Systematic review of cannabis for medical use

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LIST OF ABBREVIATIONS

BMI	Body Mass Index
Δ^9-THC	Δ^9-tetrahydrocannabinol
ACROBAT-NRS	Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies
ADL	Activities of daily living
ADHD	Attention deficit hyperactivity disorder
AE	Adverse event
AHI	Apnea hypopnea index
AIDS	Acquired immunodeficiency syndrome
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AUC	Area under curve
BDI	Beck depression inventory
BMI	Body mass index
BPI-SF	Brief pain inventory – short form
BS-11	Box score - 11
CBD	Cannabidiol
CBM	Cannabis based medicine
CI	Confidence interval
CRPS	Complex regional pain syndrome
DNP	Diabetic neuropathic pain
DPNP	Diabetic peripheral neuropathic pain
DSM	Diagnostic and statistical manual of mental disorders
ECOG	Eastern Cooperative Oncology Group
EDSS	Expanded disability status scale
FIQ	Fibromyalgia impact questionnaire
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HADS	Hospital anxiety and depression Scale
HIV	Human immunodeficiency virus
HR	Hazard ratio
HTA	Health Technology Assessment
IM	Intramuscular
ISI	Insomnia severity index
ITT	Intention to treat
IV	Intravenous
LSEQ	Leeds sleep evaluation questionnaire
MADS	Montgomery Asberg depression scale
MADRS	Montgomery Asberg depression rating scale
MedDRA	Medical dictionary for regulatory activities
MD	Mean difference
MFIS	Modified fatigue impact scale
MI	Myocardial infarction
MS	Multiple sclerosis
MSIS	Multiple sclerosis impact scale
MSSS	Multiple sclerosis spasticity scale
MSQoL	Multiple sclerosis quality of life

MSWS	Multiple sclerosis walking scale
N&V	Nausea and vomiting
NR	Not reported
NRS	Numerical ratings scale
OCB	Obsessive compulsive behaviours
OR	Odds ratio
PANSS	Positive and negative syndrome scale
PDI	Pain disability index
PGIC	Patients' global impression of change
PPMS	Primary progressive MS
PSS	Primary symptom score
QoL	Quality of life
RCT	Randomised controlled trial
ROBIS	Risk of bias in systematic reviews
RR	Relative risk
RRMS	Relapsing remitting MS
SAD	Social anxiety disorder
SCL-90-R	Symptom checklist 90 revised
SD	Standard deviation
SE	Standard error
SF36	Short form 36 health survey
SF-MPQ	Short form McGill pain questionnaire
SPMS	Secondary progressive MS
SR	Systematic review
STSSS	Shapiro tourette syndrome severity scale
THC	Tetrahydrocannabinol
THCA	THC-acid
THCV	Tetrahydrocannabivarin
TS-CGI	Tourettes syndrome clinical global impression scale
TSGS	Tourette's syndrome global scale
TSSL	Tourette syndrome symptom list
VAMS	Visual analogue mood scale
VAS	Visual analogue scale
WHO	World Health Organisation
WMD	Weighted mean difference
YGTSS	Yale global tic severity scale

EXECUTIVE SUMMARY

BACKGROUND

Cannabis is a generic term used for drugs produced from plants belonging to the genus Cannabis. It is one of the most popular recreational drugs - only tobacco, alcohol and caffeine are more popular.

Medical cannabis (or medical marijuana) refers to the use of cannabis or cannabinoids as medical therapy to treat disease or alleviate symptoms. Common conditions for which cannabis based medicine (CBM) may be indicated include chemotherapy-induced nausea and vomiting, as an appetite stimulant for AIDS and cancer patients, chronic pain, and spasticity in multiple sclerosis.

OBJECTIVE OF THE PROJECT

To conduct a systematic review, supported by GRADE summaries, of the evidence for the effects (first objective) and adverse events (second objective) of medical cannabis.

METHODS

This review followed the guidance published by the Centre for Reviews and Dissemination and the Cochrane Collaboration.

Twenty-eight databases (CDSR, DARE, HTA, NHS EED, INAHTA, NIHR Project Portfolio, GIN, NGC, NICE Guidance, TRIP Guidelines, CADTH, PROSPERO, EuroScan, Embase, Medline, Medline In-Process Citations & Daily Update, PubMed, PsycINFO, BIOSIS Citation Index, CINAHL, SCI, AMED, CENTRAL, IACM, IACM Database of Clinical Studies and Case Reports, NIH ClinicalTrials.gov, metaRegister of Controlled Trials, WHO ICTRP) were searched for randomised controlled trials, relevant observational studies and previously published systematic reviews and meta-analyses. The searches were carried out in April 2014 and were not limited by language.

Randomised trials were included if they assessed any form of medical cannabis in people with nausea and vomiting due to chemotherapy; HIV/AIDS (as appetizer); chronic pain; spasticity due to multiple sclerosis or paraplegia; depression (as antidepressant); anxiety disorder; sleep disorder; psychosis; glaucoma (reducing the intraocular pressure); or movement disorders due to Tourette's syndrome compared to usual care, placebo or no treatment. For most populations inclusion was not restricted based on outcome. Only studies in patients with HIV/AIDS that report data on outcomes related to appetite were eligible; for patients with depression only studies that report data on outcomes related to depression were eligible; and for patients with glaucoma, only studies that report data on intraocular pressure were eligible. Cross-over trials were only included if they fulfilled the following criteria that we considered to define a cross-over trial: included random treatment orders and were balanced in design i.e. participants received the same number of treatments. For populations for which no RCTs were available lower levels of evidence were considered based on the following hierarchy: 1) observational studies with concurrent

control groups; 2) observational studies with non-concurrent control groups; 3) uncontrolled studies (such as case series) with at least 25 patients.

Titles and abstracts identified through electronic database and web searching were independently screened by two reviewers. In order to minimise bias and errors, data extraction and risk of bias assessment were performed independently by two reviewers.

Results of direct comparisons of relevant treatments were presented and supplemented by narrative discussions of the study characteristics. Results of quantitative analysis and meta-analysis were also presented following the guidance by the GRADE Working Group.

RESULTS

For the first objective (clinical effects), primary searches identified 15,786 hits of which 423 were considered potentially relevant and obtained as full text studies. Depression was the only indication of interest for which no relevant RCTs were identified. Additional focused searches were conducted to identify eligible non-randomised studies for this indication. These searches did not find any potentially relevant studies even when going to the lowest level of evidence specified as eligible for the review (uncontrolled studies with at least 25 patients). A total of 76 studies available as 147 reports were included in the review of effectiveness.

The majority of the 76 included studies (6380 participants) evaluated nausea and vomiting due to chemotherapy (28 studies), chronic pain (27 studies) and spasticity due to MS and paraplegia (12 studies). All other patient categories were evaluated in less than five studies. Thirty-two studies were parallel group studies (4397 participants) and 44 were cross-over trials (1983). The parallel group trials generally enrolled greater number of participants than the cross-over trials (median 70, range 13 to 657 in the parallel group trials; median 48, range 6 to 214 in the cross-over trials). Many of the included studies were very old. Date of publication ranged from 1975 to 2014 (median 2004) with 1/3 of trials published before 1990. Studies were conducted in wide range of countries. Twenty seven studies were funded by the drug manufacturer, fifteen were mixed funded between industry and public bodies, nineteen were funded by public bodies and fifteen did not provide information on source of funding. Only four (5%) trials were judged at low risk of bias overall, 52 (68%) were judged at high risk of bias, and 20 (26%) at unclear risk of bias.

Cannabis was evaluated in a variety of different forms. These included oral formulations of cannabidiol (CBD), THC, THC/CBD, CT3, dronabinol, nabilone, or levonantradol; intramuscular levonantradol; vaporised cannabis; smoked marijuana or THC; and oromucosal spray of THC or nabiximols (a combination of THC/CBD). Of the 76 included studies, 53 included a placebo control. A variety of active comparators were included in the trials, with some including both active comparator and placebo. These included alizapride, amisulpride, amitriptyline, chlorpromazine, dihydrocodeine, domperidone, hydroxyzine, metoclopramide, megestrol acetate, ondansetron and prochlorperazine.

For the second objective (adverse events), searches identified 5085 hits of which 70 were considered potentially relevant and obtained as full text studies. Thirty-one studies available as 46 reports were included. These studies on long-term adverse events amend the data on short-term AEs reported in the studies included for objective 1 (clinical effects).

Nausea and vomiting due to chemotherapy

Twenty-eight studies (37 publications; 1772 participants) evaluated CBM for the treatment of nausea and vomiting in adults and children undergoing chemotherapy. The studies included patients with a variety of cancers. Some were restricted to single cancer types such as testicular cancer or lung cancer, others included patients with a specific type of cancer such as gastrointestinal or advanced gynaecological cancers, but most included mixed cancers. Seven studies used a parallel group design (467 participants) and twenty one (1305) were cross-over trials. None of the studies were rated as low risk of bias overall, 23 were judged at high risk of bias and five at unclear risk of bias. Therefore the results should be interpreted with some caution.

Overall there was some evidence that CBM reduces nausea and vomiting and improves appetite and functional status in patients receiving chemotherapy treatment for various types of cancer. All studies reported beneficial effects on all outcomes assessed but these did not reach statistical significance in all studies and some did report on the statistical significance of their findings. There were only sufficient data to pool results for one outcome, the number of patients showing a complete nausea and vomiting response. This showed a significant beneficial effect of CBM compared to placebo (OR 3.44, 95% CI 1.45, 8.15).

HIV/AIDS

Four studies (255 participants) evaluated CBM as a treatment for appetite stimulation in patients with HIV/AIDS. Three RCTs used a parallel group design (243 participants) and one (12 participants) was a cross-over trial. All studies were judged at high risk of bias.

There was some evidence that dronabinol is associated with an increase in weight compared to placebo. More limited evidence suggested that it may also be associated with increased appetite, greater % body fat, reduced nausea, and improved functional status. However, these outcomes were mostly assessed in single studies and failed to reach statistical significance. One trial evaluated marijuana and dronabinol, this study found significantly greater weight gain with both forms of cannabis compared to placebo. An active comparison study found that megestrol acetate was associated with greater weight gain than dronabinol and that combining dronabinol with megestrol acetate did not lead to additional weight gain.

Chronic pain

Twenty-seven studies (61 publications, 2439 participants) evaluated CBM as a treatment for chronic pain. The conditions causing the chronic pain varied between studies and included neuropathic pain (central, peripheral or not specified; 11 studies), cancer pain (three

studies), diabetic peripheral neuropathy (3 studies), fibromyalgia (2 studies), HIV associated sensory neuropathy (2 studies), refractory pain due to MS or other neurological conditions (1 study), rheumatoid arthritis (1 study), non-cancer pain (1 study), central pain (not specified further; 1 study), musculoskeletal problems (1 study) and chemotherapy induced pain (1 study). Fourteen studies were parallel group studies (1980 participants) and fourteen used a cross-over design (459 participants). The risk of bias in the included studies was variable. Only two were rated as low risk of bias for all domains while a further nine were rated as unclear risk of bias.

Overall there was some evidence that CBM may reduce pain, there was less evidence for an effect on other outcomes such as quality of life and global impression of change. Studies generally suggested a beneficial effect of CBM on measures of pain but this did not reach statistical significance in most individual studies. Summary estimates for outcomes where there were sufficient data to permit pooling suggested a beneficial effect of cannabis on all measures both dichotomous and continuous, e.g. ≥30% reduction in pain (OR 1.35, 95%-CI 0.95 to 1.93). Dichotomous data suggested a significant beneficial effect of CBM on patient global impression of change. There was some evidence to support this based on continuous data but this was not consistent across trials. Sensitivity analyses that included cross-over trials in the meta-analyses showed results consistent with those based on parallel group trials alone.

Spasticity due to multiple sclerosis (MS) or paraplegia

Twelve studies (31 reports; 2213 participants) evaluated CBM as a treatment for spasticity due to MS or paraplegia. Ten studies (2188 participants) included patients with MS and two included patients with paraplegia (25 participants) caused by spinal cord injury. Eight RCTs used a parallel group design (2091 participants) and four (122 participants) were cross-over trials. The risk of bias in the included studies was variable. Only two, by the same author, were rated as low risk of bias for all domains. A further five were rated as unclear risk of bias.

Overall there was some evidence that CBM may improve spasticity and patient global impression of change, there was less evidence for an effect on other outcomes such as quality of life, mobility/disability and general disease specific symptoms. Studies generally suggested a beneficial effect of CBM on measures of spasticity but this failed to reach statistical significance in most studies. The summary estimate for the Ashworth scale based on parallel group trials suggested a significant beneficial effect of CBM on spasticity (5 studies: WMD -0.14, 95%-CI -0.27 to -0.01). Other measures of spasticity also suggested a beneficial effect but did not reach statistical significance. Dichotomous data suggested a significant beneficial effect of CBM on patient global impression of change; this was supported by a further cross-over trial that provided continuous data for this outcome. There were no clear differences between the different types of CBM evaluated in these studies. Sensitivity analyses that included cross-over trials in the meta-analyses showed results consistent with those based on parallel group trials alone.

Depression

No studies evaluating cannabis for the treatment of depression fulfilled inclusion criteria for the review. Additional searches were carried out for this population with lower levels of evidence eligible for inclusion. These searches did not locate any eligible studies.

Five studies included for other sections of this review reported on depression as an outcome measure. Four of these studies evaluated patients with chronic pain and one was conducted in patients with MS. Three studies were parallel group trials and two were cross-over trials. Two studies were rated as unclear risk of bias while the remaining three were rated as high risk of bias.

There was no data available on the CBM for the treatment of depression. Studies included for other sections of the review that reported on depression as an outcome found little evidence of an effect of CBM on depression.

Anxiety

One parallel group trial evaluated patients with anxiety disorder. This study was conducted in 24 patients with generalised social anxiety disorder in Brazil. Participants were randomised to receive either cannabidiol or placebo before taking part in a simulated public speaking test. The study was judged at high risk of bias.

The study reported a significant beneficial effect of cannabidiol compared to placebo on change from before to during a simulated public speaking test on the anxiety factor of a visual analogue mood scale (MD change from baseline -16.52, p-value 0.012). Additional data on anxiety outcomes provided by three studies (two cross-over and one parallel group) in patients with chronic pain also suggested a beneficial effect of CBM but these studies were not restricted to patients with anxiety disorders.

Sleep disorder

Two studies evaluated patients with sleep disorders. One study enrolled patients with obstructive sleep apnoea syndrome and one included patients with fibromyalgia. One study was judged at low risk of bias the other at high risk of bias.

One study reported a significant beneficial effect of nabilone on the sleep apnoea/hypopnea index (MD change from baseline -19.64, p-value 0.018) but this should be interpreted with some caution due to the methodological limitations associated with this study. The other study in patients with sleep disorders was a cross-over trial in patients with fibromyalgia and compared nabilone with amitriptyline. This suggested some beneficial effects of nabilone on insomnia (MD change from baseline -3.25, 95%-CI -5.26 to -1.24) but greater sleep restfulness (MD change from baseline 0.48, 95%-CI 0.01 to 0.95) with amitriptyline.

Nineteen studies included for other populations (chronic pain and MS) also evaluated sleep as an outcome. Overall there was some evidence that CBM may improve sleep in these patient groups. There were sufficient data to pool results for sleep quality (WMD -0.58, 95% CI -0.87 to -0.29) and sleep disturbance (WMD -0.26, 95% CI -0.52 to 0.00), both suggested significant beneficial effects in favour of cannabis.

Psychosis

Two studies (9 reports, 71 participants) evaluated CBM as a treatment for psychosis. Both studies were conducted in Germany by the same group. One was a parallel group study (42 participants) and the other used a cross-over design (29 participants). Information on the cross-over trial was available only as conference abstracts. The two studies enrolled patients with DSM-IV criteria of acute paranoid schizophrenia or schizophreniform psychosis and ≥36 in the BPRS total score. Both trials evaluated cannabidol (max dose 600-800mg/day); the parallel group study compared this to the active comparator Amisulpride and the cross-over trial included a placebo control phase. The two studies were both rated as high risk of bias.

The trials found no difference in outcomes between treatment groups (Mental health rated by Brief Psychiatric Rating Scale and mood using PANSS).

Glaucoma

One cross-over trial (6 participants) evaluated CBM for the treatment of glaucoma. It included patients with ocular hypertension or early open angle glaucoma, with a mild visual defect in at least one eye. The study compared THC (5mg), cannabidiol (20mg), cannabidiol (40mg) and placebo all in the form of an oromucosal spray and was judged at unclear risk of bias.

This study found no evidence of an effect of CBM on intraocular pressure (MD at follow-up, THC 5mg: -0.58, 95%-CI -5.39 to 4.23; cannabidiol 20mg: 0.12, 95%-CI -5.09 to 5.33; cannabidiol 40mg: -0.25, 95%-CI -5.23 to 4.73).

Movement disorders due to Tourette syndrome

Two small studies, one parallel group and one cross-over trial, suggested that THC capsules may be associated with a significant improvement in tic severity, e.g. MD change from baseline, TSSL-global score -9.08, 95%-CI -12.87 to -5.29.

Adverse events

Sixty-two of the 76 studies included in the clinical effectiveness review provided data on short term adverse events. We found no evidence for a difference in the effect of cannabis on adverse events based on study design, population, comparator, method of cannabis administration or duration of follow-up, and so analyses were conducted for all studies combined. CBM was associated with a significantly greater risk of any AE, serious AE, withdrawals due to AE, ear and labyrinth disorders, gastrointestinal disorders, general disorders and administration site conditions, metabolism and nutrition disorders, psychiatric disorders, renal and urinary disorders, asthenia, balance problems, confusion, diarrhoea, disorientation, drowsiness, dry mouth, euphoria, fatigue, hallucination, nausea, somnolence, and vomiting. Other AEs did not show significant differences between groups.

We included an additional 31 observational studies (46 reports) to investigate the effects of cannabis on long term adverse events (cardiovascular disease, respiratory disease, cancer, psychotic disorders, and suicide or suicidal ideation). All studies examined the relationship

between recreational use of cannabis and the outcomes of interest; we did not find any studies that specifically assessed medical cannabis use and long term AEs. All studies had methodological weaknesses with none rated as low risk of bias and only four as moderate risk of bias.

CONCLUSIONS

Based on an extensive and rigorous systematic review of the literature of clinical effects and side effects of medical cannabis in ten populations which identified a total of 193 references to 76 RCTs and 31 observational studies, use of medical cannabis might be warranted for some medical conditions.

Medical cannabis showed statistically significant beneficial effects for the treatment of nausea and vomiting due to chemotherapy, chronic pain, on spasticity due multiple sclerosis (MS) or paraplegia, anxiety, sleep disorders, and movement disorders due to Tourette syndrome. However, these results should be taken with some caution due to a very heterogeneous set of included studies which also suffered from some potential risk of bias.

However, short-term side effects are relatively common and include serious adverse events. Furthermore, long-term cannabis use is linked to psychosis. However, no other association with long-term adverse events was found. Again, these findings might be restricted by methodological limitations of the identified studies on short- and long-term adverse events.

1. BACKGROUND

"Very few drugs, if any, have such a tangled history as a medicine. In fact, prejudice, superstition, emotionalism, and even ideology have managed to lead cannabis to ups and downs concerning both its therapeutic properties and its toxicological and dependence-inducing effects."

E. A. Carlini[6]

Cannabis is a generic term used for drugs produced from plants belonging to the genus Cannabis. Cannabis Sativa is the only species of the genus Cannabis but is divided into two subspecies: Cannabis Sativa and Cannabis Indica.[7] Drugs derived from these plants are produced in three broad categories: marijuana (dried leaves and flowering top of the plants), hashish (cannabis resin) and cannabis oil.[8] Cannabis is not a single drug – it consists of over 400 chemicals, over 60 of which are cannabinoids. Cannabinoid is a collective name for any compound, natural or synthetic, that can mimic the actions of plant-derived cannabinoids or that have structures that closely resemble those of plant cannabinoids.[9] They include three broad classes: endocannabinoids (produced naturally in the body by humans and animals), phytocannabinoids (found in cannabis and some other plants), and synthetic cannabinoids (manufactured chemically). The principal cannabinoid component of cannabis is Δ^9-tetrahydrocannabinol (Δ^9-THC).[9, 10] It was first isolated and synthesised in the 1960s.[6] The Δ^9-THC content of cannabis products varies according to the specific plant and conditions in which it is grown and on the cannabis product. It typically varies from around 5% in marijuana to 80% in hashish oil.[11] A large number of other biologically active cannabinoids have been identified. These include Δ^8-THC, cannabidiol (CBD), tetrahydrocannabivarin (THCV), and THC-acid (THCA).[6, 12]

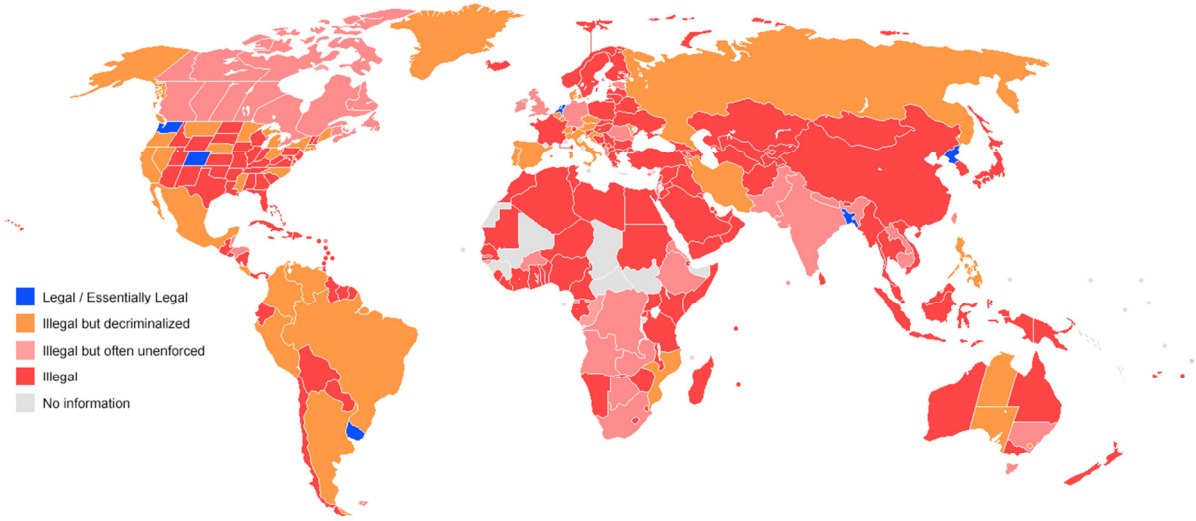
Cannabinoids act mainly via two different receptors: the prevalent CB-1 receptor and the CB-2 receptor. CB-1 is predominantly expressed on neurons, whilst CB-2 is predominantly expressed on cells of the immune system. The expression of these receptors is the biological basis for the medical use of cannabinoids in analgesia, as an anti-emetic and as an anti-inflammatory. Cannabinoids can interact with other biological pathways leading to complex physiological and pharmacological functions. Smoking and oral ingestion are the common administration routes. Smoking results in rapid absorption and onset of psychoactive effects. Ingestion leads to delayed onset and longer duration of actions.[13, 14]

Cannabis is one of the most popular recreational drugs - only tobacco, alcohol and caffeine are more popular. It can result in an alteration to mood and a feeling of "high". An estimated 141 million people use cannabis worldwide – this is equivalent to 2.5% of the world's population.[15] A review of studies that have evaluated self-reported cannabis effects found that frequently reported effects included relaxation, happiness/anti-depressant (some reported depression), cognitive benefits, respiratory benefits, creativity, socialising, sensory perception, improved sleep (some reported worse sleep), deeper thinking, laughter, exaggeration of mood, slowing of time(some reported that it goes faster), increased

appetite, increased or decreased concentration, increased or decreased talkativeness, sexual pleasure, sexual arousal, floating sensation, sociability, drowsy, creativity, memory, paranoia, anxiety, depression, dizziness, hallucinations/visions, and irritability.[16] Cannabis has also been associated with a number of short and long term adverse effects. Short term effects of cannabis include a dry mouth, blurred vision, dizziness, dysphoria, depression, ataxia, increased heart rate, paranoia, hallucinations, inability to discriminate or produce time and distance intervals, decreased vigilance, decreased ability to inhibit responses, and decreased ability to perform arithmetic tasks.[6, 8] Potential long term effects include developing cardiovascular or respiratory diseases or cancers, dependence and precipitating psychotic disorders including Schizophrenia.[8, 17, 18]

Cannabis was included as a controlled drug in the United Nations *Single Convention on Narcotic Drugs* in 1961[19], and the use of cannabis is illegal in most countries. However, in many countries it has been decriminalised or possession of small quantities is often unenforced. The only country in Europe in which possession is legal is the Netherlands. Figure 1 shows an overview of the legal status of cannabis throughout the world.

FIGURE 1: LEGAL STATUS OF CANNABIS IN COUNTRIES ACROSS THE WORLD
Source: Wikipedia[20]



In Switzerland, the production, culture, use and possession of cannabis is illegal and punishable by three years in prison or a fine.[21] Since September 2012 possession of less than 10 grams of cannabis is no longer considered a criminal offence but is still punishable by a 100 Swiss francs fine.[22] On 1 January 2012, several cantons introduced a new regulation which allowed private citizens to grow up to four hemp plants. However, this was invalidated by the Federal Court in October 2012.[23] The prevalence for cannabis consumption in Switzerland was estimated at 31% in 1998.[24]

Medical cannabis (or medical marijuana) refers to the use of cannabis or cannabinoids as medical therapy to treat disease or alleviate symptoms. There is evidence of the use of cannabis for medical purposes going back to Early Egyptian times in the 16th century BC, in China up to 4000 BC, India around 1000 years BC and in Europe around 450 BC.[25] The *pen-*

ts'ao ching the world's oldest herbal book (a collection of descriptions of plants put together for medicinal purposes), includes reference to cannabis as medicine for rheumatic pain, intestinal constipation, disorders of the female reproductive system, and malaria amongst others, this herbal book also contains the first reference to cannabis as a psychoactive drug.[25] In India the plant was used for a variety of functions including analgesia, anticonvulsant, hypnotic, tranquiliser, antibiotic, anti-parasitic, antispasmodic, appetite stimulant, diuretic, aphrodisiac or anphrodisiac, antitussive and expectorant. There are also references to it being used by women during labour to strengthen contractions and relieve pain.[26] Cannabis also has historical religious associations in countries such as India and Tibet. There are some reports of European physicians using cannabis from the early 19th century but the main introduction to Western medicine was through the works of William O'Shaughnessy, an Irish physician, who wrote a paper entitled *"On the preparations of the Indian hemp or gunjah"* which describes successful experiments using cannabis to treat rheumatism, convulsions, and muscular spasms of tetanus and rabies.[27]

Cannabinoid based medicine (CBM) can be administered orally, sublingually, smoked, inhaled, mixed with food, under the tongue as a tincture, made into tea, or administered topically. It can be taken in herbal form, extracted naturally from the plant, gained by isomerisation of cannabidol, or manufactured synthetically.[12] Prescribed CBMs include dronabinol gelatine capsules (brand name Marinol® since 1986, Abbott Products Inc.), nabilone capsules (brand name Cesamet® since 1981, Valeant Pharmaceutical International), and the sublingually administered oromucosal spray nabiximols (brand name Sativex® since 2005, GW Pharmaceuticals, UK , and partners).[12] The patent has expired on Marinol® and Cesamet® and generic versions are now available (Watson Pharmaceuticals and Pharmascience Inc respectively). Generic THC is also available, in Germany this is supplied by two companies (THC Pharm GmbH and Bionorica Ethics), allowing pharmacies to produce capsules and solutions which can be taken orally or inhaled using a vaporiser. Some countries have legalised medicinal-grade cannabis to chronically ill patients. Canada and the Netherlands have government run programmes where specialised companies supply quality controlled herbal cannabis.[28] These programmes have been running since 2001 and 2003 respectively. In the US around a third of states have introduced laws to permit the medical use of cannabis; other countries have similar laws. The Dutch programme offers pharmaceutical grade cannabis in the form of dried female flowers (Cannabis Flos) which patients are advised to administer by preparing as a tea or using a cannabis vaporiser. Prescriptions are available to patients with multiple sclerosis, cancer, HIV/AIDS, chronic pain, therapy-resistant glaucoma, and Tourette's syndrome, with costs now increasingly reimbursed by health insurance companies.[28] Israel and the Czech Republic are setting up similar programmes and Italy, Finland and Germany are importing products from the Dutch programme. In a recent decision, a court in Cologne allowed chronically ill patients to grow cannabis if all other treatment options have been used. However, this decision only affects three patients and the wider impact remains to be seen.[29] A large international survey of 953 participants in 31 countries found that smoking

marijuana was the most common mode of administration of CBM (tried by 95% of participants). A large proportion of respondents (87%) had also used herbal cannabis in foods, baked goods, or tinctures, but much smaller numbers had used the licenced medications dronabinol (11%), nabilone (2%) or nabixmols (1%). Around 5% had experience of topical use of CBM. The preferred method of intake was a herbal CBM in 97% of cases.[12]

Common conditions for which CBM may be indicated include chemotherapy-induced nausea and vomiting, as an appetite stimulant for AIDS and cancer patients, chronic pain, and spasticity in multiple sclerosis. The survey of 953 CBM users found that the most common primary conditions for which CBMs were used were back pain (12%), sleeping disorder (7%), depression (7%), pain resulting from injury or accident (6%), and multiple sclerosis (4%).[12] Similar results were found in an analysis of 1,655 applicants presenting to a marijuana specialty practice in California which found that the most common conditions were back pain (26%), sleep disorders (21%), anxiety (19%), arthritis (18%), muscle spasm (12%), and migraine (9%).[30] Other conditions for which CBMs were used in either survey included ADHD/hyperactivity, allergy, anxiety, asthma, autism, bipolar disorder, cancer, alcohol/opiate dependency, dysmenorrhea, endometriosis, epilepsy, fibromyalgia, gastrointestinal disorders, glaucoma, hepatitis, HIV/AIDS, irritable bowel disease, migraine/headache, neuropathy, post-traumatic stress disorder, seizures, and spinal cord injury. The main symptoms for which relief was sought in the international survey included chronic pain (29%), anxiety (18%), loss of appetite and/or weight (11%), depression (5%), and insomnia or sleeping disorder (5%). The Californian study reported on any symptom for which relief was sought. This study found that commonly reported reasons for taking CBM were pain (83%), to improve sleep (71%), for relaxation (56%), spasms (41%), headache (41%), anxiety (38%), and to increase appetite. Other symptoms included breathing problems, chronic inflammation, cramps, diarrhoea, lack of energy, general malaise, hyperactivity, inner unrest, irritability, itching, nausea or vomiting, panic, spasms, and spasticity.[12, 30] A smaller survey of 128 patients in German speaking countries (Germany, Austria and Switzerland) found that the most common indications for medicinal cannabis use were depression (12%), multiple sclerosis (11%), HIV (9%), migraine (7%), asthma (6%), back pain (5%), hepatitis C (5%) and sleep disorders (5%). Most patients used natural cannabis products, only five patients used a prescription based formulation (Marionol®).[31]

A large number of systematic reviews have examined the effectiveness of CBMs for the treatment of a variety of conditions including chronic pain (non-cancer, cancer pain, neuropathic pain, multiple sclerosis related, mixed),[32-40] symptoms associated with multiple sclerosis (spasticity and bladder dysfunction),[41-43] nausea and vomiting (palliative care patients, cancer patients, chemotherapy patients, and mixed),[44-47] Tourette's syndrome,[48] epilepsy,[49] dementia,[50] HIV/AIDS patients[51] post-traumatic stress disorder,[52] and one general review of medicinal use of marijuana.[53] There are also systematic reviews focussing specifically on the adverse effects of cannabis use – one on adverse effects in general[54] and

one on schizophrenia.[55] None of these reviews are up to date – the most recent search date was September 2013 in a review of cannabinoids for epilepsy.[49] Latest search dates for the other reviews ranged from 1999-2012. All except one of the reviews focused on a narrow clinical area. There is therefore a need for an up to date systematic review to evaluate the effectiveness and adverse events of CBMs in a range of conditions.

2. OBJECTIVES OF THE PROJECT

To conduct a systematic review, supported by GRADE summaries, of the evidence for the effects and adverse events of medical cannabis.

3. RESEARCH QUESTIONS

1. What are the clinical effects of medical cannabis in people with: nausea and vomiting due to chemotherapy; HIV/AIDS (as appetizer); chronic pain; spasticity due to multiple sclerosis or paraplegia; depression (as antidepressant); anxiety disorder; sleep disorder; psychosis; glaucoma (reducing the intraocular pressure); or movement disorders due to Tourette's syndrome?
2. What are the adverse events associated with medical cannabis?

4. METHODS

4.1 LITERATURE SEARCHES

Literature searches were undertaken to identify relevant studies on the use of cannabis and cannabinoid derivatives as medical treatment for a number of indications. Search methods followed best practice standards in systematic reviews.[56, 57] The search strategies combined relevant search terms comprising indexed keywords (e.g. Medical Subject Headings (MeSH) and EMTREE terms) and free text terms appearing in the titles and/or abstracts of database records. Search terms were identified through discussion between the review team, by scanning background literature and 'key articles' already known to the review team, and by browsing database thesauri. The searches were not limited by language, date or publication status (unpublished or published), and were conducted in three phases to identify existing systematic reviews, protocols, health technology assessments (HTAs) and economic evaluations; clinical effectiveness of medicinal cannabis use; and adverse events resulting from medicinal cannabis use.

4.1.1 Rapid appraisal of systematic reviews, protocols and health technology assessments

A full rapid appraisal was conducted to retrieve existing systematic reviews, protocols, HTAs, economic evaluations, guidance and guidelines relating to the use of cannabis and cannabinoid derivatives in a therapeutic context.

The following databases were searched from inception to the March/April 2014:

- Cochrane Database of Systematic Reviews (CDSR) (Wiley Online Library): issue 3/July 2014
- Database of Abstracts of Reviews of Effects (DARE) (Wiley Online Library): issue 1/January 2014
- Health Technology Assessment database (HTA) (Wiley Online Library): issue 1/January 2014
- NHS Economic Evaluations Database (NHS EED) (Wiley Online Library): issue 1/January 2014
- International Network of Agencies for Health Technology Assessment (INAHTA) (Internet) (http://www.inahta.org/): up to 2014/03/25
- NIHR Project Portfolio (Internet) (http://www.nets.nihr.ac.uk/projects/): up to 2014/03/25
- International Guidelines Network Library (GIN) (Internet) (http://www.g-i-n.net/): 2000-2014/03/25
- National Guidelines Clearinghouse (Internet) (http://www.guideline.gov/): up to 2014/03/25
- NICE Guidance (National Institute for Health and Care Excellence) (Internet) (http://guidance.nice.org.uk/): up to 2014/03/25
- TRIP - Guidelines (Internet) (http://www.tripdatabase.com/): up to 2014/03/25

- Canadian Agency for Drugs and Technologies in Health (CADTH) (Internet) (http://www.cadth.ca/): up to 2014/03/25
- PROSPERO (International Prospective Register of Systematic Reviews) (Internet) (http://www.crd.york.ac.uk/PROSPERO/): up to 2014/04/08
- International Information Network on New and Emerging Health Technologies (EuroScan) (Internet) (http://www.euroscan.org.uk/): up to 2014/04/08

4.1.2 Clinical effectiveness of medicinal cannabis

Where appropriate, database-specific objectively-derived randomised controlled trials filters, such as Wong 2006, [58] were applied to limit the searches to retrieve RCTs. No randomised trials were found for depression, so additional searches for observational studies were carried out for this indication.

The following databases were searched from inception to the April 2014:

- Embase (OvidSP): 1974-2014/wk 14
- Medline (OvidSP): 1946-2014/Mar wk 4
- Medline In-Process Citations & Daily Update (OvidSP): up to 2014/04/04
- PubMed (NLM) (Internet) (http://www.ncbi.nlm.nih.gov/pubmed): up to 2014/04/14
- PsycINFO (OvidSP): 1806-2014/Apr wk 1
- BIOSIS Citation Index (Web of Science): 1926-2014/04/11
- CINAHL (Cumulative Index to Nursing and Allied Health Literature) (EBSCO): 1981-2014/04/14
- Science Citation Index (SCI) (Web of Science): 1900-2014/04/15
- AMED (ProQuest): 1985-2014//04/07
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley Online Library): issue 3/March 2014

Supplementary searches were conducted to identify grey literature, and completed and ongoing trials in the following resources:

- International Association for Cannabinoid Medicines (IACM) (Internet) (http://www.cannabis-med.org/): up to 2014/04/07
- IACM Database of Clinical Studies and Case Reports (Internet) (http://www.cannabis-med.org/studies/study.php): up to 2014/04/04
- NIH ClinicalTrials.gov (Internet) (http://www.clinicaltrials.gov): up to 2014/04/07
- metaRegister of Controlled Trials (Internet) (http://www.controlled-trials.com): up to 2014/04/07
- WHO International Clinical Trials Registry Platform (ICTRP) (Internet) (http://www.who.int/ictrp/en): up to 2014/04/07

Full search strategies and results are presented in Appendix 1.

4.1.3 Adverse events from medicinal cannabis use

Further focussed adverse events (AEs) searches were necessary following screening of the clinical effectiveness search results. Where further information was required, topic-specific searches were conducted: cardiovascular/respiratory disease, cancer, dependence, and psychotic disorder/schizophrenia. Each search strategy was tailored to each resource searched, combining cannabis search terms with search terms for each of the indications listed above. In addition, a study design search filter for cohort and case-control studies was included. The searches were not limited by language, date or publication status (unpublished or published).

The following databases and resources were searched for AEs:

- Embase (OvidSP): 1974-2014/wk 31
- Medline (OvidSP): 1946-2014/July wk 5
- Medline In-Process Citations & Daily Update (OvidSP): up to 2014/08/06
- PubMed (NLM) (Internet) (http://www.ncbi.nlm.nih.gov/pubmed): up to 2014/08/07
- PsycINFO (OvidSP): 1806-2014/July wk 5
- BIOSIS Citation Index (Web of Science): 1926-2014/08/07
- CINAHL (Cumulative Index to Nursing and Allied Health Literature) (EBSCO): 1981-2014/08/07
- Science Citation Index (SCI) (Web of Science): 1900-2014/08/07

4.1.4 Handling of citations

As a number of databases were searched, there was some degree of duplication. In order to manage this issue, the titles and abstracts of bibliographic records were downloaded and imported into EndNote reference management software and duplicate records removed. Rigorous records were maintained as part of the searching process. Individual records within the Endnote reference libraries were tagged with searching information, such as searcher, date searched, database host, database searched, strategy name and iteration, theme or search question. This enables the information specialist to track the origin of each individual database record, and its progress through the screening and review process.

4.1.5 Quality assurance within the search process

For all searches undertaken by Kleijnen Systematic Reviews Information team, the main Embase strategy for each set of searches is independently peer reviewed by a second Information Specialist, using the CADTH checklist. [59]

4.2 Inclusion Criteria

Studies that fulfilled the following criteria were eligible for inclusion:

4.2.1 Review of clinical effectiveness:

Population

People with any of the following conditions:

1) Nausea and vomiting due to chemotherapy
2) HIV/AIDS

3) Chronic pain (e.g. neuropathic pain, migraine, back pain)
4) Spasticity due to multiple sclerosis or paraplegia
5) Depression
6) Anxiety disorder
7) Sleep disorder
8) Psychosis
9) Glaucoma
10) Movement disorders due to Tourette syndrome

Intervention

Any form of cannabis for medical use.

Comparators

Usual care, placebo or no treatment.

Outcomes

For most populations inclusion was not restricted based on outcome.

Only studies in patients with HIV/AIDS that reported data on outcomes related to appetite were eligible; for patients with depression only studies that reported data on outcomes related to depression were eligible; and for patients with glaucoma, only studies that reported data on intraocular pressure were eligible.

Study designs

Randomised controlled trials (RCTs), including randomised cross-over trials. Cross-over trials were only included if they fulfilled the following criteria that we considered to define a cross-over trial: included random treatment orders and were balanced in design i.e. participants received the same number of treatments. For populations for which no RCTs were available lower levels of evidence were considered based on the following hierarchy:

1) Observational studies with concurrent control groups
2) Observational studies with non-concurrent control groups
3) Uncontrolled studies (such as case series) with at least 25 patients

4.2.2 Review of adverse events:

All studies included for objective 1 (review of clinical effectiveness) contributed data on short term adverse events to the review of adverse events. Long term adverse events of interest included developing cardiovascular or respiratory diseases or cancers, dependence, precipitating psychotic disorders including schizophrenia. Data on long term adverse event were not available from the studies included for objective 1. We therefore included lower levels of evidence for these outcomes according to the following hierarchy:

1) Observational studies with concurrent control groups
2) Observational studies with non-concurrent control groups

3) Uncontrolled studies (such as case series) with at least 25 patients

For both review objectives, we had planned that any high quality systematic reviews (rated low risk of bias on all ROBIS domains [60] that fulfilled all review inclusion criteria and included all relevant studies for any single population would have been included. However, none of the identified reviews fulfilled these criteria and so all identified systematic reviews were used as sources of potentially relevant studies.

4.3 Methods of Study Selection, Data Extraction and Quality Assessment

4.3.1 Study selection

Titles and abstracts identified through electronic database and web searching were independently screened by two reviewers. We employed a two stage process to screen titles and abstracts. In the initial phase reviewers independently screened the full search results and selected any study that appeared to be an RCT or SR that reported on the effectiveness or adverse events of CBM in any patient group. A second mapping phase, also conducted independently by two reviewers, was then used to code the selected studies according to the population. Full text copies were obtained for all references relating to one or more of the populations specified in the inclusion criteria. These were then independently examined in detail by two reviewers in order to determine whether they met the criteria for inclusion in the review. All papers excluded at this second stage of the screening process were documented along with the reasons for exclusion (Appendix 2). Discrepancies between reviewers were resolved through discussion or the intervention of a third reviewer.

4.3.2 Data extraction

Data were extracted using standardised data extraction forms developed in Microsoft Access 2010 (Appendix 2). Data extraction forms were piloted on a small sample of papers and adapted as necessary. In order to minimise bias and errors, data extraction was performed independently by two reviewers.

We extracted baseline data on the following variables: funding sources (public, industry, mixed), study design, recruitment dates, patient category (nausea and vomiting due to chemotherapy, HIV/AIDS, chronic pain, spasticity due to multiple sclerosis or paraplegia, depression, anxiety disorder, sleep disorder, psychosis, glaucoma, movement disorders due to Tourette syndrome), inclusion and exclusion criteria, age, sex, ethnicity, weight, disease severity, disease duration, concomitant medication, previous medication, comorbidities, previous drug or tobacco use, previous cannabis use, study duration and withdrawals. We extracted results for the following outcomes:

1. Patient relevant/disease specific outcomes: nausea and/or vomiting, appetite, weight, pain, sleep, depression, anxiety, spasticity, psychosis, eye pressure, tic severity, balance and falls.
2. Activities of daily living

3. Quality of life and global impression of change
4. Adverse events (AEs): number of patients with at least one AE, withdrawals due to AEs, serious AEs, MedDRA high level group terms[61] (reproductive system and breast disorders; skin and subcutaneous tissue disorders; other body systems; ear and labyrinth disorders; blood disorders; injury, poisoning & procedural complications; metabolism & nutrition disorders; neoplasms, benign, malignant & unspecified; renal & urinary disorders; hepatobiliary disorders; investigations; mental status change; cardiac disorders; general disorders and administration site conditions; psychiatric disorders; respiratory, thoracic and mediastinal disorders; gastrointestinal disorders; infections and infestations; musculoskeletal and connective tissues disorders; nervous system disorders) and specific adverse events (anxiety, asthenia (weakness), balance, confusion, death, depression, diarrhoea, disorientation, dizziness, dry mouth, dyspnoea, euphoria, fatigue, hallucinations, nausea, paranoia, psychosis, seizures, somnolence/drowsiness, vomiting)

We extracted dichotomous data as number of patients with events and/or number of events and total number of patients in each treatment arm. For categorical data, we extracted details on the categories assessed, the total number of patients in each treatment arm and the number of patients in each outcome category. For continuous data we extracted means/medians together with ranges, standard deviations (SD), standard errors (SE) and/or confidence intervals (CIs) for the outcome at baseline, follow-up and for change from baseline in each treatment group. For all types of data, summary effect estimates together with 95% CIs and p-values for comparisons between groups together with details on the methods of analysis, any variables controlled for in the analysis and the test statistic were extracted.

For cross-over trials, we developed a hierarchy of the type of data to be extracted. This is because cross-over trials rarely reported data in the appropriate format using the appropriate analysis for studies of this design. Ideally, for continuous data we extracted the mean and associated measure of variance (SD, SE or CI) or p-value for between group differences based on a paired analysis, if this was not available we extracted continuous data in the standard format for the whole trial (periods 1 and 2 combined) and for period 1 only, if reported. For dichotomous data, our preferred data format was data to populate a 2x2 table for cross-over trials that would allow calculation of a Mantel-Haenszel OR, [62] alternatively we selected a summary effect estimate (OR or RR) with associated measure of variance (SE or CI) and p-value based on paired analysis (e.g. McNemar's test), if these were not available we extracted dichotomous data in the standard format for the whole trial and for period 1 only, if reported.

Any additional outcomes, including adverse events, reported in the studies but not specified as outcomes to extract for this review were listed but numerical results were not extracted. If data were reported for multiple time points we only extracted data for the time point defined as the "primary analysis". If this was not defined we selected the latest time point with the most complete data. We extracted data for the most complete population available i.e. we extracted intention to treat (ITT) data or modified ITT data in preference to per-protocol analysis. For trials with multiple treatment arms we extracted data for each treatment compared to the CBM; i.e. if there was an active comparator and placebo arm we did not extract data comparing the active comparator to placebo but for the CBM vs placebo, and CBM vs active comparator.

We used all sources available to extract data so if a study was available as a full journal article, abstract and clinical trial registry entry we used data from all three. We selected the journal article as the primary publication as this had been peer-reviewed i.e. if there were any discrepancies between the data reported in the journal article and the trial registry entry or study abstract we selected the data from the journal article.

4.3.3 Quality assessment

RCTs were assessed for methodological quality using the Cochrane Risk of Bias tool (Appendix 3b).[63] This includes items covering selection bias (random sequence generation and allocation concealment), performance bias (participant blinding), detection bias (blinding of outcome assessors) attrition bias (incomplete outcome data), and reporting bias (selective reporting).

We used the new Cochrane risk of bias tool for non-randomised studies (ACROBAT-NRS) to assess the risk of bias in observational studies.[64] This is currently under development and we contributed to the piloting of this tool. It includes domains covering bias due to confounding, bias in the selection of participants into the study, bias due to departures from intended interventions, bias due to missing data, bias in taking measurements, and bias in selection of the reported result.

For both tools, if at least one of the domains was rated as "high" the study was considered at high risk of bias, if all domains were judged as "low" the trial was considered at low risk of bias, otherwise the trial was considered at "unclear" risk of bias. The risk of bias assessment was conducted as part of the data extraction process. Detailed guidance on how to assess trials for risk of bias specific to this review is provided in Appendix 3.

4.4 ANALYSIS

4.4.1 Narrative synthesis methods

A narrative summary of the included studies was presented. This included a summary of the characteristics (e.g. study aim, study design, population size, geographical location, year, baseline population characteristics, outcome definition and assessments). Where data were considered too heterogeneous to pool, or not reported in a format suitable for pooling (e.g. data reported as medians), we employed a narrative synthesis. This involved the use of

descriptive text and tables to summarise data in order to allow the reader to consider outcomes in the light of differences in study designs and potential sources of bias for each of the studies being reviewed. Studies were grouped according to patient category (nausea and vomiting due to chemotherapy, HIV/AIDS, chronic pain, spasticity due to multiple sclerosis or paraplegia, depression, anxiety disorder, sleep disorder, psychosis, glaucoma, movement disorders due to Tourette syndrome), the results of the studies (range and size of the associations reported) were summarised, and the most important characteristics of the included studies were described. A detailed commentary on the results of the risk of bias assessment, including the major methodological problems or biases that affected the studies, was included.

4.4.2 Quantitative analysis and meta-analysis methods

For dichotomous data we calculated the odds ratio (OR) for each trial with the associated 95% confidence intervals (CIs). For continuous data, where sufficient information was reported, we calculated the mean difference between groups, either at follow-up or in change from baseline, and associated 95% CIs. For multi-arm studies, we compared results for each treatment compared to the CBM.

Where sufficient studies assessed similar populations and outcomes, a formal meta-analysis was used to estimate summary measures of effect. We anticipated that systematic differences between studies (heterogeneity) would be likely. Therefore, the random-effects model was used to calculate summary estimates. Heterogeneity was investigated visually using forest plots and statistically using the I^2 and Q statistics.[65] For continuous outcomes, we selected mean difference in change from baseline if available. If this was not reported and could not be calculated from available data then we used the mean difference at follow-up. In order to avoid double counting we selected a single data set from each study to contribute to meta-analyses. For studies evaluating multiple interventions we selected the intervention or dose that most similar to other interventions being evaluated in that meta-analysis.

We had planned to formally investigate heterogeneity using meta-regression, however, there were insufficient data for any single outcome to perform such analyses.

Small study effects (publication bias) was assessed using a modified linear regression test for funnel plot asymmetry as recommended by Harbord et al (2005) where there were sufficient numbers of trials (i.e. six trials).[66]

Statistical analyses were performed using Stata (version 10) and the MetaXL add on for Microsoft Excel.

4.5 GRADE Framework

GRADE presents a systematic and transparent framework for clarifying questions, determining the outcomes of interest, summarising the evidence that addresses a question, and moving from the evidence to a recommendation or decision.[67-69] It rates the quality of a complete body of evidence for a specific outcome in a specific population. The quality of

evidence was assessed for risk of bias, publication bias, imprecision, inconsistency, indirectness, magnitude of effect, dose-response gradient and the effects of any confounding.

Risk of bias describes any limitations in the design and execution of a collection of studies, for example failure to properly randomise the participants, failure to blind participants and investigators or selective reporting of outcomes (see section on Quality assessment).

Publication bias is a measure of the degree to which the available published data are skewed by selective publication of trials dependent on their results, e.g. positive trials are more likely to be published than those with negative results (see section on Analysis).

Imprecision assesses the degree to which random error influences the interpretation of the results.

Inconsistency captures the degree of heterogeneity between studies in terms of their PICO elements, i.e. how comparable are the studies to each other (see section on Analysis).

The remaining GRADE criteria can be used to rate up the quality of evidence if there is a very large effect of intervention, if there is evidence of a dose response or if the effects of any confounding would reduce rather than increase any observed effects.

Each of the GRADE criteria was described in detail in a series of papers published by the GRADE working group.[70] Appendix 4a presents GRADE definitions, categories, and factors affecting the quality of evidence. GRADE is currently the most widely accepted and used framework for developing guidelines. More than 50 organisations worldwide, many highly influential, have endorsed the framework (http://www.gradeworkinggroup.org/).

We developed GRADE evidence profiles and summary of findings tables to summarise the evidence and rate the quality of evidence separately for each population (nausea and vomiting due to chemotherapy, HIV/AIDS, chronic pain, spasticity due to multiple sclerosis or paraplegia, depression, anxiety disorder, sleep disorder, psychosis, glaucoma, movement disorders due to Tourette syndrome).

Summary of findings tables are presented at the end of the relevant results section while evidence profiles are presented in Appendix 10. Both present relevant results from parallel group studies.

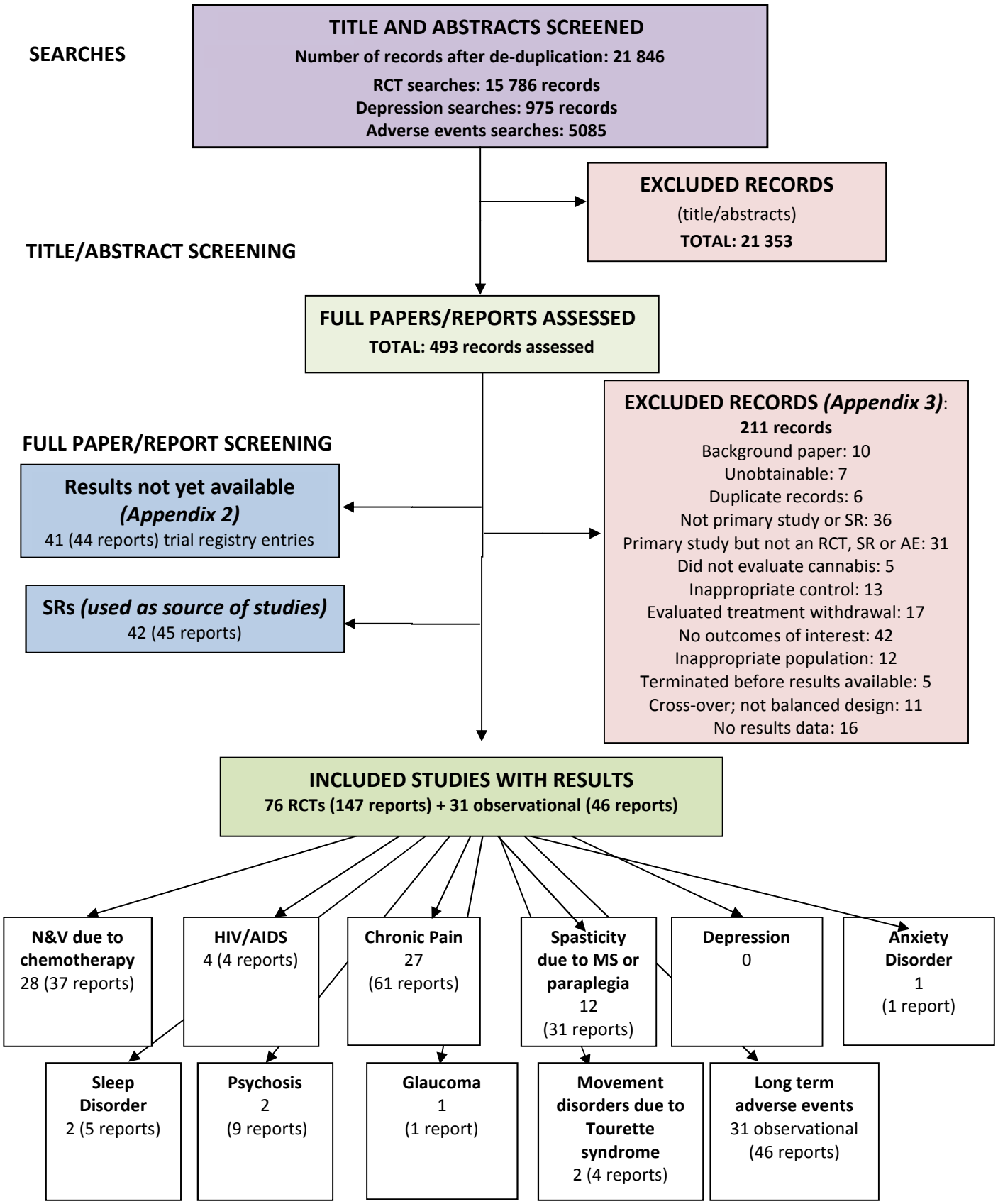
5. RESULTS

The primary searches for objective 1 identified 15,786 hits of which 423 were considered potentially relevant and obtained as full text studies. Depression was the only indication of interest for which no relevant RCTs were identified. Additional focused searches were conducted to identify eligible non-randomised studies for this indication. These searches did not find any potentially relevant studies even when going to the lowest level of evidence specified as eligible for the review (uncontrolled studies with at least 25 patients). We also conducted additional searches to identify studies on the long term adverse events associated with cannabis use. These searches identified 5085 of which 70 were considered potentially relevant and obtained as full text studies. Full details of the search strategies used are available in Appendix 1. In total we screened 21 846 titles and abstracts and retrieved 493 full text studies.

A total of 76 studies available as 147 reports were included in the review of effectiveness (objective 1) and 31 studies available as 46 reports were included in the review of long-term adverse events (objective 2). Most studies included for objective 1 also reported data on short-term adverse events and so were also included for objective 2. A further 42 studies (44 reports) appeared to fulfil the inclusion criteria but these were available only as trial registry entries and reports of results of these studies were not found. Details of these studies are reported in Appendix 2. We also identified 42 SRs (45 publications). We had specified that if high quality systematic reviews were identified for any of the patient groups of interest that fulfilled all inclusion criteria for the review and included all relevant studies then these would be eligible for inclusion. None of the SRs identified by the searches fulfilled these criteria and so identified SRs were used as a source of relevant studies.

Figure 2 summarises the flow of studies through the review process. Details of the 207 papers excluded after full text screening are listed in appendix 3 alongside the reason for exclusion. We were unable to obtain seven reports, details of these are provided in appendix 4.

FIGURE 2: FLOW OF STUDIES (NUMBER OF REPORTS) THROUGH THE REVIEW PROCESS



NRS: non-randomised study; RCT: randomised controlled trial; SR: systematic review; N&V: nausea and vomiting. NB single papers could be included in multiple categories e.g. a study in MS patients could be included for MS, pain and sleep

5.1 CLINICAL EFFECTIVENESS REVIEW

5.1.1 Overview of included studies

The majority of the 76 included studies (6,380 participants) evaluated nausea and vomiting due to chemotherapy (28 studies), chronic pain (27 studies) and spasticity due to MS and paraplegia (12 studies). All other patient categories were evaluated in less than five studies. Thirty-two studies were parallel group studies (4,397 participants) and 44 were cross-over trials (1,983). The parallel group trials generally enrolled greater number of participants than the cross-over trials (median 70, range 13 to 657 in the parallel group trials; median 48, range 6 to 214 in the cross-over trials). Many of the included studies were very old. Date of publication ranged from 1975 to 2014 (median 2004) with one third of trials published before 1990. Studies were conducted in wide range of countries including Austria, Belgium, Brazil, Canada, Czech Republic, Denmark, Ireland, Finland, France, Germany, Netherlands, Romania, Spain, Switzerland, UK, and USA. Twenty-seven studies were funded by the drug manufacturer, 15 were mixed funded between industry and public bodies, 19 were funded by public bodies and 15 did not provided information on source of funding. Seven studies were available only as conference abstracts;[1, 71-76] all other studies were available as full reports, some including multiple publications including full results available as trial registry entries. Nineteen studies were multi-centre trials, 17 of these were parallel group trials[2-5, 77-89] and two were cross-over trials.[90, 91] Sample sizes in these studies tended to be larger than in the single group studies (median 177, range 52-657 in the multi-centre studies; median 35, range 6-152). The majority of the studies were restricted to adults but two of the studies[92, 93] that evaluated CBM for nausea and vomiting due to chemotherapy were conducted in children and a further study also included children.[94] Duration of follow-up ranged from 1.47 hours in a study of anxiety[95] to 15 weeks in a study of chronic pain.[81] Full baseline details of all included studies are provided in Appendix 5, full results are provided in Appendix 7. The included studies used a wide variety of outcomes to measure the effects of CBM. On some a low score indicates a good outcome while on others this indicates a bad outcome, this can make results difficult to interpret. To facilitate interpretation of results, we have provided an overview of the outcome measures used in the included studies including the scale on which these are measures and whether a positive mean difference favours CBM or control (Appendix 9).

5.1.2 Overview of interventions evaluated in included studies

The interventions evaluated by the included trials are summarised in Table 1, full details are provided in Appendix 6. Cannabis was evaluated in a variety of different forms. These included oral formulations of cannabidiol (CBD), THC, THC/CBD, CT3, dronabinol, nabilone, or levonantradol; intramuscular levonantradol; vaporised cannabis; smoked marijuana or THC; and oromucosal spray of THC or nabiximols (a combination of THC/CBD). Of the 76 included studies, 53 included a placebo control. A variety of active comparators were included in the trials, with some including both active comparator and placebo. These included alizapride, amisulpride, amitriptyline, chlorpromazine, dihydrocodeine, domperidone, hydroxyzine, metoclopramide, megestrol acetate, ondansetron and

prochlorperazine. Active comparators were generally only evaluated in single trials, the exception was prochlorperazine which was evaluated in 15 of the nausea and vomiting due to chemotherapy trials. Most trials included only two treatment arms comparing CBM to placebo or active comparison. Some trials included multiple treatment arms comparing CBM to active comparison and placebo, comparing more than one different from of CBM to placebo or comparing different doses of the same form of CBM to placebo. One study included five treatment arms comparing four different doses of THC to placebo.[96]

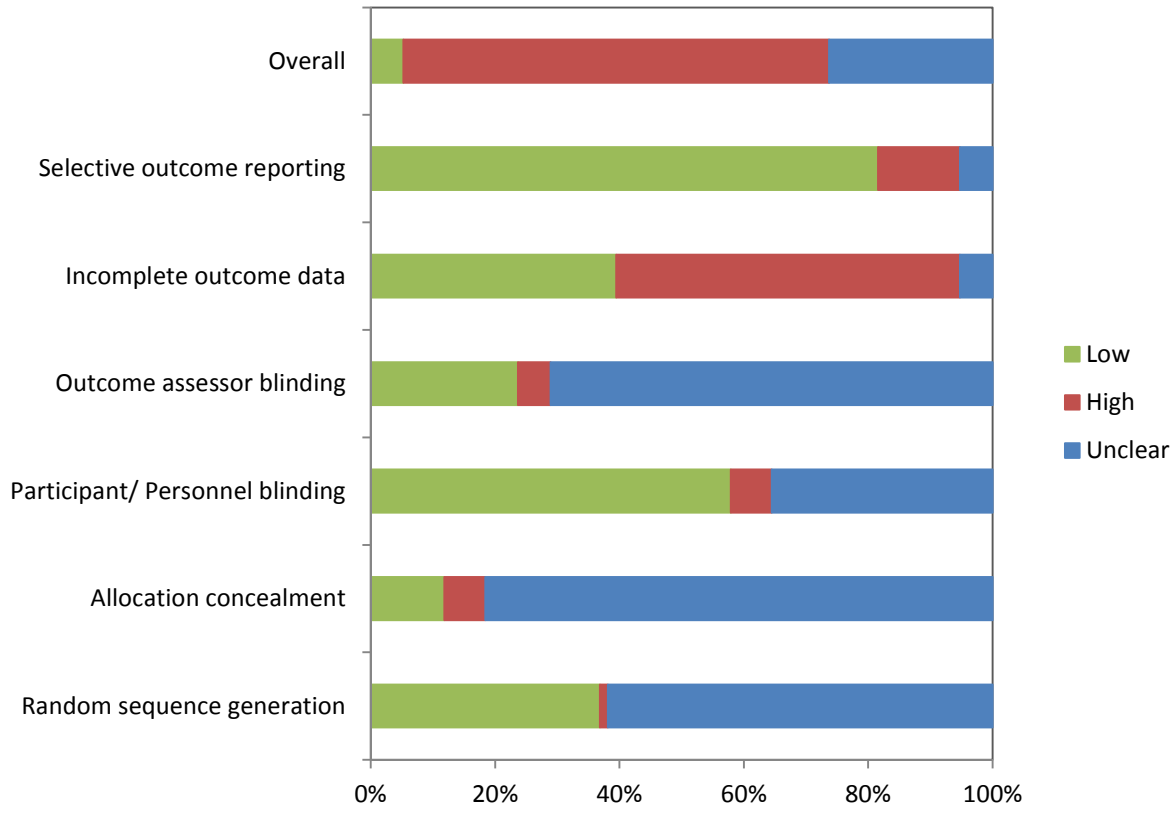
TABLE 1: INTERVENTION EVALUATED BY THE STUDIES INCLUDED IN THE REVIEW

Intervention	Administration Method	Number of studies
CBM		
Cannabidiol (CBD)	Capsules (oral)	4
THC	Capsules (oral)	10
THC/CBD	Capsules (oral)	4
CT3	Capsules (oral)	1
Dronabinol (Marinol)	Capsules (oral)	13
Nabilone (Cesamet)	Capsules (oral)	19
Levonantradol	Capsules (oral)	1
Cannabis	Vaporised	1
Marijuana	Smoked	1
THC	Smoked	5
Levonantradol	IM	3
Nabiximols (Sativex)	Oromuscosal spray	17
THC	Oromuscosal spray	6
Combination interventions		
Dronabinol (Marinol) + megestrol acetate	Capsules (oral)	1
Dronabinol (Marinol) + ondansetron	Capsules (oral)	1
Dronabinol (Marinol) + prochlorperazine	Capsules (oral)	1
Comparator interventions		
Alizapride	Capsules (oral)	1
Amisulpride	Capsules (oral)	1
Amitriptyline	Capsules (oral)	1
Chlorpromazine	IM	2
Dihydrocodeine	Capsules (oral)	1
Domperidone	Capsules (oral)	1
Domperidone	Oromuscosal spray	1
Hydroxizine	oral	1
Megestrol acetate	Capsules (oral)	1
Metoclopramide	IM	1
Ondansetron	Capsules (oral)	1
Prochlorperazine	Capsules (oral)	15
Placebo	Capsules (oral)	27
Placebo	Oromuscosal spray	19
Placebo	Smoked	5
Placebo	Vaporised	1

5.1.3 Risk of bias

Figure 3 summarises the risk of bias across included trials. Only four (5%) trials were judged at low risk of bias overall, 52 (68%) were judged at high risk of bias, and 20(26%) at unclear risk of bias. The major potential sources of bias in the trials was incomplete outcome data. Over 50% of trials reported relatively large numbers of withdrawals and did not adequately account for this in the analysis by using an appropriate intention to treat (ITT) analysis based on all randomised participants. Instead of using a full ITT analysis studies often reported a modified ITT analysis based on the number of patients randomised who received at least one dose of the study medication. Selective outcome reporting was a potential risk of bias in 16% of trials. These studies did not report data for all outcomes specified in the trial register, protocol or methods section of the review or changed the primary outcome from that which had been pre-specified. Other domains were only rated as high risk of bias in a small proportion (<7%) of trials. However, very few studies provided sufficient information to judge whether appropriate methods were used to randomise participants or conceal treatment allocation. Blinding was also poorly reported in the included studies. Almost all studies reported that they were double blinded but only 52% provided sufficient information to judge that appropriate methods had been used to blind participant/personnel and only 22% provided details that suggested that outcome assessors had been appropriately blinded. Full details of the risk of bias assessments for individual trials, including the support for judgements, are provided in Appendix 8. A summary of the risk of bias of studies included for each patient category is provided within each results section (section 5.2.1-5.2.10).

FIGURE 3: RISK OF BIAS ACROSS INCLUDED TRIALS



5.2 RESULTS OF CLINICAL EFFECTIVENESS REVIEW

5.2.1 Nausea and vomiting due to chemotherapy

Twenty-eight studies (37 publications; 1772 participants) evaluated CBM for the treatment of nausea and vomiting in adults and children undergoing chemotherapy (Table 2). [73, 74, 83, 85, 90-94, 97-124] The majority of the studies were restricted to adults but two studies were conducted in children[92, 93] and a further study also included children.[94] The studies included patients with a variety of cancers. Some were restricted to single cancer types such as testicular cancer[125] or lung cancer,[101] others included patients with a specific type of cancer such as gastrointestinal[111] or advanced gynaecological cancers,[104] but most included mixed cancers. Studies restricted inclusion based on certain chemotherapy or previous anti-emetic treatment requirements such as having failed previous anti-emetic treatment, being scheduled for two identical courses of chemotherapy, previous chemotherapy induced nausea and vomiting lasting >24 hours, receiving chemotherapy with a high or moderate emetic potential, or the same chemotherapy as previous cycles. Studies were conducted in Canada, Ireland, Finland, France, Germany, Spain, UK and USA.

Seven studies used a parallel group design (467 participants) and 21 (1305) were cross-over trials. Nineteen of the cross-over trials evaluated CBM or control for one chemotherapy cycle and then the other treatment for the next cycle, one cross-over trial was 4 days in duration for each treatment period with a 4 day washout, [112] and one did not provide any

information on the duration of the treatment period or on follow-up.[113] The parallel group trials ranged in duration from 24 hours to 6 days and one included two chemotherapy cycles.[99] Fourteen studies evaluated nabilone (max dose 2-10mg/24h, most common dose 4mg/4h), six studies evaluated THC capsules (max dose 45mg/24h or 4x7-14mg/m^2), four evaluated levonantradol (1.5-4mg/day IM or 4mg/24h oral), three evaluated dronabinol (max dose 10-4mg/24 hours) and one evaluated nabiximols (max 8 sprays in any 4 hour period every 24 hours). Most studies included an active comparator these included procholorperazine in 15 studies (max dose 15-50 mg/24 hours), most common dose 40mg/24 hours) and chlorpromazine (max 37.5mg/24 hours). Other comparators were only evaluated in a single studies and included domperidone oromucosal spray (max dose 45mg/day), oral domperidone (max dose 60mg/day), alizapride (max dose 450mg/day), hydroxyzine (max dose 300mg)/24 hours), metoclopramide (IM, max dose 30mg/24 hours, and ondansetron (max dose 15mg/24 hours). Eight studies, including three that also included an active control, included a placebo control group. Two studies included a combination therapy arm of a CBM and other treatment (dronabinol+ondansetron and dronabinol +Prochlorperazine).

5.2.1.1 Risk of bias

The risk of bias was generally high (Table 3). None of the studies were rated as low risk of bias overall, 23 were judged at high risk of bias and five at unclear risk of bias. The main limitation in the included study related to incomplete outcome data; nineteen studies were judged at high risk of bias for this domain. Other potential sources of bias included selective outcome reporting (judged at high risk of bias in two studies), concealment of treatment allocation (high risk of bias in one study) and blinding of participants (high risk of bias in two studies) and outcome assessors (high risk of bias on one study). Randomisation was rated as low or unclear risk of bias in all studies. Very few studies provided sufficient information to judge whether appropriate methods were taken to conceal treatment allocation or blind outcome assessors, these were rated as unclear in 27 and 26 of the 28 studies respectively.

TABLE 2: OVERVIEW OF STUDIES THAT EVALUATED CBM FOR NAUSEA AND VOMITING DUE TO CHEMOTHERAPY

Study Details	Country	Design	N	Duration	Cancer details	Chemotherapy criteria	Intervention 1	Intervention 2	Intervention 3	Comparator
Ahmedzai(1983}[112]	UK	Cross-over RCT	34	4 days (4 day washout)	Small cell bronchial carcinoma	Eligible for chemotherapy	Nabilone (Cesamet); Max dose 4mg/day			Proclor-perazine; Max dose 30mg/day
Broder(1982}[74]	USA	Cross-over RCT	44	1 chemo-therapy cycle	NR	Failed prior anti-emetic therapy.	THC; 10mg/m^2 every 4-6 hours			Hydroxizine; 50mg every 4-6 hours
Chan(1987}[93, 118]	Canada	Cross-over RCT	40	1 chemo-therapy cycle	Peadiatric malignancies	Repeated courses of CTx with severe drug-induced nausea and vomiting.	Nabilone (Cesamet); max dose 9mg/day (weight dependent)			Prochlor-perazine; wieght dependent
Dalzell(1986}[92]	UK	Cross-over RCT	23	1 chemo-therapy cycle	Peadiatric malignancies	scheduled to receive two identical (courses of emetogenic chemotherapy	Nabilone (Cesamet); max dose 3mg/day			Domperidone oromucosal spray; max dose 15mg 3x/day
Duran(2010}[97]	Spain	Parallel group RCT	16	5 Days	Breast, Ovary, Lung.	chemotherapy-induced nausea and vomiting > 24 h despite prophylaxis with standard anti-emetic treatment after moderately emetogenic chemotherapy	Nabiximols (Sativex); max 8 sprays in any 4h period every 24h			Placebo

Study Details	Country	Design	N	Duration	Cancer details	Chemotherapy criteria	Intervention 1	Intervention 2	Intervention 3	Comparator
Einhorn(1981}[108]	USA	Cross-over RCT	100	1 chemo-therapy cycle	Sarcoma, Hodgkin's disease, lymphoma, bladder, testicular	Combination chemotherapy with drug regimens that produce severe nausea and vomiting.	Nabilone (Cesamet); max 8mg/24 h			Prochlor-perazine; max 40mg/24h
Frytak (1979}[111, 120]	UaSA	Parallel group RCT	117	4 Days	Gastro-intestinal cancers	Initial chemotherapy with specified agents	THC; max 45mg/24h	Prochlor-perazine; max 30mg/24h		Placebo
George(1983}[104]	France	Cross-over RCT	20	1 chemo-therapy cycle	Gyn-aecological cancer (advanced)	Receiving identical courses of chemotherapy.	Nabilone (Cesamet); max 3mg/24h			Chlor-promazine; max 37.5mg/24h
Heim(1984}[102]	Germany	Cross-over RCT	57	1 chemo-therapy cycle	lung, lymphona, soft-tissue sarcoma, breast, testis, melanoma, ovarary, osteosarcoma, prostate cancer, and head and neck cancer.	Receiving chemotherapy with high emetic potential.	Levon-antradol (IM); 0.5mg x 3			Meto-clopramide (IM); 10mg x 3
Herman (1979}[123]	USA	Cross-over RCT	152	1 chemo-therapy cycle	Testicular carcinoma, non-Hodgkin's lymphoma, Hodgkin's disease.	Repeated courses of chemotherapy, all had experienced drug indeced nausea and vomiting.	Nabilone (Cesamet); max 8mg/day			Prochlor-perazine; max 40mg/day

Study Details	Country	Design	N	Duration	Cancer details	Chemotherapy criteria	Intervention 1	Intervention 2	Intervention 3	Comparator
Hutcheon(1983}[103]	UK	Parallel group RCT	108	24 Hours	NR	First course of potentially high antiemetic cytotoxic chemotherapy.	Levon-antradol (IM): 2mg/day	Levon-antradol (IM): 3mg/day	Levon-antradol (IM): 4mg/day	Chlor-promazine
Johansson(1982}[106]	Finland	Cross-over RCT	27	1 chemo-therapy cycle	Cervix, fallopian tubes, ovary, testis, head and neck, bronchus, histiocytoma, fibrosarcoma, oligoden-drioma lymphoma.	Same chemotherapy as previous cycles; uncontrolled nausea and vomiting despite use of standard antiemetic drugs.	Nabilone (Cesamet); max dose 4mg/24h			Prochlor-perazine; max dose 20mg/24h
Jones(1982}[90]	USA	Cross-over RCT	54	1 chemo-therapy cycle	Breast, lymphoma, ovary, lung, melanoma, testes, miscellaneous.	Adults with cancer receiving chemotherapy regimens likely to produce nausea and vomiting; likely to receive at least 2 identical courses of chemotherapy.	Nabilone (Cesamet); max dose 4mg/24h			Placebo
Lane(1991}[83, 116]	USA	Parallel group RCT	62	6 Days	Breast, colon, lung, lymphoma, miscellaneous	NR	Dronabinol (Marinol); max dose 40mg/24h			Proclor-perazine; max dose 40mg/24h
Levitt(1982}[117]	Canada	Cross-over RCT	58	1 chemo-therapy cycle	Lung cancer, ovarian cancer, breast cancer, other.	Not reported	Nabilone (Cesamet); max dose 4mg/24h			Placebo

Study Details	Country	Design	N	Duration	Cancer details	Chemotherapy criteria	Intervention 1	Intervention 2	Intervention 3	Comparator
Long(1982}[73]	USA	Cross-over RCT	42	1 chemo-therapy cycle	NR	strongly emetic chemotherapy	Levon-antradol (oral); max dose 4mg/24h			Prochlor-perazine; max dose 40mg/24h
McCabe (1988}[98, 122]	USA	Cross-over RCT	36	1 chemo-therapy cycle	breast; haematologic; sarcomas; gastro-intestinal; melanoma; ovarian; testicular.	Experiencing severe nausea and vomiting refractory to standard anti-emetics.	THC (oral); 14mg/m^2 every 4h			Prochlor-perazine; max dose 40mg/24h
Meiri(2007}[85, 119, 121]	USA	Parallel group RCT	64	5 days	Breast cancer, non-small cell lung cancer, colon, rectal, or gastric cancer, lung cancer, others	Moderately to highly emetogenic regimen	Dronabinol (Marinol); max dose 10mg/day	Dronabinol + ondansetron	Ondansetron; max 16mg/day	Placebo
Melhem-Bertrandt(2014}[114, 124]	USA	Parallel group RCT	62	5 Days	Breast cancer 61, lymphoma 1.	<=cyclophosphamide 1500 mg/m2 and/or doxorubicin >=40 mg/m2.	Dronabinol (Marinol); max dose 15mg/day			Placebo
Niederle(1986}[100]	Germany	Cross-over RCT	20	1 chemo-therapy cycle	Testicular cancer	NR	Nabilone (Cesamet); max dose 4mg/day			Alizapride; max dose 450mg/day
Niiranen(1985}[101]	Finland	Cross-over RCT	32	1 chemo-therapy cycle	Lung cancer	Scheduled to receive at least two identical consecutive cycles of chemptherapy	Nabilone (Cesamet); max dose 2mg/day			Prochlor-perazine; max dose 15mg/day

Study Details	Country	Design	N	Duration	Cancer details	Chemotherapy criteria	Intervention 1	Intervention 2	Intervention 3	Comparator
Orr(1980}[107, 109]	USA	Cross-over RCT	79	1 chemo-therapy cycle	Variety of neoplasms	previously demonstrated repeated vomiting from anti-cancer agents known to induce emesis; failed standeard antiemetic therapy	THC (oral); 7mg/m^2 x 4 doses		Prochlor-perazine; 7mg/m^2 x 4 doses	Placebo
Pomeroy(1986}[99]	Eire (Ireland)	Parallel group RCT	38	2 chemo-therapy cycles	Ovary, testis, bronchus, non-Hodgkin's lymphoma, Hodgkin's disease, sarcoma, breast, melanoma, nephro-blastoma	Highly emetogenic chemotherapy regimens	Nabilone (Cesamet); max dose 3mg/day			Domperidone ; max dose 60mg/day
Sallan(1980}[94]	USA	Cross-over RCT	84	1 chemo-therapy cycle	NR	Nausea and vomiting inadequately controlled by conventional anti-emetics.	THC (oal); 10mg/m^2 x 3 doses			Prochlor-perazine; max dose 30mg/24h
Sheidler(1984}[113]	USA	Cross-over RCT	20	NR	Small cell lung cancer, multiple myeloma, ovarian, adeno-carcinoma of the lung, breast cancer, diffuse histocytic lymphom, rhabdomyosarcoma	Inpatient chemotherapy	Levon-antradol (IM); max dose 4mg/24h			Prochlor-perazine; max dose 40mg/24h

Study Details	Country	Design	N	Duration	Cancer details	Chemotherapy criteria	Intervention 1	Intervention 2	Intervention 3	Comparator
Steele(1980}[110]	USA	Cross-over RCT	55	1 chemo-therapy cycle	NR	NR	Nabilone (Cesamet); max dose 10mg/24h			Prochlor-perazine; max dose 50mg/24h
Ungerleider(1982}[91]	USA	Cross-over RCT	214	1 chemo-therapy cycle	Carcinoma, sarcoma, lymphoma/ Hodgkins, and leukemia.	Previous chemotherapy associated with nausea and vomiting, or be on the first course of chemotherapy of a drug with a high emetic potential	THC (oral); max dose 50mg/24h (dependent on size)			Prochlor-perazine; max dose 40mg/24h
Wada(1982}[105]	USA	Cross-over RCT	114	1 chemo-therapy cycle	Lung, breast, ovarian, lymphoma, colonic, prostatitc, adeno-carcinoma, bladder, melanoma, pancreatic, oesophagus, stomach, sarcoma, testis, other.	Chemotherapy regimens likely to produce nausea and vomiting; likely to receive at least 2 identical courses of chemotherapy.	Nabilone (Cesamet); max dose 4mg/day			Placebo

TABLE 3: RISK OF BIAS IN NAUSEA AND VOMITING DUE TO CHEMOTHERAPY STUDIES

Study Details	RISK OF BIAS						
	Random sequence generation	Allocation concealment	Participant/ Personnel blinding	Outcome assessor blinding	Incomplete outcome data	Selective outcome reporting	Overall
Ahmedzai(1983}[112]	?	?	☺	?	☹	☺	☹
Broder(1982}[74]	?	?	?	?	?	?	?
Chan(1987}[93]	?	?	☺	?	☹	☺	☹
Dalzell(1986}[92]	?	?	☺	?	☹	☺	☹
Duran(2010}[97]	☺	?	☺	?	☺	☹	☹
Einhorn(1981}[108]	?	?	☺	?	☹	☺	☹
Frytak (1979}[111]	☺	☹	☺	?	☺	☺	☹
George(1983}[104]	☺	?	☺	?	☺	☺	?
Heim(1984}[102]	?	?	☹	?	☹	☺	☹
Herman (1979}[123]	?	?	☺	☺	☹	☺	☹
Hutcheon(1983}[103]	?	?	☺	?	☺	☺	?
Johansson(1982}[106]	?	?	?	?	☹	☺	☹
Jones(1982}[90]	?	?	?	?	☹	☺	☹
Lane(1991}[83]	?	?	☺	?	☹	☺	☹
Levitt(1982}[117]	?	?	?	?	☹	?	☹
Long(1982}[73]	?	?	?	?	☹	☹	☹
McCabe (1988}[98, 122]	?	?	☹	☹	☺	☺	☹
Meiri(2007}[85]	?	?	☺	?	☹	☺	☹
Melhem-Bertrandt(2014}[124]	☺	?	☺	?	☺	☺	?
Niederle(1986}[100]	?	?	?	?	☺	☹	☹
Niiranen(1985}[101]	?	?	☺	?	☹	☺	☹
Orr(1980}[107, 109]	?	?	☺	?	☹	☺	☹
Pomeroy(1986}[99]	?	?	☺	?	☹	☺	☹
Sallan(1980}[94]	?	?	☺	?	☹	☺	☹
Sheidler(1984}[113]	?	?	☹	☹	☹	☺	☹
Steele(1980}[110]	?	?	?	?	☹	☺	☹
Ungerleider(1982}[91]	☺	?	?	?	☺	☺	?
Wada(1982}[105]	?	?	☺	?	☹	☺	☹

5.2.1.2 Dichotomous outcome results

Ten studies provided dichotomous outcome data on various measures related to nausea and vomiting.[73, 83, 85, 93, 97, 98, 102, 108, 112, 124] All suggested beneficial effects of CBM compared to both active comparators and placebo but this did not reach statistical significance in most trials. The most commonly evaluated outcome measure, assessed in five studies, was a complete response in nausea and vomiting generally defined as no vomiting and no or very little nausea. Two studies, one parallel group and one cross over trial, compared dronabinol and THC to prochlorperazine. Both reported a greater number of patients with a complete response in the CBM group but this only reached statistical significance in the cross-over trial (OR 25.2, 95% CI 1.4, 452.2). Three parallel group studies compared dronabinol or nabiximols to placebo and provided sufficient data on this outcome to allow pooling. One of these studies included two CBM arms – dronabinol alone and dronabinol combined with ondansetron. Results were similar for both treatment arms; we selected the data for the dronabinol arm as this was most similar to the other trials.[85] The summary estimate suggested a significantly greater number of participants with complete nausea and vomiting response among those taking CBM compared to placebo (OR 3.44, 95% CI 1.45, 8.1; Figure 4).

FIGURE 4: FOREST PLOT SHOWING ORS (95% CI) FOR NUMBER OF PATIENTS REPORTING A COMPLETE RESPONSE FOR NAUSEA AND VOMITING, PARALLEL GROUP STUDIES ONLY

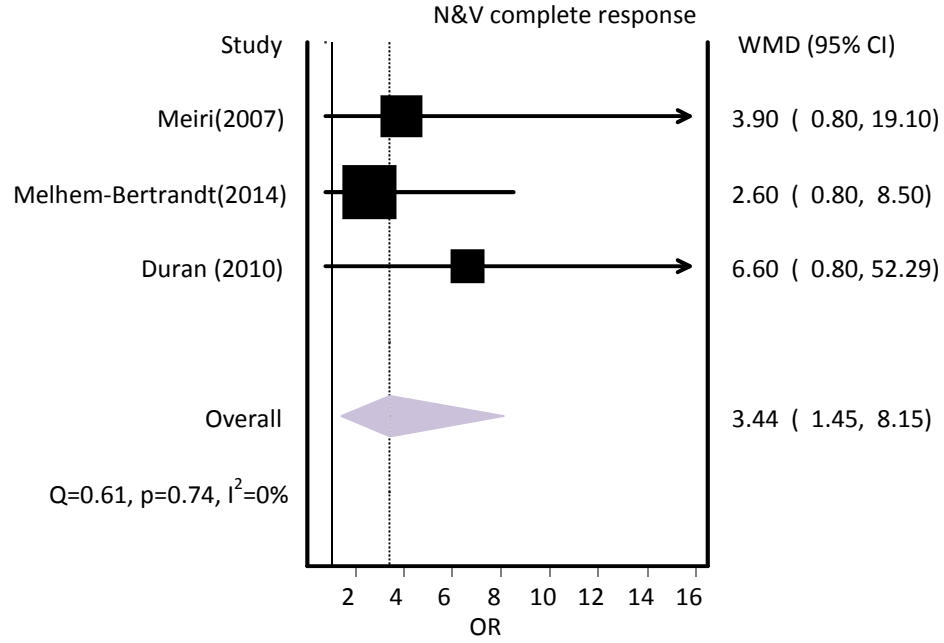


TABLE 4: RESULTS FOR DICHOTOMOUS OUTCOMES FROM STUDIES THAT EVALUATED CBM FOR NAUSEA AND VOMITING DUE TO CHEMOTHERAPY

Study Details	Intervention	Comparator	Outcome	Intervention Events/ n	Placebo Events/n	OR (95% CI)
Appetitie & Weight						
Einhorn(1981)[108] Cross-over	Nabilone (Cesamet)	Prochlorperazine	"Depressed appetite and reduced food intake"	64/80	72/80	0.46 (0.19, 1.12)
Nausea & vomiting:						
Lane(1991)[83] Parallel group	Dronabinol (Marinol)	Proclor-perazine	Complete response	7/17	6/20	1.5 (0.42, 5.94)
McCabe(1988)[98] Cross-over	THC	Proclor-perazine	Complete response	9/36	0/36	**25.2 (1.40, 452.22)**
Meiri(2007)[85] Parallel group	Dronabinol	Placebo	Complete response (no vomiting, nausea < 5 mm on a 100-mm VASP)	8/14	3/13	3.9 (0.80, 19.10)
	Dronabinol + ondansetron			7/14	3/13	3.0 (0.61, 14.52)
Melhem-Bertrandt(2014)[124] Parallel group	Dronabinol	Placebo	Complete response	11/30	5/29	2.6 (0.80, 8.52)
Duran (2010)[97] Parallel group	Nabiximols	Placebo	Complete response (no vomiting and a mean nausea VAS score of ≤10mm)	5/7	2/9	6.6 (0.83, 52.29)
Melhem-Bertrandt(2014)[124] Parallel group	Dronabinol	Placebo	Complete response (No vomiting, nausea intensity NRS >3)	14/30	9/29	1.8 (0.66, 5.38)
Duran (2010)[97] Parallel group	Nabiximols	Placebo	Partial response (vomiting on average 1-4x daily and a mean nausea VAS score of ≤25mm)	1/7	5/9	0.1 (0.02, 1.65)
Lane(1991)[83] Parallel group	Dronabinol (Marinol)	Proclor-perazine	Partial response (≤2 episodes of nausea or vomiting)	12/17	9/20	2.7 (0.73, 10.30)
Long(1982)[73] Cross-over	Levonan-tradol	Proclor-perazine	Partial response ('Significantly less nausea and vomiting')	13/34	3/34	**5.6 (1.54, 20.67)**
McCabe(1988)[98] Cross-over	THC	Proclor-perazine	Partial response (≥50% decrease in frequency and intensity)	14/36	1/36	**15.2 (2.61, 88.83)**
Nausea						
Meiri(2007)[85] Parallel group	Dronabinol	Placebo	Complete response	10/14	2/13	**10.7 (1.85, 62.25)**

Study Details	Intervention	Comparator	Outcome	Intervention Events/ n	Placebo Events/n	OR (95% CI)
	Dronabinol + ondansetron		Complete response	7/14	2/13	4.6 (0.83, 25.21)
Ahmedzai(1983)[112] Cross-over	Nabilone	Proclor-perazine	Complete response	21/26	10/30	7.6 (2.30, 25.23)
Melhem-Bertrandt(2014)[124] Parallel group	Dronabinol	Placebo	Complete response	11/30	5/29	2.6 (0.80, 8.52)
Melhem-Bertrandt(2014)[124] Parallel group	Dronabinol	Placebo	No significant nausea(NRS >3)	15/30	10/29	1.8 (0.66, 5.19)
Lane(1991)[83] Parallel group	Dronabinol (Marinol)	Proclor-perazine	Anticipatory nausea	6/20	0/20	18.3 (0.95, 352.58)
Retching						
Ahmedzai(1983)[112] Cross-over	Nabilone	Proclor-perazine	Retching: Complete response (No retching)	22/26	13/30	**6.4 (1.88, 22.31)**
Vomiting & retching						
Chan(1987)[93] Cross-over	Nabilone	Proclor-perazine	Vomiting and retching: Complete response	3/30	3/30	1.0 (0.20, 4.82)
Chan(1987)[93] Cross-over	Nabilone	Proclor-perazine	Vomiting and retching: Partial response ("Overall improvement ")	21/30	9/30	**5.1 (1.73, 15.08)**
Chan(1987)[93] Cross-over	Nabilone	Proclor-perazine	Vomiting and retching: Partial response ("Less retching and vomiting")	18/30	6/30	**5.5 (1.81, 17.16)**
Vomiting						
Melhem-Bertrandt(2014)[124] Parallel group	Dronabinol	Placebo	Vomiting: Complete response	15/30	12/29	1.4 (0.50, 3.84)
Ahmedzai(1983)[112] Cross-over	Nabilone	Proclor-perazine	Vomiting: Complete response	26/26	22/30	**20.0 (1.09, 366.45)**
Heim(1984)[102] Cross-over	Levon-antradol	Metoclo-pramide	Vomiting: Episodes of vomiting	140/45	(301)/45	NA

Study Details	Intervention	Comparator	Outcome	Intervention Events/ n	Placebo Events/n	OR (95% CI)
Melhem-Bertrandt(2014)[124] Parallel group	Dronabinol	Placebo	Vomiting: Episodes of vomiting	19/30	19/29	NA

5.2.1.3 Categorical outcome results

Nine studies, two parallel group and seven cross-over trials, provided categorical results on nausea and vomiting outcomes (Table 5).[94, 100, 101, 106, 109, 113, 123] These generally suggested a better effect of the intervention but most did not provide a p-value for the difference between groups. Only two studies provided this information, one parallel group study showed a significant difference in nausea intensity between groups in favour of nabilone compared to prochlorperazine (p=0.027)[106] and the cross-over trial showed no differences in nausea between groups.[113] For studies that did not provide a p-value for the significance of observed differences across groups we used a chi^2 test to compare results across groups. Most comparisons showed no significant differences between groups. The only exceptions were levonantradol at a dose of 2mg which was associated with significantly fewer vomiting episodes than chlorpromazine in a parallel group study,[103] THC was associated with less nausea intensity than prochlorperzine and placebo,[126] and THC and nabilone were associated with more patients experience complete and improved nausea and vomiting response than prochlorperazine.[94, 123] The latter three studies were cross-over trials.

TABLE 5: RESULTS FOR CATEGORICAL OUTCOMES FROM STUDIES THAT EVALUATED CBM FOR NAUSEA AND VOMITING DUE TO CHEMOTHERAPY

Study	Intervention	Comparator	Outcome	Categories	Inter-vention events	Compa rator event	P-value*
Frytak(1979)[111] Parallel group	THC	Placebo	Nausea & vomiting	None Nausea only Nausea and vomiting	16 2 20	7 6 24	*0.053*
	THC	Prochlor-perazine		None Nausea only Nausea and vomiting	16 2 20	17 1 24	*0.768*
Herman(1979)[123]	Nabilone	Prochlor-perazine	Nausea & vomiting	Complete response Partial response No response	9 81 23	0 36 77	***<0.01***
Hutcheon(1983)[103] Parallel group	Levonan-tradol (2mg)	Chlorpro-mazine	Appetite	Good Normal Fair Poor	2 14 6 5	4 6 7 10	*0.132*
			Nausea severity/intensity	None Mild Moderate Severe	14 6 7 0	9 13 4 1	*0.140*

Study	Intervention	Comparator	Outcome	Categories	Inter-vention events	Compa rator event	P-value*
			Number of vomiting episodes	0 1-4 5-10 10	20 3 2 2	11 9 7 0	***0.016***
	Levonantradol (3mg)		Appetite	Good Normal Fair Poor	3 2 13 10	4 6 7 10	*0.270*
			Nausea severity/intensity	None Mild Moderate Severe	8 14 5 1	9 13 4 1	*0.979*
			Number of vomiting episodes	0 1-4 5-10 10	11 11 5 1	11 9 7 0	*0.679*
	Levonantradol (4mg)		Appetite	Good Normal Fair Poor	1 9 6 9	4 6 7 10	*0.483*
			Nausea severity/ intensity	None Mild Moderate Severe	13 4 6 3	9 13 4 1	*0.076*
			Number of vomiting episodes	0 1-4 5-10 10	14 4 8 0	11 9 7 0	*0.312*
Johansson(1982)[106] Cross-over	Nabilone	Prochlor-perazine	Nausea severity/intensity	None Mild Moderate Severe	3 6 7 2	0 3 11 4	0.027
			Number of vomiting episodes	0 1-5 6-10 11-20 >20	3 3 5 4 3	0 2 2 5 9	*0.281*
Niederle(1986)[100] Cross-over	Nabilone	Alizapride	Nausea severity/ intensity	None Mild Moderate Severe	12 4 4 0	7 6 5 2	*0.281*
Niiranen (1985)[101] Cross-over RCT	Nabilone	Prochlor-perazine	Appetite	Not diminished Moderately diminished Markedly dimished	8 14 2 0	5 15 4 0	*0.498*

Study	Intervention	Comparator	Outcome	Categories	Inter-vention events	Compa rator event	P-value*
			Response	Very good (no N or V) Good Fair Poor very poor (>15 episodes of vomitting or severe nausea)	3 9 5 6 1	5 3 6 3 7	*0.059*
			Nausea severity/ intensity	None Mild Moderate Severe	1 7 9 7	4 4 10 6	*0.432*
Orr(1980)[109] Cross-over	THC	Prochlor-perazine	Nausea severity/ intensity	None Mild Severe Emesis	40 7 5 3	5 8 13 29	***<0.01***
	THC	Placebo		None Mild Severe Emesis	40 7 5 3	8 11 18 18	***<0.01***
Sallan(1980)[94] Cross-over	THC	Prochlor-perazine	Nausea and vomiting response	Complete response Partial response No response	36 10 33	16 15 47	**0.004**
Sheidler(1984)[113] Cross-over	Levonan-tradol	Prochlor-perazine	Nausea	Complete response Partial response No response	1 9 6	2 9 5	0.61

*Values in italics were calculated from the reported in the paper using a Chi^2 test

5.2.1.4 Results of cross-over trials that compared treatments within patients

Five cross-over trials compared treatments within patients by asking patients which intervention was associated with a better outcome (Table 6).[90, 102, 105, 106, 127] All evaluated nausea and found that greater number of patients reported less nausea with dronabinol or nabilone, or found no difference between treatments, with much small numbers experiencing less nausea with metoclopramide, prochlorperazine or placebo. [90, 102, 105, 127] Four trials evaluated nausea and showed similar results and one trial found a similar effect on appetite.[102]

TABLE 6: RESULTS FOR CROSS-OVER TRIALS THAT COMPARED NAUSEA AND VOMITING OUTCOMES WITHIN PATIENTS

Study	Intervention	Comparator	Outcome	No. patients reporting that intervention was associated with best outcomes			p-value
				CBM	No difference	Comparator	
Heim(1984)[102]	Dronabinol	Meto-clopramide	Nausea	28	12	5	**<0.05**
			Vomiting	25	12	8	**<0.05**
			Appetite	22	21	2	**<0.05**
Johansson(1982)[106]	Nabilone	Prochlor-perazine	Nausea	9	8	1	NR
Jones(1982)[90]	Nabilone	Placebo	Nausea	15	8	1	**<0.001**
			Vomiting	19	2	3	**<0.001**

Study	Intervention	Comparator	Outcome	No. patients reporting that intervention was associated with best outcomes			p-value
				CBM	No difference	Comparator	
Levitt(1982)[117]	Nabilone	Placebo	Nausea	26	8	2	**<0.001**
			Vomiting	29	3	4	**<0.001**
Wada(1982)[105]	Nabilone	Placebo	Nausea	56	27	9	NR
			Vomiting	53	18	21	NR

5.2.1.5 Continuous outcome results

Eighteen studies assessed nausea and vomiting using continuous outcome measures.[74, 83, 85, 90-92, 99-101, 104-106, 108, 110, 112, 117, 124, 128] All reported suggested beneficial effects in favour of CBM compared to both placebo and active comparison, but this did not reach statistical significance in all studies and some did not report on the statistical significance of the difference (Table 7). None of the studies provided information to allow calculation of confidence intervals around mean differences between treatments and so it was not possible to pool continuous data for this population.

The most commonly evaluated outcome was the number of episodes of vomiting. This was evaluated in 11 studies, two parallel group studies and three cross-over trials.[74, 85, 90, 92, 99, 101, 104-106, 108, 117] Nine studies, including one of the parallel group trials, reported significantly less ($p<0.05$) vomiting associated with CBM (THC, nabilone or dronabilon) compared to various comparators including hydrazine, domperidone, prochlorperazine, and placebo. The remaining two studies did not report on the statistical significance of the difference. Nausea severity/intensity was evaluated in nine studies, two parallel group trials and seven cross-over trials.[74, 85, 90, 92, 99, 105, 108, 112, 117] The studies compared THC, nabilone and dronabinol to hydroxyzine, domperidone, prochlorperzine, and placebo. All but one of the studies reported significant beneficial effects ($p<0.05$) of CBM compared to the comparator intervention.[99] Nausea duration was evaluated in four trials, two parallel group and two cross-over trials. One of the parallel group and one-crossover trial reported significant beneficial effects of dronabinol and nabilone compared to placebo and alizapride ($p<0.03$).

Appetite and food intake was assessed in four cross-over trials.[74, 91, 99, 117] One study found significant beneficial effects of THC compared to hydroxyzine for all three outcomes assessed,[74] one reported significantly greater food intake with nabilone compared to placebo,[117] two reported beneficial effects of CBM compared to active comparators but did not report on the statistical significance of the results.[91, 99]

Two studies provided a global interpretation of patient's functional status. Both reported significant beneficial effects in favour of CBM. One compared dronabinol alone and compared with ondansetron to placebo and reported significantly greater improvements in ECOG assessments in the dronabinol groups ($p=0.036$).[85] The other compared to nabilone to prochlorperazine and reported significantly better physician global impression in the nabilone group (<0.001).[106]

TABLE 7: RESULTS FOR CONTINUOUS OUTCOMES FROM STUDIES THAT EVALUATED CBM FOR NAUSEA AND VOMITING DUE TO CHEMOTHERAPY

Study Details	Inter-vention	Comparator	Outcome	MD at follow-up:		Analysis Details
Appetite & weight:						
Broder(1982)[74] Cross-over	THC	Hydroxizine	Anorexia	**Favoured THC**	**p<0.05**	McNemar's Test
Ungerleider(1982)[91] Cross-over	THC	Prochlor-perazine	Appetite Single day regimen	0.08		
Ungerleider(1982)[91] Cross-over	THC	Prochlor-perazine	Appetite Multiple day regimen	0.11		
Levitt(1982)[117] Cross-over	Nabilone	Placebo	Food intake (0 (no food intake) - 3 (more than usual))	**0.78**	**0.001**	NR
Broder(1982)[74] Cross-over	THC	Hydroxizine	Food intake	**Favoured THC**	**p<0.05**	McNemar's Test
Ungerleider(1982)[91] Cross-over	THC	Prochlor-perazine	Food intake Single day regimen	-0.02		
Pomeroy(1986)[99] Parallel group	Nabilone	Domperidone	Food intake	0.34	NR	Kolmagorov-Smirnov test
Ungerleider(1982)[91] Cross-over	THC	Prochlor-perazine	Food intake Multiple day regimen	0.08		
Broder(1982)[74] Cross-over	THC	Hydroxizine	Fluid intake	**Favoured THC**	**p<0.05**	McNemar's Test
Nausea						
Broder(1982)[74] Cross-over	THC	Hydroxizine	Severity/intensity	**Favoured THC**	**p<0.05**	McNemar's Test
Dalzell(1986)[92] Cross-over	Nabilone	Domperidone	Severity/intensity	**-1.0**	**<0.01**	Wilcoxen signed rank
Pomeroy(1986)[99] Parallel group	Nabilone	Domperidone	Severity/intensity	-0.5	≥0.05	Kolmagorov-Smirnov test
Einhorn(1981)[108] Cross-over	Nabilone	Prochlor-perazine	Severity/intensity		**0.003**	ANOVA
Jones[90] Cross-over	Nabilone	Placebo	Severity/intensity	**-0.8**	**<0.001**	NR
Ahmedzai(1983)[112] Cross-over	Nabilone	Proclor-perazine	Severity/intensity	**-0.5**	**≤0.05**	Mann- Whitney/ Wilcoxon test
Levitt(1982)[117] Cross-over	Nabilone	Placebo	Severity/intensity	**-1.22**	**≤0.001**	NR
Meiri(2007)[85] Parallel group	Drona-binol	Placebo	Severity/intensity	**-38.3**	**<0.05**	Wilcoxon rank sum test

Study Details	Inter-vention	Comparator	Outcome	MD at follow-up:		Analysis Details
	Drona-binol + ondan-setron			**-38.3**	**<0.05**	
Wada (1982)[105] Cross-over	Nabilone	Placebo	Severity/intensity	**-0.74**	**≤0.001**	"Non-parametric test on ranks"
Melhem-Bertr andt(2014)[124] Parallel group	Drona-binol	Placebo	Average nausea episodes/day)	**-0.24**	**0.033**	Mann-Whitney/ Wilcoxon test
Steele(1980)[110] Cross-over	Nabilone	Prochlor-perazine	Duration (days)	Medians 0.7 vs 1.0	NR	NR
Melhem-Bertr andt(2014)[124] Parallel group	Drona-binol	Placebo	Duration (days)	**-1.24**	**0.027**	Mann-Whitney/ Wilcoxon test
Niederle(1986)[100] Cross-over	Nabilone	Alizapride	Duration (hours)	**-3.8***	**<0.01**	Wilcoxen signed rank
Lane(1991)[83] Parallel group	Drona-binol	Proclor-perazine	Duration (mins)	-5	0.09	Mann-Whitney/ Wilcoxon test
Retching						
Ahmedzai(1983)[112] Cross-over	Nabilone	Proclor-perazine	**S**everity	-0.4	≥0.05	Mann- Whitney/ Wilcoxon test
Vomiting						
Broder(1982)[74] Cross-over	THC	Hydroxizine	Number of episodes	**Favoured THC**	**<0.01**	McNemar's Test
Dalzell(1986)[92] Cross-over	Nabilone	Domperidone	Number of episodes	**-10.78**	**<0.01**	Wilcoxen signed rank
Einhorn(1981)[108] Cross-over	Nabilone	Prochlor-perazine	Number of episodes		**0.003**	ANOVA
George(1983)[104] Cross-over	Nabilone	Chlor-promazine	Number of episodes	-1.9		
Johansson(1982)[106] Cross-over	Nabilone	Prochlor-perazine	Number of episodes	**-20.3**	**≤0.001**	ANOVA
Jones[90] Cross-over	Nabilone	Placebo	Number of episodes	**-11.6**	**<0.001**	NR
Levitt(1982)[117] Cross-over	Nabilone	Placebo	Number of episodes	**-4.5**	**≤0.001**	NR
Meiri(2007)[85] Parallel group	Drona-binol	Placebo	Number of episodes	-1.1		
Meiri(2007)[85] Parallel group	Drona-binol + ondan-setron	Placebo	Number of episodes	-1.1		

Study Details	Inter-vention	Comparator	Outcome	MD at follow-up:		Analysis Details
Niiranen (1985)[101] Cross-over	Nabilone	Prochlor-perazine	Number of episodes	**-4.5**	**p<0.05**	Hills and Armitage
Pomeroy(1986)[99] Parallel group	Nabilone	Domperidone	Number of episodes	**-6.28**	**≤0.01**	t-test
Wada (1982)[105] Cross-over	Nabilone	Placebo	Number of episodes	**-2.89**	**≤0.001**	NR
Ahmedzai(1983)[112] Cross-over	Nabilone	Proclor-perazine	Severity/intensity	**-0.6**	**≤0.001**	Mann- Whitney/ Wilcoxon test
Lane(1991)[83] Parallel group	Drona-binol	Proclor-perazine	Duration (mins)	-2	NR	Mann-Whitney/ Wilcoxon test
Steele(1980)[110] Cross-over	Nabilone	Prochlor-perazine	Duration (hours)	Medians 3.2 vs 5.2	NR	
Steele(1980)[110] Cross-over	Nabilone	Prochlor-perazine	Severity/intensity	Medians 1.5 vs 1.9	NR	
Steele(1980)[110] Cross-over	Nabilone	Prochlor-perazine	(Frequency (hours))	Medians 6 vs 11.5	NR	
Nausea & vomiting:						
Lane(1991)[83] Parallel group	Drona-binol	Proclor-perazine	Duration of nausea/vomiting (mins)	0	NR	Mann-Whitney/ Wilcoxon test
Ungerleider(1982)[91] Cross-over	THC	Prochlor-perazine	Severity/intensity Single day regimen	0.23		
Ungerleider(1982)[91] Cross-over	THC	Prochlor-perazine	Severity/intensity Multiple day regimen	-0.11		
Global impression						
Meiri(2007)[85] Parallel group	Drona-binol	Placebo	ECOG assessment	**-0.02***	**0.036**	ANOVA
	Drona-binol + ondan-setron	Placebo		**-0.02**	**0.036**	ANOVA
Johansson(1982)[106] Cross-over	Nabilone	Prochlor-perazine	Physician global impression (1 to 5 (scale meaning unclear - 1 appears best))	**-1.2**	**≤0.001**	ANOVA

5.2.1.6 Summary

Overall there was some evidence that CBM reduces nausea and vomiting and improves appetite and functional status in patients receiving chemotherapy treatment for various types of cancer. All studies reported beneficial effects on all outcomes assessed but these did not reach statistical significance in all studies and some did report on the statistical

significance of their findings. The majority of the studies were cross-over trials conducted in the 1980s and over 80% were judged at high risk of bias. These findings should therefore be interpreted with some caution. There were only sufficient data to pool results for one outcome, the number of patients showing a complete nausea and vomiting response. This showed a significant beneficial effect of CBM compared to placebo (OR 3.44, 95% CI 1.45, 8.15, Table 8). There were insufficient data to investigate small study effects.

