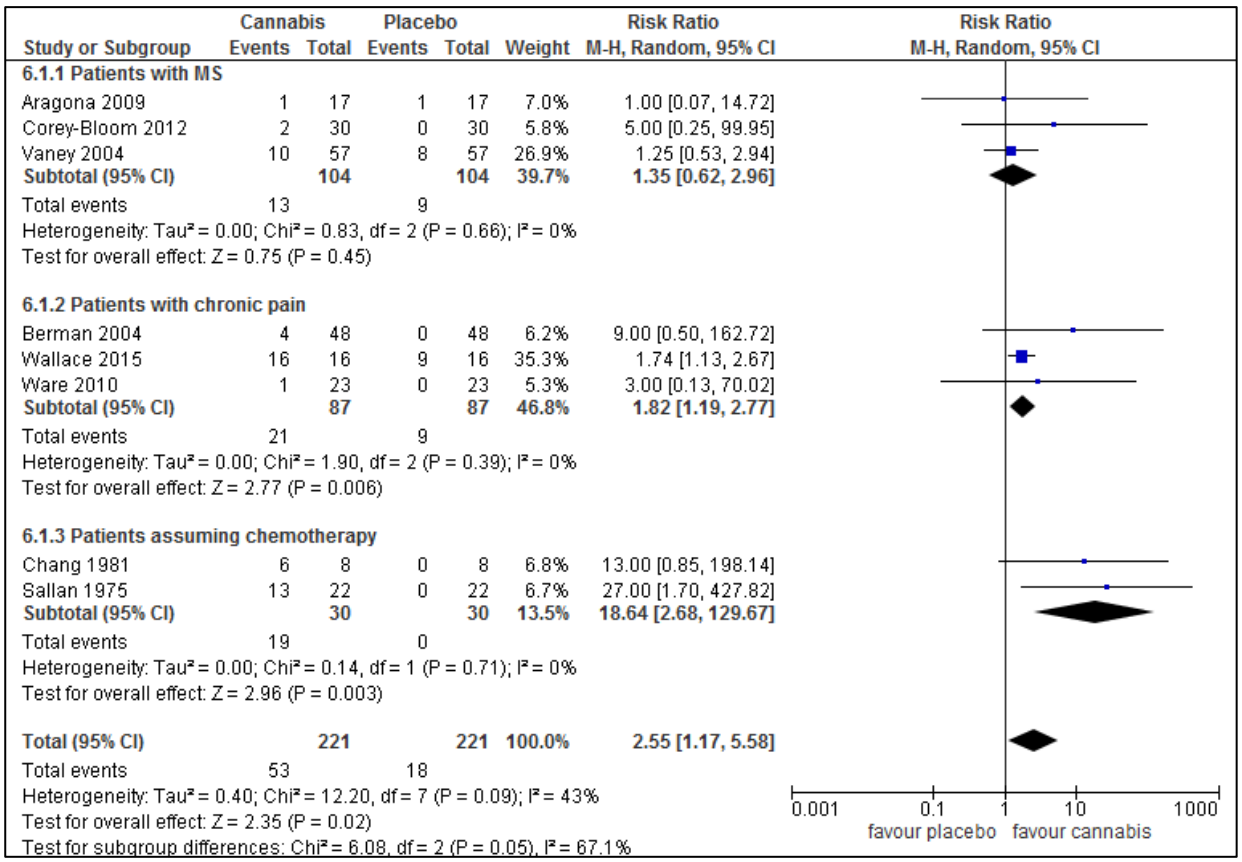


Figure 48. Outcome 6.2: Dizziness

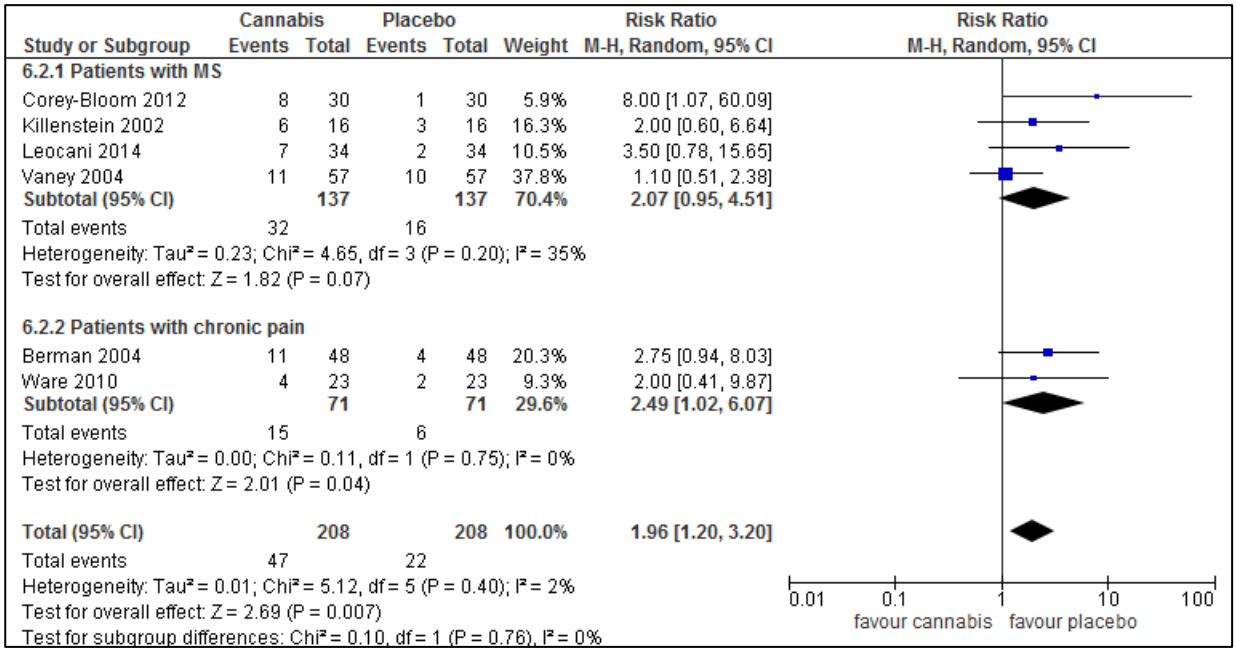


Figure 49. Outcome 6.3: Headache