TABLE 8: SUMMARY ESTIMATES FOR NAUSEA AND VOMITING TRIALS

Outcome	Number of studies	Summary estimate	Favours	I^2 (%)
N&V complete response	3	**OR=3.44(1.45, 8.15)**	CBM	0

The Grade Evidence profile for this section is given below.

TABLE 9: GRADE SUMMARY OF FINDINGS TABLE: NAUSEA AND VOMITING DUE TO CHEMOTHERAPY

Nausea and vomiting due to chemotherapy

Patient or population: patients with nausea and vomiting due to chemotherapy
Settings: Not specified
Intervention: CBM

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Control**	Corresponding risk **CBM**				
Complete response for nausea and vomiting no vomiting and no or very little nausea Follow-up: 5 days	**196 per 1000**	**456 per 1000** (261 to 665)	**OR 3.44** (1.45 to 8.15)	102 (3 studies[1])	⊕⊖⊖⊖ **very low**[2,3]	
Any adverse events Follow-up: 6 days[4]	**499 per 1000**	**777 per 1000** (687 to 847)	**OR 3.51** (2.21 to 5.56)[5]	784 (10 studies[6])	⊕⊕⊕⊖ **moderate**[7]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Duran 2010, Meiri 2007, Melham-Bertrandt 2014
[2] Risk of bias: Insufficient details on randomisation (Meiri 2007), concealment of allocation (all studies) and outcome assessor blinding (all studies); high risk of bias for incomplete outcome data (Meiri 2007) and selective outcome reporting (Duran 2010).
[3] Imprecision: 3 studies including 102 patients (34 events).
[4] Chan 1987, George 1983, Heim 1984, Johansson 1982, Pomeroy 1986, Ungerleider 1982: 1 chemotherapy cycle; Hutcheon 1983: 1 day; Duran 2010, Meiri 2004: 5 days; Lane 1991: 6 days
[5] OR across all patient populations (29 studies): 3.03, 95%-CI 2.42 to 3.80 (see section 5.3 for details)
[6] Chan 1987, Duran 2010, George 1983, Heim 1984, Hutcheon 1983, Johansson 1982, Lane 1991, Meiri 2004, Pomeroy 1986, Ungerleider 1982
[7] Risk of bias: Insufficient details on randomisation (Chan 1987, Heim 1984, Hutcheon 1983, Johansson 1982, Lane 1991, Meiri 2007, Pomeroy 1986), concealment of allocation (all studies) and blinding (all studies); high risk of bias for incomplete outcome data (Duran 1987, Heim 1984, Johansson 1982, Meiri 2007, Pomeroy 1986).

5.2.2 HIV/AIDS

Four studies (255 participants) evaluated CBM as a treatment for appetite stimulation in patients with HIV/AIDS (Table 10).[84, 88, 129, 130] Three studies (2,188 participants) included patients with MS and two included patients with paraplegia (25 participants) caused by spinal cord injury. All studies were conducted in the USA.

Three RCTs used a parallel group design (243 participants) and one (12 participants) was a cross-over trial.[130] Three trials specified a minimum weight loss as an entry criterion. This ranged from ≥2.25-2.3 kg or ≥10% of body weight. Study duration ranged from 3 to 12 weeks. All studies evaluated dronabinol, three compared to matched placebo and one compared to megestrol acetate.[88] Two studies included additional treatment arms. One of the placebo controlled trials also evaluated marijuana cigarettes[129] and the active comparison trial also included a combined dronabinol/megestrol acetate treatment arm.[88]

5.2.2.1 Risk of bias

All studies were judged at high risk of bias (Table 11). Two studies were judged at high risk of bias for participant and outcome assessor blinding; the active comparison study and the marijuana arm of the other three arm study. The other trials did not provide information on blinding. Three trials were judged at high risk of bias for incomplete outcome data as they had a large proportion of withdrawals and did not adequately account for this through use of an intention to treat analysis for all outcomes. All studies were judged at low risk of bias for selective outcome reporting. Method of randomisation and allocation concealment were only reported in one study which was judged to be at low risk of bias.[129]

TABLE 10: OVERVIEW OF STUDIES THAT EVALUATED CBM IN PATIENTS WITH HIV/AIDS

Study Details	Country	Design	N	Duration (weeks)*	HIV entry criterion	Intervention 1	Intervention 2	Comparator
Abrams(2003)[129]	USA	Parallel group	67	3	Stable antiretroviral regimen for ≥ 8 weeks; stable viral load for 16 weeks	Marijuana (smoked); (max 3 cigarettes/day, 4% THC)	Dronabinol (max 7.5mg/day)	Placebo
Beal (1995)[84]	USA	Parallel group	139	6	≥1 AIDS defining event; loss ≥2.3 kg normal body bodyweight	Dronabinol (5mg/day)		Placebo
Struwe(1993)[130]	USA	Cross-over	12	5 weeks (2 week washout)	loss of ≥2.25 kg normal body weight but were at least 70% of ideal body weight	Dronabinol (max 10mg/day)		Placebo
Timpone(1997)[88]	USA	Parallel group	37	12	>10% weight loss or BMI that was low; stable antiretroviral regimen for ≥ 4 weeks	Dronabinol (5mg/day)	Dronabinol (5mg/day) + megestrol acetate (750mg/day)	megestrol acetate (750mg/day)

TABLE 11: RISK OF BIAS IN HIV/AIDS STUDIES

Study Details	RISK OF BIAS						
	Random sequence generation	Allocation concealment	Participant/ Personnel blinding	Outcome assessor blinding	Incomplete outcome data	Selective outcome reporting	Overall
Abrams(2003)[129]	☺	☺	☹/?*	☹/?*	☺	☺	☹
Beal (1995)[84]	?	?	?	?	☹/☺$	☺	☹
Struwe(1993)[130]	?	?	?	?	☹	☺	☹
Timpone(1997)[88]	?	?	☹	☹	☹	☺	☹

*This study was judged at high risk of bias for blinding for the marijuana cigarette group and unclear for the dronabinol group

$This study was judged at high risk of bias for outcomes that were analysed on a per-protocol basis and low risk of bias for outcomes analysed on an ITT basis

5.2.2.2 Dichotomous outcome results

Only one study, a parallel group study, evaluated a dichotomous outcome related to the effectiveness of interventions for appetite stimulation in patients with HIV (Table 12).[84] This study suggested that a greater number of patients gained weight with dronabinol treatment compared to placebo but the difference did not reach statistical significance (OR 2.2, 95% CI 0.69, 7.27).

TABLE 12: RESULTS FOR DICHOTOMOUS OUTCOMES FROM STUDIES THAT EVALUATED CBM FOR APPETITE STIMULATION IN PATIENTS WITH HIV

Study Details	Intervention	Outcome	Intervention Events/ n	Placebo Events/n	OR (95% CI)*
Appetite & weight:					
Beal (1995)[84]	Dronabinol (Marinol)	Number of patients who gained ≥2kg	11/50	4/38	2.2 (0.68, 7.27)

5.2.2.3 Continuous outcome results

Appetite and weight

All four studies reported on the change in weight associated with CBM treatment (Table 13). One placebo controlled study reported a significant beneficial effect of both dronabinol and marijuana (p=0.004 and 0.021) but data were only reported as median weight at follow-up and so it was not possible to calculate an effect size for this trial.[129] Two further trials suggested a greater weight gain with dronabinol compared to placebo but this did not reach statistical significance (p=0.14 and 0.13). The active comparison trial suggested significantly greater weight gain with megestrol acetate compared to dronabinol (MD -8.5 (-9.18, -7.82)) and no difference between dronabinol and megestrol acetate combined and megestrol acetate alone.[88] There was also a suggestion of increased appetite with dronabinol based on two trials,[84, 130] one of which used a cross-over design,[130] but this did not reach statistical significance. The cross-over trial reported a significantly greater increase in the % body fat associated with dronabinol use (p=0.04).[130]

Nausea and vomiting

One placebo controlled parallel group study reported less nausea with dronabinol but the evidence for this was weak (p=0.26).[84]

Global impression

One placebo controlled parallel group study[84] also reported a suggestion of a greater improvement in Karnofsky performance status[131] in the dronabinol group compared to placebo. The cross-over trial found improvements in functional limitations associated with dronabinol.[130]

5.2.2.4 Summary

There was some evidence that dronabinol is associated with an increase in weight compared to placebo. More limited evidence suggested that it may also be associated with increased appetite, greater % body fat, reduced nausea, and improved functional status. However,

these outcomes were mostly assessed in single studies and failed to reach statistical significance. One trial evaluated marijuana and dronabinol, this study found significantly greater weight gain with both forms of cannabis compared to placebo. An active comparison study found that megestrol acetate was associated with greater weight gain than dronabinol and that combining dronabinol with megestrol acetate did not lead to additional weight gain.

TABLE 13: RESULTS FOR CONTINUOUS OUTCOMES FROM STUDIES THAT EVALUATED CBM IN PATIENTS WITH HIV/AIDS

Study Details	Intervention	Outcome	MD change from baseline:	p-value	Analysis Details
Appetite & weight:					
Abrams(2003)[129]	Dronabinol	Weight (kg)	Only medians reported	**0.004**	Mann-Whitney
	Marijuana			**0.021**	
Beal(1995)[84]	Dronabinol	Weight (kg)	0.50	0.14	ANOVA
Struwe (1993)[130]	Dronabinol	Weight (kg)	1.0*	0.13	Wilcoxen signed rank
Timpone(1997)[88]	Dronabinol	Weight (kg)	*-8.5 (-9.18, -7.82)*		
	Dronabinol + megestrol acetate		*-0.5 (-1.10, 0.10)*		
Beal(1995)[84]	Dronabinol	Appetite (VAS scale; %)	**20**	**0.05**	ANOVA
Struwe (1993)[130]	Dronabinol	Appetite (Score 0 (extremely hungry) - 100 (not hungry))	-19.5	0.14	Wilcoxen signed rank
Struwe (1993)[130]	Dronabinol	Caloric/food intake (kcal/kg/24h)	4.2*	0.50	Wilcoxen signed rank
Struwe (1993)[130]	Dronabinol	Body fat (%)	**0.76**	**0.04**	Wilcoxen signed rank
Nausea & Vomiting:					
Beal(1995)[84]	Dronabinol	Nausea severity/intensity (VAS scale; %)	-18	0.26	ANOVA
Global impression:					
Beal(1995)[84]	Dronabinol	Karnofsky performance status	0.70	0.07	ANOVA
Struwe (1993)[130]	Dronabinol	Symptoms/functional limitations (out of 340))	**-33.5**	**0.04**	Wilcoxen signed rank

TABLE 14: GRADE SUMMARY OF FINDINGS TABLE: HIV/AIDS

CBM for HIV/AIDS

Patient or population: patients with HIV/AIDS
Settings: Not specified
Intervention: CBM

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Control**	Corresponding risk **CBM**				
Weight gain Number of patients who gained ≥2kg Follow-up: 6 weeks	**105 per 1000**	**206 per 1000** (74 to 461)	**OR 2.2** (0.68 to 7.27)	88 (1 study[1])	⊕⊕⊖⊖ **low**[2,3,4]	
Weight[5] kg Follow-up: 3-12 weeks[6]	See comment	See comment	Not estimable[5]	241 (3 studies[7])	⊕⊕⊖⊖ **low**[8,9]	
Appetite VAS scale. Scale from: 0 to 100.		The mean appetite in the intervention groups was **20 higher** (0 to 0 higher)[10]		88 (1 study[1])	⊕⊕⊖⊖ **low**[2,3,4]	
Nausea severity/intensity VAS scale. Scale from: 0 to 100.		The mean nausea severity/intensity in the intervention groups was **18 lower** (0 to 0 higher)[11]		88 (1 study[1])	⊕⊕⊖⊖ **low**[2,3,4]	
Karnofsky Performance Status Scale from: 0 to 100.		The mean Karnofsky performance status in the intervention groups was **0.70 higher** (0 to 0 higher)[12]		88 (1 study[1])	⊕⊕⊖⊖ **low**[2,3,4]	
Any adverse events Follow-up: 6-12 weeks[13]	**221 per 1000**	**329 per 1000** (46 to 836)	**OR 1.73** (0.17 to 18.0)[14]	160 (2 studies[15])	⊕⊖⊖⊖ **very low**[16,17,18]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] Beal 1995
[2] Risk of bias: Insufficient details on randomisation, concealment of allocation and blinding; high risk of bias for selective outcome reporting.
[3] Inconsistency: Not applicable (single study)
[4] Imprecision: Study included only 139 patients
[5] Abrams 2003: p-value (Dronabinol vs. Placebo)=0.004, p-value (Marijuana vs. Placebo)=0.021; Beal 1995 (Dronabinol vs. Placebo): MD change from baseline 0.5 (p-value=0.14); Timpone 1997: MD change from baseline (Dronabinol vs. Placebo)=-8.5, -9.18, -.7.82); MD change from baseline (Dronabinol + megestrol acetate vs. Placebo)=-0.5, -1.10, 0.10);
[6] Abrams 2003: 3 weeks, Beal 1995: 6 weeks, Timpone 1997: 12 weeks
[7] Abrams 2003, Beal 1995, Timpone 1997
[8] Risk of bias: Insufficient details on randomisation (Beal 1995, Timpone 1997), concealment of allocation (Beal 1995, Timpone 1997) and blinding (Abrams 2003-D, Beal 1995); high risk of bias for blinding (Abrams 2003-M) and selective outcome reporting (Beal 1995, Timpone 1997).
[9] Imprecision: 3 studies including only 243 patients
[10] No 95 %-CI reported, p-value=0.05
[11] No 95 %-CI reported, p-value=0.26
[12] No 95 %-CI reported, p-value=0.07
[13] Beal 1995: 6 weeks; Timpone 1997: 12 weeks
[14] OR across all patient populations (29 studies): 3.03, 95%-CI 2.42 to 3.80 (see section 5.3 for details)
[15] Beal 1995, Timpone 1997
[16] Risk of bias: Insufficient details on randomisation (both studies), concealment of allocation (both studies) and blinding (Beal 1995); high risk of bias for blinding (Timpone 1997) and incomplete data reporting (Timpone 1997)
[17] Inconsistency: I2=79%
[18] Imprecision: Two studies including 160 patients (55 events)

5.2.3 Chronic pain (e.g. neuropathic pain, migraine, back pain)

Twenty-seven studies (61 publications, 2,439 participants) evaluated CBM as a treatment for chronic pain (Table 15).[1, 4, 76-82, 86, 96, 132-180] The conditions causing the chronic pain varied between studies and included neuropathic pain (central, peripheral or not specified; 11 studies), cancer pain (three studies), diabetic peripheral neuropathy (3 studies), fibromyalgia (2 studies), HIV associated sensory neuropathy (2 studies), refractory pain due to MS or other neurological conditions (1 study), rheumatoid arthritis (1 study), non-cancer pain (1 study), central pain (not specified further; 1 study), musculoskeletal problems (1 study) and chemotherapy induced pain (1 study).

Fourteen studies were parallel group studies (1980 participants) and 14 used a cross-over design (459 participants). Most (75%) studies specified a minimum level of pain as a study inclusion criterion. In most studies this was equivalent to a mean score ≥4 on a 0-10 NRS or VAS scale generally over the 6-7 days before study entry. Four studies specified a criterion of >4, one of >5, one of ≥3 and one a score of ≥5 on the pain intensity subscale of the Descriptor Differential Scale (DDS).[181] Study duration ranged from 4 hours in a small cross-over trial[76] to 15 weeks in a large multicentre parallel group trial.[81] Thirteen studies evaluated nabiximols(max dose 4-48 sprays/24h), one evaluated THC (1-7%) oromucosal spray, [76] two evaluated dronabinol (max dose 10-20mg/day),[139, 146] four evaluated nabilone (max dose 0.5-2mg/day),[133, 140, 141, 143] one evaluated THC capsules (5-20mg/day),[96] one evaluated CT3 capsules (max 80mg/day),[147] one evaluated vaporised cannabis (8-12 puffs per day)[134] and three evaluated THC cigarettes (one cigarette/day).[135, 137, 138, 142] Nine studies included multiple intervention arms with different doses of the intervention evaluated in different arms. One study evaluated two different doses of dronabinol (10mg and 20mg),[139] one evaluated different doses of THC (5mg, 10mg, 15mg and 20mg),[96] one evaluated different doses of nabiximols (1-4 sprays, 6-10 sprays and 11-16 sprays),[86] two evaluated nabiximols and THC spray,[82, 145] one evaluated different concentrations of THC spray (7%, 4% and 1%),[76] one evaluated different concentrations of vaporised cannabis (3.53% and 1.29%),[134] and two evaluated different concentrations of smoked THC (3.5% and 7%, and 2.5%, 6% and 9.4%).[138, 176] One study compared CBM (nabilone) to the active comparator amitriptyline,[133] all other studies compared the CBM evaluated to a matched placebo control group. One study that evaluated nabilone included an active comparator (dihydrocodeine) as well as a placebo control group.[141]

5.2.3.1 Risk of bias

The risk of bias in the included studies was variable (Table 16). Only two were rated as low risk of bias for all domains.[133, 134] A further nine were rated as unclear risk of bias. The main limitation in the included study related to incomplete outcome data; fourteen studies were judged at high risk of bias for this domain. Other potential sources of bias included selective outcome reporting (judged at high risk of bias in four studies) and concealment of treatment allocation (judged at high risk of bias in two studies). All other domains were rated as low or unclear risk of bias. Very few studies provided sufficient information to judge whether

appropriate methods were taken to conceal treatment allocation, outcome assessor blinding was also poorly reported.

TABLE 15: OVERVIEW OF STUDIES THAT EVALUATED CBM FOR CHRONIC PAIN

Study Details	Country	Design	N	Duration (weeks)*	Condition	Pain entry criterion	Intervention 1	Intervention 2	Inter-vention 3	Inter-vention 4	Comparator
Abrams (2007)[142, 157, 165]	USA	Parallel group	55	12 days	HIV-associated sensory neuropathy	Average daily pain score ≥ 30 on 100 mm VAS	THC (4%; smoked); One cigarette (0.9g) daily				Placebo cigarette
Berman(2007)[1, 164]	Romania, UK	Parallel group	117	3	Central neuropathic pain (non-acute spinal cord injury)	Average daily pain score ≥4 on NRS	Nabiximols (Sativex); max 48 sprays/24 h				Placebo
Berman(2004)[145, 159]	UK	Cross-over	48	2 (no washout)	Central neuropathic pain (brachial plexus avulsion)	Average daily pain score ≥4 on NRS	Nabiximols (Sativex); max 48 sprays/24 h	THC oromucosal spray			Placebo
Blake(2006)[78]	UK	Parallel group	58	5	Pain caused by rheaumatoid arthritis	Not specified	Nabiximols (Sativex); max 48 sprays/24 h				Placebo
Ellis(2009)[137, 162]	USA	Cross-over	34	5 days (2 week washout)	HIV-associated sensory neuropathy	average score ≥5 on the pain intensity sub-scale of the Descriptor Differential Scale (DDS)	THC (smoked); dose started at 4% and adjusted as necessary. Four daily smoking sessions.				Placebo
Frank(2008)[14, 178]	UK	Cross-over	96	6 (2 washout)	Mixed neuropathic pain	Average pain score > 40 on 0-100 mm VAS.	Nabilone (Cesamet); max 8 capsules (240ug each)	Dihydrocodeine ; max 8 capsules (30mg each)			Placebo
GW Pharma Ltd(2005)[77, 170]	Czech Republic, Romania, UK	Parallel group	297	14	Diabetic peripheral neuropathy (DPN)	Last 6 daily NRS pain scores ≥ 24;	Nabiximols (Sativex); max 24 sprays/24 h				Placebo

Study Details	Country	Design	N	Duration (weeks)*	Condition	Pain entry criterion	Intervention 1	Intervention 2	Inter-vention 3	Inter-vention 4	Comparator
GW Pharma Ltd(2012)[79]	UK	Parallel group	70	3	Chronic refractory pain due to MS or other defects of neurological origin	average score >4 on Box-Scale 11 on 4 consecutive days	Nabiximols (Sativex); max 48 sprays/24 h				Placebo
Johnson (2010)[82, 167]	Belgium; Romania; UK	Parallel group	177	2	Cancer-related pain.	Pain severity score ≥4 on 0-10 NRS	Nabiximols (Sativex); max 8 sprays/24 h	THC oromucosal spray			Placebo
Karst(2003)[147, 153]	Germany	Cross-over	21	1 (1 week washout)	Chronic neuropathic pain	Not specified	CT3 capsules; max 8 capsules (10mg each)				Placebo
Langford(2013)[4, 151]	UK, Czech Republic, Canada, Spain	Parallel group	339	14	Central neuropathic pain (CNP) due to MS.	sum score of ≥24 on a pain 0–10 point NRS on the last 6 days	Nabiximols (Sativex); max 12 sprays/24 h				Placebo
Lynch(2014)[148, 172]	Canada	Cross-over	18	4 (2 weeks)	Chemotherapy induced pain.	average 7 day pain intensity ≥4 on 11-point NRS	Nabiximols (Sativex); max 12 sprays/24 h				Placebo
Narang(2008)[139, 173]	USA	Cross-over	30	8 hours (72 hour washout)	Chronic non cancer pain	Pain > 4 NRS (0-10).	Dronabinol (Marinol); 20mg daily	Dronabinol; 10 mg daily			Placebo
Noyes (1975)[96]	USA	Cross-over	10	1 day (none)	Cancer-related pain	"continuous moderate pain"	THC Capsules; 5mg	THC Capsules; 10mg	THC Capsules; 15mg	THC Capsules; 20mg	Placebo
Nurmikko (2007)[80, 155, 168, 171, 175]	Belgium, UK	Parallel group	125	5	Neuropathic pain characterised by allodynia	pain ≥4 NRS for 4-7 days	Nabiximols (Sativex); max 48 sprays/24 h				Placebo

Study Details	Country	Design	N	Duration (weeks)*	Condition	Pain entry criterion	Intervention 1	Intervention 2	Inter-vention 3	Inter-vention 4	Comparator
Pinsger(2006) [143, 154]	Austria	Cross-over	30	4 (5 washout)	Chronic refractory pain due to problems of the musculoskeletal system	VAS>5	Nabilone (Cesamet); max 4 capsules (0.25mg each)				Placebo
Portenoy(2012)[86, 166]	Belgium, Canada, Chile, Czech Republic, Finland, France, Germany, India, Italy, Mexico, Poland, Romania, South Africa, Spain, UK, USA	Parallel group	360	9	Cancer pain	Score 4-8 on NRS pain scale, not changed by ≥2 points over 3 consecutive days in 14 days	Nabiximols (Sativex); max 4 sprays per day	Nabiximols (Sativex); 6-10 sprays per day	Nabiximols (Sativex); 11-16 sprays per day		Placebo
Rog(2005)[144, 158, 169, 180]	UK	Parallel group	66	5	Central neuropathic pain syndromes due to MS	Not specified	Nabiximols (Sativex); max 48 sprays/24 h				Placebo
Selvarajah (2010)[132, 136, 179]	UK	Parallel group	30	12	Diabetic peripheral neuropathy	Not specified	Nabiximols (Sativex); max unclear				Placebo

Study Details	Country	Design	N	Duration (weeks)*	Condition	Pain entry criterion	Intervention 1	Intervention 2	Inter-vention 3	Inter-vention 4	Comparator
Serpell(2014)[8] [1, 177]	Belgium, Canada, Czech Republic, Romania, UK	Parallel group	246	15	Peripheral neuropathic pain (PNP) associated with allodynia	≥24 on pain 0–10 NRS for ≥ 6 days during baseline	Nabiximols (Sativex); max 24 sprays/24 h				Placebo
Skrabek(2008)[140, 174]	Canada	Parallel group	40	4	Fibromylagia	Pain despite the use of other oral medications.	Nabilone (Cesamet); max 4 capsules (0.5mg each)				Placebo
Svendsen(2004)[146, 152]	Denmark	Cross-over	24	3 (3 washout)	Central pain in MS patients	Central pain at the maximal pain site with a pain intensity score ≥ 3 on a 0-10 NRS	Dronabinol (Marinol); max dose 10mg/day				Placebo
Wallace(2013)[76, 160]	USA	Cross-over	16	4 hours (washout unclear)	Painful diabetic peripheral neuropathy	> 4 on 11 point NPS	THC (7%) oromucosal spray	THC (4%) oromucosal spray	THC (1%) oromucosal spray		Placebo
Ware(2010)[132, 133, 149, 150]	Canada	Cross-over	32	2 (2 washout)	Chronic pain conditions (fibromyalgia)	Not specified	Nabilone (Cesamet); 0.5mg/day				Amitriptyline: 10mg/day
Ware(2010)[135, 176]	Canada	Cross-over	23	5 days (9 days washout)	Neuropathic pain	Average weekly pain intensity score ≥ 4 on a 10-cm VAS	THC (2.5%) smoked	THC (6%) smoked	THC (9.4%) smoked		Placebo
Wilsey(2013)[1 34, 163]	USA	Cross-over	39	6 hours (washout 3-7 days)	Peripheral neuropathic pain	VAS > 3/10	Cannabis (3.53%) vaporised; 4 puffs 1 hour from baseline, 4-8 puffs 3 hours	Cannabis (1.29%) vaporised 4 ;puffs 1 hour from baseline, 4-8 puffs 3 hours			Placebo

Study Details	Country	Design	N	Duration (weeks)*	Condition	Pain entry criterion	Intervention 1	Intervention 2	Inter-vention 3	Inter-vention 4	Comparator
Wilsey(2011)[1] [38, 161]	USA	Cross-over	38	6 hours (3-21 day washout)	Neuropathic pain	VAS > 3/10	THC (3.5%) smoked: 9 puffs following standard procedure	THC (7%) smoked: 9 puffs following standard procedure			Placebo

TABLE 16: RISK OF BIAS IN CHRONIC PAIN STUDIES

Study Details	RISK OF BIAS						
	Random sequence generation	Allocation concealment	Participant/ Personnel blinding	Outcome assessor blinding	Incomplete outcome data	Selective outcome reporting	Overall
Abrams(2007)[142]	☺	?	☺	?	☹	☺	☹
Berman(2007)[1]	?	?	☺	?	☹	☺	☹
Berman(2004)[145]	☺	☹	☺	?	☺	☺	☹
Blake(2006)[78]	☺	?	?	?	?	☺	?
Ellis(2009)[137]	?	?	?	?	☹	☹	☹
Frank(2008)[141]	?	?	☺	?	☹	☺	☹
GW Pharma Ltd(2005)[77]	?	?	?	?	☹	☺	☹
GW Pharma NCT01606176(2012)[79]	?	?	?	☺	☹	☺	☹
Johnson(2010)[82]	?	?	?	?	☹	☺	☹
Karst(2003)[147]	☺	☺	☺	☺	☹	☺	☹
Langford(2013)[4]	☺	?	☺	☺	☺	☺	?
Lynch(2014)[148]	☺	☺	☺	☺	☹	☺	☹
Narang(2008)[139]	☺	?	☺	?	☺	☹	☹
Noyes(1975)[96]	?	?	?	?	☺	☺	?
Nurmikko(2007)[80]	☺	☹	☺	?	☺	☺	☹
Pinsger(2006)[143]	?	?	?	?	☺	☺	?
Portenoy(2012)[86]	☺	?	?	?	☺	☺	?
Rog(2005)[144]	☺	?	☺	☺	☺	☺	?
Selvarajah(2010)[136]	?	?	?	?	☺	☺	?
Serpell(2014)[81]	☺	?	☺	☺	☺	☺	?
Skrabek(2008)[140]	?	?	☺	☺	☹	☺	☹
Svendsen(2004)[146]	☺	?	☺	☺	☺	☺	?
Wallace(2013)[76]	?	?	☺	?	☹	☹	☹
Ware(2010)[135]	?	?	?	?	☹	☺	☹
Ware(2010)[133]	☺	☺	☺	☺	☺	☺	☺
Wilsey(2013)[134]	☺	☺	☺	☺	☺	☺	☺
Wilsey(2011)[138]	☺	☺	☺	☺	☹	☺	☹

5.2.3.2 Dichotomous outcome results

Pain

Twelve studies provided dichotomous data for the effects of CBM on pain (Table 17). The most commonly evaluated outcome was a 30% reduction in pain scores based on NRS or VAS scales, this was evaluated in 11 studies (8 parallel group and 3 cross-over studies). In order to calculate a summary estimate for this outcome we selected one set of results from studies that evaluated multiple interventions. We selected the intervention or dose most comparable to other studies. For the study that evaluated nabiximols and THC we selected the nabiximols data, for the study that evaluated different doses of nabiximols we selected the 11-14 spray dose, for the studies that evaluated two different concentrations of smoked cannabis we selected the 3.5% concentration. The summary OR based on 8 parallel group studies suggested a beneficial effect of CBM but this did not reach statistical significance (OR 1.35, 95% CI 0.95, 1.93; Figure 5). There was moderate evidence of heterogeneity (I^2=49%, p=0.06). Sensitivity analysis including the three cross-over trials found evidence for a beneficial effect of cannabis on pain (OR 1.60, 95% CI 1.11, 2.30; Figure 6) but there was greater heterogeneity (I^2=54%, p=0.016). Differences across studies did not appear related to type of CBM, underlying cause of pain, or risk of bias. There was no evidence of small study effect based on the eight parallel group studies alone (p=0.304) or on all 11 studies (p=0.077). Three of the studies (2 parallel group and 1 cross-over) that evaluated a 30% or more improvement in pain scores also reported data for the number of participants with a 50% or more improvement in pain scores.[80, 81, 146] All suggested a beneficial effect of CBM but this only reached statistical significance in the cross-over trial.[146] Other dichotomous pain outcomes were only evaluated in single studies, these are summarised in Table 17.

Global impression

Five parallel group studies, all assessing nabiximols, evaluated patient global impression of change.[1, 4, 77, 79, 144] Three reported dichotomous data on the number of patients reporting an improvement associated with treatment[1, 4, 79] and two reported categorical data.[77, 144] We dichotomised the data from the categorical studies to calculate the number of patients who reported an improvement associated with treatment. The summary estimate suggested that nabiximols was associated with significantly greater patients reported improvement compared to placebo (OR 1.94, 95% CI 1.15, 3.28; Figure 7). There was strong evidence of heterogeneity (I^2=69%, p=0.01).

FIGURE 5: FOREST PLOT SHOWING ORS (95% CI) FOR NUMBER OF PATIENTS REPORTING AT LEAST A 30% REDUCTION IN PAIN, PARALLEL GROUP STUDIES ONLY

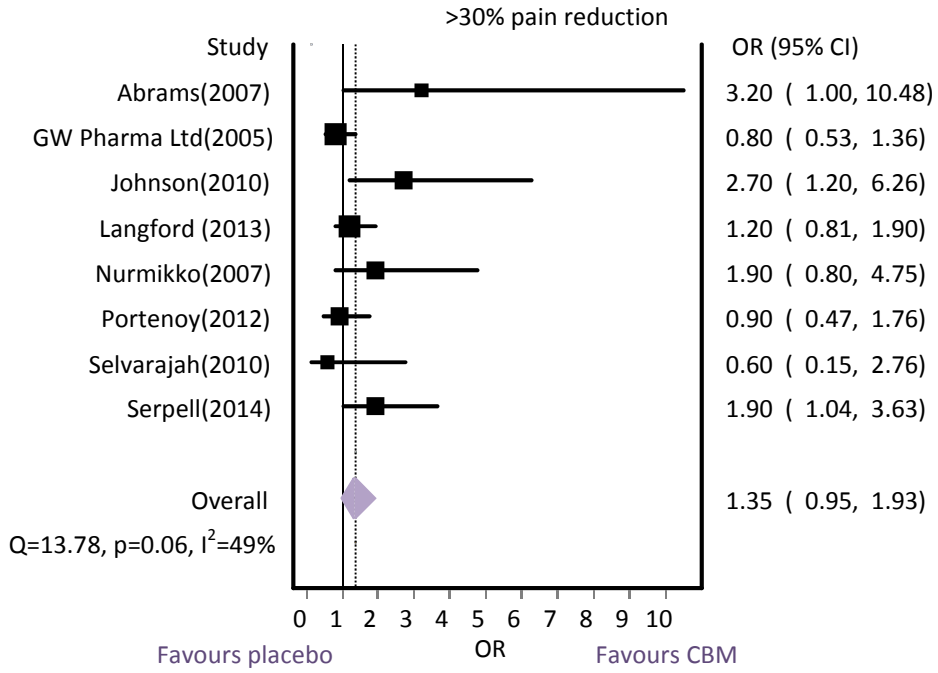


FIGURE 6: FOREST PLOT SHOWING ORS (95% CI) FOR NUMBER OF PATIENTS REPORTING AT LEAST A 30% REDUCTION IN PAIN, PARALLEL GROUP AND CROSS-SECTIONAL STUDIES

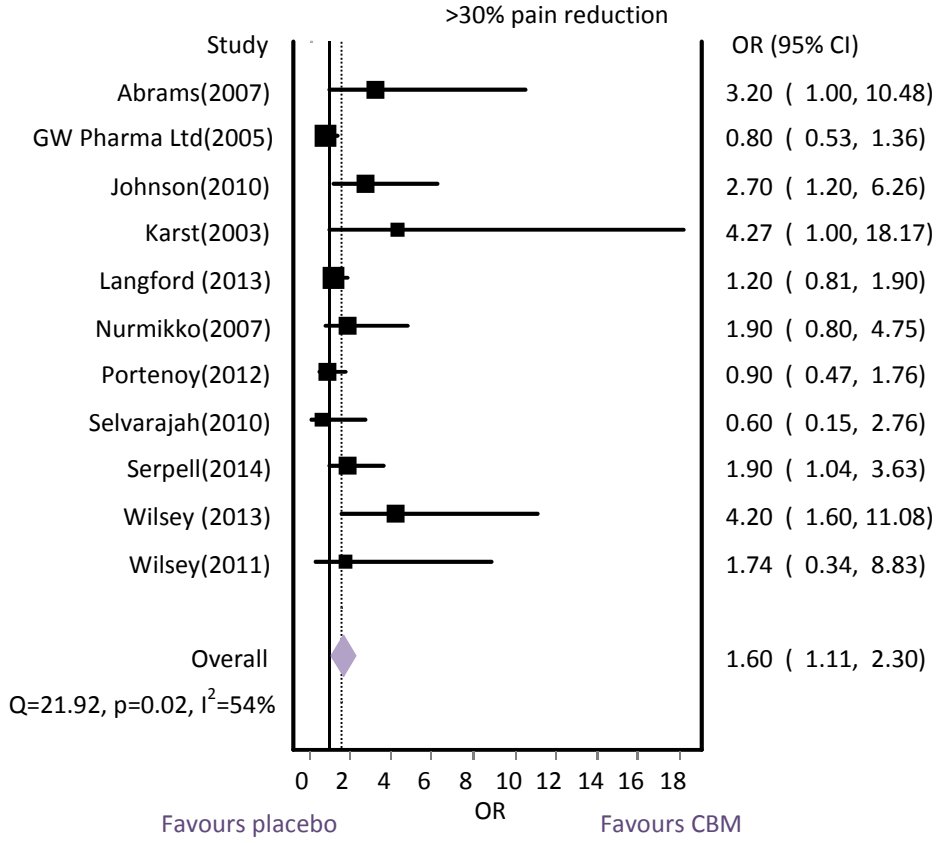


FIGURE 7: FOREST PLOT SHOWING ORS (95% CI) FOR NUMBER OF PATIENTS REPORTING AN IMPROVEMENT WITH NABIXIMOLS COMPARED TO PLACEBO

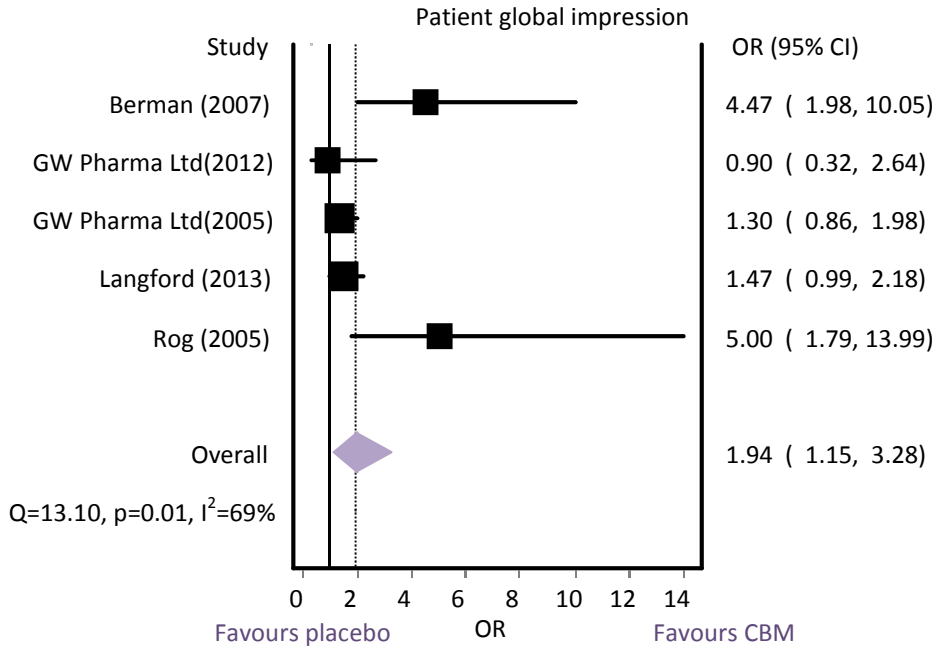


TABLE 17: RESULTS FOR DICHOTOMOUS OUTCOMES FROM STUDIES THAT EVALUATED CBM FOR CHRONIC PAIN

Study Details	Intervention	Outcome	Intervention Events/ n	Placebo Events/n	OR (95% CI)*
Pain					
Abrams(2007)[142] Parallel group	THC	Neuropathic pain scale (VAS) (>30% reduction)	13/25	6/25	**3.2 (1.00, 10.48)**
GW Pharma Ltd(2005)[77] Parallel group	Nabiximols	NRS (≥30% reduction)	54/149	59/148	0.8 (0.53, 1.36)
Johnson(2010)[82] Parallel group	Nabiximols	Pain relief (NRS) (≥30% reduction)	23/53	12/56	**2.7 (1.20, 6.26)**
	THC		12/52	12/56	1.0 (0.45, 2.68)
Karst(2003)[147] Cross-over	CT3	Neuropathic pain scale (≥30% reduction)	9/19	3/19	**4.27 (1.00, 18.17)**
Langford (2013)[4] Parallel group	Nabiximols	NRS (≥30% reduction)	84/167	77/172	1.2 (0.81, 1.90)
Nurmikko(2007)[80] Parallel group RCT	Nabiximols (Sativex)	NRS (≥30% reduction)	16/63	9/62	1.9 (0.80, 4.75)
Portenoy(2012)[86] Parallel group RCT	Nabiximols (1-4 sprays)	NRS (≥30% reduction)	30/91	24/91	1.37 (0.72, 2.58)
	(6-10 sprays)		26/87	24/91	1.19 (0.62, 2.27)
	(11-14 sprays)		22/90	24/91	0.90 (0.47, 1.76)
Selvarajah(2010)[136] Parallel group RCT	Nabiximols	Neuropathic pain scale(VAS) (≥30% reduction)	8/15	9/14	0.6 (0.15, 2.76)
Serpell(2014)[81] Parallel group RCT	Nabiximols	NRS (≥30% reduction)	34/123	19/117	**1.9 (1.04, 3.63)**

Study Details	Intervention	Outcome	Intervention Events/ n	Placebo Events/n	OR (95% CI)*
Wilsey (2013)[134] Cross-over RCT	Cannabis (1.29%)	VAS score (≥30% reduction)	21/37	10/38	**3.5 (1.36, 9.19)**
	Cannabis (3.53%)		22/36	10/38	**4.2 (1.60, 11.08)**
Wilsey(2011)[138] Cross-over RCT	THC (3.5%)	VAS score (≥30% reduction)	4/36	2/33	1.74 (0.34, 8.83)
	THC (7%)		0/34	2/33	0.18 (0.01, 3.95)
Karst(2003)[147] Cross-over	CT3	Neuropathic pain scale (≥50% reduction)	2/19	0/19	5.5 (0.24, 124.20)
Nurmikko(2007)[80] Parallel group RCT	Nabiximols (Sativex)	NRS (>50% reduction)	13/63	5/62	2.7 (0.96, 8.07)
Svendsen(2004)[146] Cross-over RCT	Dronabinol	NRS (50% pain relief)	11/24	4/24	**3.8 (1.07, 14.07)**
Serpell(2014)[81] Parallel group RCT	Nabiximols	NRS (≥50% improvement)	/123	/117	1.70 (0.65, 4.48) p-value=0.280
Portenoy(2012)[86] Parallel group RCT	Nabiximols (1-4 sprays)	Composite outcome: change in NRS and change in opioid consumption; positive response improvement in one and other stable or improved	/91	/91	1.87 p-value=0.038
	Nabiximols (6-10 sprays)		/87	/91	
	Nabiximols (11-16 sprays)		/90	/91	1.16 p-value=0.622
Johnson(2010)[82] Parallel group	Nabiximols	Breakthrough analgesia use (Number of days breakthrough medication used)	NR	NR	0.96 p-value=0.697
	THC		NR	NR	1.20 p-value=0.555
Global impression					
Berman (2007)[1] Parallel group RCT	Nabiximols	Patient global impression (number of participants reporting improvement)	30/56	12/60	**4.47 (1.98, 10.05)**
GW Pharma Ltd(2012)[79] Parallel group	Nabiximols	Patient global impression	9/36	9/34	0.9 (0.32, 2.64)
GW Pharma Ltd(2005)[77]	Nabiximols	Patient global impression	NR	NR	1.3 (0.86, 1.98)
Langford (2013)[4] Parallel group	Nabiximols	Patient global impression	NR	NR	1.47 (0.99, 2.18)
Rog (2005)[144]	Nabiximols	Patient global impression (number of participants reporting improvement)	24/34	10/32	**5.0 (1.79, 13.99)**

5.2.3.3 Continuous outcome results

The included studies reported a variety of continuous outcome measures that we grouped as covering pain, quality of life (QoL), mobility/disability, and global impression. Outcome measures reported only in single trials included various types of total pain scores, peripheral neuropathic pain, superficial pain, pain at allodynic site, pain relief, spine pain, headache

intensity, punctuate allodynia, number of headache free days, dynamic allodynia, morning pain at rest of on movement, muscular pain, deep pain, breakthrough analgesia use, unpleasantness, and radiating pain. These are summarised in Table 18 and are not considered in more detail. In order to calculate summary estimates for some outcomes it was necessary to select one set of results from studies that evaluated multiple interventions. As with the analysis for dichotomous outcomes, we selected the intervention or dose most comparable to other studies. For the study that evaluated nabiximols and THC we selected the nabiximols data, for the study that evaluated different doses of nabiximols we selected the 11-14 spray dose, for the studies that evaluated two different concentrations of smoked cannabis we selected the 3.5% concentration, for the study that evaluated two doses of dronabinol we selected the 10mg dose, and for the studies that evaluated different doses of THC we selected the 10mg dose.

Pain

The most commonly reported measure of pain was a 0-10 numerical pain ratings score. This was assessed in 11 studies, six parallel group[1, 4, 80, 82, 86, 144] and five cross-over trials.[96, 135, 139, 146, 148] All but one of the cross-over trials provided data in sufficient detail to permit pooling.[139] This study reported a significant beneficial effect of dronabinol at two different doses compared to placebo, with a greater effect for the 20mg compared to the 10mg dose (-0.9 vs -1.5).[139] The summary weighted mean different based on the six parallel group studies suggested a significant beneficial improvement in pain scores associated with CBM (WMD -0.46, 95% CI -0.80, -0.11, Figure 8). There was moderate evidence of heterogeneity (I^2=59%, p=0.03). Sensitivity analysis that included the cross-over trials also showed a significant beneficial effect of CBM (WMD -0.57, 95% CI -0.93, -0.22, Figure 9) but heterogeneity increased (I^2=67%, p<0.01). There was evidence of small study effects for the analysis based on the parallel group studies alone (p=0.02) but not for the analysis based on all 10 studies (p=0.172).

FIGURE 8: FOREST PLOT SHOWING WMD (95% CI) FOR PAIN NRS FOR PARTICIPANTS TAKING CBM COMPARED TO PLACEBO IN PARALLEL GROUP STUDIES

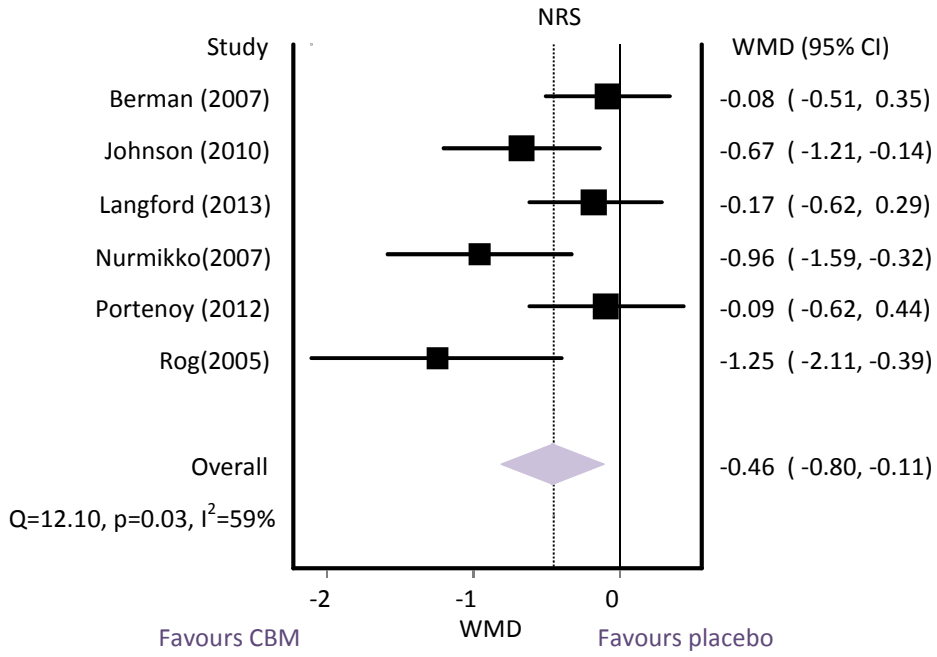
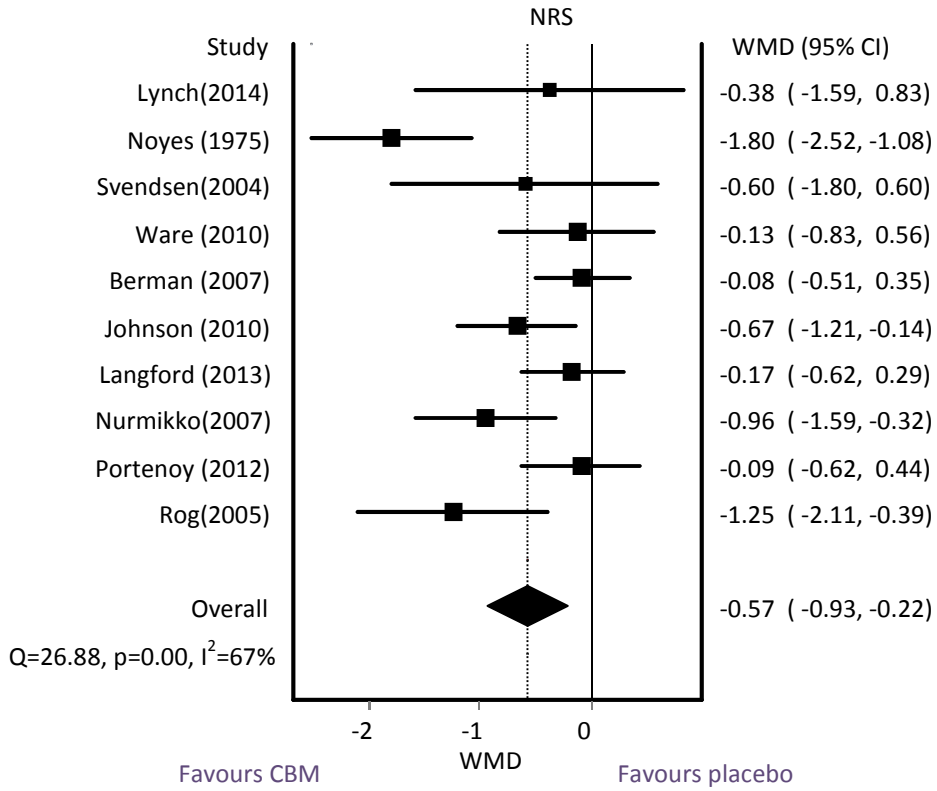


FIGURE 9: FOREST PLOT SHOWING WMD (95% CI) FOR NRS FOR PARTICIPANTS TAKING CBM COMPARED TO PLACEBO IN PARALLEL GROUP AND CROSS-OVER TRIALS



Six parallel group studies, all of which evaluated nabiximols, used the brief pain inventory short form (BPI-SF) [182] to measure pain using various scores from this tool.[4, 77, 79, 81, 82, 86] All of these suggested a beneficial effect of cannabis in reducing pain scores but this did not reach statistical significance in any of the trials. The most commonly reported subscale was the severity composite index which was evaluated in four of the six trials, with sufficient data to permit pooling in three trials. The summary effect size suggested a small beneficial effect of cannabis on pain but this did not reach statistical significance (WMD -0.17, 95% CI -0.50, 0.16, Figure 10). There was no evidence of heterogeneity (I^2=0%).

Six studies, [1, 76, 137, 138, 141, 183] five cross-over trials and one parallel group study, evaluated changes in pain using various measures on the descriptor differential scale.[181] None of these studies provided a measure of effect with associated confidence interval but all provided p-values for the difference between CBM and placebo and suggested a significant beneficial effect of CBM in reducing pain (p-values ranged from 0.04 to 0.007).

Five studies, two parallel group trials and three cross-over trials, used the McGill pain rating scale[184] to evaluate pain. Generally the studies showed no difference between CBM and placebo, although two studies found some evidence of significant beneficial effects in favour of CBM. One parallel group study showed a significant beneficial effect on the VAS scale of the McGill pain rating (MD -0.72, 95% CI -1.30, -0.14) but not on total pain intensity.[78] One of the cross-over trials that evaluated both THC and nabiximols compared to placebo reported a significantly beneficial effect of THC compared to placebo but found no significant difference for nabiximols. The only study to compare CBM (nabilone) to an active comparator (amitriptyline) assessed pain using this rating scale. This cross-over trial found no difference between nabilone and amitriptyline.

Seven parallel group trials assessed pain using the neuropathic pain scale.[4, 77, 80, 81, 136, 142, 144] Five of these trials provided data on suitable format to allow data to be pooled. [77, 80, 81, 136, 144] All but one suggested a beneficial effect of CBM but this only reached statistical significance in one. The pooled estimates suggested a significant beneficial effect of nabiximols in reduced neuropathic pain compared to placebo (WMD -3.89, 95% CI -7.32, -0.47, Figure 11). There was some evidence of heterogeneity (I^2=41%, p=0.15). One of the studies that did not contribute to the meta-analysis also suggested a significant beneficial effect of THC,[142] the other found no difference between nabiximols and placebo.[4]

Four studies, three parallel group and one-cross-over trial, measured pain using the pain disability index (PDI).[4, 79, 80, 145] All compared nabiximols to placebo. Three suggested a beneficial effect of nabiximols on the PDI although this only reach statistical significance in one (MD -5.85, 95% CI -9.62, -2.09).[80] One trial suggested a harmful effect of nabiximols but this was of borderline significance (p=0.058), this study did not report a confidence intervals and so there were insufficient data to pool results from the parallel group studies for this outcome.

Two cross-over trials evaluated pain using a VAS scale, both reported strong evidence for a beneficial effect of cannabis (p<0.002), however, these studies did not provide confidence intervals around the mean difference. Two studies, one crossover trial and one parallel group study, evaluated pain using the 11 item pain box scale.[145, 185] The cross-over trial found a significant difference between groups (p=0.005) but the parallel group study found no differences between groups (p<0.05).

FIGURE 10: FOREST PLOT SHOWING WMD (95% CI) FOR BRIEF PAIN INVENTORY-SHORT FORM FOR PARTICIPANTS TAKING CBM COMPARED TO PLACEBO

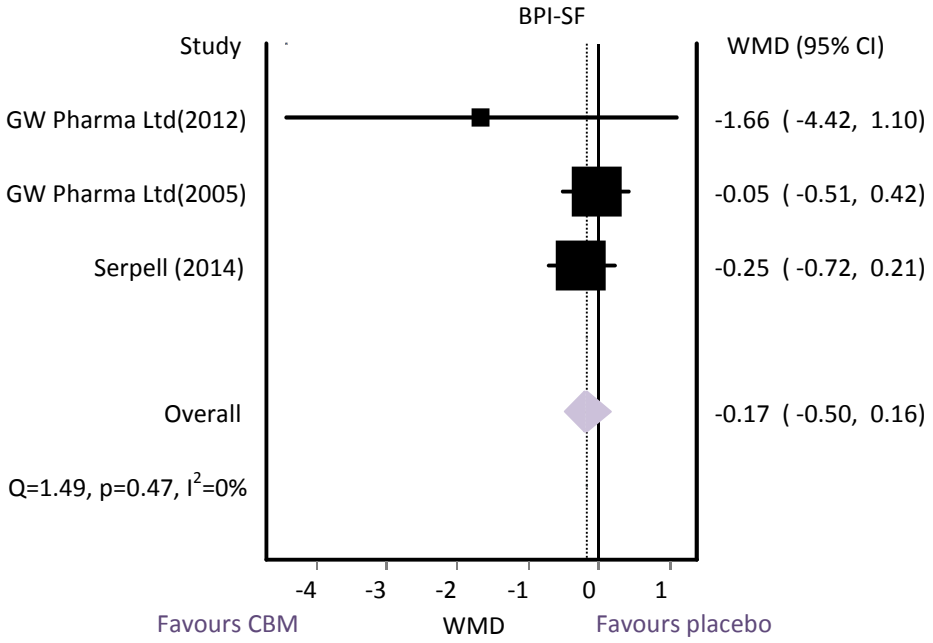
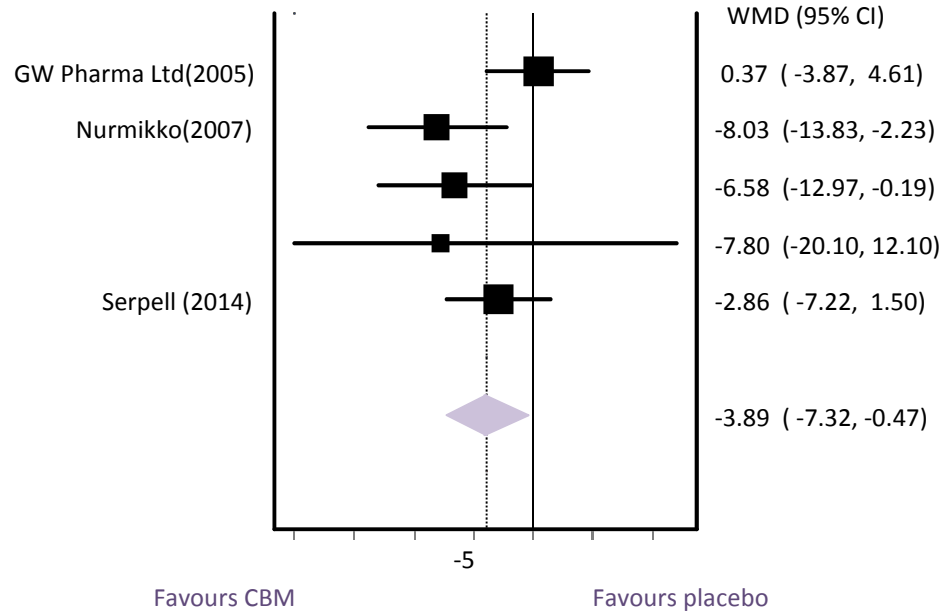


FIGURE 11: FOREST PLOT SHOWING WMD (95% CI) FOR NEUROPATHIC PAIN SCALE (NPS) FOR PARTICIPANTS TAKING CBM COMPARED TO PLACEBO

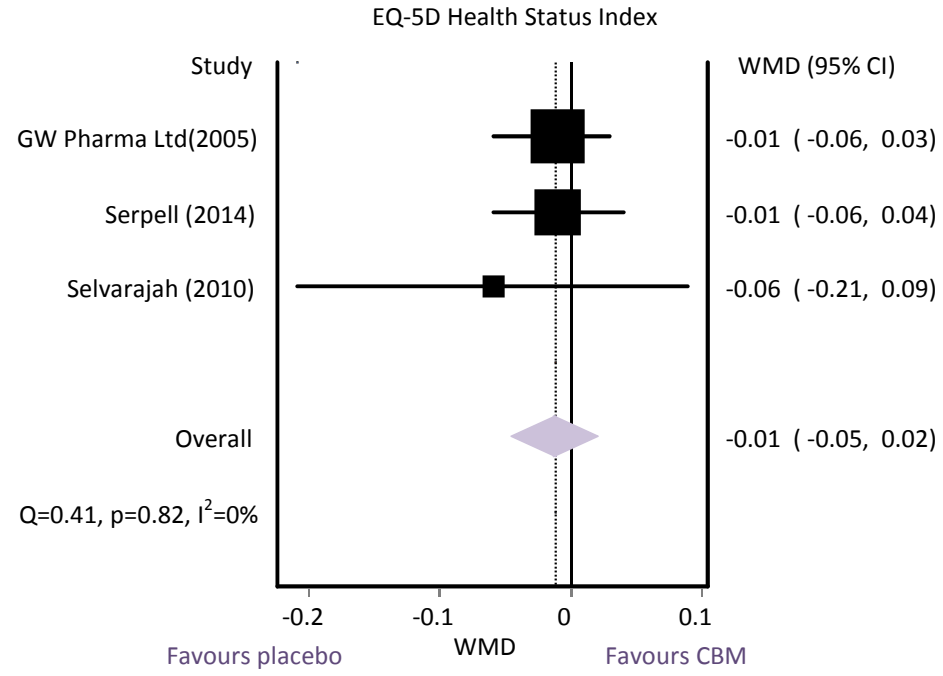


Quality of life

Thirteen of the chronic pain studies evaluated quality of life as an outcome measure.[1, 4, 77, 79, 81, 135, 136, 141, 143, 146, 148] Five studies were cross-over trials and eight were parallel group studies. Quality of life was measured using a variety of different measures. Measures used in multiple studies included EQ-5D (5 studies),[186] SF-36 (5 studies),[187] Spitzer QoL (2 studies).[188] On all these tools lower scores are associated with worse outcomes meaning that a higher score or positive MD favours CBM, this is in contrast to most pain outcomes where a lower score generally favours CBM.

Five studies, four parallel group studies and one cross-over trial, evaluated QoL using the EQ-5D with most reporting data for both the health status index and health status VAS.[4, 77, 81, 135, 136] Four parallel group studies suggested a very small negative effect nabiximols on EQ-5D health status index compared to placebo but this did not reach statistical significance in any of the studies. Three studies reported data in a format suitable for pooling. The summary estimate showed no difference between treatment groups (WMD -0.01, 95% CI -0.05, 0.02; Figure 12). There was no evidence of heterogeneity (I^2=0%, p=0.82).

FIGURE 12: FOREST PLOT SHOWING WMD (95% CI) FOR EQ-5D HEALTH STATUS INDEX FOR PARTICIPANTS TAKING CBM COMPARED TO PLACEBO



Five studies, three cross-over trials and two parallel group studies,[4, 136, 141, 146, 148] evaluated QoL using the SF-36 which included various subscales. The studies generally found little evidence for an effect of CBM on SF-36 results, with most results showing no differences between groups.

Two parallel group studies evaluated the Spritzer QoL index.[1, 79] Neither reported a significant difference between nabiximols or placebo for this outcome. One study evaluated

various scales on the EORTC QLQ-C30 measure of cancer QoL and also found no differences between nabiximols and placebo.[82]

Global impression of change

Four studies, two cross-over trials and two parallel group trials, evaluated global impression of change.[80, 86, 134, 139] Three reported significant beneficial effects in favour of CBM but one of the parallel group trials found no differences between groups.

TABLE 18: RESULTS FOR CONTINUOUS OUTCOMES FROM STUDIES THAT EVALUATED CBM FOR CHRONIC PAIN

Study Details	Intervention	Outcome	MD at follow-up	MD change from baseline:		Analysis Details
Pain						
Serpell (2014)[81] Parallel group	Nabiximols	(Peripheral neuropathic pain 0-10 NRS)		-0.34 (-0.79, 0.11)	0.139	ANCOVA
Svendsen(2004)[146] Cross-over	Dronabinol	(Radiating pain (NRS 0-10))	**-0.6 (-1.3, 0.0)**		**0.039**	
Wilsey (2013)[134] Cross-over	Cannabis (3.53%)	(Unpleasantness)			**<0.001**	Repeated measures model
GW Pharma Ltd(2005)[77] Parallel group	Nabiximols	Breakthrough analgesia use (daily number of paracetamol tablets)		-0.17(-0.59, 0.24)	0.410	ANCOVA
GW Pharma Ltd(2012)[79] Parallel group	Nabiximols	BPI-SF (severity scomposite score)	-1.66 (-4.42, 1.10)		0.233	ANCOVA
Langford (2013)[4] Parallel group	Nabiximols	BPI-SF (no further details)		-0.12	0.564	
Serpell (2014)[81] Parallel group	Nabiximols	BPI-SF (Average pain)		-0.34 (-0.71, 0.12)	0.148	ANCOVA
Johnson (2010)[82] Parallel group	Nabiximols	BPI-SF(Interference composite score)		-1.04 (-5.23, 3.15)	0.619	ANCOVA
Johnson (2010)[82] Parallel group	THC	BPI-SF(Interference composite score)		**-4.07 (-8.10, -0.05)**	**0.048**	ANCOVA
Portenoy (2012)[86]	Nabiximols (1-4 sprays)	BPI-SF (Interference composite score)			0.871	
Portenoy (2012)[86]	Nabiximols (6-10 sprays)	BPI-SF(Interference composite score)			0.088	
Portenoy (2012)[86]	Nabiximols (11-16 sprays)	BPI-SF (Interference composite score)			0.956	
Serpell (2014)[81] Parallel group	Nabiximols	BPI-SF (Interference composite score)		-0.32 (-0.80, 0.15)	0.183	ANCOVA

Study Details	Intervention	Outcome	MD at follow-up	MD change from baseline:		Analysis Details
GW Pharma Ltd(2005)[77] Parallel group	Nabiximols	BPI-SF (Severity Composite Score)		-0.05 (-0.51, 0.42)	0.841	ANCOVA
Serpell (2014)[81] Parallel group	Nabiximols	BPI-SF (Severity composite score)		-0.25 (-0.72, 0.21)	0.288	ANCOVA
Portenoy (2012)[86]	Nabiximols (1-4 sprays)	BPI-SF(Severity composite score)			0.236	
Portenoy (2012)[86]	Nabiximols (6-10 sprays)	BPI-SF(Severity composite score)			0.119	
Portenoy (2012)[86]	Nabiximols (11-16 sprays)	BPI-SF(Severity composite score)			0.861	
Serpell (2014)[81] Parallel group	Nabiximols	BPI-SF(worst pain)		-0.30 (-0.82, 0.22)	0.255	ANCOVA
Selvarajah (2010)[136] Parallel group	Nabiximols	Deep pain (100mm VAS scale)		10.50(-12.20, 30.80)	0.38	Linear regression
Ellis(2009)[137]	THC	Descriptor Differential Scale		**3.30**	**0.016**	Wilcoxon's signed rank test
Wilsey (2011)[138] Cross-over	THC 3.5%	Descriptor Differential Scale (Global impression of change (pain relief))	**0.12 (0.065, 0.18)**		**<0.01**	Linear mixed model
Wilsey (2011)[138] Cross-over	THC 7%	Descriptor Differential Scale (Global impression of change (pain relief).	**0.12 (0.064, 0.18)**		**<0.01**	
Berman (2007)[1] Parallel group	Nabiximols	Descriptor Differential Scale (least pain in the last 24h (points))	**0.79**		**0.007**	
Berman (2007)[1] Parallel group	Nabiximols	Descriptor Differential Scale (mean BPI (points))	**0.46**		**0.04**	
Wallace(2013)[76]	THC	Descriptor Differential Scale (mean lowest achieved spontaneous pain score)			**0.017**	
Wilsey (2011)[138] Cross-over	THC 3.5%	Descriptor Differential Scale (Pain unpleasantness (measure of the emotional dimension of pain by VAS)	**-0.21 (-0.33, -0.09)**		**≤0.01**	

Study Details	Intervention	Outcome	MD at follow-up	MD change from baseline:		Analysis Details
Wilsey (2011)[138] Cross-over	THC 7%	Descriptor Differential Scale (Pain unpleasantness (measure of the emotional dimension of pain by VAS).	**-0.21 (-0.33, -0.09)**		**≤0.01**	
Berman (2007)[1] Parallel group	Nabiximols	Descriptor Differential Scale (Total BPI (points))	**-1.93 (-3.69, -0.16)**		**0.032**	ANCOVA
Frank (2008)[141] Cross-over	Nabilone	Descriptor Differential Scale (VAS (0-100mm))	**6.0 (1.40, 10.50)**		**0.01**	
Skrabek (2008)[140] Cross-over	Nabilone	Descriptor Differential Scale (VAS (0-100mm))	**-0.79**		**≤0.02**	
Wilsey (2011)[138] Cross-over	THC 3.5%	Descriptor Differential Scale (VAS (0-100mm))	**-0.0036 (-0.0069, 0.0003)**		**0.03**	
Wilsey (2011)[138] Cross-over	THC 7%	Descriptor Differential Scale (VAS (0-100mm))	**-0.0035 (-0.0068, -0. 0002)**		**0.04**	
GW Pharma Ltd(2005)[77] Parallel group	Nabiximols	Diabetic Neuropathy Pain (0-10 NRS)		-0.12 (-0.60, 0.36)	0.634	ANCOVA
Selvarajah (2010)[136] Parallel group	Nabiximols	McGill Pain rating (Affective scale)		-1.3(-3.0, 2.4)	0.81	Linear regression
Ware (2010)[133] Cross-over	Nabilone **vs** Amitriptyline	McGill Pain rating (Present pain intensity)		1.4 (-4.3, 7.20)		
Selvarajah (2010)[136] Parallel group	Nabiximols	McGill Pain rating (Present pain intensity)		0.53(-0.79, 1.40)	0.57	Linear regression
Selvarajah (2010)[136] Parallel group	Nabiximols	McGill Pain rating (Sensory scale)		3.30(-5.39, 8.44)	0.65	Linear regression
Blake(2006)[78] Parallel group	Nabiximols	McGill Pain rating ((SF-MPQ): total intensity of pain		3(-3, 9)	0.302	Mann-Whitney/ Wilcoxon test;
Berman (2004)[145] Cross-over	Nabiximols	McGill Pain rating (SF-MPQ Pain Rating Index (total score=45))	-1.7 (-3.64, 0.55)		0.146	ANCOVA
Berman (2004)[145] Cross-over	THC	McGill Pain rating (SF-MPQ Pain Rating Index (total score=45))	**-2.1 (-4.29, -0.1)**		**0.04**	

Study Details	Intervention	Outcome	MD at follow-up	MD change from baseline:		Analysis Details
Berman (2004)[145] Cross-over	Nabiximols	McGill Pain rating (SF-MPQ VAS)	-7.8 (-15.78, -1.21)		0.092	ANCOVA
Berman (2004)[145] Cross-over	THC	McGill Pain rating (SF-MPQ VAS)	**-9.3 (-17.41, -0.57)**		**0.0037**	
Blake(2006)[78] Parallel group	Nabiximols	McGill Pain rating (SF-MPQ VAS)		-3(-18, 9)	0.574	Mann-Whitney/ Wilcoxon test;
Blake(2006)[78] Parallel group	Nabiximols	McGill Pain rating (SF-MPQ VAS)		**-0.72 (-1.30, -0.14)**	**0.016**	Mann-Whitney/ Wilcoxon test;
Ware (2010)[135] Cross-over	THC (2.5%)	McGill Pain rating (Total score)	1.30 (-9.19, 11.79)			
Ware (2010)[135] Cross-over	THC (6%)	McGill Pain rating (Total score)	-3.30 (-12.86, 6.26)			
Ware (2010)[135] Cross-over	THC (9.4%)	McGill Pain rating (Total score)	-4.30 (-13.82, 5.22)			
Selvarajah (2010)[136] Parallel group	Nabiximols	McGill Pain rating (VAS)		1.0(-0.91, 3.40)	0.24	Linear regression
Blake(2006)[78] Parallel group	Nabiximols	Morning pain on movement (0-10 NRS)		**-0.95(-1.83, -0.02)**	**0.044**	ANCOVA
Blake(2006)[78] Parallel group	Nabiximols	Morning pain at rest (0-10 NRS)		**-1.04(-1.90, -0.18)**	**0.018**	Mann-Whitney/ Wilcoxon test;
Selvarajah (2010)[136] Parallel group	Nabiximols	Muscular pain (100mm VAS scale)		10.3 (-9.15, 33.00)	0.26	Linear regression
Langford (2013)[4] Parallel group	Nabiximols	Neuropathic pain scale (0-100)		1.83	0.310	
Selvarajah (2010)[136] Parallel group	Nabiximols	Neuropathic pain scale (0-100)		-7.80(-20.10, 12.10)	0.62	Linear regression
Serpell (2014)[81] Parallel group	Nabiximols	Neuropathic pain scale (0-100)		-2.86 (-7.22, 1.50)	0.198	ANCOVA
Abrams (2007)[142] Parallel group	THC	Neuropathic pain scale (% median reduction in chronic neuropathic pain (VAS))		**18**	**0.03**	Mann-Whitney/ Wilcoxon test
Abrams (2007)[142] Parallel group	THC	Neuropathic pain scale (% reduction chronic pain ratings (AUC))			**≤0.001**	Mann-Whitney/ Wilcoxon test

Study Details	Intervention	Outcome	MD at follow-up	MD change from baseline:		Analysis Details
Rog(2005)[144] Parallel group	Nabiximols	Neuropathic pain scale (0-100)		**-6.58(-12.97, -0 .19)**	**0.044**	ANCOVA
GW Pharma Ltd(2005)[77] Parallel group	Nabiximols	Neuropathic pain scale (0-100)		0.37(2.153) (-3.87, 4.61)	0.865	ANCOVA
Nurmikko(200 7)[80] Parallel group	Nabiximols	Neuropathic pain scale (0-100)		**-8.03 (-13.83, -2.23)**	**0.007**	ANCOVA
Berman (2007)[1] Parallel group	Nabiximols	NRS (0-10)		-0.08 (-0.51, 0.35	0.708	ANCOVA
Johnson (2010)[82] Parallel group	Nabiximols	NRS (0-10)		**-0.67 (-1.21, -0.14)**	**0.0014**	ANCOVA
Johnson (2010)[82] Parallel group	THC	NRS (0-10)		-0.32 (-0.86, 0.22)	0.245	ANCOVA
Rog(2005)[144] Parallel group	Nabiximols	NRS (0-10)		**-1.25(-2.11, -0. 39)**	**0.005**	ANCOVA
Lynch(2014)[148] Cross-over	Nabiximols	NRS (0-10)	-0.38 (-1.59, 0.83)			
Portenoy (2012)[86]	Nabiximols (1-4 sprays)	NRS (0-10)		**-0.75 (-1.28, -0.22)**	**0.006**	ANCOVA
	Nabiximols (6-10 sprays)			-0.36 (-0.89, 0.18)	0.187	
	Nabiximols (11-16 sprays)			-0.09(-0.62, 0.44)	0.75	
Ware (2010)[135] Cross-over	THC (2.5%)	NRS (0-10)	-0.13 (-0.83, 0.56)			Generalised linear model
	THC (6%)		-0.09(-0.78, 0.60)			
	THC (9.4%)		**-0.71(-1.40, -0.02)**			
Nurmikko(200 7)[80] Parallel group	Nabiximols	NRS (Dynamic allodynia)		**-0.82 (-1.60, -0.03)**	**0.042**	ANCOVA
Pinsger(2006)[143] Cross-over	Nabilone	NRS (Increase of number of headache-free days in last 4 weeks)		0.093		Wilcoxen signed rank
Berman (2004)[145] Cross-over	Nabiximols	NRS (Mean diary BS-11 pain score)	**-0.58 (-0.98, -0.18)**		**0.005**	ANCOVA
Berman (2004)[145] Cross-over	THC	NRS (Mean diary BS-11 pain score)	**-0.64 (-1.03, -0.24)**		**0.002**	
Nurmikko(200 7)[80] Parallel group	Nabiximols	NRS (mean pain NRS score)		**-0.96 (-1.59, -0.32)**	**0.004**	ANCOVA

Study Details	Intervention	Outcome	MD at follow-up	MD change from baseline:		Analysis Details
Langford (2013)[4] Parallel group	Nabiximols	NRS (NRS 0-10 scale)		0.17(-0.62, 0.29)	0.47	
Narang(2008)[139] Cross-over	Dronabinol (10mg)	NRS (pain intensity (0-10))		**-0.9**	**<0.001**	Linear regression (fixed effects)
Narang(2008)[139] Cross-over	Dronabinol (20mg)	NRS (pain intensity (0-10))		**-1.5**	**<0.001**	Linear regression (fixed effects)
Nurmikko(2007)[80] Parallel group	Nabiximols	NRS (Punctate allodynia)		**-0.87 (-1.62, -0.13)**	**0.021**	ANCOVA
Pinsger(2006)[143] Cross-over	Nabilone	NRS (Reduction of current spine pain intensity)		0.006		Wilcoxen signed rank
Pinsger(2006)[143] Cross-over	Nabilone	NRS (Reduction of mean headache intensity in last 4 weeks)		0.241		Wilcoxen signed rank
Pinsger(2006)[143] Cross-over	Nabilone	NRS (Reduction of mean spine pain intensitiy in last 4 weeks)		0.196		Wilcoxen signed rank
Narang(2008)[139] Cross-over	Dronabinol (10mg)	NRS (SPID)		**-23.8**	**<0.01**	Linear regression (fixed effects)
Svendsen(2004)[146] Cross-over	Dronabinol	NRS (Spontaneous pain score.)	**-0.60 (-1.8, 0.0)**		**0.02**	
Noyes (1975)[96] Cross-over	THC (5mg)	NRS (Total Pain Reduction	**2.1 (1.4, 2.8)**			
	THC (10mg)		**1.8 (1.08, 2.52)**			
	THC (15mg)		**3.2 (2.56, 3.84)**			
	THC (20mg)		**8.2 (7.37, 9.03)**			
Berman (2004)[145] Cross-over	Nabiximols	Pain Box Scale-11	**-0.8 (-1.23, -0.23)**		**0.005**	ANCOVA
Berman (2004)[145] Cross-over	THC	Pain Box Scale-11	**-0.6 (-1.08, -0.09)**		**0.02**	
Ellis(2009)[137]	THC	VAS (0-10)			**<0.001**	Wilcoxon's signed rank test
Wilsey (2013)[134] Cross-over	Cannabis (3.53%)	VAS (0-100)		**-10**	**0.0018**	Repeated measures model

Study Details	Intervention	Outcome	MD at follow-up	MD change from baseline:		Analysis Details
	Cannabis (1.29)			**-11**	**0.0018**	Repeated measures model
Langford (2013)[4] Parallel group	Nabiximols	Pain disability index (PDI)		2.79	0.058	
Nurmikko(2007)[80] Parallel group	Nabiximols	Pain disability index (PDI)		**-5.85 (-9.62, -2.09)**	**0.003**	ANCOVA
GW Pharma Ltd(2012)[79] Parallel group	Nabiximols	Pain disability index (PDI)	-2.79 (-8.14, 2.56)		0.30	ANCOVA
Berman (2004)[145] Cross-over	Nabiximols	Pain disability index (PDI)	-2.0 (-4.32, 0.83)		0.181	ANCOVA
Berman (2004)[145] Cross-over	THC	Pain disability index (PDI)	0.3 (-2.12, 2.98)		0.739	
Narang(2008)[139] Cross-over	Dronabinol (10mg)	Pain relief ((integral relief scores))	**8.3**		**<0.05**	Linear regression (fixed effects)
	Dronabinol (20mg)		**10.6**		**<0.01**	
Narang(2008)[139] Cross-over	Dronabinol (10mg)	Pain relief (Average relief scale (0-10))	**0.8**		**<0.01**	Linear regression (fixed effects)
	Dronabinol (20mg)		**0.9**		**<0.01**	
Svendsen(2004)[146] Cross-over	Dronabinol	Pain relief (NRS (0-10))	**2.5 (0.5, 4.5)**		**0.035**	
Nurmikko(2007)[80] Parallel group	Nabiximols	Pain at allodynic site		**29.03 (13.79, 44.67)**	**0.001**	ANCOVA
Selvarajah (2010)[136] Parallel group	Nabiximols	Superficial pain (100mm VAS scale)		9.10(-15.30, 21.93)	0.72	Linear regression
Selvarajah (2010)[136] Parallel group	Nabiximols	Total pain score (Average of superficial, deep and muscular pain scores)		9.50(-11.30, 27.80)	0.40	Linear regression
GW Pharma Ltd(2012)[79] Parallel group	Nabiximols	Total pain score (median treatment difference, % of days)	**0.18 (-47.62, 0)**		**0.006**	
Wallace(2013)[76]	THC	Total pain score (Spontaneous pain Score (area under curve - vs time))			**0.013**	

Study Details	Intervention	Outcome	MD at follow-up	MD change from baseline:		Analysis Details
QoL						
Johnson (2010)[82] Parallel group	Nabiximols	EORTC QLQ-C30 global health status		2.47 (-3.87, 8.81)	0.443	ANCOVA
	THC			0.84 (-5.46, 7.13)	0.793	
Langford (2013)[4] Parallel group	Nabiximols	EQ-5D (health status index)		-0.01	0.396	
Selvarajah (2010)[136] Parallel group	Nabiximols	EQ-5D (Health status index)	*-0.06 (-0.21, 0.09)*		0.87	Linear regression
GW Pharma Ltd(2005)[77] Parallel group	Nabiximols	EQ-5D (Health status index)		-0.01 (0.021) (-0.06, 0.03)	0.523	ANCOVA
Serpell (2014)[81] Parallel group	Nabiximols	EQ-5D (Health status index)		-0.01 (-0.06, 0.04)	0.617	ANCOVA
Langford (2013)[4] Parallel group	Nabiximols	EQ-5D (Health status VAS)		1.94	0.383	
Selvarajah (2010)[136] Parallel group	Nabiximols	EQ-5D (Health status VAS)	*1.70 (-10.35, 13.75)*		0.92	Linear regression
Serpell (2014)[81] Parallel group	Nabiximols	EQ-5D (health status VAS)		-0.75 (-5.60, 4.09)	0.760	ANCOVA
Ware (2010)[135] Cross-over	THC (2.5%)	EQ-5D (health status VAS)	-5.50 (-16.99, 5.99)			
Ware (2010)[135] Cross-over	THC (6%)	EQ-5D (health status VAS)	-1.20 (-13.77, 11.37)			
Ware (2010)[135] Cross-over	THC (9.4%)	EQ-5D (health status VAS)	2.20 (-9.73, 14.13)			
GW Pharma Ltd(2012)[79] Parallel group	Nabiximols	MSQoL (Spitzer QoL index scores)	0.28 (-0.36, 0.91)		0.387	ANCOVA
Berman (2007)[1] Parallel group	Nabiximols	MSQoL (Spitzer QoL index scores)	-0.04 (-0.49, 0.40)		0.847	ANCOVA
Pinsger(2006)[143] Cross-over	Nabilone	Other (Score (Mezzich & Cohen, German translation 2003))		0.902		Wilcoxen signed rank
Portenoy (2012)[86]	Nabiximols (1-4 sprays)	Patient assessment of Consitpation quality of life			0.226	

Study Details	Intervention	Outcome	MD at follow-up	MD change from baseline:		Analysis Details
Portenoy (2012)[86]	Nabiximols (6-10 sprays)	Patient assessment of Consitpation quality of life			-0.10 0.493	
Portenoy (2012)[86]	Nabiximols (11-16 sprays)	Patient assessment of Consitpation quality of life			0.139	
Frank (2008)[141] Cross-over	Nabilone	SF36 (Bodily pain)	**-5.2 (-10.1, -0.4)**		**0.03**	
Langford (2013)[4] Parallel group	Nabiximols	SF36 (Bodily pain)		1.35	0.494	
Selvarajah (2010)[136] Parallel group	Nabiximols	SF36 (Bodily pain)	-5.60 (-20.98, 9.78)		0.64	Linear regression
Svendsen(2004)[146] Cross-over	Dronabinol	SF36 (Bodily pain)	**9.8 (0.0, 21.5)**		**0.037**	
Frank (2008)[141] Cross-over	Nabilone	SF36 (Change in health)	0.0 (-0.2, 0.2)		0.88	
Frank (2008)[141] Cross-over	Nabilone	SF36 (General health)	0.8 (-3.1, 4.6)		0.70	
Langford (2013)[4] Parallel group	Nabiximols	SF36 (General health)		-1.70	0.264	
Selvarajah (2010)[136] Parallel group	Nabiximols	SF36 (General health)	*4.50 (-9.25, 18.25)*		0.78	Linear regression
Svendsen(2004)[146] Cross-over	Dronabinol	SF36 (General health)	0.0 (-6, 5)		0.95	
Frank (2008)[141] Cross-over	Nabilone	SF36 (General pain)	0.8(-3.1, 4.6)		0.7	
Frank (2008)[141] Cross-over	Nabilone	SF36 (mental health)	2.5 (-2.7, 7.6)		0.35	
Langford (2013)[4] Parallel group	Nabiximols	SF36 (Mental health)		-0.56	0.733	
Selvarajah (2010)[136] Parallel group	Nabiximols	SF36 (Mental health)	5.00 (-9.90, 19.90)		0.76	Linear regression
Svendsen(2004)[146] Cross-over	Dronabinol	SF36 (Mental health)	**8(0, 12)**		**0.023**	
Lynch(2014)[148] Cross-over	Nabiximols	SF36 (Mental)	10.96 (4.03, 17.89)			
Frank (2008)[141] Cross-over	Nabilone	SF36 (Physical functioning)	-1.2 (-4.5, 2.1)		0.48	

Study Details	Intervention	Outcome	MD at follow-up	MD change from baseline:		Analysis Details
Langford (2013)[4] Parallel group	Nabiximols	SF36 (Physical Functioning)		-0.45	0.785	
Selvarajah (2010)[136] Parallel group	Nabiximols	SF36 (Physical functioning)	-6.00 (-22.86, 10.86)		0.63	Linear regression
Svendsen(2004)[146] Cross-over	Dronabinol	SF36 (Physical functioning)	5.0 (0.0, 7.5)		0.06	
Frank (2008)[141] Cross-over	Nabilone	SF36 (Role emotional)	-1.2(-11.8, 9.5)		0.83	
Langford (2013)[4] Parallel group	Nabiximols	SF36 (Role emotion)		-3.33	0.216	
Selvarajah (2010)[136] Parallel group	Nabiximols	SF36 (Role emotional)	7.20 (-27.36, 41.76)		0.76	Linear regression
Svendsen(2004)[146] Cross-over	Dronabinol	SF36 (Role emotional)	0 (-33, 0)		0.46	
Frank (2008)[141] Cross-over	Nabilone	SF36 (Role physical)	**8.9 (1.1, 16.7)**		**0.03**	
Langford (2013)[4] Parallel group	Nabiximols	SF36 (Role physical)		-0.89	0.694	
Lynch(2014)[148] Cross-over	Nabiximols	SF36 (Role physical)	-11.0 (-17.3, -4.87)			
Selvarajah (2010)[136] Parallel group	Nabiximols	SF36 (Role physical)	-26.80 (-56.60, 3.00)		0.12	Linear regression
Svendsen(2004)[146] Cross-over	Dronabinol	SF36 (Role physical)	0.0 (-25.0, 12.5)		0.73	
Frank (2008)[141] Cross-over	Nabilone	SF36 (Social functioning)	3.4 (-4.1, 10.8)		0.37	
Langford (2013)[4] Parallel group	Nabiximols	SF36 (Social functioning)		**-5.75**	**0.020**	
Selvarajah (2010)[136] Parallel group	Nabiximols	SF36 (Social functioning)	-11.60 (-30.91, 7.71)		0.08	Linear regression
Svendsen(2004)[146] Cross-over	Dronabinol	SF36 (Social functioning)	6.3 (0.0, 12.5)		0.17	
Frank (2008)[141] Cross-over	Nabilone	SF36 (Vitality)	-2.0 (-7.2, 3.3)		0.46	
Langford (2013)[4] Parallel group	Nabiximols	SF36 (Vitality)		-2.75	0.095	

Study Details	Intervention	Outcome	MD at follow-up	MD change from baseline:		Analysis Details
Selvarajah (2010)[136] Parallel group	Nabiximols	SF36 (Vitality)	-5.70 (-20.92, 9.52)		0.45	Linear regression
Svendsen(2004)[146] Cross-over	Dronabinol	SF36 (Vitality)	2.5 (-5.0, 10.0)		0.52	
Global impression						
Narang(2008)[139] Cross-over	Dronabinol (10mg)	Patient global impression		**2**	**<0.05**	Linear regression (fixed effects)
	Dronabinol (20mg)			**2**	**<0.05**	
Wilsey (2013)[134] Cross-over	Cannabis (3.53%)	Patient global impression (Global impression of pain relief scale of -3 to +3)	**0.69**		**0.0001**	Repeated measures model
	Cannabis (1.29)		**0.55**		**0.0001**	
Portenoy (2012)[86]	Nabiximols (1-4 sprays)	Patient global impression (Patient global assessment of change)			0.268	
	Nabiximols (6-10 sprays)				0.664	
	Nabiximols (11-16 sprays)				0.538	
Nurmikko(2007)[80] Parallel group	Nabiximols	Patient global impression (PGIC (all neuropathic pain))		**29.03 (13.79, 44.67)**	**≤0.001**	ANCOVA

5.2.3.4 Summary

Overall there was some evidence that CBM may improve pain, there was less evidence for an effect on other outcomes such as quality of life and global impression of change. Studies generally suggested a beneficial effect of CBM on measures of pain but this did not reach statistical significance in most individual studies. Summary estimates for outcomes where there were sufficient data to permit pooling suggested a significant beneficial effect of cannabis on all measures both dichotomous and continuous (Table 19). Dichotomous data suggested a significant beneficial effect of CBM on patient global impression of change. There was some evidence to support this based on continuous data but this was not consistent across trials. Sensitivity analyses that included cross-over trials in the meta-analyses showed results consistent with those based on parallel group trials alone. Pain measured using a numerical rating scale was the only outcome where sufficient data were available to investigate the presence of small study effects. There was no evidence of small study effect from the analysis where this outcome was dichotomised (p=0.304 for parallel group studies only). For pain NRS as a continuous measure, there was evidence of small study effects for the analysis based on the parallel group studies alone (p=0.02) but not for the analysis based on all ten studies (p=0.172).

TABLE 19: SUMMARY ESTIMATES FOR CHRONIC PAIN PARALLEL GROUP TRIALS

Outcome	Number of studies	Summary estimate	Favours	I^2 (%)
≥30% reduction in pain	8	OR=1.35 (0.95, 1.93)	CBM	49
Pain NRS (0-10)	6	**WMD =-0.46 (-0.80, -0.11)**	CBM	59
BPI-SF (severity composite index)	4	WMD=-0.17(-0.50, 0.16)	CBM	0
Patient global impression change	5	**OR=1.94 (1.15, 3.28)**	CBM	69
Neuropathic pain scale	5	**WMD=-3.89(-7.32, -0.47)**	CBM	41
EQ-5D: Health status index	3	WMD=-0.01 (-0.05, 0.02)	Placebo	0

TABLE 20: GRADE SUMMARY OF FINDINGS TABLE: CHRONIC PAIN

CBM for chronic pain

Patient or population: patients with chronic pain
Settings: Not specified
Intervention: CBM

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Control**	Corresponding risk **CBM**				
30% reduction in pain NRS or VAS Follow-up: 2-15 weeks[1]	**314 per 1000**	**382 per 1000** (303 to 469)	**OR 1.35** (0.95 to 1.93)	1370 (8 studies[2])	⊕⊕⊕⊖ **moderate**[3,4]	
Improvement with Nabiximols Patient global impression of change Follow-up: 3-14 weeks[5]	**246 per 1000**[6]	**388 per 1000** (273 to 517)[6]	**OR 1.94** (1.15 to 3.28)	252 (5 studies[7])	⊕⊕⊖⊖ **low**[8,9]	
Pain Numerical rating scale. Scale from: 0 to 10. Follow-up: 2-14 weeks[10]	See comment	See comment		948 (6 studies[11])	⊕⊕⊕⊖ **moderate**[12]	WMD -0.46 (95%-CI -0.8 to -0.11)
Pain Brief Pain Inventory-Short Form (BPI-SF). Scale from: 0 to 10. Follow-up: 3-15 weeks[13]	See comment	See comment		613 (3 studies[14])	⊕⊕⊕⊖ **moderate**[12]	WMD -0.17 (95%-CI -0.5 to 0.16)
Neuropathic pain Neuropathic Pain Scale. Scale from: 0 to 100. Follow-up: 5-15 weeks[15]	See comment	See comment		764 (5 studies[16])	⊕⊕⊕⊖ **moderate**[17]	WMD -3.89 (95%-CI -7.32 to -0.47)
Quality of life EQ-5D. Scale from: 0 to 100. Follow-up: 12-15 weeks[18]	See comment	See comment		573 (3 studies[19])	⊕⊕⊕⊖ **moderate**[20]	WMD -0.01 (95%-CI -0.05 to 0.02)
Any adverse events Follow-up: 1-15 weeks[21]	**673 per 1000**	**867 per 1000** (819 to 904)	**OR 3.17** (2.19 to 4.58)[22]	1187 (9 studies[23])	⊕⊕⊕⊖ **moderate**[24]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Abrams 2007, Johnson 2010: 2 weeks; Nurmikko 2007: 5 weeks; Portenoy 2012: 9 weeks; Selvarajah 2010: 12 weeks; GW Pharma Ltd 2005, Langford 2013: 14 weeks; Serpell 2014: 15 weeks
[2] Abrams 2007, GW Pharma Ltd 2005, Johnson 2010, Langford 2013, Nurmikko 2007, Portenoy 2012, Selvarajah 2010, Serpell 2014
[3] Risk of bias: Insufficient details on randomisation (GW Pharma Ltd 2005, Johnson 2010, Selvarajah 2010), concealment of allocation (Abrams 2007, GW Pharma Ltd 2005, Johnson 2010, Langford 2013, Portenoy 2012, Selvarajah 2010, Serpell 2014) and blinding (Abrams 2007, GW Pharma Ltd 2005, Johnson 2010, Nurmikko 2007, Portenoy 2012, Selvarajah 2010); high risk of bias for concealment of allocation (Nurmikko 2007) and incomplete outcome data (Abrams 2007, GW Pharma Ltd 2005, Johnson 2010)
[4] No evidence of small study effects (Egger test, p=0.304)
[5] Berman 2007, GW Pharma Ltd 2012: 3 weeks; Rog 2005: 5 weeks; GW Pharma Ltd 2005, Langford 2013: 14 weeks
[6] Numbers not reported for GW Pharma Ltd 2005 and Langford 2013
[7] Berman 2007, GW Pharma Ltd 2005, GW Pharma Ltd 2012, Langford 2013, Rog 2005
[8] Risk of bias: Insufficient details on randomisation (Berman 2007, GW Pharma Ltd 2005, GW Pharma Ltd 2012), concealment of allocation (all studies) and blinding (Berman 2007, GW Pharma Ltd 2005, GW Pharma Ltd 2012); high risk of bias for incomplete outcome data (Berman 2007, GW Pharma Ltd 2005, GW Pharma Ltd 2012)
[9] Inconsistency: I2=69%
[10] Johnson 2010: 2 weeks; Berman 2007: 3 weeks; Nurmikko 2007, Rog 2005: 5 weeks; Portenoy 2012: 9 weeks; Langford 2013: 14 weeks
[11] Berman 2007, Johnson 2010, Langford 2013, Nurmikko 2007, Portenoy 2012, Rog 2005
[12] Risk of bias: Insufficient details on randomisation (Berman 2007, Johnson 2010), concealment of allocation (all but Nurmikko 2007) and blinding (Berman 2007, Johnson 2010, Nurmikko 2007, Portenoy 2012); high risk of bias for concealment of allocation (Nurmikko 2007) and incomplete outcome data (Berman 2007, Johnson 2010)
[13] GW Pharma Ltd 2012: 3 weeks; GW Pharma Ltd 2005: 14 weeks; Serpell 2014: 15 weeks
[14] GW Pharma Ltd 2005, GW Pharma Ltd 2012, Serpell 2012
[15] Nurmikko 2007, Rog 2005: 5 weeks; Selvarajah 2010: 12 weeks; GW Pharma Ltd: 14 weeks; Serpell 2014: 15 weeks
[16] GW Pharma Ltd, Nurmikko 2007, Rog 2005, Selvarajah 2010, Serpell 2014
[17] Risk of bias: Insufficient details on randomisation (GW Pharma Ltd 2005, Selvarajah 2010), concealment of allocation (all but Nurmikko 2007) and blinding (GW Pharma Ltd 2005, Nurmikko 2007, Selvarajah 2010); high risk of bias for concealment of allocation (Nurmikko 2007) and incomplete outcome data (GW Pharma Ltd 2005)
[18] Selvarajah 2010: 12 weeks; GW Pharma Ltd 2005: 14 weeks; Serpell 2014: 15 weeks
[19] GW Pharma Ltd 2005, Serpell 2014, Selvarajah 2010
[20] Risk of bias: Insufficient details on randomisation (GW Pharma Ltd 2005, Selvarajah 2010), concealment of allocation (all studies) and blinding (GW Pharma Ltd 2005, Selvarajah 2010); high risk of bias for incomplete outcome data (GW Pharma Ltd 2005)
[21] Karst 2003: 1 week; Berman 2007, GW Pharma Ltd 2012, Svendsen 2004: 3 weeks; Nurmikko 2007, Rog 2005: 5 weeks; Portenoy 2012: 9 weeks; GW Pharma Ltd 2005: 12 weeks; Serpell 2014: 15 weeks
[22] OR across all patient populations (29 studies): 3.03, 95%-CI 2.42 to 3.80 (see section 5.3 for details)
[23] Berman 2007, GW Pharma Ltd 2005, GW Pharma Ltd 2012, Karst 2003, Nurmikko 2007, Portenoy 2012, Rog 2005, Serpell 2014, Svendsen 2004
[24] Risk of bias: Insufficient details on randomisation (Berman 2007, GW Pharma Ltd 2005, GW Pharma Ltd 2012), concealment of allocation (Berman 2007, GW Pharma Ltd 2005, GW Pharma Ltd 2012, Portenoy 2012, Rog 2005, Serpell 2014, Svendsen 2004) and blinding (all but Karst 2003 and Nurmikko 2007; high risk of bias for concealment of allocation (Nurmikko 2007), incomplete outcome data (Berman 2007, GW Pharma Ltd 2005, GW Pharma Ltd 2012, Karst 2003), selective outcome reporting.

5.2.4 Spasticity due to multiple sclerosis (MS) or paraplegia

Twelve studies (31 reports; 2213 participants) evaluated CBM as a treatment for spasticity due to MS or paraplegia (Table 21).[1-5, 71, 87, 89, 128, 151, 164, 189-208] Ten studies (2188 participants) included patients with MS and two included patients with paraplegia (25 participants) caused by spinal cord injury. A number of studies also provided data on outcomes relating to sleep[3-5, 87, 190, 192, 209], chronic pain[4, 87] and depression.[3] Data for these outcomes are considered under the relevant sections and are not reported further in this section.

Eight RCTs used a parallel group design (2,091 participants) and four (122 participants) were cross-over trials. Most studies specified a minimum level of spasticity for inclusion in the trial. This ranged from ≥2 or 3 on the Ashworth score with some studies specifying that this should apply to at least one limb or joint, two or more muscle groups or at the elbow, hip or knee. One study specified a score of ≥4 on a spasticity numerical rating scale (NRS) for at least 6 days.[5] Study duration ranged from 3 days for each treatment period in one of the cross-over trials to 15 weeks in one of the parallel group trials. Five studies evaluated nabiximols (max dose 12-48 sprays/24h),[1-5] three evaluated dronabinol (max dose 10-25mg/day),[71, 89, 193] two of these also evaluated CBD/THC capsules (max dose 10-25mg/day),[89, 193] an additional two evaluated CBD/THC alone (max dose 25/30mg/day),[87, 192] one evaluated nabilone (max dose 1mg/day),[128] and one evaluated THC (4%) cigarettes (one 800mg cigarette/day).[190] All studies compared the CBM evaluated to a matched placebo control group.