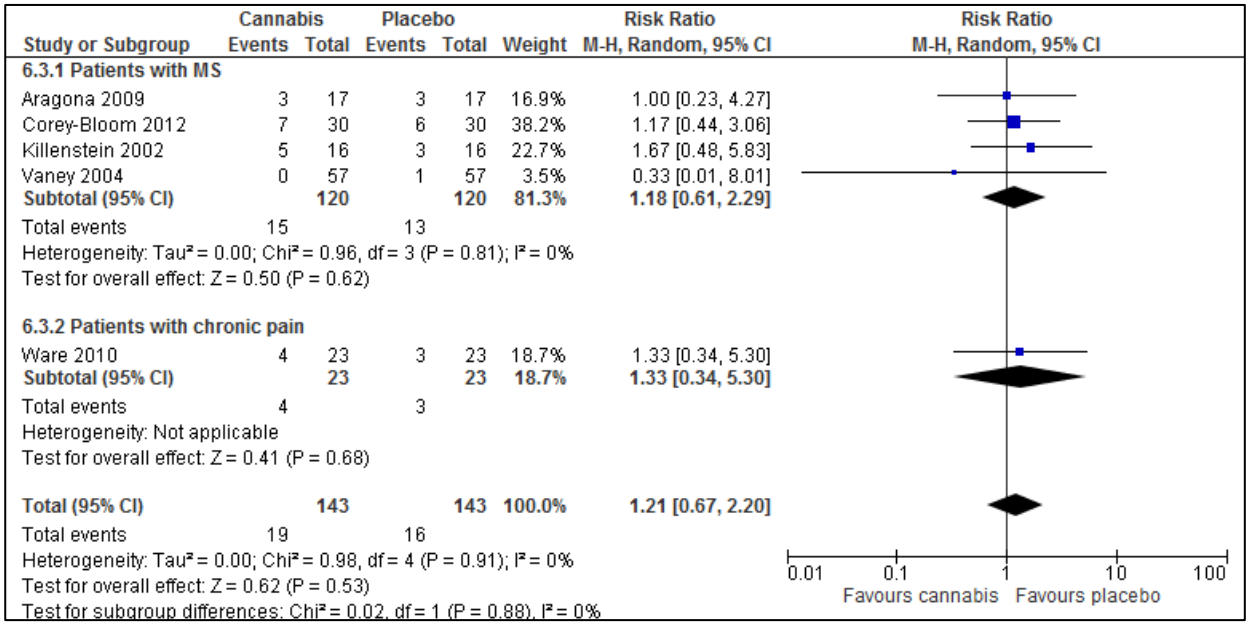


Figure 50. Outcome 6.4: Somnolence

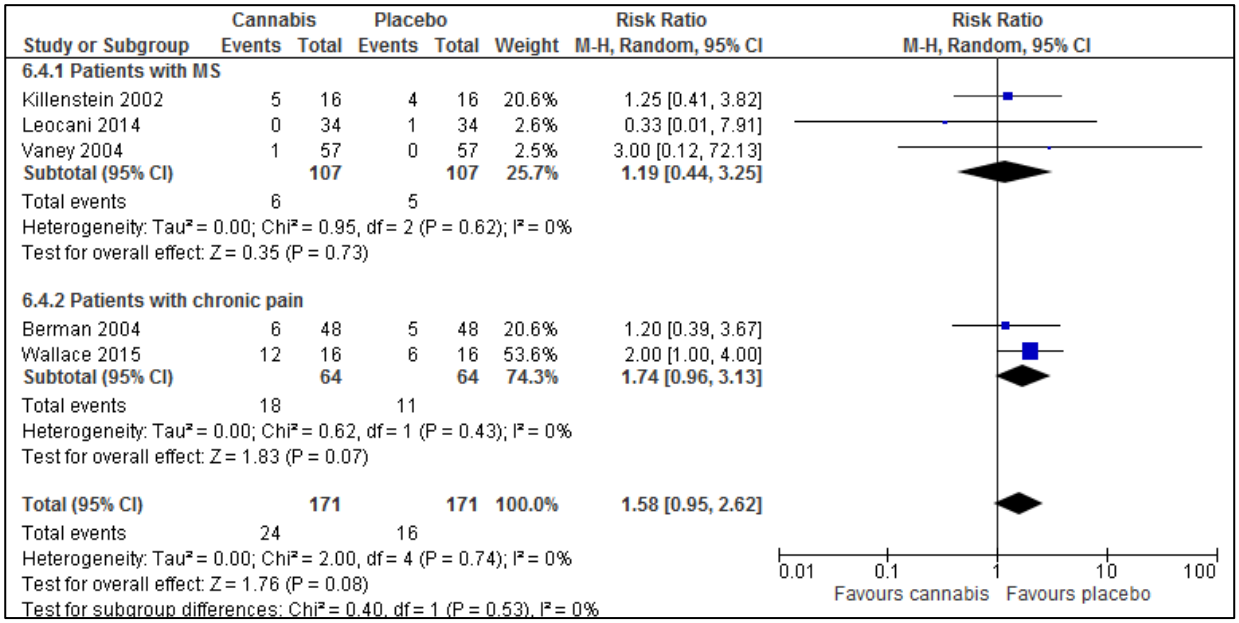


Figure 51. Outcome 6.5: Withdrawal for any reason

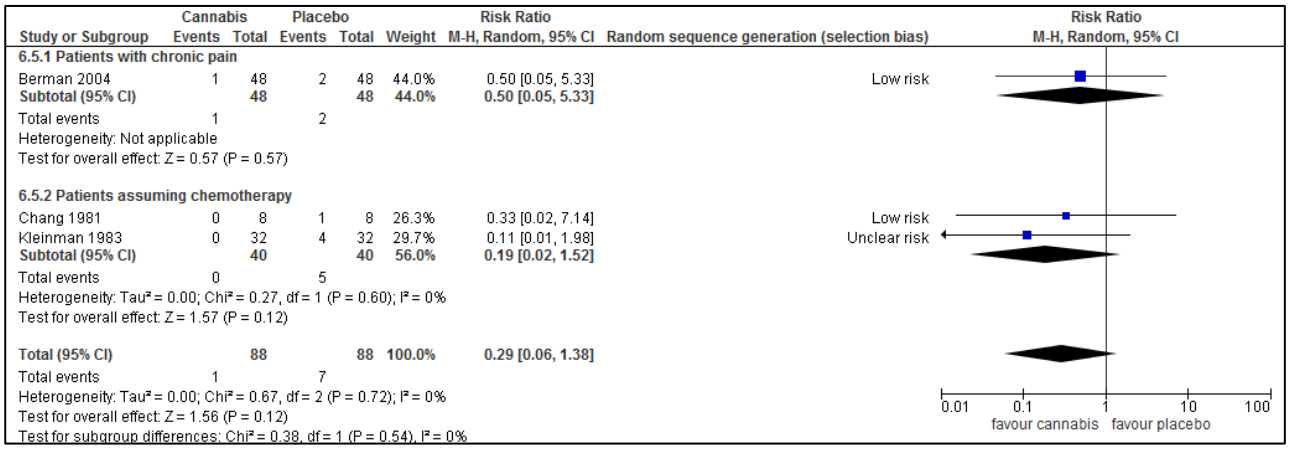


Figure 52. Outcome 6.6: Depression

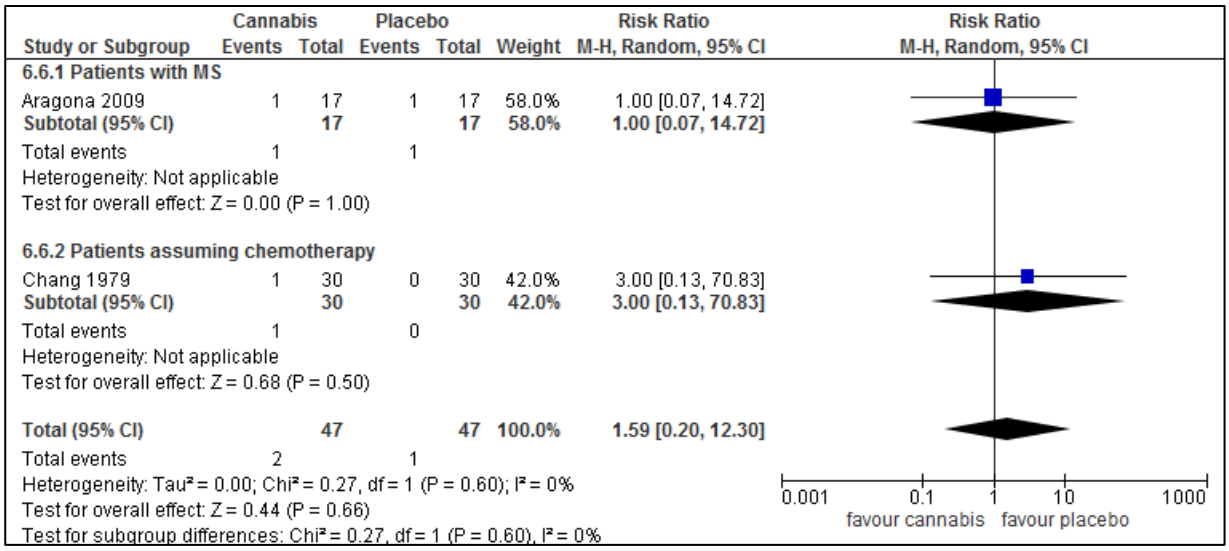


Figure 53. Outcome 6.7: Gastrointestinal disorders