5.2.4.1 Risk of bias

The risk of bias in the included studies was variable (Table 22). Only two, by the same author, were rated as low risk of bias for all domains.[87, 89] A further five were rated as unclear risk of bias. One of these, available only as a conference abstract, did not report sufficient details to allow a judgement of high or low risk of bias to be made for any of the bias domains.[71] Two were rated as low risk of bias for all domains except for allocation concealment for which insufficient details were reported to allow a judgement to be made.[4, 5] A further study did not provide details on allocation concealment of outcome assessor blinding but was rated as low risk bias for all other domains,[128] and one study did not provide details on randomisation, allocation concealment or outcome assessor blinding.[2] Five studies were judged at high risk of bias. Limitations in these studies related to incomplete outcome data and failure to use an ITT analysis to account for missing data[1, 3, 190, 192] and selective outcome reporting.[193]

TABLE 21: OVERVIEW OF STUDIES THAT EVALUATED CBM FOR SPASTICITY IN PATIENTS WITH MS AND PARAPLEGIA

Study Details	Country	Design	N	Duration (weeks)*	Condition	Spasticity entry criterion	Intervention 1	Intervention 2	Comparator
Berman(2007)[1, 164]	Romania, UK	Parallel group	117	3	MS	Not specified	Nabiximols (Sativex); Max 48 sprays/24h		Placebo
Collin(2007)[2, 202]	UK and Romania	Parallel group	189	6	MS	Spasticity in ≥2 muscle groups; Ashworth score≥2	Nabiximols (Sativex); Max 48 sprays/24h		Placebo
Collin(2010)[5, 198, 203]	UK and Czeck republic	Parallel group	337	14	MS	Mean daily score ≥4 on spasticity NRS for 6 days	Nabiximols (Sativex); max 24 sprays/24h		Placebo
Corey-Bloom(2012)[1 90, 200, 208]	USA	Cross-over	37	3 days (11 day washout)	MS	Ashworth score ≥ 3 at the elbow, hip, or knee;	THC; one 800mg cigarette		Placebo
Hagenbach(2003)[71]	Switzerland	Parallel group	13	6	Paraplegia (spinal cord injury)	Ashworth score >3	Dronabinol (Marinol); max dose unclear appeared to be 10mg daily		Placebo
Killestein(2002)[193, 196]	Netherlands	Cross-over	16	4 (4)	MS	Ashworth score ≥ 2 in at least one limb	THC/CBD capsules; max dose 10mg/day	Dronabinol (Marinol); max dose 10mg/day	Placebo
Langford(2013)[4, 151]	UK, Czech Republic, Canada, Spain	Parallel group	339	14	MS	Not specified	Nabiximols (Sativex); max 12 sprays/24h		Placebo
Pooyania(2010)[128, 205]	Canada	Cross-over	12	4 (2)	Paraplegia (Spinal cord injury)	Ashworth ≥ 3	Nabilone (Cesamet); max dose 1mg/day		Placebo
Vaney(2004)[19 2]	Switzerland	Cross-over	57	9 days (4 days)	MS	≥ one joint scoring ≥ 2 on the Ashworth scale	THC/CBD capsules; max dose 30mg/day		Placebo
Wade(2004)[3, 199, 204]	UK	Parallel group	160	6	MS	Not specified	Nabiximols (Sativex); max 48 sprays/24h		Placebo
Zajicek(2003)[8 9, 189, 191, 206]	UK (CAMS study)	Parallel group	657	15	MS	Ashworth score of ≥2 in ≥ 2 limb muscle groups	THC/CBD capsules; max 25mg/day	Dronabinol (Marinol); max 25mg/day	Placebo
Zajicek(2012)[8 7, 194, 195, 197, 201, 207]	UK (MUSEC study)	Parallel group	279	12	MS	Not specified	THC/CBD capsules; max 25mg/day		Placebo

TABLE 22: RISK OF BIAS IN MS AND PARAPLEGIA STUDIES

Study Details	RISK OF BIAS						
	Random sequence generation	Allocation concealment	Participant/ Personnel blinding	Outcome assessor blinding	Incomplete outcome data	Selective outcome reporting	Overall
Berman(2007)[1]	?	?	☺	?	☹	☺	☹
Collin(2007)[2]	?	?	☺	?	☺	☺	?
Collin(2010)[5]	☺	?	☺	☺	☺	☺	?
Corey-Bloom(2012)[190]	?	?	?	?	☹	☺	☹
Hagenbach(2003)[71]	?	?	?	?	?	?	?
Killestein(2002)[193]	?	?	☺	☺	☺	☹	☹
Langford(2013)[4]	☺	?	☺	☺	☺	☺	?
Pooyania(2010)[128]	☺	?	☺	?	☺	☺	?
Vaney(2004)[192]	☺	☺	☺	☺	☹	☺	☹
Wade(2004)[3]	☺	?	☺	☺	☹	☺	☹
Zajicek(2003)[89]	☺	☺	☺	☺	☺	☺	☺
Zajicek(2012)[87]	☺	☺	☺	☺	☺	☺	☺

5.2.4.2 Dichotomous outcome results

Spasticity

Four parallel group studies provided dichotomous data for the effects of CBM on spasticity (Table 23). All suggested a beneficial effect of CBM, this reached statistical significance in three studies.[2, 87, 89] Two parallel group studies, both by the same author and assessing nabiximols, evaluated the number of patients who reported a ≥ 50% reduction or ≥ 30% reduction in spasticity symptoms as assessed on a 0-10 NRS. Summary estimates for these outcomes suggested a beneficial effect of nabiximols but this did not reach statistical significance (Figure 13 and Figure 14).

General disease specific symptoms

One parallel group study also reported a significant beneficial effect on muscle stiffness,[87] and a further parallel group study reported a suggestion of a reduction in the incidence of MS relapses but this did not reach statistical significance for either THC/CBD capsules or dronabinol.[89]

Global impression

Four parallel group studies, all evaluating nabiximols, assessed patient global impression, one also assessed carer global impression. All suggested a beneficial effect of nabiximols but this only reached statistical significance in one. The summary estimate (

Figure 15) suggested a significant beneficial effect of nabiximols on patient global impression (OR 1.78, 95% CI 1.12, 2.82). However, there was moderate heterogeneity across studies (I^2 =58%, p=0.43) and so this should be interpreted with some caution.

TABLE 23: RESULTS FOR DICHOTOMOUS OUTCOMES FROM STUDIES THAT EVALUATED CBM FOR SPASTICITY IN PATIENTS WITH MS AND PARAPLEGIA

Study Details	Intervention	Outcome	Intervention Events/ n	Placebo Events/n	OR (95% CI)*
Spasticity					
Collin(2007)[2] Parallel group	Nabiximols	NRS(≥ 50% reduction)	21/120	6/64	1.9 (0.76, 4.95)
		NRS(≥30% reduction)	48/120	14/64	**2.3 (1.17, 4.63)**
Collin (2010)[5] Parallel group	Nabiximols	NRS(≥50% improvement)	21/166	18/169	1.2 (0.62, 2.34)
		NRS(≥30% improvement)	51/166	42/169	1.3 (0.82, 2.15)
Zajicek(2003)[89] Parallel group	THC/CBD	Patient assessment of whether there was a treatment benefit	121/197	91/198	**1.8 (1.25, 2.78)**
	Dronabinol		108/181	91/198	**1.7 (1.15, 2.60)**
Zajicek(2012)[87] Parallel group	THC/CBD	Spasm severity (0-3 on an 11 point category rating scale)	44/143	18/134	**2.8 (1.53, 5.15)**
General disease specific symptoms					
Zajicek(2012)[87] Parallel group	THC/CBD	Muscle stiffness (0-3 on an 11 point category rating scale)	42/143	21/134	**2.2 (1.23, 3.96)**
Zajicek(2003)[89] Parallel group	THC/CBD	Relapse: MS relapse or possible relapse	1 (1)/211	7 (8)/213	0.1 (0.03, 1.14)
	Dronabinol		1 (1)/206	7 (8)/213	0.2 (0.03, 1.17)
Global impression					
Berman(2007)[1] Parallel group	Nabiximols	Patient global impression	30/56	12/60	**4.47 (1.98, 10.05)**
Collin(2007)[2] Parallel group	Nabiximols	Patient global impression	66/124	31/65	1.2 (0.68, 2.26)

Study Details	Intervention	Outcome	Intervention Events/ n	Placebo Events/n	OR (95% CI)*
Langford (2013)[4] Parallel group	Nabiximols	Patient Global Impression	NR	NR	1.47 (0.99, 2.18)
Wade(2004)[3] Parallel group	Nabiximols	Patient global impression	32/79	21/77	1.7 (0.92, 3.50)
Collin (2010)[5] Parallel group	Nabiximols	Carer global impression	72/167	56/170	1.5 (0.98, 2.39)

*Estimate that showed a statistically significant difference between treatment groups (p<0.05) are shown in bold

FIGURE 13: FOREST PLOT SHOWING ORS (95% CI) FOR NUMBER OF PATIENTS REPORTING AT LEAST A 50% REDUCTION IN SPASTICITY SYMPTOMS AMONG THOSE RECEIVING CBM COMPARED TO PLACEBO

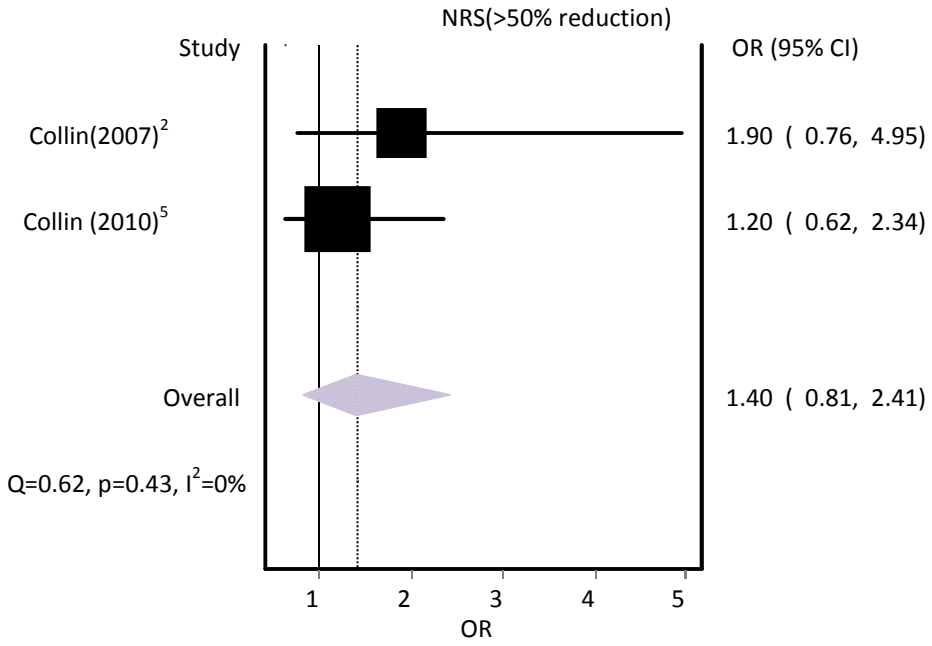


FIGURE 14: FOREST PLOT SHOWING ORS (95% CI) FOR NUMBER OF PATIENTS REPORTING AT LEAST A 30% REDUCTION IN SPASTICITY SYMPTOMS AMONG THOSE RECEIVING CBM COMPARED TO PLACEBO

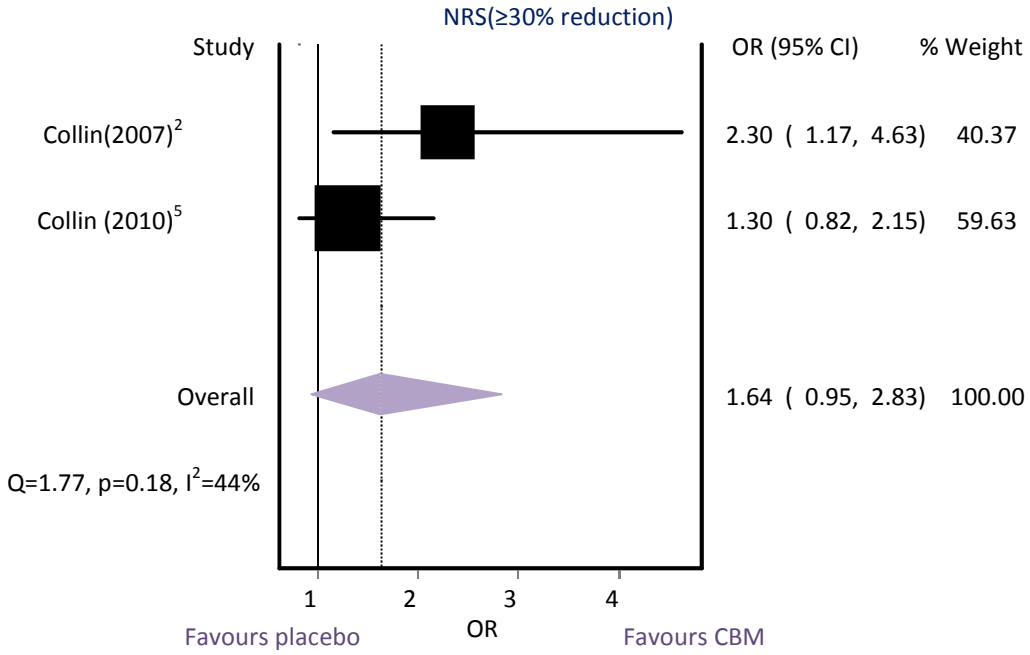
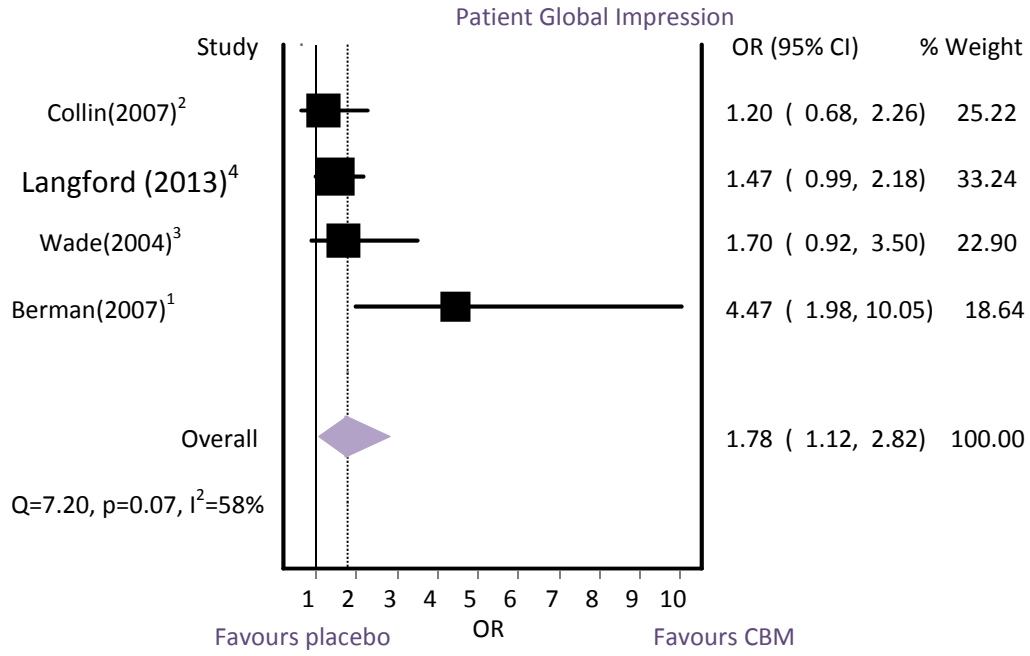


FIGURE 15: FOREST PLOT SHOWING ORS (95% CI) FOR NUMBER OF PATIENTS REPORTING A GLOBAL IMPRESSION OF CHANGE IN SYMPTOMS AMONG THOSE RECEIVING CBM COMPARED TO PLACEBO



5.2.4.3 Continuous outcome results

The twelve included studies reported a variety of continuous outcome measures that we grouped as covering spasticity, quality of life (QoL), mobility/disability, general disease

specific symptoms and global impression. Outcome measures reported only in single trials are summarised in Table 24 and are not considered in more detail.

Spasticity

The most commonly reported measure of spasticity was the Ashworth scale or modified Ashworth scale,[210] we defined this as the primary outcome measure for spasticity. This assesses spasticity on a scale ranging from 0 (no increase in muscle tone) to 5 (affected part(s) rigid in flexion and extension), a negative MD therefore indicates a beneficial effect of the CBD. All but one of the individual trials suggested a beneficial effect of CBM on the Ashworth score but this only reached statistical significance ($p<0.05$) in two trials. The summary WMB estimate based on five parallel group studies that reported data on the Ashworth scale was -0.14 (95% -0.27, -0.01; Figure 16). There was no evidence of heterogeneity (I^2=0%, p=0.52). We performed an additional sensitivity analysis where we included three cross-over trials that also reported results for spasticity assessed using the Ashworth scale. The summary WMD based on all eight (5 parallel group and 3 cross-over studies) that reported data for this outcome suggested a significant beneficial effect of CBM on spasticity assessed using the Ashworth scale (WMD -0.26 95% CI -0.47, -0.05; Figure 17). There was moderate evidence of heterogeneity (I^2 47%, p=0.07) and so this should be assessed with some caution. The Egger test for this outcome suggested no evidence of small study effects either based on the five parallel group studies alone (p=0.437) or on all eight studies (p=0.173).

FIGURE 16: FOREST PLOT SHOWING WMD (95% CI) FOR ASHWORTH SCORE FOR PARTICIPANTS TAKING CBM COMPARED TO PLACEBO IN THE PARALLEL GROUP STUDIES ONLY

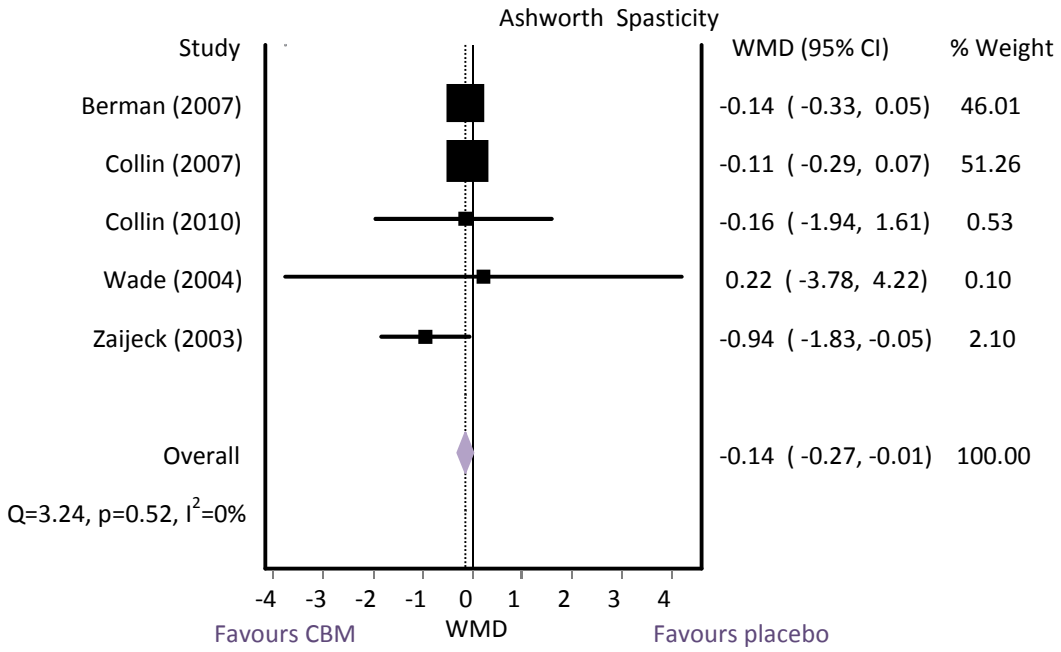
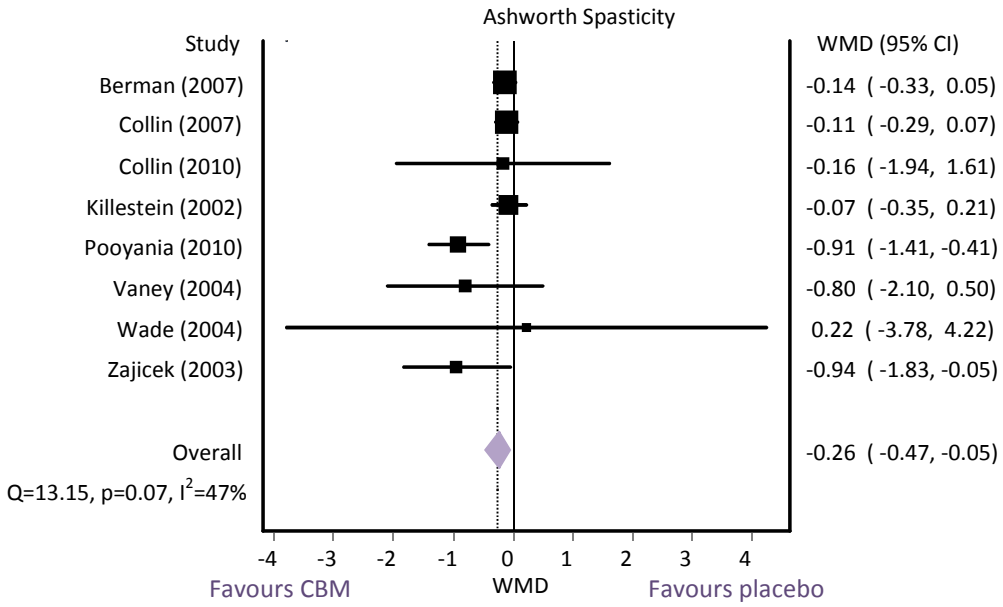


FIGURE 17: FOREST PLOT SHOWING WMD (95% CI) FOR ASHWORTH SCORE FOR PARTICIPANTS TAKING CBM COMPARED TO PLACEBO IN ALL STUDIES (PARALLEL GROUP AND CROSS-OVER TRIALS)



Three parallel group studies assessed the impact of CBM on spasticity using a 0-10 NRS[1, 2, 5] and a further two (one parallel group and one cross-over trial) used a 0-100 VAS[3, 128]; in all 0 indicated no spasticity and 10 or 100 worst spasticity. We divided the results from the studies that used the VAS scale by 10 so that results were on the same scale and could be combined with the studies that used NRS. All but one (a parallel group trial)[1] of the studies suggested a beneficial effect of CBM on spasticity but this only reached statistical significance in one parallel group trial.[3] The summary effect estimate based on the four parallel group trials suggested a significant beneficial effect of CBM on spasticity assessed using an NRS or VAS but this did not reach statistical significance (WMD -0.52, 95% CI -1.11, 0.07; Figure 18). There was strong evidence of heterogeneity (I^2=73%, p=0.01). We performed an additional sensitivity analysis where we included the cross-over trial that also reported results for spasticity assessed using a VAS score. The summary effect estimate based on all five trials suggested a significant beneficial effect of CBM on spasticity assessed using an NRS or VAS (WMD -0.57, 95% CI -1.09, -0.05; Figure 19). There was strong evidence of heterogeneity (I^2=67%, p=0.02). Other measures of spasticity were not consistently reported; they were either only reported in a small number of studies or measures of variance were not reported (Table 24). Generally the studies suggested a beneficial effect of CBM on spasticity for other outcomes but most did not reach statistical significance.

FIGURE 18: FOREST PLOT SHOWING WMD (95% CI) FOR SPASTICITY NRS/VAS FOR PARTICIPANTS TAKING CBM COMPARED TO PLACEBO IN THE PARALLEL GROUP STUDIES ONLY

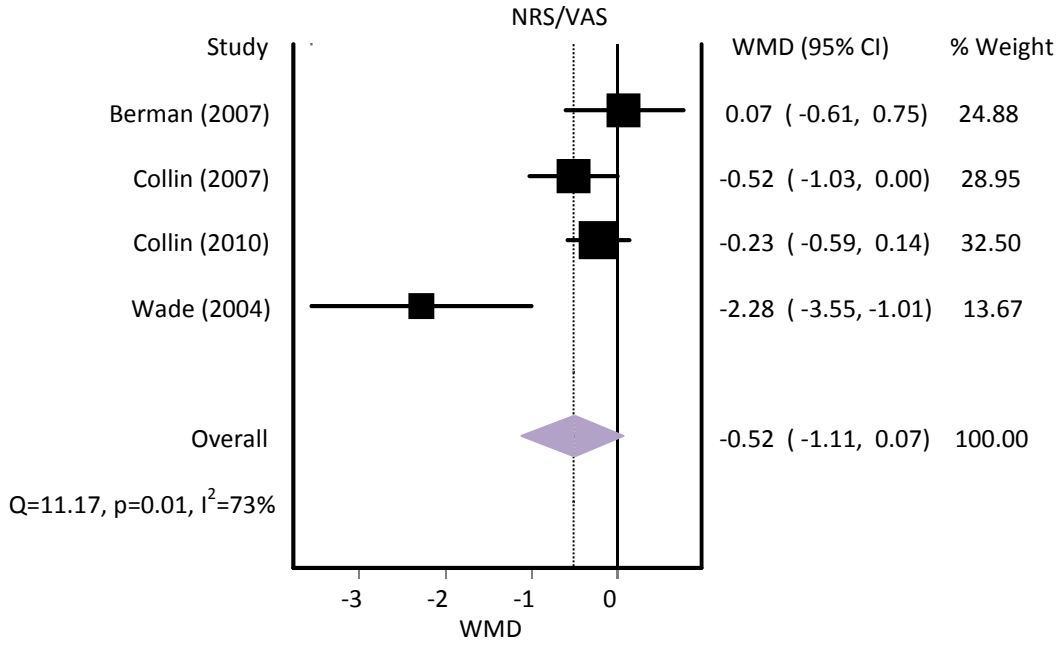
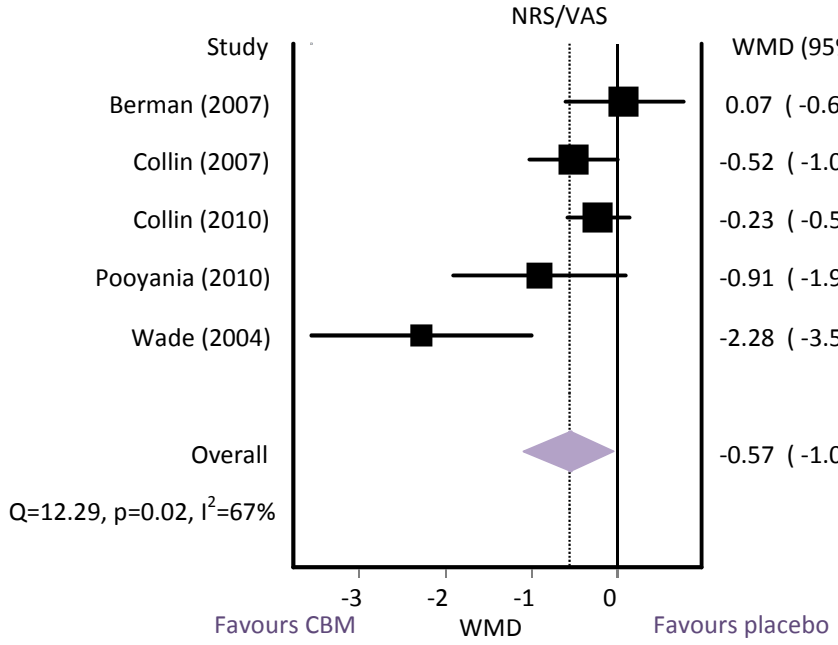


FIGURE 19. FOREST PLOT SHOWING WMD (95% CI) FOR SPASTICITY NRS/VAS FOR PARTICIPANTS TAKING CBM COMPARED TO PLACEBO IN ALL STUDIES (PARALLEL GROUP AND CROSS-OVER TRIALS)



Quality of life (QoL)

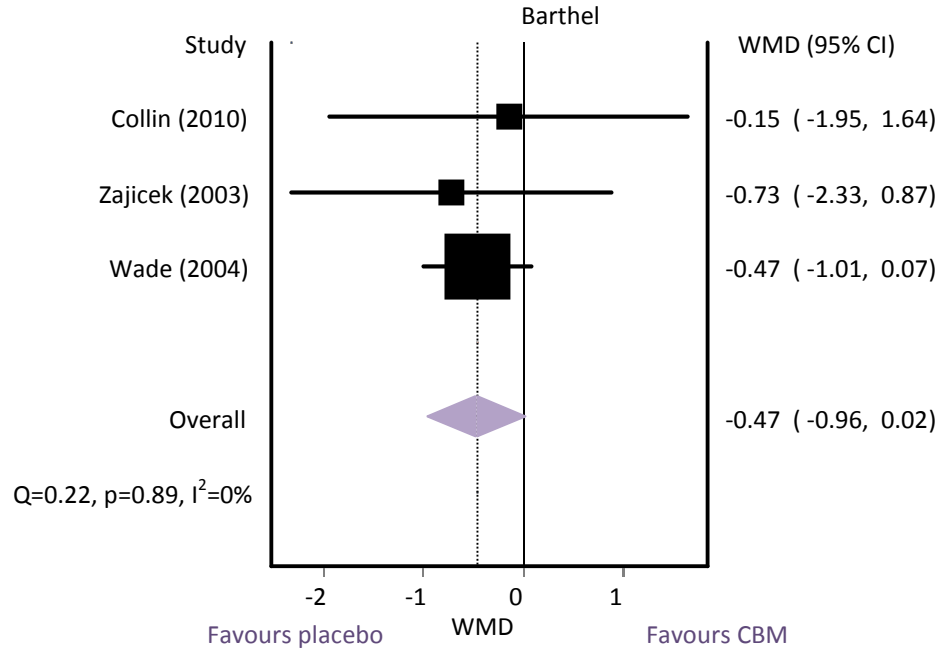
Quality of life was assessed in three parallel group trials[1, 4, 5] using various different measures including the EQ-5D, [211] MSQoL,[212] and SF36. [187] On all these scales a higher score indicates better health states therefore an MD favouring CBM would be positive. Only one study provided sufficient information to calculate a CI around the MD in change from

baseline,[1] the other two studies reported only MD and p-values. Generally there was no effect of CBM on QoL with only 1/15 measures showing a statistically significant difference between groups; this favoured placebo.

Mobility/Disability

Three parallel group trials[3, 5, 89] evaluated activities of daily living using the Barthel Index. [213] This is a 10 item scale that measures daily function and gives a score out of 20 with higher scores suggesting greater independence. All studies suggested a negative effect of CBM but this did not reach statistical significance. The summary effect estimate suggested a negative effect but this did not reach statistical significance (WMD -0.46, 95% CI -0.96, 0.02; Figure 20). There was no evidence of heterogeneity across studies (I^2=0, p=0.89).

FIGURE 20. FOREST PLOT SHOWING WMD (95% CI) FOR BARTHEL INDEX OF ACTIVITIES OF DAILY LIVING FOR PARTICIPANTS TAKING CBM COMPARED TO PLACEBO



Four studies, three parallel group trials and one cross-over trial, evaluated walk time.[3, 5, 89, 190] The summary WMD based on the two parallel group trials was -0.86 (95% CI -3.08, 1.36, Figure 21) suggested no difference between treatment groups. There was moderate evidence of heterogeneity (I^2=52%, p=0.15). A sensitivity analysis that included the cross-over trial in the meta-analysis also showed no difference between groups (WMD -0.48, -2.13, 1.17; Figure 22). Other measures of mobility and disability were only reported in single trials (Table 24).

FIGURE 21: FOREST PLOT SHOWING WMD (95% CI) FOR WALK TIME FOR PARTICIPANTS TAKING CBM COMPARED TO PLACEBO IN THE PARALLEL GROUP STUDIES ONLY

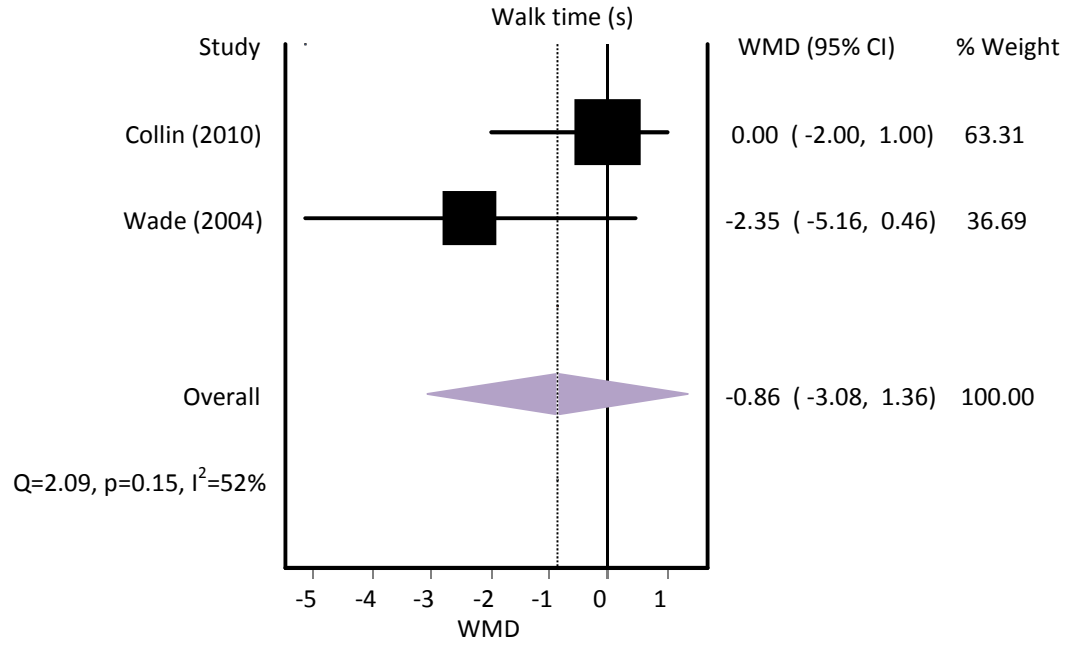
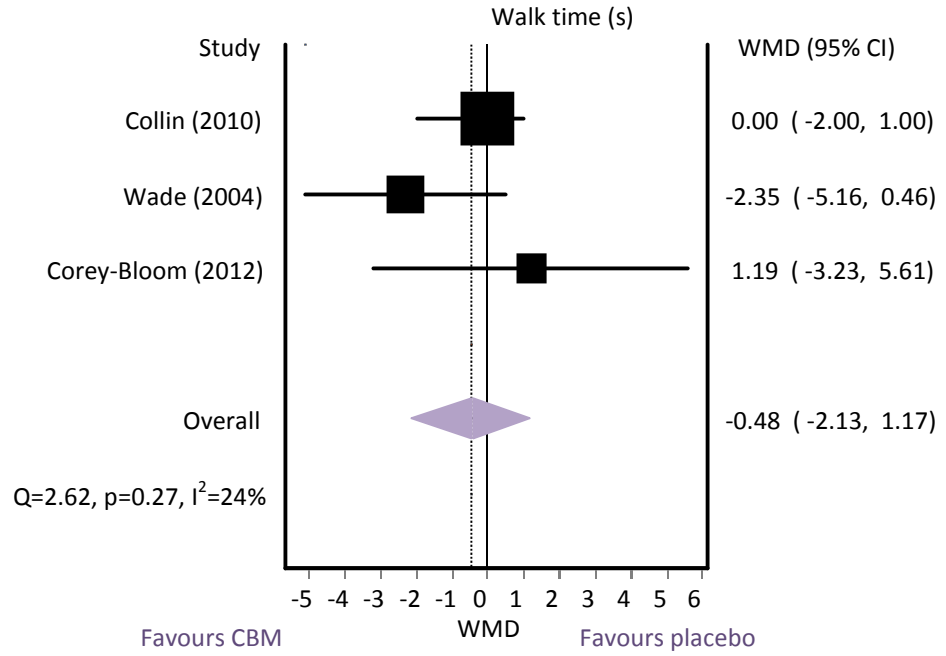


FIGURE 22: FOREST PLOT SHOWING WMD (95% CI) FOR WALK TIME FOR PARTICIPANTS TAKING CBM COMPARED TO PLACEBO IN ALL STUDIES (PARALLEL GROUP AND CROSS-OVER TRIALS)



General disease specific symptoms

General disease specific symptoms were not reported consistently across studies. There were therefore insufficient data to draw conclusions regarding the effect of CBM on these outcomes.

Global impression

Two cross-over studies[128, 193] evaluated patient global impression of change, however the scale used differed between studies and was unclear in one of the studies[193] so it was not possible to derive summary estimates for this outcome. A further two parallel group trials evaluated global impression using the general health questionnaire versions 12[3] and 30.[89] Studies generally suggested a positive effect of CBM but this did not reach statistical significance in most studies.

TABLE 24: RESULTS FOR CONTINUOUS OUTCOMES FROM STUDIES THAT EVALUATED CBM FOR SPASTICITY IN PATIENTS WITH MS AND PARAPLEGIA

Study Details	Intervention	Outcome	MD at follow-up	MD change from baseline:	p-value	Analysis Details
Spasticity:						
Berman (2007)[1]	Nabiximols	Ashworth (modified)		-0.14 (-0.33, 0.05)	0.142	ANCOVA
Collin (2007)[2]	Nabiximols	Ashworth		-0.11 (-0.29, 0.07)	0.218	ANCOVA
Collin (2010)[5]	Nabiximols	Ashworth (modified)		-0.16 (-1.94, 1.61)	0.857	ANCOVA
Killestein(2002)[193]	Dronabinol	Ashworth	-0.07 (-0.35, 0.21)		>0.05	Mixed linear model
	THC/CBD	Ashworth	-0.07 (-0.37, 0.23)		>0.05	Mixed linear model
Pooyania (2010)[128]	Nabilone	Ashworth (most involved muscle group)	**-0.91(-1.41, -0.41)**		0.003	Mann-Whitney/ Wilcoxon test
Vaney(2004)[192]	THC/CBD	Ashworth		-0.80 (-2.1, 0.5)	0.2379	Linear regression;
Wade (2004)[3]	Nabiximols	Ashworth (modified)	0.22 (-0.50, 0.94)	0.22 (-3.78, 4.22)	0.55	NR
Zajicek (2003)[89]	Dronabinol	Ashworth		**-0.94 (-1.83, -0.05)**		ANCOVA
	THC/CBD	Ashworth		-0.32 (-1.21, -0.57,)		
Berman (2007)[1]	Nabiximols	NRS (0-10)		0.07 (-0.61, 0.75)	0.830	ANCOVA
Collin (2007)[2]	Nabiximols	NRS (0-10)		**-0.52 (-1.029, -0.004)**	0.048	ANCOVA
Collin (2010)[5]	Nabiximols	NRS (0-10)		-0.23 (-0.59, 0.14)	0.220	ANCOVA
Langford (2013)[4]	Nabiximols	NRS (0-10)		-0.10	0.667	
Pooyania (2010)[128]	Nabilone	VAS score (0-100)	-9.09(-19.12, 0.94)		0.76	Mann-Whitney/ Wilcoxon test
Wade (2004)[3]	Nabiximols	VAS score (0-100)	**-22.79 (-35.52, -10.07)**		0.001	
Langford (2013)[4]	Nabiximols	Spasm severity (NRS)		-0.14	0.548	

Study Details	Intervention	Outcome	MD at follow-up	MD change from baseline:	p-value	Analysis Details
Berman (2007)[1]	Nabiximols	Spasm severeity (NRS)		0.05 (-0.54, 0.65)	0.860	ANCOVA
Collin (2010)[5]	Nabiximols	Spasm severity (NRS)		-0.01	0.955	ANCOVA
Zajicek (2012)[87]	THC/CBD	Spasm severity (NRS)	-0.70 (-1.35, -0.05	**-0.80 (-1.21, -0.39)**		
Collin (2007)[2]	Nabiximols	Spasm Frequency Scale		-0.17(-0.39, 0.06)	0.141	ANCOVA
Wade (2004)[3]	Nabiximols	Spasm Frequency Scale		-1.27(-16.90, 14.30)	0.869	ANCOVA
Pooyania (2010)[128]	Nabilone	Spasm Frequency Scale	0.0 (-0.11, 0.11)		0.369	Mann-Whitney/ Wilcoxon test
Corey-Bloom(2012)[190]	THC	Ashworth (modified) (Scores 0-30)	-2.53 (-4.08, -0.98)	-2.74 (-3.14, -2.20)		ANCOVA
Hagenbach(2003)[71]	Dronabinol	Ashworth (summed scores)	**-4.89**		0.001	NR
Pooyania (2010)[128]	Nabilone	Ashworth (Ashworth in 8 muscle groups)	**-2.55(-2.70, -2.40)**		0.001	Mann-Whitney/ Wilcoxon test
Wade (2004)[3]	Nabiximols	Spasm severity (Primary symptom VAS score)		-0.08 (-17.28, 17.11)	0.992	ANCOVA
Wade (2004)[3]	Nabiximols	Spasms	-5.30 (-19.81, 9.22)		0.464	
Berman (2007)[1]	Nabiximols	Percentage of days on which spasm was experienced		-0.64 (-0.856, 7.27)	0.873	ANCOVA
Berman (2007)[1]	Nabiximols	Percentage of days on which spasticity was experienced		0.4 (-4.08, 4.88)	0.860	ANCOVA
Collin (2007)[2]	Nabiximols	Motricity Index Score (Arms)		1.30 (-7.47, 10.07)	0.766	ANCOVA
Collin (2007)[2]	Nabiximols	Motricity Index Score (Legs)		3.86(-0.06, 7.78)	0.054	ANCOVA
Pooyania (2010)[128]	Nabilone	Wartenberg Pendulum Test (Rotational damping ratio, sitting)	-0.004(-0.21, 0.20)		0.6397	t-test
Pooyania (2010)[128]	Nabilone	Wartenberg Pendulum Test (Rotational natural frequency, sitting, pendulum variable)	0.498(-0.03, 1.02)		**0.018**	t-test
Zajicek (2012)[87]	THC/CBD	Multiple Sclerosis Spasticity Scale (MSSS-88) (Social functioning)	0.50 (-1.24, 2.24)	-0.20 (-1.15, 0.75)		

Study Details	Intervention	Outcome	MD at follow-up	MD change from baseline:	p-value	Analysis Details
Zajicek (2012)[87]	THC/CBD	MSSS-88 (Feelings)	0.20 (-2.64, 3.04)	-0.30 (-1.84, 1.24)		
Zajicek (2012)[87]	THC/CBD	MSSS-88 (Body movement)	-1.20 (-3.44, 1.04)	**-2.10 (-3.44, -0.76)**		
Zajicek (2012)[87]	THC/CBD	MSSS-88 (Ability to walk)	**-2.60 (-4.32, -0.88)**	**-1.60 (-2.31, -0.89)**		
Zajicek (2012)[87]	THC/CBD	MSSS-88 (Daily activities)	0.00 (-2.30, 2.30)	0.30 (-1.09, 1.69)		
Zajicek (2012)[87]	THC/CBD	MSSS-88 (Muscle spasms)	-1.40 (-4.13, 1.33)	**-3.10 (-4.66, -1.54)**		
Zajicek (2012)[87]	THC/CBD	MSSS-88 (Pain/discomfort)	-0.80 (-2.59, 0.99)	**-1.40 (-2.45, -0.35)**		
Zajicek (2012)[87]	THC/CBD	MSSS-88 (Muscle stiffness)	-2.40 (-4.61, -0.19)	**-3.70 (-5.04, -2.36)**		
QoL						
Collin(2010)[5]	Nabiximols	EQ-5D (Health state index)		0.02	0.175	ANCOVA
Langford (2013)[4]	Nabiximols	EQ-5D (EQ-5D health status index)		-0.01	0.396	
Collin (2010)[5]	Nabiximols	EQ-5D (Health status VAS score)		1.42	0.538	ANCOVA
Langford (2013)[4]	Nabiximols	EQ-5D (Health status VAS)		1.94	0.383	
Berman (2007)[1]	Nabiximols	MSQoL (Spitzer Quality of Life Index Score)	-0.04 (-0.49, 0.40)	0.00 (-0.33, 0.33)	0.847	ANCOVA
Collin (2010)[5]	Nabiximols	MSQoL (MSQoL-54 mental health composite)		-3.09	0.312	ANCOVA
Collin (2010)[5]	Nabiximols	MSQoL (MSQoL-54 (physical health composite))		-1.51	0.549	ANCOVA
Langford (2013)[4]	Nabiximols	SF36 (Role physical)		-0.89	0.694	
Langford (2013)[4]	Nabiximols	SF36 (Mental health)		-0.56	0.733	
Langford (2013)[4]	Nabiximols	SF36 (Role emotion)		-3.33	0.216	
Langford (2013)[4]	Nabiximols	SF36 (Social functioning)		**-5.75**	0.020	
Langford (2013)[4]	Nabiximols	SF36 (Vitality)		-2.75	0.095	
Langford (2013)[4]	Nabiximols	SF36 (Bodily pain)		1.35	0.494	
Langford (2013)[4]	Nabiximols	SF36 (Physical Functioning)		-0.45	0.785	
Langford (2013)[4]	Nabiximols	SF36 (General health)		-1.70	0.264	
Mobility/ Disability:						
Collin (2010)[5]	Nabiximols	Barthel Index of activities of daily living (ADL)		-0.15 (-1.95, 1.64)	0.867	ANCOVA

Study Details	Intervention	Outcome	MD at follow-up	MD change from baseline:	p-value	Analysis Details
Zajicek (2003)[89]	Dronabinol	Barthel Index of activities of daily living (ADL)	-0.73 (-2.33, 0.87)	0.23 (-0.13, 0.59)		
	THC/CBD	Barthel Index of activities of daily living (ADL)	-0.62 (-2.23, 0.99)	-0.03 (-0.39, 0.33)		
Wade (2004)[3]	Nabiximols	Barthel Index of activities of daily living (ADL)	-0.47 (-1.01, 0.07)		0.09	
Collin (2010)[5]	Nabiximols	Walk time (10m walk)		0.0 (-2, 1)	0.624	ANCOVA
Wade (2004)[3]	Nabiximols	Walk time (10m walk)	-2.35 (-5.16, 0.46)		0.07	Mann-Whitney/ Wilcoxon test
Corey-Bloom(2012)[190]	THC	Walk time (distance unclear)	1.19 (-3.23, 5.61)	1.20 (0.15, 4.31)		ANCOVA
Zajicek (2003)[89]	Dronabinol	Walk time (10m walk)	-1.01	-4.02		
Zajicek (2003)[89]	THC/CBD	Walk time (10m walk)	-1.01	-0.02		
Killestein(200 2)[193]	Dronabinol	Acitivities of daily living (VAS "walking score")	NR		0.08	Mixed linear model
Wade (2004)[3]	Nabiximols	Acitivities of daily living (Nine-hole peg test of manual dexterity)	-0.52 (-1.58, 0.55)		0.16	Mann-Whitney/ Wilcoxon test
Zajicek (2012)[87]	THC/CBD	Multiple sclerosis walking scale (MSWS-12) (Total score)	**-10.90 (-15.85, -5.95)**	**-7.30 (-9.40, -5.20)**		
Zajicek (2003)[89]	Dronabinol	UK neurological disability score	1.23 (-0.53, 2.99)	0.61 (-0.17, 1.39)		
Zajicek (2003)[89]	THC/CBD	UK neurological disability score	0.51 (-1.17, 2.19)	-0.35 (-1.13, 0.43)		
Zajicek (2003)[89]	Dronabinol	Rivermead Mobility Index	0.06 (-0.87, 0.99)	**0.19 (0.00, 0.38)**		
Zajicek (2003)[89]	THC/CBD	Rivermead Mobility Index	-0.18 (-1.09, 0.73)	0.01 (-0.18, 0.20)		
General disease specific symptoms:						
Corey-Bloom(2012)[190]	THC	Perceived deficits PDQ score (0-80)	2.07 (-3.70, 7.84)	1.70 (-3.23, 6.07)		ANCOVA
Corey-Bloom(2012)[190]	THC	Brief symptom inventory (BSI) score (0-208)	4.57 (-1.17, 10.31)	-2.87 (-9.63, 4.58)		ANCOVA
Wade (2004)[3]	Nabiximols	Guys Neurological Disability Scale (GNDS)	**1.81 (0.02, 3.60)**		0.048	
Wade (2004)[3]	Nabiximols	Primary Symptom Score (PSS)	-5.93 (-13.52, 1.65)		0.124	

Study Details	Intervention	Outcome	MD at follow-up	MD change from baseline:	p-value	Analysis Details
Zajicek (2012)[87]	THC/CBD	Muscle stiffness (11 point scale)	**-1.00 (-1.61, -0.39)**	**-1.10 (-1.51, -0.69)**		
Zajicek (2012)[87]	THC/CBD	Multiple Sclerosis Impact Scale (MSIS-29) (Psychological impact)	1.60 (-4.51, 7.71)	-2.50 (-6.36, 1.36)		
Zajicek (2012)[87]	THC/CBD	Multiple Sclerosis Impact Scale (MSIS-29) (Physical impact)	-3.80 (-9.50, 1.90)	**-5.90 (-9.03, -2.77)**		
Global impression						
Killestein(2002)[193]	Dronabinol	Patient global impression (scale unclear, negative indicates worsening)	**-266 (-485, -47)**		0.01	Mixed linear model
	THC/CBD	Patient global impression	**-238 (-467, -9)**		0.02	Mixed linear model
Pooyania (2010)[128]	Nabilone	Patient global impression (7 point scale)	0.49 (-0.17, 1.15)		0.312	Mann-Whitney/ Wilcoxon test
Pooyania (2010)[128]	Nabilone	Clinical global impression	0.18(-0.51, 0.87)		0.789	Mann-Whitney/ Wilcoxon test
Wade (2004)[3]	Nabiximols	General Health Questionnaire 12	0.72 (-2.38, 3.82)		0.65	
Zajicek (2003)[89]	Dronabinol	General Health Questionaire 30	0.75 (-1.65, 3.15)	-0.19 (-1.92, 1.54)		
Zajicek (2003)[89]	THC/CBD	General Health Questionaire 30	0.77 (-1.64, 3.18)	0.70 (-1.03, 2.43)		

5.2.4.4 Summary

Overall there was some evidence that CBM may improve spasticity and patient global impression of change, there was less evidence for an effect on other outcomes such as quality of life, mobility/disability and general disease specific symptoms. Studies generally suggested a beneficial effect of CBM on measures of spasticity but this failed to reach statistical significance in most studies. The summary estimate for the Ashworth scale based on parallel group trials suggested a significant beneficial effect of CBM on spasticity (Table 25). For other measures of spasticity also suggested a beneficial effect but did not reach statistical significance. Dichotomous data suggested a significant beneficial effect of CBM on patient global impression of change, this was supported by a further cross-over trial that provided continuous data for this outcome. There were no clear differences between the different types of CBM evaluated in these studies. Sensitivity analyses that included cross-over trials in the meta-analyses showed results consistent with those based on parallel group trials alone. There was no evidence of small study effect based on the Ashworth scale, the only outcome for which sufficient data were available to allow investigation of this.

TABLE 25: SUMMARY ESTIMATES FOR MS AND PARAPLEGIA PARALLEL GROUP TRIALS

Outcome	Number of studies	Summary estimate	Favours	I^2 (%)
≥50% reduction in spasticity NRS	2	OR=1.40 (0.81, 2.41)	CBM	0
≥30% reduction in spasticity NRS	2	OR=1.64 (0.95, 2.83)	CBM	44
Patient global impression of change	4	**OR=1.78 (1.12, 2.82)**	CBM	58
Ashworth spasticity scale	5	**WMD=-0.14 (-0.27, -0.01)**	CBM	0
NRS/VAS spasticity	4	WMD=-0.52 (-1.11, 0.07)	CBM	73
Barthel Index of ADL	3	WMD=-0.47 (-0.96, 0.02)	Placebo	0
Walk Time	3	WMD=-0.48 (-2.13, 1.17)	CBM	24

TABLE 26: GRADE SUMMARY OF FINDINGS TABLE: SPASTICITY DUE TO MULTIPLE SCLEROSIS OR PARAPLEGIA

CBM for spasticity due to multiple sclerosis or paraplegia

Patient or population: patients with spasticity due to multiple sclerosis or paraplegia
Settings: Not specified
Intervention: CBM

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk CBM				
30% reduction in spasticity symptoms 0-10 Numerical rating scale (NRS) Follow-up: 6-14 weeks[1]	**240 per 1000**	**307 per 1000** (204 to 433)	**OR 1.40** (0.81 to 2.41)	519 (2 studies[2])	⊕⊕⊖⊖ **low**[3]	
50% reduction in spasticity symptoms 0-10 Numerical rating scale (NRS) Follow-up: 6-14 weeks[1]	**103 per 1000**	**158 per 1000** (98 to 245)	**OR 1.64** (0.95 to 2.83)	519 (2 studies[2])	⊕⊕⊖⊖ **low**[3,4]	
Spasticity Ashworth score Follow-up: 3-15 weeks[5]	See comment	See comment		1244 (5 studies[6])	⊕⊕⊕⊖ **moderate**[7,8]	WMD -0.14 (95%-CI -0.27 to -0.01)
Spasticity: Treatment benefit (THC/CBD) Patient assessment of whether there was a treatment benefit Follow-up: 15 weeks	**460 per 1000**	**605 per 1000** (515 to 703)	**OR 1.8** (1.25 to 2.78)	395 (1 study[9])	⊕⊕⊕⊖ **moderate**[10,11]	
Spasticity: Treatment benefit (Dronabinol) Patient assessment of whether there was a treatment benefit Follow-up: 15 weeks	**460 per 1000**	**591 per 1000** (494 to 689)	**OR 1.7** (1.15 to 2.6)	379 (1 study[9])	⊕⊕⊕⊖ **moderate**[10,11]	
Global impression of change in symptoms Patient assessment Follow-up: 3-14 weeks[12]	**317 per 1000**[13]	**452 per 1000** (342 to 567)[13]	**OR 1.78** (1.12 to 2.82)	461 (4 studies[9])	⊕⊕⊖⊖ **low**[14,15]	
Any adverse events Follow-up: 6-15 weeks[16]	**712 per 1000**	**860 per 1000** (800 to 905)	**OR 2.48** (1.61 to 3.83)[17]	1300 (5 studies[18])	⊕⊕⊕⊖ **moderate**[19]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Collin 2007: 6 weeks, Collin 2010: 14 weeks
[2] Collin 2007, Collin 2010
[3] Risk of bias: Insufficient details on randomisation (Collin 2007), concealment of allocation (both studies) and blinding (Collin 2007)
[4] Imprecision: 2 studies including only 519 patients (<300 events)
[5] Berman 2007: 3 weeks; Collin 2007, Wade 2004: 6 weeks; Collin 2010: 14 weeks; Zajicek 2003: 15 weeks
[6] Berman 2007, Collin 2007, Collin 2010, Wade 2004, Zajicek 2003
[7] Risk of bias: Insufficient details on randomisation (Berman 2003, Collin 2007), concealment of allocation (all but Zajicek 2003) and blinding (Berman 2003, Collin 2007); high risk of incomplete outcome data (Berman 2007, Wade 2004)
[8] No evidence of small study effects (Egger test, p=0.437)
[9] Zajicek 2003
[10] Inconsistency: Not applicable (single study)
[11] Imprecision: Study included 657 patients (<300 events)
[12] Berman 2007: 3 weeks; Collin 2007, Wade 2004: 6 weeks; Langford 2013: 14 weeks
[13] Numbers of events and patients not reported for Langford 2013. Study reported an OR which is included in the pooled estimate.
[14] Risk of bias: Insufficient details on randomisation (Berman 2003, Collin 2007), concealment of allocation (all studies) and blinding (Berman 2003, Collin 2007); high risk of incomplete outcome data (Berman 2007, Wade 2004)
[15] Imprecision: 4 studies including only 461 patients (<300 events)
[16] Collin 2007, Wade 2004: 6 weeks; Collin 2010, Langford 2013: 14 weeks; Zajicek 2012: 15 weeks
[17] OR across all patient populations (29 studies): 3.03, 95%-CI 2.42 to 3.80 (see section 5.3 for details)
[18] Collin 2007, Collin 2010, Langford 2013. Wade 2004, Zajicek 2012
[19] Risk of bias: Insufficient details on randomisation (Collin 2007), concealment of allocation (all but Zajicek 2003) and outcome assessor blinding (Collin 2007); high risk of bias for incomplete outcome data.

5.2.5 Depression

No studies evaluating cannabis for the treatment of depression fulfilled inclusion criteria for the review. Additional searches were carried out for this population with lower levels of evidence eligible for inclusion. These searches did not locate any eligible studies.

Five studies included for other sections of this review reported on depression as an outcome measures.[3, 86, 139, 141, 144] Four of these studies evaluated patients with chronic pain[86, 139, 141, 144] and one was conducted in patients with MS.[3] Three studies[3, 86, 144] were parallel group trials and two were cross-over trials.[139, 141] Full details of these trials, including the results of the risk of bias assessment, are available in the appendices and the sections on chronic pain (section 5.2.3) and spasticity due to MS or paraplegia (section 5.2.4).

5.2.5.1 Continuous outcome results

The studies used different depression rating scales (MADS, HADS and BDI), in all scales a higher score indicated more severe depression and thus a negative MD favoured CBM while a positive MD favoured control. One of the cross-over trials reported data to calculate the MD change from baseline but did not provide any measure of variation or the statistical significance of the finding. Three studies (two parallel group trials and one cross-over trials) suggested no difference between CBM and placebo in depression outcomes (Table 27). One parallel group trial that compared different doses of nabiximols to placebo reported a negative effect of nabiximols for the highest dose (11-14 sprays per day) evaluated compared to placebo (MD from baseline 2.50, 95% CI 0.38, 4.62) but no difference compared to placebo for the two lower doses evaluated.[86]

TABLE 27: RESULTS FOR CONTINUOUS OUTCOMES FROM STUDIES THAT EVALUATED CBM FOR DEPRESSION

Study Details	Intervention	Outcome	MD at follow-up	MD change from baseline[$]:	p-value	Analysis Details
Depression outcomes reported in chronic pain/MS studies						
Portenoy (2012)[86] Parallel group	Nabiximols (1-4 sprays)	Depression (MADRS)		1.80 (-0.32, 3.92)		
	Nabiximols (6-10 sprays)			1.90 (-0.22, 4.02)		
	Nabiximols (11-14 sprays)			**2.50 (0.38, 4.62)**		
Narang(2008)[139] Cross-over	Dronabinol (10mg)	HADS depression score		-4.20		
	Dronabinol (20mg)			-2.00		
Frank (2008)[141] Cross-over	Nabilone	HADS depression score		-0.2 (1.20, 0.9)		
Rog(2005)[144] Parallel group	Nabiximols	HADS depression score		0.15 (-1.0, 1.31)		
Wade(2004)[3] Parallel group	Nabiximols	Beck Depression Inventory		0.69 (-0.76, 2.14)		

5.2.5.2 Summary

There was no data available on the CBM for the treatment of depression. Studies included for other sections of the review that reported on depression as an outcome found little evidence of an effect of CBM on depression.

TABLE 28: GRADE SUMMARY OF FINDINGS TABLE: DEPRESSION

CBM for depression

Patient or population: patients with depression
Settings: Not specified
Intervention: CBM

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Control**	Corresponding risk **CBM**				
Depression Montgomery–Åsberg depression scale (MADRS). Scale from: 0 to 54. Follow-up: 9 weeks		The mean depression in the intervention groups was **1.80 higher** (0.32 lower to 3.92 higher)[1]		182 (1 study[2])	⊕⊖⊖⊖ **very low**[3,4,5,6]	
Depression Beck Depression Inventory (BDI). Scale from: 0 to 63. Follow-up: 6 weeks		The mean depression in the intervention groups was **0.69 higher** (0.76 lower to 2.14 higher)		160 (1 study[7])	⊕⊖⊖⊖ **very low**[4,8,9,10]	
Depression Hospital Anxiety and Depression Scale (HADS). Scale from: 0 to 52. Follow-up: 5 weeks		The mean depression in the intervention groups was **0.15 higher** (1 lower to 1.31 higher)		66 (1 study[11])	⊕⊖⊖⊖ **very low**[4,9,12,13]	
Any adverse events Follow-up: 1-105 days[14]	**619 per 1000**	**831 per 1000** (797 to 860)	**OR 3.03** (2.42 to 3.80)	3489 (29 studies[15])	⊕⊕⊖⊖ **low**[16,17]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Results for 1-4 sprays nabiximols vs. placebo. Two more groups reported: 6-10 sprays vs. placebo (1.90 (-0.22 to 4.02)) and 11-14 sprays vs. placebo (2.50 (0.38 to 4.62))

[2] Portenoy 2012
[3] Risk of bias: Insufficient details on concealment of allocation and blinding
[4] Inconsistency: Not applicable (single study)
[5] Indirectness: Study included pain patients
[6] Imprecision: Study included only 182 patients
[7] Wade 2004
[8] Risk of bias: Insufficient details on concealment of allocation; high risk for incomplete outcome data.
[9] Indirectness: Study included MS/ paraplegia patients
[10] Imprecision: Study included only 160 patients
[11] Rog 2005
[12] Risk of bias: Insufficient details on concealment of allocation.
[13] Imprecision: Study included only 66 patients
[14] See Appendix 5 (Baseline details of included studies)
[15] Beal, 1995, Berman 2007, Chan 1987, Collin 2007, Collin 2010, Duran 2010, George 1983, GW Pharma Ltd 2005, GW Pharma Ltd 2012, Heim 1984, Hutcheon 1983, Johansson 1982, Karst 2003, Lane 1991, Langford 2013. Meiri 2004, Müller-Vahl 2001, Müller-Vahl 2003, Nurmikko 2007, Pomeroy 1986, Portenoy 2012, Rog 2005, Serpell 2014, Svendsen 2004, Timpone 1997, Tomida 2006, Ungerleider 1982, Wade 2004, Zajicek 2012
[16] See Appendix 8 (Results of the risk of bias assessment)
[17] Indirectness: Analysis of AEs across all patient populations, excluding anxiety, depression, psychosis and sleep disorders

5.2.6 Anxiety disorder

One parallel group trial evaluated patients with anxiety disorder (Table 29).[95] This study was conducted in patients with generalised social anxiety disorder in Brazil. Participants were randomised to receive either cannabidiol or placebo before taking part in a simulated public speaking test. A further four trials (three cross-over and one parallel group) conducted in patients with chronic pain evaluated anxiety as an outcome.[140, 141, 144] Full details of these trials, including the results of the risk of bias assessment, are available in the appendices and the section on chronic pain (section 5.2.3).

5.2.6.1 Risk of bias

This study was judged at high risk of bias (Table 30). The main limitation related to the method of randomisation and concealment of treatment allocation. The first participant were blindly allocated to one of the two treatment options available; the next participant (whose characteristics were matched to the first one's based on gender, age, years of education, and socioeconomic status) were assigned to the remaining treatment option. The study was judged to be at low risk of bias for participant blinding, incomplete outcome data, and selective outcome reporting; insufficient information was reported to judge outcome assessor blinding.

TABLE 29: OVERVIEW OF STUDY THAT EVALUATED CBM FOR ANXIETY

Study Details	Country	Design	N	Duration (weeks)*	Anxiety entry criterion	Intervention 1	Intervention 2	Comparator
Bergamaschi(2011)[95]	Brazil	Parallel group	24	Took place over public speaking event	Generalized Social Anxiety Disorder (SAD); ≥ 6 points on self-assessed short version of the Social Phobia Inventory named MINISPIN.	Cannabidiol (single dose of 600mg)		Placebo

TABLE 30: RISK OF BIAS IN ANXIETY STUDY

Study Details	RISK OF BIAS						
	Random sequence generation	Allocation concealment	Participant/ Personnel blinding	Outcome assessor blinding	Incomplete outcome data	Selective outcome reporting	Overall
Bergamaschi(2011)[95]	☹	☹	☺	?	☺	☺	☹

5.2.6.2 Dichotomous outcome results

The study did not report any dichotomous results.

5.2.6.3 Continuous outcome results

The study that enrolled patients with anxiety disorder reported a significant beneficial effect of cannabidiol compared to placebo on change from before to during a simulated public speaking test on the anxiety factor of a visual analogue mood scale (p=0.012; Table 31).[95] Four studies of patients with chronic pain also reported on anxiety as an outcome measure. It should be noted that these studies did not restrict inclusion based on symptoms of anxiety and so the included patients are not likely to have had an anxiety disorder. All four studies reported beneficial effects of CBM (nabilone, nabiximols or dronabinol) but this only reached statistical significance in one of the cross-over trials.[140] One of the cross-over trials reported results for two different doses of dronabinol compared to placebo. This study suggested a beneficial effect for the lower dose but a negative effect for the higher dose, however, neither result was statistically significant.

TABLE 31: RESULTS FOR CONTINUOUS OUTCOMES FROM STUDIES THAT EVALUATED CBM FOR ANXIETY

Study Details	Intervention	Outcome	MD at follow-up	MD change from baseline:	p-value	Analysis Details
Anxiety						
Bergamaschi(2011)[95] Parallel group	Cannabidiol	Visual analogue mood scale (VAMS): anxiety factor		**-16.52**	**0.012**	ANCOVA
Anxiety outcomes reported in chronic pain studies						
Frank (2008)[141] Cross-over	Nabilone	FIQ anxiety subscale	-0.6 (-1.4, 0.3)		0.19	
Narang(2008)[139] Cross-over	Dronabinol (10mg)	HADS anxiety		-2.6	>0.05	
	Dronabinol (20mg)			3.7	>0.05	
Rog(2005)[144] Parallel group	Nabiximols	HADS anxiety		-0.65 (-1.78, 0.47)	0.249	
Skrabeck(2008)[140] Cross-over	Nabilone	HADS anxiety		**-16.52**	**<0.02**	

*change from pre-test not baseline

5.2.6.4 Summary

There was very limited evidence on the treatment of anxiety disorder with CBM. One parallel group study that evaluated patients with social anxiety disorder reported beneficial effects of cannabidiol administered before a simulated public speaking test. However, this study was very small and was judged at high risk of bias and should be interpreted with caution. Additional data on anxiety outcomes provided by three studies (two cross-over and one parallel group) in patients with chronic pain also suggested a beneficial effect of CBM but these studies were not restricted to patients with anxiety disorders.

TABLE 32: GRADE SUMMARY OF FINDINGS TABLE: ANXIETY

CBM for anxiety disorder

Patient or population: patients with generalized Social Anxiety Disorder (SAD); ≥ 6 points on self-assessed short version of the Social Phobia Inventory named MINISPIN.
Settings: Not specified
Intervention: CBM (cannabidiol, single dose of 600mg)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Control**	Corresponding risk **CBM (cannabidiol, single dose of 600mg)**				
Anxiety Visual analogue mood scale (VAMS): anxiety factor[1]. Scale from: 0 to 100. Follow-up: 107 minutes		The mean anxiety in the intervention groups was **16.52 lower** (0 to 0 higher)[2]		24 (1 study[3])	⊕⊕⊖⊖ **low**[4,5,6]	
Any adverse events Follow-up: 1-105 days[7]	**619 per 1000**	**831 per 1000** (797 to 860)	**OR 3.03** (2.42 to 3.80)	3489 (29 studies[8])	⊕⊕⊖⊖ **low**[9,10]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Assessed during public speaking event
[2] Change from pre-test. No 95%-CI reported, p-value=0.012
[3] Bergamaschi 2011
[4] Risk of bias: High risk of bias for randomisation and allocation concealment
[5] Inconsistency: Not applicable (single study)
[6] Imprecision: Study included only 24 patients
[7] See Appendix 5 (Baseline details of included studies)
[8] Beal, 1995, Berman 2007, Chan 1987, Collin 2007, Collin 2010, Duran 2010, George 1983, GW Pharma Ltd 2005, GW Pharma Ltd 2012, Heim 1984, Hutcheon 1983, Johansson 1982, Karst 2003, Lane 1991, Langford 2013. Meiri 2004, Müller-Vahl 2001, Müller-Vahl 2003, Nurmikko 2007, Pomeroy 1986, Portenoy 2012, Rog 2005, Serpell 2014, Svendsen 2004, Timpone 1997, Tomida 2006,

Ungerleider 1982, Wade 2004, Zajicek 2012

[9] See Appendix 8 (Results of the risk of bias assessment)

[10] Indirectness: Analysis of AEs across all patient populations, excluding anxiety, depression, psychosis and sleep disorders

5.2.7 Sleep disorder

Two studies evaluated patients with sleep disorders (Table 33).[72, 133] One study enrolled patients with obstructive sleep apnoea syndrome[72] and one included patients with fibromyalgia; this study was also included in the section on chronic pain.[133] The study in patients with obstructive sleep apnoea compared to dronabinol to placebo and was conducted in the USA, it was reported only as an abstract and so only limited details were available.[72] The study in patients with fibromyalgia compared nabilone to amitriptyline and was conducted in Canada.[133] Study duration ranged from 2-3 weeks.

A further nineteen studies also reported outcomes related to sleep although did not restrict inclusion to participants with sleep disorders. Six of these studies were conducted in patients with MS[3, 5, 87, 89, 190, 192] and fourteen in patients with chronic pain.[1, 4, 77-82, 86, 135, 141, 144, 145] Full details of these trials, including the results of the risk of bias assessment, are available in the appendices and the sections on MS and paraplegia (section 5.2.4) and chronic pain (section 5.2.3).

5.2.7.1 Risk of bias

One study was judged at low risk of bias[133] the other at high risk of bias (Table 34). The study judged at high risk of bias was the one available only as a conference abstract.[72] The main limitation with this study related to incomplete outcome data. Only very limited details were reported and this included stratifying results according to the dose to which patients titrated. It was only possible to extract usable data for 8 participants who titrated to the maximum dose of 10mg. This study did not provide sufficient information to judge the risk of bias for most other domains.

TABLE 33: OVERVIEW OF STUDY THAT EVALUATED CBM FOR SLEEP DISORDERS

Study Details	Country	Design	N	Duration (weeks)	Sleep entry criterion	Intervention 1	Comparator
Prasad(2011}[72]	USA	Parallel group RCT	22	3	Obstructive sleep apnea syndrome	Dronabinol (Marinol); max 10mg/day	Placebo
Ware(2010)[132, 133, 149, 150]	Canada	Cross-over	32	2 (2 washout)	Chronic pain conditions (fibromyalgia)	Nabilone (Cesamet); 0.5mg/day	Amitriptyline: 10mg/day

TABLE 34: RISK OF BIAS IN SLEEP DISORDER STUDY

Study Details	RISK OF BIAS						
	Random sequence generation	Allocation concealment	Participant/ Personnel blinding	Outcome assessor blinding	Incomplete outcome data	Selective outcome reporting	Overall
Prasad(2011}[72]	?	?	?	?	☹	☺	☹
Ware(2010)[133]	☺	☺	☺	☺	☺	☺	☺

5.2.7.2 Dichotomous outcome results

Neither of the studies in patients with sleep disorders provided dichotomous results. One of the studies in patients with MS[87] evaluated sleep quality using a 0-10 NRS and provided information on the number of patients reporting an improvement in sleep (Table 35). A further study in MS patients by the same authors provided categorical data on sleep where patients rated their sleep as improved, the same or deteriorated.[89] We dichotomised this data to show the number of patients with improved sleep (Table 35). Both studies reported a significant improvement in sleep associated with THC/CBD compared to placebo (OR 2.1, 95% CI 1.2, 3.6 and OR 1.76, 95% CI 1.13, 2.73). There was also a suggestion of a beneficial effect of dronabinol but this was of borderline statistical significance (OR 1.54, 95% CI 0.98, 2.42).

TABLE 35: RESULTS FOR DICHOTOMOUS OUTCOMES FROM STUDIES THAT EVALUATED CBM FOR SLEEP DISORDERS

Study Details	Intervention	Outcome	Intervention Events/ n	Placebo Events/n	OR (95% CI)*
Sleep outcomes reported in MS study					
Zajicek(2012)[87] Parallel group	THC/CBD	Improvement in sleep quality	48/143	26/134	**2.1(1.2, 3.6)**
Zajicek (2003)[89]	THC/CBD	Improvement in sleep	82/164	59/163	**1.76 (1.13, 2.73)**
	Dronabinol		71/152	59/163	1.54 (0.98, 2.42)

5.2.7.3 Continuous outcome results

Sleep outcomes in studies that enrolled patients with sleep disorders

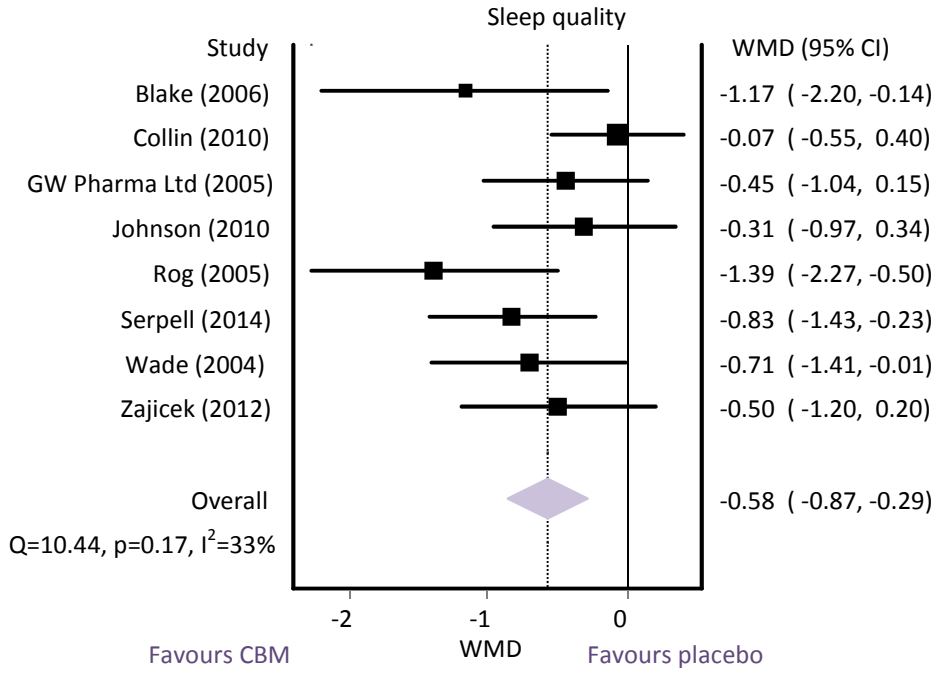
Both studies conducted in patients with sleep disorders reported continuous measures of sleep (Table 36).[72, 133] The parallel group study reported a significant improvement in the sleep apnoea/hypopnea index (-19.64, p=0.018) in patients receiving nabilone compared to those receiving placebo. The cross-over trial[133] compared nabilone with amitriptyline. This study found a significantly greater improvement in the insomnia severity index (MD -3.25, 95% CI -5.26, -1.24) during the nabilone treatment phase compared to the amitriptyline treatment phase. Amitriptyline was associated with greater restfulness of sleep as assessed by the Leeds Sleep Evaluation Questionnaire (LSEQ) (MD 0.48 (0.01, 0.95)).[214] There as a suggestion that speed and ease of getting to sleep were improved with cannabis compared to amitriptyline but these differences did not reach statistical significance.

Sleep outcomes in studies conducted in other populations

The most commonly reported measure was sleep quality assessed using a 0-10 NRS or 0-100 VAS scale (Table 36). We transformed the 0-100 VAS results to a 0-10 scale by dividing by 10 so that these were comparable to other studies evaluating this outcome. Ten studies, eight parallel group studies and two cross-over trials, evaluated sleep quality.[3-5, 77, 81, 82, 87, 144, 145, 192, 215] Most suggested improvements in sleep associated with CBM but this only reached statistical significance in three parallel group trials. One of the cross-over trials also reported a significant difference between both nabiximols and THC and placebo but it was unclear whether this favoured CBM or placebo.[145] The scale reported in the study

suggested that a positive MD (which the study reported) favoured placebo, however, the study reported that it had found improvements in sleep associated with CBM. Seven of the parallel group studies reported data in a format suitable for pooling. One of these evaluated both Nabiximols and THC and so the data for nabiximols were selected for pooling as this was the intervention most commonly evaluated by these trials: all except one evaluated nabiximols, this evaluated oral THC/CBD.[82] The summary estimate suggested a significant improvement in sleep quality associated with CBM (WMD -0.58, 95% CI -0.87, -0.29; Figure 23). There was little evidence of heterogeneity (I^2=33%, p=0.17). There was evidence of small study effects (p= 0.012).

FIGURE 23: FOREST PLOT SHOWING WMD (95% CI) FOR SLEEP QUALITY FOR PARTICIPANTS TAKING CBM COMPARED TO PLACEBO IN THE PARALLEL GROUP STUDIES ONLY



Five studies, four parallel group and one cross-over trial, evaluated changes in sleep disturbance.[1, 79, 80, 86] All but one reported reduced sleep disturbance associated with CBM, this reached statistical significance in two. Three parallel group studies reported sufficient data to pool studies. The summary estimate showed a significant beneficial effect in favour of CBM (WMD -0.26, 95% CI -0.52, 0.00, FIGURE 24). There was substantial evidence of heterogeneity (I^2=64%, p=0.06). Three studies, two parallel group studies and one cross-over trial, evaluated fatigue.[4, 5, 190] All found no differences between CBM and placebo. One study used the LSEQ and found significantly greater tiredness in the CBM group compared to placebo for the lowest dose of smoked THC evaluated (2.5%) but no difference between groups at higher doses, with a suggestion of a greater tiredness in placebo groups at the highest dose (9%). Two studies, one cross-over and one parallel group, evaluated quantity of sleep. Both showed no differences between groups (p=0.20).[3, 141]

FIGURE 24: FOREST PLOT SHOWING WMD (95% CI) FOR SLEEP DISTURBANCE FOR PARTICIPANTS TAKING CBM COMPARED TO PLACEBO IN THE PARALLEL GROUP STUDIES ONLY

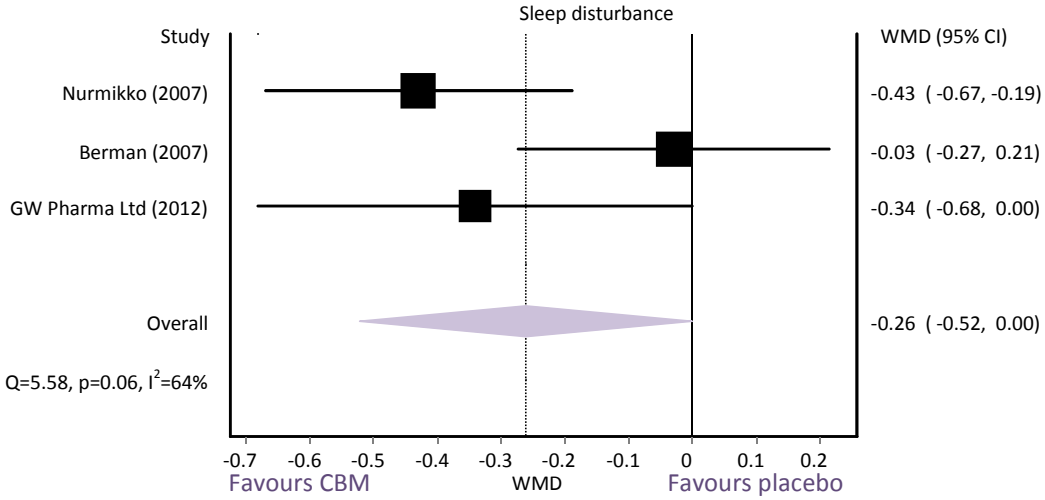


TABLE 36: RESULTS FOR CONTINUOUS OUTCOMES FROM STUDIES THAT EVALUATED CBM FOR SLEEP DISORDERS

Study Details	Intervention	Outcome	MD at follow-up	MD change from baseline[$]:	p-value	Analysis Details
Sleep:						
Prasad(2011)[7] [2] Parallel group	Dronabinol	Sleep Apnoea/hypopnea(AHI (apnea hypopnea index))		**-19.64**	**0.018**	NR
Ware(2010)[133] Cross-over	Nabilone	Insomnia severity index (ISI)()		**-3.25 (-5.26, -1.24)**		Linear regression
Ware(2010)[133] Cross-over	Nabilone	Leeds Sleep Evaluation Questionnaire (LSEQ)(Restfulness of sleep (100 mm VAS))		**0.48 (0.01, 0.95)**		Linear regression
Ware(2010)[133] Cross-over	Nabilone	Leeds Sleep Evaluation Questionnaire (LSEQ)(Speed of getting to sleep (100 mm VAS))		-0.70 (-1.36, 0.03)		Linear regression
Ware(2010)[133] Cross-over	Nabilone	Leeds Sleep Evaluation Questionnaire (LSEQ)(Ease of getting to sleep (100 mm VAS))		-0.70(-1.40, 0.02)		Linear regression

Study Details	Intervention	Outcome	MD at follow-up	MD change from baseline[$]:	p-value	Analysis Details
Sleep outcomes in studies that enrolled patienst with MS or Chronic Pain						
Corey-Bloom(2012)[190] Cross-over	THC	Fatigue (mFIS score (0-84))		-1.8 (-8.29, 3.56)		Ppaired t-test
Collin(2010)[5] Parallel group	Nabiximols	Fatigue(NRS)		0.35	0.185	ANCOVA
Langford (2013)[4] Parallel group	Nabiximols	Fatigue(NRS)		0.32	0.176	NR
Wade(2004)[3] Parallel group	Nabiximols	Feeling upon waking(VAS scale: Feeling upon waking)	-1.36 (-8.80, 6.07)		0.717	ANCOVA
Ware (2010)[135] Cross-over	THC (2.5%)	Leeds Sleep Evaluation Questionnaire (LSEQ)(Feeling now (tired - alert).	**-2.80(-3.76, -1.84)**			NR
	THC (6%)		0.80(-0.27, 1.87)			
	THC (9.4%)		-0.10(-1.06, 0.86)			
Rog(2005)[144] Parallel group	Nabiximols	Numerical rating scale(0-10)		**-1.39(-2.27, -0.5)**	**0.003**	ANCOVA
Collin(2010)[5] Parallel group	Nabiximols	Numerical rating scale(0-10)		-0.07(-0.55, 0.40)	0.734	ANCOVA
Serpell(2014)[81] Parallel group	Nabiximols	Numerical rating scale(0-10)		**-0.83(-1.43, -0.23)**	**0.007**	ANCOVA
GW Pharma Ltd(2012)[79] Parallel group	Nabiximols	Sleep disturbance(Sleep disturbance score (QoL))	-0.34(-0.68, 0.00)		0.052	ANCOVA
Nurmikko(2007)[80] Parallel group	Nabiximols	Sleep disturbance(NRS)		**-0.43(-0.67, -0.19)**	**0.001**	ANCOVA
Berman (2007)[1] Parallel group	Nabiximols	Sleep disturbance(NRS)		-0.03 (-0.27, 0.21)		NR
Vaney(2004)[192] Cross-over	THC/CBD	Sleep disturbance("Waking up again")		1.69(0.63, 4.59)	0.308	Linear regression
Berman(2004)[145] Cross-over	Nabiximols (Sativex)	Sleep disturbance(4-point-scale)		**-0.20(-0.37, -0.04)**	**0.017**	ANCOVA
	THC			**-0.30(-0.37, -0.04)**	**0.017**	

Study Details	Intervention	Outcome	MD at follow-up	MD change from baseline[$]:	p-value	Analysis Details
Portenoy(2012)[86] Parallel group	Nabiximols (1-4 sprays)	Sleep disturbance(Sleep disruption NRS)		**-2.5**	**0.003**	NR
	Nabiximols (6-10 sprays)			-0.10	0.260	
	Nabiximols(11-16 sprays)			0.10	0.784	
Wade(2004)[3] Parallel group	Nabiximols	Sleep quality(VAS scale: Quality of sleep)	**-7.1(-14.1, -0.08)**		**0.047**	ANCOVA
Blake(2006)[78] Parallel group	Nabiximols	Sleep quality(NRS (0-10))		**-1.17 (-2.20, -0.14)**	**0.027**	Linear regression
GW Pharma Ltd(2005)[77] Parallel group	Nabiximols	Sleep quality(NRS (0-10))		-0.45(-1.04, 0.15)	0.139	ANCOVA
Johnson(2010)[82] Parallel group	THC	Sleep quality(NRS (0-10))		0.02(-0.64, 0.68)	0.95	ANCOVA
	Nabiximols (Sativex)			-0.31(-0.97, 0.34)	0.346	
Vaney(2004)[192] Cross-over	THC/CBD	Sleep quality("Falling asleep fast")		2.13(0.95, 4.74)	0.073	Linear regression
Berman(2004)[145] Cross-over	Nabiximols (Sativex)	Sleep quality(Sleep Quality BS-11)		**0.60(0.09, 1.01)**	**0.019**	ANCOVA
	THC			**0.70(0.33, 1.24)**	**<0.001**	
Langford(2013)[4] Parallel group	Nabiximols (Sativex)	Sleep quality(NRS (0-10))		0.05	0.833	NR
Zajicek(2012)[87] Parallel group	THC/CBD	Sleep quality(11 point category rating scale)	-0.5(-1.20, 0.20)			NR
Wade(2004)[3] Parallel group	Nabiximols (Sativex)	Sleep quantity(VAS scale: How much sleep)	-4.53 (-11.45, 2.40)		0.198	ANCOVA
Frank(2008)[141] Cross-over	Nabilone (Cesamet)	Sleep quantity(number of hours slept per night)	0.20(-0.10, 0.5)		0.2	ANCOVA

5.2.7.4 Summary

Only two studies evaluated CBM in patients with sleep disorders. One was a very small parallel group study judged to be at high risk of bias. This study reported a significant beneficial effect of nabilone on the sleep apnoea/hypopnea index but this should be interpreted with some caution due to the methodological limitations associated with this study.[72] The other study in patients with sleep disorders was a cross-over trial in patients

with fibromyalgia and compared nabilone with amitriptyline.[133] This suggested some beneficial effects of nabilone on insomnia but greater sleep restfulness with amitriptyline.

Nineteen studies included for other populations (chronic pain and MS) also evaluated sleep as an outcome. Overall there was some evidence that CBM may improve sleep in these patient groups (Table 37). There were sufficient data to pool results for sleep quality and sleep disturbance, both suggested significant beneficial effects in favour of cannabis. There was evidence of small study effect based on sleep quality (p=0.012), the only outcome for which sufficient data were available to allow investigation of this.

TABLE 37: SUMMARY ESTIMATES FOR TRIALS THAT REPORTED SLEEP RELATED OUTCOMES

Outcome	Number of studies	Summary estimate	Favours	I^2 (%)
Sleep quality NRS/VAS	7	**WMD -0.58, 95% CI -0.87, -0.29**	CBM	33
Sleep disturbance	3	**WMD -0.26, 95% CI -0.52, 0.00**	CBM	64

TABLE 38: GRADE SUMMARY OF FINDINGS TABLE: SLEEP DISORDER

CBM for sleep disorder

Patient or population: patients with sleep disorder
Settings: Not specified
Intervention: CBM

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk CBM	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Sleep Apnoea/ hypopnea Apnea hypopnea index (AHI) Follow-up: 3 weeks		The mean sleep apnoea/ hypopnea in the intervention groups was **19.64 lower** (0 to 0 higher)[1]		22 (1 study[2])	⊕⊕⊖⊖ **low**[3,4,5]	
Sleep quality Numerical rating scale[6]. Scale from: 0 to 10. Follow-up: 2-15 weeks[7]	See comment	See comment		539 (8 studies[8])	⊕⊖⊖⊖ **very low**[9,10,11]	WMD -0.58 (95%-CI -0.87 to -0.29)
Sleep disturbance Numerical rating scale. Scale from: 0 to 10. Follow-up: 2-15 weeks[12]	See comment	See comment		1637 (3 studies[13])	⊕⊖⊖⊖ **very low**[9,14,15]	WMD -0.26 (95%-CI -0.52 to 0.0)
Any adverse events Follow-up: 1-105 days[16]	**619 per 1000**	**831 per 1000** (797 to 860)	**OR 3.03** (2.42 to 3.80)	3489 (29 studies[17])	⊕⊕⊖⊖ **low**[18,19]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] No 95 %-CI reported, p-value=0.018
[2] Prasad 2011
[3] Risk of bias: Insufficient details on randomisation, concealment of allocation and blinding; high risk of bias for incomplete outcome data

[4] Inconsistency: Not applicable (single study)
[5] Imprecision: Study included only 22 patients
[6] 0-10 or 0-100. 0-100 VAS results were transformed to a 0-10 scale by dividing by 10
[7] Johnson 2010: 2 weeks; Blake 2006, Rog 2005: 5 weeks; Wade 2004: 6 weeks; Zajicek 2012: 12 weeks; Collin 2010, GW Pharma Ltd 2005: 14 weeks; Serpell 2014: 15 weeks
[8] Blake 2006, Collin 2010, GW Pharma Ltd 2005, Johnson 2010, Rog 2005, Serpell 2014, Wade 2004, Zajicek 2012
[9] Risk of bias: Insufficient details on randomisation (Berman 2007, GW Pharma Ltd 2005), concealment of allocation (Berman 2007, GW Pharma Ltd 2005) and blinding (all three); high risk for allocation concealment (Nurmikko 2007) and incomplete outcome data (Berman 2007, GW Pharma Ltd 2005)
[10] Indirectness: Studies were conducted in patients with chronic pain (GW Pharma Ltd 2005, Nurmikko 2007) and chronic pain as well as MS/ paraplegia (Berman 2007)
[11] Evidence of small study effects (Egger test, p=0.012)
[12] Berman 2007: 3 weeks; Nurmikko 2007: 5 weeks; GW Pharma Ltd 2005: 14 weeks
[13] Berman 2007, GW Pharma Ltd 2012, Nurmikko 2007
[14] Inconsistency: I2=64%
[15] Indirectness: Studies were conducted in patients with chronic pain (Blake 2006, GW Pharma Ltd 2005, Johnson 2010, Rog 2005, Serpell 2014) and MS/ paraplegia (Collin 2010, Wade 2004, Zajicek 2012)
[16] See Appendix 5 (Baseline details of included studies)
[17] Beal, 1995, Berman 2007, Chan 1987, Collin 2007, Collin 2010, Duran 2010, George 1983, GW Pharma Ltd 2005, GW Pharma Ltd 2012, Heim 1984, Hutcheon 1983, Johansson 1982, Karst 2003, Lane 1991, Langford 2013. Meiri 2004, Müller-Vahl 2001, Müller-Vahl 2003, Nurmikko 2007, Pomeroy 1986, Portenoy 2012, Rog 2005, Serpell 2014, Svendsen 2004, Timpone 1997, Tomida 2006, Ungerleider 1982, Wade 2004, Zajicek 2012
[18] See Appendix 8 (Results of the risk of bias assessment)
[19] Indirectness: Analysis of AEs across all patient populations, excluding anxiety, depression, psychosis and sleep disorders

5.2.8 Psychosis

Two studies (9 reports, 71 participants) evaluated CBM as a treatment for psychosis.[75, 216-223] Both studies were conducted in Germany by the same group. One was a parallel group study (42 participants)[216] and the other used a cross-over design (29 participants).[75] Information on the cross-over trial was available only as conference abstract. Both studies enrolled patient with DSM-IV criteria of acute paranoid schizophrenia or schizophreniform psychosis and ≥36 in the BPRS total score. Both trials evaluated cannabidol (max dose 600-800mg/day), the parallel group study compared this to the active comparator Amisulpride[216] and the cross-over trial included a placebo control phase.[75]

5.2.8.1 Risk of bias

Both studies were judged at high risk of bias (Table 40). Neither provided sufficient information to judge whether allocation was concealed or whether the trial was appropriately blinded. The parallel group trials reported appropriate methods of randomisation but this information was not provided in the cross-over trial.[75] The cross-over trial was judged at high risk of bias for both incomplete outcome data and selective outcome reporting.[75] The parallel group trial was also judged at high risk of bias for selective outcome reporting.[216]

TABLE 39: OVERVIEW OF STUDIES THAT EVALUATED CBM PSYCHOSIS

Study Details	Country	Design	N	Duration (weeks)*	Psychosis entry criterion	Intervention 1	Intervention 2	Comparator
Leweke (2012)[75, 216-220]	Germany	Parallel group	42	4	DSM-IV criteria of acute paranoid schizophrenia or schizophreniform psychosis; ≥36 in the BPRS total score and	Cannabidiol (max 800mg/day)		Amisulpride (max 800mg/day)
Rohleder(2012)[75, 220-223]	Germany	**Cross-over**	**29**	2 (each period, washout NR)	DSM-IV criteria of acute paranoid schizophrenia or schizophreniform psychosis; ≥36 in the BPRS total score and	Cannabidiol (max 600mg/day)		Placebo

TABLE 40: RISK OF BIAS IN PSYCHOSIS STUDIES

Study Details	RISK OF BIAS						
	Random sequence generation	Allocation concealment	Participant/ Personnel blinding	Outcome assessor blinding	Incomplete outcome data	Selective outcome reporting	Overall
Leweke (2012)[216]	☺	?	?	?	☺	☹	☹
Rohleder(2012)[75]	?	?	?	?	☹	☹	☹

5.2.8.2 Dichotomous outcome results

The study did not report any dichotomous results.

5.2.8.3 Continuous outcome results

Both trials evaluated mood as assessed using the PANSS scale (Table 41). Both reported that there was no significant difference between treatment arms.[75, 216] The parallel group also assessed mental health using the brief psychiatric rating scale and found no difference in outcome between those randomised to cannabidiol and those randomised to amisulpride.

TABLE 41: RESULTS FOR CONTINUOUS OUTCOMES FROM STUDIES THAT EVALUATED CBM FOR PSYCHOSIS

Study Details	Intervention	Outcome	MD at follow-up	MD change from baseline[$]:	p-value	Analysis Details
Psychological measurements						
Leweke(2008)[216] Parallel group	Cannabidiol	Mental health (Brief Psychiatric Rating Scale)		-0.10(-9.20, 8.90)	0.977	
		Mood (PANSS (positive and negative syndrome scale))		1(-12.60, 14.60)	0.884	
Rohleder(2012)[75] Cross-over	Cannabidiol	Mood (PANSS (positive and negative syndrome scale))		2.40 (-3.48, 8.28)	NR	

5.2.8.4 Summary

There was very little data available on the treatment of psychosis with CBM. Two trials, a parallel group trial comparing cannabidiol to amisulpride and a cross-over trial comparing cannabidiol to placebo found no difference in outcomes between treatment groups.

TABLE 42: GRADE SUMMARY OF FINDINGS TABLE: PSYCHOSIS

CBM for psychosis

Patient or population: patients with psychosis
Settings: Not specified
Intervention: CBM (cannabidiol, max. 800 mg/day)
Comparison: Amisulpride (max. 800 mg/day)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Amisulpride (max. 800 mg/day)**	Corresponding risk **CBM (cannabidiol, max. 800 mg/day)**				
Mental health Brief Psychiatric Rating Scale Follow-up: 4 weeks		The mean mental health in the intervention groups was **0.10 lower** (9.2 lower to 8.9 higher)[1]		35 (1 study[2])	⊕⊕⊖⊖ **low**[3,4,5]	
Mood Positive and negative syndrome scale (PANSS). Scale from: 30 to 210. Follow-up: 4 weeks		The mean mood in the intervention groups was **1.0 higher** (12.6 lower to 14.6 higher)[6]		35 (1 study[2])	⊕⊕⊖⊖ **low**[3,4,5]	
Any adverse events Follow-up: 1-105 days[7]	**619 per 1000**	**831 per 1000** (797 to 860)	**OR 3.03** (2.42 to 3.80)	3489 (29 studies[8])	⊕⊕⊖⊖ **low**[9,10]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] p-value=0.977
[2] Leweke 2012
[3] Risk of bias: Insufficient details on concealment of allocation and blinding; high risk of bias for selective outcome reporting.
[4] Inconsistency: Not applicable (single study)
[5] Imprecision: Study included only 42 patients
[6] p-value=0.884

[7] See Appendix 5 (Baseline details of included studies)
[8] Beal, 1995, Berman 2007, Chan 1987, Collin 2007, Collin 2010, Duran 2010, George 1983, GW Pharma Ltd 2005, GW Pharma Ltd 2012, Heim 1984, Hutcheon 1983, Johansson 1982, Karst 2003, Lane 1991, Langford 2013. Meiri 2004, Müller-Vahl 2001, Müller-Vahl 2003, Nurmikko 2007, Pomeroy 1986, Portenoy 2012, Rog 2005, Serpell 2014, Svendsen 2004, Timpone 1997, Tomida 2006, Ungerleider 1982, Wade 2004, Zajicek 2012
[9] See Appendix 8 (Results of the risk of bias assessment)
[10] Indirectness: Analysis of AEs across all patient populations, excluding anxiety, depression, psychosis and sleep disorders

5.2.9 Glaucoma

One cross-over trial (6 participants) evaluated CBM for the treatment of glaucoma (Table 43).[224] It included patients with ocular hypertension or early open angle glaucoma, with a mild visual defect in at least one eye. The study compared THC (5mg), cannabidiol (20mg), cannabidiol (40mg) and placebo all in the form of an oromucosal spray.

5.2.9.1 Risk of bias

The study was judged at uncler risk of bias (Table 44). Insufficient information was provided to judge whether appropriate methods were used for randomisation, allocation conealment, and blinding. The study was judged at low risk of bias for incomplete outcome data and selective outcome reporting.

5.2.9.2 Dichotomous outcome results

The study did not report any dichotomous results.

5.2.9.3 Continuous outcome results

The trial evaluated intraocular pressure and found no differences between any of the treatment arms and placebo (Table 45).

5.2.9.4 Summary

Only one very small cross-over trial was evalauted CBM for the treatment of glaucoma. This study found no evidence of an effect of CBM on intraocular pressure.

TABLE 43: OVERVIEW OF STUDIES THAT EVALUATED CBM IN PATIENTS WITH GLAUCOMA

Study Details	Country	Design	N	Duration	Glaucoma entry criterion	Intervention 1	Intervention 2	Intervention 2	Comparator
Tomida(2006) [224]	UK	Cross-over	6	12 hours	Ocular hypertension or early open angle glaucoma, with mild visual defect in at least one eye	THC oromucosal spray (5mg)	Cannabidiol oromucosal spray (20 mg)	Cannabidiol oromucosal spray (40 mg)	Placebo

TABLE 44: RISK OF BIAS IN GLAUCOMA STUDIES

Study Details	RISK OF BIAS						
	Random sequence generation	Allocation concealment	Participant/ Personnel blinding	Outcome assessor blinding	Incomplete outcome data	Selective outcome reporting	Overall
Tomida(2006)[224]	?	?	?	?	☺	☺	?

TABLE 45: RESULTS FOR CONTINUOUS OUTCOMES FROM STUDIES THAT EVALUATED CBM FOR GLAUCOMA

Study Details	Intervention	Outcome	MD at follow-up	p-value	Analysis Details
Spasticity:					
Tomida(2006) [224] Cross-over	THC (5mg)	Intraocular pressure (Average of both eyes per patient)	-0.58 (-5.39, 4.23)		
	Cannabidiol (20 mg)		0.12 (-5.09, 5.33)		
	Cannabidiol (40 mg)		-0.25 (-5.23, 4.73)		

TABLE 46: GRADE SUMMARY OF FINDINGS TABLE: GLAUCOMA

CBM for glaucoma

Patient or population: patients with glaucoma
Settings: Not specified
Intervention: CBM

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk **Control**	Corresponding risk **CBM**				
Any adverse events Follow-up: 12 hours	**333 per 1000**	**500 per 1000** (87 to 912)	**OR 2.00** (0.19 to 20.61)[1]	12 (1 study)	⊕⊖⊖⊖ **very low**[2,3,4]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] OR across all patient populations (29 studies): 3.03, 95%-CI 2.42 to 3.80 (see section 5.3 for details)
[2] Risk of bias: Insufficient details on randomisation, concealment of allocation and blinding
[3] Inconsistency: Not applicable (single study)
[4] Imprecision: Study included only 42 patients (cross-over design)

5.2.10 Movement disorders due to Tourette syndrome

Two studies (four publications, 36 participants) evaluated CBM for the treatment of movement disorders due to Tourette syndrome (Table 47).[225-228] Both studies were conducted in Germany by the same group. One was a parallel group trial (24 participants)[225] and the other used a cross-over design (12 participants).[227] Both trials compared THC capsules (maximum dose 10mg/day) to placebo.

5.2.10.1 Risk of bias

The parallel group study was judged at high risk of bias[225] and the cross-over trial at unclear risk of bias (Table 48).[227] Insufficient information was provided to judge whether appropriate methods were used for randomisation and allocation concealment. Both studies were judged to have used appropriate methods to blind patients and study personnel to treatment group and the parallel group study was also judged as having used appropriate methods to blind outcome assessors; details on this were not provided in the cross-over trial. Both were judged at low risk of bias for selective outcome reporting. The parallel group study was judged at high risk of bias as the modified ITT analyses conducted excluded results for 7/24 randomised participants.

TABLE 47: OVERVIEW OF STUDIES THAT EVALUATED CBM IN PATIENTS WITH TOURETTE SYNDROME

Study Details	Country	Design	N	Duration (weeks)	Tourette's entry criteria	Intervention 1	Comparator
Müller-Vahl(2003)[225, 226]	Germany	Parallel group	24	6	Tourettes syndrome DSM-III R criteria	THC capsules (max dose 10mg)	Placebo
Müller-Vahl (2001)[227, 228]	Germany	Cross-over	12	2 days	Tourettes syndrome DSM-III R criteria	THC capsules (max dose 10mg)	Placebo

TABLE 48: RISK OF BIAS IN TOURETTE SYNDROME STUDIES

Study Details	RISK OF BIAS						
	Random sequence generation	Allocation concealment	Participant/ Personnel blinding	Outcome assessor blinding	Incomplete outcome data	Selective outcome reporting	Overall
Müller-Vahl(2003)[225]	?	?	☺	☺	☹	☺	☹
Müller-Vahl (2001)[227]	?	?	☺	?	☺	☺	?

5.2.10.2 Dichotomous outcome results

The studies did not report any dichotomous results.

5.2.10.3 Continuous outcome results

Both studies used the same four scales to assess tic severity (Table 49); on each of these scale a high score indicates more severe tics therefore a negative MD favours CBM. The parallel group study reported data to calculate MD in change from baseline but did not provide sufficient data to allow calculation of confidence limits around these estimates. However, it did report p-values for the Mann-Whitney/Wilcoxon test comparing change from baseline between group. There was a statistically significant benefical effect of CBM on tick severity on three of the four measures evaluated ($p<0.05$); the four measure was of borderline statistical significance ($p=0.061$).[225] The cross-over trial reported sufficient data to caluclated the MD in change form baseline for the same four outcomes and reported a statistically signficiant benefical effect on all four outcomes. It also assessed one additional outcome, obsessive compulsive behaviours, but found no difference in follow-up results between groups.[227]

TABLE 49: RESULTS FOR CONTINUOUS OUTCOMES FROM STUDIES THAT EVALUATED CBM FOR TOURETTE SYNDROME

Study Details	Intervention	Outcome	MD at follow-up	MD change from baseline	p-value	Analysis Details
General disease specific symptoms						
Müller-Vahl(2003)[225, 226] Parallel group	THC capsule	Tic severity (Shapiro Tourette Syndrome Severity Scale (STSSS))		**-0.70**	**0.033**	Mann-Whitney/ Wilcoxon test
Müller-Vahl(2003)[225, 226] Parallel group	THC capsule	Tic severity (Tourette syndrome symptom list (tic rating) TSSL)		**-16.2**	**<0.05**	Mann-Whitney/ Wilcoxon test
Müller-Vahl(2003)[225, 226] Parallel group	THC capsule	Tic severity (Yale Global Tic Severity Scale (YGTSS))		-12.03	0.061	Mann-Whitney/ Wilcoxon test
Müller-Vahl(2003)[225, 226] Parallel group	THC capsule	Tic severity (Tourettes syndrome clinical global impression scale (TS-CGI))		**-0.57**	**0.008**	Mann-Whitney/ Wilcoxon test
Müller-Vahl, (2001)[227]Cross -over	THC capsule	Tic severity (Tourette's syndrome symptoms list (TSSL) - Global score)		**-9.08 (-12.87, -5.29)**		
Müller-Vahl, (2001)[227]Cross -over	THC capsule	Tic severity (Shapiro Tourette's syndrome severity scale)		**-0.67 (-1.04, -0.30)**		

Study Details	Intervention	Outcome	MD at follow-up	MD change from baseline	p-value	Analysis Details
Müller-Vahl, (2001)[227]Cross -over	THC capsule	Tic severity (Tourette's syndrome global scale (TSGS))		**-6.50 (-10.76, -2.24)**		
Müller-Vahl, (2001)[227]Cross -over	THC capsule	Tic severity (Yale global tic severtiy scale (YGTSS)- perfomed by an examiner)		**-6.50 (-11.66, -1.34)**		
Müller-Vahl, (2001)[227]Cross -over	THC capsule	Obsessive compulsive behaviours (OCB), (SCL-90-R checklist)	4.40 (-4.49, 13.29)			

5.2.10.4 Summary

Two small studies, one parallel group and one cross-over trial, suggested that THC capsules may be associated with a significant improvement in tic severity.