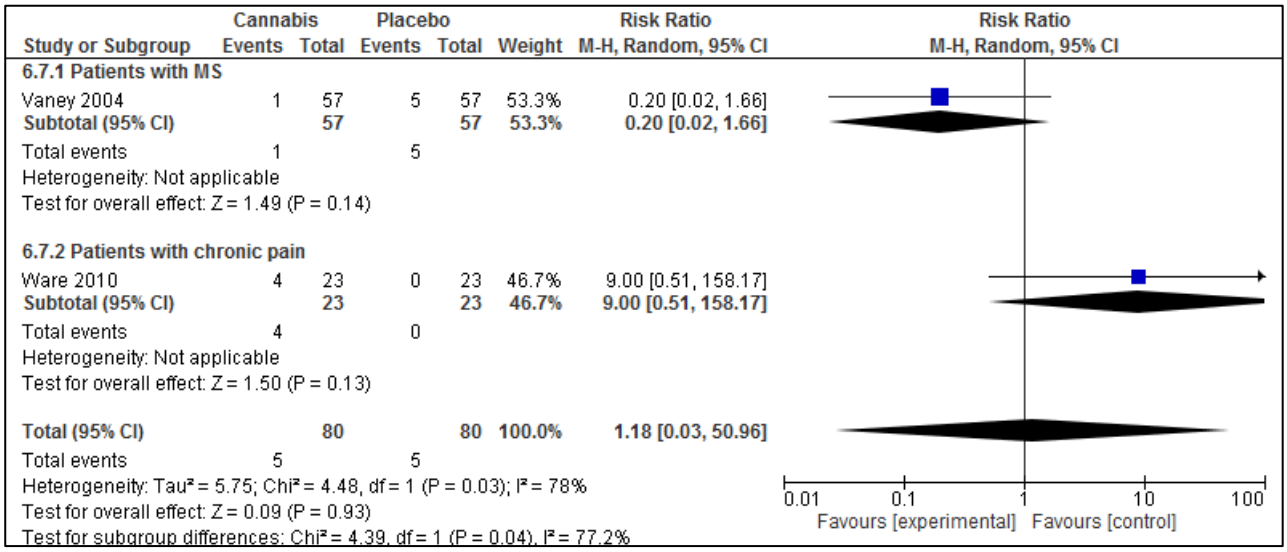


Figure 54. Outcome 6.8: Dry mouth

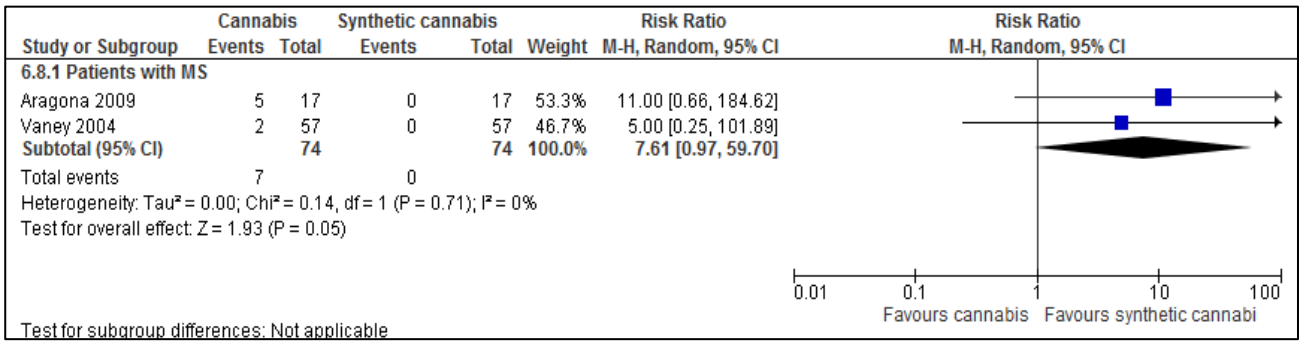


Figure 55. Outcome 6.9: Dysgeusia (bad taste)