TABLE 50: GRADE SUMMARY OF FINDINGS TABLE: MOVEMENT DISORDERS DUE TO TOURETTE SYNDROME

CBM for movement disorders due to Tourette syndrome

Patient or population: patients with Movement disorders due to Tourette syndrome
Settings: Not specified
Intervention: CBM

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk CBM	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Tic severity Shapiro Tourette Syndrome Severity Scale (STSSS). Scale from: 0 to 6. Follow-up: 6 weeks		The mean tic severity in the intervention groups was **0.70 lower** (0 to 0 higher)[1]		17 (1 study[2])	⊕⊕⊖⊖ **low**[3,4,5]	
Tic severity Tourette syndrome symptom list (TSSL) - tic rating Follow-up: 6 weeks		The mean tic severity in the intervention groups was **16.2 lower** (0 to 0 higher)[6]		17 (1 study[2])	⊕⊕⊖⊖ **low**[3,4,5]	
Tic severity Yale Global Tic Severity Scale (YGTSS). Scale from: 0 to 100. Follow-up: 6 weeks		The mean tic severity in the intervention groups was **12.03 lower** (0 to 0 higher)[7]		18 (1 study[2])	⊕⊕⊖⊖ **low**[3,4,5]	
Tic severity Tourettes syndrome clinical global impression scale (TS CGI). Scale from: 0 to 6. Follow-up: 6 weeks		The mean tic severity in the intervention groups was **0.57 lower** (0 to 0 higher)[8]		17 (1 study[2])	⊕⊕⊖⊖ **low**[3,4,5]	
Any adverse events Follow-up: 2-42 days[9]	**217 per 1000**	**489 per 1000** (202 to 784)	**OR 3.45** (0.91 to 13.08)[10]	44 (2 studies[11])	⊕⊖⊖⊖ **very low**[12,13]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] No 95 %-CI reported, p-value=0.033
[2] Müller-Vahl 2003
[3] Risk of bias: Insufficient information on randomisation and allocation concealment; high risk for incomplete outcome data
[4] Inconsistency: Not applicable (single study)
[5] Imprecision: Study included only 24 patients
[6] No 95 %-CI reported, p-value<0.05
[7] No 95 %-CI reported, p-value=0.061
[8] No 95 %-CI reported, p-value=0.008
[9] Müller-Vahl 2001: 2 days; Müller-Vahl 2003: 6 weeks
[10] OR across all patient populations (29 studies): 3.03, 95%-CI 2.42 to 3.80 (see section 5.3 for details)
[11] Müller-Vahl 2001, Müller-Vahl 2003
[12] Risk of bias: Insufficient details on randomisation (both studies), concealment of allocation (both studies) and blinding (Müller-Vahl 2001); high risk of bias for incomplete outcome data (Müller-Vahl 2003)
[13] Imprecision: 2 studies including 44 patients (16 events)

5.3 RESULTS OF ADVERSE EVENTS REVIEW

5.3.1 Short-term adverse events

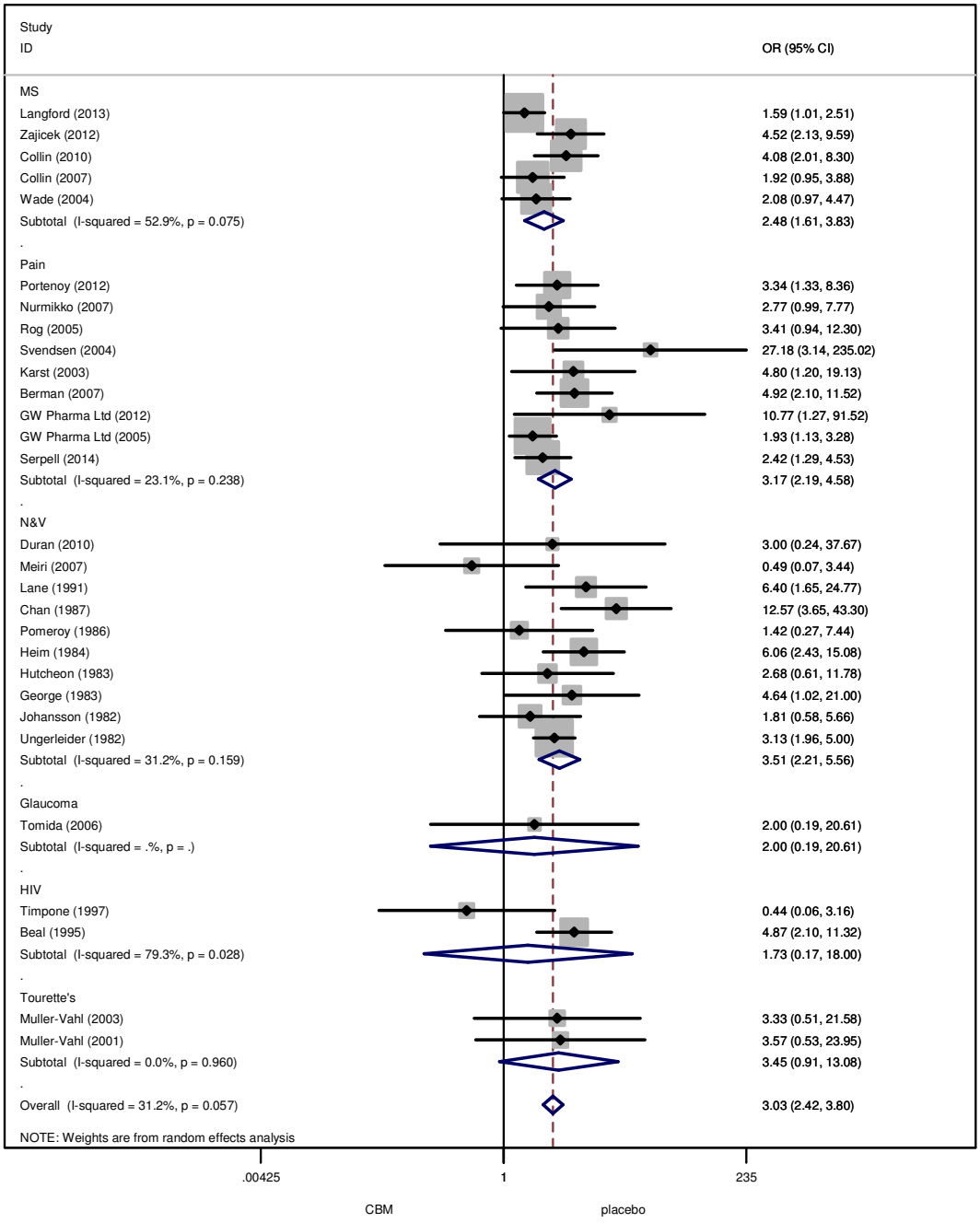
Sixty-two of the 76 studies included in the clinical effectiveness review provided dichotomous data on the number of participants in each intervention group who experienced various short term adverse events.[1-5, 72-74, 77-93, 96, 97, 99, 100, 102-106, 109-113, 117, 123, 124, 128, 133-135, 138-148, 190, 192, 224, 225, 227]

Thirty-one studies evaluated the number of participants experiencing at least one adverse event. We pooled data for all studies to investigate the associated between CBM use and experiencing any adverse events. We used meta-regression to investigate the influence of study design (parallel group vs cross-over trial), population (each of the population categories included in this report), comparator (active vs placebo), method of cannabis administration (oral, oromucosal spray, smoked or vapourised) and duration of follow-up (<24 hours, 24hours-1 week, 1-4 weeks, >4 weeks). We also performed stratified meta-analysis. None of the variables showed a significant association with effect of cannabis on adverse events (p>0.05). Stratified analysis showed similar pooled estimates the different subgroups investigated (Table 51). Figure 25 shows the OR for any adverse event among participants taking CBM compared to placebo or active comparison stratified according to population category.

TABLE 51: SUMMARY ESTIMATES FROM STRATIFIED META-ANALYSES FOR NUMBER OF PARTICIPANTS EXPERIENCING ANY AE IN THOSE TAKING CBM COMPARED TO THOSE TAKING PLACEBO OR ACTIVE COMPARISON

Variable	Category	Number of studies	Summary OR (95% CI)	I^{2} (%)
Study design	Parallel	20	2.66 (2.09, 3.38)	24.3
	Cross-over	9	4.37 (2.78, 6.87)	31.2
Comparator	Placebo	20	2.82 (2.21, 3.61)	24.9
	Active	9	3.50 (2.12, 5.76)	40.3
Duration of follow-up	<24 hours	5	3.53 (2.40, 5.17)	0.0
	1-4 weeks	10	4.11 (2.07, 8.15)	42.4
	>4 weeks	14	2.64 (2.05, 3.39)	28.9
Administration	Oral	13	3.57 (2.30, 5.55)	41.1
	IM	3	4.80 (2.41, 9.57)	0.0
	Oromucosal spray	13	2.37 (1.90, 2.94)	0.2
OVERALL		29	3.03 (2.42, 3.80)	31.2

FIGURE 25: FOREST PLOT SHOWING INDIVIDUAL STUDY RESULTS AND SUMMARY ESTIMATES FROM STRATIFIED META-ANALYSES FOR NUMBER OF PARTICIPANTS EXPERIENCING ANY AE IN THOSE TAKING CBM COMPARED TO THOSE TAKING PLACEBO OR ACTIVE COMPARISON



As the primary adverse event analysis based on the number of participants experiencing any adverse events showed no difference in the effects of cannabis on adverse events based on study design, population, comparator, method of cannabis administration or duration of follow-up, further analysis were conducted for data from all studies combined. Table 52 shows summary estimates for each of the AEs assessed. CBM was associated with a significantly greater risk of serious AEs (Figure 26), withdrawals due to AE, ear and labyrinth

disorders, gastrointestinal disorders, general disorders and administration site conditions, metabolism and nutrition disorders, psychiatric disorders, renal and urinary disorders, asthenia, balance problems, confusion, diarrhoea, disorientation, drowsiness, dry mouth, euphoria, fatigue, hallucination, nausea, somnolence, and vomiting. Other AEs did not show significant differences between groups.

TABLE 52: SUMMARY ESTIMATES FROM META-ANALYSES FOR EACH ADVERSE EVENT ASSESSED SHOWING ORS FOR PARTICIPANTS EXPERIENCING AE IN THOSE TAKING CBM COMPARED TO THOSE TAKING PLACEBO OR ACTIVE COMPARISON

Adverse event	Number of studies	Summary OR (95% CI)	I^{2} (%)
General AE categories			
Any AE	29	**3.03 (2.42, 3.80)**	31.2
Serious AE	33	**1.44 (1.06, 1.96)**	0
Withdrawal due to AE	23	**2.73 (1.99, 3.73)**	29
MedDRA high level grouping[61]			
Blood disorders	3	1.42 (0.20, 10.25)	0
Cardiac disorders	7	1.42 (0.58, 3.48)	18
Death	5	1.01 (0.51, 2.00)	0
Ear and labyrinth disorders	3	**2.72 (1.55, 4.75)**	0
Gastrointestinal disorders	10	**1.78 (1.43, 2.22)**	0
General disorders and administration site conditions	6	**1.78 (1.34, 2.36)**	0
Hepatobiliary disorders	11	3.07 (0.12, 76.29)	NA
Infections and infestations	7	1.13 (0.87, 1.46)	0
Injection site pain	1	2.49 (0.92, 6.68)	NA
Injury, poisoning & procedural complications	3	1.18 (0.48, 2.93)	0
Investigations	2	1.55 (0.36, 6.71)	0
Mental status change	3	2.49 (0.49, 12.64)	0
Metabolism and nutrition	2	**2.37 (1.00, 5.61)**	0
Musculoskeletal and connective tissues disorders	7	1.32 (0.75, 2.32)	34
Neoplasms, benign, malignant & unspecified	2	0.99 (0.47, 2.08)	0
Nervous system disorders	10	**3.17 (2.20, 4.58)**	46
Other body systems	1	2.59 (0.34, 19.47)	NA
Psychiatric disorders	8	**3.10 (1.81, 5.29)**	55
Renal and urinary disorders	3	**2.45 (2.27, 2.65)**	NA
Reproductive system	1	1.55 (0.20, 11.92)	0
Respiratory, thoracic, and mediastinal disorders	5	0.80 (0.46, 1.39)	0
Skin & subcutaneous	3	0.85 (0.34, 2.13)	24
Individual AEs			
Anxiety	12	1.98 (0.73, 5.35)	54
Asthenia	14	**1.88 (1.26, 2.79)**	0
Balance	6	**2.62 (1.12, 6.13)**	31
Confusion	13	**4.03 (2.05, 7.97)**	0
Depression	15	1.32 (0.87, 2.01)	0
Diarrhoea	17	**1.65 (1.04, 2.62)**	15
Disorientation	12	**5.41 (2.61, 11.19)**	0
Dizziness	41	**5.09 (4.10, 6.32)**	18
Drowsiness	18	**3.68 (2.24, 6.01)**	44
Dry mouth	36	**3.50 (2.58, 4.75)**	28

Adverse event	Number of studies	Summary OR (95% CI)	I^{2} (%)
Dyspnea	4	0.83 (0.26, 2.63)	0
Euphoria	28	**3.65 (2.00, 6.69)**	35
Eye disorders	1	1.42 (0.46, 4.33)	NA
Fatigue	20	**2.00 (1.54, 2.62)**	0
Hallucination	10	**2.19 (1.02, 4.68)**	0
Nausea	30	**2.08 (1.63, 2.65)**	0
Paranoia	4	2.05 (0.42, 10.10)	0
Psychosis	2	1.09 (0.07, 16.35)	25
Seizures	2	0.91 (0.05, 15.66)	0
Somnolence	25	**2.97 (2.14, 4.12)**	24
Vomiting	17	**1.67 (1.13, 2.47)**	0
Weakness	1	7.24 (0.36, 145.29)	NA

FIGURE 26: FOREST PLOT SHOWING NUMBER OF PARTICIPANTS EXPERIENCING A SERIOUS AE IN THOSE TAKING CBM COMPARED TO THOSE TAKING PLACEBO OR ACTIVE COMPARISON

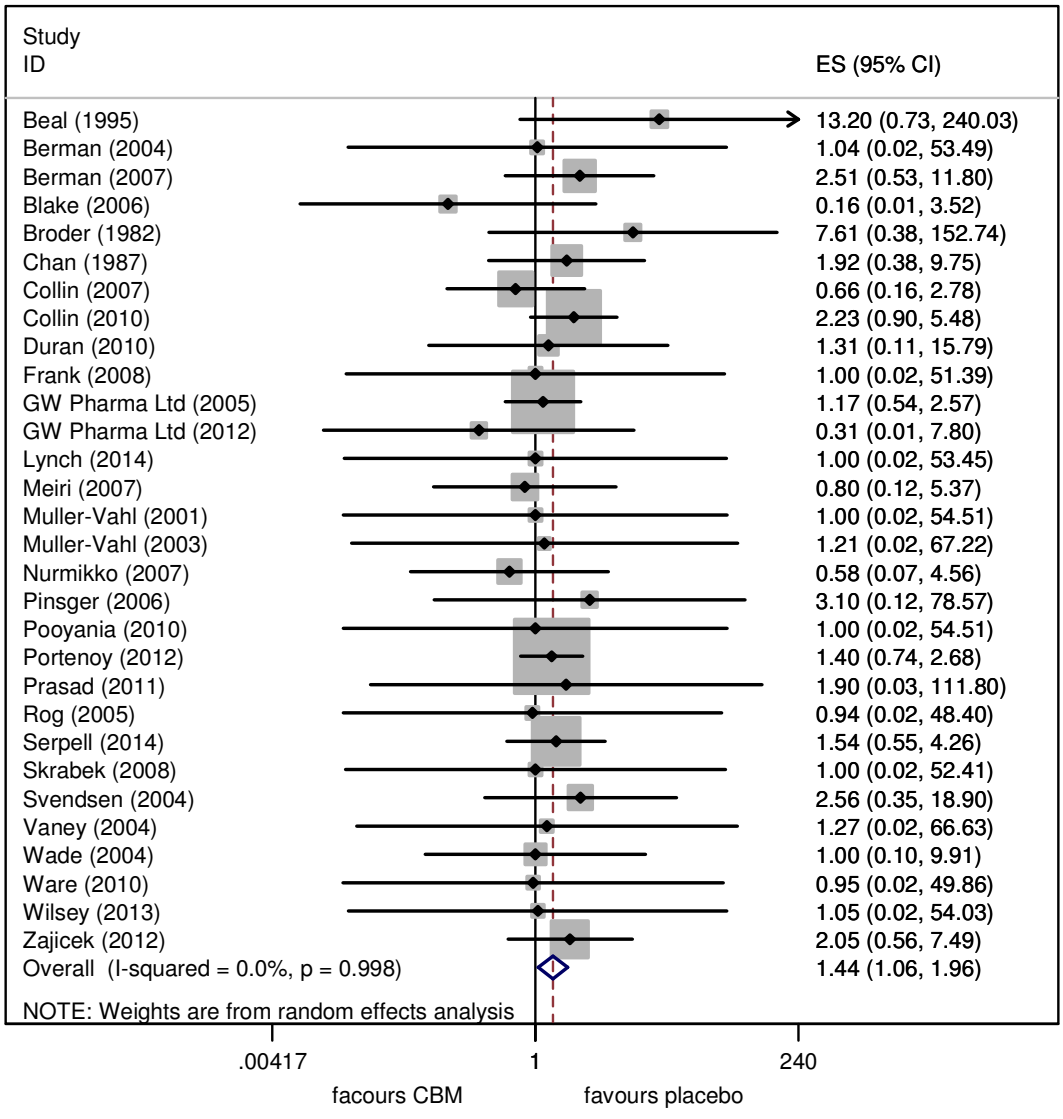
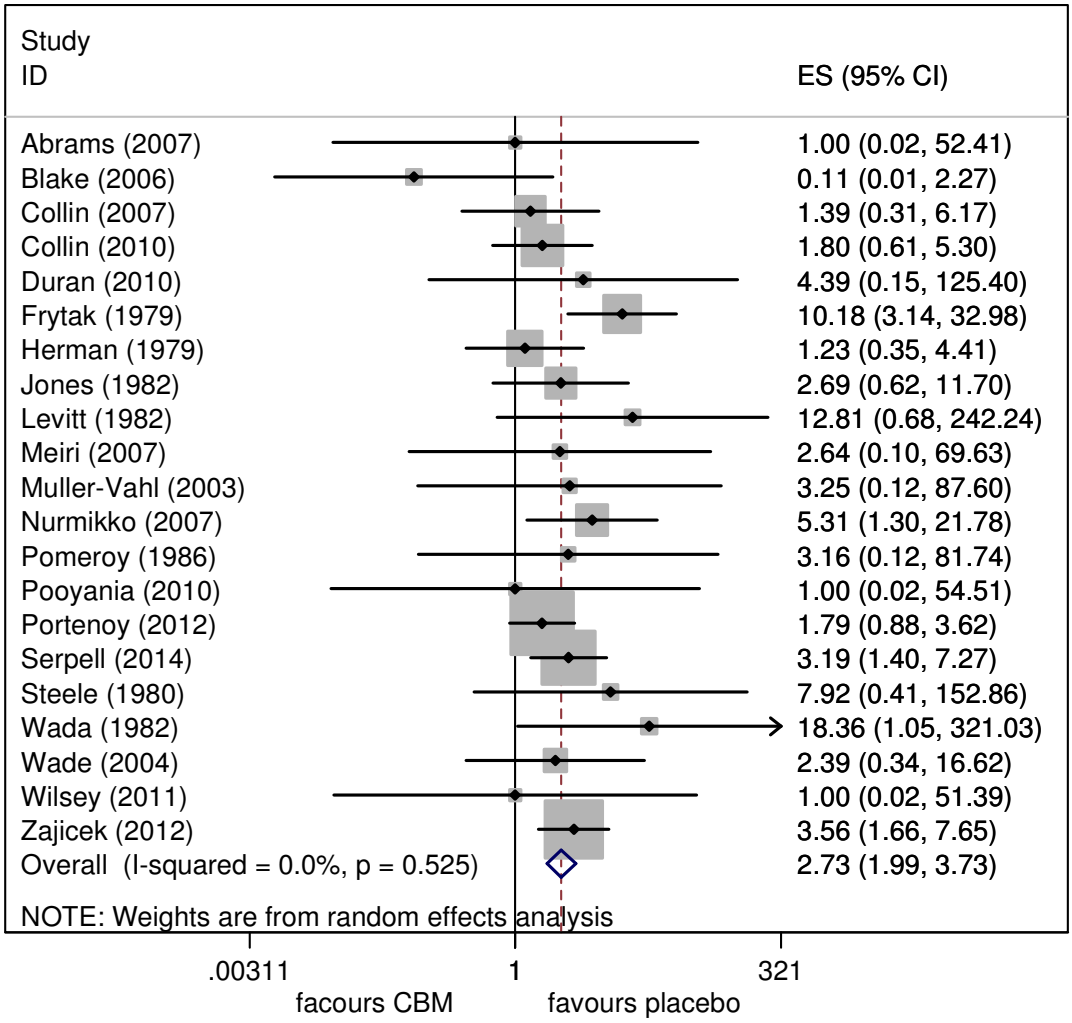


FIGURE 27: FOREST PLOT SHOWING NUMBER OF PARTICIPANTS WITH WITHDRAWAL DUE TO AE AMONG THOSE TAKING CBM COMPARED TO THOSE TAKING PLACEBO OR ACTIVE COMPARISON



5.3.2 Long-term adverse events

We included 31 observational studies (46 reports) that reported data on the relationship between cannabis use and long-term adverse events (cardiovascular disease, respiratory disease, cancer, psychotic disorders, and suicide or suicidal ideation).[229-259] It is important to note that all studies have limited applicability to CBM, as all examined the relationship between recreational use of cannabis and long-term adverse events; we did not identify any studies that reported long-term adverse events data for medicinal cannabis use. Full details of the included studies can be found in Appendix 5 (baseline details) and Appendix 7 (results).

5.3.2.1 Risk of bias

All studies had methodological limitations; none were judged at low risk of bias overall (Figure 28; Table 53). Four studies were judged at moderate risk of bias, four at serious risk of bias and 23 at critical risk of bias. The main limitation in the included studies related to

measurement of interventions with 20 studies judged at critical risk of bias for this domain as cannabis exposure was assessed retrospectively generally using self-reported questionnaire which often related to lifetime use and so were likely to be prone to recall bias. Full details of the ACROBAT-NRS assessment can be found in Appendix 8.

FIGURE 28: RISK OF BIAS ACROSS INCLUDED OBSERVATIONAL STUDIES

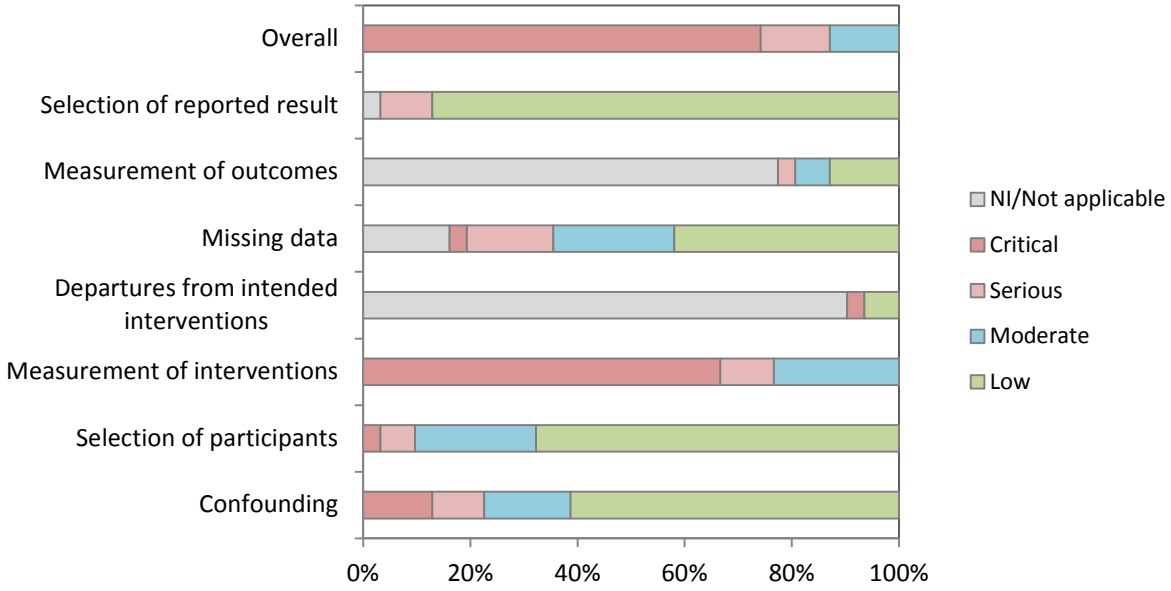


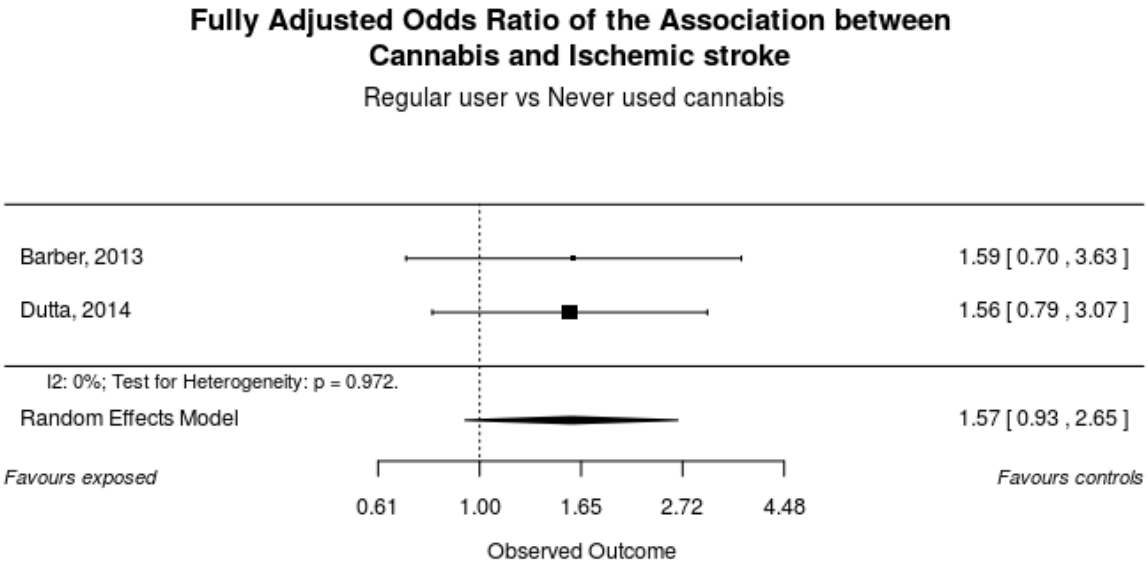
TABLE 53: RISK OF BIAS IN NAUSEA AND VOMITING DUE TO CHEMOTHERAPY STUDIES

Study	Confounding	Selection of participants	Measurement of interventions	Departures from intended interventions	Missing data	Measurement of outcomes	Selection of reported result	Overall
Agrawal(2011)[229]	Critical	Moderate	Critical	NI	NI	Not applicable	Serious	Critical
Aldington(2008)[231]	Moderate	Low	Critical	NI	Low	Not applicable	Low	Critical
Aldington(2008)[230]	Low	Low	Critical	NI	Low	Not applicable	Low	Critical
Barber(2013)[232]	Low	Low	Serious	NI	Moderate	Not applicable	Low	Serious
Beautrais(1999)[233]	Low	Low	Moderate	NI	Moderate	Not applicable	Low	Moderate
Berthiller(2009)[260]	Low	Low	Critical	NI	Low	Not applicable	Low	Critical
Daling(2009)[235]	Low	Low	Critical	NI	Moderate	Not applicable	Low	Critical
Davis(2013)[236]	Critical	Moderate	Moderate	NI	Low	Moderate	Low	Critical
Di Forti(2009)[237]	Low	Low	Critical	NI	Serious	Not applicable	Low	Critical
Dutta (2014)[238]	Low	Moderate	Criticall	NI	NI	Not applicable	NI	Critical
Giordano(2014)[239]	Critical	Low	Serious	NI	NI	Not applicable	Serious	Critical
Hashibe(2006)[240]	Low	Low	Critical	NI	Moderate	Not applicable	Low	Critical
Lacson(2012)[241]	Moderate	Serious	Critical	NI	Low	Not applicable	Serious	Critical
Liang(2009)[242]	Low	Low	Critical	Low	Serious	Not applicable	Low	Critical
Llewellyn(2004)[243]	Serious	Low	Moderate	NI	Serious	Not applicable	Low	Serious
Llewellyn(2004)[244]	Moderate	Low	Moderate	NI	Serious	Not applicable	Low	Serious
Manrique-Garcia(2012)[245]	Low	Low	Critical	NI	Critical	Low	Low	Critical
Marks (2014)[246]	Low	Low	Critical	NI	Low	Not applicable	Low	Critical
McGrath(2010)[247]	Low	Moderate	Critical	Critical	Low	Serious	Low	Critical
Pederson(2008)[248]	Moderate	Low	Critical	NI	Moderate	Low	Low	Critical
Rolfe(1993)[249]	Serious	Low	Serious	NI	NI	Not applicable	Low	Serious
Rosenblatt(2004)[250]	Low	Low	Critical	NI	Moderate	Not applicable	Low	Critical
Sasco(2002)[251]	Serious	Moderate	Moderate	NI	Low	Not applicable	Low	Moderate
Tan(2009)[252]	Low	low	Critical	NI	Serious	Low	Low	Critical
Trabert(2011)[253]	Low	Moderate	Moderate	NI	Low	Not applicable	Low	Moderate
van Os(2002)[254]	Low	Low	Moderate	NI	Low	Low	Low	Moderate
Veling (2008)[255]	Low	Low	Critical	NI	Low	Not applicable	Low	Critical
Voirin(2006)[256]	Low	Low	Critical	Low	Low	Not applicable	Low	Critical
Weller(1985)[257]	Critical	Critical	Critical	NI	Moderate	Moderate	Low	Critical
Zhang(1999)[258]	low	Moderate	Critical	NI	Low	Not applicable	Low	Critical
Zhang(2014)[259]	Moderate	Serious	Critical	NI	NI	Not applicable	Low	Critical

Cardiovascular disease

Two studies assessed the relationship between cardiovascular events and cannabis use.[232, 238] Both of these studies were case-control studies. Both studies included only relatively young patients aged 18 to 55 years[232] and 15 to 49 years.[238] In one study cases were defined as younger (age 18 to 55 years) people admitted to hospital for ischemic stroke or TIA,[232] and in the other cases were defined as people with ischemic stroke.[238] Both studies had substantial methodological weaknesses, particularly in relation to the determination of exposure status. One study was rated as at serious risk of bias overall, because exposure status was determined by urine toxicology screen on entry to the study; whilst this is an objective measure it can only provide data for a very limited time window and may misclassify people with a history of cannabis use.[232] The second study was rated as at critical risk of bias overall, because exposure status determined in relation to historical use and was therefore likely to have been susceptible to recall bias.[238] There was no statistical evidence of between study heterogeneity, with both individual studies and the summary estimate indicating no statistically significant association between regular cannabis use and ischemic stroke/TIA; both studies showed a tend towards more strokes in regular cannabis users (Figure 29).

FIGURE 29: FOREST PLOT SHOWING RISK OF ISCHEMIC STROKE AMONG REGULAR USERS OF CBM COMPARED TO NEVER USERS



Respiratory disease

One study assessed the relationship between respiratory disease (COPD) and cannabis use.[252] This study was a retrospective cohort study and reported data for both objective (spirometry) and subjective (participant report of symptoms and participant report of physician diagnosis) outcome determinations. The study was rated as at critical risk of bias overall, because exposure status determined in relation to historical use and was therefore

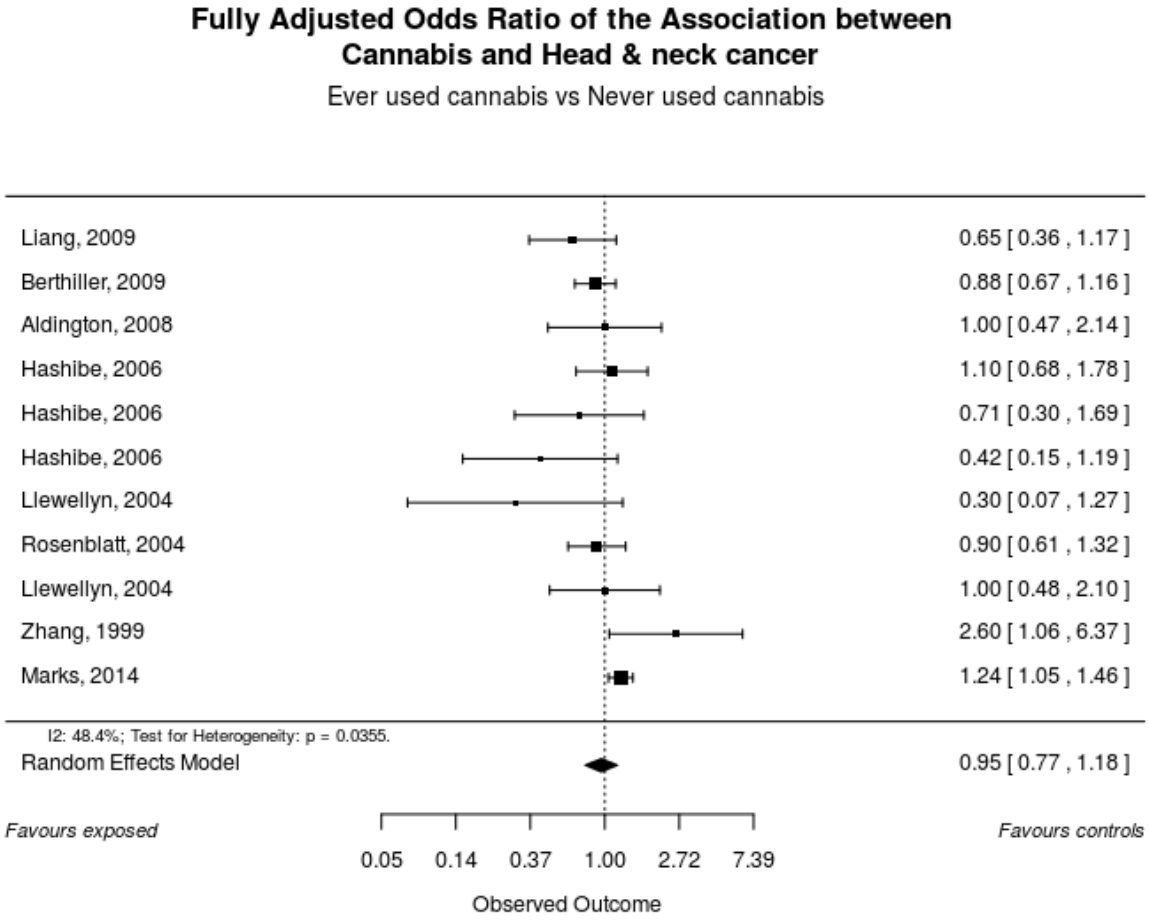
likely to have been susceptible to recall bias. After adjusting for age, sex, ethnicity, BMI, education, asthma and other co-morbidities, and concurrent tobacco smoking, this study found that a history of marijuana use (lifetime exposure of at least 50 cigarettes) was associated with an increased risk of COPD defined by spirometric testing, but the effect size did not reach statistical significance (OR 1.66 (95% CI: 0.52 to 5.26)).[252] A history of marijuana smoking was not associated with increased risk of COPD, where COPD was defined subjectively.[252]

Cancer

Seventeen case-control studies examined the relationship between cannabis use and various cancer diagnoses.[230, 231, 235, 240-246, 250, 251, 253, 256, 258-260].

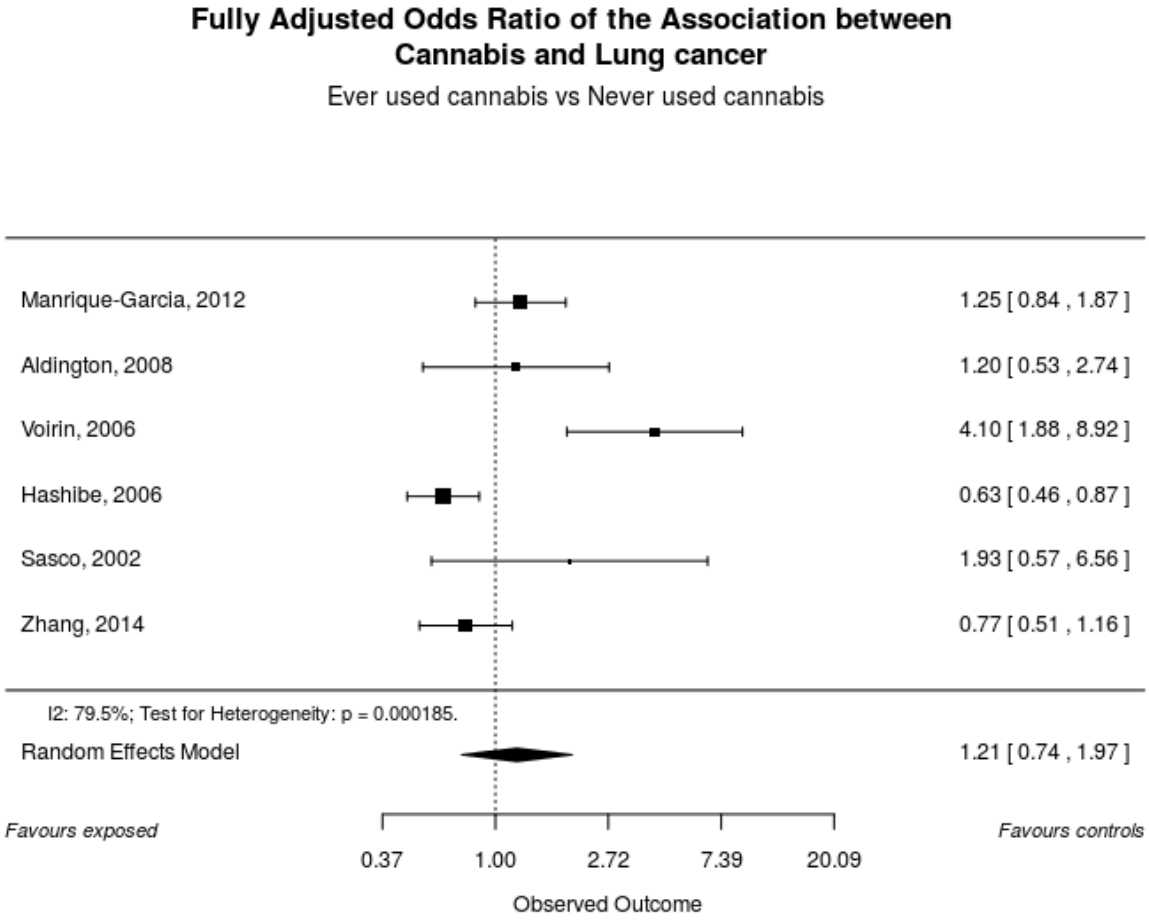
Nine studies reported data on head and neck cancers (including oral and oropharyngeal cancer).[231, 240, 242-244, 246, 250, 258, 260] Seven of these studies were rated as at critical risk of bias overall, because exposure status determined in relation to historical use and was therefore likely to have been susceptible to recall bias. The remaining two studies, by the same research group, were both rated as at moderate risk of bias overall, because it was unclear to what time period exposure assessment referred and exposure data were missing for some study participants.[243, 244] Results varied across studies with some suggesting a protective effect of cannabis and other a harmful effect. Overall there was no evidence of an association between cannabis use and head and neck cancer (Figure 32).

FIGURE 30: FOREST PLOT SHOWING RISK OF HEAD AND NECK AMONG REGULAR USERS OF CBM COMPARED TO NEVER USERS



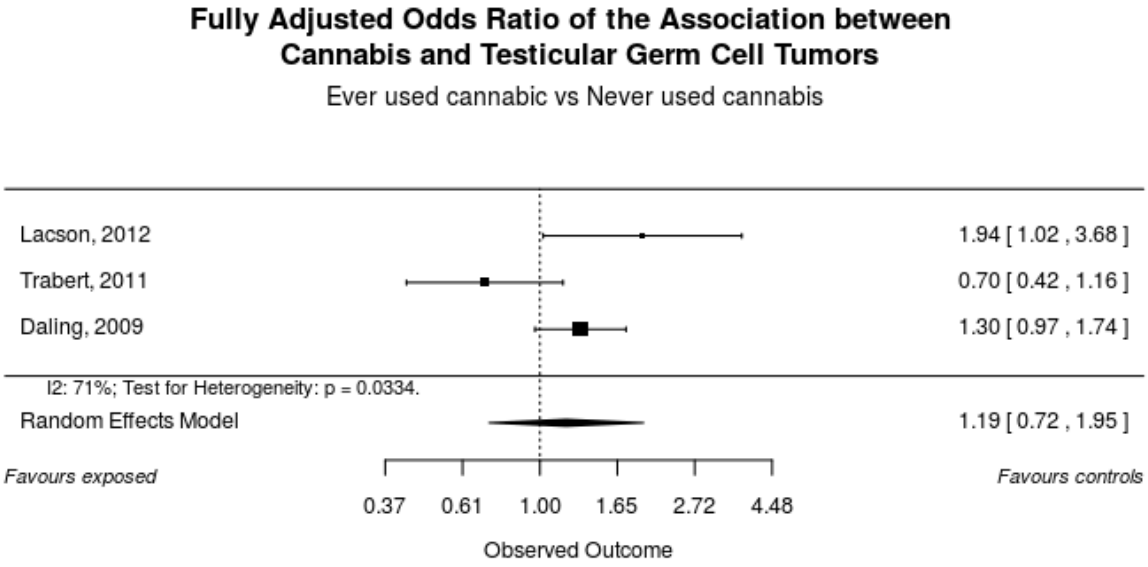
Six studies reported data on lung cancer. [230, 240, 245, 251, 256, 259] All but one [251] of these studies was rated as at critical risk of bias overall, because exposure status determined in relation to historical use and was therefore likely to have been susceptible to recall bias. The remaining study was rated as moderate risk of bias overall, because it was unclear to what time period exposure assessment referred and some potentially important confounders were not adjusted for in determining the effect size.[251] Between study heterogeneity was high and the summary estimate showed no statistically significant association between cannabis use (ever vs. never) and lung cancer, after adjusting for critical confounders (Figure 31).

FIGURE 31: FOREST PLOT SHOWING RISK OF LUNG CANCER AMONG REGULAR USERS OF CBM COMPARED TO NEVER USERS



Three studies reported data on testicular germ cell tumours.[235, 241, 253] Two of these studies were rated as at critical risk of bias overall, because exposure status determined in relation to historical use and was therefore likely to have been susceptible to recall bias.[235, 241] and the remaining study was rated as moderate risk of bias overall, because it was unclear to what time period exposure assessment referred and controls were not similar to cases on some socio-economic characteristics.[253] All three studies adjusted for all specified critical confounders in their analyses. The summary estimate showed no statistically significant association between cannabis use (ever vs. never) and TGCT; data were limited and between study heterogeneity was high (Figure 31).

FIGURE 32: FOREST PLOT SHOWING RISK OF TESTICULAR GERM CELL TUMOURS AMONG REGULAR USERS OF CBM COMPARED TO NEVER USERS

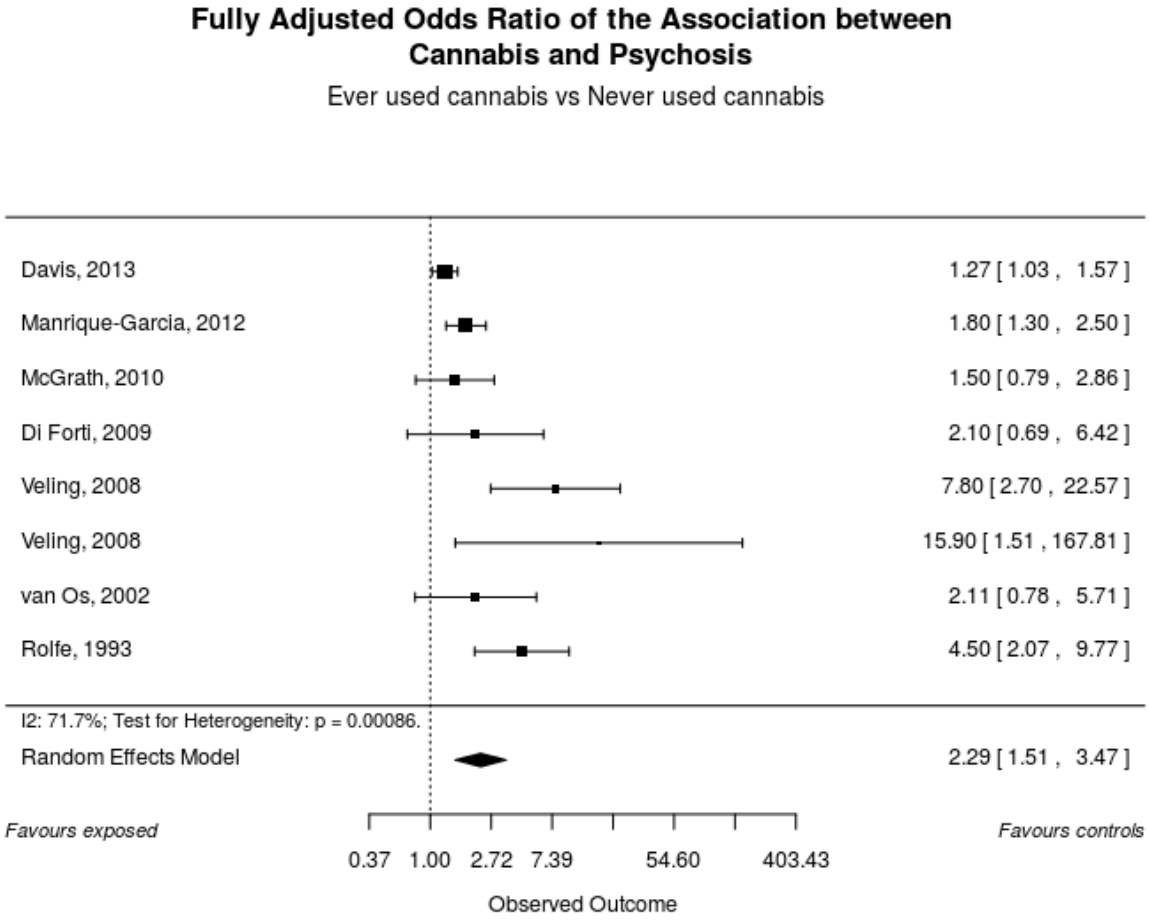


Psychotic disease

Ten studies examined the relationship between cannabis use and psychotic disease.[229, 236, 237, 239, 245, 247, 249, 254, 255, 257] Five studies used a case-control design,[229, 237, 239, 249, 255] four were prospective cohorts,[245, 247, 254, 257] and one was a historical cohort.[236] One study assessed psychosis in bipolar disorder,[229] and the remainder reported data on all psychoses and/or schizophrenia. Eight studies were rated as at critical risk of bias overall.[229, 236, 237, 239, 245, 247, 255, 257] For six studies, this rating was applied because exposure status determined in relation to historical use and was therefore likely to have been susceptible to recall bias;[229, 237, 245, 247, 255, 257] one of these studies also had a substantial amount of missing data on exposure status,[245] another showed a strong association between other illicit drug use during the study and duration of cannabis use (exposure measure),[247] and a third failed to consider possible confounders in the analysis.[257] Two studies were rated as at critical risk of bias because specified critical confounders were not adjusted for in the analyses,[236, 239] in one of these studies exposure was defined as "registered cannabis user" which may have resulted in other users being misclassified.[239] The remaining two studies were rated as serious[249] and moderate[254] risk of bias overall, due to concerns about the measurement of interventions,[249, 254] and adjustment for confounders.[249]

All studies suggested that cannabis use was associated with an increased risk of psychosis. The summary estimate based on six studies that compared ever use to never use of cannabis showed a strong association between ever use of cannabis and psychosis (Figure 33).

FIGURE 33: FOREST PLOT SHOWING RISK OF PSYCHOSIS AMONG REGULAR USERS OF CBM COMPARED TO NEVER USERS

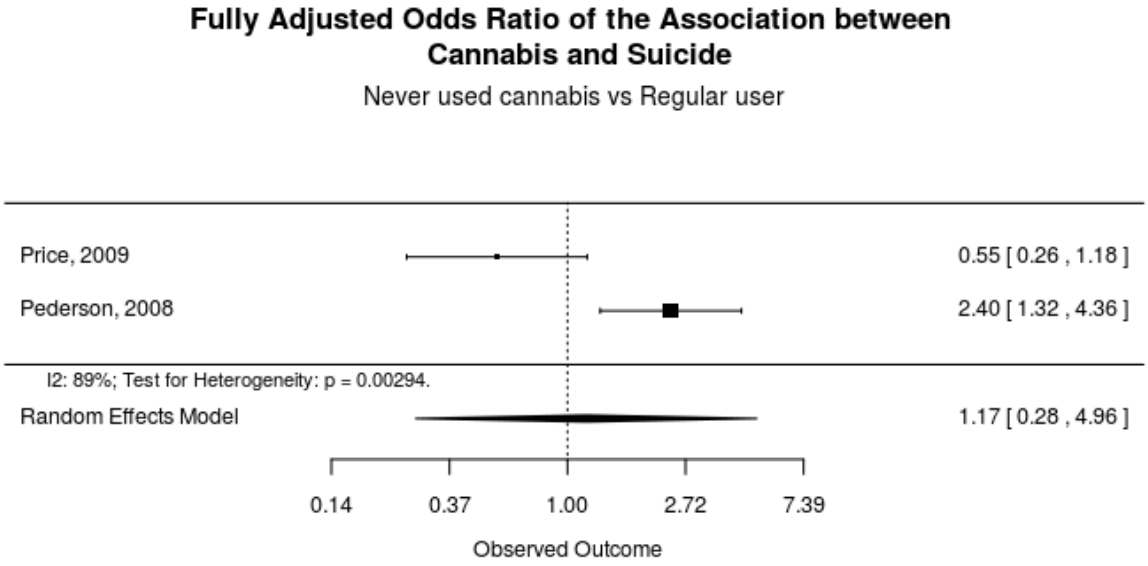


Suicide and suicidal ideation

Three studies examined the relationship between cannabis use and suicide/suicidal ideation.[233, 245, 248] Two prospective cohort studies reported data on suicide or possible suicide outcomes,[245] and suicide attempts and suicidal ideation[248] Both of these studies were rated as at critical risk of bias overall, because exposure status determined in relation to historical use and was therefore likely to have been susceptible to recall bias. The remaining study used a case-control design to assess the relationship between cannabis use and serious suicide attempts.[233] This study was rated as at moderate risk of bias overall, due to concerns about possible recall bias in the assessment of exposure and some missing data on exposure.[233] A summary estimate was calculated for the two prospective cohort studies, which indicated that regular cannabis use has no statistically significant effect on suicide outcomes (Figure X). However, statistical between study heterogeneity was high and the outcome definitions varied between studies; the study which assessed suicide attempts and suicidal ideation reported data suggesting a significant association of these outcomes with regular cannabis use (more than 10 times), OR 2.40 (95% CI: 1.32 to 4.36), after adjusting for critical confounders.[248] the case-control study reported a statistically significant association between cannabis abuse/dependency and serious suicide attempts, after adjusting for

sociodemographic and childhood factors (OR 3.2 (95% CI: 1.7 to 6.0)); when psychiatric co-morbidities were also adjusted for, the association was no longer statistically significant (OR 2.0, 95% CI: 0.97 to 5.3; Figure 34).[261]

FIGURE 34: FOREST PLOT SHOWING RISK OF SUICIDE AMONG REGULAR USERS OF CBM COMPARED TO NEVER USERS



5.3.2.2 Summary

Thirty one observational studies provided data on the relationship between cannabis use and long-term adverse events (cardiovascular disease, respiratory disease, cancer, psychotic disorders, and suicide or suicidal ideation). All studies had methodological limitations; none were judged at low risk of bias overall. Four studies were judged at moderate risk of bias, four at serious risk of bias and 23 at critical risk of bias. The only adverse event to show a significant association with cannabis use (ever use vs never use) was psychosis (OR 2.29, 95% CI 1.51, 3.47; Table 54). Ischemic stroke, head and neck cancer, lung cancer, testicular germ cell tumours and suicide were not associated with ever use of cannabis.

TABLE 54: SUMMARY ESTIMATES FOR LONG TERM AES ASSOCIATED WITH CBM

Outcome	Number of studies	Summary estimate	Favours	I^2 (%)
Ischemic Stroke	2	1.57 (0.93, 2.65)	No use	0
Head & neck cancer	9	0.95 (0.77, 1.18)	No use	48
Lung cancer	6	1.21 (0.74, 1.97)	No use	80
Testicular germ cell tumours	3	1.19 (0.72, 1.95)	No use	71
Psychosis	7	**2.29 (1.51, 3.47)**	No use	72
Suicide and suicidal ideation	2	1.17 (0.28, 4.96)	No use	89

6. DISCUSSION

This systematic review aimed to assess the evidence for the effects and adverse events of medical cannabis.

An extensive review of the available literature using 28 databases was conducted in order to identify studies that were relevant to the question of this report. A total of 193 references to 76 RCTs and 31 observational studies were included and presented in this report.

6.1 SUMMARY OF MAIN FINDINGS

Two research questions were of interest for this systematic review:

1. What are the clinical effects of medical cannabis in people with: nausea and vomiting due to chemotherapy; HIV/AIDS (as appetizer); chronic pain; spasticity due to multiple sclerosis or paraplegia; depression (as antidepressant); anxiety disorder; sleep disorder; psychosis; glaucoma (reducing the intraocular pressure); or movement disorders due to Tourette's syndrome?
2. What are the adverse events associated with medical cannabis?

For the first objective (clinical effects), primary searches identified 15,786 hits of which 423 were considered potentially relevant and obtained as full text studies. Depression was the only indication of interest for which no relevant RCTs were identified. Additional focused searches were conducted to identify eligible non-randomised studies for this indication. These searches did not find any potentially relevant studies even when going to the lowest level of evidence specified as eligible for the review (uncontrolled studies with at least 25 patients). A total of 76 studies available as 147 reports were included in the review of effectiveness.

The majority of the 76 included studies (6380 participants) evaluated nausea and vomiting due to chemotherapy (28 studies), chronic pain (27 studies) and spasticity due to MS and paraplegia (12 studies). All other patient categories were evaluated in less than five studies. Thirty-two studies were parallel group studies (4,397 participants) and 44 were cross-over trials (1,983). The parallel group trials generally enrolled greater number of participants than the cross-over trials (median 70, range 13 to 657 in the parallel group trials; median 48, range 6 to 214 in the cross-over trials). Many of the included studies were very old. Date of publication ranged from 1975 to 2014 (median 2004) with one third of trials published before 1990. Studies were conducted in wide range of countries. Twenty-seven studies were funded by the drug manufacturer, 15 were mixed funded between industry and public bodies, 19 were funded by public bodies and 15 did not provided information on source of funding. Only four (5%) trials were judged at low risk of bias overall, 52 (68%) were judged at high risk of bias, and 20 (26%) at unclear risk of bias.

Cannabis was evaluated in a variety of different forms. These included oral formulations of cannabidiol (CBD), THC, THC/CBD, CT3, dronabinol, nabilone, or levonantradol; intramuscular levonantradol; vaporised cannabis; smoked marijuana or THC; and

oromucosal spray of THC or nabiximols (a combination of THC/CBD). Of the 76 included studies, 53 included a placebo control. A variety of active comparators were included in the trials, with some including both active comparator and placebo. These included alizapride, amisulpride, amitriptyline, chlorpromazine, dihydrocodeine, domperidone, hydroxyzine, metoclopramide, megestrol acetate, ondansetron and prochlorperazine.

For the second objective (adverse events), searches identified 5085 of which 70 were considered potentially relevant and obtained as full text studies. Thirty-one studies available as 46 reports were included. These studies on long-term adverse events amend the data on short-term AEs reported in the studies included for objective 1 (clinical effects).

6.1.1 Nausea and vomiting due to chemotherapy

Twenty-eight studies (37 publications; 1,772 participants) evaluated CBM for the treatment of nausea and vomiting in adults and children undergoing chemotherapy. The studies included patients with a variety of cancers. Some were restricted to single cancer types such as testicular cancer[125] or lung cancer,[101] others included patients with a specific type of cancer such as gastrointestinal[111] or advanced gynaecological cancers,[104] but most included mixed cancers. Seven studies used a parallel group design (467 participants) and 21 (1,305) were cross-over trials. None of the studies were rated as low risk of bias overall, 23 were judged at high risk of bias and five at unclear risk of bias. Therefore the results should be interpreted with some caution.

Overall there was some evidence that CBM reduces nausea and vomiting and improves appetite and functional status in patients receiving chemotherapy treatment for various types of cancer. All studies reported beneficial effects on all outcomes assessed but these did not reach statistical significance in all studies and some did report on the statistical significance of their findings. There were only sufficient data to pool results for one outcome, the number of patients showing a complete nausea and vomiting response. This showed a significant beneficial effect of CBM compared to placebo (OR 3.44, 95% CI 1.45, 8.15).

6.1.2 HIV/AIDS

Four studies (255 participants) evaluated CBM as a treatment for appetite stimulation in patients with HIV/AIDS. Three RCTs[84, 88, 129] used a parallel group design (243 participants) and one[130] (12 participants) was a cross-over trial. All studies were judged at high risk of bias.

There was some evidence that dronabinol is associated with an increase in weight compared to placebo. More limited evidence suggested that it may also be associated with increased appetite, greater % body fat, reduced nausea, and improved functional status. However, these outcomes were mostly assessed in single studies and failed to reach statistical significance. One trial evaluated marijuana and dronabinol, this study found significantly greater weight gain with both forms of cannabis compared to placebo.[129] An active comparison study found that megestrol acetate was associated with greater weight gain

than dronabinol and that combining dronabinol with megestrol acetate did not lead to additional weight gain.[88]

6.1.3 Chronic pain

Twenty-seven studies (61 publications, 2,439 participants) evaluated CBM as a treatment for chronic pain. The conditions causing the chronic pain varied between studies and included neuropathic pain (central, peripheral or not specified; 11 studies), cancer pain (three studies), diabetic peripheral neuropathy (3 studies), fibromyalgia (2 studies), HIV associated sensory neuropathy (2 studies), refractory pain due to MS or other neurological conditions (1 study), rheumatoid arthritis (1 study), non-cancer pain (1 study), central pain (not specified further; 1 study), musculoskeletal problems (1 study) and chemotherapy induced pain (1 study). Fourteen studies were parallel group studies (1980 participants) and fourteen used a cross-over design (459 participants). The risk of bias in the included studies was variable. Only two were rated as low risk of bias for all domains[133, 134] while a further nine were rated as unclear risk of bias.

Overall there was some evidence that CBM may improve pain, there was less evidence for an effect on other outcomes such as quality of life and global impression of change. Studies generally suggested a beneficial effect of CBM on measures of pain but this did not reach statistical significance in most individual studies. Summary estimates for outcomes where there were sufficient data to permit pooling suggested a significant beneficial effect of cannabis on all measures both dichotomous and continuous, e.g. ≥30% reduction in pain (OR 1.35, 95%-CI 0.95 to 1.93; see Table 19 for details). Dichotomous data suggested a significant beneficial effect of CBM on patient global impression of change. There was some evidence to support this based on continuous data but this was not consistent across trials. Sensitivity analyses that included cross-over trials in the meta-analyses showed results consistent with those based on parallel group trials alone.

6.1.4 Spasticity due to multiple sclerosis (MS) or paraplegia

Twelve studies (31 reports; 2,213 participants) evaluated CBM as a treatment for spasticity due to MS or paraplegia (Table 21). Ten studies (2,188 participants) included patients with MS and two included patients with paraplegia (25 participants) caused by spinal cord injury. Eight RCTs used a parallel group design (2,091 participants) and four (122 participants) were cross-over trials. The risk of bias in the included studies was variable. Only two, by the same author, were rated as low risk of bias for all domains.[87, 89] A further five were rated as unclear risk of bias.

Overall there was some evidence that CBM may improve spasticity and patient global impression of change, there was less evidence for an effect on other outcomes such as quality of life, mobility/disability and general disease specific symptoms. Studies generally suggested a beneficial effect of CBM on measures of spasticity but this failed to reach statistical significance in most studies. The summary estimate for the Ashworth scale based on parallel group trials suggested a significant beneficial effect of CBM on spasticity (5 studies: WMD -0.14, 95%-CI -0.27 to -0.01). For other measures of spasticity also suggested

a beneficial effect but did not reach statistical significance (Table 25). Dichotomous data suggested a significant beneficial effect of CBM on patient global impression of change, this was supported by a further cross-over trial that provided continuous data for this outcome. There were no clear differences between the different types of CBM evaluated in these studies. Sensitivity analyses that included cross-over trials in the meta-analyses showed results consistent with those based on parallel group trials alone.

6.1.5 Depression

No studies evaluating cannabis for the treatment of depression fulfilled inclusion criteria for the review. Additional searches were carried out for this population with lower levels of evidence eligible for inclusion. These searches did not locate any eligible studies.

Five studies included for other sections of this review reported on depression as an outcome measures.[3, 86, 139, 141, 144] Four of these studies evaluated patients with chronic pain[86, 139, 141, 144] and one was conducted in patients with MS.[3] Three studies[3, 86, 144] were parallel group trials and two were cross-over trials.[139, 141] Two studies[86, 144] were rated as unclear risk of bias while the remaining three were rated as high risk of bias.

There was no data available on the CBM for the treatment of depression. Studies included for other sections of the review that reported on depression as an outcome found little evidence of an effect of CBM on depression.

6.1.6 Anxiety

One parallel group trial evaluated patients with anxiety disorder.[95] This study was conducted in 24 patients with generalised social anxiety disorder in Brazil. Participants were randomised to receive either cannabidiol or placebo before taking part in a simulated public speaking test. The study was judged at high risk of bias.

The study a significant beneficial effect of cannabidiol compared to placebo on change from before to during a simulated public speaking test on the anxiety factor of a visual analogue mood scale (MD change from baseline -16.52, p-value 0.012). Additional data on anxiety outcomes provided by three studies (two cross-over and one parallel group) in patients with chronic pain also suggested a beneficial effect of CBM but these studies were not restricted to patients with anxiety disorders.

6.1.7 Sleep disorder

Two studies evaluated patients with sleep disorders.[72, 133] One study enrolled patients with obstructive sleep apnoea syndrome[72] and one included patients with fibromyalgia.[133] One study was judged at low risk of bias[133] the other at high risk of bias.[72]

Only two studies evaluated CBM in patients with sleep disorders. One study reported a significant beneficial effect of nabilone on the sleep apnoea/hypopnea index (MD change from baseline -19.64, p-value 0.018) but this should be interpreted with some caution due to the methodological limitations associated with this study.[72] The other study in patients with sleep disorders was a cross-over trial in patients with fibromyalgia and compared nabilone with amitriptyline.[133] This suggested some beneficial effects of nabilone on

insomnia (MD change from baseline -3.25, 95%-CI -5.26 to -1.24) but greater sleep restfulness (MD change from baseline 0.48, 95%-CI 0.01 to 0.95) with amitriptyline.

Nineteen studies included for other populations (chronic pain and MS) also evaluated sleep as an outcome. Overall there was some evidence that CBM may improve sleep in these patient groups (Table 37). There were sufficient data to pool results for sleep quality (WMD -0.58, 95% CI -0.87 to -0.29) and sleep disturbance (WMD -0.26, 95% CI -0.52 to 0.00), both suggested significant beneficial effects in favour of cannabis.

6.1.8 Psychosis

Two studies (9 reports, 71 participants) evaluated CBM as a treatment for psychosis.[75, 216-223] Both studies were conducted in Germany by the same group. One was a parallel group study (42 participants)[216] and the other used a cross-over design (29 participants).[75] Information on the cross-over trial was available only as conference abstracts. The two studies enrolled patient with DSM-IV criteria of acute paranoid schizophrenia or schizophreniform psychosis and ≥36 in the BPRS total score. Both trials evaluated cannabidol (max dose 600-800mg/day), the parallel group study compared this to the active comparator Amisulpride[216] and the cross-over trial included a placebo control phase.[75]. The two studies were both rated as high risk of bias.

There was very little data available on the treatment of psychosis with CBM. Two trials, a parallel group trial comparing cannabidiol to amisulpride and a cross-over trial comparing cannabidiol to placebo found no difference in outcomes between treatment groups (Mental health rated by Brief Psychiatric Rating Scale and mood using PANSS).

6.1.9 Glaucoma

One cross-over trial (6 participants) evaluated CBM for the treatment of glaucoma.[224] It included patients with ocular hypertension or early open angle glaucoma, with a mild visual defect in at least one eye. The study compared THC (5mg), cannabidiol (20mg), cannabidiol (40mg) and placebo all in the form of an oromucosal spray and was judged at unclear risk of bias.

Only one very small cross-over trial was evalauted CBM for the treatment of glaucoma. This study found no evidence of an effect of CBM on intraocular pressure (MD at follow-up, THC 5mg: -0.58, 95%-CI -5.39 to 4.23; cannabidiol 20mg: 0.12, 95%-CI -5.09 to 5.33; cannabidiol 40mg: -0.25, 95%-CI -5.23 to 4.73).

6.1.10 Movement disorders due to Tourette syndrome

Two studies (four publications, 36 participants) evaluated CBM for the treatment of movement disorders due to Tourette syndrome.[225-228] Both studies were conducted in Germany by the same group. One was a parallel group trial (24 participants)[225] and the other used a cross-over design (12 participants).[227] Both trials compared THC capsules (maximum dose 10mg/day) to placebo. The parallel group study was judged at high risk of bias[225] and the cross-over trial at unclear risk of bias (Table 48).[227]

Two small studies, one parallel group and one cross-over trial, suggested that THC capsules may be associated with a significant improvement in tic severity, e.g. MD change from baseline, TSSL-global score -9.08, 95%-CI -12.87 to -5.29. [225]

6.1.11 Adverse events

Sixty-two of the 76 studies included in the clinical effectiveness review provided data on short term adverse events. We found no evidence for a difference in the effect of cannabis on adverse events based on study design, population, comparator, method of cannabis administration or duration of follow-up, and so analyses were conducted for all studies combined. CBM was associated with a significantly greater risk of any AE, serious AE, withdrawals due to AE, ear and labyrinth disorders, gastrointestinal disorders, general disorders and administration site conditions, metabolism and nutrition disorders, psychiatric disorders, renal and urinary disorders, asthenia, balance problems, confusion, diarrhoea, disorientation, drowsiness, dry mouth, euphoria, fatigue, hallucination, nausea, somnolence, and vomiting. Other AEs did not show significant differences between groups.

We included an additional 31 observational studies (46 reports) to investigate the effects of cannabis on long term adverse events (cardiovascular disease, respiratory disease, cancer, psychotic disorders, and suicide or suicidal ideation). All studies examined the relationship between recreational use of cannabis and the outcomes of interest; we did not find any studies that specifically assessed medical cannabis use and long term AEs. All studies had methodological weaknesses with none rated as low risk of bias and only four as moderate risk of bias.

6.2 COMPARISON WITH OTHER REVIEWS

A number of systematic reviews assessed the use of medical cannabis in populations relevant to and discussed in this report. Appendix 10 presents a brief overview of these reviews. In contrast to this report most of the other systematic reviews are based solely on observational studies and only a small number (n=4) addressed more than one relevant population. It appears as if this report offers the most comprehensive review of the literature on the use of medical cannabis in the pre-specified populations relevant to this report.

6.3 STRENGTHS, LIMITATIONS AND UNCERTAINTIES

This review sought wherever possible to reduce the risk of bias during the review processes and analyses. One of the main strengths of the review is the adherence to the most rigorous methods for systematic reviews.

In order to try and identify all of the potentially relevant evidence relating to the review question and reduce the risk of publication bias, an extensive range of resources were searched including electronic databases, guidelines and systematic reviews. Both published and unpublished trials were eligible for inclusion. There were no date or language restrictions. An extensive review of the available literature using 28 databases was conducted in order to identify studies that are relevant to the question of this report.

Search methods followed best practice standards in systematic reviews.[56, 57] Titles and abstracts identified through electronic database and web searching were independently screened by two reviewers. In order to minimise bias and errors, data extraction and risk of bias assessment were performed independently by two reviewers.

A further strength of the review is that different approaches were combined:

- Results of direct comparisons of relevant treatments were presented and supplemented by narrative discussions of the study characteristics.
- Results of quantitative analysis and meta-analysis were also presented following the guidance by the GRADE Working Group.[67-69]

However, despite all efforts to ensure the risk of bias and error was minimised, the findings of the review may still be subject to limitations and uncertainties. Many of these were beyond our control and many related to the quality and quantity of the available evidence base.

One primary limitation is the quality of the primary studies included in the review. We carried out a detailed risk of bias assessment of both the included trials and observational studies. We used the Cochrane risk of bias tool to assess the included RCTs and the new ACROBAT-NRS tool for the observational studies included for long-term adverse events. Both are domain-based tools which provided an assessment of the risk of bias (internal validity) of the included studies. Using the Cochrane risk of bias tool, only four (5%) trials included for the assessment of clinical effects were judged at low risk of bias overall, 52 (68%) were judged at high risk of bias, and 20 (26%) at unclear risk of bias. The major potential source of bias in the trials was incomplete outcome data. Over 50% of trials reported relatively large numbers of withdrawals and did not adequately account for this in the analysis by using an appropriate intention to treat (ITT) analysis based on all randomised participants. Based on the new ACROBAT-NRS tool, none of the included observational studies were judged as low risk of bias and only four were judged at moderate risk of bias; most were judged at critical risk of bias. The main limitation in these studies related to how cannabis exposure was measured.

There were a number of issues which made the data analysis complex. The included studies used a large variety of measures to evaluate outcomes, and even very similar outcomes were often assessed using a variety of different measures. For instance when assessing chronic pain a number of different instruments have been used (see Table 18). Furthermore, a wide range of timepoints were reported in the included trials, limiting the applicability of the findings of these studies. The majority of the studies were two arm trials with a placebo control arm, however, some studies included active comparisons and multiple arms comparing more than one form of CBM, different doses of CBM, or active and placebo comparator arms. This necessitated selecting a single result from each trial to contribute to meta-analyses to avoid double counting of studies. Where possible, we selected the result most similar for the treatment or dose most similar to the other studies

contributing to that meta-analysis and for placebo controlled comparisons rather than active comparisons. For the short term AE analysis we selected the highest reported CBM dose as we hypothesised that this would be most likely to be associated with AEs and so this analysis would present a "worst case" scenario. Studies evaluated various different forms of cannabis administered via various different routes (oral capsules, smoked, vapourised, oromucosal spray, intramuscular injection) and active comparators differed across trials. This combined with the variety of outcome measures and the broad population groupings considered by this review resulted in a very heterogeneous set of included studies which meant that meta-analysis was not always possible or appropriate. Even where meta-analysis may have been appropriate, studies often failed to report the required information (i.e. measure of effect and estimate of variation such as mean and standard deviation for each treatment group) to permit pooling. Such studies often only reported p-values for differences between groups, sometimes without even reporting on the method of analysis performed, this made it very difficult to interpret and synthesise results from these trials. A further difficulty with the continuous data were that, even for the same outcomes, some studies reported results as difference between groups at follow-up and others reported results for differences in change from baseline. As advised by Cochrane, we combined both types of data when estimating summary mean differences.[56]

A potential problem with RCTs using cross-over designs is the possible unblinding due to strong treatment or side effects. Therefore, we presented the results of parallel group as the prime outcome alongside the findings of cross-over RCTs in the same populations as sensitivity analysis.

6.4 Recommendations for future research

Further large, robust, randomised controlled trials are needed. These trials need to adhere to CONSORT (Consolidated Standards of Reporting Trials)[262], reporting standards and report outcome data in a form that can be incorporated into meta-analyses. Although it can be challenging to conduct randomised trials well, e.g. due to slow recruitment of participants, paucity of funding or ethical considerations, this report identified 76 completed and 46 ongoing RCTs (see Appendix 2) as well as 31 observational studies relevant for long-term adverse events. This indicates that it is possible to plan and perform those trials. Systematic reviews including meta-analyses of results from randomised controlled trials are widely accepted as the highest level of evidence and hence the 'gold standard' for making treatment and reimbursement decisions.

Future studies need to assess relevant outcomes (including disease-specific endpoints, quality of life, and adverse events) using standardised outcome measures at similar time points to ensure inclusion in future meta-analyses.

All ongoing or future trials should be registered, e.g. on clinicaltrials.gov, to make them known to the scientific community, to allow planning of research efforts, and to avoid duplication of work.

7. CONCLUSIONS

Based on an extensive and rigorous systematic review of the literature of clinical effects and side effects of medical cannabis in ten populations which identified a total of 193 references to 76 RCTs and 31 observational studies, use of medical cannabis might be warranted for some medical conditions.

Medical cannabis showed statistically significant beneficial effects for the treatment of nausea and vomiting due to chemotherapy, chronic pain, on spasticity due multiple sclerosis (MS) or paraplegia, anxiety, sleep disorders, and movement disorders due to Tourette syndrome. However, these results should be taken with some caution due to a very heterogeneous set of included studies which also suffered from some potential risk of bias.

However, short-term side effects are relatively common and include serious adverse events. Furthermore, long-term cannabis use is linked to psychosis. However, no other association with long-term adverse events was found. Again, these findings might be restricted by methodological limitations of the identified studies on short- and long-term adverse events.

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APPENDIX 1: SEARCH STRATEGIES

Cochrane Database of Systematic Reviews (CDSR) (Wiley Online Library). Issue 3: March/2014
Database of Abstracts of Reviews of Effects (DARE) (Wiley Online Library). Issue 1: January/2014
Health Technology Assessment Database (HTA) (Wiley Online Library). Issue 1: January/2014
NHS Economic Evaluation Database (NHS EED) (Wiley Online Library). Issue 1: January/2014
Cochrane Methodology Register (CMR) (Wiley Online Library). Issue 3: July/2012
Searched 25.3.14

#1 MeSH descriptor: [Cannabinoids] explode all trees 485
#2 MeSH descriptor: [Cannabis] this term only 255
#3 MeSH descriptor: [Cannabaceae] this term only 0
#4 (marijuana or marihuana or cannabis or canabis):ti,ab,kw 1320
#5 (Hashish or hash or bhang or ganja or ganjah or hemp or charas):ti,ab,kw 21
#6 (cannador or eucannabinolide or "8001-45-4" or "8063-14-7" or "38458-58-1"):ti,ab,kw 1
#7 ("9tetrahydrocannabinol*" or "delta3-thc" or "sp-104" or "sp104" or "1972-08-3"):ti,ab,kw 3
#8 (Dronabinol or Marinol or "ea-1477" or "ea1477" or tetranabinex or "qcd-84924" or "qcd84924" or "7663-50-5"):ti,ab,kw 474
#9 ("delta-9-THC" or "5957-75-5"):ti,ab,kw 66
#10 (THC or CBD or AEA):ti,ab 543
#11 (nabidiolex or "13956-29-1"):ti,ab,kw 1
#12 (dexanabinol or "Hu-210" or "Hu-211" or "hu210" or "hu211" or "112924-45-5"):ti,ab,kw 7
#13 (Cannabichromene or "521-35-7"):ti,ab,kw 1
#14 (Nabilone or Cesamet or cesametic or "cpd109514" or "cpd-109514" or "lilly-109514" or "lilly109514" or "51022-71-0"):ti,ab,kw 72
#15 (Nabiximols or Sativex or "Gw-1000" or "gw1000" or "sab-378" or "sab378" or "56575-23-6"):ti,ab,kw 33
#16 (Anandamide or "N-arachidonoylethanolamine"):ti,ab,kw 18
#17 (canabinoid* or canabidiol* or cannabinoid* or Tetrahydrocannabinol* or tetra-hydrocannabinol* or endocannabinoid* or Cannabidiol or cannabinol):ti,ab 653
#18 (nantradol or "cp-44001" or "cp-44001-1" or "cp440011" or "cp44001-1" or "72028-54-7"):ti,ab,kw 5
#19 {or #1-#18) 1823

CDSR search retrieved 30 references
DARE search retrieved 20 references
HTA search retrieved 17 references
NHS EED search retrieved 5 references
CMR search retrieved 8 references

International Network of Agencies for Health Technology Assessment (INAHTA) (Internet): up to 2014/3/25
Searched 25.3.14
http://www.inahta.org/

Search terms	Records
marijuana	0
Cannabis	1
Cannabinoid	1
Cannabinol	0
Cannador	0
Dronabinol OR marinol	74
THC OR nabidiolex or Dexanabinol	74/74
Cannabichromene OR Nabilone OR Cesamet OR Cesametic	74/74
Nabiximols OR Sativex OR Anandamide OR nantradol OR Cannabidiol	74/74
Total	**76**

NIHR Project Portfolio (Internet): up to 2014/3/25
Searched 25.3.14
http://www.nets.nihr.ac.uk/projects/

Search terms	Records
marijuana	0
Cannabis	6
Cannabinoid	2
Cannabinol	0
Cannador	0
Dronabinol	0
Marinol	0
THC	6
nabidiolex	0
Dexanabinol	0
Cannabichromene	0
Nabilone	0
Cesamet	0
Cesametic	0
Nabiximols	0
Sativex	0
Anandamide	0
nantradol	0
Cannabidiol	0
Total	**14**

International Guidelines Library (GIN) (Internet): 2000-2014/3/25
Searched 25.3.14
http://www.g-i-n.net

Search terms	Records
Marijuana OR Cannabis OR Cannabinoid	9
Cannabinol OR Cannador OR Dronabinol OR Marinol	0
THC OR nabidiolex OR Dexanabinol OR Cannabichromene	0
Nabilone OR Cesamet* OR Nabiximols	0
Sativex OR Anandamide OR nantradol OR Cannabidiol OR tetrahydrocannabin*	0
Total	**9**

National Guidelines Clearinghouse (Internet): up to 2014/3/25
Searched 25.3.14
http://www.guideline.gov/search/advanced-search.aspx

Search terms	Records
Marijuana OR Cannabis OR Cannabinoid	24
Dronabinol OR marinol OR Cannabinol OR Cannador	5/2
THC OR nabidiolex or Dexanabinol	2/2
Cannabichromene OR Nabilone OR Cesamet OR Cesametic	3/1
Nabiximols OR Sativex OR Anandamide OR nantradol OR Cannabidiol	0
Total	**34/5**
Total after dedup	**29**

National Institute for Social and Care Excellence (NICE) Guidance (Internet): up to 2014/3/25
Searched 25.3.14
http://guidance.nice.org.uk/

Search terms (limited to guidance only)	Records
marijuana	0
Cannabis	9
Cannabinoid	1
Cannabinol	0
Cannador	0
Dronabinol	0
Marinol	0
THC	0
nabidiolex	0
Dexanabinol	0
Cannabichromene	0
Nabilone	0
Cesamet	0

Cesametic	0
Nabiximols	0
Sativex	1/1
Anandamide	0
nantradol	0
Cannabidiol	0
Total	**10**

TRIP (Internet): up to 2014/3/25
Searched 25.3.14
http://www.tripdatabase.com/

Search terms – Guidelines only	**Records**
(Marijuana OR Cannabis OR Cannabinoid) TITLE ONLY	2
(Dronabinol OR marinol OR Cannabinol OR Cannador) TITLE ONLY	2/2
THC OR nabidiolex OR Dexanabinol	19
Cannabichromene OR Nabilone OR Cesamet OR Cesametic	10/9
Nabiximols OR Sativex OR Anandamide OR nantradol OR Cannabidiol	6/6
Total	**39/17**
Total after dedup	**22**

Canadian Agency for Drugs and Technologies in Health (CADTH) (Internet): up to 2014/3/25
Searched 25.3.14
http://www.cadth.ca/http://guidance.nice.org.uk/

Filter by: Result type - Publication

Search terms	**Records**
Marijuana OR Cannabis OR Cannabinoid	7
Cannabinol OR Cannador OR Dronabinol OR Marinol	2/2
THC OR nabidiolex OR Dexanabinol OR Cannabichromene	2/2
Nabilone OR Cesamet OR Nabiximols	8/3
Sativex OR Anandamide OR nantradol OR Cannabidiol OR tetrahydrocannabinoid	5/5
Total	**24/12**
Total after dedup	**12**

PROSPERO (Internet): Up to 8/4/2014
Searched 8.4.14
http://www.crd.york.ac.uk/prospero/

Search; Combine these selections with 'OR'; five search boxes; 'in 'All fields''

Terms searched	Records
Marijuana OR Cannabis OR Cannabinoid OR Cannabinol OR Cannador	10
Dronabinol OR Marinol OR THC OR nabidiolex OR Dexanabinol	1/1
Cannabichromene OR Nabilone OR Cesamet* OR Nabiximols OR Sativex	1/1
Anandamide OR nantradol OR Cannabidiol OR tetrahydrocannabin*	1/1
Total	**13**
Total after dedup	**10**

International Information Network on New and Emerging Health Technologies (EuroScan) (Internet): up to 2014/4/8
Searched 8.4.14
http://www.euroscan.org.uk/

Terms Searched	Records
Marijuana OR Cannabis OR Cannabinoid OR Cannabinol OR Cannador OR Dronabinol OR Marinol OR THC OR nabidiolex OR Dexanabinol OR Cannabichromene OR Nabilone OR Cesamet* OR Nabiximols OR Sativex OR Anandamide OR nantradol OR Cannabidiol OR tetrahydrocannabin*	**7**

Randomised controlled trial (RCT) searches

Embase (OvidSP): 1974-2014/wk 14
Searched 7.4.14

1 Cannabaceae/ (50)
2 exp cannabinoid/ (42621)
3 (marijuana or marihuana or cannabis or canabis).ti,ab,ot,hw. (31642)
4 (Hashish or hash or bhang or ganja or ganjah or hemp or charas).ti,ab,ot,hw. (1677)
5 (cannador or eucannabinolide or 8001-45-4 or 8063-14-7 or 38458-58-1).ti,ab,ot,hw,rn. (21214)
6 (9tetrahydrocannabinol$ or delta3-thc or sp-104 or sp104 or 1972-08-3).ti,ab,ot,hw,rn. (4813)
7 (Dronabinol or Marinol or dronabinolum or deltanyne or ea-1477 or ea1477 or tetranabinex or qcd-84924 or qcd84924 or 7663-50-5).ti,ab,ot,hw,rn. (5501)
8 (delta-9-THC or 5957-75-5 or 1972-08-3).ti,ab,ot,hw,rn. (5095)
9 delta9?11?tetrahydrocannabinol.ti,ab,ot,hw. (0)
10 (THC or CBD or AEA).ti,ab,ot. (13066)
11 (nabidiolex or 13956-29-1).ti,ab,ot,hw,rn. (1877)
12 (dexanabinol or Hu-210 or Hu-211 or hu210 or hu211 or 112924-45-5).ti,ab,ot,hw,rn. (1107)
13 (Cannabichromene or 521-35-7).ti,ab,ot,hw,rn. (967)
14 (Nabilone or Cesamet or cesametic or cpd109514 or cpd-109514 or lilly-109514 or lilly109514 or 51022-71-0).ti,ab,ot,hw,rn. (970)

15 (Nabiximols or Sativex or Gw-1000 or gw1000 or sab-378 or sab378 or 56575-23-6).ti,ab,ot,hw,rn. (271)
16 (Anandamide or N-arachidonoylethanolamine).ti,ab,ot,hw. (4956)
17 (canabinoid$ or canabidiol$ or cannabinoid$ or Tetrahydrocannabinol$ or tetra-hydrocannabinol$ or endocannabinoid$ or Cannabidiol or cannabinol).ti,ab,ot. (20827)
18 (nantradol or cp-44001 or cp44001 or cp-44001-1 or cp 440011 or cp440011 or cp44001-1 or 72028-54-7).ti,ab,ot,hw,rn. (99)
19 or/1-18 (59963)
20 Random$.tw. or clinical trial$.mp. or exp health care quality/ (3194786)
21 animal/ (1561691)
22 animal experiment/ (1762194)
23 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5594752)
24 or/21-23 (5594752)
25 exp human/ (14638299)
26 human experiment/ (323203)
27 or/25-26 (14639727)
28 24 not (24 and 27) (4487234)
29 20 not 28 (3040232)
30 19 and 29 (8561)

Trials filter:
Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. J Med Libr Assoc 2006;94(1):41-7.

Medline (OvidSP): 1946-2014/Mar wk 4
Searched 7.4.14

1 exp cannabinoids/ (10137)
2 cannabis/ or cannabaceae/ (6725)
3 (marijuana or marihuana or cannabis or canabis).ti,ab,ot,hw. (18912)
4 (Hashish or hash or bhang or ganja or ganjah or hemp or charas).ti,ab,ot,hw. (1156)
5 (cannador or eucannabinolide or 8001-45-4 or 8063-14-7 or 38458-58-1).ti,ab,ot,hw,rn. (4)
6 (9tetrahydrocannabinol$ or delta3-thc or sp-104 or sp104 or 1972-08-3 or dronabinol or marinol or dronabinolum or deltanyne or ea-1477 or ea1477 or tetranabinex or qcd-84924 or qcd84924 or 7663-50-5).ti,ab,ot,hw,rn. (5822)
7 (delta-9-THC or 5957-75-5 or 1972-08-3).ti,ab,ot,hw,rn. (906)
8 delta9?11?tetrahydrocannabinol.ti,ab,ot,hw. (0)
9 (THC or CBD or AEA).ti,ab,ot. (8631)
10 (nabidiolex or 13956-29-1).ti,ab,ot,hw,rn. (0)
11 (dexanabinol or Hu-210 or Hu-211 or hu210 or hu211 or 112924-45-5).ti,ab,ot,hw,rn. (442)
12 (Cannabichromene or 521-35-7).ti,ab,ot,hw,rn. (74)
13 (Nabilone or Cesamet or cesametic or cpd109514 or cpd-109514 or lilly-109514 or lilly109514 or 51022-71-0).ti,ab,ot,hw,rn. (222)

14 (Nabiximols or Sativex or Gw-1000 or gw1000 or sab-378 or sab378 or 56575-23-6).ti,ab,ot,hw,rn. (85)
15 (Anandamide or N-arachidonoylethanolamine).ti,ab,ot,hw. (2881)
16 (canabinoid$ or canabidiol$ or cannabinoid$ or Tetrahydrocannabinol$ or tetra-hydrocannabinol$ or endocannabinoid$ or Cannabidiol or cannabinol).ti,ab,ot. (15670)
17 (nantradol or cp-44001 or cp44001 or cp-44001-1 or cp 440011 or cp440011 or cp44001-1 or 72028-54-7).ti,ab,ot,hw,rn. (65)
18 or/1-17 (36120)
19 randomized controlled trial.pt. (369234)
20 controlled clinical trial.pt. (88013)
21 randomized.ab. (268291)
22 placebo.ab. (144614)
23 randomly.ab. (190765)
24 trial.ab. (278176)
25 groups.ab. (1228275)
26 or/19-25 (1802726)
27 exp Animals/ not (exp Animals/ and Humans/) (3917948)
28 26 not 27 (1469645)
29 18 and 28 (3953)

Based on Trials filter:
Lefebvre C, Manheimer E, Glanville J. Chapter 6: searching for studies. Box 6.4.c: Cochrane Highly sensitive search strategy for identifying randomized controlled trials in Medline: Sensitivity-maximizing version (2008 version); OVID format. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

Medline In-Process & Daily Update (OvidSP): up to 4 April 2014
Searched 7.4.14

1 exp cannabinoids/ (4)
2 cannabis/ or cannabaceae/ (8)
3 (marijuana or marihuana or cannabis or canabis).ti,ab,ot,hw. (1185)
4 (Hashish or hash or bhang or ganja or ganjah or hemp or charas).ti,ab,ot,hw. (154)
5 (cannador or eucannabinolide or 8001-45-4 or 8063-14-7 or 38458-58-1).ti,ab,ot,hw,rn. (1)
6 (9tetrahydrocannabinol$ or delta3-thc or sp-104 or sp104 or 1972-08-3 or dronabinol or marinol or dronabinolum or deltanyne or ea-1477 or ea1477 or tetranabinex or qcd-84924 or qcd84924 or 7663-50-5).ti,ab,ot,hw,rn. (19)
7 (delta-9-THC or 5957-75-5 or 1972-08-3).ti,ab,ot,hw,rn. (8)
8 delta9?11?tetrahydrocannabinol.ti,ab,ot,hw. (0)
9 (THC or CBD or AEA).ti,ab,ot. (636)
10 (nabidiolex or 13956-29-1).ti,ab,ot,hw,rn. (0)
11 (dexanabinol or Hu-210 or Hu-211 or hu210 or hu211 or 112924-45-5).ti,ab,ot,hw,rn. (10)
12 (Cannabichromene or 521-35-7).ti,ab,ot,hw,rn. (2)

13 (Nabilone or Cesamet or cesametic or cpd109514 or cpd-109514 or lilly-109514 or lilly109514 or 51022-71-0).ti,ab,ot,hw,rn. (7)
14 (Nabiximols or Sativex or Gw-1000 or gw1000 or sab-378 or sab378 or 56575-23-6).ti,ab,ot,hw,rn. (20)
15 (Anandamide or N-arachidonoylethanolamine).ti,ab,ot,hw. (146)
16 (canabinoid$ or canabidiol$ or cannabinoid$ or Tetrahydrocannabinol$ or tetra-hydrocannabinol$ or endocannabinoid$ or Cannabidiol or cannabinol).ti,ab,ot. (1099)
17 (nantradol or cp-44001 or cp44001 or cp-44001-1 or cp 440011 or cp440011 or cp44001-1 or 72028-54-7).ti,ab,ot,hw,rn. (0)
18 or/1-17 (2557)
19 randomized controlled trial.pt. (1006)
20 controlled clinical trial.pt. (107)
21 randomized.ab. (21876)
22 placebo.ab. (8164)
23 randomly.ab. (19607)
24 trial.ab. (23129)
25 groups.ab. (112735)
26 or/19-25 (149459)
27 exp Animals/ not (exp Animals/ and Humans/) (2777)
28 26 not 27 (149048)
29 18 and 28 (337)

Based on Trials filter:
Lefebvre C, Manheimer E, Glanville J. Chapter 6: searching for studies. Box 6.4.c: Cochrane Highly sensitive search strategy for identifying randomized controlled trials in Medline: Sensitivity-maximizing version (2008 version); OVID format. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

PubMed (https://www.ncbi.nlm.nih.gov/pubmed): up to 14.4.2014
Searched 14.4.14
PubMed not Medline searched to ensure 'ahead-of-print' records retrieved

#27 (#25 AND #26)105
#26 (pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb]) 1734578
#25 (#16 AND #24) 2280
#24 (#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23) 898472
#23 trial [ti] 124602
#22 randomly [tiab] 212281
#21 clinical trials as topic [mesh: noexp] 166928
#20 placebo [tiab] 156432
#19 randomized [tiab] 312453
#18 controlled clinical trial [pt] 87163
#17 randomized controlled trial [pt] 362893
#16 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15) 35874

#15 nantradol[tiab] OR nantradol[ot] OR cp-44001[tiab] OR cp44001[tiab] OR cp-44001-1[tiab] OR "cp 440011"[tiab] OR cp440011[tiab] OR cp44001-1[tiab] 19
#14 canabinoid*[tiab] OR canabinoid*[ot] OR canabidiol*[tiab] OR cannabinoid*[tiab] OR cannabinoid*[ot] OR tetrahydrocannabinol*[tiab] OR tetra-hydrocannabinol*[tiab] OR endocannabinoid* OR cannabidiol*[tiab] OR cannabinol*[tiab] 17035
#13 anandamide[tiab] OR anandamide[ot] OR n-arachidonoylethanolamine[tiab] 3021
#12 nabiximols[tiab] OR nabiximols[ot] OR sativex[tiab] OR sativex[ot] OR gw-1000[tiab] OR gw1000[tiab] OR sab-378[tiab] OR sab378[tiab] 109
#11 nabilone[tiab] OR nabilone[ot] OR cesamet[tiab] OR cesametic[tiab] OR cpd109514[tiab] OR cpd-109514[tiab] OR lilly-109514[tiab] OR lilly109514[tiab] 200
#10 cannabichromene[tiab] OR cannabichromene[ot] 71
#9 dexanabinol[tiab] OR dexanabinol[ot] OR Hu-210[tiab] OR Hu-211[tiab] OR hu210[tiab] OR hu211[tiab] 397
#8 nabidiolex[tiab] OR nabidiolex[ot] Schema: all 0
#7 nabidiolex[tiab] OR nabidiolex[ot] 0
#6 THC[tiab] OR THC[ot] OR CBD[tiab] OR AEA[tiab] 9274
#5 delta-9-THC[tiab] OR delta-9-THC[ot] OR delta-9-11-tetrahydrocannabinol[tiab] 990
#4 9tetrahydrocannabinol*[tiab] OR delta3-thc[tiab] OR sp-104[tiab] OR sp104[tiab] OR dronabinol[tiab] OR marinol[tiab] OR dronabinolum[tiab] OR deltanyne[tiab] OR ea-1477[tiab] OR ea1477[tiab] OR tetranabinex[tiab] OR qcd-84924[tiab] OR qcd84924[tiab] 251
#3 cannador[tiab] OR eucannabinolide[tiab] 4
#2 hashish[tiab] OR hash[tiab] OR bhang[tiab] OR ganja[tiab] OR ganjah[tiab] OR hemp[tiab] OR charas[tiab] 1319
#1 marijuana[tiab] OR marijuana[ot] OR marihuana[tiab] OR cannabis[tiab] OR cannabis[ot] OR canabis[tiab]16607

Trials filter (best sensitivity and specificity) from:
Lefebvre C, Manheimer E, Glanville J. Chapter 6: searching for studies. Box 6.4.b: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); PubMed format. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

PsycINFO (OvidSP): 1806-2014/April wk 1
Searched 7.4.14

1 exp cannabis/ (4802)
2 exp cannabinoids/ (3454)
3 (marijuana or marihuana or cannabis or canabis).ti,ab,ot,hw. (12570)
4 (Hashish or hash or bhang or ganja or ganjah or hemp or charas).ti,ab,ot,hw. (464)
5 (cannador or eucannabinolide or 8001-45-4 or 8063-14-7 or 38458-58-1).ti,ab,ot,hw. (1)
6 (9tetrahydrocannabinol$ or delta3-thc or sp-104 or sp104 or 1972-08-3).ti,ab,ot,hw. (7)
7 (dronabinol or marinol or dronabinolum or deltanyne or ea-1477 or ea1477 or tetranabinex or qcd-84924 or qcd84924 or 7663-50-5).ti,ab,ot,hw. (59)

8 (delta-9-THC or 5957-75-5 or 1972-08-3).ti,ab,ot,hw. (45)
9 delta9?11?tetrahydrocannabinol.ti,ab,ot,hw. (0)
10 (THC or CBD or AEA).ti,ab,ot. (1926)
11 (nabidiolex or 13956-29-1).ti,ab,ot,hw. (0)
12 (dexanabinol or Hu-210 or Hu-211 or hu210 or hu211 or 112924-45-5).ti,ab,ot,hw. (90)
13 (Cannabichromene or 521-35-7).ti,ab,ot,hw. (11)
14 (Nabilone or Cesamet or cesametic or cpd109514 or cpd-109514 or lilly-109514 or lilly109514 or 51022-71-0).ti,ab,ot,hw. (43)
15 (Nabiximols or Sativex or Gw-1000 or gw1000 or sab-378 or sab378 or 56575-23-6).ti,ab,ot,hw. (24)
16 (Anandamide or N-arachidonoylethanolamine).ti,ab,ot,hw. (555)
17 (canabinoid$ or canabidiol$ or cannabinoid$ or Tetrahydrocannabinol$ or tetra-hydrocannabinol$ or endocannabinoid$ or Cannabidiol or cannabinol).ti,ab,ot. (4517)
18 (nantradol or cp-44001 or cp44001 or cp-44001-1 or cp 440011 or cp440011 or cp44001-1 or 72028-54-7).ti,ab,ot,hw. (6)
19 or/1-18 (16362)
20 (double-blind or random$ asigned or control).tw. (327645)
21 animal.de,po. (306778)
22 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or canine or feline or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).mp. (324199)
23 or/21-22 (360550)
24 human.po. (3001848)
25 23 not (23 and 24) (298604)
26 20 not 25 (285937)
27 19 and 26 (1663)

Based on RCT Filter (optimised sensitivity & specificity):
Eady AM, Wilczynski NL, Haynes RB. PsycINFO search strategies identified methodologically sound therapy studies and review articles for use by clinicians and researchers. J Clin Epidemiol 2008;61(1):34-40.

BIOSIS Citation Index (Web of Knowledge): 1926-2014/04/11
Searched 15.4.14

# 22	**2,799**	**#21 AND #18**
# 21	3,976,203	#19 OR #20
# 20	3,962,866	TS=((clinic* SAME trial*) OR (placebo* OR random* OR control* OR prospectiv*))
# 19	107,744	TS=((singl* or doubl* or trebl* or tripl*) SAME (blind* or mask*))
# 18	12,315	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
# 17	0	TS=(dronabinolum or deltanyne or cp44001 or "cp 440011")
# 16	205	TS=(Dronabinol or Marinol)
# 15	68	TS=(nantradol or "cp-44001" or "cp-44001-1" or cp440011 or "cp44001-1" or "72028-54-7")

14 915 TS=((Medical or medicinal or therapeutic* or therapy or therapies*) NEAR/5 (canabinoid* or canabidiol* or cannabinoid* or Tetrahydrocannabinol* or "tetra-hydrocannabinol*" or endocannabinoid* or Cannabidiol or cannabinol))
13 3,833 TS=(Anandamide or "N-arachidonoylethanolamine")
12 80 TS=(Nabiximols or Sativex or "Gw-1000" or gw1000 or "sab-378" or sab378 or "56575-23-6")
11 194 TS=(Nabilone or Cesamet or cesametic or cpd109514 or "cpd-109514" or "lilly-109514" or lilly109514 or "51022-71-0")
10 103 TS=(Cannabichromene or "521-35-7")
9 521 TS=(dexanabinol or "Hu-210" or "Hu-211" or hu210 or hu211 or "112924-45-5")
8 1 TS=(nabidiolex or "13956-29-1")
7 770 TI=(THC)
6 1 TS=("delta9 11 tetrahydrocannabinol" or "delta9-11-tetrahydrocannabinol" or delta911tetrahydrocannabinol)
5 1,284 TS=("delta-9-THC" or "5957-75-5" or "1972-08-3")
4 24 TS=(9tetrahydrocannabinol* or "delta3-thc" or "sp-104" or sp104 or "1972-08-3")
3 12 TS=(cannador or eucannabinolide or "8001-45-4" or "8063-14-7" or "38458-58-1")
2 3,781 TS=(Hashish or hash or bhang or ganja or ganjah or hemp or charas)
1 2,034 TS=((Medical or medicinal or therapeutic* or therapy or therapies*) NEAR/15 (marijuana or marihuana or cannabis or canabis))

CINAHL (Cumulative Index to Nursing and Allied Health Literature) (EBSCO): 1981-2014/04/14
Searched 16.4.14

S1 TX (Hashish or hash) 835
S2 TX (marijuana or marihuana or cannabis or canabis) 10,313
S3 (MH "Cannabis") 3,220
S4 TX (bhang or ganja or ganjah or hemp or charas) 455
S5 TX (cannador or eucannabinolide or "8001-45-4" or "8063-14-7" or "38458-58-1") 3
S6 TX (9tetrahydrocannabinol* or "delta3-thc" or "sp-104" or sp104 or "1972-08-3") 213
S7 TX ("delta-9-THC" or "5957-75-5" or "1972-08-3" or nantradol or "cp-44001" or "cp-44001-1" or cp440011 or "cp44001-1" or "72028-54-7" or cp44001 or "cp 440011") 53
S8 TX (delta911tetrahydrocannabinol) 0
S9 TX ("delta9 11 tetrahydrocannabinol" or "delta9-11-tetrahydrocannabinol") 0
S10 TX (THC or canabinoid? or canabidiol? or cannabinoid? or Tetrahydrocannabinol? or "tetra-hydrocannabinol?" or endocannabinoid? or Cannabidiol or cannabinol) 2,694
S11 TX (nabidiolex or "13956-29-1" or Dronabinol or Marinol or dronabinolum or deltanyne) 194
S12 TX (dexanabinol or "Hu-210" or "Hu-211" or hu210 or hu211 or "112924-45-5") 15
S13 TX (Cannabichromene or "521-35-7") 3

S14 TX (Nabilone or Cesamet or cesametic or cpd109514 or "cpd-109514" or "lilly-109514" or lilly109514 or "51022-71-0") 80
S15 TX (Nabiximols or Sativex or "Gw-1000" or gw1000 or "sab-378" or sab378 or "56575-23-6") 48
S16 TX (Anandamide or "N-arachidonoylethanolamine") 117
S17 S16 or S15 OR S14 OR S13 OR S12 OR S11 OR S10 OR S9 OR S8 OR S7 OR S6 OR S5 OR S4 OR S3 OR S2 OR S1 13,283
S18 (ZT "clinical trial") 51,270
S19 TX (randomized) 123,929
S20 (MH "Treatment Outcomes+") 119,323
S21 S18 OR S19 OR S20 244,116
S22 S17 AND S21 2,049

Trials filter (Optimised sensitivity & specificity):
Wong SS, Wilczynski NL, Haynes RB. Optimal CINAHL search strategies for identifying therapy studies and review articles. J Nurs Scholarsh 2006;38(2):194-199.

Science Citation Index (Web of Knowledge): 1900-2014/04/15
Searched 15.4.14

 # 20 3,471 #19 AND #16
19 4,316,298 #18 OR #17
18 4,278,702 TS=((clinic* SAME trial*) OR (placebo* OR random* OR control* OR prospectiv*))
17 196,259 TS=((singl* or doubl* or trebl* or tripl*) SAME (blind* or mask*))
16 16,442 #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
15 19 TS=(nantradol or "cp-44001" or "cp-44001-1" or cp440011 or "cp44001-1" or cp44001 or "cp 440011" or "72028-54-7")
14 1,203 TS=((Medical or medicinal or therapeutic* or therapy or therapies*) NEAR/10 (canabinoid* or canabidiol* or cannabinoid* or Tetrahydrocannabinol* or "tetra-hydrocannabinol*" or endocannabinoid* or Cannabidiol or cannabinol))
13 4,830 TS=(Anandamide or "N-arachidonoylethanolamine" or Dronabinol or Marinol or dronabinolum or deltanyne)
12 129 TS=(Nabiximols or Sativex or "Gw-1000" or gw1000 or "sab-378" or sab378 or "56575-23-6")
11 222 TS=(Nabilone or Cesamet or cesametic or cpd109514 or "cpd-109514" or "lilly-109514" or lilly109514 or "51022-71-0")
10 78 TS=(Cannabichromene or "521-35-7")
9 466 TS=(dexanabinol or "Hu-210" or "Hu-211" or hu210 or hu211 or "112924-45-5")
8 0 TS=(nabidiolex or "13956-29-1")
7 1,341 TI=(THC)
6 1 TS=("delta9 11 tetrahydrocannabinol" or "delta9-11-tetrahydrocannabinol" or delta911tetrahydrocannabinol)
5 1,190 TS=("delta-9-THC" or "5957-75-5" or "1972-08-3")

4 14 TS=(9tetrahydrocannabinol* or "delta3-thc" or "sp-104" or sp104 or "1972-08-3")
3 6 TS=(cannador or eucannabinolide or "8001-45-4" or "8063-14-7" or "38458-58-1")
2 7,845 TS=(Hashish or hash or bhang or ganja or ganjah or hemp or charas)
1 986 TS=((Medical or medicinal or therapeutic* or therapy or therapies*) NEAR/15 (marijuana or marihuana or cannabis or canabis))

AMED (ProQuest): 1985-2014/04/07
Searched 7.4.14

S1 SU.EXACT.EXPLODE("CANNABINOIDS") OR SU.EXACT.EXPLODE("CANNABIS") 413
S2 (marijuana OR marihuana OR cannabis OR canabis) OR (hashish OR hash OR bhang OR ganja OR ganjah OR hemp OR charas) OR (cannador OR eucannabinolide OR "8001-45-4" OR "8063-14-7" OR "38458-58-1") OR (9tetrahydrocannabinol* OR "delta3-thc" OR "sp-104" OR sp104 OR "1972-08-3" OR dronabinol OR marinol OR dronabinolum OR deltanyne OR "ea-1477" OR ea1477 OR tetranabinex OR "qcd-84924" OR qcd84924 OR "7663-50-5") 244
S3 ("delta-9-THC" OR "5957-75-5" OR "1972-08-3") OR (delta9*11*tetrahydrocannabinol) OR (THC OR CBD OR AEA) OR (nabidiolex OR "13956-29-1") 59
S4 (dexanabinol OR "hu-210" OR "hu-211" OR hu210 OR hu211 OR "112924-45-5") OR (cannabichromene OR "521-35-7") OR (nabilone OR cesamet OR cesametic OR cpd109514 OR "cpd-109514" OR "lilly-109514" OR lilly109514 OR "51022-71-0") OR (nabiximols OR sativex OR "gw-1000" OR gw1000 OR "sab-378" OR sab378 OR "56575-23-6") 8
S5 (anandamide OR "n-arachidonoylethanolamine") OR (cannabinoid* OR canabidiol* OR cannabinoid* OR tetrahydrocannabinol* OR "tetra-hydrocannabinol*" OR endocannabinoid* OR cannabidiol OR cannabinol) OR (nantradol OR "cp-44001" OR cp44001 OR "cp-44001-1" OR "cp 440011" OR cp440011 OR "cp44001-1" OR "72028-54-7") 103
S6 S1 OR S2 OR S3 OR S4 OR S5 525
S7 SU.EXACT.EXPLODE("CLINICAL TRIALS") OR (clinic* NEAR/2 trial*) OR (placebo* OR random* OR control* OR prospectiv*) OR ((singl* or doubl* or trebl* or tripl*) NEAR/2 (blind* or mask*)) 41230
S8 S6 AND S7 109

Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley Online Library). Issue 3/12: March 2014
Searched 7.4.14

#1 MeSH descriptor: [Cannabinoids] explode all trees 488
#2 MeSH descriptor: [Cannabis] this term only 255
#3 MeSH descriptor: [Cannabaceae] this term only 0
#4 (marijuana or marihuana or cannabis or canabis):ti,ab,kw 1343
#5 (Hashish or hash or bhang or ganja or ganjah or hemp or charas):ti,ab,kw 21
#6 (cannador or eucannabinolide or "8001-45-4" or "8063-14-7" or "38458-58-1"):ti,ab,kw 1

#7 ("9tetrahydrocannabinol*" or "delta3-thc" or "sp-104" or "sp104" or "1972-08-3"):ti,ab,kw 3
#8 (dronabinol or marinol or dronabinolum or deltanyne or "ea-1477" or "ea1477" or tetranabinex or "qcd-84924" or "qcd84924" or "7663-50-5"):ti,ab,kw 474
#9 ("delta-9-THC" or "5957-75-5"):ti,ab,kw 66
#10 (THC or CBD or AEA):ti,ab 556
#11 (nabidiolex or "13956-29-1"):ti,ab,kw 1
#12 (dexanabinol or "Hu-210" or "Hu-211" or "hu210" or "hu211" or "112924-45-5"):ti,ab,kw 7
#13 (Cannabichromene or "521-35-7"):ti,ab,kw 1
#14 (Nabilone or Cesamet or cesametic or "cpd109514" or "cpd-109514" or "lilly-109514" or "lilly109514" or "51022-71-0"):ti,ab,kw 71
#15 (Nabiximols or Sativex or "Gw-1000" or "gw1000" or "sab-378" or "sab378" or "56575-23-6"):ti,ab,kw 36
#16 (Anandamide or "N-arachidonoylethanolamine"):ti,ab,kw 18
#17 (canabinoid* or canabidiol* or cannabinoid* or Tetrahydrocannabinol* or tetra-hydrocannabinol* or endocannabinoid* or Cannabidiol or cannabinol):ti,ab 665
#18 (nantradol or "cp-44001" or "cp44001" or "cp-44001-1" or "cp440011" or "cp 440011" or "cp44001-1" or "72028-54-7"):ti,ab,kw 0
#19 {or #1-#18} 1861

CENTRAL search retrieved 1781 references.

International Association for Cannabinoid Medicines (IACM) (Internet): up to 2014/04/07
Searched 4.4.14 & 7.4.14
http://www.cannabis-med.org/

Browsed website:

Medicine
Science
Laws and Politics
Archive
Current Studies
Newsletter: IACM-Bulletin
Journal: Cannabinoids; Journal of Cannabis Therapeutics
Conference: Former (2013, 2011, 2009)

IACM Database of Clinical Studies and Case Reports (Internet): up to 2014/04/04
Searched 4.4.14
http://www.cannabis-med.org/studies/study.php

Clinical Studies and Case Reports

Copied entire list (including URL link to detailed record); 360 records

NIH Clinicaltrials.gov (Internet): up to 2014/4/7

Searched 7.4.14
http://clinicaltrials.gov/ct2/search/advanced

Advanced search option – search terms box

	Results
(marijuana OR marihuana OR cannabis OR canabis OR hashish OR hash OR bhang OR ganja OR ganjah OR hemp OR charas)	396
(cannador OR eucannabinolide OR dronabinol OR dronabinolum OR deltanyne OR marinol OR THC OR tetranabinex OR nantradol)	169
(nabidiolex OR dexanabinol OR cannabichromene OR nabilone OR cesamet OR cesametic OR nabiximols OR sativex OR anandamide)	339
(canabinoid* OR canabidiol* OR cannabinoid* OR tetrahydrocannabinol* OR tetra-hydrocannabinol* OR endocannabinoid* OR cannabidiol OR cannabinol)	216
Total	**1120**
Total after dedup	**522**

metaRegister of Controlled Trials (mRCT) (Internet): up to 2014/4/7
Searched 7.4.14
http://www.controlled-trials.com/

Advanced search option – search terms box.

NIH Clinical Trials register option not ticked as already searched separately.

	Results
(marijuana OR marihuana OR cannabis OR canabis OR hashish OR hash OR bhang OR ganja OR ganjah OR hemp OR charas)	14
(cannador OR eucannabinolide OR dronabinol OR dronabinolum OR deltanyne OR marinol OR THC OR tetranabinex OR nantradol)	6
(nabidiolex OR dexanabinol OR cannabichromene OR nabilone OR cesamet OR cesametic OR nabiximols OR sativex OR anandamide)	4
(canabinoid* OR canabidiol* OR cannabinoid* OR tetrahydrocannabinol* OR tetra-hydrocannabinol* OR endocannabinoid* OR cannabidiol OR cannabinol)	9
Total	**33**
Total after dedup	**12**

WHO International Clinical Trials Register Portfolio (ICTRP) (Internet): up to 7/04/14
Searched 8.4.14
http://www.who.int/ictrp/en/

Advanced search option.

Intervention	Results
(marijuana OR marihuana OR cannabis OR canabis OR hashish OR hash OR bhang OR ganja OR ganjah OR hemp OR charas)	311 records for 236 trials found
(cannador OR eucannabinolide OR dronabinol OR dronabinolum OR deltanyne OR marinol OR THC OR tetranabinex OR nantradol)	182 records for 124 trials found
(nabidiolex OR dexanabinol OR cannabichromene OR nabilone OR cesamet OR cesametic OR nabiximols OR sativex OR anandamide)	136 records for 82 trials found
(canabinoid* OR canabidiol* OR cannabinoid* OR tetrahydrocannabinol* OR tetra-hydrocannabinol* OR endocannabinoid* OR cannabidiol OR cannabinol)	203 records for 142 trials found
Total	**584 trials**
Total after dedup	**422 trials**

Additional searches

Observational studies: depression

Embase (OvidSP): 1974-2014/wk 24
Searched 20.6.14

1 Cannabaceae/ (53)
2 exp cannabinoid/ (43393)
3 (marijuana or marihuana or cannabis or canabis).ti,ab,ot,hw. (32185)
4 (Hashish or hash or bhang or ganja or ganjah or hemp or charas).ti,ab,ot,hw. (1703)
5 (cannador or eucannabinolide or 8001-45-4 or 8063-14-7 or 38458-58-1).ti,ab,ot,hw,rn. (21449)
6 (9tetrahydrocannabinol$ or delta3-thc or sp-104 or sp104 or 1972-08-3).ti,ab,ot,hw,rn. (4841)
7 (Dronabinol or Marinol or dronabinolum or deltanyne or ea-1477 or ea1477 or tetranabinex or qcd-84924 or qcd84924 or 7663-50-5).ti,ab,ot,hw,rn. (5560)
8 (delta-9-THC or 5957-75-5 or 1972-08-3).ti,ab,ot,hw,rn. (5125)
9 delta9?11?tetrahydrocannabinol.ti,ab,ot,hw. (0)
10 (THC or CBD or AEA).ti,ab,ot. (13410)
11 (nabidiolex or 13956-29-1).ti,ab,ot,hw,rn. (1902)
12 (dexanabinol or Hu-210 or Hu-211 or hu210 or hu211 or 112924-45-5).ti,ab,ot,hw,rn. (1109)
13 (Cannabichromene or 521-35-7).ti,ab,ot,hw,rn. (973)
14 (Nabilone or Cesamet or cesametic or cpd109514 or cpd-109514 or lilly-109514 or lilly109514 or 51022-71-0).ti,ab,ot,hw,rn. (982)
15 (Nabiximols or Sativex or Gw-1000 or gw1000 or sab-378 or sab378 or 56575-23-6).ti,ab,ot,hw,rn. (287)
16 (Anandamide or N-arachidonoylethanolamine).ti,ab,ot,hw. (5035)
17 (canabinoid$ or canabidiol$ or cannabinoid$ or Tetrahydrocannabinol$ or tetra-hydrocannabinol$ or endocannabinoid$ or Cannabidiol or cannabinol).ti,ab,ot. (21248)
18 (nantradol or cp-44001 or cp44001 or cp-44001-1 or cp 440011 or cp440011 or cp44001-1 or 72028-54-7).ti,ab,ot,hw,rn. (99)
19 or/1-18 (61191)

20 exp Depression/ (312811)
21 mood disorder/ (27013)
22 exp mania/ (48510)
23 affective psychosis/ (1233)
24 (depression$ or depressive$ or depressed or melancholˆ$ or dysthymia or dysthymic or dysphori$ or seasonal affective).ti,ab,ot,hw. (506888)
25 ((mood or affective or delusion$ or schizotypal$ or personality or obsessive or compulsive or cogniti$) adj2 (disorder$ or psychosis)).ti,ab,ot,hw. (106716)
26 (bipolar$ adj2 (disorder$ or illness$ or disease$ or episod$)).ti,ab,hw,ot. (44168)
27 (mania or manic or hypomanic or hypomania).ti,ab,hw,ot. (31649)
28 cyclothym$.ti,ab,hw,ot. (1297)
29 or/20-28 (587704)
30 19 and 29 (6249)
31 exp case control study/ (85596)
32 cohort analysis/ (169422)
33 longitudinal study/ (66952)
34 prospective study/ (252519)
35 follow up/ (803875)
36 case study/ (26350)
37 cohort$.ti,ab,ot. (399335)
38 (case$ adj5 control$).ti,ab,ot. (148042)
39 (case$ and series).ti,ab,ot. (159529)
40 (observational adj3 (study or studies)).ti,ab,ot. (82216)
41 or/31-40 (1677823)
42 30 and 41 (805)
43 animal/ (1567887)
44 animal experiment/ (1779185)
45 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5648556)
46 or/43-45 (5648556)
47 exp human/ (14853038)
48 human experiment/ (325857)
49 or/47-48 (14854467)
50 46 not (46 and 49) (4521909)
51 42 not 50 (803)

Study design filter based on:
BMJ Evidence Centre Information Specialists. Study design search filter: Embase cohort, case-control, and case series strategy [Internet]. London: BMJ Publishing Group Limited, 2012 [accessed 20.6.14]. Available from: http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.html

Medline (OvidSP): 1946-2014/Jun wk 2
Searched 20.6.14
1 exp cannabinoids/ (10255)
2 cannabis/ or cannabaceae/ (6787)

3 (marijuana or marihuana or cannabis or canabis).ti,ab,ot,hw. (19255)
4 (Hashish or hash or bhang or ganja or ganjah or hemp or charas).ti,ab,ot,hw. (1166)
5 (cannador or eucannabinolide or 8001-45-4 or 8063-14-7 or 38458-58-1).ti,ab,ot,hw,rn. (4)
6 (9tetrahydrocannabinol$ or delta3-thc or sp-104 or sp104 or 1972-08-3 or dronabinol or marinol or dronabinolum or deltanyne or ea-1477 or ea1477 or tetranabinex or qcd-84924 or qcd84924 or 7663-50-5).ti,ab,ot,hw,rn. (5867)
7 (delta-9-THC or 5957-75-5 or 1972-08-3).ti,ab,ot,hw,rn. (907)
8 delta9?11?tetrahydrocannabinol.ti,ab,ot,hw. (0)
9 (THC or CBD or AEA).ti,ab,ot. (8765)
10 (nabidiolex or 13956-29-1).ti,ab,ot,hw,rn. (0)
11 (dexanabinol or Hu-210 or Hu-211 or hu210 or hu211 or 112924-45-5).ti,ab,ot,hw,rn. (447)
12 (Cannabichromene or 521-35-7).ti,ab,ot,hw,rn. (75)
13 (Nabilone or Cesamet or cesametic or cpd109514 or cpd-109514 or lilly-109514 or lilly109514 or 51022-71-0).ti,ab,ot,hw,rn. (224)
14 (Nabiximols or Sativex or Gw-1000 or gw1000 or sab-378 or sab378 or 56575-23-6).ti,ab,ot,hw,rn. (89)
15 (Anandamide or N-arachidonoylethanolamine).ti,ab,ot,hw. (2923)
16 (canabinoid$ or canabidiol$ or cannabinoid$ or Tetrahydrocannabinol$ or tetra-hydrocannabinol$ or endocannabinoid$ or Cannabidiol or cannabinol).ti,ab,ot. (15944)
17 (nantradol or cp-44001 or cp44001 or cp-44001-1 or cp 440011 or cp440011 or cp44001-1 or 72028-54-7).ti,ab,ot,hw,rn. (65)
18 or/1-17 (36767)
19 exp Depressive Disorder/ (80881)
20 Depression/ (76260)
21 Mood Disorders/ (10833)
22 exp Affective Disorders, Psychotic/ (33139)
23 (depression$ or depressive$ or depressed or melanchol$ or dysthymia or dysthymic or dysphori$ or seasonal affective).ti,ab,ot,hw. (345553)
24 ((mood or affective or delusion$ or schizotypal$ or personality or obsessive or compulsive or cogniti$) adj2 (disorder$ or psychosis)).ti,ab,ot,hw. (131279)
25 (bipolar$ adj2 (disorder$ or illness$ or disease$ or episod$)).ti,ab,hw,ot. (35360)
26 (mania or manic or hypomanic or hypomania).ti,ab,hw,ot. (13482)
27 cyclothym$.ti,ab,hw,ot. (968)
28 or/19-27 (458575)
29 exp Cohort Studies/ (1357184)
30 cohort$.ti,ab,ot. (256807)
31 Epidemiologic Methods/ (29801)
32 exp case-control studies/ (665073)
33 (case$ adj5 control$).ti,ab,ot. (111641)
34 (case$ and series).ti,ab,ot. (112325)
35 (observational adj3 (study or studies)).ti,ab,ot. (51370)
36 or/29-35 (1732497)
37 18 and 28 and 36 (601)
38 exp Animals/ not (exp Animals/ and Humans/) (3951750)
39 37 not 38 (601)

Study design filter based on:
BMJ Evidence Centre Information Specialists. Study design search filter: Medline cohort, case-control, and case-series strategy [Internet]. London: BMJ Publishing Group Limited, 2012 [accessed 20.6.14]. Available from: http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.html

Medline In-Process & Daily Update (OvidSP): up to 19 June 2014
Searched 20.6.14

1 exp cannabinoids/ (6)
2 cannabis/ or cannabaceae/ (0)
3 (marijuana or marihuana or cannabis or canabis).ti,ab,ot,hw. (1263)
4 (Hashish or hash or bhang or ganja or ganjah or hemp or charas).ti,ab,ot,hw. (163)
5 (cannador or eucannabinolide or 8001-45-4 or 8063-14-7 or 38458-58-1).ti,ab,ot,hw,rn. (1)
6 (9tetrahydrocannabinol$ or delta3-thc or sp-104 or sp104 or 1972-08-3 or dronabinol or marinol or dronabinolum or deltanyne or ea-1477 or ea1477 or tetranabinex or qcd-84924 or qcd84924 or 7663-50-5).ti,ab,ot,hw,rn. (20)
7 (delta-9-THC or 5957-75-5 or 1972-08-3).ti,ab,ot,hw,rn. (7)
8 delta9?11?tetrahydrocannabinol.ti,ab,ot,hw. (0)
9 (THC or CBD or AEA).ti,ab,ot. (692)
10 (nabidiolex or 13956-29-1).ti,ab,ot,hw,rn. (0)
11 (dexanabinol or Hu-210 or Hu-211 or hu210 or hu211 or 112924-45-5).ti,ab,ot,hw,rn. (8)
12 (Cannabichromene or 521-35-7).ti,ab,ot,hw,rn. (1)
13 (Nabilone or Cesamet or cesametic or cpd109514 or cpd-109514 or lilly-109514 or lilly109514 or 51022-71-0).ti,ab,ot,hw,rn. (7)
14 (Nabiximols or Sativex or Gw-1000 or gw1000 or sab-378 or sab378 or 56575-23-6).ti,ab,ot,hw,rn. (23)
15 (Anandamide or N-arachidonoylethanolamine).ti,ab,ot,hw. (147)
16 (canabinoid$ or canabidiol$ or cannabinoid$ or Tetrahydrocannabinol$ or tetra-hydrocannabinol$ or endocannabinoid$ or Cannabidiol or cannabinol).ti,ab,ot. (1153)
17 (nantradol or cp-44001 or cp44001 or cp-44001-1 or cp 440011 or cp440011 or cp44001-1 or 72028-54-7).ti,ab,ot,hw,rn. (0)
18 or/1-17 (2711)
19 exp Depressive Disorder/ (65)
20 Depression/ (78)
21 Mood Disorders/ (3)
22 exp Affective Disorders, Psychotic/ (13)
23 (depression$ or depressive$ or depressed or melanchol$ or dysthymia or dysthymic or dysphori$ or seasonal affective).ti,ab,ot,hw. (20691)
24 ((mood or affective or delusion$ or schizotypal$ or personality or obsessive or compulsive or cogniti$) adj2 (disorder$ or psychosis)).ti,ab,ot,hw. (3947)
25 (bipolar$ adj2 (disorder$ or illness$ or disease$ or episod$)).ti,ab,hw,ot. (1972)
26 (mania or manic or hypomanic or hypomania).ti,ab,hw,ot. (1004)
27 cyclothym$.ti,ab,hw,ot. (38)

28 or/19-27 (24371)
29 exp Cohort Studies/ (1370)
30 cohort$.ti,ab,ot. (25177)
31 Epidemiologic Methods/ (6)
32 exp case-control studies/ (879)
33 (case$ adj5 control$).ti,ab,ot. (9465)
34 (case$ and series).ti,ab,ot. (10925)
35 (observational adj3 (study or studies)).ti,ab,ot. (7335)
36 or/29-35 (50613)
37 18 and 28 and 36 (22)
38 exp Animals/ not (exp Animals/ and Humans/) (1993)
39 37 not 38 (22)

Study design filter based on:
BMJ Evidence Centre Information Specialists. Study design search filter: Medline cohort, case-control, and case-series strategy [Internet]. London: BMJ Publishing Group Limited, 2012 [accessed 20.6.14]. Available from: http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.html

PubMed (https://www.ncbi.nlm.nih.gov/pubmed): up to 20.6.2014
Searched 20.6.14
PubMed not Medline searched to ensure 'ahead-of-print' records retrieved

#36 (#34 AND #35) 7
#35 ((pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb])) 1776397
#34 (#15 AND #25 AND #33) 413
#33 (#26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32) 1596164
#32 "observational study"[tiab] OR "observational studies"[tiab] 46492
#31 "case series"[tiab] 37458
#30 "case control"[tiab] OR "case controls"[tiab] OR "case controlled"[tiab] 80139
#29 "Case-Control Studies"[Mesh] 651645
#28 "Epidemiologic Methods"[Mesh:NoExp] 29260
#27 cohort *[tiab] OR cohort*[ot] 117113
#26 "Cohort Studies"[Mesh] 1330158
#25 (#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24) 389094
#24 mania[tiab] OR manic[tiab] OR hypomanic[tiab] OR hypomania[tiab] OR cyclothym*[tiab] 15061
#23 "bipolar disorder"[tiab] OR "bipolar disorders"[tiab] OR "bipolar illness"[tiab] OR "bipolar episode"[tiab] OR "bipolar episodes"[tiab] 17339
#22 "mood psychosis"[tiab] OR "affective psychosis"[tiab] OR "delusion psychosis"[tiab] OR "delusional psychosis"[tiab] OR "schizotypal psychosis"[tiab] OR "personality psychosis"[tiab] OR "obsessive psychosis"[tiab] OR "compulsive psychosis"[tiab] OR "cognitive psychosis"[tiab] 706
#21 "mood disorder"[tiab] OR "mood disorders"[tiab] OR "affective disorder"[tiab] OR "affective disorders"[tiab] OR "delusion disorder"[tiab] OR "delusion disorders"[tiab] OR "delusional disorder"[tiab] OR "delusional disorders"[tiab] OR "schizotypal disorder"[tiab] OR "schizotypal disorders"[tiab] OR "personality disorder"[tiab] OR "personality

disorders"[tiab] OR "obsessive disorder"[tiab] OR "obsessive disorders"[tiab] OR "compulsive disorder"[tiab] OR "compulsive disorders"[tiab] OR "cognitive disorder"[tiab] OR "cognitive disorders"[tiab] 47697
#20 (depression*[tiab] OR depressive*[tiab] OR depressed[tiab] OR melanchol*[tiab] OR dysthymia[tiab] OR dysthymic[tiab] OR dysphori*[tiab] OR "seasonal affective"[tiab]) 303941
#19 "Affective Disorders, Psychotic"[Mesh] 32460
#18 "Mood Disorders"[Mesh:NoExp] 10584
#17 "Depression"[Mesh] 74443
#16 "Depressive Disorder"[Mesh] 79352
#15 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14) 36515
#14 nantradol[tiab] OR nantradol[ot] OR cp-44001[tiab] OR cp44001[tiab] OR cp-44001-1[tiab] OR "cp 440011"[tiab] OR cp440011[tiab] OR cp44001-1[tiab] 19
#13 canabinoid*[tiab] OR canabinoid*[ot] OR canabidiol*[tiab] OR cannabinoid*[tiab] OR cannabinoid*[ot] OR tetrahydrocannabinol*[tiab] OR tetra-hydrocannabinol*[tiab] OR endocannabinoid* OR cannabidiol*[tiab] OR cannabinol*[tiab] 17329
#12 anandamide[tiab] OR anandamide[ot] OR n-arachidonoylethanolamine[tiab] 3061
#11 nabiximols[tiab] OR nabiximols[ot] OR sativex[tiab] OR sativex[ot] OR gw-1000[tiab] OR gw1000[tiab] OR sab-378[tiab] OR sab378[tiab] 111
#10 nabilone[tiab] OR nabilone[ot] OR cesamet[tiab] OR cesametic[tiab] OR cpd109514[tiab] OR cpd-109514[tiab] OR lilly-109514[tiab] OR lilly109514[tiab] 200
#9 cannabichromene[tiab] OR cannabichromene[ot] 71
#8 (dexanabinol[tiab] OR dexanabinol[ot] OR Hu-210[tiab] OR Hu-211[tiab] OR hu210[tiab] OR hu211[tiab]) 397
#7 nabidiolex[tiab] OR nabidiolex[ot] 0
#6 THC[tiab] OR THC[ot] OR CBD[tiab] OR AEA[tiab] 9407
#5 delta-9-THC[tiab] OR delta-9-THC[ot] OR delta-9-11-tetrahydrocannabinol[tiab] 994
#4 9tetrahydrocannabinol*[tiab] OR delta3-thc[tiab] OR sp-104[tiab] OR sp104[tiab] OR dronabinol[tiab] OR marinol[tiab] OR dronabinolum[tiab] OR deltanyne[tiab] OR ea-1477[tiab] OR ea1477[tiab] OR tetranabinex[tiab] OR qcd-84924[tiab] OR qcd84924[tiab] 256
#3 cannador[tiab] OR eucannabinolide[tiab] 4
#2 hashish[tiab] OR hash[tiab] OR bhang[tiab] OR ganja[tiab] OR ganjah[tiab] OR hemp[tiab] OR charas[tiab] 1339
#1 (marijuana[tiab] OR marijuana[ot] OR marihuana[tiab] OR cannabis[tiab] OR cannabis[ot] OR canabis[tiab]) 16924

Study design filter based on:
BMJ Evidence Centre Information Specialists. Study design search filter: Medline cohort, case-control, and case-series strategy [Internet]. London: BMJ Publishing Group Limited, 2012 [accessed 20.6.14]. Available from: http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.html

PsycINFO (OvidSP): 1806-2014/June wk 3
Searched 20.6.14

1 exp cannabis/ (4911)
2 exp cannabinoids/ (3495)
3 (marijuana or marihuana or cannabis or canabis).ti,ab,ot,hw. (12817)
4 (Hashish or hash or bhang or ganja or ganjah or hemp or charas).ti,ab,ot,hw. (472)
5 (cannador or eucannabinolide or 8001-45-4 or 8063-14-7 or 38458-58-1).ti,ab,ot,hw. (1)
6 (9tetrahydrocannabinol$ or delta3-thc or sp-104 or sp104 or 1972-08-3).ti,ab,ot,hw. (7)
7 (dronabinol or marinol or dronabinolum or deltanyne or ea-1477 or ea1477 or tetranabinex or qcd-84924 or qcd84924 or 7663-50-5).ti,ab,ot,hw. (61)
8 (delta-9-THC or 5957-75-5 or 1972-08-3).ti,ab,ot,hw. (45)
9 delta9?11?tetrahydrocannabinol.ti,ab,ot,hw. (0)
10 (THC or CBD or AEA).ti,ab,ot. (1954)
11 (nabidiolex or 13956-29-1).ti,ab,ot,hw. (0)
12 (dexanabinol or Hu-210 or Hu-211 or hu210 or hu211 or 112924-45-5).ti,ab,ot,hw. (90)
13 (Cannabichromene or 521-35-7).ti,ab,ot,hw. (11)
14 (Nabilone or Cesamet or cesametic or cpd109514 or cpd-109514 or lilly-109514 or lilly109514 or 51022-71-0).ti,ab,ot,hw. (44)
15 (Nabiximols or Sativex or Gw-1000 or gw1000 or sab-378 or sab378 or 56575-23-6).ti,ab,ot,hw. (30)
16 (Anandamide or N-arachidonoylethanolamine).ti,ab,ot,hw. (564)
17 (canabinoid$ or canabidiol$ or cannabinoid$ or Tetrahydrocannabinol$ or tetra-hydrocannabinol$ or endocannabinoid$ or Cannabidiol or cannabinol).ti,ab,ot. (4585)
18 (nantradol or cp-44001 or cp44001 or cp-44001-1 or cp 440011 or cp440011 or cp44001-1 or 72028-54-7).ti,ab,ot,hw. (6)
19 or/1-18 (16670)
20 exp major depression/ (92849)
21 "depression (emotion)"/ (21582)
22 affective disorders/ (11431)
23 exp mania/ (5100)
24 exp bipolar disorder/ (19434)
25 (depression$ or depressive$ or depressed or melanchol$ or dysthymia or dysthymic or dysphori$ or seasonal affective).ti,ab,ot,hw. (219629)
26 ((mood or affective or delusion$ or schizotypal$ or personality or obsessive or compulsive or cogniti$) adj2 (disorder$ or psychosis)).ti,ab,ot,hw. (74881)
27 (bipolar$ adj2 (disorder$ or illness$ or disease$ or episod$)).ti,ab,hw,ot. (24495)
28 (mania or manic or hypomanic or hypomania).ti,ab,hw,ot. (17263)
29 cyclothym$.ti,ab,hw,ot. (1013)
30 or/20-29 (281328)
31 cohort analysis/ (1025)
32 exp longitudinal studies/ (15291)
33 followup studies/ (12310)
34 Retrospective Studies/ (342)
35 Observation Methods/ (4491)
36 (followup study or retrospective study or longitudinal study).md. (141170)
37 ((cohort or panel) adj3 (study or studies or analy$)).ti,ab,hw,ot. (16142)
38 (longitudinal adj3 (study or studies or survey or surveys or analy$ or pattern$ or data)).ti,ab,hw,ot. (58323)

39 ((follow up or followup) adj3 (study or studies or survey or surveys or analy$ or data)).ti,ab,hw,ot. (28315)
40 ((retrospective or prospective) adj3 (study or studies or survey or surveys or analy$ or pattern$ or data)).ti,ab,hw,ot. (32586)
41 (case adj3 (control$ or comparison$ or series or group$)).ti,ab,hw,ot. (13206)
42 or/31-41 (203602)
43 19 and 30 and 42 (376)
44 animal.de,po. (309848)
45 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or canine or feline or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).mp. (327789)
46 44 or 45 (364602)
47 human.po. (3045312)
48 46 not (46 and 47) (301326)
49 43 not 48 (376)

BIOSIS Citation Index (Web of Knowledge): 1926-2014/06/20
Searched 24.6.14

30 32 #29 AND #23 AND #18
29 499,659 #28 OR #27 OR #26 OR #25 OR #24
28 153,266 TS=(case* NEAR/5 (control* or series or comparison* or group*))
27 235,545 TS=((retrospective or prospective) NEAR/3 (study or studies or survey or surveys or analy* or pattern* or data))
26 56,499 TS=(("follow up" or followup) NEAR/3 (study or studies or survey or surveys or analy* or data))
25 47,743 TS=(longitudinal NEAR/3 (study or studies or survey or surveys or analy* or pattern* or data))
24 80,312 TS=((cohort or panel) NEAR/3 (study or studies or analy*))
23 391,433 #22 OR #21 OR #20 OR #19
22 12,921 TS=(mania or manic or hypomanic or hypomania or cyclothym*)
21 20,570 TS=(bipolar* NEAR/2 (disorder* or illness* or disease* or episod*))
20 77,995 TS=((mood or affective or delusion* or schizotypal* or personality or obsessive or compulsive or cogniti*) NEAR/2 (disorder* or psychosis))
19 325,146 TS=(depression* or depressive* or depressed or melanchol* or dysthymia or dysthymic or dysphori* or "seasonal affective")
18 12,460 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
17 0 TS=(dronabinolum or deltanyne or cp44001 or "cp 440011")
16 209 TS=(Dronabinol or Marinol)
15 68 TS=(nantradol or "cp-44001" or "cp-44001-1" or cp440011 or "cp44001-1" or "72028-54-7")

14 941 TS=((Medical or medicinal or therapeutic* or therapy or therapies*) NEAR/5 (canabinoid* or canabidiol* or cannabinoid* or Tetrahydrocannabinol* or "tetra-hydrocannabinol*" or endocannabinoid* or Cannabidiol or cannabinol))
13 3,876 TS=(Anandamide or "N-arachidonoylethanolamine")
12 85 TS=(Nabiximols or Sativex or "Gw-1000" or gw1000 or "sab-378" or sab378 or "56575-23-6")
11 195 TS=(Nabilone or Cesamet or cesametic or cpd109514 or "cpd-109514" or "lilly-109514" or lilly109514 or "51022-71-0")
10 103 TS=(Cannabichromene or "521-35-7")
9 525 TS=(dexanabinol or "Hu-210" or "Hu-211" or hu210 or hu211 or "112924-45-5")
8 1 TS=(nabidiolex or "13956-29-1")
7 784 TI=(THC)
6 1 TS=("delta9 11 tetrahydrocannabinol" or "delta9-11-tetrahydrocannabinol" or delta911tetrahydrocannabinol)
5 1,287 TS=("delta-9-THC" or "5957-75-5" or "1972-08-3")
4 24 TS=(9tetrahydrocannabinol* or "delta3-thc" or "sp-104" or sp104 or "1972-08-3")
3 12 TS=(cannador or eucannabinolide or "8001-45-4" or "8063-14-7" or "38458-58-1")
2 3,801 TS=(Hashish or hash or bhang or ganja or ganjah or hemp or charas)
1 2,079 TS=((Medical or medicinal or therapeutic* or therapy or therapies*) NEAR/15 (marijuana or marihuana or cannabis or canabis))

CINAHL (Cumulative Index to Nursing and Allied Health Literature) (EBSCO): 1981-2014/06/20
Searched 24.6.14

S1 TX (Hashish or hash)
javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl00$linkResults','')
(843)javascript:showShDetails(%22ctl00_ctl00_FindField_FindField_historyControl_ctrlPopup%22, %22S1%22);
http://eds.b.ebscohost.com.ezproxy.stir.ac.uk/Legacy/Views/UserControls/EHOST/
S2 TX (marijuana or marihuana or cannabis or canabis)
javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl01$linkResults','') (10,506)
javascript:showShDetails(%22ctl00_ctl00_FindField_FindField_historyControl_ctrlPopup%22, %22S2%22);http://eds.b.ebscohost.com.ezproxy.stir.ac.uk/Legacy/Views/UserControls/EHOST/
S3 (MH "Cannabis")
javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl02$linkResults','') (3,278)

S4 TX (bhang or ganja or ganjah or hemp or charas)
javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl03$linkResults','') (456)
S5 TX (cannador or eucannabinolide or "8001-45-4" or "8063-14-7" or "38458-58-1")
javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl04$linkResults','') (3)
S6 TX (9tetrahydrocannabinol* or "delta3-thc" or "sp-104" or sp104 or "1972-08-3")
javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl05$linkResults','') (218)
http://eds.b.ebscohost.com.ezproxy.stir.ac.uk/Legacy/Views/UserControls/EHOST/
S7 TX ("delta-9-THC" or "5957-75-5" or "1972-08-3" or nantradol or "cp-44001" or "cp-44001-1" or cp440011 or "cp44001-1" or "72028-54-7" or cp44001 or "cp 440011")
javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl06$linkResults','') (53)
S8 TX (delta911tetrahydrocannabinol)
javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl07$linkResults','') (0)
S9 TX ("delta9 11 tetrahydrocannabinol" or "delta9-11-tetrahydrocannabinol")
javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl08$linkResults','') (0)
S10 TX (THC or canabinoid? or canabidiol? or cannabinoid? or Tetrahydrocannabinol? or "tetra-hydrocannabinol?" or endocannabinoid? or Cannabidiol or cannabinol)
javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl09$linkResults','') (2,720)
S11 TX (nabidiolex or "13956-29-1" or Dronabinol or Marinol or dronabinolum or deltanyne)
javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl10$linkResults','') (196)
S12 TX (dexanabinol or "Hu-210" or "Hu-211" or hu210 or hu211 or "112924-45-5")
javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl11$linkResults','') (15)
S13 TX (Cannabichromene or "521-35-7")
javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl12$linkResults','') (3)
S14 TX (Nabilone or Cesamet or cesametic or cpd109514 or "cpd-109514" or "lilly-109514" or lilly109514 or "51022-71-0")
javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl13$linkResults','') (81)
S15 TX (Anandamide or "N-arachidonoylethanolamine")
javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl14$linkResults','') (119)
S16 TX (Nabiximols or Sativex or "Gw-1000" or gw1000 or "sab-378" or sab378 or "56575-23-6")
javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl15$linkResults','') (53)
S17 S16 or S15 OR S14 OR S13 OR S12 OR S11 OR S10 OR S9 OR S8 OR S7 OR S6 OR S5 OR S4 OR S3 OR S2 OR S1

javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl16$linkResults','') (13,486)
S18 (MH "Prospective Studies")
javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl17$linkResults','') (159,810)
S19 (MH "Case Control Studies+")
javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl18$linkResults','') (31,181)
S20 (MH "Correlational Studies")
javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl19$linkResults','') (16,019)
S21 (MH "Nonconcurrent Prospective Studies")
javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl20$linkResults','') (158)
S22 (MH "Cross Sectional Studies")
javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl21$linkResults','') (62,924)
S23 TX (cohort N2 (study or studies))
javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl22$linkResults','') (43,280)
S24 TX (observational N2 (study or studies))
javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl23$linkResults','') (25,050)
S25 S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24
javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl24$linkResults','') (285,677)
S26 (MH "Affective Disorders, Psychotic+")
javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl25$linkResults','') (4,310)
S27 (MH "Depression+")
javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl26$linkResults','') (44,891)
S28 TI (depression* or depressive* or depressed or melanchol* or dysthymia or dysthymic or dysphoric* or "seasonal affective") OR AB (depression* or depressive* or depressed or melanchol* or dysthymia or dysthymic or dysphoric* or "seasonal affective")
javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl27$linkResults','') (48,560)
S29 TI ((mood or affective or delusion* or schizotypal* or personality or obsessive or compulsive or cogniti*) N2 (disorder* or psychosis)) OR AB ((mood or affective or delusion* or schizotypal* or personality or obsessive or compulsive or cogniti*) N2 (disorder* or psychosis))
javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl28$linkResults','') (7,143)
S30 TI (bipolar* N2 (disorder* or illness* or disease* or episode*)) OR AB (bipolar* N2 (disorder* or illness* or disease* or episode*))
javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl29$linkResults','') (2,688)

S31 TI (mania or manic or hypomanic or hypomania or cyclothym*) OR AB (mania or manic or hypomanic or hypomania or cyclothym*)
javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl30$linkResults','') (1,150)
S32 S26 OR S27 OR S28 OR S29 OR S30 OR S31
javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl31$linkResults','') (71,147)
S33 S17 AND S25 AND S32
javascript: doPostBack('ctl00$ctl00$FindField$FindField$historyControl$HistoryRepeater$ctl32$linkResults','') (430)
javascript:showShDetails(%22ctl00_ctl00_FindField_FindField_historyControl_ctrlPopup%22,%22S33%22);
http://eds.b.ebscohost.com.ezproxy.stir.ac.uk/Legacy/Views/UserControls/EHOST/Trials filter (Observational Studies) based on:
Scottish Intercollegiate Guidelines Network (SIGN). Search filters: observational studies [CINAHL (OvidSP)]. Edinburgh: SIGN, Last modified 26/04/13 Available from: http://www.sign.ac.uk/methodology/filters.html#obs

Science Citation Index (Web of Knowledge): 1900-2014/06/20
Searched 24.6.14

28 13 #27 AND #22 AND #16
27 364,947 #26 OR #25 OR #24 OR #23
26 15,767 TS=(mania or manic or hypomanic or hypomania or cyclothym*)
25 30,634 TS=(bipolar* NEAR/2 (disorder* or illness* or disease* or episod*))
24 62,651 TS=((mood or affective or delusion* or schizotypal* or personality or obsessive or compulsive or cogniti*) NEAR/2 (disorder* or psychosis))
23 312,944 TS=(depression* or depressive* or depressed or melanchol* or dysthymia or dysthymic or dysphori* or "seasonal affective")
22 735,952 #21 OR #20 OR #19 OR #18 OR #17
21 204,235 TS=(case* NEAR/5 (control* or series or comparison* or group*))
20 376,205 TS=((retrospective or prospective) NEAR/3 (study or studies or survey or surveys or analy* or pattern* or data))
19 76,766 TS=(("follow up" or followup) NEAR/3 (study or studies or survey or surveys or analy* or data))
18 73,338 TS=(longitudinal NEAR/3 (study or studies or survey or surveys or analy* or pattern* or data))
17 122,450 TS=((cohort or panel) NEAR/3 (study or studies or analy*))
16 16,732 #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
15 19 TS=(nantradol or "cp-44001" or "cp-44001-1" or cp440011 or "cp44001-1" or cp44001 or "cp 440011" or "72028-54-7")
14 1,238 TS=((Medical or medicinal or therapeutic* or therapy or therapies*) NEAR/10 (canabinoid* or canabidiol* or cannabinoid* or Tetrahydrocannabinol* or "tetra-hydrocannabinol*" or endocannabinoid* or Cannabidiol or cannabinol))
13 4,906 TS=(Anandamide or "N-arachidonoylethanolamine" or Dronabinol or Marinol or dronabinolum or deltanyne)

12 136 TS=(Nabiximols or Sativex or "Gw-1000" or gw1000 or "sab-378" or sab378 or "56575-23-6")
11 225 TS=(Nabilone or Cesamet or cesametic or cpd109514 or "cpd-109514" or "lilly-109514" or lilly109514 or "51022-71-0")
10 79 TS=(Cannabichromene or "521-35-7")
9 467 TS=(dexanabinol or "Hu-210" or "Hu-211" or hu210 or hu211 or "112924-45-5")
8 0 TS=(nabidiolex or "13956-29-1")
7 1,357 TI=(THC)
6 1 TS=("delta9 11 tetrahydrocannabinol" or "delta9-11-tetrahydrocannabinol" or delta911tetrahydrocannabinol)
5 1,197 TS=("delta-9-THC" or "5957-75-5" or "1972-08-3")
4 14 TS=(9tetrahydrocannabinol* or "delta3-thc" or "sp-104" or sp104 or "1972-08-3")
3 6 TS=(cannador or eucannabinolide or "8001-45-4" or "8063-14-7" or "38458-58-1")
2 7,984 TS=(Hashish or hash or bhang or ganja or ganjah or hemp or charas)
1 1,016 TS=((Medical or medicinal or therapeutic* or therapy or therapies*) NEAR/15 (marijuana or marihuana or cannabis or canabis))

AMED (ProQuest): 1985-2014/04/07
Searched 20.6.14

S1 SU.EXACT.EXPLODE("CANNABINOIDS") OR SU.EXACT.EXPLODE("CANNABIS") 416
S2 (marijuana OR marihuana OR cannabis OR canabis) OR (hashish OR hash OR bhang OR ganja OR ganjah OR hemp OR charas) OR (cannador OR eucannabinolide OR "8001-45-4" OR "8063-14-7" OR "38458-58-1") OR (9tetrahydrocannabinol* OR "delta3-thc" OR "sp-104" OR sp104 OR "1972-08-3" OR dronabinol OR marinol OR dronabinolum OR deltanyne OR "ea-1477" OR ea1477 OR tetranabinex OR "qcd-84924" OR qcd84924 OR "7663-50-5") 245
S3 ("delta-9-THC" OR "5957-75-5" OR "1972-08-3") OR (delta9*11*tetrahydrocannabinol) OR (THC OR CBD OR AEA) OR (nabidiolex OR "13956-29-1") 59
S4 (dexanabinol OR "hu-210" OR "hu-211" OR hu210 OR hu211 OR "112924-45-5") OR (cannabichromene OR "521-35-7") OR (nabilone OR cesamet OR cesametic OR cpd109514 OR "cpd-109514" OR "lilly-109514" OR lilly109514 OR "51022-71-0") OR (nabiximols OR sativex OR "gw-1000" OR gw1000 OR "sab-378" OR sab378 OR "56575-23-6") 8
S5 (anandamide OR "n-arachidonoylethanolamine") OR (cannabinoid* OR canabidiol* OR cannabinoid* OR tetrahydrocannabinol* OR "tetra-hydrocannabinol*" OR endocannabinoid* OR cannabidiol OR cannabinol) OR (nantradol OR "cp-44001" OR cp44001 OR "cp-44001-1" OR "cp 440011" OR cp440011 OR "cp44001-1" OR "72028-54-7") 103
S6 S1 OR S2 OR S3 OR S4 OR S5 528
S7 SU.EXACT("DEPRESSIVE DISORDER") OR SU.EXACT("AFFECTIVE DISORDERS PSYCHOTIC") OR SU.EXACT("AFFECTIVE DISORDERS") 1259

S8 (depression* OR depressive* OR depressed OR melanchol* OR dysthymia OR dysthymic OR dysphori* OR "seasonal affective")
6035
S9 ((mood OR affective OR delusion* OR schizotypal* OR personality OR obsessive OR compulsive OR cogniti*) NEAR/2 (disorder* OR psychosis))
2915
S10 (bipolar* NEAR/2 (disorder* OR illness* OR disease* OR episod*) 113
S11 (mania OR manic OR hypomanic OR hypomania OR cyclothym*) 94
S12 S7 OR S8 OR S9 OR S10 OR S11
8559
S13 S6 AND S12 13

Adverse events searches

Embase (OvidSP): 1974-2014/week 31
Searched 7.8.14

1 Cannabaceae/ (54)
2 exp cannabinoid/ (43922)
3 (marijuana or marihuana or cannabis or canabis).ti,ab,ot,hw. (32602)
4 (Hashish or hash or bhang or ganja or ganjah or hemp or charas).ti,ab,ot,hw. (1716)
5 (cannador or eucannabinolide or 8001-45-4 or 8063-14-7 or 38458-58-1).ti,ab,ot,hw,rn. (21608)
6 (9tetrahydrocannabinol$ or delta3-thc or sp-104 or sp104 or 1972-08-3).ti,ab,ot,hw,rn. (4869)
7 (Dronabinol or Marinol or dronabinolum or deltanyne or ea-1477 or ea1477 or tetranabinex or qcd-84924 or qcd84924 or 7663-50-5).ti,ab,ot,hw,rn. (5602)
8 (delta-9-THC or 5957-75-5 or 1972-08-3).ti,ab,ot,hw,rn. (5154)
9 delta9?11?tetrahydrocannabinol.ti,ab,ot,hw. (0)
10 (THC or CBD or AEA).ti,ab,ot. (13569)
11 (nabidiolex or 13956-29-1).ti,ab,ot,hw,rn. (1923)
12 (dexanabinol or Hu-210 or Hu-211 or hu210 or hu211 or 112924-45-5).ti,ab,ot,hw,rn. (1114)
13 (Cannabichromene or 521-35-7).ti,ab,ot,hw,rn. (975)
14 (Nabilone or Cesamet or cesametic or cpd109514 or cpd-109514 or lilly-109514 or lilly109514 or 51022-71-0).ti,ab,ot,hw,rn. (990)
15 (Nabiximols or Sativex or Gw-1000 or gw1000 or sab-378 or sab378 or 56575-23-6).ti,ab,ot,hw,rn. (293)
16 (Anandamide or N-arachidonoylethanolamine).ti,ab,ot,hw. (5078)
17 (canabinoid$ or canabidiol$ or cannabinoid$ or Tetrahydrocannabinol$ or tetra-hydrocannabinol$ or endocannabinoid$ or Cannabidiol or cannabinol).ti,ab,ot. (21498)
18 (nantradol or cp-44001 or cp44001 or cp-44001-1 or cp 440011 or cp440011 or cp44001-1 or 72028-54-7).ti,ab,ot,hw,rn. (99)
19 or/1-18 (62000)
20 animal/ (1572807)
21 animal experiment/ (1790507)

22 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,ot,hw. (5680014)
23 or/20-22 (5680014)
24 exp human/ (14987475)
25 human experiment/ (327602)
26 or/24-25 (14988904)
27 23 not (23 and 26) (4542926)
28 19 not 27 (49483)
29 cohort analysis/ (173685)
30 longitudinal study/ (68253)
31 prospective study/ (257286)
32 follow up/ (819010)
33 cohort$.tw. (409068)
34 exp case control study/ (87021)
35 (case$ adj5 control$).tw. (150156)
36 (observational adj3 (study or studies)).ti,ab,ot. (84439)
37 or/29-36 (1575314)
38 28 and 37 (5073)
39 exp Cardiovascular Diseases/ (2992283)
40 ((cardiovascular or cardio or vascular or peripheral) adj3 (disease$ or disorder$ or failure$)).ti,ab,ot,hw. (370939)
41 ((heart or cardiac or myocardi$ or coronary) adj3 (disease$ or disorder$ or failure$ or attack$ or arrest$ or infarc$ or syndrome$)).ti,ab,ot,hw. (924228)
42 (CVD or CHD).ti,ab,ot. (48001)
43 (ami or mi).ti,ab,ot. (67293)
44 (circulatory adj3 (disease$ or disorder$)).ti,ab,ot,hw. (4947)
45 angina$.ti,ab,ot,hw. (90993)
46 atrial fibril$.ti,ab,ot,hw. (62348)
47 exp Stroke/ (82584)
48 (stroke$ or poststroke$).ti,ab,ot,hw. (260703)
49 (cerebrovascular or cerebro vascular or cerebralvascular or cerebral vascular).ti,ab,ot,hw. (161132)
50 ((brain$ or cerebral$ or lacunar) adj3 (accident$ or infarc$)).ti,ab,ot,hw. (51742)
51 apoplexy.ti,ab,ot,hw. (3009)
52 (CVA or CVAs).ti,ab,ot. (3714)
53 or/39-52 (3176222)
54 exp respiratory tract disease/ (1757553)
55 ((respirat$ or airway$ or air way$ or bronchia$ or broncho$) adj3 (disease$ or disorder$ or illness$ or infect$ or inflamm$ or injury or injuries or malform$ or tumo?r$ or failure$ or impair$)).ti,ab,ot,hw. (256749)
56 ((lung$ or pulmon$ or pleural$) adj3 (disease$ or disorder$ or illness$ or infect$ or inflamm$ or injury or injuries or malform$ or tumo?r$ or failure$ or impair$)).ti,ab,ot,hw. (349301)
57 or/54-56 (1816382)
58 exp neoplasm/ (3414496)

59 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$).ti,ab,ot. (3472213)
60 or/58-59 (4439222)
61 exp psychosis/ (217343)
62 (psychosis or psychoses or psychotic$ or hallucinat$ or delusion$ or deluded or catatonia or catatonic or paranoia or paranoid or paracusia or Phantosmia or paracusia).ti,ab,ot,hw. (147173)
63 (schizophren$ or schizoaffect$ or schizo-affect$ or (dementia adj2 praecox) or hebephreni$ or oligophreni$).ti,ab,ot,hw. (156539)
64 or/61-63 (253619)
65 cannabis addiction/ (6647)
66 ((marijuana or marihuana or cannabis or canabis) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (9826)
67 ((Hashish or hash or bhang or ganja or ganjah or hemp or charas) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (127)
68 ((cannador or eucannabinolide or 8001-45-4 or 8063-14-7 or 38458-58-1) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (0)
69 ((9tetrahydrocannabinol$ or delta3-thc or sp-104 or sp104 or 1972-08-3) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (0)
70 ((Dronabinol or Marinol or dronabinolum or deltanyne or ea-1477 or ea1477 or tetranabinex or qcd-84924 or qcd84924 or 7663-50-5) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (24)
71 ((delta-9-THC or 5957-75-5 or 1972-08-3) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (5)
72 ((THC or CBD or AEA) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (637)
73 ((nabidiolex or 13956-29-1) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (0)
74 ((dexanabinol or Hu-210 or Hu-211 or hu210 or hu211 or 112924-45-5) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (31)
75 ((Cannabichromene or 521-35-7) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (0)
76 ((Nabilone or Cesamet or cesametic or cpd109514 or cpd-109514 or lilly-109514 or lilly109514 or 51022-71-0) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (11)
77 ((Nabiximols or Sativex or Gw-1000 or gw1000 or sab-378 or sab378 or 56575-23-6) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (12)
78 ((Anandamide or N-arachidonoylethanolamine) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (146)
79 ((canabinoid$ or canabidiol$ or cannabinoid$ or Tetrahydrocannabinol$ or tetra-hydrocannabinol$ or endocannabinoid$ or Cannabidiol or cannabinol) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (1160)

80 ((nantradol or cp-44001 or cp44001 or cp-44001-1 or cp 440011 or cp440011 or cp44001-1 or 72028-54-7) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (1)
81 or/65-80 (11449)
82 37 and 81 (1598)
83 82 not 27 (1591)
84 53 or 57 or 60 or 64 (8258053)
85 38 and 84 (1766)
86 83 or 85 (2884)

Study design filter based on:
BMJ Evidence Centre Information Specialists. Study design search filter: Embase cohort and case-control strategy [Internet]. London: BMJ Publishing Group Limited, 2012 [accessed 4.8.14]. Available from: http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.html

Medline (OvidSP): 1946-2014/July week 5
Searched 7.8.14

1 exp cannabinoids/ (10441)
2 cannabis/ or cannabaceae/ (6957)
3 (marijuana or marihuana or cannabis or canabis).ti,ab,ot,hw. (19684)
4 (Hashish or hash or bhang or ganja or ganjah or hemp or charas).ti,ab,ot,hw. (1194)
5 (cannador or eucannabinolide or 8001-45-4 or 8063-14-7 or 38458-58-1 or Dronabinol or Marinol or ea-1477 or ea1477 or tetranabinex or qcd-84924 or qcd84924 or 7663-50-5).ti,ab,ot,hw,rn. (5997)
6 (9tetrahydrocannabinol$ or delta3-thc or sp-104 or sp104 or 1972-08-3).ti,ab,ot,hw,rn. (17)
7 (delta-9-THC or 5957-75-5 or 1972-08-3).ti,ab,ot,hw,rn. (919)
8 delta9?11?tetrahydrocannabinol.ti,ab,ot,hw. (0)
9 (THC or CBD or AEA).ti,ab,ot. (8907)
10 (nabidiolex or 13956-29-1).ti,ab,ot,hw,rn. (0)
11 (dexanabinol or Hu-210 or Hu-211 or hu210 or hu211 or 112924-45-5).ti,ab,ot,hw,rn. (451)
12 (Cannabichromene or 521-35-7).ti,ab,ot,hw,rn. (75)
13 (Nabilone or Cesamet or cesametic or cpd109514 or cpd-109514 or lilly-109514 or lilly109514 or 51022-71-0).ti,ab,ot,hw,rn. (224)
14 (Nabiximols or Sativex or Gw-1000 or gw1000 or sab-378 or sab378 or 56575-23-6).ti,ab,ot,hw,rn. (100)
15 (Anandamide or N-arachidonoylethanolamine).ti,ab,ot,hw. (2957)
16 (canabinoid$ or canabidiol$ or cannabinoid$ or Tetrahydrocannabinol$ or tetra-hydrocannabinol$ or endocannabinoid$ or Cannabidiol or cannabinol).ti,ab,ot. (16256)
17 (nantradol or cp-44001 or cp-44001-1 or cp440011 or cp44001-1 or 72028-54-7).ti,ab,ot,hw,rn. (65)
18 or/1-17 (37453)
19 animals/ not (animals/ and humans/) (3900724)
20 18 not 19 (28244)

21 exp Cohort Studies/ (1386404)
22 cohort$.ti,ab,ot. (265294)
23 controlled clinical trial.pt. (89591)
24 exp case-control studies/ (681412)
25 (case$ adj5 control$).ti,ab,ot. (114273)
26 (observational adj3 (study or studies)).ti,ab,ot. (53408)
27 or/21-26 (1754515)
28 20 and 27 (4497)
29 exp Cardiovascular Diseases/ (1895636)
30 ((cardiovascular or cardio or vascular or peripheral) adj3 (disease$ or disorder$ or failure$)).ti,ab,ot,hw. (261066)
31 ((heart or cardiac or myocardi$ or coronary) adj3 (disease$ or disorder$ or failure$ or attack$ or arrest$ or infarc$ or syndrome$)).ti,ab,ot,hw. (637103)
32 (CVD or CHD).ti,ab,ot. (30866)
33 (ami or mi).ti,ab,ot. (40549)
34 (circulatory adj3 (disease$ or disorder$)).ti,ab,ot,hw. (4317)
35 angina$.ti,ab,ot,hw. (60392)
36 atrial fibril$.ti,ab,ot,hw. (45402)
37 exp Stroke/ (87651)
38 (stroke$ or poststroke$).ti,ab,ot,hw. (177220)
39 (cerebrovascular or cerebro vascular or cerebralvascular or cerebral vascular).ti,ab,ot,hw. (112279)
40 ((brain$ or cerebral$ or lacunar) adj3 (accident$ or infarc$)).ti,ab,ot,hw. (38501)
41 apoplexy.ti,ab,ot,hw. (2283)
42 (CVA or CVAs).ti,ab,ot. (1858)
43 or/29-42 (2102254)
44 exp Respiratory Tract Diseases/ (1070235)
45 ((respirat$ or airway$ or air way$ or bronchia$ or broncho$) adj3 (disease$ or disorder$ or illness$ or infect$ or inflamm$ or injury or injuries or malform$ or tumo?r$ or failure$ or impair$)).ti,ab,ot,hw. (157191)
46 ((lung$ or pulmon$ or pleural$) adj3 (disease$ or disorder$ or illness$ or infect$ or inflamm$ or injury or injuries or malform$ or tumo?r$ or failure$ or impair$)).ti,ab,ot,hw. (235213)
47 or/44-46 (1144417)
48 exp Neoplasms/ (2593679)
49 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$).ti,ab,ot. (2636444)
50 or/48-49 (3396785)
51 exp Psychotic Disorders/ (38857)
52 exp Schizophrenia/ (86224)
53 (psychosis or psychoses or psychotic$ or hallucinat$ or delusion$ or deluded or catatonia or catatonic or paranoia or paranoid or paracusia or Phantosmia or paracusia).ti,ab,ot,hw. (87303)
54 (schizophren$ or schizoaffect$ or schizo-affect$ or (dementia adj2 praecox) or hebephreni$ or oligophreni$).ti,ab,ot,hw. (110615)
55 or/51-54 (165616)
56 Marijuana Abuse/ (4542)

57 ((marijuana or marihuana or cannabis or canabis) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (6487)
58 ((Hashish or hash or bhang or ganja or ganjah or hemp or charas) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (77)
59 ((cannador or eucannabinolide or 8001-45-4 or 8063-14-7 or 38458-58-1) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (0)
60 ((9tetrahydrocannabinol$ or delta3-thc or sp-104 or sp104 or 1972-08-3) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (0)
61 ((Dronabinol or Marinol or dronabinolum or deltanyne or ea-1477 or ea1477 or tetranabinex or qcd-84924 or qcd84924 or 7663-50-5) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (21)
62 ((delta-9-THC or 5957-75-5 or 1972-08-3) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (65)
63 ((THC or CBD or AEA) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (461)
64 ((nabidiolex or 13956-29-1) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (0)
65 ((dexanabinol or Hu-210 or Hu-211 or hu210 or hu211 or 112924-45-5) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (26)
66 ((Cannabichromene or 521-35-7) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (0)
67 ((Nabilone or Cesamet or cesametic or cpd109514 or cpd-109514 or lilly-109514 or lilly109514 or 51022-71-0) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (5)
68 ((Nabiximols or Sativex or Gw-1000 or gw1000 or sab-378 or sab378 or 56575-23-6) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (7)
69 ((Anandamide or N-arachidonoylethanolamine) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (116)
70 ((canabinoid$ or canabidiol$ or cannabinoid$ or Tetrahydrocannabinol$ or tetra-hydrocannabinol$ or endocannabinoid$ or Cannabidiol or cannabinol) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (912)
71 ((nantradol or cp-44001 or cp44001 or cp-44001-1 or cp 440011 or cp440011 or cp44001-1 or 72028-54-7) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (1)
72 or/56-71 (7735)
73 27 and 72 (1556)
74 73 not 19 (1553)
75 43 or 47 or 50 or 55 (6055738)
76 28 and 75 (942)
77 74 or 76 (2175)

Study design filter based on:
BMJ Evidence Centre Information Specialists. Study design search filter: Medline cohort and case-control strategy [Internet]. London: BMJ Publishing Group Limited, 2012 [accessed

6.8.14]. Available from: http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.html

MEDLINE In-Process & Other Non-Indexed Citations; MEDLINE Daily Update. August 06, 2014
Searched 7.8.14

1 exp cannabinoids/ (3)
2 cannabis/ or cannabaceae/ (4)
3 (marijuana or marihuana or cannabis or canabis).ti,ab,ot,hw. (1328)
4 (Hashish or hash or bhang or ganja or ganjah or hemp or charas).ti,ab,ot,hw. (172)
5 (cannador or eucannabinolide or 8001-45-4 or 8063-14-7 or 38458-58-1 or Dronabinol or Marinol or ea-1477 or ea1477 or tetranabinex or qcd-84924 or qcd84924 or 7663-50-5).ti,ab,ot,hw,rn. (19)
6 (9tetrahydrocannabinol$ or delta3-thc or sp-104 or sp104 or 1972-08-3).ti,ab,ot,hw,rn. (2)
7 (delta-9-THC or 5957-75-5 or 1972-08-3).ti,ab,ot,hw,rn. (7)
8 delta9?11?tetrahydrocannabinol.ti,ab,ot,hw. (0)
9 (THC or CBD or AEA).ti,ab,ot. (729)
10 (nabidiolex or 13956-29-1).ti,ab,ot,hw,rn. (0)
11 (dexanabinol or Hu-210 or Hu-211 or hu210 or hu211 or 112924-45-5).ti,ab,ot,hw,rn. (6)
12 (Cannabichromene or 521-35-7).ti,ab,ot,hw,rn. (1)
13 (Nabilone or Cesamet or cesametic or cpd109514 or cpd-109514 or lilly-109514 or lilly109514 or 51022-71-0).ti,ab,ot,hw,rn. (7)
14 (Nabiximols or Sativex or Gw-1000 or gw1000 or sab-378 or sab378 or 56575-23-6).ti,ab,ot,hw,rn. (17)
15 (Anandamide or N-arachidonoylethanolamine).ti,ab,ot,hw. (160)
16 (canabinoid$ or canabidiol$ or cannabinoid$ or Tetrahydrocannabinol$ or tetra-hydrocannabinol$ or endocannabinoid$ or Cannabidiol or cannabinol).ti,ab,ot. (1215)
17 (nantradol or cp-44001 or cp-44001-1 or cp440011 or cp44001-1 or 72028-54-7).ti,ab,ot,hw,rn. (0)
18 or/1-17 (2861)
19 animals/ not (animals/ and humans/) (1067)
20 18 not 19 (2853)
21 exp Cohort Studies/ (887)
22 cohort$.ti,ab,ot. (26596)
23 controlled clinical trial.pt. (57)
24 exp case-control studies/ (595)
25 (case$ adj5 control$).ti,ab,ot. (9930)
26 (observational adj3 (study or studies)).ti,ab,ot. (7804)
27 or/21-26 (42373)
28 20 and 27 (122)
29 exp Cardiovascular Diseases/ (666)
30 ((cardiovascular or cardio or vascular or peripheral) adj3 (disease$ or disorder$ or failure$)).ti,ab,ot,hw. (13423)

31 ((heart or cardiac or myocardi$ or coronary) adj3 (disease$ or disorder$ or failure$ or attack$ or arrest$ or infarc$ or syndrome$)).ti,ab,ot,hw. (27453)
32 (CVD or CHD).ti,ab,ot. (3935)
33 (ami or mi).ti,ab,ot. (3311)
34 (circulatory adj3 (disease$ or disorder$)).ti,ab,ot,hw. (131)
35 angina$.ti,ab,ot,hw. (1871)
36 atrial fibril$.ti,ab,ot,hw. (3623)
37 exp Stroke/ (46)
38 (stroke$ or poststroke$).ti,ab,ot,hw. (13246)
39 (cerebrovascular or cerebro vascular or cerebralvascular or cerebral vascular).ti,ab,ot,hw. (2577)
40 ((brain$ or cerebral$ or lacunar) adj3 (accident$ or infarc$)).ti,ab,ot,hw. (1362)
41 apoplexy.ti,ab,ot,hw. (147)
42 (CVA or CVAs).ti,ab,ot. (170)
43 or/29-42 (55605)
44 exp Respiratory Tract Diseases/ (314)
45 ((respirat$ or airway$ or air way$ or bronchia$ or broncho$) adj3 (disease$ or disorder$ or illness$ or infect$ or inflamm$ or injury or injuries or malform$ or tumo?r$ or failure$ or impair$)).ti,ab,ot,hw. (7669)
46 ((lung$ or pulmon$ or pleural$) adj3 (disease$ or disorder$ or illness$ or infect$ or inflamm$ or injury or injuries or malform$ or tumo?r$ or failure$ or impair$)).ti,ab,ot,hw. (10475)
47 or/44-46 (16880)
48 exp Neoplasms/ (1057)
49 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$).ti,ab,ot. (175457)
50 or/48-49 (175638)
51 exp Psychotic Disorders/ (12)
52 exp Schizophrenia/ (27)
53 (psychosis or psychoses or psychotic$ or hallucinat$ or delusion$ or deluded or catatonia or catatonic or paranoia or paranoid or paracusia or Phantosmia or paracusia).ti,ab,ot,hw. (4506)
54 (schizophren$ or schizoaffect$ or schizo-affect$ or (dementia adj2 praecox) or hebephreni$ or oligophreni$).ti,ab,ot,hw. (6350)
55 or/51-54 (9269)
56 Marijuana Abuse/ (7)
57 ((marijuana or marihuana or cannabis or canabis) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (347)
58 ((Hashish or hash or bhang or ganja or ganjah or hemp or charas) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (7)
59 ((cannador or eucannabinolide or 8001-45-4 or 8063-14-7 or 38458-58-1) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (0)
60 ((9tetrahydrocannabinol$ or delta3-thc or sp-104 or sp104 or 1972-08-3) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (0)

61 ((Dronabinol or Marinol or dronabinolum or deltanyne or ea-1477 or ea1477 or tetranabinex or qcd-84924 or qcd84924 or 7663-50-5) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (1)
62 ((delta-9-THC or 5957-75-5 or 1972-08-3) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (0)
63 ((THC or CBD or AEA) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (43)
64 ((nabidiolex or 13956-29-1) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (0)
65 ((dexanabinol or Hu-210 or Hu-211 or hu210 or hu211 or 112924-45-5) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (1)
66 ((Cannabichromene or 521-35-7) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (0)
67 ((Nabilone or Cesamet or cesametic or cpd109514 or cpd-109514 or lilly-109514 or lilly109514 or 51022-71-0) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (0)
68 ((Nabiximols or Sativex or Gw-1000 or gw1000 or sab-378 or sab378 or 56575-23-6) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (2)
69 ((Anandamide or N-arachidonoylethanolamine) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (7)
70 ((canabinoid$ or canabidiol$ or cannabinoid$ or Tetrahydrocannabinol$ or tetra-hydrocannabinol$ or endocannabinoid$ or Cannabidiol or cannabinol) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (72)
71 ((nantradol or cp-44001 or cp44001 or cp-44001-1 or cp 440011 or cp440011 or cp44001-1 or 72028-54-7) adj5 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$)).ti,ab,ot,hw. (0)
72 or/56-71 (448)
73 27 and 72 (33)
74 73 not 19 (33)
75 43 or 47 or 50 or 55 (244483)
76 28 and 75 (32)
77 74 or 76 (53)

Study design filter based on:
BMJ Evidence Centre Information Specialists. Study design search filter: Medline cohort and case-control strategy [Internet]. London: BMJ Publishing Group Limited, 2012 [accessed 6.8.14]. Available from: http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.html

PubMed (https://www.ncbi.nlm.nih.gov/pubmed): up to 7.8.2014
Searched 7.8.14

#37 Search (#35 and #36) 76
#36 Search (pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb]) 1801169
#35 Search (#17 AND #34) 1172

#34 Search (#25 or #28 or #29 or #32 or #33) 7936671
#33 Search depend*[tiab] or addict*[tiab] or abus*[tiab] or misus*[tiab] or user[tiab] or users[tiab] or habit*[tiab] 1975203
#32 Search (#30 or #31) 125279
#31 Search schizophren*[tiab] or schizoaffect*[tiab] or schizo-affect*[tiab] 93097
#30 Search psychosis[tiab] or psychoses[tiab] or psychotic*[tiab] 48998
#29 Search (cancer*[tiab] or neoplas*[tiab] or oncolog*[tiab] or malignan*[tiab] or tumor*[tiab] or tumour*[tiab] or carcinoma*[tiab] or adenocarcinoma*[tiab] or sarcoma*[tiab] or adenom*[tiab] or lesion*[tiab] 2814536
#28 Search (#26 or #27) 4823137
#27 Search ((lung*[tiab] or pulmon*[tiab] or pleural*[tiab]) AND (disease*[tiab] or disorder*[tiab] or illness*[tiab] or infect*[tiab] or inflamm*[tiab] or injury[tiab] or injuries[tiab] or malform*[tiab] or tumor*[tiab] or tumour*[tiab] or failure*[tiab] or impair*[tiab] 4793908
#26 Search ((respirat*[tiab] or airway*[tiab] or "air way*"[tiab] or bronchia*[tiab] or broncho*[tiab]) AND (disease*[tiab] or disorder*[tiab] or illness*[tiab] or infect*[tiab] or inflamm*[tiab] or injury[tiab] or injuries[tiab] or malform*[tiab] or tumo?r*[tiab] or tumour*[tiab] or failure*[tiab] or impair*[tiab] 3927083
#25 Search (#18 or #19 or #20 or #21 or #22 or #23 or #24) 875951
#24 Search ((brain*[tiab] or cerebral*[tiab] or lacunar[tiab]) AND (accident*[tiab] or infarc*[tiab] 217960
#23 Search cerebrovascular[tiab] or "cerebro vascular"[tiab] or cerebralvascular[tiab] or "cerebral vascular"[tiab] 43158
#22 Search angina*[tiab] or "atrial fibrilation"[tiab] or stroke*[tiab] or poststroke*[tiab] 198144
#21 Search "circulatory disease"[tiab] or "circulatory diseases"[tiab] or "circulatory disorder"[tiab] or "circulatory disorders"[tiab] 3279
#20 Search CVD[tiab] or CHD[tiab] or ami[tiab] 47209
#19 Search ((heart[tiab] or cardiac[tiab] or myocardi*[tiab] or coronary[tiab]) AND (disease*[tiab] or disorder*[tiab] or failure*[tiab] or attack*[tiab] or arrest*[tiab] or infarc*[tiab] or syndrome*[tiab])) 586510
#18 Search "cardiovascular disease"[tiab] or "cardiovascular diseases"[tiab] or "cardiovascular disorder"[tiab] or "cardiovascular disorders"[tiab] or "cardiovascular failure"[tiab] or "cardiovascular failures"[tiab] or "cardio disease"[tiab] or "cardio diseases"[tiab] or "cardio disorder"[tiab] or "cardio disorders"[tiab] or "cardio failure"[tiab] or "cardio failures"[tiab] or "vascular disease"[tiab] or "vascular diseases"[tiab] or "vascular disorder"[tiab] or "vascular disorders"[tiab] or "vascular failure"[tiab] or "vascular failures"[tiab] 137536
#17 Search (#15 AND #16) 1653
#16 Search cohort*[tiab] OR (case*[tiab] AND control*[tiab]) OR (observational[tiab] AND (study[tiab] or studies[tiab])) 652767
#15 Search (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14) 36900
#14 Search (nantradol[tiab] OR nantradol[ot] OR cp-44001[tiab] OR cp44001[tiab] OR cp-44001-1[tiab] OR "cp 440011"[tiab] OR cp440011[tiab] OR cp44001-1[tiab]) 19
#13 Search canabinoid*[tiab] OR canabinoid*[ot] OR canabidiol*[tiab] OR cannabinoid*[tiab] OR cannabinoid*[ot] OR tetrahydrocannabinol*[tiab] OR tetra-

hydrocannabinol*[tiab] OR endocannabinoid* OR cannabidiol*[tiab] OR cannabinol*[tiab] 17499
#12 Search anandamide[tiab] OR anandamide[ot] OR n-arachidonoylethanolamine[tiab] 3083
#11 Search nabiximols[tiab] OR nabiximols[ot] OR sativex[tiab] OR sativex[ot] OR gw-1000[tiab] OR gw1000[tiab] OR sab-378[tiab] OR sab378[tiab] 111
#10 Search nabilone[tiab] OR nabilone[ot] OR cesamet[tiab] OR cesametic[tiab] OR cpd109514[tiab] OR cpd-109514[tiab] OR lilly-109514[tiab] OR lilly109514[tiab] 202
#9 Search cannabichromene[tiab] OR cannabichromene[ot] 71
#8 Search (dexanabinol[tiab] OR dexanabinol[ot] OR Hu-210[tiab] OR Hu-211[tiab] OR hu210[tiab] OR hu211[tiab]) 397
#7 Search nabidiolex[tiab] OR nabidiolex[ot] 0
#6 Search THC[tiab] OR THC[ot] OR CBD[tiab] OR AEA[tiab] 9498
#5 Search delta-9-THC[tiab] OR delta-9-THC[ot] OR delta-9-11-tetrahydrocannabinol[tiab] 1001
#4 Search 9tetrahydrocannabinol*[tiab] OR delta3-thc[tiab] OR sp-104[tiab] OR sp104[tiab] OR dronabinol[tiab] OR marinol[tiab] OR dronabinolum[tiab] OR deltanyne[tiab] OR ea-1477[tiab] OR ea1477[tiab] OR tetranabinex[tiab] OR qcd-84924[tiab] OR qcd84924[tiab] 260
#3 Search cannador[tiab] OR eucannabinolide[tiab] 4
#2 Search (hashish[tiab] OR hash[tiab] OR bhang[tiab] OR ganja[tiab] OR ganjah[tiab] OR hemp[tiab] OR charas[tiab]) 1359
#1 Search (marijuana[tiab] OR marijuana[ot] OR marihuana[tiab] OR cannabis[tiab] OR cannabis[ot] OR canabis[tiab]) 17110

PsycINFO (OvidSP): 1806-2014/July week 5
Searched 7.8.14

1 exp cannabis/ (4968)
2 exp cannabinoids/ (3524)
3 (marijuana or marihuana or cannabis or canabis).ti,ab,ot,hw. (12936)
4 (Hashish or hash or bhang or ganja or ganjah or hemp or charas).ti,ab,ot,hw. (475)
5 (cannador or eucannabinolide or 8001-45-4 or 8063-14-7 or 38458-58-1).ti,ab,ot,hw. (1)
6 (9tetrahydrocannabinol$ or delta3-thc or sp-104 or sp104 or 1972-08-3).ti,ab,ot,hw. (7)
7 (Dronabinol or Marinol or ea-1477 or ea1477 or tetranabinex or qcd-84924 or qcd84924 or 7663-50-5).ti,ab,ot,hw. (61)
8 (delta-9-THC or 5957-75-5 or 1972-08-3).ti,ab,ot,hw. (45)
9 delta9?11?tetrahydrocannabinol.ti,ab,ot,hw. (0)
10 (THC or CBD or AEA).ti,ab,ot. (1971)
11 (nabidiolex or 13956-29-1).ti,ab,ot,hw. (0)
12 (dexanabinol or Hu-210 or Hu-211 or hu210 or hu211 or 112924-45-5).ti,ab,ot,hw. (90)
13 (Cannabichromene or 521-35-7).ti,ab,ot,hw. (11)
14 (Nabilone or Cesamet or cesametic or cpd109514 or cpd-109514 or lilly-109514 or lilly109514 or 51022-71-0).ti,ab,ot,hw. (47)
15 (Nabiximols or Sativex or Gw-1000 or gw1000 or sab-378 or sab378 or 56575-23-6).ti,ab,ot,hw. (31)
16 (Anandamide or N-arachidonoylethanolamine).ti,ab,ot,hw. (565)

17 (canabinoid$ or canabidiol$ or cannabinoid$ or Tetrahydrocannabinol$ or tetra-hydrocannabinol$ or endocannabinoid$ or Cannabidiol or cannabinol).ti,ab,ot. (4626)
18 (nantradol or cp-44001 or cp-44001-1 or cp440011 or cp44001-1 or 72028-54-7).ti,ab,ot,hw. (6)
19 or/1-18 (16825)
20 animal.de,po. (311650)
21 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or canine or feline or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).mp. (329622)
22 or/20-21 (366704)
23 human.po. (3068015)
24 22 not (22 and 23) (302678)
25 19 not 24 (13785)
26 cohort analysis/ (1028)
27 Experiment Controls/ (736)
28 exp longitudinal studies/ (15312)
29 followup studies/ (12310)
30 cohort$.ti,ab,hw,ot,id. (42646)
31 (longitudinal adj3 (study or studies or survey or surveys or analy$ or pattern$ or data)).ti,ab,hw,ot,id. (59378)
32 ((follow up or followup) adj3 (study or studies or survey or surveys or analy$ or data)).ti,ab,hw,ot,id. (28745)
33 (case adj5 (control$ or comparison$ or series or group$)).ti,ab,hw,ot,id. (16720)
34 (observational adj3 (study or studies)).ti,ab,id. (6973)
35 or/26-34 (142733)
36 25 and 35 (1700)
37 exp Cardiovascular Disorders/ (43079)
38 ((cardiovascular or cardio or vascular or peripheral) adj3 (disease$ or disorder$ or failure$)).ti,ab,ot,hw. (14350)
39 ((heart or cardiac or myocardi$ or coronary) adj3 (disease$ or disorder$ or failure$ or attack$ or arrest$ or infarc$ or syndrome$)).ti,ab,ot,hw. (17489)
40 (CVD or CHD).ti,ab,ot. (3070)
41 (ami or mi).ti,ab,ot. (3976)
42 (circulatory adj3 (disease$ or disorder$)).ti,ab,ot,hw. (284)
43 angina$.ti,ab,ot,hw. (927)
44 atrial fibril$.ti,ab,ot,hw. (683)
45 cerebrovascular accidents/ (13532)
46 (stroke$ or poststroke$).ti,ab,ot,hw. (21354)
47 (cerebrovascular or cerebro vascular or cerebralvascular or cerebral vascular).ti,ab,ot,hw. (17752)
48 ((brain$ or cerebral$ or lacunar) adj3 (accident$ or infarc$)).ti,ab,ot,hw. (2308)
49 apoplexy.ti,ab,ot,hw. (112)
50 (CVA or CVAs).ti,ab,ot. (352)
51 or/37-50 (66039)
52 exp respiratory tract disorders/ (10733)

53 ((respirat$ or airway$ or air way$ or bronchia$ or broncho$) adj3 (disease$ or disorder$ or illness$ or infect$ or inflamm$ or injury or injuries or malform$ or tumo?r$ or failure$ or impair$)).ti,ab,ot,hw. (3542)
54 ((lung$ or pulmon$ or pleural$) adj3 (disease$ or disorder$ or illness$ or infect$ or inflamm$ or injury or injuries or malform$ or tumo?r$ or failure$ or impair$)).ti,ab,ot,hw. (3384)
55 or/52-54 (13826)
56 exp Neoplasms/ (35042)
57 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or adenom$ or lesion$).ti,ab,ot. (93978)
58 or/56-57 (96029)
59 exp psychosis/ (92273)
60 (psychosis or psychoses or psychotic$ or hallucinat$ or delusion$ or deluded or catatonia or catatonic or paranoia or paranoid or paracusia or Phantosmia or paracusia).ti,ab,ot,hw. (83959)
61 (schizophren$ or schizoaffect$ or schizo-affect$ or (dementia adj2 praecox) or hebephreni$ or oligophreni$).ti,ab,ot,hw. (101197)
62 or/59-61 (154985)
63 exp drug dependency/ (21620)
64 (depend$ or addict$ or abus$ or misus$ or user or users or problem$ or habit$).ti,ab,ot,hw. (804602)
65 or/63-64 (804602)
66 51 or 55 or 58 or 62 or 65 (1060036)
67 36 and 66 (1254)

BIOSIS Citation Index (Web of Knowledge): 1926-2014/08/07
Searched 7.8.14

 # 41 235 #40 AND #25
40 7,350,501 #39 OR #38 OR #37 OR #36 OR #35 OR #34 OR #33 OR #32 OR #31 OR #30 OR #29 OR #28 OR #27 OR #26
39 2,808,509 TS=((depend* or addict* or abus* or misus* or user or users or problem* or habit*))
38 91,387 TS=((schizophren* or schizoaffect* or schizo-affect* or (dementia NEAR/2 praecox) or hebephreni* or oligophreni*))
37 54,804 TS=((psychosis or psychoses or psychotic* or hallucinat* or delusion* or deluded or catatonia or catatonic or paranoia or paranoid or paracusia or phantosmia or paracusia))
36 3,486,991 TS=((cancer* or neoplas* or oncolog* or malignan* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion*))
35 275,593 TS=(((lung* or pulmon* or pleural*) NEAR/3 (disease* or disorder* or illness* or infect* or inflamm* or injury or injuries or malform* or tumor* or tumour* or failure* or impair*)))
34 555,051 TS=(((respirat* or airway* or "air way*" or bronchia* or broncho*) NEAR/3 (disease* or disorder* or illness* or infect* or inflamm* or injury or injuries or malform* or tumor* or tumour* or failure* or impair*)))
33 2,904 TS=((apoplexy or CVA or CVAs))

32 19,778 TS=(((brain* or cerebral* or lacunar) NEAR/3 (accident* or infarc*)))
31 83,067 TS=((cerebrovascular or "cerebro vascular" or "cerebral vascular" or cerebralvascular))
30 207,601 TS=((angina* or "atrial fibril*" or stroke* or poststroke*))
29 70,158 TS=((circulatory NEAR/3 (disease* or disorder*)))
28 66,859 TS=((CVD or CHD or ami or mi))
27 696,771 TS=(((heart or cardiac or myocard* or coronary) NEAR/3 (disease* or disorder* or failure* or attack* or arrest* or infarc* or syndrome$)))
26 1,031,071 TS=(((cardiovascular or cardio or vascular or peripheral) NEAR/3 (disease* or disorder* or failure*)))
25 279 #24 AND #18
24 593,776 #23 OR #22 OR #21 OR #20 OR #19
23 154,389 TS=((case* NEAR/5 (control* or series or comparison* or group*)))
22 237,471 TS=(((retrospective or prospective) NEAR/3 (study or studies or survey or surveys or analy* or pattern* or data)))
21 56,850 TS=((("follow up" or followup) NEAR/3 (study or studies or survey or surveys or analy* or data)))
20 48,190 TS=((longitudinal NEAR/3 (study or studies or survey or surveys or analy* or pattern* or data)))
19 192,419 TS=(cohort*)
18 12,521 #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
17 0 TS=((dronabinolum or deltanyne or cp44001 or "cp 440011"))
16 211 TS=((Dronabinol or Marinol))
15 68 TS=((nantradol or "cp-44001" or "cp-44001-1" or cp440011 or "cp44001-1" or "72028-54-7"))
14 950 TS=(((Medical or medicinal or therapeutic* or therapy or therapies*) NEAR/5 (canabinoid* or canabidiol* or cannabinoid* or Tetrahydrocannabinol* or "tetra-hydrocannabinol*" or endocannabinoid* or Cannabidiol or cannabinol)))
13 3,893 TS=((Anandamide or "N-arachidonoylethanolamine"))
12 88 TS=((Nabiximols or Sativex or "Gw-1000" or gw1000 or "sab-378" or sab378 or "56575-23-6"))
11 195 TS=((Nabilone or Cesamet or cesametic or cpd109514 or "cpd-109514" or "lilly-109514" or lilly109514 or "51022-71-0"))
10 103 TS=((Cannabichromene or "521-35-7"))
9 525 TS=((dexanabinol or "Hu-210" or "Hu-211" or hu210 or hu211 or "112924-45-5"))
8 1 TS=((nabidiolex or "13956-29-1"))
7 789 TITLE: ((THC))
6 1 TS=(("delta9 11 tetrahydrocannabinol" or "delta9-11-tetrahydrocannabinol" or delta911tetrahydrocannabinol))
5 1,289 TS=(("delta-9-THC" or "5957-75-5" or "1972-08-3"))
4 24 TS=((9tetrahydrocannabinol* or "delta3-thc" or "sp-104" or sp104 or "1972-08-3"))
3 12 TS=((cannador or eucannabinolide or "8001-45-4" or "8063-14-7" or "38458-58-1"))
2 3,812 TS=((Hashish or hash or bhang or ganja or ganjah or hemp or charas))

1 2,103 TS=(((Medical or medicinal or therapeutic* or therapy or therapies*) NEAR/15 (marijuana or marihuana or cannabis or canabis)))

CINAHL (Cumulative Index to Nursing and Allied Health Literature) (EBSCO): 1981-2014/08/07
Searched 7.8.14

S55 S26 AND S54 760
S54 S38 OR S42 OR S45 OR S50 OR S53 813,284
S53 S51 OR S52 230,573
S52 TI (depend* or addict* or abus* or misus* or user or users or problem* or habit*) or AB (depend* or addict* or abus* or misus* or user or users or problem* or habit*) 228,615
S51 (MH "Substance Dependence") 5,669
S50 S46 OR S47 OR S48 OR S49 56,810
S49 TI (schizophren* or schizoaffect* or schizo-affect* or (dementia N2 praecox) or hebephreni* or oligophreni*) or AB (schizophren* or schizoaffect* or schizo-affect* or (dementia N2 praecox) or hebephreni* or oligophreni*) 7,945
S48 TI (psychosis or psychoses or psychotic* or hallucinat* or delusion* or deluded or catatonia or catatonic or paranoia or paranoid or paracusia or phantosmia or paracusia) or AB (psychosis or psychoses or psychotic* or hallucinat* or delusion* or deluded or catatonia or catatonic or paranoia or paranoid or paracusia or phantosmia or paracusia) 7,009
S47 (MH "Schizophrenia+") 9,380
S46 (MH "Psychotic Disorders+") 53,094
S45 S43 OR S44 238,926
S44 TI (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion*) or AB (cancer* or neoplas* or oncolog* or malignan* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion*) 171,781
S43 (MH "Neoplasms+") 181,006
S42 S39 OR S40 OR S41 130,463
S41 TI ((lung* or pulmon* or pleural*) N3 (disease* or disorder* or illness* or infect* or inflamm* or injury or injuries or malform* or tumo?r* or failure* or impair*)) or AB ((lung* or pulmon* or pleural*) N3 (disease* or disorder* or illness* or infect* or inflamm* or injury or injuries or malform* or tumo?r* or failure* or impair*)) 15,588
S40 TI ((respirat* or airway* or "air way*" or bronchia* or broncho*) N3 (disease* or disorder* or illness* or infect* or inflamm* or injury or injuries or malform* or tumo?r* or failure* or impair*)) or AB ((respirat* or airway* or "air way*" or bronchia* or broncho*) N3 (disease* or disorder* or illness* or infect* or inflamm* or injury or injuries or malform* or tumo?r* or failure* or impair*)) 12,614
S39 (MH "Respiratory Tract Diseases+") 123,216
S38 S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 266,748
S37 TI (apoplexy or CVA or CVAs) or AB (apoplexy or CVA or CVAs) 538
S36 TI ((brain* or cerebral* or lacunar) N3 (accident* or infarc*)) or AB ((brain* or cerebral* or lacunar) N3 (accident* or infarc*)) 2,420

S35 TI (cerebrovascular or "cerebro vascular" or "cerebral vascular" or cerebralvascular) or AB (cerebrovascular or "cerebro vascular" or "cerebral vascular" or cerebralvascular) 4,345
S34 TI (stroke* or poststroke*) or AB (stroke* or poststroke*) 35,883
S33 (MH "Stroke+") 32,085
S32 TI (angina* or "atrial fibril*") or AB (angina* or "atrial fibril*") 11,594
S31 TI (circulatory N3 (disease* or disorder*)) or AB (circulatory N3 (disease* or disorder*)) 290
S30 TI (CVD or CHD) or AB (CVD or CHD) 5,698
S29 TI ((heart or cardiac or myocardi* or coronary) N3 (disease* or disorder* or failure* or attack* or arrest* or infarc* or syndrome*)) or AB ((heart or cardiac or myocardi* or coronary) N3 (disease* or disorder* or failure* or attack* or arrest* or infarc* or syndrome*)) 61,683
S28 TI ((cardiovascular or cardio or vascular or peripheral) N3 (disease* or disorder* or failure*)) or AB ((cardiovascular or cardio or vascular or peripheral) N3 (disease* or disorder* or failure*)) 22,132
S27 (MH "Cardiovascular Diseases+") 242,191
S26 S17 AND S25 1,224
S25 S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 266,226
S24 TX (observational N2 (study or studies)) 12,898
S23 TX (cohort N2 (study or studies)) 24,099
S22 (MH "Cross Sectional Studies") 63,520
S21 (MH "Nonconcurrent Prospective Studies") 158
S20 (MH "Correlational Studies") 16,145
S19 (MH "Case Control Studies+") 31,407
S18 (MH "Prospective Studies") 161,158
S17 S16 or S15 OR S14 OR S13 OR S12 OR S11 OR S10 OR S9 OR S8 OR S7 OR S6 OR S5 OR S4 OR S3 OR S2 OR S1 5,681
S16 TX (Nabiximols or Sativex or "Gw-1000" or gw1000 or "sab-378" or sab378 or "56575-23-6") 16
S15 TX (Anandamide or "N-arachidonoylethanolamine") 46
S14 TX (Nabilone or Cesamet or cesametic or cpd109514 or "cpd-109514" or "lilly-109514" or lilly109514 or "51022-71-0") 28
S13 TX (Cannabichromene or "521-35-7") 2
S12 TX (dexanabinol or "Hu-210" or "Hu-211" or hu210 or hu211 or "112924-45-5") 4
S11 TX (nabidiolex or "13956-29-1" or Dronabinol or Marinol or dronabinolum or deltanyne) 64
S10 TX (THC or canabinoid? or canabidiol? or cannabinoid? or Tetrahydrocannabinol? or "tetra-hydrocannabinol?" or endocannabinoid? or Cannabidiol or cannabinol) 460
S9 TX ("delta9 11 tetrahydrocannabinol" or "delta9-11-tetrahydrocannabinol") 0
S8 TX (delta911tetrahydrocannabinol) 0
S7 TX ("delta-9-THC" or "5957-75-5" or "1972-08-3" or nantradol or "cp-44001" or "cp-44001-1" or cp440011 or "cp44001-1" or "72028-54-7" or cp44001 or "cp 440011") 21
S6 TX (9tetrahydrocannabinol* or "delta3-thc" or "sp-104" or sp104 or "1972-08-3") 92
S5 TX (cannador or eucannabinolide or "8001-45-4" or "8063-14-7" or "38458-58-1") 2

S4 TX (bhang or ganja or ganjah or hemp or charas) 35
S3 (MH "Cannabis") 3,306
S2 TX (marijuana or marihuana or cannabis or canabis) 5,388
S1 TX (Hashish or hash) 86

Study design filter (Observational Studies) based on:
Scottish Intercollegiate Guidelines Network (SIGN). Search filters: observational studies [CINAHL (OvidSP)]. Edinburgh: SIGN, Last modified 26/04/13 Available from: http://www.sign.ac.uk/methodology/filters.html#obs

Science Citation Index (Web of Knowledge): 1900-2014/08/07
Searched 7.8.14

 # 46 152 #27 and #45
45 9,634,629 #36 or #39 or #40 or #43 or #44
44 5,750,900 TS=(depend* or addict* or abus* or misus* or user or users or problem* or habit*)
43 195,162 #41 or #42
42 146,086 TS=(schizophren* or schizoaffect* or schizo-affect* or (dementia NEAR/2 praecox) or hebephreni* or oligophreni*)
41 80,141 TS=(psychosis or psychoses or psychotic* or hallucinat* or delusion* or deluded or catatonia or catatonic or paranoia or paranoid or paracusia or phantosmia or paracusia)
40 3,037,890 TS=(cancer* or neoplas* or oncolog* or malignan* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or adenom* or lesion*)
39 294,396 #37 or #38
38 195,611 TS=((lung* or pulmon* or pleural*) NEAR/3 (disease* or disorder* or illness* or infect* or inflamm* or injury or injuries or malform* or tumor* or tumour* or failure* or impair*))
37 133,435 TS=((respirat* or airway* or "air way*" or bronchia* or broncho*) NEAR/3 (disease* or disorder* or illness* or infect* or inflamm* or injury or injuries or malform* or tumor* or tumour* or failure* or impair*))
36 1,063,441 #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35
35 3,857 TS=(apoplexy or CVA or CVAs)
34 25,136 TS=((brain* or cerebral* or lacunar) NEAR/3 (accident* or infarc*))
33 42,953 TS=(cerebrovascular or "cerebro vascular" or "cerebral vascular" or cerebralvascular)
32 289,761 TS=(angina* or "atrial fibril*" or stroke* or poststroke*)
31 2,112 TS=(circulatory NEAR/3 (disease* or disorder*))
30 123,580 TS=(CVD or CHD or ami or mi)
29 625,082 TS=((heart or cardiac or myocard* or coronary) NEAR/3 (disease* or disorder* or failure* or attack* or arrest* or infarc* or syndrome$))
28 212,501 TS=((cardiovascular or cardio or vascular or peripheral) NEAR/3 (disease* or disorder* or failure*))
27 229 #25 not #26

26 4,113,450 TS=(rat or rats or mouse or mice or murine or hamster or hamsters or animal or animals or dogs or dog or pig or pigs or cats or bovine or cow or sheep or ovine or porcine or monkey)
25 269 #18 and #24
24 965,383 #19 or #20 or #21 or #22 or #23
23 225,995 TS=(case* NEAR/5 (control* or series or comparison* or group*))
22 393,922 TS=((retrospective or prospective) NEAR/3 (study or studies or survey or surveys or analy* or pattern* or data))
21 85,241 TS=(("follow up" or followup) NEAR/3 (study or studies or survey or surveys or analy* or data))
20 105,650 TS=(longitudinal NEAR/3 (study or studies or survey or surveys or analy* or pattern* or data))
19 316,407 TS=(cohort*)
18 23,252 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
17 0 TS=(dronabinolum or deltanyne or cp44001 or "cp 440011")
16 295 TS=(Dronabinol or Marinol)
15 19 TS=(nantradol or "cp-44001" or "cp-44001-1" or cp440011 or "cp44001-1" or "72028-54-7")
14 900 TS=((Medical or medicinal or therapeutic* or therapy or therapies*) NEAR/5 (canabinoid* or canabidiol* or cannabinoid* or Tetrahydrocannabinol* or "tetra-hydrocannabinol*" or endocannabinoid* or Cannabidiol or cannabinol))
13 4,741 TS=(Anandamide or "N-arachidonoylethanolamine")
12 145 TS=(Nabiximols or Sativex or "Gw-1000" or gw1000 or "sab-378" or sab378 or "56575-23-6")
11 235 TS=(Nabilone or Cesamet or cesametic or cpd109514 or "cpd-109514" or "lilly-109514" or lilly109514 or "51022-71-0")
10 80 TS=(Cannabichromene or "521-35-7")
9 472 TS=(dexanabinol or "Hu-210" or "Hu-211" or hu210 or hu211 or "112924-45-5")
8 0 TS=(nabidiolex or "13956-29-1")
7 1,435 TI=(THC)
6 1 TS=("delta9 11 tetrahydrocannabinol" or "delta9-11-tetrahydrocannabinol" or delta911tetrahydrocannabinol)
5 1,245 TS=("delta-9-THC" or "5957-75-5" or "1972-08-3")
4 14 TS=(9tetrahydrocannabinol* or "delta3-thc" or "sp-104" or sp104 or "1972-08-3")
3 6 TS=(cannador or eucannabinolide or "8001-45-4" or "8063-14-7" or "38458-58-1")
2 14,138 TS=(Hashish or hash or bhang or ganja or ganjah or hemp or charas)
1 1,360 TS=((Medical or medicinal or therapeutic* or therapy or therapies*) NEAR/15 (marijuana or marihuana or cannabis or canabis))

IACM Database of Clinical Studies (Internet)
http://www.cannabis-med.org/studies/study.php

For the RCT search the entire database was downloaded into Excel spreadsheet (including URL links to detailed records). No further records had been added to the IACM Database since the RCT search was conducted.