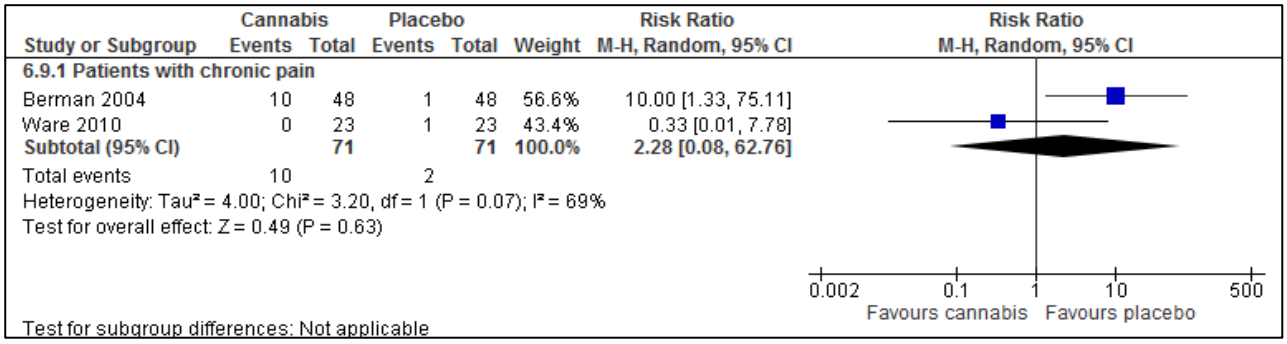


Figure 56. Outcome: 6.10 General psychiatric disorders

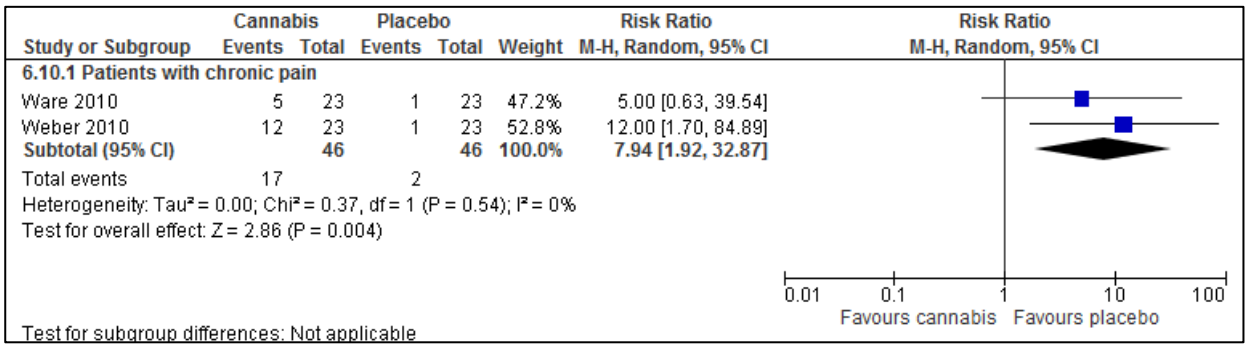


Figure 57. Outcome 6.11: Dysphoria

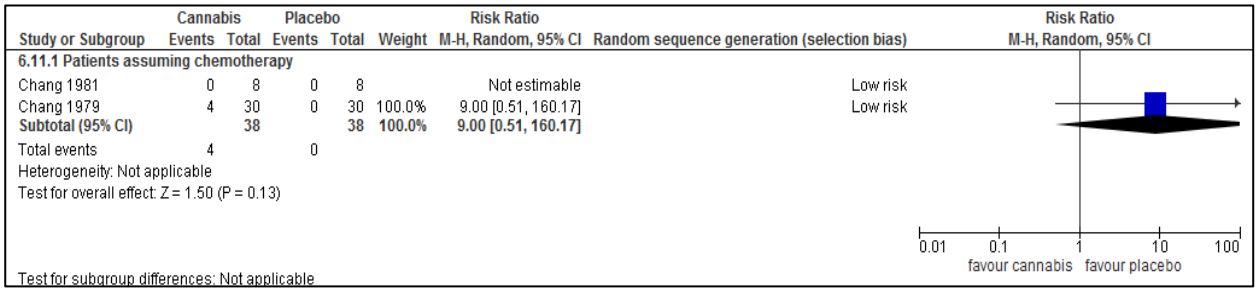


Figure 58. Outcome 6.12: Fatigue

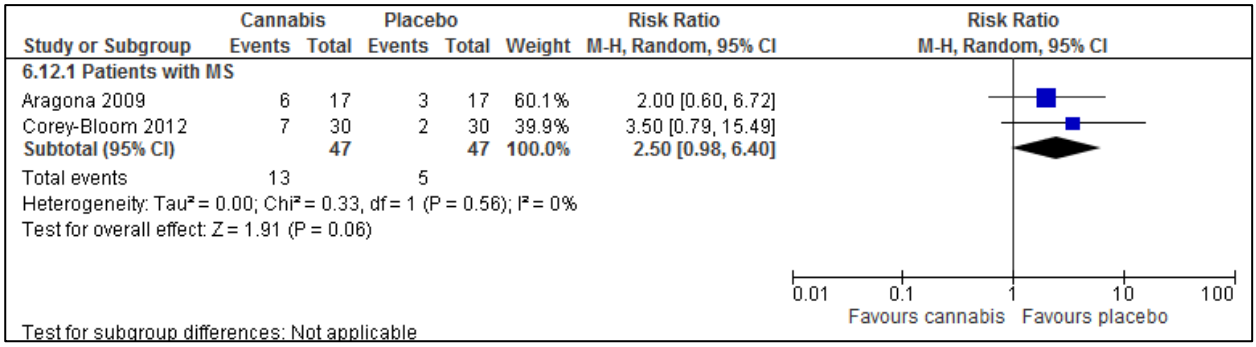
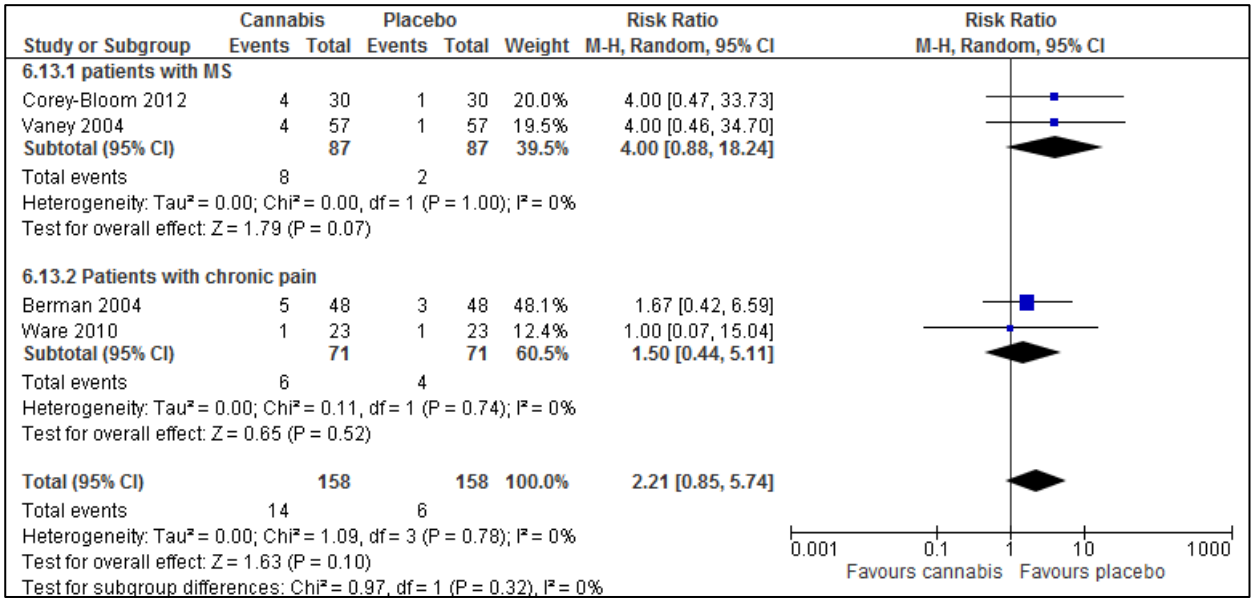