APPENDIX 2: STUDIES AVAILABLE ONLY AS TRIAL REGISTRY ENTRIES

Sponsor	Study number	Condition	Intervention	Enrolment	Study dates
Anxiety					
Hadassah Medical Organization, Israel[263] Arieh Y. Shalev	ClinicalTrials.gov: NCT00965809 Other study ID: THC09	Posttraumatic Stress Disorder (PTSD)	Tetrahydrocannabinol Placebo	70	Start: October 2009 Estimated completion: April 2013
University of Michigan, USA[264] Christine A. Rabinak	ClinicalTrials.gov: NCT02069366 Other study ID: HUM00069772	Posttraumatic Stress Disorder (PTSD)	Dronabinol Placebo	120	Start: March 2014 Estimated completion: March 2018
HIV/AIDS					
Solvay Pharmaceuticals, USA[265] Vickie Baranowski	ClinicalTrials.gov: NCT00642499 Other study ID: S175.2.101	Highly Active Antiretroviral Therapy (HAART)-Related Nausea and Vomiting	Dronabinol Placebo	103	Start: August 2003 End: April 2005
Spasticity in Multiple sclerosis					
Bionorica Research GmbH, Germany[266, 267] Sebastian Schimrigk	ClinicalTrials.gov: NCT00959218 EudraCT: 2006-004255-38 Other study ID: cnp-MS-0601, MC-2006-01	Central neuropathic pain in Multiple Sclerosis	Dronabinol Placebo	240	Start: June 2007 End: April 2010
Echo Pharmaceuticals B.V., Netherlands[268] NR	EudraCT: 2010-022033-28 Other study ID: CHDR1015	Multiple Sclerosis patients suffering from spasticity and pain	Dronabinol Placebo	24	Start: January 2011 Completed
GW Pharma Ltd, UK[269] NR	EudraCT: 2004-002509-63 Other study ID: GWCL0403	Spasticity in Multiple Sclerosis	Sativex Placebo	284	Start: March 2005 Ongoing
GW Pharma Ltd, UK[270] NR	EudraCT: 2005-005265-11 Other study ID: GWMS0501	Central neuropathic pain in Multiple Sclerosis	Sativex Placebo	312	Start: April 2006 Ongoing
GW Pharma Ltd, UK[271] NR	EudraCT: 2006-005910-11 Other study ID: GWSP0604	Spasticity in Multiple Sclerosis	Sativex Placebo	488	Start: January 2008 End: September 2008
GW Pharma Ltd, UK[272] NR	EudraCT: 2011-000926-31 Other study ID: GWMS1137	Spasticity in Multiple Sclerosis	Sativex Placebo	120	Start: June 2011 End: May 2013

Sponsor	Study number	Condition	Intervention	Enrolment	Study dates
GW Pharma Ltd, UK[273] NR	ClinicalTrials.gov: NCT01868048 Other study ID: GWMS1315	Spasticity in Multiple Sclerosis	Sativex Placebo	711	Start: September 2014 Estimated completion: December 2016
University of Roma La Sapienza, Italia[274] Maurizio Inghilleri	ClinicalTrials.gov: NCT00202423 Other study ID: GWMS1315	Spasticity in Multiple Sclerosis	Sativex Placebo	20	Start: July 2005 Estimated completion: NR
University of California, Davis, USA[275] Mark Agius	ClinicalTrials.gov: NCT00682929 Other study ID: 200311404, MS Society Award # RG 3781-A-1	Spasticity in Multiple Sclerosis	Smoked Cannabis Smoked Cannabis and oral marinol Placebo	60	Start: March 2003 Estimated completion: June 2013
University of Manitoba, Canada[276] Michael P. Namaka	ClinicalTrials.gov: NCT00480181 Other study ID: B2007:051	Neuropathic pain in Multiple Sclerosis	Nabilone Placebo	50	Start: June 2007 End: July 2012
Nausea and vomiting due to chemotherapy					
Fundació Institut Català de Farmacologia, Spain[277] NR	EudraCT: 2004-003824-36 Other study ID: SATEME-08	Chemotherapy induced nausea and vomiting	Sativex Placebo	60	Start: September 2005 Ongoing
M.D. Anderson Cancer Center, USA[278] Steven M. Grunberg, Amal I. Melhem-Bertrandt	ClinicalTrials.gov: NCT00553059 Other study ID: 2006-0841, MDA-2006-0841, CDR0000573510, NCI-2009-00637	Chemotherapy induced nausea and vomiting	Dexamethasone Dronabinol Palonosetron hydrochloride Placebo	200	Start: October 2007 Estimated completion: March 2015
Chronic pain					
Azienda Ospedaliera Policlinico di Modena, Italy[279] NR	EudraCT: 2007-007873-22 Other study ID: 148/07	Headache	Nabilone Ibuprofen	60	Start: February 2009 End: March 2011
Bionorica Research GmbH, Germany[266, 267] Sebastian Schimrigk	ClinicalTrials.gov: NCT00959218 EudraCT: 2006-004255-38 Other study ID: cnp-MS-0601, MC-2006-01	Central neuropathic pain in Multiple Sclerosis	Dronabinol Placebo	240	Start: June 2007 End: April 2010
GW Pharma Ltd, UK[280, 281] Babara Hoggart	ClinicalTrials.gov: NCT00713817 EudraCT: 2004-004395-36 Other study ID: GWCL0404 Part B	Neuropathic pain	Sativex Placebo	19	Start: March 2007 End: July 2007

Sponsor	Study number	Condition	Intervention	Enrolment	Study dates
GW Pharma Ltd, UK[282] NR	EudraCT: 2006-001598-10 Other study ID: GWDN0603	Diabetic Neuropathy	Sativex Placebo	218	Start: September 2006 Ongoing
GW Pharma Ltd, UK[283] NR	EudraCT: 2006-003655-20 Other study ID: GWPHN0602	Post-herpetic neuralgia	Sativex Placebo	218	Start: November 2008 Ongoing
GW Pharma Ltd, UK[270] NR	EudraCT: 2005-005265-11 Other study ID: GWMS0501	Central neuropathic pain in Multiple Sclerosis	Sativex Placebo	312	Start: April 2006 Ongoing
GW Pharma Ltd, UK[284] NR	EudraCT: 2007-005225-30 Other study ID: GWCA0701	Pain due to advanced cancer	Sativex Placebo	336	Start: January 2008 Ongoing
GW Pharma Ltd, UK[285, 286] NR	ClinicalTrials.gov: NCT01361607 EudraCT: 2009-016065-29 Other study ID: GWCA0962, SPRAY III	Cancer-related pain	Sativex Placebo	380	Start: May 2011 End: January 2015
GW Pharma Ltd, UK[287] NR	ClinicalTrials.gov: NCT01424566 Other study ID: GWCA1103, 2010-022905-17, SPRAY	Cancer-related pain	Sativex Placebo	540	Start: January 2012 End: December 2015
GW Pharma Ltd, UK[288] NR	ClinicalTrials.gov: NCT01262651 Other study ID: GWCA0958, 2009-016064-36, SPRAY	Cancer-related pain	Sativex Placebo	380	Start: December 2010 End: January 2015
Hadassah Medical Organization, Israel[289] Elyad Davidson	ClinicalTrials.gov: NCT01149018 Other study ID: THC-FMS-HMO-CTIL	Fibromyalgia	Tetrahydrocannabinol Placebo	80	Start: June 2010 End: October 2012
Heidelberg University, Germany[290] Justus Benrath	ClinicalTrials.gov: NCT00176163 Other study ID: kfg107	Chronic back pain Fibromyalgia	Behavioral therapy and dronabinol Behavioral therapy and placebo Behavioral therapy Standard medical therapy	240	Start: August 2005 End: May 2009
Ludwig-Maximilians-University of Munich, Germany[291] Shahnaz C. Azad	ClinicalTrials.gov: NCT00377468 Other study ID: 2310106, Eudra-CT: 2006-000439-85	Complex Regional Pain Syndromes (CRPS)	Delta9-Tetrahydrocannabinol Placebo	100	Start: September 2006 End: December 2008
Radboud University, The Netherlands[292] Harry van Goor	ClinicalTrials.gov: NCT01562483 Other study ID: HEEL-2011-03	Persistent post-surgical abdominal pain	Tetrahydrocannabinol (Namisol, Dronabinol) Placebo	68	Start: October 2012 End: October 2013

Sponsor	Study number	Condition	Intervention	Enrolment	Study dates
Radboud University, The Netherlands[293] Harry van Goor	ClinicalTrials.gov: NCT01551511 Other study ID: HEEL-2011-02	Persistent abdominal pain	Tetrahydrocannabinol Placebo	68	Start: October 2012 End: October 2013
Radboud University, The Netherlands[294] Harry van Goor	ClinicalTrials.gov: NCT01318369 Other study ID: HEEL-2011-01	Chronic abdominal pain	Tetrahydrocannabinol Placebo	24	Start: October 2011 End: May 2013
Sheffield Teaching Hospitals NHS Foundation Trust, UK[295] Solomon Tesfaye	ClinicalTrials.gov: NCT00238550 Other study ID: 02/343, BDA:RD03/0002590	Diabetic neuropathy	Cannabis based medicine extract (CBME) Existing treatment regime	36	Start: October 2003 End: March 2006
Solvay Pharmaceuticals, USA[296] NR	ClinicalTrials.gov: NCT00123201 Other study ID: S175.2.103	Migraine headache	Dronabinol MDI Placebo	NR	Start: September 2005 Completed
Spinal Cord Injury Centre of Western Denmark, Denmark[297]	EudraCT: 2012-005328-14 Other study ID: SATIVEX-2013	Neuropathic pain and spasticity due to spinal cord injury	Sativex Placebo	60	Start: April 2013 Ongoing
University of California, Davis, USA[298] Barth Wilsey	ClinicalTrials.gov: NCT01555983 Other study ID: 256412-3, 1R01DA030424-01A1	Spinal cord injury	Cannabis (high dose) Cannabis (low dose) Placebo	52	Start: July 2012 End: June 2014
University of Manitoba, Canada[299] Ryan Q. Skrabek	ClinicalTrials.gov: NCT00699634 Other study ID: 1975, REB: B2007:129, Impact: RI07:119, Health Canada: 116697	Phantom limb pain Neuropathic pain	Nabilone Placebo	50	Start: January 2009 End: April 2011
University of Manitoba, Canada[276] Michael P. Namaka	ClinicalTrials.gov: NCT00480181 Other study ID: B2007:051	Neuropathic pain in Multiple Sclerosis	Nabilone Placebo	50	Start: June 2007 End: July 2012
University of Manitoba, Canada[300] Karen D. Ethans	ClinicalTrials.gov: NCT01222468 Other study ID: 1976	Neuropathic pain	Nabilone Placebo	40	Start: June 2012 Estimated end: December 2014
Zentrum für interdisziplinäre Schmerztherapie, Klagenfurt, Austria[301] NR	EudraCT: 2009-011862-27 Other study ID: SATIVEX-2013	Cancer-related pain	Nabilone Placebo	40	Start: September 2009 Ongoing

Sponsor	Study number	Condition	Intervention	Enrolment	Study dates
Paraplegia					
University of California, Davis, USA[298] Barth Wilsey	ClinicalTrials.gov: NCT01555983 Other study ID: 256412-3, 1R01DA030424-01A1	Spinal cord injury	Cannabis (high dose) Cannabis (low dose) Placebo	52	Start: July 2012 End: June 2014
University of Manitoba, Canada[300] Karen D. Ethans	ClinicalTrials.gov: NCT01222468 Other study ID: 1976	Neuropathic pain	Nabilone Placebo	40	Start: June 2012 Estimated end: December 2014
Psychosis					
Central Institute of Mental Health, Mannheim, Germany[302, 303] F. Markus Leweke	ClinicalTrials.gov: NCT00959218 EudraCT: 2012-004335-23 Other study ID: CBD-FEP	Schizophrenia	Cannabidiol Olanzapine Placebo	150	Start: March 2014 Estimated end: December 2015
GW Pharma Ltd, UK[304, 305] Philip McGuire	ClinicalTrials.gov: NCT02006628 EudraCT: 2013-000212-22 Other study ID: GWAP1241	Schizophrenia and related psychotic disorders	Cannabidiol Placebo	78	Start: February 2014 Estimated end: August 2016
University of British Columbia, Canada[306] Allan H. Young	ClinicalTrials.gov: NCT00397605 Other study ID: H06-00239	Bipolar Affective Disorder	Synthetic cannabinoids Placebo	50	Start: November 2006 End: December 2013
Yale University 2014[307] Mohini Ranganathan	ClinicalTrials.gov: NCT00588731 Other study ID: 0710003164, 07TGS-1082	Schizophrenia	Cannabidiol Placebo	36	Start: February 2009 End: December 2013
Sleep Disorders					
University of Illinois at Chicago, USA[308] David W. Carley	ClinicalTrials.gov: NCT01755091 Other study ID: UM1HL112856 2011-06400	Obstructive Sleep Apnea	Dronabinol Placebo	120	Start: December 2012 Estimated end: May 2015

APPENDIX 3: STUDIES EXCLUDED AFTER FULL TEXT SCREENING

Study	Reason for exclusion
(2010)[1]	Not available
(2009)[2]	Not primary study or SR
(2000)[3]	Not primary study or SR
Abrams(2003)[4]	Not primary study or SR
Adekanmi(2004)[5]	Not available
Aisner(1982)[6]	No results data
Aldana(2011)[7]	Not primary study or SR
Almirall(2014)[8]	Withdrawal
Ambler(2009)[9]	Withdrawal
Aragona(2009)[10]	Wrong outcome: No spasticity data
Auther(2010)[11]	AE; No outcomes of interest
Azienda Universitaria Policlinico Umberto(2007)[12]	Wrong outcome: No spasticity data
Barnes(2001)[13]	Not primary study or SR
Barnes(2002)[14]	Not primary study or SR
Beal(1997)[15]	Not RCT
Beard(2003)[16]	Did not assess cannabis
Bionorica research Gmb(2007)[17]	Terminated early
Boon(2006)[18]	Wrong outcome: No spasticity data
Bovasso(2001)[19]	AE; No outcomes of interest
Brady(2002)[20]	Not RCT
Brady(2001)[21]	Not primary study or SR
Brady(2001)[22]	Not RCT
Bredt(2002)[23]	Inappropriate control
Cambridge Laboratories(2007)[24]	Not RCT
Carlini(1981)[25]	Background
Cascini(2012)[26]	Background
Center for Medicinal Cannabis(2007)[27]	Terminated early
Center for Medicinal Cannabis(2006)[28]	Wrong Population
Center for Spiseforstyrrelse(2008)[29]	Wrong Population
Central Institute of Mental Health(2013)[30]	Inappropriate control
Central Institute of Mental Health(2014)[31]	Wrong Population
Chagas(2013)[32]	Wrong Population
Chang(1979)[33]	Cross-over; not balanced design
Chang(1979)[34]	Cross-over; not balanced design
Chang(1981)[35]	Cross-over; not balanced design
Chong(2006)[36]	Not RCT
Chrubasik(2006)[37]	Not primary study or SR
Chung(2008)[38]	No results data
Chung(2009)[39]	No results data (intervention group only)
Citron(1983)[40]	Inappropriate control (cannabis vs cannabis)
Citron(1985)[41]	Inappropriate control (cannabis v cannabis)
Clark(2005)[42]	Not primary study or SR

Study	Reason for exclusion
Colls(1980)[43]	Cross-over; not balanced design
Cooper(2013)[44]	Background
Corcoran(1999)[45]	Not primary study or SR
Crawford(1986)[46]	Cross-over; not balanced design
Cunha(1988)[47]	Not available
Cunningham(1988)[48]	Did not assess cannabis
Cunningham(1987)[49]	Did not assess cannabis
Cunningham(1985)[50]	Inappropriate control
Cunningham(1987)[51]	Duplicate
Cunningham(1985)[52]	Inappropriate control
Curtis(2009)[53]	Duplicate
Dartmouth-Hitchcock Medical(2013)[54]	Inappropriate control
Davis(2008)[55]	Not primary study or SR
de Lange de Klerk(2002)[56]	Not primary study or SR
de Ridder(2006)[57]	Wrong outcome: No spasticity data
Degenhardt(2003)[58]	AE; Not primary
Degenhardt(2013)[59]	AE; No outcomes of interest
Degenhardt(2008)[60]	Not primary study or SR
D'Souza(1998)[61]	Ongoing, preliminary results only; Number of patients and results not reported
D'Souza(1999)[62]	Ongoing, preliminary results only; Number of patients and results not reported
Ekert(1979)[63]	Cross-over; not balanced design
Ernst(2005)[64]	No results data
Evans(2013)[65]	Not primary study or SR
Fabre(1981)[66]	Background
Fabre(1978)[67]	Not RCT
Ferdinand(2005)[68]	AE; No outcomes of interest
Ferdinand(2005)[69]	AE; No outcomes of interest
Fergusson(2005)[70]	AE; No outcomes of interest
Fergusson(2008)[71]	Background
Fergusson(2000)[72]	AE: dependency not medical cannabis
Fox(2001)[73]	Not available
Fox(2002)[74]	Wrong outcome: No spasticity data
Fox(2004)[75]	Wrong outcome: No spasticity data
Freeman(2004)[76]	Wrong outcome: No spasticity data
Gaille(2011)[77]	Background
Gorter(1992)[78]	Not RCT
Gralla(1982)[79]	Ongoing, preliminary results only; Number of patients and results not reported
Green(1989)[80]	Not primary study or SR
Greenberg(1990)[81]	Not RCT
Grotenhermen(2004)[82]	Not primary study or SR
Grotenhermen(1996)[83]	Not primary study or SR
Grotenhermen(2010)[84]	Not primary study or SR

Study	Reason for exclusion
Grotenhermen(2010)[85]	Not primary study or SR
GW Pharma Ltd(2013)[86]	Withdrawal
GW Pharma Ltd(2007)[87]	Withdrawal
GW Pharma Ltd(2013)[88]	Not RCT
GW Pharma Ltd(2012)[89]	Not RCT
GW Pharma Ltd(2013)[90]	Wrong outcome: No spasticity data
GW Pharma Ltd(2013)[91]	Withdrawal
GW Pharma Ltd(2013)[92]	Not RCT
GW Pharma Ltd(2005)[93]	Not RCT
GW Pharma Ltd(2013)[94]	Wrong outcome: No spasticity data
Haney(2005)[95]	Inappropriate control
Hartlapp(1984)[96]	Not RCT
Hauser(2013)[97]	Not primary study or SR
Hayatbakhsh(2007)[98]	AE; No outcomes of interest
Hemming(1993)[99]	Not RCT
Higi(1982)[100]	Inappropriate control
Ho(2012)[101]	Background
Honarmand(2011)[102]	Not primary study or SR
Istituto Nazionale Per Lo Studio(2012)[103]	Inappropriate control
Johnson(2013)[104]	Not RCT
Jungmayr(2004)[105]	Not primary study or SR
Katagigiotis(2012)[106]	Wrong outcome: No spasticity data
Kavia(2007)[107]	Wrong outcome: No spasticity data
Kavia(2006)[108]	Wrong outcome: No spasticity data
Kavia(2010)[109]	Wrong outcome: No spasticity data
Kivimies(2012)[110]	AE; Not appropriate design
Kleinman(1983)[111]	Cross-over; not balanced design
Kluin-Neleman(1979)[112]	Not RCT
Kluin-Nelemans(1980)[113]	Not primary study or SR
Kotin(1973)[114]	Not RCT
Kuepper(2011)[115]	AE; No outcomes of interest
Kuepper(2011)[116]	AE; No outcomes of interest
Kuepper(2010)[117]	AE; No outcomes of interest
Kuepper(2011)[118]	AE; No outcomes of interest
Kuspinar(2012)[119]	Wrong outcome: No spasticity data
Levitt(1980)[120]	No results data
Levitt(1981)[121]	No results data
Levitt(1984)[122]	Inappropriate control
Levitt(1981)[123]	Wrong outcome: No N&V data
Leweke(2010)[124]	Wrong Population
Manrique-Garcia(2012)[125]	AE; No outcomes of interest
Marcus(2013)[126]	AE; Not primary
McGrath(2011)[127]	AE; Not appropriate design
Medical Research Council (MRC)2005)[128]	Wrong outcome: No spasticity data
Meinck(1989)[129]	Not RCT

Study	Reason for exclusion
Merritt(1981)[130]	Not RCT
Mills(2007)[131]	Wrong outcome: No spasticity data
Montalban(2009)[132]	Withdrawal
Muller-Vahl(2003)[133]	Background
Murray(2011)[134]	AE; No results data
Musty(2001)[135]	Background
National Horizon Scanning Centre (NHSC)2009)[136]	Not primary study or SR
National Horizon Scanning Centre (NHSC)2009)[137]	Not primary study or SR
National Institute on Drug(2008)[138]	Inappropriate control
Nct(2009)[139]	Duplicate
Nct(2002)[140]	Duplicate
Nct(2003)[141]	Duplicate
Nct(2007)[142]	Duplicate
Neidhart(1981)[143]	Cross-over; not balanced design
New York State Psychiatric(2009)[144]	Wrong Population
Niiranen(1987)[145]	Did not assess cannabis
Nocon(2006)[146]	AE: dependency not medical cannabis
Notcutt(2009)[147]	Withdrawal
Notcutt(2004)[148]	Withdrawal
Notcutt(2012)[149]	Withdrawal
Notcutt(2009)[150]	Withdrawal
Notcutt(2009)[151]	Withdrawal
Novotna(2011)[152]	Withdrawal
Noyes(1976)[153]	Wrong outcome: No pain data
Paparelli(2010)[154]	AE; No outcomes of interest
Pierre(2010)[155]	AE; Not primary
Pini(2012)[156]	Inappropriate control
Puhan(2008)[157]	Not primary study or SR
Radboud(2014)[158]	Wrong population
Rafa(2007)[159]	Terminated early
Rog(2007)[160]	Not RCT
Rosenberg(2001)[161]	AE; Not appropriate design
Rossler(2012)[162]	AE; No outcomes of interest
Rotblatt(2006)[163]	Not primary study or SR
Roxburgh(2010)[164]	Not RCT
Russo(2005)[165]	Not RCT
Russo(2003)[166]	Not primary study or SR
Sallan(1975)[167]	Cross-over; not balanced design
Sallan(1975)[168]	Cross-over; not balanced design
Schuette(1985)[169]	Not available
Schulz(2009)[170]	Not primary study or SR
Sedgwick(2012)[171]	Background
Serpell(2013)[172]	Not RCT

Study	Reason for exclusion
Snedecor(2013)[173]	Did not assess cannabis
Stambaugh(1981)[174]	Not RCT
Stambaugh(1984)[175]	Not RCT
Stambaugh(1982)[176]	Not RCT
Staud(2008)[177]	Not primary study or SR
Steele(1979)[178]	Not available
Struwe(1992)[179]	Not available
Tiedeman(1981)[180]	Wrong Population
Toth(2012)[181]	Withdrawal
Toth(2012)[182]	Withdrawal
Toth(2012)[183]	Withdrawal
Turcotte(2011)[184]	No results data
Turcotte(2010)[185]	No results data
Turcotte(2013)[186]	No results data
Turcotte(2011)[187]	No results data
Turcotte(2009)[188]	No results data
Ungerleider(1987)[189]	Cross-over; not balanced design
University Health Network(2006)[190]	No results data
University of Colorado(2013)[191]	Terminated early
University of Colorado(2009)[192]	Withdrawal
van der Pol(2013)[193]	AE: dependency not medical cannabis
van Laar(2007)[194]	AE; No outcomes of interest
van Ours(2013)[195]	AE; exposure outcome relationship not clear
Wade(2003)[196]	Withdrawal
Wade(2006)[197]	Not RCT
Wasan(2009)[198]	Wrong outcome: No pain data
Washington University School(2011)[199]	Terminated early
Williams(1980)[200]	Not primary study or SR
Wissel(2004)[201]	Wrong population
Wissel(2004)[202]	Wrong population
Wissel(2004)[203]	Wrong population
Wissel(2006)[204]	Wrong population
Wittchen(2007)[205]	AE; No outcomes of interest
Wright(2013)[206]	Wrong outcome: No spasticity data
Wright(2012)[207]	Not primary study or SR
Wright(2006)[208]	Not primary study or SR
Zajicek(2013)[209]	Wrong outcome: No spasticity data
Zeltzer(1980)[210]	Not RCT
Zvolensky(2008)[211]	AE; No outcomes of interest

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APPENDIX 4: UNOBTAINABLE STUDIES

We were unable to access seven reports, these are summarised below. However, five of these appear to be conference abstracts of studies for which we have alternative reports. One study was an ongoing HTA identified through the HTA database as an ongoing project but no record of this is available on the NIHR HTA website and so this project may no longer be in existence. This means that there were only two potentially relevant study that we have not been able to obtain. This was a study of cannabidiol for anxiety.[309]

Overview of reports that we were not able to obtain:

Design	Author	Title	Comments
SR	2010 [1]	Cannabinoids (cannabis derivatives) for treatment of the symptoms of multiple sclerosis	Ongoing HTA, identified through HTA database link takes to NIHR HTA website but no details of relevant project on website.
RCT?	Cunha 1988[2]	Anti-anxiety activity of canabidiol: double-blind, comparative trial with diazepan and placebo	Full text article, no abstract, cannot access; unclear from title whether randomised.
RCT	Schuette 1985[3]	Randomized crossover trial comparing the antiemetic efficacy of nabilone versus alizapride in patients (pts) with nonseminomatous testicular cancer (NSTC) receiving low-dose cisplatin therapy	Conference abstract only; cannot access. Appears to be same study as Niederle[4] – included for nausea and vomiting due to chemotherapy
	Fox 2001[5]	A multicentre randomised controlled trial of cannabinoids in multiple sclerosis	Conference abstract only; cannot access. Includes Zajicek as author; likely to be publication of CAMS study[6] – included for MS
	Adekanmi 2004[7]	The effect of cannabinoids on lower urinary tract symptoms in multiple sclerosis: a randomised placebo controlled trial (CAMS-LUTS study)	Conference abstract only; cannot access. CAMS-LUTS study – excluded as did not report spasticity data
	Struwe 1992[8]	Randomized study of dronabinol in HIV related weight loss	Conference abstract only; cannot access. Same study as Struwe 1993[9] – included for HIV
	Steele 1979[10]	Double-blind comparison of the antiemetic effects of Nabilone and Prochlorperazine on chemotherapy-induced emesis	Conference abstract only; cannot access. Same study as Steele 1980[11] – included for nausea and vomitting

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APPENDIX 5: BASELINE DETAILS OF INCLUDED STUDIES

A. CLINICAL EFFECTIVENESS REVIEW

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Abrams(2003)[129] **Country:** USA **Funding:** Mixed **Recruitment:** May 1998 - May 2000 **Design:** Parallel group RCT **Number randomised:** 67 **Study duration:** 21 days	**Patient category:** HIV **Inclusion criteria** ≥ 18 yrs; documented HIV infection; stable antiretroviral treatment regimen for ≥ 8 weeks; stable viral load for 16 weeks **Exclusion criteria** Opportunistic infection or malignant condition requiring acute treatment; unintentional loss of ≥10% body weight in 6 months; current substance dependence (drug, alcohol), methadone maintenance; use of tobacco or cannabinoids ≤ 30 days; history of serious pulmonary disease; pregnancy; ≥stage II AIDS dementia Complex; hematocrit < 0.25 & hepatic aminotransferase levels > 5x upper limit of normal; use of anabolic hormones, prednisone, interleukin-2, or other immune system function agents in 8 weeks.	**Age (Median, range):** 43 (26, 80) **Median BMI (range):** 25.5 (14.8-53.3) **% Male:** 89 **% White:** 50	**Disease severity:** Median HIV RNA level (range), $\log_{10}$ copies/ml: 3.6 (1.7–4.6) Undetectable HIV RNA levels: 58% CD4+ cell count < 200 x 10^9 cells/l: 24% **Disease duration:** NR	**Concomitant medication:** Indinavir (45%) & nelfinavir (55%). No additional protease inhibitors **Previous medication:** Stable antiretroviral treatment regimen (indinavir or nelfinavir) for at least 8 weeks.	**Previous cannabis use:** All ≥ 6 times smoking marijuana (not within 30 days before enrollment) **Previous drug or tobacco use:** NR	*Marijuana*: 1 (AE) *Dronabinol*: 3 (2 AE, 1 personal reasons) *Placebo*: 1 (personal reasons).

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Abrams (2007)[142, 157, 165] **Country:** USA **Funding:** Public **Recruitment:** May 2003 - May 2005 **Design:** Parallel group RCT **Number randomised:** 55 **Study duration:** 12 days	**Patient category:** Pain **Pain details:** HIV-associated sensory neuropathy (SN) Cause of neuropathy: HIV n=17, nucleosides n=26, both n=12. **Inclusion criteria** Adults with HIV infection; symptomatic HIV-SN with; average daily pain score ≥ 30 on 100 mm VAS; stable health; stable medication regimen for pain and HIV for ≥ 8 weeks prior; >6 times experience smoking cannabis; current users asked to discontinue cannabis. **Exclusion criteria** Family history of polyneuropathy; neuropathy due to causes other than HIV or dideoxynucleosides; use of isoniazid, dapsone, or metronidazole <8 weeks; current substance abuse (including tobacco)	*CBD group:* **Age (mean, sd):** 50(6) **% Male:** 81 **% White:** 52 *Placebo group:* **Age (mean, sd):** 47(7) **% Male:** 93 **% White:** 39	**Disease severity:** >30mm VAS **Disease duration:** neuropathy: median = 7 years (range 3-9).	**Concomitant medication:** 56.5% taking any type of concomitant medication (gapapentin, opiod and others). Preadmission analgesics continued throughout the study.	**Previous cannabis use:** 100% **Previous drug or tobacco use:** No current tobacco smokers.	*Prior to intervention phase:* 1 (upset with nursing care). *CBM:* 2 (1 environmental surroundings, 1 family problems). *Placebo:* 2 (1 influenza, 1 treatment failure).

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Ahmedzai(1983)[112] **Country:** UK **Funding:** Industry - drug manufacturer **Recruitment:** NR **Design:** Cross-over RCT **Number randomised:** 34 **Study duration:** *Period 1:* 4 days *Period 2:* 4 days *Washout*: NR	**Patient category:** N&V **Cancer details:** Small cell bronchial carcinoma **Inclusion criteria** Small cell bronchial carcinoma; eligible for chemotherapy **Exclusion criteria** Active psychiatric disease (unclear if entry restricted on this basis)	**Age (Median, range):** 58 (27, 72) **% Male:** 56	**Disease severity:** ECOG status median 2: 0 (2), 1 (10), 2 (14), 3 (7), 4 (1) **Disease duration:** NR	**Chemotherapy:** cyclophosphamide, adriamycin, etoposide on days 2 and 3; vincristine with methotrexact on day 10 folowed by folinic acid rescue. Rescue medication of metoclopramide (10mg) or chlopromazine (50mg) given as required.	**Previous cannabis use:** Thought that none of the patients had prior experience of marijuana. **Previous drug or tobacco use:** NR	8 (5 died during first chemotherapy cycle, 1 withdrawn from chemo-therapy, 2 AEs)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Beal (1995)[84] **Country:** USA **Funding:** Industry - drug manufacturer **Recruitment:** NR **Multicentre study** **Design:** Parallel group RCT **Number randomised:** 139 **Study duration:** 6 weeks	**Patient category:** HIV **Inclusion criteria** ≥1 AIDS defining event (CDC 1987); loss ≥2.3 kg from normal body bodyweight; ability to feed oneself and consume normal diet. **Exclusion criteria** Acute infections; diabetes; Candida oesophagitis; ascites; pleural effusion; oedema; uncontrolled diarrhoea; dementia; biliary, pancreatic, or gastrointestinal obstruction; marijuana use ≤30 days.	**Age (Mean, CI):** 39 (22, 64) **% Male:** 93 **% White:** 78	**Disease severity:** Initial T4 cell count: mean 47 Pretherapy body weight loss: mean 9.9 kg **Disease duration:** HIV symptoms mean 32.4 months	**Concomitant medication:** Antiretrovirals allowed if patient had tolerated medication for at least 4 weeks and was on same dose for at least 2 weeks prior to trial start. Megastrol acetate, tube feedings, corticosteroids and marijuana not allowed during the trial.	**Previous cannabis use:** None (45%), <1 monthly (25%), 1-3 times monthly (13%), ≥4 times monthly (17%) **Previous drug or tobacco use:** NR	*CBM:* 22 (1 protocol violation, 2 refused further treatment, 6 toxicity, 4 intercurrent illness, 8 noncompliance with study medications, 2 other) *Placebo:* 29 (15 protocol violation, 4 lost to follow-up, 3 toxicity, 3 intercurrent illness, 3 noncompliance with study medications, 1 other)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Bergamaschi(2011)[95] **Country:** Brazil **Funding:** Public **Recruitment:** NR **Design:** Parallel group RCT **Number randomised:** 24 **Study duration:** During public speaking task	**Patient category:** Anxiety **Anxiety details** Generalized social anxiety disorder **Inclusion criteria** Generalized Social Anxiety Disorder (SAD); ≥, who 6 points on self-assessed short version of the Social Phobia Inventory named MINISPIN. **Exclusion criteria** History of head trauma; neurological illness; ECT; substance abuse; major medical illnesses (based on a semi-standardized medical questionnaire and physical examination).	% Male**:** 50 *CBD:* **Mean Age(sd):** 24.6(3.6) *Placebo***:** **Mean Age (sd):** 22.9(2.4)	**Disease severity:** MINI-SPIN Mean (sd): placebo = 36.3 (11.2); CBD = 30.9 (12). **Disease duration:** Mean (sd) age of SAD onset: placebo 12.2 (5.8) yrs; CBD 9.6 (6.9) yrs.	**Concomitant medication:** No medications taken for at least 3 months before the study. **Previous medication:** All treatment-naıve (either with pharmacotherapy or psychotherapy).	**Previous cannabis use:** All ≤5 times in their lives (no use in the last year). **Previous drug or tobacco use:** No previous illegal drug use. Non-smokers of tobacco.	NR **Comments** 12 healthy volunteers were also included, they received no medication.

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Berman(2007)[1, 164] **Country:** Romania, UK **Funding:** Industry - drug manufacturer **Recruitment:** NR **Only available as conference abstract** **Design:** Parallel group RCT **Number randomised:** 117 **Study duration:** 3 weeks	**Patient category:** MS Pain **Pain details:** Central neuropathic pain due to non-acute spinal cord injury **Inclusion criteria** >18 years; non-acute spinal cord injury; central neuropathic pain not wholly relieved by current therapy with mean NRS score ≥4 during last 7 days; stable neurology for last 6 months; stable medication for last 4 weeks; not used canncabis for previous 7 days and willing to abstain during study. **Exclusion criteria** History of schizophrenia, or other significant psychiatric disorder other than depression associated with underlying condition; history of alcohol or substance abuse; autonomic dysreflexia; epilepsy; severe cardiovascular disorder; pregnancy or lactating; renal or hepatic impairment; elective surgery or other procedures requiring general anaesthesia; terminal illness ; regular levodopa therapy <7days; sildenafil treatment.	**Age (Mean, SD):** 48.1 (12.69) **% Male:** 91	**Disease severity:** ≥4 central neuropathic pain severity score on 11 point NRS **Disease duration:** > 6 months	**Concomitant medication:** NR	NR	10 patients withdrew during the study (intervention 7, control 3)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Berman(2004)[145, 159] **Country:** UK **Funding:** Mixed **Recruitment:** December 2001 - July 2002 **Design:** Cross-over RCT **Number randomised:** 48 **Study duration:** *Period 1:* 2 weeks *Period 2:* 2 weeks *Washout:* None	**Patient category:** Pain **Pain details:** Central neuropathic pain from brachial plexus avulsion **Inclusion criteria** ≥ 18 years; ≥ 1 avulsed brachial plexus root injury ≥ 18 mths; ≥ 4 on 0-10 pain scale; stable pain pattern for 4 wks; permitted medication stable for 4 weeks **Exclusion criteria** History of schizophrenia, other psychotic illness or significant psychiatric illness, other than depression associated with chronic illness; serious cardiovascular disease; significant renal or hepatic impairment; epilepsy or convulsions; history of substance abuse; known adverse reaction to cannabis or the product excipients; surgery within 2 months (6 months for nerve repair); pregnant, lactating or at risk of pregnancy; concurrent use of levodopa, sildenafil and fentanyl; maximum dose of amitriptyline 75 mg/day; no analgesics ; no cannabis use for ≥ 7 days.	**Age (Mean, range):** 39 (23, 63) **% Male:** 95.8	**Disease severity:** Number of root avulsions (mean, range): 3.6 (1–5) **Disease duration:** Time since last surgical intervention (mean, range): 5 (0.9–18.6)	**Concomitant medication:** Gabapentin (33%), opiates (29%), TCA (20%), tramadol (19%), paracetamol (13%), other anticonvulsants (8%), NSAIDs (4%), SSRI (4%), Alpha II blockers (2%)	**Previous cannabis use:** 46% previously used CBM, 60% recreationally. **Previous drug or tobacco use:** NR	*Total: 4 withdrawals* *GW-1000-02 (Sativex):* 1 AE *GW-2000-02 (THC):* 0 *Placebo:* 2 (1 AE, 1 withdrew consent)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Blake(2006)[78] **Country:** UK **Funding:** Industry - drug manufacturer **Recruitment:** NR **Multicentre study:** **Design:** Parallel group RCT **Number randomised:** 58 **Study duration:** 5 weeks	**Patient category:** Pain **Pain details:** Pain caused by RA (rhaumatoid arthritis) **Inclusion criteria** RA (ACR criteria); not adequately controlled by standard medication; stable NSAID and prednisolone regimes for 1 month and DMARDs for 3 months; and were maintained constant throughout the study. **Exclusion criteria** History of psychiatric disorders or substance misuse; severe cardiovascular, renal or hepatic disorder; history of epilepsy.	**Age (Mean, SD):** 62.8(9.8) **Weight (Mean, SD):** 74(19.2) **% Male:** 21	**Disease severity:** NR **Disease duration:** NR	**Concomitant medication:** NSAID, prednisolone and DMARDs **Previous medication:** NR	**Previous cannabis use:** 3% reported recreational cannabis use, 2% medicinal cannabis use **Previous drug or tobacco use:** 88% smokers	*CBM:* 1 (unrelated surgery) *Placebo:* 3 (AE)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Broder(1982)[74] **Country:** USA **Funding:** Not stated **Recruitment:** NR **Only available as conference abstract** **Design:** Cross-over RCT **Number randomised:** 44 **Study duration:** *Period 1:* 1 chemotherapy cycle *Period 2:* 1 chemotherapy cycle	**Patient category:** N&V **Cancer details:** NR **Inclusion criteria** Cancer patients who had failed prior anti-emetic therapy. **Exclusion criteria** NR	NR	**Disease severity:** NR **Disease duration:** NR	**Concomitant medication:** NR **Previous medication:** All had failed anti-emetic therapy	**Previous cannabis use:** NR **Previous drug or tobacco use:** NR	9 withdrawals but no further details.

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Chan(1987)[93, 118] **Country:** Canada **Funding:** Industry - drug manufacturer **Recruitment:** February 1982 - April 1983 **Design:** Cross-over RCT **Number randomised:** 40 **Study duration:** *Period 1:* 1 chemo-therapy cycle *Period 2:* 1 chemo-therapy cycle *Washout:* NR	**Patient category:** N&V **Cancer details:** Various paediatric malignancies (no further details) with severe drug-induced vomiting **Inclusion criteria** Repeated courses of chemotherapy with severe drug-induced nausea and vomiting; never received nabilone or PCP. **Exclusion criteria** NR	**Age (Mean, range):** 11.8 (3.5, 17.8)	**Disease severity:** NR **Disease duration:** NR	**Chemotherapy regimens:** Various chemo-therapy regimens, none of the patients received cis-platinum-based regimens.	**Previous cannabis use:** Not previously treated with nabilone.	*Total:* 10 (4 change of chemotherapy after cycle 1, 2 unable to cope with diagnosis and treatment, 2 received other antiemetics, 2 cycle 2 of AE following CBM).

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Collin(2007)[2, 202] **Country:** UK and Romania **Funding:** Industry - drug manufacturer **Recruitment:** April 2002 - March 2004 **Multicentre study** **Design:** Parallel group RCT **Number randomised:** 189 **Study duration:** 6 Weeks	**Patient category:** MS **Inclusion criteria** Age >18 years; diagnosis of MS; stable disease for >3 months; significant spasticity in at least two muscle groups with an Ashworth score≥2; failed to gain adequate relief using current therapy; stable treatment for ≥30 days. **Exclusion criteria** Psychosis or severe psychiatric disorder other than depression; known alcohol or substance abuse; severe cardiovascular disorder including poorly controlled hypertension; history of seizures; pregnancy or lactation; sensitivity to cannabinoids.	**Age (Mean, SD, CI):** 49.1(9.9)(20, 69) **% Male:** 39.7 **% White:** 99	**Disease severity:** NR **Disease duration:** 12.6 years	**Concomitant medication:** Concomitant medications and therapies (NR) maintained during the study. Most common: baclofen (32 %) and tizanidine (16 %) for spasticity, paracetamol (14 %) for pain, and evening primrose oil (13 %).	**Previous cannabis use:** 41.8% had previoulsy used cannabis. **Previous drug or tobacco use:** NR	*CBM*: 12 (6 AE, 1 non-complianc, 4 withdrawal of consent, 1 lost to follow-up). *Placebo*: 3 (2 AE, 1 protocol deviation).

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Collin(2010)[5, 198, 203] **Country:** UK and Czeck republic **Funding:** Industry - drug manufacturer **Recruitment:** NR **Multicentre study** **Design:** Parallel group RCT **Number randomised:** 337 **Study duration:** 14 weeks	**Patient category:** MS **Inclusion criteria** Any MS subtype; ≥6 months duration; ≥3 months spasticity not wholly relieved by current therapy; mean daily score ≥4 on spasticity NRS for 6 days; stable anti-spasticity regimen ≥ 30 days **Exclusion criteria** Spasticity not due to MS; concurrent history of significant psychiatric, renal, hepatic, cardiovascular or convulsive disorders.	**Age (Mean, SD):** 47.5(9.6) **% Male:** 39	**Disease severity:** Mean EDSS score 6 (sd 1.53) **Disease duration:** Mean MS duration 15.2 (sd 8.4) years, mean spasiticty duration 7.7 (sd 5.3) years	**Concomitant medication:** Baclofen (80%), dantrolene (7%), tizanidine (43%), benzodiazepines (28%), gabapentin (15%), botulinum toxin (4%), other (61%), no previous/concomitt ant antispasticity medication (3%). **Previous medication:** NR	**Previous cannabis use:** 24% **Previous drug or tobacco use:** NR	*CBM:* 17 (9 AE, 3 other, 2 withdrew consent, 2 lack of efficacy, 1 lost to follow-up) *Placebo:* 15 (5 AE, 2 other, 1 withdrew consent, 4 lack of efficacy, 2 lost to follow-up, 1 pregnancy)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Corey-Bloom(2012)[190, 200, 208] **Country:** USA **Funding:** Public **Recruitment:** NR **Design:** Cross-over RCT **Number randomised:** 37 **Study duration:** *Period 1:* 3 days *Period 2:* 3 days *Washout:* 11 days	**Patient category:** MS **MS details** Secondary progressive 67%; relapsing-remitting 33%. **Inclusion criteria** MS; ≥ 3 points on the Ashworth scale at the elbow, hip, or knee; abstinence from cannabis smoking for≥1 month. **Exclusion criteria** History of major psychiatric disorder (othere than depression); history of substance abuse; substantial neurologic disease other than MS; severe or unstable medical illness; known pulmonary disorders; use of benzodiazapines to control spasticity, or high dose narcotic medications to control pain; pregnancy or lactation; positive toxicological screening.	**Age (Mean, SD):** 51(8) **% Male:** 37	**Disease severity:** Mean (SD) EDSS score 5.3 (1.5) **Disease duration:** 8.5 (7.4) yrs	**Concomitant medication:** 9 Interferon beta-1a; 6 interferon beta-1b; 6 glatiramer; 14 baclofen; 4 tizanidine **Previous medication:** NR	**Previous cannabis use:** 24 Any exposure; 10 exposure in previous yr; 14 more than 1 yr since last use **Previous drug or tobacco use:** NR	Total: 7 (1 did not attend treatment, 3 unavailable for time commitment, 2 cannabis AE, 1 lightheadedness after smoking/ blood drawn)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Dalzell(1986)[92] **Country:** UK **Funding:** Not stated **Recruitment:** NR **Design:** Cross-over RCT **Number randomised:** 23 **Study duration:** *Period 1*: 1 chemotherapy cycle *Period 2*: 1 chemotherapy cycle	**Patient category:** N&V **Cancer details:** Rhabdomyosarcomas (10), Ewing's tumours (5), acute non-lymphocytic leukaemias (4), Hodgkin's disease (1), medulloblastoma (1), neuroblastoma (1) and nasopharyngeal carcinoma (1). **Inclusion criteria** ≤ 17 years old; undergoing emetogenic antineoplastic chemotherapy for malignant disease; scheduled to receive two identical (drugs, doses, and duration) courses of emetogenic chemotherapy. **Exclusion criteria** NR	**Age range:** 1, 17 **% Male:** 83	**Disease severity:** NR **Disease duration:** NR	**Concomitant medication:** 5 patients required additional IV antiemetic treatment **Chemotherapy regimens:** Vincristinc/Actinonlycin/Cyclophosphamidc (n=14), Cisplatinum VP16(n=2), Mustine/Vincristine/Procarhbazine/Prednisolone (n=1), M-AMSA/VPI6/5-Azacytidine (n=1). High Dose Cytarabine (n=1), Vincristine/Cyclophosphimide/Cisplatinum/VM26 (n=1), Daunorubican/Cytarahine/Thioguanine (n=2), CCNU (n=1).	**Previous cannabis use:** NR	*Total:* 5 (2 uncontrolled vomiting, both on nabilone), 1 hallucinations (on nabilone), 1 received two cycles of domperidone in error, 1 received differing doses of cisplatin on the two cycles).

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Duran(2010)[97] **Country:** Spain **Funding:** Public **Recruitment:** January 2006 - December 2007 **Design:** Parallel group RCT **Number randomised:** 16 **Study duration:** 5 days	**Patient category:** N&V **Cancer details** Primary cancer diagnosis: Breast (12), Ovary (2), Lung (2). Cancer extension: Localized (13), metastasized (3) **Inclusion criteria** >18 years; Karnofsky score ≥70; chemotherapy-induced nausea and vomiting > 24 h according to the MANE questionnaire, despite prophylaxis with standard anti-emetic treatment after the administration of 1-day MEC [moderately emetogenic cancer chemotherapy]. **Exclusion criteria** Current use of illicit drugs, THC or alcohol abuse; abnormal laboratory values, multiple-day chemotherapy in a single cycle; radiation therapy on the abdomen or pelvis ≤ 1 week before; cannabinoid use ≤ 30 days; history of major psychiatric disorder; severe cardiovascular disease; seizures; pregnant or lactating; suspected hypersensitivity to cannabinoids.	*CBM:* **Age:** 50.0 (41.0, 70.0) **% Male:** .0 *Placebo:* **Age:** 50.0 (34.0, 76.0) **% Male:** 11.0	**Disease severity:** Basal Morrow assessment of nausea and emesis (MANE). Nausea Severity mean (SD): CBM 63.6 (26.5), PCB 56.22 (20.3). Duration (h) mean (SD): CBM 15 (7.9), PCB 15.3 (10.9). Vomiting Severity mean (SD): CBM 52.3 (32.9), PCB, 64.3 (22.8) Duration (h) mean (SD): CBM 11.6 (11), PCB 11.1 (10). **Disease duration:** NR	**Concomitant medication:** Corticosteroid +5-HT3 antagonists, 5-HT3 antagonists, ortopramide.	**Previous cannabis use:** 2/16 **Previous drug or tobacco use:** NR	*CBM:* 1

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Einhorn(1981)[108] **Country:** USA **Funding:** NR **Recruitment:** NR **Design:** Cross-over RCT **Number randomised:** 100 **Study duration:** / *Period 1:* 1 chemotherapy cycle *Period 2:* 1 chemotherapy cycle *Washout:* 3 weeks	**Patient category:** N&V **Cancer Details:** Sarcoma (1), Hodgkin's disease (2), lymphoma (4), bladder (3), testicular (70) **Inclusion criteria** Combination chemotherapy for neoplastic diseases with drug regimens that produce severe nausea and vomiting. **Exclusion criteria** History or drug abuse; cardiovascular disease; psychiatric distrubance.	**Age (Median, range):** 28 (15, 74)	**Disease severity:** NR **Disease duration:** NR	**Chemotherapy regimens:** ADR (doxyrubin hydrochloride), CTX (cyclo-phosphamide), HN2 (nitrogen mustard), VCR (vincristine), DDP (cisplatin), 5-FU (5-fluouracil), VLB (vinblastine), BLEO (bleomycin), PRED (prednisone), PC (procarbazine). **Previous medication:** NR	**Previous cannabis use:** No "history of drug abuse" **Previous drug or tobacco use:** No "history of drug abuse"	*Total:* 20 (1 early death, 7 change of chemotherapy prior to cross-over, 8 insufficient data, 3 failure to cross-over-presumed nabilone toxicity, 1 toxcitiy both arms).

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Ellis(2009)[137, 162] **Country:** USA **Funding:** Public **Recruitment:** February 2002 - November 2006 **Design:** Cross-over RCT **Number randomised:** 34 **Study duration:** *Period 1:* 5 days *Period 2:* 5 days *Washout:* 14 days	**Patient category:** Pain **Pain details:** Neuopathic pain in HIV **Inclusion criteria** Adults; doccumented HIV infection; neuropathic pain refractory to at least 2 previous analgesics; average score of at least 5 on the pain intensity sub-scale of the Descriptor Differential Scale (DDS) **Exclusion criteria** Current DSM-IV substance abuse disorder; history of dependence on cannabinoids; previous psychosis or intolerance to cannabinoids; concurrent use of approved cannabinoid medications; positive toxicology screen for cannabinoids during the two-week pre-treatment phase; serious medical condition	**Age (Mean, SD):** 49.1 (6.9) **% Male:** 97 **% White:** 71	**Disease severity:** Advanced HIV disease (93%) Mean baseline Total Neoropthay score 16 (range 9-34), corresponding to mild to moderately severe **Disease duration:** >5 yrs	**Concomitant medication:** Combination ART 32 (94%); non-narcotic analgesis 12 (35%); antidepressants 8 (24%); anticonvulsants 21 (62%); opioids 22 (65%) **Previous medication:** dideoxynucleoside reverse transcriptase inhibitors (72%)	**Previous cannabis use:** 31 (91%) **Previous drug or tobacco use:** 21 (72%)	6 Withdrawals: 1 acute cannabis-induce psychosis; 1 intractable smoking-related cough; 1 intractable diarrhea; 1 discontinued due to un-anticipated personal commirments; 1 loss to follow-up; 1 protocol violation (positive metamphetamine screen)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Frank(2008)[141, 178] **Country:** UK **Funding:** Industry - drug manufacturer **Recruitment:** July 2001 – November 2002 **Design:** Cross-over RCT **Number randomised:** 96 **Study duration:** *Period 1:* 6 weeks *Period 2:* 6 weeks *Washout:* 2 weeks	**Patient category:** Pain **Pain details:** Mixed neuropathic pain (such as burning, stabbing, or paraesthesia within the distribution of a peripheral nerve). **Inclusion criteria** Neuropathic pain; clear clinical history of its cause; age 18-90 years; mean pain score > 40 (0-100 mm VAS). **Exclusion criteria** History of epilepsy, liver disease, psychosis, bipolar disorder, substance misuse, or renal failure; adverse reactions to dihydrocodeine or nabilone; pregnancy or lactation; use of following during study: dihydrocodeine, antipsychotic drugs, benzodiazepine drugs, (except stable doses of night-time sedatives), monoamine oxidase inhibitors, cannabinoid preparations.	**Age range:** 23, 84	**Disease severity:** NR **Disease duration:** NR	**Concomitant medication:** Stable analgesics (except dihydrocodeine) **Previous medication:** NR	**Previous cannabis use:** NR **Previous drug or tobacco use:** NR	NR

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Frytak (1979)[111, 120] **Country:** USA **Funding:** Not stated **Recruitment:** NR **Design:** Parallel group RCT **Number randomised:** 117 **Study duration:** 4 days	**Patient category:** N&V **Cancer details:** Gastrointestinal cancers, primary neoplasm: colorectal (84), gastric (26), liver (5), other (1). **Inclusion criteria** Initial chemotherapy with combined 5-fluoracil and semustine as 2-drug combination or in 3 drug combinations with vincristine, doxorubicin, razxane or triazante; age >21 years; unresectable gastrointestinal cancer or participants in gastrointestinal cancer surgical adjuvant programs; ambulatory outpatients; pretreatment oral intake of >=1500 calories/day **Exclusion criteria** Nausea or vomiting before study entry; past history of drug dependence; significant psychological disturbance.	**Age (Median):** 61 **% Male:** 60.3	**Disease severity:** ECOG score at baseline: 0 (32), 1 (63), 2 (18), 3 (3). **Disease duration:** NR	**Chemotherapy regimens:** First course of chemotherapy. Strong emetic stimulus (chemotherapy) on day 1, weaker stimulus on days 2 and 4. Combined 5-fluoracil and semustine as 2-drug combination or in 3 drug combinations with vincristine, doxorubicin, razxane or triazante. **Concomitant medication:** Appears that patients were not allowed to take other anti-emetics during the study. **Previous medication:** NR	**Previous cannabis use:** None known **Previous drug or tobacco use:** NR	Day 1: 1 after inadvertently taking another antiemetic agent. Days 2-4: 18 (intolerable CNS toxicity or excessive vomiting).

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
George(1983)[104] **Country:** France **Funding:** Industry - drug manufacturer **Recruitment:** October 1981 - March 1982 **Design:** Cross-over RCT **Number randomised:** 20 **Study duration:** *Period 1:* 1 chemotherapy cycle *Period 2:* 1 chemotherapy cycle	**Patient category:** N&V **Cancer details:** Gynaecological cancer (advanced); cervix (n=10), ovarian (n=6), endometrial (n=2); fallopian tube (n=1), vagina (n=1). **Inclusion criteria** Age 18-70; life expectancy >2 months; advanced gynaecological cancer receiving identical courses of chemotherapy. **Exclusion criteria** Psychotropic medication; general analgesics. Use of other anti-emetic drug during study.	**Age (mean, SD):** 54.1 (11.7)	**Disease severity:** Median Karnofsky index = 80 (range 70-100). **Disease duration:** NR	**Chemotherapy regimens:** Adriamycine/cyclophospahmide/ cis-platinum (n=11), cyclophosphamide/ cis-platinum (n=3), cis-platinum (n=6). **Previous medication:** Had all received one cycle of chemotherapy before start of trial.	**Previous cannabis use:** NR **Previous drug or tobacco use:** NR	*CBM:* 4 (2 did not take medication, 1 anxiety, 1 feeling unwell) *Chlorpromazine:* 2 (1 refused injection, 1 disease progression)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
GW Pharma Ltd(2005)[77, 170] **Country:** Czech Republic, Romania, UK **Funding:** Industry - drug manufacturer **Recruitment:** NR **Multicentre study** **Design:** Parallel group RCT **Number randomised:** 297 **Study duration:** 98 days	**Patient category:** Pain **Pain details:** Diabetic peripheral neuropathy (DPN) **Inclusion criteria** Age ≥ 18 yrs; diabetes (WHO criteria). DPN ≥ 6 mths (NDS ≥ 4, confirmed by ≥ 2 different tests); pain not wholly relieved with current therapy; last 6 daily NRS pain scores ≥ 24; stable dose of pain medication and non-pharmacological therapies for 14 days. **Exclusion criteria** Concomitant pain likely to interfere with pain assessment; uncontrolled diabetes; prohibited medication; use of CBM ≤60 days or cannabis ≤30 days; history of schizophrenia or other significant psychiatric disorder other than depression; history of alcohol or substance abuse; history of epilepsy, recurrent seizures or gastroparesis; hypersensitivity to cannabinoids; postural drop of 20mmHg or more in systolic blood pressure at screening; cardiomyopathy, MI or clinically relevant cardiac dysfunction ≤ 12 months; elevated QT interval; secondary or tertiary AV block or sinus bradycardia (HR <50bpm) or tachycardia (HR>110bpm); diastolic blood pressure <50 or >105 mmHg; impaired renal or hepatic function; pregnant or lactating; IMP ≤12 weeks.	**Age (Mean, SD):** 59.5 (10.5) **% Male:** 61.6	**Disease severity:** Last six daily NRS pain scores ≥ 24 **Disease duration:** DPN ≥ 6 mths	**Concomitant medication:** Rescue analgesia **Previous medication:** NR	**Previous cannabis use:** No use within 30 days before study **Previous drug or tobacco use:** NR	*CBM:* 44 (30 AE; 4 lack of efficacy; 5 withdrawal by participant; 5 other). *Placebo:* 23 (12 AE; 5 lack of efficacy; 3 withdrawal by participant; 1 lost to follow up; 2 other).

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
GW Pharma Ltd(2012)[79] **Country:** UK **Funding:** Industry - drug manufacturer **Recruitment:** March 2002 - August 2002 **Multicentre study** **Design:** Parallel group RCT **Number randomised:** 70 **Study duration:** 3 weeks	**Patient category:** Pain **Pain details** Chronic refractory pain due to MS or other defects of neurological origin **Inclusion criteria** Age ≥18yrs; chronic refractory pain due to MS or other defects of neurological origin; pain not wholly alleviated with current analgesia; average score >4 on Box-Scale 11 on 4 consecutive days; stable dose of analgesia ≥2 weeks; willing to abstain from cannabis during the study. **Exclusion criteria** Cannabis use ≤7 days; history of schizophrenia, other psychotic illness, severe personality disorder or other significant psychiatric disorder other than depression associated with underlying condition; known history of alcohol or substance abuse; severe cardiovascular disorder; poorly controlled hypertension or severe heart failure; history of epilepsy; pregnant or lactating; significant renal or hepatic impairment; procedures requiring general anaesthesia during the study; terminally ill or inappropriate for placebo medication; regular levadopa; hypersensitivity or adverse reaction to cannabinoids; receiveing viagra.	**Age (Mean, SD):** 54.6 (11.6) **% Male:** 41.4	**Disease severity:** Pain > 4 on 0-11 scale **Disease duration:** NR	**Concomitant medication:** Pain relieving medication (no further details) **Previous medication:** NR	**Previous cannabis use:** NR **Previous drug or tobacco use:** NR	*CBM:* 4 (2 AE, 1 disease progression, 1 withdrawal by participant) *Placebo:* 3 (3 AE)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Hagenbach(2003)[71] **Country:** Switzerland **Funding:** Industry - drug manufacturer **Recruitment:** NR **Only available as conference abstract** **Design:** Parallel group RCT **Number randomised:** 13 **Study duration:** 6 weeks	**Patient category:** Paraplegia **Details:** Spasticity in patients with spinal cord injury. **Inclusion criteria** Spasticity in patients with spinal cord injury; >3 points on Ashworth scale without therapy; negative urine drug screening; >18 years old. **Exclusion criteria** NR	NR	**Comorbidities:** NR **Disease severity:** NR **Disease duration:** NR	**Concomitant medication:** NR **Previous medication:** NR	**Previous cannabis use:** NR **Previous drug or tobacco use:** NR	NR

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Heim(1984)[102] **Country:** Germany **Funding:** NR **Recruitment:** NR **Design:** Cross-over RCT **Number randomised:** 57 **Study duration:** *Period 1:* 24h of 1 chemotherapy cycle *Period 2:* 24h of 1 chemotherapy cycle	**Patient category:** N&V **Cancer details:** Advanced carcinomas of the following: lung (20), lymphona (10), soft-tissue sarcoma (9), breast (4), testis (4), melanoma (4), ovarary (3), osteosarcoma (1), prostate cancer (1), and head and neck cancer (1). **Inclusion criteria** Patients with various advanced malignancies who were receiving chemotherapy with high emetic potential. **Exclusion criteria** NR	**Age (Median, range):** 49 (18, 73) **% Male:** 77.2	**Disease severity:** NR **Disease duration:** NR	**Concomitant medication:** No brain or spinal irradiation, other antiemetics, or pschoactive drugs were given concomitantly. **Chemotherapy regimens:** Cisplatinum (24), dacarbazine (5), ifosfamide (2), adriamycin-cyclophosphamide combinations (14). **Previous medication:** No previous chemotherapy	**Previous cannabis use:** NR **Previous drug or tobacco use:** NR	*Total:* 7 completed only one chemotherapy cycle: 2 received other antiemetic drugs simultaneously; 3 treated by different chemotherapy

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Herman (1979)[123] **Country:** USA **Funding:** Mixed **Recruitment:** NR **Design:** Cross-over RCT **Number randomised:** 152 **Study duration:** Period 1: 1 chemotherapy cycle Period 2: 1 chemotherapy cycle Washout: NR	**Patient category:** N&V **Details:** Testicular carcinoma (n=70, 46%), non-Hodgkin's lymphoma (n=12, 8%), Hodgkin's disease 11/152 (7%). Other cancers: n/% not reported. **Inclusion criteria** Repeated courses of chemotherapy; all had experienced drug indeced nausea and vomiting. **Exclusion criteria** Psychiatric or cardiovascular disease	**Age (Median, range):** 33 (15, 74) **% Male:** 83	**Disease severity:** NR **Disease duration:** NR	**Chemotherapy regimens:** Cisplatin, vinblasine and bleomycin; cyclophsphamide, doxorubicin, vincristine and prednisone (CHOP); nitrogen mustart, vincristine, procarbazine and prednisone (MOPP); other chemotherapy regimens included dactionmycin, dacarbazine, 5-fluouracil, melphalan, and nitrosurea. **Previous medication:** NR	**Previous cannabis use:** NR **Previous drug or tobacco use:** NR	*Total:* 39 (19 chemotherapy changed after one course, 9 AEs (5 nabilone, 4 prochloperazine), 8 insufficient data available, 3 vomitted prior to chemotherapy).

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Hutcheon(1983)[103] **Country:** UK **Funding:** Mixed **Recruitment:** NR **Multicentre study** **Design:** Parallel group RCT **Number randomised:** 108 **Study duration:** 24 hours	**Patient category:** N&V **Cancer details:** NR **Inclusion criteria** Malignant disease; first course of potentially high antiemetic cytotoxic chemotherapy. **Exclusion criteria** Preganant women; history of psychiatric disturbance or cardiovascular disease.	*Intervention 1:* **Mean age (range):** 50.4 (21, 72) **% Male:** 80 *Intervention 2:* **Mean age (range):** 53 (25, 80) **% Male:** 38 *Intervention 3:* **Mean age (range):** 49 (17, 70) **% Male:** 50 *Placebo:* **Mean age (range):** 48.7 (21, 80) **% Male:** 48	**Disease severity:** NR **Disease duration:** NR	**Chemotherapy regimens:** Cis-platinum, fluorouracil/ doxorubin/ mitomycin, cylcophosphamide/ doxorubicin/ vincristine, cylcophosphamide/ doxorubicin/ VP16, cylcophosphamide/ methotrexate/ fluorouracil, mustine/ vinblastine/ procarbazine plus 'others'. **Previous medication:** NR	**Previous cannabis use:** NR **Previous drug or tobacco use:** NR	None reported.

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Johansson(1982)[106] **Country:** Finland **Funding:** NR **Recruitment:** September 1981 - April 1982 **Design:** Cross-over RCT **Number randomised:** 27 **Study duration:** *Period 1:* 1 chemotherapy cycle *Period 2:* 1 chemotherapy cycle	**Patient category:** N&V **Cancer details:** Primary tumour site: cervix (2, 8%), fallopian tubes (2, 8%), ovary (13, 50%), testis (2, 8%), head and neck (1, 4%), bronchus (1, 4%), histiocytoma (1, 4%), fibrosarcoma (1, 4%), oligodendrioma (1, 4%), lymphoma (2, 8%). **Inclusion criteria** Age 18-70 years; ECOG <2; same chemotherapy as previous cycles; uncontrolled nausea and vomiting despite use of standard antiemetic drugs. **Exclusion criteria** Known psychotic or cardiovascular diseases; currently under medication (i.e. with phenothiazines); previous usage of marijuana.	NR	**Disease severity:** NR **Disease duration:** NR	**Chemotherapy regimens:** Cisplatinum, adriamycin, cyclophosphamide (in combination with vinblastine, vincristine or ftorafur). Chemotherapy was of 1 day duration. **Concomitant medication:** No other antiemetic or psychotropic treatment while on study. **Previous medication:** NR	**Previous cannabis use:** Previous marijuana use excluded. **Previous drug or tobacco use:** NR	*Total:* 9 (1 insufficient data, 2 change of chemotherapy regime during cross-over, 1 concomtant antiemetic therapy, 1 inefficacy of treatment, 4 nabilone toxicity)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Johnson (2010)[82, 167] SPRAY **Country:** Belgium; Romania; UK **Funding:** Industry - drug manufacturer **Recruitment:** NR **Multicentre study** **Design:** Parallel group RCT **Number randomised:** 177 **Study duration:** 2 weeks	**Patient category:** Pain **Pain details:** Cancer-related pain. Primary cancer site: breast (16%); prostate (14%); lung (11%). Pain classification: mixed (50%); bone (37%); neuropathic (22%); visceral (21%); somatic/incident (10%) **Inclusion criteria** Adults; intractable malignancy-related pain; use of strong opioids ≥1 week; pain severity score ≥4 on 0-10 NRS, on 2 consecutive days **Exclusion criteria** Cancers of of the oral cavity; radiotherapy to the floor of the mouth; major psychiatric or cardiovascular disorder; epilepsy; hepatic or renal inpairment; pregnant, lactating, or not using adequate contraception; receipt of epidural analgesia ≤48 hrs; receipt of palliative radiotherapy, chemotherapy, or hormonal therapy ≤2 wks; taking levodopa, sildenafil, or fentanyl; hypersensitivity to CBM	**Age (Mean, SD):** 60.2 (12.3) **% Male:** 54 **% White:** 98	**Disease severity:** Pain score of ≥ 4 on a 0-10 NRS **Disease duration:** Mean (SD) duration of cancer 3.5 (4.4) yrs	**Concomitant medication:** Opioids Mean (SD) baseline morphine equivalents: 271.2 mg (698.98) **Previous medication:** NR	**Previous cannabis use:** 11% **Previous drug or tobacco use:** NR	*THC:CBD:* 12 (10 10, 1 consent withdrawal, 1 other) *THC: 13* (7 AE, 2 consent withdrawal, 1 sponsor decision, 1 protocol violation, 1 other) Placebo: 8 (3 AE, 2 consent withdrawal, 3 other)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Jones(1982)[90] **Country:** USA **Funding:** Industry - drug manufacturer **Recruitment:** NR **Multicentre study** **Design:** Cross-over RCT **Number randomised:** 54 **Study duration:** *Period 1*: 1 chemotherapy cycle *Period 2*: 1 chemotherapy cycle	**Patient category:** N&V **Details:** Cancer type: breast (15), lymphoma (12), ovary (8), lung (7), melanoma (3), testes (2), miscellaneous (7). **Inclusion criteria** Adults with cancer receiving chemotherapy regimens likely to produce nausea and vomiting; no serious contraindication to nabilone; likely to receive at least 2 identical courses of chemotherapy. **Exclusion criteria** ≥100 mg/m^2/day of cis-platinum; pregnant women or women not using medically acceptable contraceptive measures; clinically significant cardiovascular, hepatic or renal disease; major CNS disease; psychosis; progressive disease of the eye; weight of less than 45 kg; alcohol or drug addiction.	**Age:** 9 patients 20-37yrs; 23 38-57; 22 ≥58 **% Male:** 65	**Disease severity:** NR **Disease duration:** NR	**Chemotherapy regimens:** Adriacycin based (25), cisplatinum based (14), other (12). **Concomitant medication:** No other antiemetics permitted. **Previous medication:** NR	**Previous cannabis use:** NR **Previous drug or tobacco use:** NR	*Total:* 30 (6 protocol violations, 24 did not complete at least 24h of study drug on 2 consecutive identical courses of chemotherapy).

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Karst(2003)[147, 153] **Country:** Germany **Funding:** Industry - drug manufacturer **Recruitment:** May 2002 - September 2002 **Design:** Cross-over RCT **Number randomised:** 21 **Study duration:** *Phase 1:*1 week *Phase 2:* 1 week *Washout:* 1 week followed by 1 week baseline	**Patient category:** Pain **Pain details:** Chronic neuropathic pain with hyper-algesia(21) and allodynia in some (7). Location of neuropathic pain: arm (7); facial pain (4); behind ear (n=1); leg (n=7); sole of foot (n=1); whole-body (n=1). **Inclusion criteria** Pain ≥6 months; stable pain medications for at least 2 months; age 18-65. **Exclusion criteria** Severe organic or psychiatric disease; pregnancy or lactation; use of investigational drug ≤ 30 days; somatic pain; N-methyl-D-aspartate receptor antagonists and cannabinoids were not permitted.	**Age (Mean, SD, CI):** 50.9 (11.69) (29, 65) **% Male:** 61.9	**Disease severity:** NR **Disease duration:** Duration of pain 11.48 (7.15) years	**Concomitant medication:** Antipyretic and opioid analgesics, flupirtine, anticonvulsants, and antidepressants Regular use of concomitant analgesics: 10/11 **Previous medication:** NR	**Previous cannabis use:** None **Previous drug or tobacco use:** NR	*Placebo:* 1 (AE) *CBM:* 1 (AE)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Killestein(2002)[193, 196] **Country:** Netherlands **Funding:** Public **Recruitment:** NR **Design:** Cross-over RCT **Number randomised:** 16 **Study duration:** *Period 1*: 4 weeks *Period 2*: 4 weeks *Washout:*4 weeks	**Patient category:** MS **Details:** Primary Progressive MS: 37.5%; Secondary Progressive MS: 62.5% **Inclusion criteria** Progressive MS pts (according to Poser); disease duration >1 year; severe spasticity (mean Ashworth spasticity score ≥ 2 in at least one limb); EDSS score 4 - 7.5. **Exclusion criteria** Other disease of clinical importance; use of other investigational drug; disease exacerbation;, steroid treatment or use of cannabinoids ≤ 2 months; history of alcohol or drug abuse, depression, psychosis, or schizophrenia.	**Age (Mean, SD):** 46 (7.9) **% Male:** NR	**Disease severity:** Mean EDSS score: 6.2 (SD 1.2) **Disease duration:** Mean disease duration: 15 years (SD 10.7).	**Concomitant medication:** NR **Previous medication:** NR	**Previous cannabis use:** 6 patients had used cannabis before, none on a regular basis. **Previous drug or tobacco use:** NR	

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Lane(1991)[83, 116] **Country:** USA **Funding:** Industry - drug manufacturer **Recruitment:** NR **Multicentre study** **Design:** Parallel group RCT **Number randomised:** 62 **Study duration:** 6 days	**Patient category:** N&V **Cancer details:** Primary tumours: Breast (24), colon (3), lung (8), lymphoma (17), miscellaneous (10) **Inclusion criteria** Age 18-69 years; treated for cancer with chemotherapy other than investigational agents or high dose (>60mg/m^2) cisplatin **Exclusion criteria** CNS primaries or metastases	**Age (Median, range):** 52 (20, 68) **% Male:** 47 **% White:** 58	**Disease severity:** 27% experienced <2 episodes of nausea/vomiting with their prior chemotehrapy/anti emetic regimens, 52% had 2-10 episodes and 21% had >10 episodes. **Disease duration:** NR	**Chemotherapy regimens:** Most common: cyclophosphamide & doxorubicin, 5-fluourcail, cincristine, and etoposide. 48 had a high emeto-genicity chemo-therapy and 8 had low. **Previous medication:** All had received prior chemo-therapy and prior anti-emetic therapy	**Previous cannabis use:** No patient had previously received dronabinol or any other cannabinoid. **Previous drug or tobacco use:** NR	*Dronabinol:* 14 (10 AEs, 2 insufficient therapeutic effect, 2 other) *Prochlorperazine:* 4 (2 insufficient therapeutic effect, 2 other) *Combination:* 5 (4 AEs, 1 other)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Langford(2013)[4, 151] **Country:** UK, Czech Republic, Canada, Spain **Funding:** Industry - drug manufacturer **Recruitment:** NR **Multicentre study** **Design:** Parallel group RCT **Number randomised:** 339 **Study duration:** 14 weeks	**Patient category:** MS Pain **Pain details:** Central neuropathic pain (CNP) due to MS. MS subtype: Primary progressive (12%), secondary progressive (40%), relapsing/remitting (46%), progressive relapsing (2%). **Inclusion criteria** CNP due to MS for ≥3 months; sum score of ≥24 on a pain 0–10 point NRS on the last 6 days during the baseline period; stable analgesic for ≥2 weeks. **Exclusion criteria** Severe pain from other concomitant conditions; pain that was not of a central neuropathic origin thought by the investigator to be of a nature or severity to interfere with the patient's assessment of neuropathic pain due to MS; history of significant psychiatric, renal, hepatic, cardiovascular, or convulsive disorders; sensitivity to cannabis or cannabinoids.	**Age (Mean, SD):** 49(10.5) **% Male:** 32 **% White:** 98	**Disease severity:** NR **Disease duration:** MS duration mean 11.99 (sd 8.26) years. CNP duration mean 5.46 (sd 5.49) years.	**Concomitant medication:** 59% of patients took disease modifying treatments. 92% were taking medications other than analgesic medications. Paracetamol provided as rescue analgesic. Other analgesics incuded anticonvulsants, NSAIDs, tricyclic anti-depressants, opiods, antiarrhytmics, other. **Previous medication:** NR	**Previous cannabis use:** 6% had used cannabis in last year. **Previous drug or tobacco use:** NR	*CBM* arm: 26 (14 AE, 3 withdrew consent, 3 lack of efficacy, 6 other) *Placebo*: 16 (9 AE, 2 withdrew consent, 4 lack of efficacy, 1 other).

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Levitt(1982)[117] **Country:** Canada **Funding:** Not reported **Recruitment:** NR **Design:** Cross-over RCT **Number randomised:** 58 **Study duration:** *Period 1:* 1 chemotherapy cycle *Period 2:* 1 chemotherapy cycle	**Patient category:** N&V **Details:** Lung cancer (36%), ovarian cancer (19%), breast cancer (17%), other (28%). **Inclusion criteria** Not reported **Exclusion criteria** Not reported	**Age range:** 17, 78 **% Male:** 33	**Disease severity:** NR **Disease duration:** NR	**Chemotherapy regimens:** Adriamycin, bleomycin, cis-platinum, cyclophophamide, dactinomycin, melphalan, mitomycin C, methotrexate, tamoxifen, vincristine, VP-16, 5-fluorouracil. **Previous medication:** NR	**Previous cannabis use:** NR **Previous drug or tobacco use:** NR	*Total:* 20 (7 related to AEs).

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Leweke (2012)[75, 216-220] **Country:** Germany **Funding:** Public **Recruitment:** NR **Design:** Parallel group RCT **Number randomised:** 42 **Study duration:** 4 weeks	**Patient category:** Psychosis **Psychosis details:** 37 acute paranoid schizophrenia, 5 paranoid schizophrenia **Inclusion criteria** Age 18–50 years; DSM-IV criteria of acute paranoid schizophrenia or schizophreniform psychosis; acutely psychotic patients with a total Brief Psychiatric Rating Scale (BPRS) score ≥36 and a BPRS THOT factor (thought disorders) score ≥12; ≥3 antipsychotic free days. **Exclusion criteria** Positive urine drug screening for illicit drugs including cannabinoids; substance use disorders; previous treatment with a depot antipsychotic ≤3 months; history of treatment resistance; relevant and/or unstable medical condition; pregnancy or breast-feeding.	*Intervention 1:* **Mean age(sd):** 29.7(8.3) **Mean weight (sd):** 81.8(16.0) **% Male:** 75.0 *Control:* **Mean age(sd):** 30.6(9.4) **Mean weight (sd):** 73.3(11.4) **% Male:** 89**:**	**Disease severity:** NR **Disease duration:** NR	**Concomitant medication:** Lorazepam (up to 7.5mg/day). **Previous medication:** NR	**Previous cannabis use:** None **Previous drug or tobacco use:** NR	*CBM* arm: 3 (1 withdrawal of consent, 1 psychogenic sizure, 1 persisting suicidal ideation) *Control*: 1 (withdrawal of consent)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Long(1982)[73] **Country:** USA **Funding:** Not stated **Recruitment:** NR **Only available as conference abstract** **Design:** Cross-over RCT **Number randomised:** 42 **Study duration:** *Period 1:* 1 course of chemotherapy *Period 2:* 1 course of chemotherapy	**Patient category:** N&V **Cancer details:** NR **Inclusion criteria** Cancer patients receiving strongly emetic chemotherapy **Exclusion criteria** NR	**Age (Median, IQR):** 55 (20, 67) **% Male:** 90.4	**Disease severity:** Median (range) Karnofsky performance score 60 (50-100) **Disease duration:** NR	**Concomitant medication:** NR **Previous medication:** 81% had received chemotherapy (including cisplatin >70mg/m2).	**Previous cannabis use:** NR **Previous drug or tobacco use:** NR	36 patients (86%) have completed the study and 34 (81%) have been evaluated. Assumed 6/42 (14%) withdrawals.

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Lynch(2014)[148, 172] **Country:** Canada **Funding:** Industry - drug manufacturer (provided CBM only) **Recruitment:** NR **Design:** Cross-over RCT **Number randomised:** 18 **Study duration:** *Period 1:* 4 weeks *Period 2:* 4 weeks *Washout:* 2 weeks	**Patient category:** Pain **Pain details:** Chemotherapy induced pain. Cancer site: ovary (5, 28%), cervix (2, 11%), lung (1, 5.5%), uterus (3, 17%), breast (3, 17%), testicle (2, 11%), blood (1, 5.5%), lymphoma (1, 5.5%). **Inclusion criteria** Neuropathic pain; > three months after chemotherapy with paclitaxel, vincristine, or cisplatin; average 7 day pain intensity ≥4 on 11-point NRS; sensory abnormalities comprising allodynia, hyperalgesia, or hypesthesia; stable concurrent analgesics ≥ 14 days. **Exclusion criteria** Ischemic heart disease; epilepsy; personal or family history of schizophrenia, or psychotic disorder; substance abuse or dependency within the previous two years; pregnancy or other medical condition that might compromise safety in the trial.	**Age (Mean, SD):** 56 (10.8) **% Male:** 17	**Disease severity:** Mean baseline NRS pain intensity: 6.78 (sd 1.17) **Disease duration:** Mean pain duration: 17 months	**Concomitant medication:** Permitted during trial. Chemotherapetic agent: cisplating (3), oxaliplatin (1), paclitaxel (7), vincristine (1), combination 6). Mean number of chemotherapy cycles 5.72. **Previous medication:** Anitconvulsants (10), antidepressants (1), NSAIDs (2), opioids (2).	**Previous cannabis use:** 5 patients (28%) had previously used cannabis. **Previous drug or tobacco use:** NR	Total: 2 (reasons not reported).

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
McCabe (1988)[98, 122] **Country:** USA **Funding:** Public **Recruitment:** NR **Design:** Cross-over RCT **Number randomised:** 36 **Study duration:** *Period 1*: 1 chemotherapy cycle *Period 2*: 1 chemotherapy cycle	**Patient category:** N&V **Details:** Primary cancer sites: breast (11/36 - 31%); haematologic malignancies (9/36 - 25%); sarcomas (6/36 - 17%); gastrointestinal malignancies (5/36 - 14%); melanoma (2/36 - 5.5%); ovarian (2/36 - 5.5%); testicular (1/36 - 3%). **Inclusion criteria** Adults ≥18 years; no prior history of psychiatric illness or cardiac disease; performance status 0-1; agree to refrain from smoking marijuana during study; severe nausea and vomiting refractory to standard anti-emetics. **Exclusion criteria** History of psychiatric illness or cardiac disease; current users of inhaled marijuana.	**Age (Median, range):** 48 (18, 69) **% Male:** 25	**Disease severity:** Performance status 0-1: 100%; **Disease duration:** NR	**Chemotherapy regimen:** CMF, MOPP, platinum combinations, 5-FU or doxorubicin, DTIC and 5-azacytadine. **Previous medication:** Previous anti-emetics: 100% (94% prochlor-perazine, 6% thiethylperazine).	**Previous cannabis use:** NR **Previous drug or tobacco use:** NR	None

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Meiri(2007)[85, 119, 121] **Country:** USA **Funding:** Industry - drug manufacturer **Recruitment:** NR **Multicentre study** **Design:** Parallel group RCT **Number randomised:** 64 **Study duration:** 5 days	**Patient category:** N&V **Cancer details:** Breast cancer 26 (41%); non-small cell lung cancer 14 (22%); colon, rectal, or gastric cancer 6 (9%); lung cancer + others 18 (28%) **Inclusion criteria** Aged ≥ 18 years; malignancy excluding bone marrow; undergoing chemotherapy including a moderately to highly emetogenic regimen; could receive concomitant radiation therapy other than abdominal radiation, or be changing to a new moderately or highly emetogenic agent alone or in combination with other agents; life expectancy > 6 weeks postchemotherapy; ECOG performance status 0–2 . **Exclusion criteria** Antiemetic therapy ≤7 days; history of anticipatory nausea and/or vomiting; primary malignancy or metastases of the brain, spinal cord, or nervous system; history of brain surgery, brain trauma, or other neurological disorder; marijuana use ≤30 days; antiemetic agents ≤7 days; unstable dosage of opiates, propoxyphene, or benzodiazepines; no corticosteroids (except dexamethasone) at time of chemotherapy; chemotherapy agents with taxoid family antineoplastic agents; history or current diagnosis of psychotic disorder; evidence of substance abuse disorder; unstable medical conditions.	**Age (mean, sd, range):** 57.9 (12) (24, 81) **% Male:** 39 **% White:** 77	**Disease severity:** 41–69% of all patients had ECOG score of 0 or 1 at screening. **Disease duration:** NR	**Concomitant medication:** Metoclopramide, prochlorperazine, and prochlor-perazine, used as rescue medication **Previous medication:** Prior chemo-therapy: 16%. **Chemotherapy regimen** NR	**Previous cannabis use:** 6 (10%) **Previous drug or tobacco use:** NR	*CBM*: 5 (1 AE, 2 protocol violations, 1 other). *Ondansetron:* 4 (2 AE, 1 protocol violations, 1 other). *Combination:* 4 (3 AE, 1 other). *Placebo:* 4 (2 withdrew consent, 1 lethargy, 1 other).

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Melhem-Bertrandt(2014)[114, #10222, 124] **Country:** USA **Funding:** Public **Recruitment:** March 2009 - September 2011 **Multicentre study** **Design:** Parallel group RCT **Number randomised:** 62 **Study duration:** 5 days	**Patient category:** N&V **Cancer details:** Breast cancer 61, lymphoma 1. **Inclusion criteria** Adult solid tumour patients receiving ≤cyclophosphamide 1500 mg/m^2 and/or doxorubicin ≥40 mg/m^2. **Exclusion criteria** Cranial, abdominal or pelvic radiotherapy; chemotherapy-induced vomiting or chemotherapy-induced nausea with previous chemotherapy; other causes for nausea/vomiting besides chemotherapy; scheduled to receive other antiemetics; habitual cannabinoid use.	**Age (Mean, SD range):** 56.1 (11.1) (29, 76) **% Male:** 1.6 **% White:** 72.6	**Disease severity:** NR **Disease duration:** NR	**Chemotherapy regimen:** Cyclophosphamide and/or doxorubicin **Concomitant medication:** All pts received palonosetron 0.25 mg (PALO) and dexamethasone 10 mg (DXM) IV before chemotherapy. **Previous medication:** NR	**Previous cannabis use:** NR **Previous drug or tobacco use:** NR	*Total:* 1 treatment regime changed 1 physician included prednisone 1 inadequate drug supply at site

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Müller-Vahl (2001)[227, 228] **Country:** Germany **Funding:** Public **Recruitment:** NR **Design:** Cross-over RCT **Number randomised:** 12 **Study duration:** *Period 1:* 2 days *Period 2:* 2 days *Washout:* 28 days	**Patient category:** Tourette's **Inclusion criteria** Patients with Tourettes syndrome according to DSM -III R criteria. **Exclusion criteria** NR	**Age (Mean, SD, CI):** 34 (13) (range 18, 66) **% Male:** 92	**Disease severity:** NR **Disease duration:** NR	**Concomitant medication:** Pimozide (2), tiaprode (1), diazepam (1), pimozide/clonazepam/fluoxetin (1). Medication was stable for 3 months before trial. **Previous medication:** NR	**Previous cannabis use:** 7 patients **Previous drug or tobacco use:** NR	None

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Müller-Vahl(2003)[225, 226] **Country:** Germany **Funding:** Mixed **Recruitment:** NR **Design:** Parallel group RCT **Number randomised:** 24 **Study duration:** 6 weeks	**Patient category:** Tourette's **Inclusion criteria** Tourettes syndrome DSM-III R criteria **Exclusion criteria** Significant concomitant illness, history of psychosis or schizophrenia, pregnancy or breast-feeding, cannabis use 4-6 weeks before the study.	**Age (Mean, SD, CI):** 33 (11)(range 18 to 68) **% Male:** 79	**Disease severity:** NR **Disease duration:** NR	**Concomitant medication:** 9 (neuroleptics, serotonin-reuptake inhibitors, clonazepam), stable ≥1 year before and during study	**Previous cannabis use:** Never (17), 1-4 times monthly(4), >twice weekly (3) during t last year. **Previous drug or tobacco use: NR**	*Total:* 4 (1 AE, 2 non-compliance, 1 repeated cannabis use unrelated to study)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Narang(2008)[139, 173] **Country:** USA **Funding:** Mixed **Recruitment:** NR **Design:** Cross-over RCT **Number randomised:** 30 **Study duration:** *Period 1:* 8 hours *Period 2:* 8 hours *Washout:* 72 hours	**Patient category:** Pain **Details:** Chronic non cancer pain. Neuropathic (7), nociceptive (7), mixed neuropathic and nociceptive (11), uncategorized (5) pain. Back or neck surgery (57%). Pain location: low back (67%), lower extremity (47%), cervical (43%), abdominal/pelvic (43%), shoulder (37%), upper extremity (10%), and head (2 %). **Inclusion criteria** Chronic non-cancer pain; stable doses of opioid analgesics ≥6 months; pain > 4 NRS (0-10). **Exclusion criteria** Pain due to cancer; using a transdermal fentanyl patch or intrathecally administered opioid treatmentl; required opioid dosing > every 8 hours; unstable psychiatric disorder; current substance abuse; significant depression and/or anxiety (> 11 on the Hospital Anxiety and Depression Scale); marijuana use ≤1 month.	**Age (Median, IQR):** 43.5 (11.8) (21, 67) **% Male:** 46.7 **% White:** 96.7	**Disease severity:** NR **Disease duration:** Pain duration >5 years: 67%	**Concomitant medication:** Opioid medication: Methadone (30%), Morphine – long-acting (30%), Oxycodone – long-acting (17%), oxycodone – short-acting (37%), morphine – short-acting (17%), hydrocodone (7%), hydromorphone (7%). Use of breakthrough pain medication was allowed. **Previous medication:** NR	**Previous cannabis use:** 63%	1 dropout in the group of 10mg donabinol.

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Niederle(1986)[100] **Country:** Germany **Funding:** Not stated **Recruitment:** 1982 - 1984 **Design:** Cross-over RCT **Number randomised:** 20 **Study duration:** *Period 1*: 1 chemotherapy cycle *Period 2*: 1 chemotherapy cycle	**Patient category:** N&V **Details:** Testicular cancer **Inclusion criteria** Patient with nonseminomatous testicular cancer **Exclusion criteria** NR	**Age (Median, range):** 25 (19, 45)	**Disease severity:** Median performance status 0 (range 0-1) **Disease duration:** NR	**Chemotherapy regimen:** 2 subsequent courses of low-dose cisplatin and adriamycin therapy. **Concomittant medication:** Patients were not permitted to receive drugs with sedative-hypnotic, tranquilizing, and/or possibly antiemetic activity. **Previous medication:** 8 patients pre-treated with vinblastine/ bleomycin	**Previous cannabis use:** NR **Previous drug or tobacco use:** NR	None

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Niiranen(1985)[101] **Country:** Finland **Funding:** Industry - drug manufacturer **Recruitment:** NR **Design:** Cross-over RCT **Number randomised:** 32 **Study duration:** *Period 1:* 1 chemotherapy cycle *Period 2:* 1 chemotherapy cycle Washout: NR	**Patient category:** Nausea and vomitting **Cancer details:** Lung cancer **Inclusion criteria** Lung cancer; scheduled to receive at least two identical consecutive cycles of chemotherapy **Exclusion criteria** Clinically significant hepatic, renal, or CNS disease; alcohol or drug addiction	**Age (Mean, range):** 61 (48, 78) **Weight (Mean, range):** 72 (56, 97) **% Male:** 83	**Disease severity:** Median Karnofsky % (range): 80 (60-100) **Disease duration:** NR	**Chemotherapy regimens**: Combinations of cyclophosphamide, etoposide, vincristine, adriamiycin, cisplatinum, vindesine **Concomitant medication:** No other anti-emetics or tranquilizers were used whilst on study medication **Previous medication:** Previously untreated (10)	**Previous cannabis use:** NR **Previous drug or tobacco use:** NR	*Total:* 8 (1 cancer death, 3 refused chemotherapy before the second cycle, 1 protocol violation, 3 AE from nabilone)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Noyes (1975)[96] **Country:** USA **Funding:** Public **Recruitment:** NR **Design:** Cross-over RCT **Number randomised:** 10 **Study duration:** Period 1: 1 day Period 2: 1 day Washout: None All patients received all treatments in random order.	**Patient category:** Pain **Pain details:** Cancer-related pain (5 (50%) breast, 2 (20%) lymphoma, 1 (10%) cervix, 1 (10%) colon, 1 (10%) lymphoepithelmioma) **Inclusion criteria** Continuous moderate pain due to advanced cancer; patients volunteered to participate. **Exclusion criteria** Large doses of narcotics	**Age (Mean):** 51 **Weight (Mean):** 62 kg **% Male:** 20	**Disease severity:** Advanced cancer with moderate pain. **Disease duration:** NR	**Concomitant medication:** Usual analgesic program (no further information) **Previous medication:** NR	**Previous cannabis use:** NR **Previous drug or tobacco use:** NR	No details reported

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Nurmikko (2007)[80, 155, 168, 171, 175] **Countries:** Belgium, UK **Funding:** Industry - drug manufacturer **Recruitment:** NR **Multicentre study** **Design:** Parallel group RCT **Number randomised:** 125 **Study duration:** 5 weeks	**Patient category:** Pain **Pain details:** Neuropathic pain charaterised by allodynia. Underlying diagnosis: Postherpetic neuralgia (17), peripheral neuropathy (25), focal nerve lesion (54), Radiculopathy (13), CRPS type II (15), Other (1) **Inclusion criteria** Unilateral peripheral neuropathic pain and allodynia; ≥18years; ≥6 months of pain due to a nerve lesion; mechanical allodynia and impaired sensation within the territory of affected nerve(s); complex regional pain syndrome (CRPS) with evidence of peripheral nerve lesion; pain ≥4mm NRS for 4-7 days; stable analgesic medication ≥2 weeks, female patients of childbearing age had to agree to use contraception. **Exclusion criteria** Cannabinoid use <7 days; schizophrenia, psychosis, or other major psychiatric condition beyond depression; concomitant severe non-neuropathic pain; history of alcohol or substance abuse; severe cardiovascular condition; poorly controlled hypertension; epilepsy; pregnancy; lactation; significant hepatic or renal impairment; scheduled surgery or anaesthesia; terminal illness or participants inappropriate for placebo therapies; hypersensitivity to CBM; participation within another trial in last 12 weeks.	**Mean age (sd):** CBM: 52.4 (15.8) Placebo: 54.3 (15.2) **Weight:** NR **% Male:** 41 **% White:** 97	**Disease severity:** NR **Disease duration:** Duration of pain (years; mean (SD)): CBM 6.4 (5.7), placebo 6.2 (6.4)	**Concomitant medication:** Antiepileptic (42), tricyclic (37), opioid (86), analgesic, non-opioid (16), anti-inflammatory (25). **Previous medication:** NR	**Previous cannabis use:** n=25 **Previous drug or tobacco use:** NR	*CBM*: 13 (11 AE, 1 non-compliance, 1 lack of efficacy) *Placebo:* 7 (2 AE, 5 lack of efficacy)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Orr(1980)[107, 109] **Country:** USA **Funding:** Not stated **Recruitment:** NR **Design:** Cross-over RCT **Number randomised:** 79 **Study duration:** Period 1: 1 chemotherapy cycle Period 2: 1 chemotherapy cycle Washout: NR	**Patient category:** N&V **Cancer details:** "A variety of neoplasms" - 100% (no other detail reported) **Inclusion criteria** Neoplasms who previously demonstrated repeated vomiting from anti-cancer agents known to induce emesis; failed standard antiemetic therapy including phenothiazines, antihistamines and sedatives. **Exclusion criteria** Pregnant women; those receiving abdominal irradiation and individuals with a short life expectancy were excluded.	**Age (Mean, CI):** 46 (22, 71) **Weight:** NR **% Male:** 35.4	**Disease severity:** Previously demonstrated repeated vomiting from anti-cancer agents known to induce emesis **Disease duration:** NR	**Concomitant medication:** Chemotherapy agents used included: doxorubicin hydrochloride, cyclophosphamide, fluorouracil (with methotrexate), mechlorethamine hydrochloride, dacarbazine nitrosureas and cytarabine (proportions not reported). **Previous medication:** NR	**Previous cannabis use:** NR **Previous drug or tobacco use:** NR	24 (3 because of moral issues with use of marijuana 2 intense vomiting after taking study drugs 19 for other reasons of uncertainty about the drug and study design)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Pinsger(2006)[143, 154] **Country:** Austria **Funding:** Not stated **Recruitment:** 2003 - 2004 **Design:** Cross-over RCT **Number randomised:** 30 **Study duration:** Period 1: 4 weeks Period 2: 4 weeks Washout: 5 weeks	**Patient category:** Pain **Pains details:** Chronic refractory pain due to problems of the musculoskeletal system, especially spine (VAS >5), 80% with headache **Inclusion criteria** Chronic refractory pain due to problems of the musculoskeletal system (VAS >5) **Exclusion criteria** Change of analgesic treatment in last 4 weeks. Cancer-related pain. Chronic headache unrelated to spinal deformation CS>5.	**Age (Median, IQR):** 55 (50, 63) **Weight (Median, IQR):** 69 (64, 93) **% Male:** 23	**Disease severity:** Median (IQR) spine pain intensity in last four weeks (VAS): 7.9 (6-9) **Disease duration:** Spine pain in years (Median, IQR): 20 (10,30)	**Concomitant medication:** CBM as add-on to opioids 63%, antirheumatics 50% (no further details) **Previous medication:** NR	**Previous cannabis use:** NR **Previous drug or tobacco use:** NR	7 participants ended participation for "various reasons"; 2 changed their base medication.

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Pomeroy(1986)[99] **Country:** Ireland **Funding:** NR **Recruitment:** NR **Design:** Parallel group RCT **Number randomised:** 38 **Study duration:** 2 chemotherapy cycles	**Patient category:** N&V **Details:** Tumour types: Ovary 11/38 (29%); Testis 9/38 (24%); Bronchus 8/38 (21%); Non-Hodgkin's lymphoma 3/38 (8%); Hodgkin's disease 2/38 (5%); Sarcoma 2/38 (5%); Breast 1/38 (3%), Melanoma 1/38 (3%); Nephroblastoma 1/38 (3%). **Inclusion criteria** Patients with advanced malignant disease receiving highly emetogenic chemotherapy regimens (70% containing cisplatin). **Exclusion criteria** NR	**Age (Mean, Range):** 42 (21, 66) **% Male:** 61	**Disease severity:** Advanced malignant disease (100%) **Disease duration:** NR	**Chemotherapy regimen:** Cisplatin containing chemotherapy: 70%, Non cisplatin-containing chemotherapy: 30% (combinations of adriamycin, bleomycin, vincristine, DTIC, cyclophosphamide, prednisone, etoposide, ifosfamide, methotrexate, S-fluorouracil, vindesine, CCNU). **Previous medication:** NR	**Previous cannabis use:** NR **Previous drug or tobacco use:** NR	*CBM:* 3 (2 disease progression, 1 AE) *Domperidone:* 4 (3 lack of efficacy, 1 chemotherapy toxicity)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Pooyania(2010)[128, 205] **Country:** Canada **Funding:** Mixed **Recruitment:** NR **Design:** Cross-over RCT **Number randomised:** 12 **Study duration:** Period 1: 4 weeks Period 2: 4 weeks Washout: 2 weeks	**Patient category:** Paraplegia **Details:** Spinal cord injury (SCI) and spasticity. Injury (C5 or below, ASIA grade A-D). 5 patients with paraplegia, 6 with tetraplegia. **Inclusion criteria** SCI; age 18-65; injury level C5 (ASIA grade A–D) or below; injury occurred ≥ 1 year; no change in ASIA neurologic level ≤ 6 months; Ashworth ≥ 3; spasticity medications unchanged for ≥ 30 days; no botulinum toxin for ≥ 4 months. **Exclusion criteria** Heart disease; history of psychotic disorders, schizophrenia, or any active psychologic disorder; sensitivity to marijuana or other cannabinoid agents; severe liver dysfunction; cognitive impairment; major illness; pregnant or nursing; history of drug dependency; smoked cannabis ≤ 30 days before study or unwilling not to smoke during the study; fixed tendon contractures.	**Age (Mean):** 42.36 **% Male:** 100	**Disease severity:** Ashworth ≥ 3 **Disease duration:** SCI occurred ≥ 1 yr	**Concomitant medication:** Spasticity medications allowed if unchanged for ≥ 30 days before inclusion **Previous medication:** NR	**Previous cannabis use:** No smoked cannabis ≤ 30 days before study **Previous drug or tobacco use:** NR	*Total:* 1 (received diagnosis of urinary stricture)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Portenoy(2012)[86, 166] **Countries:** Belgium, Canada, Chile, Czech Republic, Finland, France, Germany, India, Italy, Mexico, Poland, Romania, South Africa, Spain, UK, USA **Funding:** Mixed **Recruitment:** NR **Multicentre study** **Design:** Parallel group RCT **Number randomised:** 360 **Study duration:** 9 weeks	**Patient category:** Pain **Details:** Cancer pain - primary cancer sites: breast (15%), gastrointestinal (18%), lung (18%), other/unknown (37%) Pain classification: bone (24%), mixed (42%), neuropathic (11%), somatic (9%), visceral (15%) **Inclusion criteria** Active cancer and chronic pain that was moderate or severe despite a stable opioid regimen (oral modified-release opioid formulation or transdermal fentanyl) that could not be made more effective by further opioid dose titration; score 4-8 on NRS pain scale, not changed by ≥2 points over 3 consecutive days in 14 days. **Exclusion criteria** Long-term methadone therapy; major psychiatric or cardiovascular disorder; epilepsy; significant renal or hepatic impairment; therapies expected to change the pain (e.g. radiotherapy, chemotherapy or hormonal therapy); had used marijuana, cannabinoid based medications or rimonabant ≤30 days.	**Age (Mean, SD, CI):** 58(12)(20, 93) **% Male:** 51.7 **% White:** 77.2	**Disease severity:** Average pain at baseline on NRS 5.8 (1.2) **Disease duration:** Cancer duration mean 3.6 (4.8) years; pain duration mean 1.9 (2.8) years	**Concomitant medication:** Median dose of opiods 120 mg (range 0-16660). Patients allowed to take breakthrough opiod analgesic as required. **Previous medication:** NR	**Previous cannabis use:** 10.6% **Previous drug or tobacco use:** NR	*Low dose CBM*: 20 (5 AE, 4 withdrew consent, 1 lack of efficacy, 7 disease progression, 3 other) *Medium dose CBM*: 21 (6 AE, 5 withdrew consent, 7 disease proogression, 2 other, 1 lost to follow-up) *High dose CBM*: 31 (20 AE, 4 withdrew consent, 7 disease proogression) *Placebo*: 25 (9 AE, 6 withdrew consent, 7 disease proogression, 1 other, 1 lost to follow-up, 1 lack of efficacy)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Prasad(2011)[72] **Country:** USA **Funding:** Industry - drug manufacturer **Recruitment:** NR **Only available as conference abstract** **Design:** Parallel group RCT **Number randomised:** 22 **Study duration:** 21 days	**Patient category:** Sleep **Details:** Obstructive sleep apnea syndrome (OSAS) **Inclusion criteria** Patients with obstructive sleep apnea syndrome; no further details **Exclusion criteria** NR	*CBM:* **Mean age (sd):** 51.6(7.9) **% Male:** 35 **% White:** 24 *Placebo:* **Mean age (sd):** 49.2(12.9) **% Male:** 80 **% White:** 60	**Disease severity:** Apnea Hypopnea Index: D=49(sd 25), P=30.5 (sd=15) **Disease duration:** NR	**Concomitant medication:** Continuous positive airway pressure. **Previous medication:** NR	**Previous cannabis use:** NR **Previous drug or tobacco use:** NR	

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Rohleder(2012)[75, 220-223] **Country:** Germany **Funding:** Public **Recruitment:** NR **Only available as conference abstract** **Design:** Cross-over RCT **Number randomised:** 29 **Study duration:** Period 1: 2 weeks Period 2: 2 weeks Washout: NR	**Patient category:** Psychosis **Psychosis details:** Acute paranoid schizophrenia or schizophreniform psychosis **Inclusion criteria** DSM-IV criteria of acute paranoid schizophrenia or schizophreniform psychosis; ≥36 in the BPRS total score and ≥12 in the BPRS Psychosis Cluster, including items 4 (conceptional disorganisation), 8 (exaggerated self-esteem), 12 (hallucinatory behaviour), and 15 (unusual thought content). **Exclusion criteria** Lack of accountability; pregnancy or lactation; interferences of axis 1 according to diagnostic evaluation through MINI including undifferentiated residual forms of schizophrenia; treatment with depot-antipsychotics ≤3months; severe internal or neurological illness; positive hepatitis-serology; QTc-elongation; acute suicidal tendency; hazard to others by the patient.	*NR*	**Disease severity:** NR **Disease duration:** NR	**Concomitant medication:** NR **Previous medication:** NR	**Previous cannabis use:** NR **Previous drug or tobacco use:** NR	

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Rog(2005)[144, 158, 169, 180] **Country:** UK **Funding:** Industry - drug manufacturer **Recruitment:** NR **Design:** Parallel group RCT **Number randomised:** 66 **Study duration:** 5 weeks	**Patient category:** Pain **Details:** MS spasticity and pain. **Inclusion criteria** Adults with central neuropathic pain syndromes due to MS; MS (Poser criteria) >6 months; central dysthetic pain or painful tonic spams ≥3 months for which a nociceptive cause appeared unlikely; expected to remain otherwise stable during the study. **Exclusion criteria** Chronic visceral pain, headache, spasticity-associated aching pain, secondary entrapment syndromes, or acute MS-related pains; major psychiatric disorder other than depression associated with their underlying condition; severe concomitant illness, seizures, history or suspicion of substance abuse; concomitant severe nonneuropathic pain or the presence of illness such as diabetes mellitus that could cause peripheral neuropathic pain; scheduled procedures re-quiring general anesthesia during study; pregnant or lactating; levodopa therapy ≤ 7 days; known or suspected hypersensitivity to cannabinoids.	Age (Mean, SD, CI): 49.2 (8.3) (26.9, 71.4)	**Disease severity:** Mean EDSS at study entry 5.9 (sd 1.3). Mean baseline NRS-11 pain score 6.5 (sd 1.6). **Disease duration:** Mean MS duration 11.6 (sd 7.7) years	**Concomitant medication:** Patients taking amitriptyline or other tricyclic antidepressants required to reduce to or maintain a maximum dose of 75 mg/day. Concomitant analgesics: paracetamol (8), tricyclic antidepressant (18), anaesthetic (1), anticonvulsant (13), benzodiazepine (3), evening primrose oil (n), combination opiod (22), opioid (5), strong opiod (3), oral NSAID (17), topical NSAID (2), muscle relxant (25) **Previous medication:** NR	**Previous cannabis use:** No cannabinoid use ≤7days or during study. Previous medicinal cannabis use 47%, previous recreational cannabis use 17%. **Previous drug or tobacco use:** NR	*CBM*: 2 (1 AE, 1 withdrew consent) *Placebo*: 0

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Sallan(1980)[94] **Country:** USA **Funding:** Public **Recruitment:** NR **Design:** Cross-over RCT **Number randomised:** 84 **Study duration:** Randomised to 3 courses (each lasting 1 chemotherapy cycle): 2 of one drug one of the other in all different permutations.	**Patient category:** N&V **Details:** NR **Inclusion criteria** Neoplasms; nausea and vomiting inadequately controlled by conventional anti-emetics. **Exclusion criteria** History of emotional instability; untoward reactions to pschoactive drugs.	**Age (mean, range):** 32.5 (9, 70) **% Male:** 61	**Disease severity:** NR **Disease duration:** NR	**Chemotherapy regimens:** Combinations of the following: cisplastin, decarbazine, doxorubicin, cyclo-phosphamide, high-dose methotrexacte, antinomycin D. **Previous medication:** All but 2 patients had received previous chemotherapy	**Previous cannabis use:** 5 patients known to use marihuana agreed not to smoke it during the study. **Previous drug or tobacco use:** NR	84 enrolled of which 38 completed 3 courses of treatment 11 excluded before medication (4 vomited before chemotherapy, insufficient data for 7) 27 excluded as received only 1 dose (15 CBM, 12 PCP). 8 excluded as received only 2 doses (all THC+PCP)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Selvarajah (2010)[132, 136, 179] **Country:** UK **Funding:** Public **Recruitment:** NR **Design:** Parallel group RCT **Number randomised:** 30 **Study duration:** 12 weeks	**Patient category:** Pain **Details:** Diabetic peripheral neuropathy (DPN); 24/30 had type 2 diabetes. **Inclusion criteria** Chronic painful DPN; Total Symptom Score 6 (>4 and <16) for >= 6 months with stable glycemic control (A1C<11%); persistent pain, despite an adequate trial of tricyclic antidepressants. **Exclusion criteria** NR	*CBM:* **Mean age (sd):** 58.2(8.8) **% Male:** 73 *Placebo:* **Mean age (sd):** 54.4(11.6) **% Male:** 50	**Disease severity:** NR **Disease duration:** Mean diabetes duration 11.2 (sd 8.4) years in Sativex and 13.7 (sd=6) years in placebo.	**Concomitant medication:** Patients continued preexisting neuropathic pain treatment during the study. **Previous medication:** NR	**Previous cannabis use:** 2 **Previous drug or tobacco use:** NR	Total: 6 (AEs); groups not specified.