Figure 59. Outcome 6.13: Nausea for patients with MS or chronic pain



Figures 60- 61 Comparison 7. Side effects Cannabis vs other antiemetic drugs in patient receiving chemotherapy

Figure 60. Outcome 7.1: Feeling high

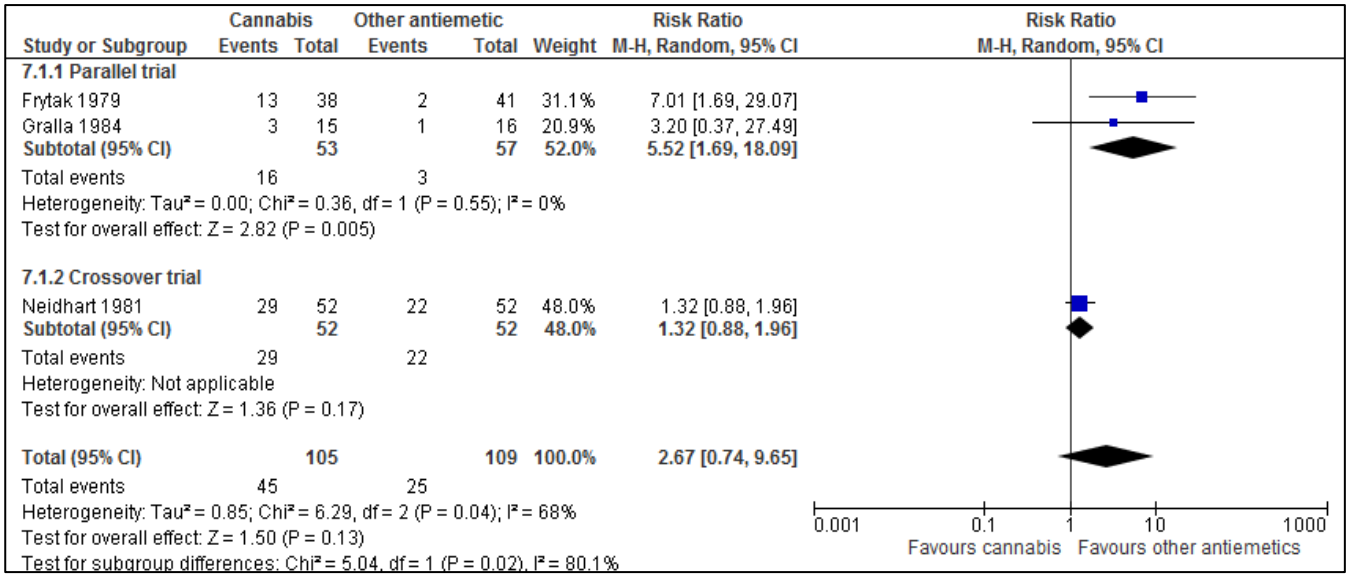
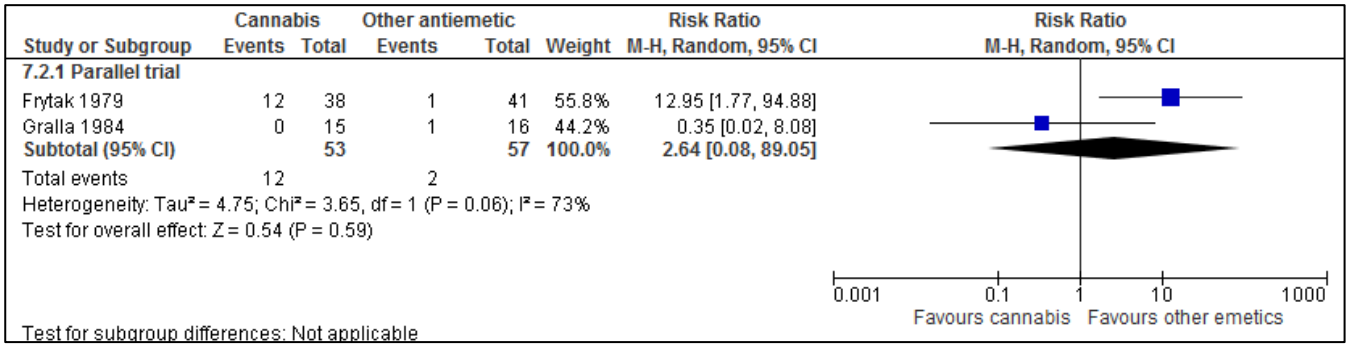


Figure 61. Outcome 7.2: Withdrawal for any reason



Appendix 7. Description of validated tools utilized to assess outcomes presented in meta-Analysis

Tool	No of items	Reference
Ashworth Scale/ Modified Ashworth Scale	5 point scale (range 0 to 4); MAS uses 6 point scale (range 0 to 4)	Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. Physical Therapy 1987; 67(2):206-7.
Numerical rating scale (NRS) for spasticity:	11-point numeric scale, where 0 = no spasticity and 10 = worst possible spasticity.	Farrar et al. 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 May; 30(5):974-85. Farrar et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001; 94:149–58.
Numerical rating scale (NRS) for sleep quality:	11-point numeric scale, where 0 = best possible sleep and 10 = worst possible sleep.	Arnold et al. Time to improvement of pain and sleep quality in clinical trials of pregabalin for the treatment of fibromyalgia. Pain Med. 2015 Jan;16(1):176-85. Cappelleri et al. Psychometric properties of a single-item scale to assess sleep quality among individuals with fibromyalgia. Health Qual Life Outcomes. 2009 Jun 17;7:54.
Numerical rating scale (NRS) for pain:	11-point numeric scale, where 0 = no pain and 10 = worst possible pain.	Downie et al. Studies with pain rating scales. Ann Rheum Dis 1978; 37: 378–81.
Visual Analog Scale for Pain (VAS Pain):	a single-item scale measuring pain intensity where 0 = no pain and 100 = worst possible pain.	Hawker et al. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res (Hoboken). 2011 Nov; 63 Suppl 11:S240-52.
Neuropathic Pain Scale (NPS):	10- point numeric scale. All the items are rated on a 0 to 10 scale	Galer et al. Development and preliminary validation of a pain measure specific to neuropathic pain. The neuropathic pain scale. Neurology 1997;48:332-338. Rog et al. Validation and reliability of the Neuropathic Pain Scale (NPS) in multiple sclerosis. Clin J Pain. 2007 Jul-Aug;23(6):473-81.

Tool	No of items	Reference
Visual Analog Scale for Sleep Quality (VAS Sleep):	a five-point severity scale	Zisapel et al. Determination of the minimal clinically significant difference on a patient visual analog sleep quality scale. J Sleep Res. 2003 Dec;12(4):291-8.
Visual Analog Scale for Spasticity (VAS Spasticity):		Hsieh et al. Spasticity outcome measures in spinal cord injury: psychometric properties and clinical utility. Spinal Cord. 2008 Feb;46(2):86-95.
Tremor Index	Individual score from 0 to 10 for each arms and a total score from 0 to 60.	Alusi et al. Evaluation of three different ways of assessing tremor in multiple sclerosis. J Neurol Neurosurg Psychiatry. 2000 Jun;68(6):756-60.
Ataxia Rating Score:	Severity of arm ataxia scored for each arm on a 0 to 4 clinical ataxia scale.	Alusi et al. Evaluation of three different ways of assessing tremor in multiple sclerosis. J Neurol NeurosurgPsychiatry. 2000 Jun;68(6):756-60.
The 88-item Multiple Sclerosis Spasticity Scale (MSSS-88)	88-item instrument with eight subscales	Hobart et al. Getting the measure of spasticity in multiple sclerosis: the Multiple Sclerosis Spasticity Scale (MSSS-88). Brain. 2006 Jan;129(Pt 1):224-34.
BS-11 scale for Pain intensity	A standard eleven point ordinal pain severity scale ranging from zero 'Best Imaginable' to 10 'Worst Imaginable',	Jensen et al. The measurement of clinical pain intensity: a comparison of six methods. Pain 1986;27:117–26. Jensen et al. The subjective experience of acute pain. An assessment of the utility of 10 indices. Clin J Pain 1989;5:153–9.
Pain disability index	Ranging from minimal index: 0 "none Disability" to maximal index: 70 "Worst Disability". The scale consists of 7 categories of life activity and for each ones the score ranging from 0 that means no disability at all, and a score of 10.	Tait et al.. The Pain Disability Index: psychometric and validity data. Arch Phys Med Rehabil 1987;68:438–41.
Minimum pain scores	an 11-item numeric rating scale, with "no pain" and "worst pain possible" as anchors.	Jensen et al. The measurement of clinical pain intensity: a comparison of six methods. Pain 1986;27:117–26.