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Serpell(2014)[81, 177] **Country:** Belgium, Canada, Czech Republic, Romania, UK **Funding:** Industry - drug manufacturer **Recruitment:** September 2005 - October 2006 **Multicentre study** **Design:** Parallel group RCT **Number randomised:** 246 **Study duration:** 15 weeks	**Patient category:** Pain **Details:** Peripheral neuropathic pain (PNP) associated with allodynia. Underlying condition: post-herpetic neuralgia (26%), peripheral neuropathy (24%), focal nerve lesion (39%), complex regional pain syndrome-II (13%). **Inclusion criteria** aged ≥18; mechanical allodynia; ≥ 6-month PNP; appropriate PNP treatment; cause of PNP: post-herpetic neuralgia, peripheral neuropathy, focal nerve lesion, radiculopathy or Complex Regional Pain Syndrome (CRPS) type 2; ≥24 on pain 0–10 NRS for ≥ 6 days during baseline; pain not wholly relieved by current therapy; stable analgesia ≥ 2 weeks. **Exclusion criteria** Severe pain from other concomitant conditions; history of significant psychiatric, renal, hepatic, cardiovascular or convulsive disorders; hypersensitivity to study medication; receiving a prohibited medication (including cannabis or CBM, analgesics taken when required, paracetamol-containing medications), history of alcohol or substance abuse.	**Age (Mean, SD):** 57.3 (14.2) **% Male:** 39 **% White:** 99	**Disease severity:** NR **Disease duration:** Mean pain duration 6.3 (sd 6.6; range 0.4-39.3) years. Mean duration of peripheral neuropathic condition 5.5 years (sd 5.9 years).	**Concomitant medication:** No analgesics on a when required basis; any new analgesic medication or altered dosage prohibited during the study. Rescue analgesis was parcetamol 500mg (max dose 2 tablets). 90% of patients continued to take analgesics: tricyclic antidepressants (26%), pregabalin (20%), gabapentin (23%), natural opium alkaloids (19%), other opioids (18%). Non-analgesic medications included proton pump inhibitors (18%), statins (15%), ACE inhibitors (14%), and beta blockers (13%).	**Previous cannabis use:** 25%, 10% had used cannabis in last year **Previous drug or tobacco use:** Known history of alcohol or tobacco abuse excluded.	*CBM*: 49 withdrawals (24 AE, 7 withdrew consent, 7 lost to follow-up, 11 lack of efficacy) *Placebo*: 24 withdrawals (7 AE, 3 withdrew consent, 1 lost to follow-up, 12 lack of efficacy, 1 other)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Sheidler(1984)[113] **Country:** USA **Funding:** Industry - drug manufacturer **Recruitment:** NR **Design:** Cross-over RCT **Number randomised:** 20 **Study duration:** No details of period duration/time of outcome assessment were reported	**Patient category:** N&V **Cancer details:** 4 small cell lung cancer; 4 multiple myeloma; 3 ovarian; 2 adenocarcinoma of the lung; 1 breast cancer; 1 diffuse histocytic lymphoma; 1 rhabdomyosarcoma **Inclusion criteria** Adults (18-70 yrs); new or previously treated cancer; receiving inpatient chemotherapy **Exclusion criteria** Brain metastases; neurological impairment; severe cardiac, renal, or hepatic disease; history of emotional instability; treatment with psychoactive drugs; pregnancy	**% Male:** 45	**Disease severity:** NR **Disease duration:** NR	**Concomitant medication:** High dose single agent or combination chemotherapy with cisplatin, cyclophosphamide and/or adriamycin **Previous medication:** NR	**Previous cannabis use:** NR **Previous drug or tobacco use:** NR	*Total:* 4 (2 cesation of chemotherapy secondary, 1 severe AE after first injection of prochlorperazine, 1 AE from levonantrodol)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Skrabek(2008)[140, 174] **Country:** Canada **Funding:** Mixed **Recruitment:** NR **Design:** Parallel group RCT **Number randomised:** 40 **Study duration:** 4 weeks	**Patient category:** Pain **Details:** Fibromylagia **Inclusion criteria** The American College of Rheumatology (1990) criteria for the classification of fibromyalgia; age 18 -70; pain despite the use of other oral medications. **Exclusion criteria** Pain better explained by a diagnosis other than fibromyalgia; abnormalities on routine baseline blood work; heart disease; schizophrenia or other psychotic disorder; severe liver dysfunction; history of untreated nonpsychotic emotional disorders; cognitive impairment; major illness in another organ system; pregnancy; nursing mothers; history of drug dependency; known sensitivity to marijuana or other cannabinoid agents; previous use of oral cannabinoids for pain management.	*CBM:* **Mean age (sd):** 47.6 (9.1) **Mean weight (sd):** 89.42 (24.54) *Placebo:* **Mean age (sd):** 50.1 (5.9) **Mean weight (sd):** 79.85 (14.36) **% Male:** 7.5	**Disease severity:** NR **Disease duration:** NR	**Concomitant medication:** Continuation of current treatments for fibromyalgia, including breakthrough medication, was allowed (no details reported). **Previous medication:** NR	**Previous cannabis use:** None **Previous drug or tobacco use:** NR	*CBM*: 5 (3 AE; 2= not stated). *Placebo*: 2 (1 AE, 1 not stated)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Steele(1980)[110] **Country:** USA **Funding:** Mixed **Recruitment:** April 1978 - January 1979 **Design:** Cross-over RCT **Number randomised:** 55 **Study duration:** Period 1: 1 chemotherapy cycle Period 2: 1 chemotherapy	**Patient category:** N&V **Cancer details:** NR **Inclusion criteria** Patients receiving cancer chemotherapy (no futher details) **Exclusion criteria** Known cardiac disease; psychotic episodes; regualr marijuana use	**Age (Median, range):** 50 (19, 65)	**Disease severity:** NR **Disease duration:** NR	**Chemotherapy regimen:** Primary emetic stimulus: cis-dichlorodiammineplatinum (II), mechlorethamine, streptoxotocin, actinomycin D, or DTIC. **Previous medication:** NR	**Previous cannabis use:** NR **Previous drug or tobacco use:** NR	*Total*: 18 (7 change in chemotherapy, 3 inadequate data collection, 1 died before second treatment period, 4 AE, 3 lack of efficacy).

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Struwe(1993)[130] **Country:** USA **Funding:** Mixed **Recruitment:** December 1990 - October 1991 **Design:** Cross-over RCT **Number randomised:** 12 **Study duration:** Period 1: 5 weeks Period 2: 5 weeks Washout: 2 weeks	**Patient category:** HIV **Inclusion criteria** HIV infected men; loss of >=2.25 kg of usual body weight but were at least 70% of ideal body weight **Exclusion criteria** Marijuana use ≤1 month; acute, concomitant medical complication; history of HIV dementia; recent histroy of substance abuse; unable to feed themselves and/or tolerate a regular diet; using steroids; frequent medicatgion changes for gastrointestinal symptoms tube feeding or parenteral nutrition.	**Age (mean, sd, CI):** 38 (7.3) (30, 48) **% White:** 80	**Disease severity:** Baseline CD 4 count 9-712 ul. % of ideal body weight 72-93%. **Disease duration:** NR	**Concomitant medication:** Omeprazole, metoclopramise, sucalfate, ranitidine, famotifine, donnagel, ADV then ddI cimetidfine/interferon, ddI, diphenoxylate, loperamide **Previous medication:** NR	**Previous cannabis use:** Patients who had used marijuana in month preceding study excluded. **Previous drug or tobacco use:** NR	Total: 7 (2 could not tolerate dronabinol, 2 HIV progression, 2 inability to comply with scheduled study visits, 1 start of experimental antiretrociral therapy).

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Svendsen(2004)[146, 152] **Country:** Denmark **Funding:** Mixed **Recruitment:** Feburary 2002 - May 2002 **Design:** Cross-over RCT **Number randomised:** 24 **Study duration:** Period 1: 3 weeks Period 2: 3 weeks Washout: 3 weeks	**Patient category:** Pain **Details:** Central Pain; MS - 9 relapsing remitting, 9 secondary progressive, 6 primary progressive. Site of pain: 16 lower extremities, 4 upper extremities, 2 back, 2 chest. Description of pain: 17 pricking, 13 hot or burning, 3 tingling, 3 tight, 3 dull, 7 other. **Inclusion criteria** Diagnosis of MS (clinical definite MS and laboratory supported definite MS); age 18-55 years; central pain at the maximal pain site with a pain intensity score ≥ 3 on a 0-10 NRS. Central pain was pain in a body territory with abnormal sensation to pinprick, touch, warmth, or cold, evaluated by the bedside or with quantitative sensory testing, corresponding to at least one lesion in the central nervous system. Concurrent spasm related pain or other pain was allowed if the patient was able to distinguish it from central pain. **Exclusion criteria** Marihuana use ≤3 months; unwilling to stop using marijuana during study.	**Age (Median, range):** 50 (23, 55) **% Male:** 42	**Disease severity:** Median EDSS 6 (2.5-6.5). Median pain intensity (NRS) 5.5 (3, 8). **Disease duration:** Median duration of pain 4.5(0.3-12) years.	**Concomitant medication:** Any analgesic drug (except paracetamol) was discontinued ≥1week before the first visit. **Previous medication:** NR	**Previous cannabis use:** Patients who had used marihuana within the last 3 months were excluded. **Previous drug or tobacco use:** NR	None

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Timpone(1997)[88] **Country:** USA **Funding:** Mixed **Recruitment:** NR **Multicentre study** **Design:** Parallel group RCT **Number randomised:** 37 **Study duration:** 12 weeks Study also included 13 participants randomised to combination of megestrol acetate 250 mg/day and dronabinol.	**Patient category:** HIV **Inclusion criteria** Clinical diagnosis of HIV wasting syndrome with anorexia and no severe diarrhea; either >10% weight loss or BMI that was low with respect to an age-based suggested range; age ≥18 years; Karnofsky performance status >60%; life expectancy >4 months; adequate organ function as measured by specified laboratory parameters; able to tolerate oral intake, and stable dose of any concomitant medications (≥4 weeks for antiretroviral therapy or ≥1week for all other medications). **Exclusion criteria** Hospitalization in ≤2 weeks; major opportunistic infections ≤2 months; dronabinol or megestrol acetate therapy ≤2 months; marijuana use ≤1 month; anabolic steroid use ≤3 months, pregnancy, active neoplasms (except cutaneous Kaposi's sarcoma or localized skin carcinoma), history of allergy to study drugs, history of psychiatric disorders (except depression), history of thromboembolic events, current drug or alcohol abuse, cardiac arrhythmias, congestive heart failure, diabetes, clinical ascites, uncontrolled hypertension, or requirement for anticonvulsants.	**Age (Mean, SD):** 40 (8) **Weight (Mean, SD):** 62.2 (10.7) **% Male:** 88 **% White:** 64	**Disease severity:** >10% weight loss: 52% Low BMI: 48%. CD4 (cells/ul): Overall = 59 % patients Karnofsky >=90: overall = 42. % patients Karnofsky <=80: overall = 58 **Disease duration:** NR	**Concomitant medication:** 86% receiving a stable dose of antiretroviral therapy. **Previous medication:** NR	**Previous cannabis use:** NR **Previous drug or tobacco use:** NR	2 excluded at baseline: 1 failure to appear for scheduled appointments and 1 prohibition against use of dronabinol. *Dronabinol:* 5 (4 AE, 1 unspecified) *M750:* 2 (AE) *M750+D:* 3 (2AE, 1 unspecified)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Tomida(2006)[224] **Country:** UK **Funding:** Industry - drug manufacturer **Recruitment:** NR **Design:** Cross-over RCT **Number randomised:** 6 **Study duration:** Period 1: 12 hours Period 2: 12 hours Washout: 1 week	**Patient category:** Glaucoma **Details:** Ocular hypertension or early open angle glaucoma, with mild visual defect (MD <6 dB and IOP >24 and <36 mm Hg) in at least one eye **Inclusion criteria** NR **Exclusion criteria** NR	**Age (Mean, SD):** 55.3 (5) **% Male:** 100	**Disease severity:** 3 ocular hypertension both eyes, no visual field defect; 2 primary open angle glaucona both eyes, no visual field defect; 1 primary open angle glaucoma both eyes, mild arcuate scotoma **Disease duration:** NR	**Concomitant medication:** None; concventional glaucoma therapy ceased for the duration of the study (washout period 4-6 wks before study) **Previous medication:** 1 timolol both eyes; 1 latanoprost both eyes; 1 timolol and latanoprost both eyes; 3 none	**Previous cannabis use:** NR **Previous drug or tobacco use:** NR	None

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Ungerleider(1982)[9] [1] **Country:** USA **Funding:** Public **Recruitment:** July 1977 - March 1980 **Multicentre study** **Design:** Cross-over RCT **Number randomised:** 214 **Study duration:** Period 1: 1 chemotherpay course Period 2: 1 chemotherpay course	**Patient category:** N&V **Details:** Tumours included: carcinoma (n=162, 76%), sarcoma (n=25, 12%), lymphoma/ Hodgkins (n=23, 11%), and leukemia (n=4). **Inclusion criteria** Patients with a wide variety of neoplasms and chemotherapeutic Regimens; >18 years of age; received a course of chemotherapy associated with a documented history of nausea and vomiting, or be on the first course of chemotherapy of a drug with a high emetic potential such as cisplatinum or dacarbazine. **Exclusion criteria** Concurrent radiation; history of allergy or severe side effects to prochlorperazine; pregnancy; use of other antiemetics or marijuana during the study.	**Age (Median, range):** 47 (18, 82) **% Male:** 50	**Disease severity:** NR **Disease duration:** NR	**Chemotherapy regimens:** 23 different agents, alone and in various combinations. These included: antibiotics (70), nitrosoureas (21), alkylating agents (119), antimetabolites (82), vinca-alkaloids (60), hormones (13), miscellaneous (33). High emetic potential (66%), moderate emetic potential (27%), and low emetic potential (7%). **Previous medication:** prior chemo-therapy (83%), prochlorperazine (73%).	**Previous cannabis use:** Approximately 50% **Previous drug or tobacco use:** NR	*CBD: 33* *Prochlorperazine (PCP): 42* The most frequent reason was discomfort about the uncertainty of which drug they had received. 2 cases of dysphoria THC and 2 cases of dysphoria PCP.

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Vaney(2004)[192] **Country:** Switzerland **Funding:** Public **Recruitment:** April 2000 - April 2001 **Design:** Cross-over RCT **Number randomised:** 57 **Study duration:** Group A (early treatment): 5 days titration, 9 days treatment, 4 days washout, 7 days placebo. Group B (late treatment): 7 days placebo, 5 days titration, 9 days treatment, 4 days washout.	**Patient category:** MS **Details:** Whole group: 29 primary progressive, 26 secondary progressive, 2 relapsing MS. **Inclusion criteria** Clinically confirmed MS and clinically stable spasticity; ≥ one joint scoring ≥ 2 on the Ashworth scale **Exclusion criteria** Significant neurological (other than MS), cardiovascular or infectious diseases; clinical disease exacerbation or treatment with steroids ≤two months preceding; history of alcohol or drug abuse; depression (Beck Depression Index > 11); history of psychosis; use of cannabinoids ≤1 week; significant cognitive impairment (Short Orientation Memory Concentration Test < 21)	**Age (Mean, SD):** 54.9 (10) **% Male:** 49	**Disease severity:** EDSS score, median (SD): 7 (6) **Disease duration:** Mean (SD): 17 (8.4) years	**Concomitant medication:** Anti-spasticity medication was continued without change **Previous medication:** NR	**Previous cannabis use:** 33 (58%) **Previous drug or tobacco use:** NR	*Total*: 7 (4 withdrawal of informed consent, 3 AE)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Wada(1982)[105] **Country:** USA **Funding:** Industry - drug manufacturer **Recruitment:** NR **Design:** Cross-over RCT **Number randomised:** 114 **Study duration:** Period 1: 1 chemotherapy cycle Period 2: 1 chemotherapy cycle	**Patient category:** N&V **Details:** Tumour types: lung (23, 20%), breast (18, 16%), ovarian (16, 14%), lymphoma (12, 11%), colonic (7, 6%), prostatitc (5, 4%), adenocarcinoma (5, 4%), bladder (3, 3%), melanoma (3, 3%), pancreatic (3, 3%), oesophagus (3, 3%), stomach (3, 3%), sarcoma (2, 2%), testis (2, 2%), other (9, 8%). **Inclusion criteria** Cancer receiving chemotherapy regimens likely to produce nausea and vomiting; no serious contrainidcation to nabilone; likely to receive at least 2 identical courses of chemotherapy. **Exclusion criteria** Significant cardiovascular, hepatic, renal or central nervous system disease; known psychosis or alcohol or drug addiction.	**Age (Mean, range):** 57 (18, 81) **% Male:** 41	**Disease severity:** NR **Disease duration:** NR	**Concomitant medication:** No other psychotropic drugs. **Chemotherapy regimens:** Cisplatinum based (22), adriamycin based (43), DTIC based (7), HN2 based (4), nitrosoureas based (8), others (13). **Previous medication:** Prior chemotherapy (50%)	**Previous cannabis use:** NR **Previous drug or tobacco use:** NR	*Total:* 30 (8 nabilone related AEs, 9 lack of efficacy of placebo, 4 progressive cancer that required change/discontinuation of chemotherapy, 3 cancer related deaths, 4 lost to follow-up, 2 change of mind after randomisation before starting treatment).

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Wade(2004)[3, 199, 204] **Country:** UK **Funding:** Industry - drug manufacturer **Recruitment:** NR **Multicentre study** **Design:** Parallel group RCT **Number randomised:** 160 **Study duration:** 6 weeks	**Patient category:** MS **MS Details:** Clinically confirmed MS of any type **Inclusion criteria** MS clinically stable with no relapse ≤4 weeks; stable regular medication unchanged ≤4 weeks; abstaining from alternative cannabinoid use for 7 days prior to screening and throughout the study; have one of five target symptoms: spasticity, spasms, bladder problems, tremor or pain that was not obviously musculoskeletal. The most troublesome to be identified as the primary symptom. **Exclusion criteria** Primary symptom was rated < 50% of maximal severity; current or past history of drug or alcohol abuse; significant psychiatric illness other than depression associated with MS; serious cardiovascular disorder; significant renal or hepatic impairment or history of epilepsy; specific contraindications to CBME excluded.	**Age (Mean, SD, CI):** 50.7(9.3)(27, 74) **% Male:** 38	**Disease severity:** NR **Disease duration:** NR	**Concomitant medication:** Continued concomitant medications throughout the study (no other detail given). **Previous medication:** NR	**Previous cannabis use:** Previous medicinal cannabis (39%). Previous recreational cannabis (21%). **Previous drug or tobacco use:** NR	*CBM*: 3 (AE) *Placebo:* 3 (1 AE, 1 withdrew consent, 1 used other cannabis)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Wallace(2013)[76, 160] **Country:** USA **Funding:** Public **Recruitment:** NR **Only available as conference abstract** **Design:** Cross-over RCT **Number randomised:** 16 **Study duration:** 4 hours per session. No details on time between session (washout)	**Patient category:** Pain **Details:** Painful diabetic peripheral neuropathy (DPN). **Inclusion criteria** History of diabetes mellitus type 1 or type 2; stable glycemia maintained by diet or a stable regimen of diabetic therapy for > 12 weeks prior to screening; DPNP> 6 months, symmetrical onset confirmed by neurological exam; score > 3 on the investigator section (physical exam) of the MNSI (Michigan Neuropathy Screening Instrument); > 4 on 11 point NPS; HbA1C<11%. **Exclusion criteria** Current or past cannabis abuse/ dependence; current other psychoactive drug use disorder; significant cardiac or pulmonary disease; pregnancy; current serious mental illness; other medical conditions that may lead to peripheral neuropathy; lower extremity amputations other than toes; no phantom pain from amputated toes; other painful conditions or pain of vascular origin; unstable blood glucose level (Fasting< 70mg/dL or random blood glucose level > 250 mg/dL)	**% Male:** 56	**Disease severity:** NR **Disease duration:** NR	**Concomitant medication:** NR **Previous medication:** NR	**Previous cannabis use:** NR **Previous drug or tobacco use:** NR	NR

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Ware(2010)[132, 133, 149, 150] **Country:** Canada **Funding:** Industry - drug manufacturer **Recruitment:** August 2005 - January 2007 **Design:** Cross-over RCT **Number randomised:** 32 **Study duration:** Period 1: 2 weeks Period 2: 2 weeks Washout: 2 weeks	**Patient category:** Pain Sleep **Details:** Sleep disorders in patients with chronic pain conditions (fibromyalgia) **Inclusion criteria** ≥18yrears; diagnosis of fibromyalgia; self-reported chronic insomnia (disturbed sleep for a minimum of every other night, for at least 6 months); negative urine test for cannabinoids at screening; 2 week washout period if using cannabinoids or amitriptyline **Exclusion criteria** Pregnancy; cancer pain; unstable cardiac disease; history of psychosis, schizophrenia or manic episode in the past year; seizure disorder; glaucoma; urinary retention; hypersensitivity to cannabinoids, amitriptyline or related tricyclic antidepressants; use of monamine oxidase inhibitors	**Age (Mean, SD, CI):** 49.5 (11.2)(26, 76) **% Male:** 16	**Disease severity:** Baseline: ISI 18.3 (5.2) McGill pain questionnaire (PPI) 2.3 (0.8); Fibromyalgia impact questionnaire total score 62.6 (15.2) **Disease duration:** NR	**Concomitant medication:** NR **Previous medication:** 5 Participants were taking tricyclic antidepressants at screening (4 amitriptyline, 1 nortriptyline); all withdrew from these medications before randomisation	**Previous cannabis use:** None at screening **Previous drug or tobacco use:** NR	Total: 3 (1 non-compliance with protocol, 1 lack of effects; 1 AE)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Ware(2010)[135, 176] **Country:** Canada **Funding:** Public **Recruitment:** August 2003 - January 2006 **Design:** Cross-over RCT **Number randomised:** 23 **Study duration:** 4 periods: each involved 5 days on study drug and 9 days of washout	**Patient category:** Pain **Details:** Neuropathic pain ≥3 months duration caused by trauma or surgery **Inclusion criteria** Age 18-70; neuropathic pain (≥3 mths) due to trauma or surgery with allodynia or hyperalgesia, (average weekly pain intensity score ≥ 4 on a 10-cm VAS); stable analgesic regimen; no cannabis use in year before study; normal liver and renal function; normal hematocrit. **Exclusion criteria** Pain due to cancer or nociceptive causes; presence of significant cardiac or pulmonary disease; current substance abuse or dependence (including cannabis), history of psychotic disorder, current suicidal ideation; pregnancy or breastfeeding.	**Age (Mean, SD, range):** 45.4 (12.3)(25, 77) **% Male:** 47.8	**Disease severity:** Average weekly pain intensity score ≥ 4 on a 10-cm VAS (inclusion criteria) **Disease duration:** Pain for at least 3 months (inclusion criteria)	**Concomitant medication:** Routine medications (61% opioids, 52% antidepressants, 43% anticonvulsants, 43% NSAIDs) were continued throughout the trial. Use of breakthrough analgesia (acetaminophen) was allowed. **Previous medication:** NR	**Previous cannabis use:** 81.8% ever used cannabis **Previous drug or tobacco use:** 34.8% never smoked, 39.1% current smoker, 26.1% ex-smoker. 61% used alcohol.	2 (1 positive result on urinary screening for cannabinoid, 1 increased pain)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Wilsey(2013)[134, 163] **Country:** USA **Funding:** Public **Recruitment:** December 2009 - March 2011 **Design:** Cross-over RCT **Number randomised:** 39 **Study duration:** Period 1: 6 hours Period 2: 6 hours Washout: minimum 3 days, mean 7 days (SD 1.8)	**Patient category:** Pain **Details:** Most patients had peripheral neuropathic pain: complex regional pain syndrome (CRPS) type I (6), causalgia (2), diabetic neuropathy (6), idiopathic peripheral neuropathy (3), postherpetic neuralgia (3), brachial plexopathy (3), lumbrosacral radiculopathy (3). 13 patients ahd central neuropathic pain: pain related to spinal cord injury (9), involvement of the central neuroaxis by MS (3), thalamic pain (1). **Inclusion criteria** Age18-70; VAS > 3/10; neuropathic pain disorder; previous cannabis exposure was required; no evidence of IV drug abuse. **Exclusion criteria** Painful condition of greater serverity than neuropathic pain; moderate-severe depression; suidical ideation; history or diagnosis of serious mental illness; uncontrolled hypertension; cardiovascular disease; chronic pulmonary disease; TB; active substance abuse; unstable type 1 or 2 diabetes (glucose > 156 mg/dl); traumatic brain injury; opportunistic infection; malignancy requiring active treatment; pregnancy; marijuana ≤ 30 days.	Age (Mean, SD, CI): 50(11) **% Male:** 72 **% White:** 72	**Disease severity:** Mean baseline pain at each treatment period ranged from 53.4 (sd 23.4) to 57.5 (sd 22.8) on 0-100 VAS scale. **Disease duration:** Median duration of pain 9 (0.5-43) years.	**Concomitant medication:** Patients were instructed to take all other concurrent medications normal. Concomitant medications included opioids (20), anticonvulsants (20), antidepressants (8), NSAIDs (4). **Previous medication:** NR	**Previous cannabis use:** None ≤30 days. All patients had used cannabis before. The median (range) time from most recent exposure to cannabis was 9.6 years (1 day to 45 years). Of the 39 patients who completed at least 1 study visit, 16 were current marijuana users and 23 were ex-users. **Previous drug or tobacco use:** Patients with active substance abuse excluded.	*Low dose CBM:* 2 (1 transportation issue, 1 scheduling conflict) *Medium dose CBM:* 3 (1 unrelated medical condition, 1 scheduling conflict, 1 discintinued interest). *Placebo:* 1 (transportation issue)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Wilsey(2011)[138, 161] **Country:** USA **Funding:** Public **Recruitment:** June 2004 - February 2006 **Design:** Cross-over RCT **Number randomised:** 38 **Study duration:** Phase 1: 6 hours Phase 2: 6 hours Phase 3: 6 hours Washout: 3 to 21 days apart (mean 7.8, sd=3.4 days).	**Patient category:** Pain **Details:** Neuropathic pain due to: complex regional pain syndrome (CRPS) type I (22), Spinal cord injury (6), Multiple sclerosis (4), Diabetic neuropathy (3), Ilioinguinal neuralgia (2), Lumbosacral plexopathy (1). **Inclusion criteria** Age > 18 and < 70yrs; VAS > 3/10; history of previous marijuana use; negative urine drug screening test; CRPS type I, spinal cord injury, peripheral neuropathy, or nerve injury. **Exclusion criteria** Presence of another painful condition of greater severity than the neuropathic pain condition; unstable Type 1 or 2 diabetes; diabetic patients maintained on insulin with a stable blood glucose and HbA1C: history of traumatic brain injury, history of schizophrenia or a past or current history of a serious psychiatric disorder; uncontrolled medical condition (coronary artery disease, hypertension, cerebrovascular disease, asthma, TB, COPD, opportunistic infection, malignancy requiring active treatment), active substance abuse.	**Age (Median, range):** 46 (21, 71) **% Male:** 53 **% White:** 87	**Disease severity:** Baseline mean pain intensity (VAS scale): 5.6 (SD 2.1) **Disease duration:** mean 6 yrs (range 10-290 months)	**Concomitant medication:** Opioids (31), antidepressants (19), NSAIDS (9), anticonvulsants (22). **Previous medication:** NR	**Previous cannabis use:** 100%. Median (range) time from previous exposure: 1.7 years (31 days to 30 years) **Previous drug or tobacco use:** NR	3.5% THC: 2 (1 elevated BP, 1 no explanation) 7% THC: 4 (2 lost interest, 2 no explanation) Placebo: 6 (1 childcare issues, 2 lost interest, 2 no explanation)

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Zajicek(2003)[89, 189, 191, 206] CAMS study **Country:** UK **Funding:** Public **Recruitment:** December 2000 - December 2002 **Multicentre study** **Design:** Parallel group RCT **Number randomised:** 657 **Study duration:** 15 weeks	**Patient category:** MS **Details:** 33 RRMS (5%), 145 PPMS (23%), 452 SPMS (72%) **Inclusion criteria** Age 18–64 years; confirmed MS; stable for ≥6 months; spasticity (Ashworth score of ≥2 in ≥ 2 limb muscle groups). **Exclusion criteria** Ischaemic heart disease; physiotherapy regimen or medication likely to affect spasticity ≤30 days; active infection; illness which could affect spasticity; immunisations associated with foreign travel; unable to avoid driving; fixed-tendon contractures; severe cognitive impairment; past history of psychotic illness; major illness in another body area; pregnancy; use of Δ9-THC at any time; use of cannabis ≤30 days.	*THC/CBD:* **Mean age (sd):** 50.5 (7.6) **Mean weight (sd):** 71.70 (15.90) *Dronabinol:* **Mean age (sd):** 50.2 (8.2) **Mean weight (sd):** 71.20(16.50) *Placebo:* **Mean age (sd):**50.9 (7.6) **Mean weight (sd):** 71.60 (15.90) **% Male:** 34	**Disease severity:** EDSS score. 0-3-5 1%, 4-5.5 4%, 6-6.5 47%, 7-9 47%, missing 1%. Able to walk with or without aid: 48%; unable to walk 52%. **Disease duration:** NR	**Concomitant medication:** No drugs "which could affect spasticity" **Previous medication:** NR	**Previous cannabis use:** No use of Δ9-THC at any time or cannabis in the 30 days before study start **Previous drug or tobacco use:** NR	*Total:* 27 did not receive allocated treatment, 19 lost to follow-up. *THC/CBD:* 8 did not receive allocated treatment, 4 lost to follow-up. *Dronabinol:* 10 did not receive allocated treatment, 9 lost to follow-up. *Placebo:* 9 did not receive allocated treatment, 6 lost to follow-up.

Study details	Selection criteria	Participant details	Disease severity/duration	Medication	Previous drug use	Withdrawals
Zajicek(2012)[87, 194, 195, 197, 201, 207] MUSEC study **Country:** UK **Funding:** Mixed **Recruitment:** June 2006 - September 2008 **Multicentre study** **Design:** Parallel group RCT **Number randomised:** 279 **Study duration:** 12 weeks	**Patient category:** MS **Details:** Relapsing-remitting (8%), primary progressive (24%), secondary progressive (69%) **Inclusion criteria** 18-64 years; diagnosis of MS (McDonald 2001 criteria); stable disease 6 months; muscle stiffness for at >=3 months (disability score of at least 4 on an 11 point category rating scale) **Exclusion criteria** Active sources of infection; taking immunomodulatory drugs that might affect spasticity (eg, b-interferon, but not azathioprine); fixed tendon contractures; severe cognitive impairment; history of psychosis; major illness; pregnancy; cannabis use ≤30 days before study start.	*CBM:* **Mean age (sd)(CI):** 51.9(7.7) (32, 64) **Mean weight (sd):** 75.31(16.52) **% Male:** 38.5 **% White:** 99.3 *Placebo:* **Mean age (sd)(CI):** 52.0(7.9) (28.0, 64.0) **Mean weight (sd):** 74.31(16.97) **% Male:** 35.1 **% White:** 99.3	**Disease severity:** At screening 77% were walking. At baseline: body pain high in 63%, muscle spasms high in 78%, quality of sleep high in 64% **Disease duration:** Time since first diagnosis median 14 (range 0-40 years).	**Concomitant medication:** Physiotherapy regimens or medications likely to affect spasticity were adjusted, where necessary, before study entry and not altered in the 30 days before study start. **Previous medication:** 61% were taking spasticity medication at baseline; 57% were taking analgesia.	**Previous cannabis use:** Not reported **Previous drug or tobacco use:** Not reported	*Did not receive allocated treatment:* 2 (participation in another study, consent withdrawn). *CBM*: 34 (30 AE, 3 consent withdrawn, 1 other reason) *Placebo*: 19 (9 AE, 7 consent withdrawn, 3 other reason)

Study details	Design	Participants	Intervention /Comparator	Outcome
Agrawal(2011)[229] **Study Name:** DIGS 4.0 / The Bipolar Genome Study **Country** USA **Funding sources** Public	**Study design** Case-control	**Cases:** DSM-IV bipolar disorder/ bipolar disorder spectrum disorder. **Controls:** Matched on gender and ethnicity; did not fulfill diagnostic criteria for major depression; did not report a history of schizophrenia, bipolar disorder or psychosis.	**Intervention** Cannabis **Details** Lifetime history of cannabis use	Psychotic disease (Bipolar disorder)
Aldington(2008)[231] **Country** New Zealand **Funding sources** Public	**Study design** Case-control	**Cases:** Age 55 years and under; diagnosed between 2001 and 2005, identified from hospital databases and the New Zealand Cancer Registry; no lung metastasis from other primary tumor; no carcinoid or melanoma. **Controls:** No respiratory tract cancer, head and neck cancer, or lung cancer; randomly selected from the electoral roll in the same geographic areas as cases; matched in five-year age groups.	**Intervention** Cannabis **Details** >10.5 joint years 1.39 - 10.5 joint years <1.39 joint years Never	Cancer (head and neck cancer)

Study details	Design	Participants	Intervention /Comparator	Outcome
Aldington(2008)[230] **Country** New Zealand **Funding sources** Public	**Study design** Case-control	**Cases:** Age 55 years and under; diagnosed between 2001 and 2005, identified from hospital databases and the New Zealand Cancer Registry; no lung metastasis from other primary tumor; no carcinoid or melanoma. **Controls:** No respiratory tract cancer, head and neck cancer, or lung cancer; randomly selected from the electoral roll in the same geographic areas as cases; matched in five-year age groups.	**Intervention** Cannabis **Details** >10.5 joint years 1.39 - 10.5 joint years <1.39 joint years Never	Cancer (lung cancer)
Barber(2013)[232, 310-312] **Country** New Zealand **Funding sources** Public	**Study design** Case-control	**Cases:** Consecutive patients; age 18 to 55; admission for ischemic stroke / TIA; asked to provide a urine sample within 72 hours of admission. **Controls:** admission for Internal Medicine without cardiovascular or neurological conditions	**Intervention** Cannabis **Details** Regular defined as up to 72 hours after a single exposure and =< 10 weeks with daily use	Cardiovascular disease (ischemic stroke / transient ischemic attack)

Study details	Design	Participants	Intervention /Comparator	Outcome
Beautrais(1999)[233] **Country** New Zealand **Funding sources** Public	**Study design** Case-control	**Cases:** Medically serious suicide attempts (hospitalised for >24 hours and were treated in a specialized unit or received surgery under general anaesthesia or received medical treatment beyond gastric lavage/ activated charcoal/ routine neurological observations). **Controls:** selected from the electoral role; frequency-matched on age group and gender.	**Intervention** Cannabis **Details** Defined as dependent / abuse according to DSM3.	Suicide (suicide attempt)
Berthiller(2009)[260] **Study Name:** INHANCE **Country** USA and Brazil **Funding sources** Public	**Study design** Case-control	Pooled IPD from five studies. **Cases:** Patients with head and neck cancer diagnoses, from five studies. Two sites restricted eligibility to squamous cell carcinomas. **Controls:** Matched on age and gender in all studies. The Brazil study also matched on study centre.	**Intervention** Marijuana **Details** Never 0-1 time per day vs never 1-3 times per day vs never >3 times per day vs never	Cancer (head and neck cancer)

Study details	Design	Participants	Intervention /Comparator	Outcome
Daling(2009)[235] **Study Name:** ATLAS **Country** USA **Funding sources** Public	**Study design** Case-control	**Cases:** Men; age 18 - 44; invasive TGCT, diagnosed between January 1999 and January 2006; landline residential telefone; English-speaking. **Controls:** Men without a history of TGCT; resident in the same geographic areas as cases; identified by random digit dialing; matched by 5-year age groups.	**Intervention** Marijuana **Details** Never <once per week vs never Daily or >once per week	Cancer (Testicular Germ Cell Tumors)
Davis(2013)[236] **Study Name:** NESARC **Country** USA **Funding sources** Public	**Study design** Retrospective Cohort	Participation in wave 1 of NESARC; non-institutionalised adults (aged at least 18 years); persons without mental or physical impairment; persons not on active duty in the armed forces; persons not deceased or deported. (NIAAA report, page 12)	**Intervention** Cannabis **Details** No use Regular defined as "abuse" Regular defined as "dependence"	Psychotic disease (schizotypical personality disorder)

Study details	Design	Participants	Intervention /Comparator	Outcome
Di Forti(2009)[237, 313-316] **Country** U.K. **Funding sources** Public	**Study design** Case-control	**Cases:** Adults (age 18 - 65 years); first episode of psychosis; in-patient units of the South London and Maudsley Mental Health NHS Foubdation Trust, between December 2005 and October 2008. **Controls:** Healthy control group recruited from the local population, recruited by advertisements which did not mention cannabis. Controls were matched on age, gender ethnicity, educational qualifications and employment status.	**Intervention** Cannabis **Details** - daily vs less than daily - 0-5 years vs over 5 years - age at first use: under 17 vs 17 and over	Psychotic disease (Psychosis using ICD10 criteria)

Study details	Design	Participants	Intervention /Comparator	Outcome
Dutta(2014)[238] **Country** USA **Funding sources** Not stated **Available only as conference abstract**	**Study design** Case-control	**Cases:** Ischaemic stroke patients from the greater Baltimore-Washington area; aged 15-49 years; presenting between 1992 and 2008 **Controls:** aged 15-49 years; from the same geographic area Participants who used any illicit drug, other than marijuana or hashish were excluded from the analyis.	**Intervention** Marijuana or hashish **Details** Exposure determined by self-report	Cardiovascular disease (Ischemic stroke)
Giordano(2014)[239] **Country** Sweden **Funding sources** Public	**Study design** Case-control	**Cases:** People in Sweden diagnosed with schizophrenia over the period 2000–2010; aged under 50 years at the time initial diagnosis. **Controls:** No diagnosis of schizophrenia from 1987 to 2010; matched for gender, age and country of birth	**Intervention** Cannabis **Details** Registered cannabis abuse as distinct from any use of cannabis	Psychotic disease (Schizophrenia)
Hashibe(2006)[240] **Country** USA	**Study design** Case-control	**Cases:** Residents of Los Angeles County; 18-65 years old; spoke English or Spanish; histologically confirmed new	**Intervention** Marijuana **Details**	Cancer (esophageal cancer) Cancer (oral cancer)

Study details	Design	Participants	Intervention /Comparator	Outcome
Funding sources Public		cases of lung and UAT (upper aerodigestive tract) cancers, diagnosed in the previous six months; identified by the rapid ascertainment system of the Cancer Surveillance Program for Los Angeles County. **Controls:** Residents of Los Angeles County; 18-65 years old; spoke English or Spanish; no history of lung or UAT cancers; individually matched to cases on age decade, gender, and residential neighborhood.	0-1 joint-years	Cancer (pharyngeal cancer) Cancer (laryngeal cancer) Cancer (lung cancer)

Study details	Design	Participants	Intervention /Comparator	Outcome
Lacson(2012)[241] **Country** USA **Funding sources** Public	**Study design** Case-control	**Cases:** men; diagnosed with TGCT between December 20, 1986 and April 4, 1991 in Los Angeles County; aged 18 to 35 years at diagnosis; spoke English; were born either in the United States, Europe, Canada, or the Middle East. **Controls:** matched on age, race, ethnicity, and neighborhood of residence at the time of diagno- sis.	**Intervention** Marijuana **Details** Exposure details were obtained by trained interviews, using structured questionnaires, administered at the participants' homes. Information was requested for the period of 1 year before the diagnosis of TGCT - defined as < 1 times / week - defined as > once per week - <10 years - ≥ 10 years - Current use	Cancer (Testicular Germ Cell Tumour (TGCT))
Liang(2009)[242] **Country** USA **Funding sources** Public	**Study design** Case-control	**Cases:** HNSCC, pathologically confirmed no more than six months before inclusion; age at least 18 years; no recurrent disease. **Controls:** Matched on age, gender and town of residence.	**Intervention** Marijuana **Details** Never Current Former use 0.5-1.5 times per week 1.5-4.5 times per week >4.5 times per week	Cancer (head and neck squamous cell carcinoma)

Study details	Design	Participants	Intervention /Comparator	Outcome
Llewellyn(2004)[243] **Country** U.K. **Funding sources** Public	**Study design** Case-control	**Cases:** Age 45 years or under; ICD-10 diagnoses of squamous cell carcinoma of lip, intra-oral or oropharyn. **Controls:** Matched, through general practitioners, for age, sex, and area of residence.	**Intervention** Cannabis **Details** Never Ever	Cancer (oral squamous cell carcinoma)
Llewellyn(2004)[244] **Country** U.K. **Funding sources** Public	**Study design** Case-control	**Cases:** Age 45 years or under; pathologically confirmed ICD-10 diagnosis of squamous cell carcinoma of lip, intra-oral or oropharynx / tonsil; identified through the Thames Cancer Registry (TCR) database. **Controls:** Matched, through general practitioners, on age, gender and area of residence.	**Intervention** Cannabis **Details** Never Ever	Cancer (oral squamous cell carcinoma)
Manrique-Garcia(2012)[245, 317-322] **Country** Sweden	**Study design** Prospective Cohort	Swedish men; aged 18-20; conscripted for military service in the year 1969 to 1970	**Intervention** Cannabis **Details** Exposure during late	Psychotic disease (Brief psychosis) Psychotic disease (Schizophrenia) Lung cancer

Study details	Design	Participants	Intervention /Comparator	Outcome
Funding sources Public			adolescence (before conscription) assessed by questionnaire (at conscription) - Once - 2-4 times - 5-10 times - 11-50 times >50 times	Suicide (Suicide or possible suicide)
Marks(2014)[246] **Study Name:** INHANCE **Country** USA and Latin America **Funding sources** Public	**Study design** Case-control	Pooled IPD analysis of nine case control studies. **Cases:** ICD diagnosis of oropharyngeal or oral tongue cancers. **Controls:** Matched on age and gender in all studies; five studies additionally matched on race and ethnicity; two studies additionally matched on area of residence.	**Intervention** Marijuana	Cancer (Oral tongue) Cancer (Oropharyngeal)

Study details	Design	Participants	Intervention /Comparator	Outcome
McGrath(2010)[247] **Study Name:** Mater-University Study of Pregnancy **Country** Australia **Funding sources** Public	**Study design** Prospective Cohort	Participants in Mater-University Study of Pregnancy; singleton offspring of 7223 women who received antenatal care at a major public hospital in Brisbane.	**Intervention** Cannabis **Details** - ≤ 3 years since start of usage - 4-5 years since first usage of cannabis - >6 years since first usage	Psychotic disease (schizophrenia (ICD-10 code F20) / persistent delusional disorder (ICD-10 code F22) / acute and transient psychotic disorders (ICD-10 code F23))
Pederson(2008)[248]{ **Study Name:** Young in Norway Longitudinal Study	**Study design** Prospective Cohort	All schools in the country were included in the register from which the schools were selected. The schools were stratified according to	**Intervention** Cannabis **Details** 1-10 times	Suicide (suicide ideation) Suicide (suicide attempt)

Study details	Design	Participants	Intervention /Comparator	Outcome
Country Norway **Funding sources** Public		geographical region and school size, which in Norway is closely related to the degree of urbanization. The number of sampled students in each stratum was proportional to the total number of students in the stratum (proportional allocation). A cohort of students in the compulsory lower school system in Norway was recruited.	**Intervention levels** Occasional Never	Psychotic disease (depression)

Study details	Design	Participants	Intervention /Comparator	Outcome
Rolfe(1993)[249] **Country** The Gambia **Funding sources** Public	**Study design** Case-control	**Cases:** Patients admitted to Campama psychiatric unit over 12 months; diagnosis of psychosis where the family was unable to cope or there was thought to be a danger to the patient or the general public; diagnosis of schizophrenia was based on the DSM-III classification (symptoms longer than six months). **Controls:** friends or relatives visiting patients at the Royal Victoria Hospital, a general medical and surgical referral centre; matched for age, sex and place of residence.	**Intervention** Cannabis **Details** Cannabinoids urine test	Psychotic disease (Psychotic illness)

Study details	Design	Participants	Intervention /Comparator	Outcome
Rosenblatt(2004)[250] **Country** USA **Funding sources** Not stated	**Study design** Case-control	Report based on data from two case-control studies. **Cases:** Age 18-65; first incident oral squamous cell carcinoma; identified through population-based Cancer Surveillance System; able to communicate in English; residential telephones. **Controls:** Identified through random digit dialing; matched on sex and five year age group.	**Intervention** Marijuana **Details** <1 times per week 1-7 times per week >7 times per week	Cancer (oral squamous cell carcinoma)
Sasco(2002)[251] **Country** Morocco **Funding sources** Public	**Study design** Case-control	**Cases:** Incident lung cancer; diagnosed between January 1996 and January 1998 in a single hospital. **Controls:** Hospital controls; matched on age, sex and place of residence.	**Intervention** Cannabis	Cancer (lung cancer)

Study details	Design	Participants	Intervention /Comparator	Outcome
Tan(2009)[252] **Study Name:** BOLD **Country** Canada **Funding sources** Public	**Study design** Retrospective Cohort	Adults aged 40 years and over; living in the health service delivery area of vancouver; sampled by random digit dialing	**Intervention** Marijuana **Details** Exposure was determined using standardised questionnaires, administered by interviewers	Respiratory disease (COPD defined by self-report of physician diagnosis)
Trabert(2011)[253] **Country** USA **Funding sources** Public	**Study design** Case-control	**Cases:** TGCT patients; age between 18 and 50; resident of Texas, Louisiana, Arkansas, or Oklahoma. **Controls:** Friend referral of case.	**Intervention** Marijuana **Details** <1 / day daily or more >10 y <10 y	Cancer (Testicular germ cell tumors)
van Os(2002)[254] **Study Name:** NEMESIS **Country** The Netherlands **Funding sources** Public	**Study design** Prospective Cohort	General population; age 18-65 years; not residing in institutions.	**Intervention** Cannabis	Psychotic disease (psychosis)

Study details	Design	Participants	Intervention /Comparator	Outcome
Veling(2008)[255] **Country** The Netherlands **Funding sources** Public	**Study design** Case-control	**Cases:** Data taken from a study of ethnic minorities in the Hague; first or second generation imigrants from non-Western countries; aged 18-54 years; DSM-IV diagnosis of schizophrenia, schizophreniform disorder or schizo-affective disorder between October 2000 and July 2005. **Controls:** Two control groups, group 1 was sibling controls and group 2 was recruited from the general ethnic minority community of the Hague who made contact with non-psychiatric secondary health care services. Controls were matched for 5-year age group, sex and ethnicity (including first- or second-generation immigrant status).	**Intervention** Cannabis **Details** Lifetime use of cannabis was assessed with the section on drugs of the Comprehensive Assessment of Symptoms and History (CASH)	Psychotic disease (Schizophrenia)

Study details	Design	Participants	Intervention /Comparator	Outcome
Voirin(2006)[256] **Country** Tunisia **Funding sources** Not stated	**Study design** Case-control	**Cases:** Men; primary incident lung cancer, confirmed by histologic or cytologic examination except for two cases that were diagnosed radiographically. **Controls:** Men; admission, at the same time and to the same institution, for nonmalignant disease of genitourinary system or endocrine disease.	**Intervention** Cannabis	Cancer (lung cancer)
Weller(1985)[257] **Country** U.S.A **Funding sources** Not stated	**Study design** Prospective Cohort	Participation in previous study; being a marihuana user (minimum 50 times in 6 months) or being a relative of an exposed individual	**Intervention** Marijuana **Details** Minimum 50 times in a 6 month period	Psychotic disease (Schizophrenia/ schizoaffective disorder) Psychotic disease (Schizophrenia/ Psychotic disorder)

Study details	Design	Participants	Intervention /Comparator	Outcome
Zhang(1999)[258] **Country** USA **Funding sources** Public	**Study design** Case-control	**Cases:** Untreated new patients with a histologically confirmed diagnosis of first primary squamous cell carcinoma of the head and neck; seen at Memorial Sloan-Kettering Cancer Center from 1992 to 1994. **Controls:** No history of cancer; identified from the Blood Bank Center of Memorial Sloan-Kettering Cancer Center during the same period.	**Intervention** Marijuana	Cancer (Head and neck cancer)
Zhang(2014)[259] **Study Name:** ILCCO studies **Country** USA, Canada, UK, NZ **Funding sources** Public	**Study design** Case-control	Pooled IPD analysis of six case-control studies. **Cases:** Primary, incident and histologically confirmed lung cancers. **Controls:** Matched on age, sex and area of residence.	**Intervention** Cannabis **Details** Non habitual those with cumulative cannabis consumprion of less than 1-joint/year < 1 joint per day ≥ 1 joints per day	Cancer (Lung cancer)

APPENDIX 6: INTERVENTIONS EVALUATED IN INCLUDED STUDIES

Study details	Intervention	Regimen	Number of participants
Abrams(2003)[129]	**Intervention 1:** Marijuana **Administration route:** Smoked **Details:** Marijuana cigarettes (mean weight 0.9 g), containing 3.95% delta-9-tetrahydrocannabinol. Research staff monitored participants while they followed the uniform puff procedure.	**Titration:** No Up to 3 capsules/ complete complete marijuana cigarettes daily, as tolerated, 1 hour before meals.	**Randomised:** 25 **Treated:** 25
	Intervention 2: Dronabinol (Marinol) **Administration route:** Capsules (oral)		**Randomised:** 21 **Treated:** 21
	Control: Placebo **Administration route:** Capsules (oral)		**Randomised:** 21 **Treated:** 21
Abrams(2007)[142]	**Intervention 1:** THC **Administration route:** Smoked **Details:** Pre-rolled cannabis and placebo cigarettes weighed on average 0.9 g. To maximize standardization of inhaled doses, patients followed a uniform puff procedure. **THC concentration:** 3.56%	**Titration:** No One cigarette smoked at 2pm on day 1 and 5. Days 2-4: as tolerated, one cigarette three times daily (8 am, 2 pm, 8 pm).	**Randomised:** 27 **Treated:** 27
	Control: Placebo **Administration route:** Smoked **Details:** Identical-appearing placebo cannabis cigarettes from which the active components had been extracted. **THC concentration:** 0		**Randomised:** 28 **Treated:** 27
Ahmedzai(1983)[112]	**Intervention 1:** Nabilone (Cesamet) **Administration route:** Capsules (oral)	**Titration:** No First dose (2x1mg capsules) 10 pm day before treatment. Subsequent doses (2x 1mg) given at 10am and 10pm on days 1-3.	**Randomised:** 34 **Treated:** 34
	Control: Proclorperazine **Administration route:** Capsules (oral)	First dose (2x5mg) 10pm night before treatment. Subsequent doses (2 x 5mg) at 6am, 2pm and 10pm.	
Beal(1995)[84]	**Intervention 1:** Dronabinol (Marinol) **Administration route:** Capsules (oral)	**Titration:** No 2.5 mg twice daily (before lunch and supper). Patients who could not tolerate the full dose were eligible for rechallenge with a reduced dose of 2.5mg once daily after toxicity resolved.	**Randomised:** 72 **Treated:** 72
	Control: Placebo **Administration route:** Capsules (oral)		**Randomised:** 67 **Treated:** 67

Study details	Intervention	Regimen	Number of participants
Bergamaschi(2011)[95]	**Intervention 1:** Cannabidiol (CBD) **Administration route:** Capsules (oral) **Details:** CBD (600 mg) in powder, approx. 99.9% pure dissolved in corn oil.	**Titration:** No Single dose	**Randomised:** 12 **Treated:** 12
	Control: Placebo **Administration route:** Capsules (oral)		**Randomised:** 12 **Treated:** 12
Berman(2007)[1]	**Intervention 1:** Nabiximols (Sativex) **Administration route:** Oromuscosal spray **Details:** Each Sativex oromucosal spray delivered 2.7mg THC and 2.5mg CBD.	**Titration:** Yes Titrated to maximum permitted dose of 8 actuations in any three hour period, and 48 actuations in any 24 hour period.	**Randomised:** 57 **Treated:** 57
	Control: Placebo **Administration route:** Oromuscosal spray		**Randomised:** 60 **Treated:** 60
Berman(2004)[145]	**Intervention 1:** Nabiximols (Sativex) **Administration route:** Oromuscosal spray	**Titration:** Yes Titrated to maximum permitted dose of 8 actuations in any three hour period, and 48 actuations in any 24 hour period.	**Randomised:** 48 **Treated:** 47
	Intervention 2: THC **Administration route:** Oromuscosal spray		**Randomised:** 48 **Treated:** 46
	Control: Placebo **Administration route:** Oromuscosal spray		**Randomised:** 48 **Treated:** 46
Blake(2006)[78]	**Intervention 1:** Nabiximols (Sativex) **Administration route:** Oromuscosal spray	**Titration:** Yes Starting dose: one actuation within 0.5 h of retiring, increased by one actuation every 2 days to a maximum of six actuations. Stable dosing maintained for 3 weeks.	**Randomised:** 31 **Treated:** 30
	Control: Placebo **Administration route:** Oromuscosal spray		**Randomised:** 27 **Treated:** 27
Broder(1982)[74]	**Intervention 1:** THC **Administration route:** oral **Dose:** 10mg/m^2	**Titration:** No One dose every 4-6 hrs, beginning 4 hours prior to chemotherapy and adjusted for individual tolerance.	**Randomised:** 44 **Treated:** 44
	Intervention 2: Hydroxizine **Administration route:** oral **Dose:** 50mg		**Randomised:** 44 **Treated:** 44

Study details	Intervention	Regimen	Number of participants
Chan(1987)[93]	**Intervention 1:** Nabilone (Cesamet) **Administration route:** Capsules (oral) **Dose:** 1 mg capsules **Details:** Daily dose (2-3 mg) according to weight. Original schedule; 1 (18-27 kg): 1bid 76 µg/kg, 6 (27.1-36 kg): 1 tid 90-110 µg/kg, 6 (>36 kg): 2 bid 48-97 µg/kg. Modified schedule; 1 (<18 kg): 0,5 bid 86 µg/kg, 5 (18-30 kg): 1 bid 68-92 µg/kg, 11 (>30 kg): 1 tid 25-110 µg/kg.	**Titration:** No Single dose 8-12 hours before chemotherapy. Same dose was repeated 2 or 3x daily, according to a dosage schedule based on the patient's weight, for as long as antiemetic coverage was required after a particular chemotherapy regimen.	**Randomised:** 40 **Treated:** 40
	Control: Prochlorperazine **Administration route:** Capsules (oral) **Dose: 5 mg capsules** **Details:** Daily dose (2-3 mg) according to weight. Original schedule; 1 (18-27 kg): 5bid 379 µg/kg, 6 (27.1-36 kg): 5 tid 452-551 µg/kg, 6 (>36 kg): 10 bid 242-485 µg/kg. Modified schedule; 1 (<18 kg): 2,5 bid 431 µg/kg, 5 (18-30 kg): 5 bid 340-459 µg/kg, 11 (>30 kg): 5 tid 198-553 µg/kg.		**Randomised:** 40 **Treated:** 40
Collin(2007)[2]	**Intervention 1:** Nabiximols (Sativex) **Administration route:** Oromuscosal spray **Details:** Each 100 ul of actuation delivered 2.7mg THC and 2.5mg CBD.	**Titration:** Yes Patients titrated their daily dose steadily as required over 2 weeks, to a maximum of 48 sprays per day.	**Randomised:** 124 **Treated:** 120
	Control: Placebo **Administration route:** Oromuscosal spray		**Randomised:** 65 **Treated:** 64
Collin(2010)[5]	**Intervention 1:** Nabiximols (Sativex) **Administration route:** Oromuscosal spray **Details:** Each 100 ul of actuation delivered 2.7mg THC and 2.5mg CBD.	**Titration:** Yes Self titrated to optimum dose based on efficacy & tolerability. Maximum dose 8 actuation in any 3 hour period and 24 actuations in any 24 hour period.	**Randomised:** 167 **Treated:** 167
	Control: Placebo **Administration route:** Oromuscosal spray		**Randomised:** 170 **Treated:** 170
Corey-Bloom(2012)[190]	**Intervention 1:** THC **Administration route:** Smoked **Details:** 800 mg cigarette **THC concentration:**4%	**Titration:** No One pre-rolled cigarette, smoked using the Foltin uniform puff procedure, under supervision, in a ventilated room. Participants completed an average of 4 puffs per cigarette	**Randomised:** 37 **Treated:** 33
	Intervention 2: Placebo **Administration route:** Smoked **Details:** 800 mg cigarette		**Randomised:** 37 **Treated:** 33

Study details	Intervention	Regimen	Number of participants
Dalzell(1986)[92]	**Intervention 1:** Nabilone (Cesamet) **Administration route:** Capsules (oral) **Dose:** <18kg = 0.5 mg 2x/day; 18-36kg = 1 mg 2x/day 1; > 36kg = 1 mg 3x/day day.	**Titration:** No **Total daily dose (mg):** 15-45 **Regimen:** The first dose was taken the night before beginning chemotherapy, and the last dose 24 hours after stopping it. Doses given 2 or 3x/day	**Randomised:** 23 **Treated:** 23
	Intervention 2: Domperidone **Administration route:** Oromuscosal spray **Details:** If vomiting prevented oral therapy then parenteral (intravenous) domperidone was allowed. **Dose:** Patients were stratified according to weight and received drug as follows: <18kg = 5 mg 3x/day; 18-36kg =10 mg 3x/day ; > 36kg = 15 mg 3x/day		**Randomised:** 23 **Treated:** 23
Duran (2010)[97]	**Intervention 1:** Nabiximols (Sativex) **Administration route:** Oromuscosal spray	**Titration:** Yes **Total daily dose (mg):** 0 **Regimen:** Day 0: up to three sprays were delivered in a 2 h period. If no signs of intoxication were observed, a second and third spray were administered after 30 & 120 min. Self-titrated to day 4 up to 8 sprays within any 4 h period every 24 h.	**Randomised:** 7 **Treated:** 7
	Control: Placebo **Administration route:** Oromuscosal spray		**Randomised:** 9 **Treated:** 9
Einhorn(1981)[108]	**Intervention 1:** Nabilone (Cesamet) **Administration route:** Capsules (oral) **Dose:** 2mg	**Titration:** No Dose every 6 hours as required. Initially drug administered 30 mins before chemotherapy. For last 44 patients design altered to allow for 3 doses starting 12 hours before chemotherapy.	**Randomised:** 100 **Treated:** 100
	Control: Prochlorperazine **Administration route:** Capsules (oral) **Dose:** 10mg		**Randomised:** 100 **Treated:** 100
Ellis(2009)[137]	**Intervention 1:** THC **Administration route:** Smoked	**Titration:** Yes Titration, on day 1 of the 5 day treatment perios, starting at 4% THC and titrated upwards if pain relief was incomplete, or downwards if side-effects were intolerable. The optimised dose was administered for the remaining 4 treatment days. Four daily, nurse-supervised smoking sessions, separated by 90-120 mins.	**Randomised:** 34 **Treated:** 28
	Control: Placebo **Administration route:** Smoked		**Randomised:** 34 **Treated:** 28

Study details	Intervention	Regimen	Number of participants
Frank(2008)[141]	**Intervention 2:** Dihydrocodeine **Administration route:** Capsules (oral) **Dose:** 1 capsule (30mg)	**Titration:** Yes One capsule in the first week, two capsules in the third week, four capsules in the third and fourth week and then eight capsules in week five and six. If the patient developed side effects, the dosage was reduced to the previous value for the remainder of the trial period.	**Randomised:** 96 **Treated:** 96
	Intervention 1: Nabilone (Cesamet) **Administration route:** Capsules (oral) **Dose:** 1 capsule (240ug)		**Randomised:** 96 **Treated:** 96
Frytak(1979)[111]	**Intervention 1:** THC **Administration route:** Capsules (oral) **Dose:** 15 mg	**Titration:** No Day 1: initial dose given 2h before chemotherapy; subsequent doses given 2h and 8h after initiation of chemotherapy. On remaining 3 days antimetic agents given 3 times daily 0.5 hours before a meal.	**Randomised:** 38 **Treated:** 38
	Intervention 2: Prochloperazine **Administration route:** Capsules (oral) **Dose:** 10 mg		**Randomised:** 41 **Treated:** 41
	Control: Placebo **Administration route:** Capsules (oral) **Titration:** No		**Randomised:** 37 **Treated:** 37
George(1983)[104]	**Intervention 2:** Chlorpromazine + placebo **Administration route:** IM **Dose:** 12.5mg	**Titration:** No Given 15min before chemotherapy. The injection was repeated if requested by the patient.	**Randomised:** 20 **Treated:** 20
	Intervention 1: Nabilone (Cesamet) + placebo **Administration route:** Capsules (oral) **Titration:** No **Dose:** 1mg	1mg given 24 hrs before chemotherapy and continued next day for 3x /day	**Randomised:** 20 **Treated:** 20
GW Pharma Ltd(2012)[79]	**Intervention 1:** Nabiximols (Sativex) **Administration route:** Oromuscosal spray	**Titration:** Yes **Titrated to** maximum dose of eight actuations in any three hour period and 48 actuations in any 24 hour period.	**Randomised:** 36 **Treated:** 36
	Intervention 2: Placebo **Administration route:** Oromuscosal spray		**Randomised:** 34 **Treated:** 34
GW Pharma Ltd(2005)[77]	**Intervention 1:** Nabiximols (Sativex) **Administration route:** Oromuscosal spray	**Titration:** Not reported Maximum permitted dose was 24 actuations in 24 hours	**Randomised:** 149 **Treated:** 149
	Control: Placebo **Administration route:** Oromuscosal spray		**Randomised:** 148 **Treated:** 148
Hagenbach(2003)[71]	**Intervention 1:** Dronabinol (Marinol) **Administration route:** Capsules (oral) **Dose:** 10mg	**Titration:** No Treatment given for six weeks “with an individual dose”.	**Randomised:** 13 **Treated:** NR

Study details	Intervention	Regimen	Number of participants
	Control: Placebo **Administration route:** Capsules (oral)		**Randomised:** 13 **Treated:** NR
Heim(1984)[102]	**Intervention 1:** Levonantradol **Administration route:** IM **Dose:** 0.5mg	**Titration:** No 1 dose 1 hour before and 2 and 6 hours after chemotherapy	**Randomised:** 57 **Treated:** 45
	Intervention 2: Metoclopramide **Administration route:** IM **Dose:** 10mg		**Randomised:** 57 **Treated:** 45
Herman(1979)[123]	**Intervention 1:** Nabilone (Cesamet) **Administration route:** Capsules (oral) **Dose:** 2 capsules (2mg)	**Titration:** No 2 capsules orally (2mg) every 6 or 8 hours, first dose before administration of chemotherapy. Treatment duration varied depending on chemotherapy regimen from 1.5 to 5 days.	**Randomised:** 152 **Treated:** 152
	Control: Prochlorperazine **Administration route:** Capsules (oral) **Dose:** 2 capsules (10mg)		**Randomised:** 152 **Treated:** 152
Hutcheon1983)[103]	**Intervention 1:** Levonantradol **Administration route:** IM **Dose:** 0.5mg **Total daily dose (mg):** 2	**Titration:** No 2 hrs before chemotherapy, 2hrs after the start of chemotherapy and a further two doses at 4 hour intervals.	**Randomised:** 27 **Treated:** 27
	Intervention 2: Levonantradol **Administration route:** IM **Dose:** 0.75mg **Total daily dose (mg):** 3		**Randomised:** 26 **Treated:** 26
	Intervention 3: Levonantradol **Administration route:** IM **Dose:** 1mg **Total daily dose (mg):** 4		**Randomised:** 28 **Treated:** 28
	Control: Chlorpromazine **Administration route:** IM **Dose:** 25mg **Total daily dose (mg):** 100		**Randomised:** 27 **Treated:** 27
Johansson(1982)[106]	**Intervention 1:** Nabilone (Cesamet) **Administration route:** Capsules (oral) **Dose:** 2mg	**Titration:** No Treatment every 12h for 4 consecutive doses with first dose night before chemotherapy and last dose	**Randomised:** 27 **Treated:** 27

Study details	Intervention	Regimen	Number of participants
	Control: Prochlorperazine **Administration route:** Capsules (oral) **Dose:** 10mg	the morning after. On the day of chemotherapy the drugs were taken 1-3 hours before the anticancer treatment.	**Randomised:** 27 **Treated:** 27
Johnson(2010)[82]	**Intervention 1:** Nabiximols (Sativex) **Administration route:** Oromuscosal spray **Details:** Each 100 uL actuation contained 2.7 mg THC and 2.5 mg CBD	**Titration:** Yes **Regimen:** Self-titration to optimal dose over wk 1, maximum permitted dose 8 actuations in 24 hrs	**Randomised:** 60 **Treated:** 60
	Intervention 2: THC **Administration route:** Oromuscosal spray **Details:** Each 100 uL actuation contained 2.7 mg THC		**Randomised:** 58 **Treated:** 58
	Control: Placebo **Administration route:** Oromuscosal spray		**Randomised:** 59 **Treated:** 59
Jones(1982)[90]	**Intervention 1:** Nabilone (Cesamet) **Administration route:** Capsules (oral) **Dose:** 2mg	**Titration:** No Dose evening before chemotherapy, morning of chemotherapy and every 12h therafter for at least 24h.	**Randomised:** 54 **Treated:** NR
	Control: Placebo **Administration route:** Capsules (oral)		**Randomised:** 54 **Treated:** NR
Karst(2003)[147]	**Intervention 1:** CT3 **Administration route:** Capsules (oral) **Dose:** 1 capsules (10mg) **Details:** Synthetic analog of tetrahydrocannabinol (THC)-11-oic acid, one of the endogenous transformation products of THC, in which a dimethylheptyl sidechain is substituted for the pentyl sidechain.	**Titration:** No 2 daily doses (2 capsules) were given during the first 4 days and 8 capsules per day in 2 daily doses during the following 3 days.	**CT3-placebo sequence:** 10 randomised and treated **Placebo-CT3 sequence:** 11 randomised and treated
	Intervention 2: Placebo **Administration route:** Capsules (oral)		
Killestein(2002)[193]	**Intervention 2:** THC/CBD **Administration route:** Capsules (oral) **Details:** Plant extract containing same level of THC as dronabinol **Dose:** 2.5mg-5mg	**Titration:** Yes During the first 2 weeks, study medication was administered in two daily doses of 2.5 mg. If well tolerated, the dose was elevated to 5 mg twice a day for the next 2 weeks.	**Randomised:** 16 **Treated:** 16
	Intervention 1: Dronabinol (Marinol) **Administration route:** Capsules (oral) **Dose:** 2.5mg-5mg		**Randomised:** 16 **Treated:** 16

Study details	Intervention	Regimen	Number of participants
	Control: Placebo **Administration route:** Capsules (oral) **Titration:** Not reported		**Randomised:** 16 **Treated:** 16
Lane,(1991)[83]	**Intervention 1:** Dronabinol (Marinol) + placebo **Administration route:** Capsules (oral) **Dose:** 10 mg	**Titration: N**o **Regimen:** Dose every 6 hours. Medication started 24 hours prior to chemotherapy. Antiemetics continued for 24 hours after last dose of chemo-therapy up to a total of 6 days.	**Randomised:** 21 **Treated:** 18
	Intervention 2: Proclorperazine + placebo **Administration route:** Capsules (oral) **Dose:** 10mg		**Randomised:** 21 **Treated:** 20
Langford(2013)[4]	**Intervention 1:** Nabiximols (Sativex) **Administration route:** Oromuscosal spray **Details:** Each 100 uL activation delivers 2.7mg of THC and 2.5mg of CBD	**Titration:** Yes Maximum of 12 sprays per 24hour period. Self titrated during baseline period to reach optimal dose depending on efficacy, tolerability, and maximum permitted dose.	**Randomised:** 167
	Control: Placebo **Administration route:** Oromuscosal spray		**Randomised:** 172
Levitt(1982)[117]	**Intervention 1:** Nabilone (Cesamet) **Administration route:** Capsules (oral) **Dose:** 2mg	**Titration:** No First dose taken evening before chemotherapy. Second dose given in morning 1-3 hours before chemotherapy, further dose given on day of chemotherapy. If patients received multiple days of chemotherapy the same dose was used.	**Randomised:** 58 **Treated:** 58
	Control: Placebo **Administration route:** Capsules (oral)		**Randomised:** 58 **Treated:** 58
Leweke(2008)[216]	**Intervention 1:** Cannabidiol (CBD) **Administration route:** Capsules (oral) **Dose:** 200mg	**Titration:** Yes 200mg/day, increased stepwise by 200mg/day to a daily dose of 200mg four times daily (total 800mg/day) each within the first week. A reduction of each treatment to 600mg/day was allowed for clinical reasons (eg AE).	**Randomised:** 21 **Treated:** 21
	Control: Amisulpride **Administration route:** Capsules (oral) **Dose:** 200mg		**Randomised:** 21 **Treated:** 21
Long(1982)[73]	**Intervention 1:** Levonantradol **Administration route:** Capsules (oral) **Dose:** 1mg	**Titration:** No 1 dose orally 2hours before chemotherapy and then every 4 hrs for a total of 4 doses.	**Randomised:** 42 **Treated:** 42
	Control: Prochlorperazine **Administration route:** Capsules (oral) **Dose:** 10mg		**Randomised:** 42 **Treated:** 42

Study details	Intervention	Regimen	Number of participants
Lynch(2014)[148]	**Intervention 1:** Nabiximols (Sativex) **Administration route:** Oromuscosal spray	**Titration:** Yes 2 weeks up titration, 4 weeks stable, 1 week down titration. If no improvement patients could reduce stable phase to 1 rather than 4 weeks. Day 1: 1 spray before bed; increased by 1-2 sprays per day until reached a dose that helped their pain, asked to stop increasing if limiting side effects were encountered. Maximum 12 sprays per day.	**Randomised:** 18 **Treated:** 16
	Control: Placebo **Administration route:** Oromuscosal spray		**Randomised:** 18 **Treated:** 16
McCabe(1988)[98]	**Intervention 1:** THC **Administration route:** Capsules (oral) **Dose (mg):** 15mg/m^2	**Titration:** No Drug given one hour prior to chemotherapy and every four hours after for 24 hours.	**Randomised:** 36 **Treated:** 36
	Control: Prochlorperazine **Administration route:** Capsules (oral) **Dose:** 10 mg		**Randomised:** 36 **Treated:** 36
Meiri(2007)[85]	**Intervention 1:** Dronabinol (Marinol) **Administration route:** Capsules (oral)	**Titration:** No All groups received: Day 1 (prechemo); 20mg dexamethasone PO + 16mg ondansetron IV + 2.5mg dronabinol. Day 1 (postchemo); 2.5mg dronabinol. Day 2; 2.5mg x4/day, Days 3-5, 2.5-5mg x4/day.	**Randomised:** 17 **Treated:** 17
	Intervention 2: Ondansetron **Administration route:** Capsules (oral)	Day 1 (postchemo); 2.5mg dronabinol. Day 2, 8mg ondansetron x2/day, Days 3-5, 4-8mg ondansetron x2/day.	**Randomised:** 16 **Treated:** 16
	Intervention 3: Dronabinol + ondansetron **Administration route:** Capsules (oral)	Day 1 (postchemo); 2.5mg dronabinol. Day 2, 2.5mg dronabinol x4/day + 8mg ondansetron x2/day, Days 3-5, 2.5-5mg dronabinol x4/day + 4-8mg ondansetron x2/day.	**Randomised:** 17 **Treated:** 17
	Control: Placebo **Administration route:** Capsules (oral)	Day 1 (postchemo); placebo. Day 2, placebo x4/day. Days 3-5, placebo x4/day.	**Randomised:** 14 **Treated:** 14
Melhem-Bertrandt(2014)[124]	**Intervention 1:** Dronabinol (Marinol) **Administration route:** Capsules (oral) **Dose:** 5mg	**Titration:** No **Regimen:** 1 tablet (mg) by mouth 3 times a day for 5 days beginning 30 minutes before chemotherapy	**Randomised:** NR **Treated:** 30

Study details	Intervention	Regimen	Number of participants
	Control: Placebo **Administration route:** Capsules (oral)		**Randomised:** NR **Treated:** 29
Müller-Vahl(2001)[227]	**Intervention 1:** THC **Administration route:** Capsules (oral)	**Single daily dose** **Regimen:** Patients received 5 or 7.5 or 10 mg according to body weight, sex and prior use; 4 patients received 5mg, 6 received 7.5mg and 2 received 10mg.	**Randomised:** 12 **Treated:** 12
	Control: Placebo **Administration route:** Capsules (oral)		**Randomised:** 12 **Treated:** 12
Müller-Vahl(2003)[225]	**Intervention 1:** THC **Administration route:** Capsules (oral) **Control:** Placebo **Administration route:** Capsules (oral)	**Titration:** Yes Titrated to a target dose f 10.0 mg, starting at 2.5 mg/day, increased by 2.5 mg/day every 4 days. If dose was not tolerated it was adjusted untile an acceptable dose was reached. Medication taken once a day. Dosages: 10mg (6), 7.5mg (2), 2.5 (1)	**Randomised (total):** 24 **Treated:** 9
			Randomised (total): 24 **Treated:** 11
Narang(2008)[139]	**Intervention 1:** Dronabinol (Marinol) **Administration route:** Capsules (oral) **Dose:** 20mg	**Titration:** No **Total daily dose (mg):** up to 20 mg **Regimen:** Patients received study drug together with the morning dose of their regular prescribed opioid medication. Subsequently, they had breakfast.	**Randomised:** 30 **Treated:** 30
	Intervention 2: Dronabinol (Marinol) **Administration route:** Capsules (oral) **Dose:** 10mg		**Randomised:** 30 **Treated:** 29
	Control: Placebo **Administration route:** Capsules (oral)		**Randomised:** 30 **Treated:** 30
Niederle(1986)[100]	**Intervention 1:** Nabilone (Cesamet) **Administration route:** Capsules (oral) **Dose:** 2mg	**Total daily dose (mg):** 4mg **Regimen:** Night before chemotherapy, 2mg at 8am and 6pm on days 1-5.	**Randomised:** 20 **Treated:** 20
	Control: Alizapride **Administration route:** Capsules (oral) **Titration:** No **Dose:** 150mg	**Total daily dose (mg):** 450mg **Regimen:** Night before chemotherapy, 8am, 12am and 6pm on days 1-5.	**Randomised:** 20 **Treated:** 20
Niiranen (1985)[101]	**Intervention 1:** Nabilone (Cesamet) **Administration route:** Capsules (oral) **Titration:** No **Dose:** 1 capsule (1mg)	**Titration:** No **Regimen:** One capsule the night before chemotherapy, 1 hr before chemotherapy, and at 12	**Randomised:** 32 **Treated:** 24

Study details	Intervention	Regimen	Number of participants
	Intervention 2: Prochlorperazine **Administration route:** Capsules (oral) **Dose:** 1 capsule (7.5mg)	hr intervals up to 24 hrs after cehmotherapy	**Randomised:** 32 **Treated:** 24
Noyes (1975)[96]	**Intervention 1:** THC **Administration route:** Capsules (oral) **Details:** Δ-9-THC in capsules containing a sesame oil vehicle. **Dose:** 5mg	**Titration:** No **Total daily dose (mg):** 5 **Regimen:** Regular analgesics withheld after 4am, test medication once daily at approx. 8.30am (1 hr after eating).	**Randomised:** 10 **Treated:** 10
	Intervention 2: THC **Administration route:** Capsules (oral) **Dose:** 10mg		**Randomised:** 10 **Treated:** 10
	Intervention 3: THC **Administration route:** Capsules (oral) **Dose:** 15mg		**Randomised:** 10 **Treated:** 10
	Intervention 4: THC **Administration route:** Capsules (oral) **Dose:** 20mg		**Randomised:** 10 **Treated:** 10
	Control: Placebo **Administration route:** Capsules (oral)		**Randomised:** 10 **Treated:** 10
Nurmikko(2007)[80]	**Intervention 1:** Nabiximols (Sativex) **Administration route:** Oromuscosal spray	**Titration:** Yes Patients home titrated to a maximum dose of 8 sprays/3-hr interval and a maximum of 48 sprays /24 h.	**Randomised:** 63 **Treated:** 63
	Control: Placebo **Administration route:** Oromuscosal spray		**Randomised:** 62 **Treated:** 62
Orr(1980)[109]	**Intervention 1:** THC **Administration route:** Capsules (oral) **Details:** THC suspended on 0.12ml of sesame oil in gelatin capsules **Dose:** 7mg/m^2	**Titration:** No Every four hours for four doses, ingested one hour before chemotherapy.	**Randomised:** 79 **Treated:** 55
	Intervention 2: Prochlorperazine **Administration route:** Capsules (oral) Dose: 7mg/m^2		**Randomised:** 79 **Treated:** 55
	Control: Placebo **Administration route:** Capsules (oral)		**Randomised:** 79 **Treated:** 55
Pinsger(2006)[143]	**Intervention 1:** Nabilone (Cesamet) **Administration route:** Capsules (oral) Dose: 1 capsule (0.25mg)	**Titration:** No Patients were allowed to take between 1-4 capsules, max. increase 1 capsule/day.	**Randomised:** 30 **Treated:** 30

Study details	Intervention	Regimen	Number of participants
	Control: Placebo **Administration route:** Capsules (oral)		**Randomised:** 30 **Treated:** 30
Pomeroy(1986)[99]	**Intervention 1:** Nabilone (Cesamet) **Administration route:** Capsules (oral) **Dose:** 1mg	**Titration:** No 1 dose the night before chemotherapy and 8-hourly on each chemotherapy day for two consecutive cycles of treatment	**Randomised:** 19 **Treated:** 16
	Control: Domperidone **Administration route:** Capsules (oral) **Dose:** 20mg		**Randomised:** 19 **Treated:** 15
Pooyania (2010)[128]	**Intervention 1:** Nabilone (Cesamet) **Administration route:** Capsules (oral) **Dose:** 0.5 mg	**Titration:** No **Regimen:** Once or twice daily. Pending tolerance of side effects, option to increase dose to 2 capsules daily (1 mg).	**Randomised:** 12 **Treated:** 11
	Control: Placebo **Administration route:** Capsules (oral)		**Randomised:** 12 **Treated:** 11
Portenoy(2012)[86]	**Intervention 1:** Nabiximols (Sativex) **Administration route:** Oromuscosal spray **Dose:** 1-4 sprays per day	**Titration:** Yes 1 week titration period until maximum target dose (4 sprays/day) achieved unless intolerable side effects prevent dose escalation	**Randomised:** 91 **Treated:** 91
	Intervention 2: Nabiximols (Sativex) **Administration route:** Oromuscosal spray **Dose:** 6-10 spray per day		**Randomised:** 88 **Treated:** 87
	Intervention 3: Nabiximols (Sativex) **Administration route:** Oromuscosal spray **Dose:** 11-16 sprays/day		**Randomised:** 90 **Treated:** 90
	Control: Placebo **Administration route:** Oromuscosal spray		**Randomised:** 91 **Treated:** 91
Prasad(2011)[72]	**Intervention 1:** Dronabinol (Marinol) **Administration route:** Capsules (oral) **Dose:** 2.5mg	**Titration:** Yes Administered daily, 30 min before bedtime. Escalating weekly as tolerated from 2.5 to 5 to 10mg.	**Randomised:** 17 **Treated:** 17
	Control: Placebo **Administration route:** Capsules (oral)		**Randomised:** 5 **Treated:** 5
Rohleder(2012)[75]	**Intervention 1:** Cannabidiol (CBD) **Administration route:** Capsules (oral) **Dose:** 600mg	**Titration:** No Single daily dose	**Randomised:** 29 **Treated:** 29
	Control: Placebo **Administration route:** Capsules (oral)		**Randomised:** 29 **Treated:** 29

Study details	Intervention	Regimen	Number of participants
Rog(2005)[144]	**Intervention 1:** Nabiximols (Sativex) **Administration route:** Oromuscosal spray	**Titration:** Yes Patients advised to increase the number of sprase on consecutive days to a maximum of 48 sprays in 24 hours, with no more than 8 sprays in 3 hours based on efficacy and tolerability.	**Randomised:** 34 **Treated:** 34
	Control: Placebo **Administration route:** Oromuscosal spray		**Randomised:** 32 **Treated:** 32
Sallan(1980)[94]	**Intervention 1:** THC **Administration route:** Capsules (oral) **Dose:** Dose 10mg/m^2 body area - 15mg most common dose.	**Titration:** No 3 doses given every 4 hours, first dose 1 h before chemo, and the other 2 were given 3 and 7 hours after chemotherapy.	**Randomised:** 84 **Treated:** 73
	Control: Prochlorperazine **Administration route:** Capsules (oral) **Dose:** 10mg		**Randomised:** 84 **Treated:** 73
Selvarajah(2010)[136]	**Intervention 1:** Nabiximols (Sativex) **Administration route:** Oromuscosal spray	**Titration:** Yes Administered in divided doses up to four times a day. Dose titrated over 2 weeks followed by 10 week maintenance phase.	**Randomised:** 15 **Treated:** 15
	Control: Placebo **Administration route:** Oromuscosal spray		**Randomised:** 15 **Treated:** 14
Serpell(2014)[81]	**Intervention 1:** Nabiximols (Sativex) **Administration route:** Oromuscosal spray	**Titration:** Yes Maximum 8 sprays in a 3-h period up to a maximum of 24 sprays per 24-h period. Patients began at a maximum of one spray per 4-h period then self-titrated to symptom relief or maximum dose, but increases were limited to a maximum of 50% of the previous day's dose.	**Randomised:** 128 **Treated:** 122
	Control: Placebo **Administration route:** Oromuscosal spray		**Randomised:** 118 **Treated:** 117
Sheidler(1984)[113]	**Intervention 1:** Levonantradol **Administration route:** IM **Dose:** 1 mg	**Titration:** No Dose, given 2 hrs before, and 2, 6 and 10 hrs after chemotherapy	**Randomised:** 20 **Treated:** 20
	Intervention 2: Prochlorperazine **Dose:** 10mg		**Randomised:** 20 **Treated:** 20
Skrabek(2008)[140]	**Intervention 1:** Nabilone (Cesamet) **Administration route:** Capsules (oral) **Titration:** Yes **Dose:** 0.5mg	**Total daily dose (mg):** 0.5-2 Week 1: single dose at bedtime. Week 2: single dose twice day. Week 3: single dose in morning, two doses at bedtime Week 4: 2 doses twice a day.	**Randomised:** 20 **Treated:** 20
	Control: Placebo		**Randomised:** 20 **Treated:** 20

Study details	Intervention	Regimen	Number of participants
Steele(1980)[110]	**Intervention 1:** Nabilone (Cesamet) **Administration route:** Capsules (oral) **Dose:** 2mg	**Titration:** No **Regimen:** 1 dose every 12 hours for 3-5 doses, first dose night before chemotherapy.	**Randomised:** 55 **Treated:** 55
	Control: Prochlorperazine **Administration route:** Capsules (oral) **Titration:** No **Dose:** 10mg		**Randomised:** 55 **Treated:** 55
Struwe (1993)[130]	**Intervention 1:** Dronabinol (Marinol) **Administration route:** Capsules (oral) **Dose:** 5mg	**Titration:** No One dose twice daily before lunch and dinner. Two dosage reductions (2.5mg bid or 2.5mg/d) were permitted if intolerable AEs occurred.	**Randomised:** 12 **Treated:** 12
	Control: Placebo **Administration route:** Capsules (oral)		**Randomised:** 12 **Treated:** 12
Svendsen(2004)[146]	**Intervention 1:** Dronabinol (Marinol) **Administration route:** Capsules (oral) **Dose:** 2.5mg	**Titration:** Yes Initial dose 2.5mg daily increased by 2.5mg every other day to maximum dose of 5mg twice daily.	**Randomised:** 24 **Treated:** 24
	Control: Placebo **Administration route:** Capsules (oral)		**Randomised:** 24 **Treated:** 24
Timpone(1997)[88]	**Intervention 1:** Dronabinol (Marinol) **Administration route:** Capsules (oral) **Dose:** 2.5mg	**Titration:** No Twice per day (1hr before lunch and 1 hr before supper)	**Randomised:** 12 **Treated:** 11
	Intervention 2: Dronabinol + megestrol acetate 750mg **Administration route:** Capsules (oral) Dose: Dronabinol (2.5mg), megestrol acetate (750mg)	As above	**Randomised:** 13 **Treated:** 13
	Control: megestrol acetate **Administration route:** Capsules (oral) **Dose:** 750mg	Once per day 1 hr before lunch	**Randomised:** 12 **Treated:** 11
Tomida (2006)[224]	**Intervention 1:** THC **Administration route:** Oromuscosal spray **Dose:** 5mg	**Titration:** No **Regimen:** Single dose at 08:00 on treatment day ("Each dose was applied sublingually by means of a pump-action oromucosal spray with a 100 ml actuator valve in 4 actuations at 5 minutes intervals")	**Randomised:** 6 **Treated:** 6
	Intervention 2: Cannabidiol (CBD) **Administration route:** Oromuscosal spray **Dose:** 20 mg		**Randomised:** 6 **Treated:** 6

Study details	Intervention	Regimen	Number of participants
	Intervention 3: Cannabidiol (CBD) **Administration route:** Oromuscosal spray **Dose:** 40 mg		**Randomised:** 6 **Treated:** 6
	Control: Placebo **Administration route:** Oromuscosal spray		**Randomised:** 6 **Treated:** 6
Ungerleider(1982)[91]	**Intervention 2:** Prochlorperazine **Administration route:** Capsules (oral) **Dose:** 10mg	**Titration:** No Administered 1 hour before chemotherapy, every 4 hours thereafter for a total of four doses/day on each day of chemotherapy.	**Randomised:** 214 **Treated:** 214
	Intervention 1: THC **Administration route:** Capsules (oral) **Dose:** 7.5 mg/body surface area <l.4m^2; 10 mg/body surface area 1.4-1.8 m^2; 12.5 mg/body surface area >1.8 m^2.		**Randomised:** 214 **Treated:** 214
Vaney(2004)[192]	**Intervention 1:** THC/CBD **Administration route:** Capsules (oral) **Dose:** 1 capsule (2.5mg)	**Titration: Y**es **Regimen:** Dose escalation starting with 6 capsules/day increasing to a maximum 12 capsules/day over 5 days. 12 capsules were given in three divided doses (four capsules: at noon, in the late afternoon and at bedtime)	**Randomised:** 28 **Treated:** 22
	Control: Placebo **Administration route:** Capsules (oral)		**Randomised:** 29 **Treated:** 28
Wada(1982)[105]	**Intervention 1:** Nabilone (Cesamet) **Administration route:** Capsules (oral) **Dose:** 1 capsule (2mg)	**Titration:** No **Regimen:** One capsule taken at 8pm on the evening before chemotherapy, one at 8am on morning of chemotherapy. Chemotherapy given within 1-3 hours of second dose. Additional doses given every 12h for 1 dose after the final administration of chemotherapy.	**Randomised:** 114 **Treated:** 114
	Control: Placebo **Administration route:** Capsules (oral)		**Randomised:** 114 **Treated:** 114
Wade(2004)[3]	**Intervention 1:** Nabiximols (Sativex) **Administration route:** Oromuscosal spray **Titration:** Yes	**Titration:** Yes **Regimen:** Up to a maximum of 120 mg THC and 120 mg CBD per day with no more than 20 mg of each in any 3-hour period.	**Randomised:** 80 **Treated:** 80
	Control: Placebo **Administration route:** Oromuscosal spray **Titration:** Not reported		**Randomised:** 80 **Treated:** 80
Wallace(2013)[76]	**Intervention 1:** THC **Administration route:** Oromuscosal spray **THC concentration:**7%	**Titration:** No **Regimen:** administered via the Volcano vaporizer 1x per study visit	**Randomised:** 16 **Treated:** 16

Study details	Intervention	Regimen	Number of participants
	Intervention 2: THC **Administration route:** Oromuscosal spray **THC concentration:**4%	**Daily dose:** 400 mg	**Randomised:** 16 **Treated:** 16
	Intervention 3: THC **Administration route:** Oromuscosal spray **THC concentration:**1%		**Randomised:** 16 **Treated:** 16
	Control: Placebo **Administration route:** Oromuscosal spray		**Randomised:** 16 **Treated:** 16
Ware(2010)[133]	**Intervention 1:** Nabilone (Cesamet) **Administration route:** Capsules (oral) **Dose:** 0.5mg	**Titration:** Yes **Single daily dose** on day 7 of the study physician could increase to two doses if required	**Randomised:** 32 **Treated:** 32
	Intervention 2: Amitriptyline **Administration route:** Capsules (oral) **Dose:** 10mg		**Randomised:** 32 **Treated:** 32
Ware(2010)[135]	**Intervention 1:** THC **Administration route:** Smoked **THC concentration:** 2.5%	**Titration:** No **Regimen:** 3x/day Participants were instructed to inhale for five seconds while the cannabis was lit, hold the smoke in their lungs for ten seconds, and then exhale.	**Randomised:** 23 **Treated:** 21
	Intervention 2: THC **Administration route:** Smoked **THC concentration:** 6%		**Randomised:** 23 **Treated:** 22
	Intervention 3: THC **Administration route:** Smoked **THC concentration:** 9.4%		**Randomised:** 23 **Treated:** 21
	Control: Placebo **Administration route:** Smoked		**Randomised:** 23 **Treated:** 21
Wilsey (2013)[134]	**Intervention 1:** Cannabis (not specified) **Administration route:** Vapourised **Details:** 0.8 g cannabis thawed and humidified. Cannabis was vaporized using the Volcano vaporizer (Storz & Bickel America, Inc, Oakland, CA). **THC concentration:** 3.53%	**Titration:** No **Total daily dose (mg):** **Regimen:** 4 puffs 1 hour from baseline, 4-8 puffs 3 hours from baseline A cued-puff procedure known as the ''Foltin Puff Procedure'' standardized the administration of the cannabis.	**Randomised:** 39 **Treated:**
	Intervention 2: Cannabis (not specified) **Administration route:** Vapourised **THC concentration:**1.29%		**Randomised:** 39 **Treated:**

Study details	Intervention	Regimen	Number of participants
	Control: Placebo **Administration route:** Vapourised **Titration:** No		**Randomised:** 39 **Treated:**
Wilsey(2011)[138]	**Intervention 1:** THC **Administration route:** Smoked **THC concentration:**3.5%	**Titration:** No Participants completed a standardized cued-puff procedure of 2 puffs after baseline measurements, 3 puffs an hour later, and 4 puffs an hour after that (total 9 puffs)	**Randomised:** 38 **Treated:** 38
	Intervention 2: THC **Administration route:** Smoked **Titration:** No **THC concentration:** 7%		**Randomised:** 38 **Treated:** 38
	Control: Placebo **Administration route:** Smoked		**Randomised:** 38 **Treated:** 38
Zajicek(2003)[89]	**Intervention 1:** THC/CBD **Administration route:** Capsules (oral) **Titration:** Yes **Dose:** Capsules contained 2·5 mg of Δ9-THC equivalent, 1·25 mg of cannabidiol, and less than 5% other cannabinoids per capsule.	**Total daily dose (mg):** **Regimen:** 5 week titration phase, dose increases of one capsule twice daily at weekly intervals. Twice daily after food. Dose of study medication based on bodyweight. Maximum dose 25 mg/ day.	**Randomised:** 219 **Treated:** 211
	Intervention 2: Dronabinol (Marinol) **Administration route:** Capsules (oral) **Titration:** Yes **Dose:** one capsule		**Randomised:** 216 **Treated:** 206
	Control: Placebo **Administration route:** Capsules (oral) **Titration:** Yes		**Randomised:** 222 **Treated:** 213
Zajicek(2012)[87]	**Intervention 1:** THC/CBD **Administration route:** Capsules (oral) **Details:** Soft gelatine capsules each containing cannabidiol (range 0.8-1.8 mg) and 2.5 mg D9- tetrahydrocannabinol (THC) **Dose:** 1 capsule (2.5mg)	**Titration:** Yes 2 week dose titration phase and 10 week maintenance phase. Starting dose 1 capsule twice daily titrated upwards by 2 capsules/day every 3 days to maximum dose of 10 capsules	**Randomised:** 144 **Treated:** 143
	Control: Placebo **Administration route:** Capsules (oral)		**Randomised:** 135 **Treated:** 134

APPENDIX 7: RESULTS OF INCLUDED STUDIES

A. DICHOTOMOUS OUTCOMES

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
Abrams(2007)[142] **Study design:** Parallel group RCT	**Intervention:** THC **Comparator:** Placebo **Follow-up:** 5 days **Analysis**: Per protocol	**Adverse events**: Anxiety (transient grade 3)	1/25	1/25	1.(0.10, 10.29)		
		Adverse events: Dizziness (grade 3)	1/25	0/25	3.12 (0.12, 80.40)		
		Adverse events: Withdrawal due to AEs	0/25	0/25	1.0 (0.01, 52.36)		
		Pain: Neuropathic pain scale (>30% reduction (VAS))	13/25	6/25	3.2 (1.00, 10.48)		
Ahmedzai(1983)[112] **Study design:** Cross-over RCT	**Intervention:** Nabilone (Cesamet) **Comparator:** Proclorperazine **Follow-up:** 3 days **Analysis**: Per-protocol	**Adverse events**: Confusion (Confusion/disorientation)	3/28	0/26	7.2 (0.35, 147.98)		
		Adverse events: Dizziness (Postural dizziness)	10/28	1/26	9.6 (1.57, 59.10)		
		Adverse events: Drowsiness	16/28	7/26	3.4 (1.12, 10.49)		
		Adverse events: Dry mouth	3/28	1/26	2.3 (0.31, 17.06)		
		Adverse events: Euphoria	4/28	0/26	9.7 (0.49, 190.31)		
		Adverse events: Nausea	1/28	0/26	2.8 (0.11, 74.17)		
	Intervention: Nabilone (Cesamet) **Comparator:** Proclorperazine **Follow-up:** 3 days **Analysis**: Modified ITT,	**Nausea & vomiting**: Complete response (no nausea)	21/26	10/30	7.6 (2.30, 25.23)		
		Nausea & vomiting: Complete response (No retching)	22/26	13/30	6.4 (1.88, 22.31)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
	28 out of 34 patients	**Nausea & vomiting**: Complete response (No vomiting)	26/26	22/30	20.0 (1.09, 366.45)		
Beal (1995)[84] **Study design:** Parallel group RCT	**Intervention:** Dronabinol (Marinol) **Comparator:** Placebo **Follow-up:** 6 weeks **Analysis**: ITT	**Adverse events**: At least one (All drug related)	31/72	9/67	4.6 (2.04, 10.69)		
		Adverse events: Cardiac disorders (COSTART cardiovascular)	1/72	0/67	2.8 (0.11, 70.73)		
		Adverse events: Gastrointestinal disorders (COSTART digestive)	6/72	2/67	2.5 (0.57, 11.45)		
		Adverse events: Nervous system disorders (COSTART)	25/72	6/67	5.0 (1.98, 13.01)		
		Adverse events: Serious AE	6/72	0/67	13.1 (0.73, 239.0)		
	Analysis: Per-protocol	**Appetite & weight**: Weight (Number of patients who gained ≥≥2kg)	11/50	4/38	2.2 (0.68, 7.27)		
Berman (2007)[1] **Study design:** Parallel group RCT	**Intervention:** Nabiximols (Sativex) **Comparator:** Placebo **Follow-up:** 51 days **Analysis**: ITT	**Adverse events**: At least one (The number of patients who experienced an adverse event)	46/56	29/60	4.7 (2.04, 10.92)		
		Adverse events: Blood disorders ("Blood and lymphatic system disorders")	1/56	0/60	3.2 (0.13, 82.0)		
		Adverse events: Confusion	3/56	0/60	7.9 (0.4, 156.8)		
		Adverse events: Dizziness	14/56	6/60	2.8 (1.0, 7.8)		
		Adverse events: Dry mouth	4/56	0/60	10.3 (0.54, 197.18)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Adverse events: Infections and infestations	9/56	6/60	1.6 (0.57, 4.89)		
		Adverse events: Injury, poisoning & procedural complications	1/56	1/60	1.0 (0.11, 10.61)		
		Adverse events: Musculoskeletal and connective tissue disorders	0/56	2/60	0.2 (0.01, 4.41)		
		Adverse events: Nausea	6/56	3/60	2.1 (0.54, 8.18)		
		Adverse events: Serious AE	5/56	2/60	2.4 (0.53, 11.67)		
		Adverse events: Skin and subcutaneuous tissue disorders	0/56	1/60	0.3 (0.01, 8.80)		
		Adverse events: Somnoloence	7/56	0/60	18.3 (1.02, 328.98)		
		Adverse events: Vomiting	2/56	0/60	5.5 (0.26, 118.18)		
		Global impression: Patient global impression (number of participants reporting improvement)	30/56	12/60	4.4 (1.98, 10.05)		
Berman(2004)[145] **Study design:** Cross-over RCT	**Intervention:** THC **Comparator:** Placebo **Follow-up:** 2 weeks **Analysis**: modified ITT; 3 randomised participants that withdrew not analysed in all arms	**Adverse events**: Dizziness	11/47	4/48	3.1 (0.96, 10.08)		
		Adverse events: Nausea	5/47	3/48	1.6 (0.41, 6.84)		
		Adverse events: Serious AE	0/47	0/48	1.0 (0.01, 52.52)		
		Adverse events: Somnoloence	6/47	5/48	1.2 (0.36, 4.16)		
	Intervention: Nabiximols (Sativex)	**Adverse events**: Dizziness	9/46	4/48	2.5 (0.75, 8.34)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
	Comparator: Placebo	**Adverse events**: Nausea	1/46	3/48	0.4 (0.06, 3.03)		
		Adverse events: Serious AE	0/46	0/48	1.0 (0.02, 53.66)		
		Adverse events: Somnoloence	7/46	5/48	1.5 (0.46, 4.89)		
Blake(2006)[78] **Study design:** Parallel group RCT	**Intervention:** Nabiximols (Sativex) **Comparator:** Placebo **Follow-up:** 5 weeks **Analysis**: ITT	**Adverse events**: Balance ("Fall")	2/31	0/27	4.6 (0.21, 101.47)		
		Adverse events: Dizziness	8/31	1/27	6.3 (1.03, 39.53)		
		Adverse events: Drowsiness	1/31	1/27	0.8 (0.08, 8.86)		
		Adverse events: Dry mouth ("Dry mouth")	4/31	0/27	9.0 (0.46, 175.29)		
		Adverse events: Nausea (Not specified if patient-reported)	2/31	1/27	1.4 (0.18, 12.11)		
		Adverse events: Serious AE ("Serious adverse events" (not specified))	0/31	2/27	0.1 (0.00, 3.52)		
		Adverse events: Vomiting (Not specified if patient-reported)	0/31	2/27	0.1 (0.00, 3.52)		
		Adverse events: Withdrawal due to AEs	0/31	3/27	0.1 (0.00, 2.25)		
Broder(1982)[74] **Study design:** Cross-over RCT	**Intervention:** THC **Comparator:** Hydroxizine **Timing:** 1 chemotherapy cycle **Analysis:** Modified ITT (35 out of 44 patients)	**Adverse events**: Serious AE	3/35	0/35	7.6 (0.38, 153.8)		
Chan(1987)[93]	**Intervention:** Nabilone (Cesamet)	**Adverse events**: At least one	32/36	14/36	11.2(3.42, 36.71)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
Study design: Cross-over RCT	**Comparator:** Prochlorperazine **Follow-up:** 1 cycle **Analysis**: modified ITT; results for 36 out of 40 patients reported.	**Adverse events**: Dizziness	18/36	1/36	23.6 (4.09, 137.05)		
		Adverse events: Drowsiness	24/36	6/36	9.1 (3.10, 27.26)		
		Adverse events: Euphoria	4/36	1/36	3.2 (0.48, 22.08)		
		Adverse events: Serious AE	4/36	2/36	1.9 (0.38, 9.64)		
	Analysis: modified ITT; 30 patients who completed both cycles included.	**Nausea & vomiting**: Complete response ("Total elimination of retching and vomiting")	3/30	3/30	1.0 (0.20, 4.82)		
		Nausea & vomiting: Partial response ("Overall improvement of retching and vomiting")	21/30	9/30	5.1 (1.73, 15.08)		
		Nausea & vomiting: Partial response ("Less retching and vomiting")	18/30	6/30	5.5 (1.81, 17.16)		
Collin(2007)[2] **Study design:** Parallel group RCT	**Intervention:** Nabiximols (Sativex) **Comparator:** Placebo **Follow-up:** 52 days **Analysis**: ITT	**Adverse events**: At least one (An adverse event during the course of the study)	102/124	46/65	1.9 (0.95, 3.84)		
	Follow-up: 6 weeks	**Adverse events**: Balance (impaired balance)	9/124	1/65	3.5 (0.61, 20.32)		
		Adverse events: Confusion	6/124	2/65	1.3 (0.31, 6.18)		
		Adverse events: Depression	6/124	0/65	7.1 (0.39, 129.58)		
		Adverse events: Diarrhoea	7/124	2/65	1.3 (0.45, 4.30)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Adverse events: Disorientation	5/124	1/65	1.9 (0.31, 12.34)		
		Adverse events: Dizziness	40/124	7/65	3.7 (1.60, 8.72)		
		Adverse events: Dry mouth	11/124	4/65	1.6 (0.38, 7.01)		
		Adverse events: Euphoria	4/124	2/65	0.9 (0.19, 4.58)		
		Adverse events: Fatigue	13/124	4/65	1.6 (0.54, 5.02)		
		Adverse events: Nausea	9/124	4/65	1.1 (0.35, 3.59)		
		Adverse events: Serious AE	4/124	3/65	0.6 (0.15, 2.78)		
		Adverse events: Somnoloence	6/124	1/65	2.3 (0.38, 14.28)		
		Adverse events: Withdrawal due to AEs	6/124	2/65	1.3 (0.31, 6.18)		
		Global impression: Patient global impression (No. patients rating global impression of change as improved. 7 point scale very much improved to very much worse.)	66/124	31/65	1.2 (0.68, 2.26)		
	Analysis: modified ITT; intention-to-treat (ITT) population, defined as	**Spasticity**: Numerical rating scale (≥ 50% reduction)	21/120	6/64	1.9 (0.76, 4.95)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
	all randomized participants receiving at least one dose of study medication with recorded post- **Intervention:** Nabiximols (Sativex) **Comparator:** Placebo **Follow-up:** 6 weeks	**Spasticity**: Numerical rating scale (≥ 30% reduction)	48/120	14/64	2.3 (1.17, 4.63)		
Collin (2010)[5] **Study design:** Parallel group RCT	**Intervention:** Nabiximols (Sativex) **Comparator:** Placebo **Follow-up:** 99 days **Analysis**: ITT (all randomised participants)	**Adverse events**: Anxiety	1/167	5/170	0.2 (0.04, 1.67)		
		Adverse events: Asthenia	26/167	11/170	2.5 (1.25, 5.38)		
		Adverse events: At least one (At least one AE)	156/167	132/170	3.9 (1.96, 7.94)		
		Adverse events: Confusion	3/167	0/170	7.2 (0.37, 141.55)		
		Adverse events: Depression (Depressed mood)	2/167	1/170	1.7 (0.22, 13.06)		
		Adverse events: Depression	4/167	2/170	1.8 (0.38, 8.83)		
		Adverse events: Disorientation	2/167	0/170	5.1 (0.24, 108.10)		
		Adverse events: Dizziness	53/167	17/170	4.0 (2.26, 7.40)		
		Adverse events: Dry mouth	24/167	7/170	3.7 (1.59, 8.69)		
		Adverse events: Ear and labyrinth disorders	19/167	7/170	2.8 (1.19, 6.83)		
		Adverse events: Euphoria (Euphoric moods)	0/167	3/170	0.1 (0.00, 2.78)		
		Adverse events: Fatigue	42/167	32/170	1.4 (0.86, 2.41)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Adverse events: Gastrointestinal disorders	58/167	34/170	2.1 (1.29, 3.45)		
		Adverse events: General disorders and administration site conditions	76/167	48/170	2.1 (1.34, 3.31)		
		Adverse events: Hallucinations	2/167	1/170	1.7 (0.22, 13.06)		
		Adverse events: Infections and infestations	37/167	37/170	1.0 (0.61, 1.70)		
		Adverse events: Musculoskeletal and connective tissues disorders	24/167	15/170	1.7 (0.87, 3.36)		
		Adverse events: Nausea	53/167	17/170	4.0 (2.26, 7.40)		
		Adverse events: Nervous system disorders	115/167	57/170	4.3 (2.75, 6.84)		
		Adverse events: Paranoia	1/167	1/170	1.0 (0.10, 9.88)		
		Adverse events: Psychiatric disorders	28/167	18/170	1.6 (0.89, 3.15)		
		Adverse events: Serious AE	15/167	7/170	2.2 (0.90, 5.44)		
		Adverse events: Somnoloence	24/167	7/170	3.7 (1.59, 8.69)		
		Adverse events: Withdrawal due to AEs	9/167	5/170	1.8 (0.61, 5.27)		
	Analysis: modified ITT; all patients who received at least one dose of study medication and had on treatment efficacy data	**Global impression**: Carer global impression (7 point scale; very much improved - very much worse. Number of carers who reported an improvement.)	72/167	56/170	1.5 (0.98, 2.39)	OR: 1.25 (0.84, 1.85) p-value=0.270	**Analysis Method** Logistic regression

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Spasticity: Numerical rating scale (≥50% improvement)	21/166	18/169	1.2 (0.62, 2.34)	OR: 1.22 (0.62, 2.37) p-value=0.569	**Analysis Method** ANCOVA
		Spasticity: Numerical rating scale (≥30% improvement in mean spasticity score)	51/166	42/169	1.3 (0.82, 2.15)	OR: 1.34 (0.83, 2.17) p-value=0.231	**Analysis Method** ANCOVA
Corey-Bloom(2012)[190] **Study design:** Cross-over RCT	**Intervention:** THC **Comparator:** Placebo **Follow-up:** 3 days **Analysis**: ITT	**Adverse events**: Dizziness	8/37	1/37	7.0 (1.15, 42.51)		
		Adverse events: Fatigue	7/37	2/37	3.4 (0.77, 15.82)		
		Adverse events: Nausea	4/37	1/37	3.2 (0.48, 21.99)		
Dalzell (1986)[92] **Study design:** Cross-over RCT	**Intervention:** Nabilone (Cesamet) **Comparator:** Domperidone **Follow-up:** 1 chemotherapy cycle **Analysis**: Modified ITT, 22 out 23 participants included	**Adverse events**: Dizziness	8/22	1/22	8.4 (1.31, 53.93)		
		Adverse events: Drowsiness	12)22	6/22	3.0 (0.89, 10.27)		
		Adverse events: Dry mouth	1/22	0/22	3.1 (0.12, 81.36)		
		Adverse events: Hallucinations	1/22	0/22	3.1 (0.12, 81.36)		
Duran (2010)[97] **Study design:** Parallel group RCT	**Intervention:** Nabiximols (Sativex) **Comparator:** Placebo **Follow-up:** 5 days **Analysis**: ITT	**Adverse events**: Anxiety	2/7	0/9	8.6 (0.34, 214.62)		
		Adverse events: At least one	6 (22)/7	6 (25)/9	2.3 (0.25, 21.06)		
		Adverse events: Confusion	2/7	0/9	8.6 (0.34, 214.62)		
		Adverse events: Depression	1/7	0/9	4.3 (0.15, 125.29)		
		Adverse events: Dizziness	3/7	1/9	4.4 (0.47, 40.90)		
		Adverse events: Dry mouth	2/7	3/9	0.8 (0.11, 6.11)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Adverse events: Euphoria	0/7	1/9	0.3 (0.01, 10.74)		
		Adverse events: Fatigue (fatigue)	1/7	4/9	0.2 (0.03, 2.46)		
		Adverse events: Psychosis (psychosis)	1/7	0/9	4.3 (0.15, 125.29)		
		Adverse events: Serious AE (serious)	0/7	0/9	1.2 (0.02, 71.63)		
		Adverse events: Serious AE (severe)	1/7	1/9	1.3 (0.10, 15.66)		
		Adverse events: Somnoloence	4/7	4/9	1.5 (0.24, 10.21)		
		Adverse events: Vomiting (Vomiting after administration)	0/7	2/9	0.2 (0.00, 4.90)		
		Adverse events: Withdrawal due to AEs	1/7	0/9	4.3 (0.15, 125.29)		
		Global impression: Patient global impression (patients satisfied with treatment)	4/7	8/9	0.2 (0.02, 2.10)		
		Nausea & vomiting: Complete response (no vomiting and a mean nausea VAS score of ≤10mm)	5/7	2/9	6.6 (0.83, 52.29)		
		Nausea & vomiting: Partial response (vomiting on average 1-4x daily and a mean nausea VAS score of ≤25mm)	1/7	5/9	0.1 (0.02, 1.65)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
Einhorn(1981)[108] **Study design:** Cross-over RCT	**Intervention:** Nabilone (Cesamet) **Comparator:** Prochlorperazine **Timing:** 5 days **Analysis:** Per protocol	**Appetite & weight:** "Depressed appetite and reduced food intake"	64/80	72/80	0.4 (0.19, 1.12)		
Frank(2008)[141] **Study design:** Cross-over RCT	**Intervention:** Nabilone (Cesamet) **Comparator:** Dihydrocodeine **Timing:**14 weeks **Analysis**: Per protocol	**Adverse events**: Serious AE ("major adverse events")	0/73	0/73	1.0 (0.02, 51.08)		
Frytak(1979)[111] **Study design:** Parallel group RCT	**Intervention:** THC **Comparator:** Placebo **Follow-up:** 4 days **Analysis**: modified ITT (1 out of 117 patients was disqualified on day 1)	**Adverse events**: Euphoria	22/38	0/37	102.2 (5.84, 1788.83)		
	Intervention: THC **Comparator:** Prochlorperazine	**Adverse events**: Euphoria	22/38	5/41	9.0 (3.01, 27.15)		
	Intervention: THC **Comparator:** Placebo	**Adverse events**: Withdrawal due to AEs	22/38	4/37	10.1 (3.15, 32.75)		
	Intervention: THC **Comparator:** Prochlorperazine	**Adverse events**: Withdrawal due to AEs	22/38	6/41	7.4 (2.61, 21.29)		
George(1983)[104] **Study design:** Cross-over RCT	**Intervention:** Nabilone (Cesamet) **Comparator:** Chlorpromazine **Follow-up:** 24 hours	**Adverse events**: At least one	17/20	11/20	4.1 (0.98, 17.32)		
		Adverse events: Balance (difficulty of coordination)	(3)/20	(0)/20			

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
	Analysis: ITT	**Adverse events**: Disorientation	(2)/20	(0)/20			
		Adverse events: Dry mouth	(16)/20	(8)/20			
		Adverse events: Euphoria	(1)/20	(0)/20			
		Adverse events: Somnoloence	(12)/20	(7)/20			
GW Pharma Ltd(2005)[77] **Study design:** Parallel group RCT	**Intervention:** Nabiximols (Sativex) **Comparator:** Placebo **Follow-up:** 133 days **Analysis**: modified ITT	**Adverse events**: At least one (Not including SAE)	120/149	101/148	1.9 (1.12, 3.24)		
		Adverse events: Depression	5/149	2/148	2.2 (0.49, 10.12)		
		Adverse events: Diarrhoea	10/149	14/148	0.6 (0.30, 1.59)		
		Adverse events: Disorientation	8/149	1/148	5.9 (1.02, 34.02)		
		Adverse events: Dizziness	42/149	7/148	7.4 (3.29, 16.86)		
		Adverse events: Dry mouth	12/149	4/148	2.9 (0.96, 8.79)		
		Adverse events: Fatigue	10/149	4/148	2.4 (0.78, 7.47)		
		Adverse events: Nausea	25/149	15/148	1.7 (0.89, 3.47)		
		Adverse events: Nausea (Defined as SAE)	0/149	1/148	.3 (0.01, 8.13)		
		Adverse events: Serious AE	14/149	12/148	1.1 (0.52, 2.58)		
		Adverse events: Somnoloence	11/149	7/148	1.5 (0.60, 4.04)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Adverse events: Treatment related AE (All-causality relationship to study medication)	120/149	101/148	1.9 (1.12, 3.24)		
		Adverse events: Treatment related AE (Plausibly related to study medication)	96/149	52/148	3.3 (2.06, 5.32)		
		Adverse events: Vomiting	14/149	11/148	1.2 (0.56, 2.87)		
		Adverse events: Vomiting (Defined as SAE)	0/149	1/148	0.3 (0.01, 8.13)		
		Pain: NRS (Number of Responders at the 30% Improvement Level, defined as a reduction of at least 30% in the mean NRS average pain score)	54/149	59/148	0.8 (0.53, 1.36)	OR: 0.85 (0.53, 1.37) p-value=0.521	**Analysis Method** Ordinal logistic regression
GW Pharma Ltd(2012)[79] **Study design:** Parallel group RCT	**Intervention:** Nabiximols (Sativex) **Comparator:** Placebo **Follow-up:** 3 weeks **Analysis**: modified ITT	**Adverse events**: Asthenia ("weakness")	2/36	0/34	5.0 (0.23, 108.01)		
		Adverse events: At least one (All adverse events)	35/36	26/34	7.5 (1.24, 46.25)		
		Adverse events: Confusion ("Confusional state")	3/36	0/34	7.2 (0.35, 144.96)		
		Adverse events: Diarrhoea	0/36	3/34	0.1 (0.00, 2.47)		
		Adverse events: Dizziness	20/36	5/34	6.6 (2.17, 20.37)		
		Adverse events: Dry mouth	4/36	0/34	9.5 (0.49, 184.52)		
		Adverse events: Euphoria ("Euphoric mood")	2/36	0/34	5.0 (0.23, 108.01)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Adverse events: Fatigue	4/36	0/34	9.5 (0.49, 184.52)		
		Adverse events: Nausea	5/36	2/34	2.2 (0.47, 10.94)		
		Adverse events: Paranoia	2/36	0/34	5.0 (0.23, 108.01)		
		Adverse events: Serious AE (SAEs: Infections and Infestations)	0/36	1/34	0.3 (0.01, 7.77)		
		Adverse events: Serious AE (Total SAEs)	0/36	1/34	0.3 (0.01, 7.77)		
		Adverse events: Somnoloence (Somnolence)	2/36	0/34	5.0 (0.23, 108.01)		
		Adverse events: Vomiting	2/36	0/34	5.0 (0.23, 108.01)		
		Global impression: Patient global impression	9/36	9/34	0.9 (0.32, 2.64)		
Heim(1984)[102] **Study design:** Cross-over RCT	**Intervention:** Levonantradol **Comparator:** Metoclopramide **Follow-up:** 24 hours **Analysis**: Per-protocol	**Adverse events**: Anxiety	2/45	0/45	5.2 (0.24, 112.06)		
		Adverse events: Asthenia	0/45	2/45	0.1 (0.01, 4.10)		
		Adverse events: At least one	32/45	13/45	5.7 (2.36, 14.21)		
		Adverse events: Diarrhoea	0/45	3/45	0.1 (0.00, 2.66)		
		Adverse events: Disorientation	1/45	0/45	3.0 (0.12, 77.32)		
		Adverse events: Dizziness	13/45	0/45	37.8 (2.16, 658.98)		
		Adverse events: Somnoloence	18/45	0/45	61.2 (3.54, 1056.93)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Nausea & vomiting: Vomiting severity/intensity (Episodes of vomiting)	(140)/45	(301)/45			
Herman (1979)[123] **Study design:** Cross-over RCT	**Intervention:** Nabilone (Cesamet) **Comparator:** Prochlorperazine **Follow-up:** 1 chemotherapy cycle **Analysis**: Per-protocol	**Adverse events**: Anxiety	3/113	12/113	0.2 (0.07, .86)		
		Adverse events: Depression	23/113	30/113	0.7 (0.38, 1.31)		
		Adverse events: Dizziness	78/113	34/113	5.0 (2.90, 8.94)		
		Adverse events: Dry mouth	95/113	39/113	9.7 (5.18, 18.27)		
		Adverse events: Euphoria	18/113	0/113	43.9 (2.61, 739.38)		
		Adverse events: Serious AE	(96)/113	(32)/113			
		Adverse events: Somnoloence	96/113	54/113	6.0 (3.21, 11.28)		
		Adverse events: Withdrawal due to AEs	5/113	4/113	1.2 (0.34, 4.40)		
		Nausea & vomiting: Complete response (Total absense of nausea and vomiting during a complete cycle of chemotherapy)	9/113	0/113	20.6 (1.18, 358.99)		
		Nausea & vomiting: Partial response (Reduction of 50% or more in duration or severity of nausea nd number of vomiting episodes compared to previous courses of identical chemotherapy)	81/113	36/113	5.3 (3.02, 9.37)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
Hutcheon (1983)[103] **Study design:** Parallel group RCT	**Intervention:** Levonantradol (2mg) **Comparator:** chlorpromazine **Follow-up:** 24 hours **Analysis**: ITT	**Adverse events**: At least one (AE common to levonantradol and chlorpromazine)	19/27	20/27	0.8 (0.26, 2.68)		
		Adverse events: Confusion	1/27	0/27	3.1 (0.12, 79.87)		
		Adverse events: Depression	0/27	0/27	1.0 (0.01, 52.22)		
		Adverse events: Dizziness (AE common to levonantradol and chlorpromazine)	9/27	8/27	1.1 (0.38, 3.62)		
		Adverse events: Drowsiness (AE of levonantradol and cAE common to levonantradol and chlorpromazinehlor-promazine)	10/27	15/27	0.4 (0.16, 1.40)		
		Adverse events: Euphoria	1/27	0/27	3.1 (0.12, 79.87)		
		Adverse events: Hallucinations	2/27	0/27	5.3 (0.24, 117.77)		
		Adverse events: Injection site pain (AE common to levonantradol and chlorpromazine)	3/27	2/27	1.4 (0.26, 8.09)		
		Adverse events: Mental status change (Personality change)	1/27	0/27	3.1 (0.12, 79.87)		
	Intervention: Levonantradol (3mg) **Comparator:** chlorpromazine	**Adverse events**: At least one (AE common to levonantradol and chlorpromazine)	25/28	20/27	2.66 (0.66, 10.76)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
	Follow-up: 24 hours **Analysis**: ITT	**Adverse events**: Confusion	1/28	0/27	3.0 (0.11, 76.90)		
		Adverse events: Depression	2/28	0/27	5.1 (0.23, 113.22)		
		Adverse events: Dizziness (AE common to levonantradol and chlorpromazine)	16/28	8/27	3.0 (1.01, 9.01)		
		Adverse events: Drowsiness (AE of levonantradol and cAE common to levonantradol and chlorpromazinehlor-promazine)	13/28	15/27	0.7 (0.24, 1.99)		
		Adverse events: Euphoria	3/28	0/27	7.5 (0.37, 153.43)		
		Adverse events: Hallucinations	6/28	0/27	15.8 (0.84, 297.54)		
		Adverse events: Injection site pain (AE common to levonantradol and chlorpromazine)	3/28	2/27	1.4 (0.25, 7.76)		
		Adverse events: Mental status change (Personality change)	1/28	0/27	3.0 (0.11, 76.90)		
	Intervention: Levonantradol (4mg) **Comparator:** chlorpromazine **Follow-up:** 24 hours **Analysis**: ITT	**Adverse events**: At least one (AE common to levonantradol and chlorpromazine)	23/26	20/27	2.46 (0.61, 9.96)		
		Adverse events: Confusion	1/26	0/27	3.2 (0.12, 83.08)		
		Adverse events: Depression	2/26	0/27	5.6 (0.25, 122.70)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Adverse events: Dizziness (AE common to levonantradol and chlorpromazine)	10/26	8/27	1.4 (0.47, 4.46)		
		Adverse events: Drowsiness (AE of levonantradol and cAE common to levonantradol and chlorpromazinehlor-promazine)	9/26	15/27	0.4 (0.14, 1.29)		
		Adverse events: Euphoria	0/26	0/27	1.0 (0.01, 54.22)		
		Adverse events: Hallucinations	6/26	0/27	17.4 (0.92, 327.50)		
		Adverse events: Injection site pain (AE common to levonantradol and chlorpromazine)	6/26	2/27	3.2 (0.67, 15.54)		
		Adverse events: Mental status change (Personality change)	2/26	0/27	5.6 (0.25, 122.70)		
Johansson (1982)[106] **Study design:** Cross-over RCT	**Intervention:** Nabilone (Cesamet) **Comparator:** Prochlorperazine **Follow-up:** 1 chemotherapy cycle **Analysis**: modified ITT; 26/27 patients took nabilone at least once and 23/27 took prochlorperazine at least once and were included in analysis.	**Adverse events**: Asthenia (Powerless, general weakness)	1/26	1/23	0.8 (0.08, 9.09)		
		Adverse events: At least one	14/26	9/23	1.7 (0.58, 5.39)		
		Adverse events: Depression	1/26	1/23	0.8 (0.08, 9.09)		
		Adverse events: Dizziness	6/26	2/23	2.7 (0.56, 13.22)		
		Adverse events: Drowsiness	1/26	0/23	2.7 (0.10, 71.25)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
	Intervention: Nabilone (Cesamet) **Comparator:** Prochlorperazine **Follow-up:** 1 chemotherapy cycle **Analysis**: Per-protocol	**Nausea & vomiting**: Complete response (No vomiting episodes)	3/18	0/18	8.3 (0.40, 174.50)		
		Nausea & vomiting: Vomiting severity/intensity (Number of patients with >20 episodes)	3/18	9/18	0.2 (0.05, 0.97)		
Johnson(2010)[82] **Study design:** Parallel group RCT	**Intervention:** Nabiximols (Sativex) **Comparator:** Placebo **Follow-up:** 2 weeks **Analysis**: Not specified	**Adverse events**: Confusion	4/60	1/59	3.1 (0.47, 20.43)		
		Adverse events: Dizziness	7/60	3/59	2.2 (0.60, 8.49)		
		Adverse events: Nausea	6/60	4/59	1.4 (0.41, 5.17)		
		Adverse events: Somnoloence	8/60	6/59	1.3 (0.44, 3.96)		
		Adverse events: Vomiting	3/60	2/59	1.4 (0.26, 7.39)		
	Intervention: THC **Comparator:** Placebo **Follow-up:** 2 weeks **Analysis**: Not specified	**Adverse events**: Confusion	1/58	1/59	1.0 (0.10, 10.06)		
		Adverse events: Dizziness	7/58	3/59	2.3 (0.62, 8.83)		
		Adverse events: Nausea	4/58	4/59	1.0 (0.26, 3.96)		
		Adverse events: Somnoloence	8/58	6/59	1.3 (0.46, 4.12)		
		Adverse events: Vomiting	4/58	2/59	1.8 (0.38, 9.31)		
	Intervention: Nabiximols (Sativex) **Comparator:** Placebo **Follow-up:** 2 weeks **Analysis**: modified ITT;	**Pain**: Breakthrough analgesia use (Number of days break-through medication used)	NR	NR	NA	OR: 0.96 p-value=0.697	Logistic regression (No further details)

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
	Randomised patients with ≥ 1 actuation of study medication and efficacy data	**Pain**: Pain relief (Number with reduction from baseline NRS of at least 30%)	23/53	12/56	2.7 (1.20, 6.26)	OR: 2.81 (1.22, 6.50) p-value=0.006	
	Intervention: THC **Comparator:** Placebo **Follow-up:** 2 weeks **Analysis**: modified ITT; Randomised patients with ≥ 1 actuation of study medication and efficacy data	**Pain**: Breakthrough analgesia use (Number of days breakthrough medication used)	NR	NR	NA	OR: 1.20 p-value=0.555	
		Pain: Pain relief (Number with reduction from baseline NRS of at least 30%)	12/52	12/56	1.0 (0.45, 2.68)	OR: 1.10 (0.44, 2.73) p-value=0.28	
Jones(1982)[90] **Study design:** Cross-over RCT	**Intervention:** Nabilone (Cesamet) **Comparator:** Placebo **Follow-up:** 1 chemotherapy cycle **Analysis**: Modified ITT, results of 49 out of 54 patients	**Adverse events**: Asthenia	1/49	0/49	1.5 (0.06, 38.59)		
		Adverse events: Drowsiness	5/49	1/49	6 (0.32, 114.19)		
		Adverse events: Dry mouth	3/49	0/49	3.6 (0.18, 74.33)		
		Adverse events: Euphoria	1/49	0/49	1.5 (0.06, 38.59)		
		Adverse events: Hallucinations	1/49	0/49	1.5 (0.06, 38.59)		
		Adverse events: Nausea	3/49	0/49	3.6 (0.18, 74.33)		
		Adverse events: Vomiting	4/49	0/49	4.8 (0.25, 93.78)		
		Adverse events: Withdrawal due to AEs	11/49	2/49	2.6 (0.62, 11.61)		
Karst(2003)[147]	**Intervention:** CT3 **Comparator:** Placebo	**Adverse events**: At least one	12/19	5/19	4.3 (1.15, 16.70)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
Study design: Cross-over RCT	**Follow-up:** 1 week **Analysis**: modified ITT (1 dropout in each arm not analysed)	**Pain**: Neuropathic pain scale (30% reduction in pain)	9/19	3/19	4.2 (1.00, 18.17)		
		Pain: Neuropathic pain scale (50% reduction in pain)	2/19	0/19	5.5 (0.24, 124.20)		
Killestein(2002)[193] **Study design:** Cross-over RCT	**Intervention:** Dronabinol (Marinol) **Comparator:** Placebo **Follow-up:** 4 weeks **Analysis**: ITT	**Adverse events**: At least one	(20)/16	(20)/16			
		Adverse events: Dizziness	(0)/16	(3)/16			
		Adverse events: Dry mouth	(5)/16	(0)/16			
		Adverse events: Serious AE (SAE: all)	(0)/16	(0)/16			
		Adverse events: Somnoloence (Somnolence)	(0)/16	(4)/16			
	Intervention: THC/CBD **Comparator:** Placebo **Follow-up:** 4 weeks **Analysis**: ITT	**Adverse events**: At least one (AEs: Others)	(41)/16	(20)/16	1.9; p=0.01		
		Adverse events: Dizziness	(6)/16	(3)/16			
		Adverse events: Dry mouth	(3)/16	(0)/16			
		Adverse events: Serious AE (SAE: all)	(1)/16	(0)/16			
		Adverse events: Somnoloence (Somnolence)	(5)/16	(4)/16			
Lane(1991)[83] **Study design:** Parallel group RCT	**Intervention:** Dronabinol (Marinol) **Comparator:** Proclorperazine **Follow-up:** 6 days **Analysis**: ITT (all	**Adverse events**: Anxiety	1/21	0/21	3.1 (0.12, 81.74)		
		Adverse events: Asthenia	2/21	1/21	1.7 (0.21, 14.55)		
		Adverse events: At least one	16/21	7/21	5.8 (1.56, 21.43)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
	randomised patients)	**Adverse events**: Cardiac disorders	3/21	1/21	2.5 (0.34, 19.36)		
		Adverse events: Confusion	2/21	0/21	5.5 (0.24, 122.08)		
		Adverse events: Depression	2/21	0/21	5.5 (0.24, 122.08)		
		Adverse events: Diarrhoea	2/21	0/21	5.5 (0.24, 122.08)		
		Adverse events: Dizziness	7/21	1/21	7.0 (1.08, 46.21)		
		Adverse events: Dry mouth	2/21	0/21	5.5 (0.24, 122.08)		
		Adverse events: Dyspnea	0/21	1/21	0.3 (0.01, 8.25)		
		Adverse events: Gastrointestinal disorders	5/21	0/21	14.3 (0.73, 278.08)		
		Adverse events: Nervous system disorders	13/21	6/21	3.7 (1.07, 13.28)		
		Adverse events: Other body systems (Other body systems)	3/21	1/21	2.5 (0.34, 19.36)		
		Adverse events: Paranoia	1/21	0/21	3.1 (0.12, 81.74)		
		Adverse events: Respiratory, thoracic, and mediastinal disorders	0/21	1/21	0.3 (0.01, 8.25)		
		Adverse events: Somnoloence	4/21	3/21	1.3 (0.29, 6.35)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
	Intervention: Dronabinol (Marinol) **Comparator:** Proclorperazine **Follow-up:** 1 day **Analysis**: Per-protocol; 2 patients excluded	**Nausea & vomiting**: Anticipatory nausea (Anticipatory nausea)	6/20	0/20	18.3 (0.95, 352.58)		
	Intervention: Dronabinol (Marinol) **Comparator:** Proclorperazine **Follow-up:** 6 days **Analysis**: modified ITT(54/62 patients who received chemotherapy)	**Nausea & vomiting**: Complete response (No nausea or vomitting)	7/17	6/20	1.5 (0.42, 5.94)		
		Nausea & vomiting: Partial response (≤2 episodes of nausea or vomiting)	12/17	9/20	2.7 (0.73, 10.30)		
Langford (2013)[4] **Study design:** Parallel group RCT	**Intervention:** Nabiximols (Sativex) **Comparator:** Placebo **Follow-up:** 98 days **Analysis**: ITT	**Adverse events**: Asthenia (Muscular weakness)	1/167	1/172	1.0 (0.10, 10.00)		
		Adverse events: At least one	120/167	106/172	1.5 (1.00, 2.49)		
		Adverse events: Balance (Balance disorder)	5/167	2/172	2.3 (0.50, 10.45)		
		Adverse events: Depression	2/167	0/172	5.2 (0.24, 109.37)		
		Adverse events: Diarrhoea	7/167	5/172	1.4 (0.46, 4.36)		
		Adverse events: Dizziness	34/167	7/172	5.7 (2.50, 12.97)		
		Adverse events: Dry mouth	12/167	10/172	1.2 (0.53, 2.90)		
		Adverse events: Ear and labyrinth disorders	20/167	9/172	2.3 (1.07, 5.32)		
		Adverse events: Eye disorder	7/167	5/172	1.4 (0.46, 4.36)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Adverse events: Fatigue	16/167	9/172	1.8 (0.81, 4.29)		
		Adverse events: Gastrointestinal disorders	54/167	40/172	1.5 (0.97, 2.53)		
		Adverse events: General disorders and administration site conditions	40/167	30/172	1.4 (0.87, 2.51)		
		Adverse events: Infections and infestations	34/167	27/172	1.3 (0.78, 2.37)		
		Adverse events: Musculoskeletal and connective tissues disorders	17/167	20/172	0.8 (0.43, 1.70)		
		Adverse events: Nausea	13/167	7/172	1.9 (0.76, 4.83)		
		Adverse events: Nervous system disorders	73/167	51/172	1.8 (1.17, 2.86)		
		Adverse events: Psychiatric disorders	27/167	12/172	2.5 (1.24, 5.09)		
		Adverse events: Respiratory, thoracic, and mediastinal disorders	8/167	11/172	0.7 (0.30, 1.86)		
		Adverse events: Somnoloence	16/167	3/172	5.2 (1.63, 17.06)		
		Adverse events: Vomiting	5/167	5/172	1.0 (0.31, 3.42)		
		Global impression: Subject Global Impression of Change	NR	NR		OR: 1.47 (0.99, 2.18) p-value=0.055	
		Pain: NRS (≥30% improvement in mean NRS score)	84/167	77/172	1.2 (0.81, 1.90)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
Levitt(1982)[117] **Study design:** Cross-over RCT	**Intervention:** Nabilone (Cesamet) **Comparator:** Placebo **Follow-up:** 1 chemotherapy cycle **Analysis**: Per protocol	**Adverse events**: Withdrawal due to AEs	5/36	0/36	12.7 (0.67, 239.68)		
Long(1982)[73] **Study design:** Cross-over RCT	**Intervention:** Levonantradol **Comparator:** Prochlorperazine **Follow-up:** 1 chemo-therapy cycle **Analysis**: Per-protocol	**Adverse events**: Anxiety	4/34	0/34	10.1 (0.52, 196.87)		
		Adverse events: Depression	4/34	1/34	3.2 (0.48, 22.29)		
		Adverse events: Disorientation	9/34	1/34	8.3 (1.37, 50.20)		
		Adverse events: Dizziness	14/34	2/34	9.1 (2.15, 39.26)		
		Adverse events: Dry mouth	15/34	6/34	3.4 (1.18, 10.28)		
		Adverse events: Euphoria	8/34	0/34	22.1 (1.22, 400.94)		
		Adverse events: Somnoloence	23/34	7/34	7.4 (2.56, 21.89)		
		Nausea & vomiting: Partial response ('Significantly less nausea and vomiting')	13/34	3/34	5.6 (1.54, 20.67)		
Lynch(2014)[148] **Study design:** Cross-over RCT	**Intervention:** Nabiximols (Sativex) **Comparator:** Placebo **Follow-up:** 6 weeks **Analysis**: Per-protocol	**Adverse events**: Anxiety	1/16	0/16	3.1 (0.12, 84.43)		
		Adverse events: Confusion	1/16	0/16	3.1 (0.12, 84.43)		
		Adverse events: Diarrhoea	2/16	0/16	5.6 (0.25, 128.50)		
		Adverse events: Dizziness	6/16	0/16	20.4 (1.03, 401.68)		
		Adverse events: Dry mouth	5/16	1/16	4.9 (0.69, 35.08)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Adverse events: Fatigue	7/16	0/16	26.0 (1.33, 508.81)		
		Adverse events: Nausea	6/16	1/16	6.3 (0.91, 44.53)		
		Adverse events: Serious AE	0/16	0/16	1.0 (0.01, 53.46)		
McCabe(1988)[98] **Study design:** Cross-over RCT	**Intervention:** THC **Comparator:** Prochlorperazine **Follow-up:** Chemotherapy cycle **Analysis**: ITT	**Nausea & vomiting**: Complete response (Patients with complete response, defined as complete absence of N&V)	9/36	0/36	25.2 (1.40, 452.22)		
		Nausea & vomiting: Partial response (Patients with partial response, defined as at least a 50% decrease in frequency and intensity of N&V)	14/36	1/36	15.2 (2.61, 88.83)		
Meiri(2007)[85] **Study design:** Parallel group RCT	**Intervention:** Dronabinol (Marinol) **Comparator:** Placebo **Follow-up:** 5 days **Analysis**: ITT	**Adverse events**: Patients with at least one severe TEAE	2/17	3/14	0.5 (0.08, 3.18)		
		Adverse events: Asthenia	2/17	1/14	1.4 (0.17, 12.48)		
		Adverse events: Death	0/17	1/14	0.2 (0.01, 6.82)		
		Adverse events: Diarrhoea	4/17	1/14	3 (0.41, 22.08)		
		Adverse events: Dizziness	1/17	0/14	2.6 (0.09, 69.88)		
		Adverse events: Fatigue	2/17	1/14	1.4 (0.17, 12.48)		
		Adverse events: Serious AE	2/17	2/14	0.8 (0.12, 5.41)		
		Adverse events: Treatment related AE	14/17	7/14	4.1 (0.88, 19.42)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Adverse events: Withdrawal due to AEs	1/17	0/14	2.6 (0.09, 69.88)		
	Intervention: Dronabinol (Marinol) **Comparator:** Placebo **Follow-up:** 5 days **Analysis**: modified ITT; 2-5 days (LOCF, values from a premature discontinuation visit included)	**Nausea & vomiting**: Complete response (Total response = no vomiting and/ or retching, intensity of nausea < 5 mm on a 100-mm VAS, and no use of rescue medication.)	8/14	3/13	3.9 (0.80, 19.10)		
		Nausea & vomiting: Nausea (patient perception) (Absence of nausea during active treatment)	10/14	2/13	10.7 (1.85, 62.25)		
	Intervention: Dronabinol + ondansetron **Comparator:** Placebo **Follow-up:** 5 days **Analysis**: ITT	**Adverse events**: At least one (Patients with at least one Severe TEAE)	2/17	3/14	0.5 (0.08, 3.18)		
		Adverse events: Asthenia	0/17	1/14	0.26 (0.01, 6.82)		
		Adverse events: Death	0/17	1/14	0.26 (0.01, 6.82)		
		Adverse events: Diarrhoea	1/17	1/14	0.82 (0.08, 8.79)		
		Adverse events: Dizziness	4/17	0/14	9.6 (0.47, 196.96)		
		Adverse events: Fatigue	3/17	1/14	2.17 (0.28, 16.90)		
		Adverse events: Serious AE	1/17	2/14	0.4 (0.05, 3.91)		
		Adverse events: Treatment related AE	12/17	7/14	2.2 (0.54, 9.44)		
		Adverse events: Withdrawal due to AEs	3/17	0/14	7.0 (0.33, 148.00)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
	Intervention: Dronabinol + ondansetron **Comparator:** Placebo **Follow-up:** 5 days **Analysis**: modified ITT; 2-5 days (LOCF, values from a premature discontinuation visit included)	**Nausea & vomiting**: Complete response (Total response = no vomiting and/ or retching, intensity of nausea < 5 mm on a 100-mm VAS, and no use of rescue medication.)	7/14	3/13	3.0 (0.61, 14.52)		
		Nausea & vomiting: Nausea (patient perception) (Absence of nausea during active treatment)	7/14	2/13	4.6 (0.83, 25.21)		
Melhem-Bertrandt(2014)[124] **Study design:** Parallel group RCT	**Intervention:** Dronabinol (Marinol) **Comparator:** Placebo **Follow-up:** 5 days **Analysis**: ITT	**Adverse events**: Diarrhoea	5/31	0/31	13.0 (0.69, 247.54)	p-value=0.053	**Analysis Method** Fisher's exact test
		Adverse events: Dizziness	10/31	2/31	5.7 (1.30, 25.49)	p-value=0.022	
		Adverse events: Euphoria	2/31	3/31	0.6 (0.12, 3.78)	p-value=0.999	
		Adverse events: Fatigue	6/31	3/31	2.0 (0.50, 8.45)	p-value=0.473	
		Adverse events: General disorders and administration site conditions (other)	4/31	1/31	3.3 (0.48, 22.65)	p-value=0.354	
		Adverse events: Somnoloence	3/31	2/31	1.4 (0.26, 7.95)	p-value=0.707	
	Intervention: Dronabinol (Marinol) **Comparator:** Placebo **Follow-up:** 120 hours **Analysis**: modified ITT (59 out of 62, 3 withdrawals)	**Nausea & vomiting**: Complete response (No vomiting or resuce medication)	15/30	12/29	1.4 (0.50, 3.84)	p-value=0.604	**Analysis Method** Fisher's exact test
		Nausea & vomiting: Complete response (No vomiting, no resuce medication, no nausea)	11/30	5/29	2.6 (0.80, 8.52)	p-value=0.143	

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Nausea & vomiting: Complete response (No vomiting or resuce medication, nausea intensity NRS > 3)	14/30	9/29	1.8 (0.66, 5.38)	p-value=0.288	
		Nausea & vomiting: Frequency of nausea (No nausea)	11/30	5/29	2.6 (0.80, 8.52)	p-value=0.143	
		Nausea & vomiting: Frequency of nausea (no significant nausea, NRS >3)	15/30	10/29	1.8 (0.66, 5.19)	p-value=0.295	
		Nausea & vomiting: Number of vomiting episodes	19/30	19/29	0.9 (0.32, 2.59)	p-value=0.999	
Müller-Vahl (2001)[227]	**Intervention:** THC **Comparator:** Placebo **Timing:** 2 days **Analysis:** ITT	**Adverse events**: At least one	5/12	2/12	3.08 (0.53, 17.98)		
		Adverse events: Serious AE	0/12	0/12	1.0 (0.02, 54.47)		
Müller-Vahl (2003)[225] **Study design:** Parallel group RCT	**Intervention:** THC **Comparator:** Placebo **Follow-up:** 6 weeks **Analysis**: Per-protocol	**Adverse events**: At least one	5/9	3/11	2.97 (0.51, 17.27)		
		Adverse events: Serious AE	0/9	0/11	1.21 (0.02, 66.96)		
	Intervention: THC **Comparator:** Placebo **Follow-up:** 6 weeks **Analysis**: ITT	**Adverse events**: Withdrawal due to AEs	1/12	0/12	3.26 (0.12, 88.35)		
Narang(2008)[139] **Study design:** Cross-over RCT	**Intervention:** Dronabinol (Marinol) (10 mg) **Comparator:** Placebo **Follow-up:** 8 hours **Analysis**: Per protocol	**Adverse events**: Anxiety	5/30	1/30	4.2 (0.64, 27.84)		
		Adverse events: Asthenia	6/30	3/30	2.0 (0.50, 8.52)		
		Adverse events: Confusion	3/30	1/30	2.5 (0.34, 18.16)		
		Adverse events: Depression	3/30	2/30	1.4 (0.26, 7.98)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Adverse events: Dizziness	14/30	1/30	17.2 (2.89, 103.07)		
		Adverse events: Drowsiness	16/30	8/30	3.0 (1.05, 8.68)		
		Adverse events: Dry mouth	15/30	2/30	11.4 (2.61, 49.68)		
		Adverse events: Euphoria	14/30	1/30	17.2 (2.89, 103.07)		
		Adverse events: Nausea	3/30	1/30	2.5 (0.34, 18.16)		
		Adverse events: Vomiting	1/30	0/30	3.1 (0.12, 79.23)		
	Intervention: Dronabinol (Marinol) (20 mg) **Comparator:** Placebo **Follow-up:** 8 hours **Analysis**: Per protocol	**Adverse events**: Anxiety	12/30	1/30	13.2 (2.21, 79.63)		
		Adverse events: Asthenia	6/30	3/30	2.0 (0.50, 8.52)		
		Adverse events: Confusion	12/30	1/30	13.2 (2.21, 79.63)		
		Adverse events: Depression	4/30	2/30	1.9 (0.37, 9.92)		
		Adverse events: Dizziness	15/30	1/30	19.6 (3.29, 117.22)		
		Adverse events: Drowsiness	20/30	(8)/30	5.1 (1.75, 15.29)		
		Adverse events: Dry mouth	14/30	2/30	10.0 (2.29, 43.69)		
		Adverse events: Euphoria	11/30	1/30	11.5 (1.92, 69.82)		
		Adverse events: Nausea	6/30	1/30	5.2 (0.81, 33.33)		
		Adverse events: Vomiting	0/30	0/30	1.0 (0.01, 52.03)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
Niederle(1986)[100] **Study design:** Cross-over RCT	**Intervention:** Nabilone (Cesamet) **Comparator:** Alizapride **Follow-up:** 5 days **Analysis**: ITT	**Adverse events**: Drowsiness	16/20	4/20	13.4 (3.07, 58.71)		
		Adverse events: Dry mouth	13/20	0/20	73.8 (3.88, 1401.64)		
		Adverse events: Euphoria	2/20	0/20	5.5 (0.24, 123.08)		
		Adverse events: Hallucinations	1/20	0/20	3.1 (0.12, 82.16)		
Noyes(1975)[96] **Study design:** Cross-over RCT	**Intervention:** THC (5 mg) **Comparator:** Placebo **Follow-up:** 6 hours **Analysis**: ITT	**Adverse events**: Dizziness	2/10	1/10	1.8 (0.20, 17.25)		
		Adverse events: Drowsiness	7/10	3/10	4.5 (0.76, 27.62)		
		Adverse events: Euphoria	0/10	0/10	1.0 (0.01, 55.27)		
		Adverse events: Hallucinations (Visual hallucinations)	0/10	0/10	1.0 (0.01, 55.27)		
	Intervention: THC (10 mg) **Comparator:** Placebo **Follow-up:** 7 hours **Analysis**: ITT	**Adverse events**: Diarrhoea (following a single dose)	1/44	2/44	0.5 (0.07, 4.63)		
		Adverse events: Disorientation (following a single dose)	6/44	3/44	2.0 (0.50, 7.88)		
	Intervention: THC (10 mg) **Comparator:** Placebo **Follow-up:** 6 hours **Analysis**: ITT	**Adverse events**: Dizziness	4/10	1/10	4.3 (0.53, 35.80)		
	Intervention: THC (10 mg) **Comparator:** Placebo **Follow-up:** 7 hours **Analysis**: ITT	**Adverse events**: Dizziness (following a single dose)	24/44	10/44	3.9 (1.58, 9.71)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
	Intervention: THC (10 mg) **Comparator:** Placebo **Follow-up:** 6 hours **Analysis**: ITT	**Adverse events**: Drowsiness	5/10	3/10	2.1 (0.37, 12.13)		
	Intervention: THC (10 mg) **Comparator:** Placebo **Follow-up:** 7 hours **Analysis**: Not specifiedITT	**Adverse events**: Dry mouth (following a single dose)	33/44	20/44	3.4 (1.42, 8.48)		
	Intervention: THC (10 mg) **Comparator:** Placebo **Follow-up:** 6 hours **Analysis**: ITT	**Adverse events**: Euphoria	1/10	0/10	3.3 (0.12, 91.60)		
	Intervention: THC (10 mg) **Comparator:** Placebo **Follow-up:** 6 hours **Analysis**: ITT	**Adverse events**: Hallucinations (Visual hallucinations)	1/10	0/10	3.3 (0.12, 91.60)		
	Intervention: THC (10 mg) **Comparator:** Placebo **Follow-up:** 7 hours **Analysis**: Not specifiedITT	**Adverse events**: Nausea (following a single dose)	10/44	7/44	1.5 (0.53, 4.32)		
		Adverse events: Somnoloence (following a single dose)	30/44	15/44	4.0 (1.66, 9.62)		
		Adverse events: Vomiting (following a single dose)	2/44	2/44	1.0 (0.16, 6.07)		
	Intervention: THC (15 mg) **Comparator:** Placebo **Follow-up:** 6 hours	**Adverse events**: Dizziness	4/10	1/10	4.3 (0.53, 35.80)		
		Adverse events: Drowsiness	7/10	3/10	4.5 (0.76, 27.62)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
	Analysis: ITT	**Adverse events**: Euphoria	4/10	0/10	14.5 (0.66, 316.71)		
		Adverse events: Hallucinations (Visual hallucinations)	0/10	0/10	1.0 (0.01, 55.27)		
	Intervention: THC (20 mg) **Comparator:** Placebo **Follow-up:** 7 hours **Analysis**: Not specifiedITT	**Adverse events**: Diarrhoea (following a single dose)	5/44	2/44	2.3 (0.49, 11.22)		
		Adverse events: Disorientation (following a single dose)	14/44	3/44	5.6 (1.60, 19.82)		
	Intervention: THC (20 mg) **Comparator:** Placebo **Follow-up:** 6 hours **Analysis**: ITT	**Adverse events**: Dizziness	6/10	1/10	9.1 (1.12, 74.70)		
	Intervention: THC (20 mg) **Comparator:** Placebo **Follow-up:** 7 hours **Analysis**: Not specifiedITT	**Adverse events**: Dizziness (following a single dose)	39/44	10/44	23.5 (7.63, 72.92)		
	Intervention: THC (20 mg) **Comparator:** Placebo **Follow-up:** 6 hours **Analysis**: ITT	**Adverse events**: Drowsiness	10/10	3/10	45.0 (2.01, 1006.80)		
	Intervention: THC (20 mg) **Comparator:** Placebo **Follow-up:** 7 hours **Analysis**: Not specifiedITT	**Adverse events**: Dry mouth (following a single dose)	36/44	20/44	5.1 (1.98, 13.26)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
	Intervention: THC (20 mg) **Comparator:** Placebo **Follow-up:** 6 hours **Analysis**: ITT	**Adverse events**: Euphoria	5/10	0/10	21.0 (0.97, 453.93)		
		Adverse events: Hallucinations (Visual hallucinations)	3/10	0/10	9.8 (0.43, 219.25)		
	Intervention: THC (20 mg) **Comparator:** Placebo **Follow-up:** 7 hours **Analysis**: ITT	**Adverse events**: Nausea (following a single dose)	9/44	7/44	1.3 (0.46, 3.86)		
		Adverse events: Somnoloence (following a single dose)	36/44	15/44	8.1 (3.10, 21.49)		
		Adverse events: Vomiting (following a single dose)	5/44	2/44	2.3 (0.49, 11.22)		
Nurmikko(2007)[80] **Study design:** Parallel group RCT	**Intervention:** Nabiximols (Sativex) **Comparator:** Placebo **Follow-up:** 5 weeks **Analysis**: ITT	**Adverse events**: At least one	57/63	48/62	2.6 (0.97, 7.19)		
		Adverse events: Diarrhoea	4/63	0/62	9.4 (0.49, 179.41)		
		Adverse events: Dizziness	18/63	9/62	2.2 (0.95, 5.50)		
		Adverse events: Dry mouth	11/63	3/62	3.7 (1.06, 13.03)		
		Adverse events: Fatigue	13/63	5/62	2.7 (0.96, 8.07)		
		Adverse events: Gastrointestinal disorders	31/63	20/62	2.0 (0.97, 4.12)	p-value=0.003	**Analysis Method** Fisher's exact test
		Adverse events: Nausea	14/63	7/62	2.1 (0.82, 5.66)		
		Adverse events: Nervous system disorders	33/63	23/62	1.8 (0.90, 3.74)	p-value=p>0.1	**Analysis Method** Fisher's exact test
		Adverse events: Psychiatric disorders	7/63	4/62	1.7 (0.50, 5.87)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Adverse events: Serious AE	1/63	2/62	0.5 (0.07, 4.53)		
		Adverse events: Somnoloence	4/63	1/62	3.1 (0.47, 20.36)		
		Adverse events: Vomiting	8/63	3/62	2.6 (0.71, 9.52)		
		Adverse events: Withdrawal due to AEs	11/63	2/62	5.3 (1.28, 21.86)		
		Pain: NRS (>30% reduction in pain score)	16/63	9/62	1.9 (0.80, 4.75)		
		Pain: NRS (>50% reduction in pain score)	13/63	5/62	2.7 (0.96, 8.07)		
Orr(1980)[109] **Study design:** Cross-over RCT	**Intervention:** THC **Comparator:** Prochlorperazine **Follow-up:** 24hrs **Analysis**: Per protocol	**Adverse events**: Dizziness	(0)/55	(12)/55			
		Adverse events: Drowsiness ("sedation")	(15)/55	(14)/55			
		Adverse events: Dry mouth	(0)/55	(6)/55			
		Adverse events: Euphoria ("Elevation of affect")	(45)/55	(0)/55			
		Adverse events: Nausea	(0)/55	(1)/55			
	Intervention: THC **Comparator:** Placebo **Follow-up:** 24hrs **Analysis**: Per protocol	**Adverse events**: Drowsiness ("sedation")	(15)/55	(0)/55			
		Adverse events: Euphoria ("Elevation of affect")	(45)/55	(0)/55			
		Adverse events: Nausea	0/55	(6)/55			

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
Pinsger(2006)[143] **Study design:** Cross-over RCT	**Intervention:** Nabilone (Cesamet) **Comparator:** Placebo **Follow-up:** 4 weeks **Analysis**: ITT	**Adverse events**: Drowsiness	(10)/30	(3)/30			
		Adverse events: Dry mouth	(6)/30	(1)/30			
		Adverse events: Fatigue ("Müdigkeit")	(9)/30	(4)/30			
		Adverse events: Serious AE	1/30	0/30	3.1 (0.12, 79.23)		
Pomeroy(1986)[99] **Study design:** Parallel group RCT	**Intervention:** Nabilone (Cesamet) **Comparator:** Domperidone **Follow-up:** 2 cycles **Analysis**: ITT	**Adverse events**: Asthenia	1/19	0/19	3.1 (0.12, 82.64)		
		Adverse events: At least one	16/19	15/19	1.3 (0.28, 6.50)		
		Adverse events: Confusion	1/19	0/19	3.1 (0.12, 82.64)		
		Adverse events: Dizziness	11/19	4/19	4.6 (1.17, 18.41)		
		Adverse events: Drowsiness	11/19	9/19	1.4 (0.42, 5.20)		
		Adverse events: Dry mouth	10/19	8/19	1.4 (0.42, 5.20)		
		Adverse events: Euphoria	2/19	0/19	5.5 (0.24, 124.20)		
		Adverse events: Nausea	1/19	0/19	3.1 (0.12, 82.64)		
	Intervention: Nabilone (Cesamet) **Comparator:** Domperidone **Follow-up:** 1 cycle **Analysis**: ITT	**Adverse events**: Withdrawal due to AEs	1/19	0/19	3.1 (0.12, 82.64)		
Pooyania(2010)[128]	**Intervention:** Nabilone (Cesamet)	**Adverse events**: Serious AE	0/11	0/11	1.0 (0.01, 54.83)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
Study design: Cross-over RCT	**Comparator:** Placebo **Follow-up:** 4 weeks **Analysis**: modified ITT (results for all treated patients reported)	**Adverse events**: Withdrawal due to AEs	0/11	0/11	1.0 (0.01, 54.83)		
Portenoy(2012)[86] **Study design:** Parallel group RCT	**Intervention:** Nabiximols (Sativex) (1-4 sprays) **Comparator:** Placebo **Follow-up:** 7 weeks **Analysis**: ITT	**Adverse events**: Asthenia	6/91	6/91	1.0 (0.32, 3.08)		
		Adverse events: At least one	70 (319)/91	71 (238)/91	0.9 (0.47, 1.87)		
		Adverse events: Blood disorders	4/91	2/91	1.8 (0.38, 8.88)		
		Adverse events: Cardiac disorders	0/91	1/91	0.3 (0.01, 8.20)		
		Adverse events: Death	25/91	16/91	1.7 (0.86, 3.53)		
		Adverse events: Diarrhoea	5/91	4/91	1.2 (0.34, 4.45)		
		Adverse events: Disorientation	5/91	1/91	3.8 (0.61, 23.89)		
		Adverse events: Dizziness	10/91	12/91	0.8 (0.34, 1.96)		
		Adverse events: Dry mouth	7/91	7/91	1.0 (0.34, 2.87)		
		Adverse events: Fatigue	4/91	4/91	1.0 (0.26, 3.81)		
		Adverse events: Gastrointestinal disorders	1/91	2/91	0.5 (0.07, 4.58)		
		Adverse events: General disorders and administration site conditions	4/91	2/91	1.8 (0.38, 8.88)		
		Adverse events: Hallucinations	1/91	5/91	0.2 (0.04, 1.62)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Adverse events: Hepatobiliary disorders	0/91	0/91	1.0 (0.01, 50.94)		
		Adverse events: Infections and infestations	4/91	2/91	1.8 (0.38, 8.88)		
		Adverse events: Injury, poisoning & procedural complications	1/91	1/91	1.0 (0.10, 9.79)		
		Adverse events: Investigations	0/91	0/91	1.0 (0.01, 50.94)		
		Adverse events: Metabolism & Nutrition disorders (Metabolism)	1/91	1/91	1.0 (0.10, 9.79)		
		Adverse events: Musculoskeletal and connective tissues disorders	0/91	1/91	0.3 (0.01, 8.20)		
		Adverse events: Nausea	16/91	12/91	1.3 (0.62, 3.09)		
		Adverse events: Neoplasms, benign, malignant & unspecified	26/91	15/91	1.9 (0.98, 4.05)		
		Adverse events: Nervous system disorders	1/91	0/91	3.0 (0.12, 75.44)		
		Adverse events: Psychiatric disorders	1/91	0/91	3.0 (0.12, 75.44)		
		Adverse events: Renal & urinary disorders	0/91	1/91	0.3 (0.01, 8.20)		
		Adverse events: Respiratory, thoracic, and mediastinal disorders	1/91	1/91	1.0 (0.10, 9.79)		
		Adverse events: Serious AE	34/91	22/91	1.9 (1.03, 3.66)		
		Adverse events: Somnoloence	8/91	4/91	1.9 (0.60, 6.45)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Adverse events: Treatment-related AE	(270)/91	(215)/91			
		Adverse events: Vomiting	9/91	7/91	1.2 (0.47, 3.54)		
		Adverse events: Weight (Decreased)	5/91	2/91	2.2 (0.49, 10.44)		
		Adverse events: Withdrawal due to AEs	13/91	16/91	0.7 (0.35, 1.72)		
		Pain: NRS (≥30% reduction in pain)	30/91	24/91	1.3 (0.72, 2.58)	OR: 1.37 p-value=0.33	Logistic regression with region and treatment groups as factors
		Pain: Composite outcome: change in NRS and change in opioid consumption; positive response improvement in one and other stable or improved	/91	/91		OR: 1.87 p-value=0.038	
	Intervention: Nabiximols (Sativex) (6-10 sprays) **Comparator:** Placebo **Follow-up:** 7 weeks **Analysis**: ITT	**Adverse events**: Asthenia	7/87	6/91	1.2 (0.41, 3.65)		
		Adverse events: At least one	74 (352)/87	71 (238)/91	1.5 (0.74, 3.38)		
		Adverse events: Blood disorders	0/87	2/91	0.2 (0.00, 4.32)		
		Adverse events: Cardiac disorders	0/87	1/91	0.3 (0.01, 8.57)		
		Adverse events: Death	14/87	16/91	0.9 (0.41, 1.95)		
		Adverse events: Diarrhoea	4/87	4/91	1.0 (0.27, 4.00)		
		Adverse events: Disorientation	5/87	1/91	4.0 (0.64, 25.07)		
		Adverse events: Dizziness	21/87	12/91	2.0 (0.95, 4.43)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Adverse events: Dry mouth	8/87	7/91	1.2 (0.43, 3.36)		
		Adverse events: Fatigue	4/87	4/91	1.0 (0.27, 4.00)		
		Adverse events: Gastrointestinal disorders	3/87	2/91	1.4 (0.28, 7.72)		
		Adverse events: General disorders and administration site conditions	1/87	2/91	0.6 (0.08, 4.80)		
		Adverse events: Hallucinations	1/87	5/91	0.2 (0.04, 1.69)		
		Adverse events: Hepatobiliary disorders	1/87	0/91	3.1 (0.12, 78.96)		
		Adverse events: Infections and infestations	5/87	2/91	2.3 (0.51, 10.96)		
		Adverse events: Injury, poisoning & procedural complications	1/87	1/91	1.0 (0.10, 10.25)		
		Adverse events: Investigations	0/87	0/91	1.0 (0.02, 53.28)		
		Adverse events: Metabolism & Nutrition disorders (Metabolism)	1/87	1/91	1.0 (0.10, 10.25)		
		Adverse events: Musculoskeletal and connective tissues disorders	0/87	1/91	0.3 (0.01, 8.57)		
		Adverse events: Nausea	18/87	12/91	1.6 (0.77, 3.71)		
		Adverse events: Neoplasms, benign, malignant & unspecified	12/87	15/91	0.8 (0.36, 1.83)		
		Adverse events: Nervous system disorders	1/87	0/91	3.1 (0.12, 78.96)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Adverse events: Psychiatric disorders	1/87	0/91	3.1 (0.12, 78.96)		
		Adverse events: Renal & urinary disorders	0/87	1/91	0.3 (0.01, 8.57)		
		Adverse events: Respiratory, thoracic, and mediastinal disorders	2/87	1/91	1.7 (0.22, 13.64)		
		Adverse events: Serious AE	18/87	22/91	0.8 (0.40, 1.65)		
		Adverse events: Somnoloence	16/87	4/91	4.4 (1.51, 13.32)		
		Adverse events: Treatment-related AE	(311)/91	(215)/91			
		Adverse events: Vomiting	14/87	7/91	2.2 (0.87, 5.66)		
		Adverse events: Weight (Decreased)	1/87	2/91	0.6 (0.08, 4.80)		
		Adverse events: Withdrawal due to AEs	15/87	16/91	0.9 (0.45, 2.10)		
		Pain: NRS (≥30% reduction in pain)	26/87	24/91	1.1 (0.62, 2.27)	OR: 1.19 p-value=0.61	Logistic regression with region and treatment groups as factors
		Pain: Composite outcome: change in NRS and change in opioid consumption; positive response improvement in one and other stable or improved	/87	/91		OR: 1.70 p-value=0.079	
	Intervention: Nabiximols (Sativex)(11-16 sprays) **Comparator:** Placebo **Follow-up:** 7 weeks **Analysis**: ITT	**Adverse events**: Asthenia	5/90	6/91	0.8 (0.26, 2.73)		
		Adverse events: At least one	83 (399)/90	71 (238)/91	3.1 (1.30, 7.80)		
		Adverse events: Blood disorders	0/90	2/91	0.1 (0.00, 4.17)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Adverse events: Cardiac disorders	0/90	1/91	0.3 (0.01, 8.29)		
		Adverse events: Death	17/90	16/91	1.0 (0.51, 2.29)		
		Adverse events: Diarrhoea	8/90	4/91	2.0 (0.61, 6.52)		
		Adverse events: Disorientation	8/90	1/91	6.2 (1.06, 36.17)		
		Adverse events: Dizziness	20/90	12/91	1.8 (0.85, 4.00)		
		Adverse events: Dry mouth	7/90	7/91	1.0 (0.35, 2.91)		
		Adverse events: Fatigue	5/90	4/91	1.2 (0.34, 4.50)		
		Adverse events: Gastrointestinal disorders	4/90	2/91	1.8 (0.38, 8.98)		
		Adverse events: General disorders and administration site conditions	4/90	2/91	1.8 (0.38, 8.98)		
		Adverse events: Hallucinations	6/90	5/91	1.2 (0.37, 3.91)		
		Adverse events: Hepatobiliary disorders	1/90	0/91	3.0 (0.12, 76.29)		
		Adverse events: Infections and infestations	2/90	2/91	1.0 (0.17, 5.98)		
		Adverse events: Injury, poisoning & procedural complications	0/90	1/91	0.3 (0.01, 8.29)		
		Adverse events: Investigations	1/90	0/91	3.0 (0.12, 76.29)		
		Adverse events: Metabolism & Nutrition disorders (Metabolism)	3/90	1/91	2.4 (0.34, 16.71)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Adverse events: Musculoskeletal and connective tissues disorders	0/90	1/91	0.3 (0.01, 8.29)		
		Adverse events: Nausea	25/90	12/91	2.4 (1.16, 5.25)		
		Adverse events: Neoplasms, benign, malignant & unspecified	13/90	15/91	0.8 (0.38, 1.90)		
		Adverse events: Nervous system disorders	3/90	0/91	7.3 (0.37, 143.78)		
		Adverse events: Psychiatric disorders	2/90	0/91	5.1 (0.24, 109.20)		
		Adverse events: Renal & urinary disorders	4/90	1/91	3.1 (0.48, 20.39)		
		Adverse events: Respiratory, thoracic, and mediastinal disorders	1/90	1/91	1.0 (0.10, 9.90)		
		Adverse events: Serious AE	27/90	22/91	1.4 (0.74, 2.70)		
		Adverse events: Somnoloence	15/90	4/91	3.9 (1.33, 11.91)		
		Adverse events: Treatment-related AE	(334)/90	(215)/91			
		Adverse events: Vomiting	19/90	7/91	3.0 (1.25, 7.55)		
		Adverse events: Weight (Decreased)	2/90	2/91	1.0 (0.17, 5.98)		
		Adverse events: Withdrawal due to AEs	25/90	16/91	1.7 (0.88, 3.59)		
		Pain: NRS (≥30% reduction in pain)	22/90	24/91	0.90(0.47, 1.76)	OR: 0.90 p-value=0.76	Logistic regression with

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Pain: Composite outcome: change in NRS and change in opioid consumption; positive response improvement in one and other stable or improved	/90	/91		OR: 1.16 p-value=0.622	region and treatment groups as factors
Prasad(2011)[72] **Study design:** Parallel group RCT	**Intervention:** Dronabinol (Marinol) **Comparator:** Placebo **Follow-up:** 3 weeks	**Adverse events**: Serious AE	0/4	0/8	1.8 (0.03, 112.07)		
Rog(2005)[144] **Study design:** Parallel group RCT	**Intervention:** Nabiximols (Sativex) **Comparator:** Placebo **Follow-up:** 5 weeks **Analysis**: ITT; All randomised patients	**Adverse events**: At least one (At least one)	30/34	22/32	3.1 (0.92, 10.83)		
		Adverse events: Diarrhoea	2/34	0/32	5.0 (0.23, 108.26)		
		Adverse events: Dizziness	18/34	5/32	5.6 (1.80, 17.36)		
		Adverse events: Dry mouth	4/34	0/32	9.5 (0.49, 185.67)		
		Adverse events: Dyspnea	0/34	1/32	0.3 (0.01, 7.74)		
		Adverse events: Euphoria	2/34	0/32	5.0 (0.23, 108.26)		
		Adverse events: Fatigue	2/34	2/32	0.9 (0.15, 5.80)		
		Adverse events: Nausea	3/34	2/32	1.3 (0.24, 7.40)		
		Adverse events: Serious AE	0/34	0/32	0.9 (0.01, 48.88)		
		Adverse events: Somnoloence	3/34	0/32	7.2 (0.35, 145.56)		
		Adverse events: Vomiting	1/34	0/32	2.9 (0.11, 74.08)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Adverse events: Weakness	3/34	0/32	7.2 (0.35, 145.56)		
Selvarajah(2010)[136] **Study design:** Parallel group RCT	**Intervention:** Nabiximols (Sativex) **Comparator:** Placebo **Follow-up:** 12 weeks **Analysis**: modified ITT; 29/30 randomised patients - 1 placebo patient excluded due to protocol violations	**Pain**: Neuropathic pain scale (≥30% VAS score improvement)	8/15	9/14	0.6 (0.15, 2.76)	OR: 0.63 (0.14, 2.82) p-value=0.55	**Analysis Method** Logistic regression
Serpell(2014)[81] **Study design:** Parallel group RCT	**Intervention:** Nabiximols (Sativex) **Comparator:** Placebo **Follow-up:** 15 weeks **Analysis**: ITT	**Adverse events**: Anxiety	4/128	1/118	2.8 (0.44, 18.28)		
		Adverse events: At least one	109/128	83/118	2.3 (1.28, 4.4)		
		Adverse events: Balance	4/128	2/118	1.6 (0.35, 8.07)		
		Adverse events: Blood and lymphatic sytem disorders	2/128	0/118	4.6 (0.22, 98.58)		
		Adverse events: Cardiac disorders	2/128	2/118	0.9 (0.16, 5.41)		
		Adverse events: Depression	6/128	0/118	12.5 (0.70, 225.72)		
		Adverse events: Diarrhoea	12/128	6/118	1.8 (0.70, 4.96)		
		Adverse events: Disorientation	8/128	0/118	16.7 (0.95, 292.93)		
		Adverse events: Dizziness	52/128	12/118	5.8 (2.95, 11.58)		
		Adverse events: Dry mouth	11/128	4/118	2.4 (0.81, 7.63)		
		Adverse events: Dyspnea	4/128	3/118	1.1 (0.29, 4.93)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Adverse events: Ear and labyrinth disorders	6/128	1/118	4.1 (0.69, 24.98)		
		Adverse events: Fatigue	20/128	8/118	2.4 (1.06, 5.70)		
		Adverse events: Gastrointestinal disorders	60/128	43/118	1.5 (0.92, 2.55)		
		Adverse events: General disorders and administration site conditions	45/128	30/118	1.5 (0.91, 2.73)		
		Adverse events: Infections and infestations	35/128	26/118	1.3 (0.74, 2.37)		
		Adverse events: Injury, poisoning & procedural complications	9/128	6/118	1.3 (0.49, 3.86)		
		Adverse events: Investigations	3/128	2/118	1.2 (0.25, 6.72)		
		Adverse events: Metabolism & Nutrition disorders	15/128	6/118	2.3 (0.91, 6.13)		
		Adverse events: Musculoskeletal and connective tissues disorders	11/128	8/118	1.2 (0.51, 3.20)		
		Adverse events: Nausea	23/128	14/118	1.6 (0.79, 3.26)		
		Adverse events: Neoplasms, benign, malignant & unspecified	3/128	1/118	2.1 (0.32, 15.04)		
		Adverse events: Nervous system disorders	79/128	34/118	3.9 (2.31, 6.69)		
		Adverse events: Psychiatric disorders	36/128	11/118	3.6 (1.80, 7.57)		
		Adverse events: Renal & urinary disorders	3/128	2/118	1.2 (0.25, 6.72)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Adverse events: Reproductive system and breast disorders	2/128	1/118	1.5 (0.20, 11.90)		
		Adverse events: Respiratory, thoracic, and mediastinal disorders	15/128	16/118	0.8 (0.40, 1.78)		
		Adverse events: Serious AE	10/128	6/118	1.50 (0.56, 4.22)		
		Adverse events: Skin and subcutaneuous tissue disorders	9/128	9/118	0.90 (0.36, 2.34)		
		Adverse events: Somnoloence	5/128	2/118	2.0 (0.46, 9.45)		
		Adverse events: Vomiting	13/128	7/118	1.7 (0.69, 4.40)		
		Adverse events: Withdrawal due to AEs	25/128	8/118	3.2 (1.41, 7.28)		
	Intervention: Nabiximols (Sativex) **Comparator:** Placebo **Follow-up:** 15 weeks **Analysis**: modified ITT; 240/246 patients for whom on treatment efficacy data were available	**Pain**: NRS (0-10 NRS; ≥50% improvement)	/123	/117		OR: 1.70 (0.65, 4.48) p-value=0.280	
		Pain: NRS (0-10 NRS; ≥30% improvement)	34/123	19/117	1.9 (1.04, 3.63)	OR: 1.97 (1.05, 3.7) p-value=0.034	
Sheidler(1984)[113] **Study design:** Cross-over RCT	**Intervention:** Levonantradol **Comparator:** Prochlorperazine **Follow-up:** 12hrs **Analysis**: ITT	**Adverse events:** Anxiety	2/16	1/16	1.7 (0.21, 15.25)		
		Adverse events: Disorientation	1/16	0/16	3.1 (0.12, 84.43)		
		Adverse events: Dizziness	5/16	2/16	2.7 (0.51, 14.93)		
		Adverse events: Dry mouth	5/16	4/16	1.3 (0.30, 5.84)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Adverse events: Euphoria	0/16	1/16	0.3 (0.01, 8.27)		
		Adverse events: Injection site pain	3/16	0/16	8.5 (0.40, 180.52)		
		Adverse events: Mental status change (Altered perception)	2/16	0/16	5.6 (0.25, 128.50)		
		Adverse events: Somnoloence	9/16	7/16	1.6 (0.41, 6.21)		
Skrabek(2008)[140] **Study design:** Parallel group RCT	**Intervention:** Nabilone (Cesamet) **Comparator:** Placebo **Follow-up:** 4 weeks **Analysis**: Per protocol	**Adverse events**: Confusion	2/15	1/18	2.1 (0.25, 18.45)		
		Adverse events: Depression	0/15	1/18	0.3 (0.01, 9.93)		
		Adverse events: Drowsiness	7/15	1/18	10.2 (1.48, 71.28)		
		Adverse events: Dry mouth	5/15	1/18	6.1 (0.86, 43.42)		
		Adverse events: Euphoria	1/15	1/18	1.2 (0.11, 12.88)		
		Adverse events: Hallucinations	0/15	0/18	1.1 (0.02, 63.72)		
		Adverse events: Serious AE	0/20	0/20	1.0 (0.01, 52.85)		
Steele (1980)[110] **Study design:** Cross-over RCT	**Intervention:** Nabilone (Cesamet) **Comparator:** Prochlorperazine **Follow-up:** 1 chemotherapy cycle **Analysis**: modified ITT; Patients who received the drug included in the analysis (43 and 53	**Adverse events**: Dizziness	19/53	4/43	4.9 (1.61, 15.23)		
		Adverse events: Dry mouth	13/53	2/43	5.5 (1.34, 22.82)		
		Adverse events: Hallucinations	2/53	0/43	4.2 (0.19, 90.35)		
		Adverse events: Nausea	3/53	0/43	6.0 (0.30, 120.00)		
		Adverse events: Somnoloence	25/53	15/43	1.6 (0.72, 3.72)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
	out of 55 patients)	**Adverse events**: Withdrawal due to AEs	4/53	0/43	7.9 (0.41, 151.12)		
Svendsen(2004)[146] **Study design:** Cross-over RCT	**Intervention:** Dronabinol (Marinol) **Comparator:** Placebo **Follow-up:** 3 weeks **Analysis**: ITT	**Adverse events**: At least one	23/24	11/24	18.3 (2.95, 114.46)	p-value=0.001	**Analysis Method** Mainland-Gart test
		Adverse events: Balance (Balance difficulty)	2 (2)/24	0 (0)/24	5.4 (0.24, 119.63)	p-value>0.05	
		Adverse events: Cardiac disorders	4 (8)/24	2 (4)/24	1.9 (0.37, 10.36)	p-value>0.05	
		Adverse events: Dizziness (Dizziness or lightheadedness)	14 (26)/24	4 (5)/24	6.2 (1.72, 22.92)	p-value<0.05	
		Adverse events: Drowsiness (Tiredness/drowsiness)	10 (12)/24	6 (10)/24	2.0 (0.62, 6.81)	p-value>0.05	
		Adverse events: Dry mouth	3 (3)/24	0 (0)/24	7.9 (0.38, 163.34)	p-value>0.05	
		Adverse events: Euphoria	3 (3)/24	0 (0)/24	7.9 (0.38, 163.34)	p-value>0.05	
		Adverse events: Fatigue	1 (2)/24	0 (0)/24	3.1 (0.12, 80.69)	p-value>0.05	
		Adverse events: Gastrointestinal disorders	5 (7)/24	4 (8)/24	1.2 (0.31, 5.16)	p-value>0.05	
		Adverse events: Musculoskeletal and connective tissues disorders (Musculoskeletal system)	9 (13)/24	2 (2)/24	5.5 (1.18, 25.63)	p-value>0.05	
		Adverse events: Nausea	3 (4)/24	4 (5)/24	0.7 (0.16, 3.39)	p-value>0.05	
		Adverse events: Nervous system disorders (Central nervous system)	19 (61)/24	8 (20)/24	6.8 (1.95, 24.19)	p-value>0.05	
		Adverse events: Psychiatric disorders	3 (4)/24	1 (1)/24	2.5 (0.34, 18.84)	p-value>0.05	

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Adverse events: Serious AE	3 (3)/24	1 (1)/24	2.5 (0.34, 18.84)	p-value>0.05	
		Medication frequency: Treatment rescue (Number of paracetamol)	0/24	0/24	1.0 (0.01, 52.44)		
		Pain: NRS (50% pain relief)	11/24	4/24	3.8 (1.07, 14.07)		
Timpone (1997)[88] **Study design:** Parallel group	**Intervention:** Dronabinol (Marinol) **Comparator:** megestrol acetate **Follow-up:** 12 weeks **Analysis**: modified ITT (Results for 34 out of 37 participants reported)	**Adverse events**: Asthenia (Grade 3 or 4)	2/11	1/10	1.6 (0.18, 15.26)		
		Adverse events: At least one (all body systems combined, grade 3 or 4)	7/11	8/10	0.4 (0.07, 3.06)		
		Adverse events: Death	0/11	1/10	0.2 (0.01, 7.57)		
		Adverse events: Diarrhoea (Grade 3 or 4)	0/11	0/10	0.9 (0.01, 50.26)		
		Adverse events: Dyspnea (Grade 3 or 4)	0/11	0/10	0.9 (0.01, 50.26)		
		Adverse events: Hallucinations (Grade 3 or 4)	1/11	0/10	3.0 (0.10, 82.40)		
		Adverse events: Mental status change (Grade 3 or 4)	1/11	1/10	0.9 (0.07, 10.25)		
		Adverse events: Nausea (Grade 3 or 4)	0/11	1/10	0.2 (0.01, 7.57)		
		Adverse events: Nervous system disorders (Grade 3 or 4)	2/11	2/10	0.8 (0.12, 6.49)		
		Adverse events: Psychosis (Grade 3 or 4)	0/11	1/10	0.2 (0.01, 7.57)		
		Adverse events: Seizures (Grade 3 or 4)	0/11	0/10	1.1 (0.02, 63.97)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Adverse events: Vomiting (Grade 3 or 4)	0/11	0/10	0.9 (0.01, 50.26)		
Tomida(2006)[224] **Study design:** Cross-over RCT	**Intervention:** Cannabidiol (CBD) (20 mg) **Comparator:** Placebo **Follow-up:** 12 hours **Analysis**: ITT	**Adverse events**: At least one	2/6	2/6	1.0 (0.11, 8.90)		
		Adverse events: Dizziness	1/6	0/6	3.5 (0.11, 105.82)		
		Adverse events: Nausea	0/6	0/6	1.0 (0.01, 58.43)		
	Intervention: Cannabidiol (CBD) (40 mg) **Comparator:** Placebo **Follow-up:** 12 hours **Analysis**: ITT	**Adverse events**: At least one	5/6	2/6	6.6 (0.61, 71.09)		
		Adverse events: Dizziness	0/6	0/6	1.0 (0.01, 58.43)		
		Adverse events: Nausea	0/6	0/6	1.0 (0.01, 58.43)		
	Intervention: THC **Comparator:** Placebo **Follow-up:** 12 hours **Analysis**: ITT	**Adverse events**: At least one	3/6	2/6	1.8 (0.21, 15.32)		
		Adverse events: Dizziness	1/6	0/6	3.5 (0.11, 105.82)		
		Adverse events: Nausea	1/6	0/6	3.5 (0.11, 105.82)		
Ungerleider(1982)[91] **Study design:** Cross-over RCT	**Intervention:** THC **Comparator:** Prochlorperazine **Follow-up:** 1 chemotherapy cycle **Analysis**: Per-protocol	**Adverse events**: At least one	136/172	99/181	3.1 (1.94, 4.94)	p-value<0.01	**Analysis Method:** Chi-square test
		Adverse events: Drowsiness (“sedation”)	78/172	56/181	1.84 (1.20, 2.85)	p<0.01	
		Adverse events: Euphoria (high)	13/172	6/181	2.2 (0.87, 5.96)		
		Adverse events: Psychiatric disorders (Psychological AE)	59/172	10/181	8.5 (4.26, 17.20)	p-value<0.01	
Vaney(2004)[192] **Study design:** Cross-over RCT	**Intervention:** THC/CBD **Comparator:** Placebo **Follow-up:** 9 days **Analysis**: ITT	**Adverse events**: Dizziness	(11)/22	(10)/28			
		Adverse events: Dry mouth	(2)/22	(0)/28			

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Adverse events: Euphoria ("Euphoria, 'high'")	(10)/22	(8)/28			
		Adverse events: Nausea	(4)/22	(1)/28			
		Adverse events: Serious AE	0/22	0/28	1.2 (0.02, 66.36)		
		Adverse events: Somnoloence ("Sleepiness")	(1)/22	(0)/28			
Wada(1982)[105] **Study design:** Cross-over RCT	**Intervention:** Nabilone (Cesamet) **Comparator:** Placebo **Follow-up:** 1 chemotherapy cycle **Analysis**: ITT	**Adverse events**: Withdrawal due to AEs	8/114	0/114	18.3 (1.04, 320.55)		
	Intervention: Nabilone (Cesamet) **Comparator:** Placebo **Follow-up:** 1 chemotherapy cycle **Analysis**: Per-protocol	**Nausea & vomiting**: Complete response (Complete relief of nausea and vomiting)	32/92	10/92	4.2 (1.95, 9.12)		
Wade(2004)[3] **Study design:** Parallel group RCT	**Intervention:** Nabiximols (Sativex) **Comparator:** Placebo **Follow-up:** 6 weeks **Analysis**: ITT	**Adverse events**: At least one	67/80	57/80	2.0 (0.95, 4.35)		
		Adverse events: Diarrhoea	6/80	2/80	2.7 (0.61, 12.18)		
		Adverse events: Euphoria	3/80	0/80	7.2 (0.36, 143.09)		
		Adverse events: Disorientation	6/80	0/80	14.0 (0.77, 253.68)		
		Adverse events: Dizziness	26/80	10/80	3.2 (1.47, 7.24)		
		Adverse events: Dry mouth	3/80	0/80	7.2 (0.36, 143.09)		
		Adverse events: Fatigue	12/80	3/80	4.0 (1.18, 13.81)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Adverse events: Nausea	7/80	5/80	1.4 (0.44, 4.40)		
		Adverse events: Serious AE	1/80	1/80	1.0 (0.10, 9.82)		
		Adverse events: Somnoloence	7/80	1/80	5.4 (0.91, 32.11)		
		Adverse events: Withdrawal due to AEs	3/80	1/80	2.3 (0.34, 16.62)		
		Global impression: Patient global impression (better and much better at end of treatment)	32/79	21/77	1.7 (0.92, 3.50)	OR: 1.36 (0.77, 2.43) p-value=0.293	**Analysis Method** Fisher's exact test
Ware(2010)[133] **Study design:** Cross-over RCT	**Intervention:** Nabilone (Cesamet) **Comparator:** Amitriptyline **Follow-up:** 2 weeks **Analysis**: ITT	**Adverse events**: Diarrhoea	(2)/32	(2)/32			
		Adverse events: Disorientation	(2)/32	(0)/32			
		Adverse events: Dizziness	(10)/32	(4)/32			
		Adverse events: Drowsiness	(6)/32	(1)/32			
		Adverse events: Dry mouth	(7)/32	(3)/32			
		Adverse events: Fatigue	(2)/32	(1)/32			
		Adverse events: Nausea	(9)/32	(1)/32			
		Adverse events: Vomiting	(3)/32	(0)/32			
Ware(2010)[135] **Study design:** Cross-over RCT	**Intervention:** THC (2.5%) **Comparator:** Placebo **Follow-up:** 5 days	**Adverse events**: Anxiety ("Anxiety")	(0)/22	(0)/21			
		Adverse events: Asthenia	(3)/22	(1)/21			

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
	Analysis: Per protocol	**Adverse events**: At least one	(61)/22	(46)/21			
		Adverse events: Dizziness	(3)/22	(2)/21			
		Adverse events: Drowsiness	(2)/22	(1)/21			
		Adverse events: Dry mouth	(0)/22	(0)/21			
		Adverse events: Euphoria	(1)/22	(0)/21			
		Adverse events: Fatigue	(3)/22	(2)/21			
		Adverse events: Gastrointestinal disorders	(5)/22	(2)/21			
		Adverse events: General disorders and administration site conditions	(13)/22	(12)/21			
		Adverse events: Infections and infestations	(1)/22	(0)/21			
		Adverse events: Musculoskeletal and connective tissues disorders	(1)/22	(4)/21			
		Adverse events: Nausea	(2)/22	(1)/21			
		Adverse events: Nervous system disorders	(18)/22	(14)/21			
		Adverse events: Paranoia	(0)/22	(0)/21			
		Adverse events: Psychiatric disorders	(5)/22	(1)/21			
		Adverse events: Renal & urinary disorders	(1)/22	(0)/21			

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Adverse events: Respiratory, thoracic, and mediastinal disorders	(5)/22	(5)/21			
		Adverse events: Serious AE	0 (0)/22	0 (0)/21	0.9 (0.01, 50.34)		
		Adverse events: Skin and subcutaneuous tissue disorders	(0)/22	(0)/21			
		Adverse events: Somnoloence ("Tiredness")	(1)/22	(1)/21			
		Adverse events: Vomiting	(1)/22	(0)/21			
	Intervention: THC (6%) **Comparator:** Placebo **Follow-up:** 5 days **Analysis**: Per protocol	**Adverse events**: Anxiety ("Anxiety")	(1)/21	(0)/21			
		Adverse events: Asthenia	(0)/21	(1)/21			
		Adverse events: At least one	(65)/21	(46)/21			
		Adverse events: Dizziness	(4)/21	(2)/21			
		Adverse events: Drowsiness	(2)/21	(1)/21			
		Adverse events: Dry mouth	(0)/21	(0)/21			
		Adverse events: Euphoria	(0)/21	(0)/21			
		Adverse events: Fatigue	(3)/21	(2)/21			
		Adverse events: Gastrointestinal disorders	(6)/21	(2)/21			
		Adverse events: General disorders and administration site conditions	(14)/21	(12)/21			

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Adverse events: Infections and infestations	(0)/21	(0)/21			
		Adverse events: Musculoskeletal and connective tissues disorders	(2)/21	(4)/21			
		Adverse events: Nausea	(2)/21	(1)/21			
		Adverse events: Nervous system disorders	(18)/21	(14)/21			
		Adverse events: Paranoia	(0)/22	(0)/21			
		Adverse events: Psychiatric disorders	(5)/21	(1)/21			
		Adverse events: Renal & urinary disorders	(0)/21	(0)/21			
		Adverse events: Respiratory, thoracic, and mediastinal disorders	(7)/21	(5)/21			
		Adverse events: Serious AE	0 (0)/21	0 (0)/21	1.0 (0.01, 52.73)		
		Adverse events: Skin and subcutaneuous tissue disorders	(0)/21	(0)/21			
		Adverse events: Somnoloence ("Tiredness")	(1)/21	(1)/21			
		Adverse events: Vomiting	(0)/21	(0)/21			
	Intervention: THC (9.4%) **Comparator:** Placebo **Follow-up:** 5 days **Analysis**: Per protocol	**Adverse events**: Anxiety ("Anxiety")	(0)/22	(0)/21			
		Adverse events: Asthenia	(2)/22	(1)/21			
		Adverse events: At least one	(82)/22	(46)/21			

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Adverse events: Dizziness	(4)/22	(2)/21			
		Adverse events: Drowsiness	(0)/22	(1)/21			
		Adverse events: Dry mouth	(1)/22	(0)/21			
		Adverse events: Euphoria	(1)/22	(0)/21			
		Adverse events: Fatigue	(2)/22	(2)/21			
		Adverse events: Gastrointestinal disorders	(4)/22	(2)/21			
		Adverse events: General disorders and administration site conditions	(13)/22	(12)/21			
		Adverse events: Infections and infestations	(0)/22	(0)/21			
		Adverse events: Musculoskeletal and connective tissues disorders	(2)/22	(4)/21			
		Adverse events: Nausea	(1)/22	(1)/21			
		Adverse events: Nervous system disorders	(18)/22	(14)/21			
		Adverse events: Paranoia	(1)/22	(0)/21			
		Adverse events: Psychiatric disorders	(12)/22	(1)/21			
		Adverse events: Renal & urinary disorders	(0)/22	(0)/21			
		Adverse events: Respiratory, thoracic, and mediastinal disorders	(7)/22	(5)/21			

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Adverse events: Serious AE	0 (0)/22	0 (0)/21	0.9 (0.01, 50.34)		
		Adverse events: Skin and subcutaneuous tissue disorders	(1)/22	(0)/21			
		Adverse events: Somnoloence ("Tiredness")	(0)/22	(1)/21			
		Adverse events: Vomiting	(0)/22	(0)/21			
Wilsey (2013)[134] **Study design:** Cross-over RCT	**Intervention:** Cannabis (not specified)(1.29%) **Comparator:** Placebo **Follow-up:** 5 hours **Analysis**: Per-protocol	**Adverse events**: Serious AE	0/37	0/38	1.0 (0.01, 53.09)		
		Pain: VAS score (VAS score; ≥30% reduction in pain)	21/37	10/38	3.5 (1.36, 9.19)		
	Intervention: Cannabis (not specified) (3.53%) **Comparator:** Placebo **Follow-up:** 5 hours **Analysis**: Per-protocol	**Adverse events**: Serious AE	0/36	0/38	1.0 (0.02, 54.56)		
		Pain: VAS score (VAS score; ≥30% reduction in pain)	22/36	10/38	4.2 (1.60, 11.08)	p-value=0.0023	**Analysis Method** Chi-squared
Wilsey(2011)[138] **Study design:** Cross-over RCT	**Intervention:** THC 3.5% **Comparator:** Placebo **Follow-up:** 4 hours **Analysis**: Per protocol	**Adverse events**: Cardiac disorders	0/34	0/33	0.9 (0.02, 50.37)		
		Adverse events: Withdrawal due to AEs	0/38	0/38	1.0 (0.02, 51.70)		
		Pain: VAS score (VAS score; ≥30% reduction in pain)	4/36	2/33	1.7 (0.34. 8.83)		
	Intervention: THC 7% **Comparator:** Placebo **Follow-up:** 4 hours **Analysis**: Per protocol	**Adverse events**: Cardiac disorders	0/36	0/33	0.9 (0.02, 47.57)		
		Adverse events: Withdrawal due to AEs	0/38	0/38	1.0 (0.02, 51.70)		
		Pain: VAS score (VAS score; ≥30% reduction in pain)	0/34	2/33	0.1 (0.01, 3.95)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
Zajicek(2003)[89] **Study design:** Parallel group RCT	**Intervention:** THC/CBD **Comparator:** Placebo **Follow-up:** 15 weeks **Analysis**: ITT	**Adverse events**: Death	0 (0)/211	0 (0)/213	1.0 (0.01, 51.11)		
		Adverse events: Depression and anxiety	20 (29)/211	18 (20)/213	1.1 (0.59, 2.19)		
		Adverse events: Dry mouth	42 (47)/211	14 (15)/213	3.4 (1.83, 6.47)		
		Adverse events: Gastrointestinal disorders ("Gastrointestinal tract")	79 (132)/211	42 (65)/213	2.4 (1.56, 3.74)		
		Adverse events: Infections and infestations ("Infections")	34 (40)/211	36 (40)/213	0.9 (0.56, 1.57)		
		Adverse events: Serious AE	(12)/211	(20)/211			
		Relapse: Other (MS relapse or possible relapse)	1 (1)/211	7 (8)/213	0.1 (0.03, 1.14)		
		Spasticity: (Patient assessment of whether there was a treatment benefit)	121/197	91/198	1.8 (1.25, 2.78)		
	Intervention: Dronabinol (Marinol) **Comparator:** Placebo **Follow-up:** 15 weeks **Analysis**: ITT	**Adverse events**: Death	1 (1)/206	0 (0)/213	3.1 (0.12, 76.95)		
		Adverse events: Depression and anxiety	20 (22)/206	18 (20)/213	1.2 (0.60, 2.25)		
		Adverse events: Dry mouth	54 (60)/206	14 (15)/213	4.9 (2.65, 9.10)		
		Adverse events: Gastrointestinal disorders ("Gastrointestinal tract")	62 (96)/206	42 (65)/213	1.7 (1.11, 2.73)		
		Adverse events: Infections and infestations ("Infections")	30 (37)/206	36 (40)/213	0.8 (0.49, 1.41)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		Adverse events: Serious AE	(18)/211	(20)/211			
		Relapse: Other (MS relapse or possible relapse)	1 (1)/206	7 (8)/213	0.2 (0.03, 1.17)		
		Spasticity: (Patient assessment of whether there was a treatment benefit)	108/181	91/198	1.7 (1.15, 2.60)		
Zajicek(2012)[87] **Study design:** Parallel group RCT	**Intervention:** THC/CBD **Comparator:** Placebo **Follow-up:** 12 weeks **Analysis**: modified ITT (all patients treated)	**Adverse events**: Asthenia	25/143	11/134	2.3 (1.10, 4.84)		
		Adverse events: At least one	133 (628)/143	100 (289)/134	4.3 (2.08, 9.12)		
		Adverse events: Death	0/143	0/134	0.9 (0.01, 47.57)		
		Adverse events: Dizziness	89/143	10/134	19.4 (9.53, 39.77)		
		Adverse events: Dry mouth	34/143	10/134	3.7 (1.78, 7.80)		
		Adverse events: Fatigue	25/143	9/134	2.8 (1.29, 6.23)		
		Adverse events: Serious AE	7/143	3/134	2.0 (0.56, 7.50)		
		Adverse events: Withdrawal due to AEs	30/143	9/134	3.5 (1.64, 7.67)		

Study details	Intervention, follow-up duration	Outcome	Intervention	Comparator	Crude OR (95% CI)	Adjusted effect estimate (95% CI)	Analysis details
		General disease specific symptoms: Muscle stiffness (0-3 on an 11 point category rating scale)	42/143	21/134	2.2 (1.23, 3.96)	OR: 2.26 (1.24, 4.13) p-value=0.004	**Analysis Method** Conditional logistic regression, controlled for treatment, ambulatory status at screening, use of spasticity medication and geographical region.
		Pain: Bodily pain (0-3 on an 11 point category rating scale)	40/143	25/134	1.6 (0.95, 2.95)		
		Sleep: Sleep quality (0-3 on an 11 point category rating scale)	48/143	26/134	2.0 (1.20, 3.59)		
		Spasticity: Spasm severity (0-3 on an 11 point category rating scale)	44/143	18/134	2.8 (1.53, 5.15)		

B. CONTINUOUS OUTCOMES

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
Abram(2003)[129] **Study design:** Parallel group RCT	**Intervention:** Dronabinol (Marinol) **Comparator:** Placebo **Timing:** 21 days **Analysis:** modified ITT	**Appetite & weight:** Weight (Change in weight)			3.2 (-1.4, 7.6) *(22)*	1.1 (-1.4, 5.2) *(20)*			p-value=0.004	Median, range reported **Analysis Method:** Mann-Whitney tests
	Intervention: Marijuana **Comparator:** Placebo				3.0 (-0.75, 8.60) *(20)*	1.1(-1.4, 5.2) *(20)*			p-value=0.021	
Abrams (2007)[142] **Study design:** Parallel group RCT	**Intervention:** THC **Comparator:** Placebo **Timing:**5 days **Analysis:** modified ITT (All patients who remained in the study at each time point were included in the analyses.)	**Adverse events**: Anxiety			0.25 (0.14, 0.44)	0.10 (0.05, 0.22)			p-value<0.05	**Analysis Method:** Mann-Whitney/ Wilcoxon test; Multivariable repeated measures model.
		Adverse events: Confusion			0.17 (0.07, 0.39)	0.01 (0.00, 0.06)			p-value<0.001	
		Adverse events: Disorientation			0.16 (0.07, 0.34)	0.01 (0.00, 0.04)			p-value<0.001	
		Adverse events: Dizziness			0.15 (0.07, 0.31)	0.02 (0.01, 0.05)			p-value<0.001	
		Adverse events: Nausea			0.11 (0.04, 0.30)	0.03 (0.01, 0.14)			Not significant (no further details)	
		Adverse events: Paranoia			0.13 (0.03, 0.45)	0.04 (0.01, 0.14)			Not significant (no further details)	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		Adverse events: Somnolence ("sedation")			0.54 (0.36, 0.81)	0.08 (0.04, 0.17)			p-value<0.001	
		Pain: Neuropathic pain scale (% median reduction in chronic neuropathic pain (VAS))	52(38, 71) *(27)*	57(40, 74)*(28)*	(*25*)	*(25)*	-34 (-71, -16)	-17 (-29, 8)	**MD change from baseline**: 18 p-value=0.03	Median, IQR reported **Analysis Method:** Mann-Whitney/Wilcoxon test
		Pain: Neuropathic pain scale (% reduction chronic pain ratings (AUC))	*(27)*	*(28)*	(*25*)	*(25)*	51	5	p-value≤0.001	
		Psychological Measurements: Mood (% median reduction in profile of mood states.)			(*25*)	*(25)*	-33	-29	p-value=0.28	
		Psychological Measurements: Mood (% median reduction in profile of mood states (depression- dejection subscale))			(*25*)	*(25)*	-63	-76	p-value=0.05	
Ahmedzai(1983)[112] **Study design:**	**Intervention:** Nabilone (Cesamet)	**Nausea & vomiting:** Retching severity			0.1 (*26*)	0.5*(26)*			p-value≥0.05	**Analysis Method:** Mann-Whitney/Wilcoxon test

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
Cross-over RCT	**Comparator:** Proclorperazine **Timing:** 3 days **Analysis:** Per protocol;	**Nausea & vomiting:** Vomiting severity/intensity			0.0 (*26)*	0.6*(26)*			p-value≤0.001	
		Nausea & vomiting: Nausea severity/intensity			0.1 (*26)*	.6*(26)*			p-value≤0.05	
Beal(1995)[84] **Study design:** Parallel group RCT	**Intervention:** Dronabinol (Marinol) **Comparator:** Placebo **Timing:** 6 weeks **Analysis:** Per protocol	**Appetite & weight:** Weight (Weight gain (kg))					0.1	-0.4	p-value=0.14	**Analysis Method:** ANOVA (adjusted for site, treatment, and their interaction)
		Nausea & vomiting: Nausea severity/intensity (Patient reported VAS scale; %)					-22	-4	p-value=0.26	
		Global impression: Karnofsky performance status					-1.0	0.3	p-value=0.07	
		Appetite & weight: Appetite (Patient reported VAS scale; %)					37	17	p-value=0.05	
Bergamaschi (2011)[95] **Study design:** Parallel group RCT	**Intervention:** Cannabidiol (CBD) **Comparator:** Placebo **Timing:** 1.47 Hours (during speech performance) **Analysis:** ITT	**Psychological Measurements:** Anxiety (visual analogue mood scale (VAMS))	*(12)*				20.94	37.46	p-value=0.012	ANOVA NB values change from pre-test not from baseline

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
Berman (2007)[1] **Study design:** Parallel group RCT	**Intervention:** Nabiximols (Sativex) **Comparator:** Placebo **Timing:** 3 weeks **Analysis:** Not specified	**Pain:** Descriptor Differential Scale (mean BPI (points))	*(56)*	*(60)*					**MD at follow-up**: 0.46 p-value=0.04	
		Pain: Descriptor Differential Scale (least pain in the last 24h (points))	*(56)*	*(60)*					**MD at follow-up**: 0.79 p-value=0.007	
	Intervention: Nabiximols (Sativex) **Comparator:** Placebo **Timing:** 51 days **Analysis:** modified ITT (all randomised patients who received at least one dose of treatment and have on-treatment efficacy data)	**Pain:** NRS	*(56)*	*(60)*	*(55)*	*(59)*	-0.74 (1.12)	-0.69 (1.39)	**MD change from baseline:** -0.08 (-0.51, 0.35) p-value=0.708	**Analysis Method:** ANCOVA including treatment and centre as factors and baseline NRS pain mean score as a covariate
		Pain: Descriptor Differential Scale (Total BPI (points))	*(56)*	*(60)*	*(53)*	*(57)*	-3.1 (5.22)	-1.2 (4.64)	**MD at follow-up**: -1.93 (-3.69, -0.16) p-value=0.032	**Analysis Method:** ANCOVA including treatment and centre as factors and baseline BPI score as a covariate

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		QoL: MSQoL (Spitzer Quality of Life Index Score)	*(56)*	*(60)*	(*55*)	*(58)*	0.10 (1.41)	0.10 (1.30)	**MD at follow-up**: -0.04 (-0.49, 0.40) p-value=0.847	**Analysis Method:** ANCOVA including treatment and centre as factors and baseline Spitzer QoL index score as a covariate
		Sleep: Sleep disturbance (Numerical Rating Scale)	*(56)*	*(60)*	(*55*)	*(59)*	-0.41 (0.59)	-0.38 (0.73)		
		Spasticity: Modified Ashworth scale	*(56)*	*(60)*	(*40*)	*(44)*	-0.13 (0.43)	-0.01 (0.42)	**MD change from baseline**: -0.14 (-0.33, 0.05) p-value=0.142	**Analysis Method:** ANCOVA including treatment and centre as factors and Modified Ashworth Scale score as a covariate
		Spasticity: Spasm severeity (NRS 0-10)	*(56)*	*(60)*	(*42*)	*(48)*	-0.5 (1.46)	-0.69 (1.59)	**MD change from baseline**: 0.05 (-0.54, 0.65) p-value=0.860	**Analysis Method:** ANCOVA including treatment and centre as factors and baseline spasm severity NRS as a covariate
		Spasticity: Percentage of days on which spasm was experienced	*(56)*	*(60)*	(*52*)	*(59)*	-1.92 (20.01)	-1.57 (22.62)	**MD change from baseline**: -0.64 (-0.856, 7.27) p-value=0.873	**Analysis Method:** ANCOVA including treatment and centre as factors and Spasm percentage of days on which spasm was experienced as a covariate

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		Spasticity: Spasticity severeity (NRS 0-10)	*(56)*	*(60)*	(*35)*	*(43)*	-0.37 (1.25)	-0.46 (1.8)	**MD change from baseline**: 0.07 (-0.61, 0.75) p-value=0.830	**Analysis Method:** ANCOVA including treatment and centre as factors and baseline spasticity severity NRS as a covariate
		Spasticity: Percentage of days on which spasticity was experienced	*(56)*	*(60)*	(*50)*	*(59)*	0.86 (6.71)	0.48 (14.76)	**MD change from baseline**: 0.4 (-4.08, 4.88) p-value=0.860	**Analysis Method:** ANCOVA including treatment and centre as factors and Spasm percentage of days on which spasticity was experienced as a covariate
Berman (2004)[145] **Study design:** Cross-over RCT	**Intervention:** Nabiximols (Sativex) **Comparator:** Placebo **Timing:**2 weeks **Analysis:** modified ITT; 3 randomised participants that withdrew not analysed in all arms	**Pain:** Pain disability index (PDI) (Total score) **Whole group:**	35.8 *(48)*	35.8 *(48)*	30.3 (*46)*	32.3*(48)*			**MD follow-up:** -2.0 (-4.32, 0.83) p-value=0.181	**Analysis Method:** ANOVA; The model included factors for patient, treatment and period.
		Pain: McGill Pain rating (SF-MPQ Pain Rating Index (total score=45))	17.3 *(48)*		13.8 (*46)*	15.5 *(48)*			**MD follow-up:** -1.7 (-3.64, 0.55) p-value=0.146	
		Global impression: General Health Questionnaire 12	13.4 *(48)*		10.9 (*46)*	13.5 *(48)*			**MD follow-up:** -2.6 (-4.01, 0.45) p-value=0.015	
		Sleep: Sleep disturbance (4-point-scale)	1.3 *(48)*		1.1 (*46)*	1.3 *(48)*			**MD follow-up:** -0.2 (-0.37, -0.04) p-value=0.017	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		Sleep: Sleep quality (Sleep Quality BS-11)	4.8 *(48)*		5.9 (*46*)	5.3 *(48)*			**MD follow-up:** 0.6 (0.09, 1.01) p-value=0.019	
		Pain: Other (Pain Review BS-11 Score)	7.5 *(48)*		6.1 (*46*)	6.9 *(48)*			**MD follow-up:** -0.8 (-1.23, -0.23) p-value=0.005	
		Pain: NRS (Mean diary BS-11 pain score)			(*46*)	*(48)*			**MD follow-up:** -0.58 (-0.98, -0.18) p-value=0.005	
		Pain: McGill Pain rating (SF-MPQ VAS (mm))	60.9 *(48)*		45.1 (*46*)	52.9 *(47)*			**MD follow-up:** -7.8 (-15.78, -1.21) p-value=0.092	
	Intervention: THC **Comparator:** Placebo	**Pain:** Pain disability index (PDI) (Total score)	35.8 *(48)*		32.6 (*47*)	32.3 *(48)*			**MD follow-up:** 0.3 (-2.12, 2.98) p-value=0.739	
		Pain: Other body systems (Pain Review BS-11 Score)	7.5 *(48)*		6.3 (*47*)	6.9 *(48)*			**MD follow-up:** -0.6 (-1.08, -0.09) p-value=0.02	
		Sleep: Sleep quality (Sleep Quality BS-11)	4.8 *(48)*		6.0 (*47*)	5.3 *(48)*			**MD follow-up:** 0.7 (0.33, 1.24) p-value<0.001	
		Sleep: Sleep disturbance (4-point-scale)	1.3 *(48)*		1.0 (*47*)	1.3 *(48)*			**MD follow-up:** -0.3 (-0.37, -0.04) p-value=0.017	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		Pain: NRS (Mean diary BS-11 pain score)			*(47)*	*(48)*			**MD follow-up**: -0.64 (-1.03, -0.24) p-value=0.002	
		Global impression: General Health Questionnaire 12	13.4 *(48)*	13.4 *(48)*	12.3 (*47)*	13.4 *(48)*			**MD follow-up:** -1.1 (-2.97, 0.56) p-value=0.178	
		Pain: McGill Pain rating (SF-MPQ VAS (mm))	60.9 *(48)*	60.9*(48)*	43.6 (*47)*	52.9 *(48)*			**MD follow-up:** -9.3 (-17.41, -0.57) p-value=0.0037	
		Pain: McGill Pain rating (SF-MPQ Pain Rating Index (total score=45))	17.3 *(48)*	17.3 *(48)*	13.4 (*47)*	15.5 *(48)*			**MD follow-up:** -2.1 (-4.29, -0.1) p-value=0.04	
Blake(2006)[78] **Study design:** Parallel group RCT	**Intervention:** Nabiximols (Sativex) **Comparator:** Placebo **Timing:**5 weeks **Analysis:** ITT;	**Pain:** Other ("Morning pain at rest", 0-10 NRS)	5.3 *(31)*	5.3*(27)*	3.1 (*31)*	4.1*(27)*			**MD change from baseline**: -1.04(-1.90, -0.18) p-value=0.018	**Analysis Method:** Mann-Whitney/ Wilcoxon test; Hodges–Lehmann median difference and 95% CI
		Pain: McGill Pain rating (Short-Form McGill Pain Questionnaire (SF-MPQ): verbal rating scale, 'none' to 'excruciating')	3.2 *(31)*	3.2*(27)*	2.6 (*31)*	3.3*(27)*			**MD change from baseline**: -0.72 (-1.30, -0.14) p-value=0.016	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		Pain: McGill Pain rating (SF-MPQ): intensity of pain at present (single VAS score))	48 *(31)*	50(*27*)	33 (*31*)	50(*27*)			**MD change from baseline**: -3(-18, 9) p-value=0.574	
		Pain: McGill Pain rating ((SF-MPQ): total intensity of pain	15 *(31)*	20(*27*)	10.5 (*31*)	13(*27*)			**MD change from baseline**: 3(-3, 9) p-value=0.302	
		Mobility/ Disability: Morning stiffness (0-10 NRS)	3.5 *(31)*	3.80*(27)*	3.00 (*31*)	3.20*(27)*			**MD change from baseline**: -0.09(-0.58, .23) p-value=0.454	
		Pain: Morning pain on movement (0-10 NRS)	7.0 *(31)*	6.7*(27)*	4.8 (*31*)	5.3*(27)*			**MD change from baseline**: -0.95(-1.83, -0.02) p-value=0.044	**Analysis Method:** ANCOVA; Baseline score included as covariate.
		Sleep: Sleep quality (0-10 NRS)	5.7 *(31)*	5.8*(27)*	3.4 (*31*)	4.6*(27)*			**MD change from baseline**: -1.17(-2.20, -0.14) p-value=0.027	
		General disease specific symptoms: Other (28-joint disease activity score (DAS28))	5.9 *(31)*	6.0(*27*)	5.0 (*31*)	5.9*(27)*			**MD change from baseline**: -0.76(-1.23, -0.28) p-value=0.002	**Analysis Method:** ANOVA

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
Broder(1982)[74] **Study design:** Cross-over RCT	**Intervention:** THC **Comparator:** Hydroxizine **Timing:** NR **Analysis:** Modified ITT (35 out of 44 patients)	**Nausea & vomiting:** Number of vomiting episodes			*(35)*	*(35)*			p-value<0.01	**Analysis Method:** McNemar's Test All favoured THC
		Nausea & vomiting: nausea severity/intensity (degree of nausea at 4 hours)			*(35)*	*(35)*			p<0.05	
		Appetite & weight: Anorexia			*(35)*	*(35)*			p<0.05	
		Appetite & weight: Food intake			*(35)*	*(35)*			p<0.05	
		Appetite & weight: Fluid intake			*(35)*	*(35)*			p<0.05	
Collin (2007)[2] **Study design:** Parallel group RCT	**Intervention:** Nabiximols (Sativex) **Comparator:** Placebo **Timing:** 52 days	**Spasticity:** Motricity Index Score (Arms)			*(25)*	*(15)*	3.64 (14.82)	3.07 (10.08)	**MD change from baseline**: 1.30 (-7.47, 10.07) p-value=0.766	**Analysis Method:** ANCOVA Adjusted for baseline severity.
		Spasticity: Spasm Frequency Scale			*(120)*	*(64)*	-0.370 (0.770)	-0.260 (0.740)	**MD change from baseline**: -0.17(.11)(-0.39, .06) p-value=0.141	
		Spasticity: Motricity Index Score (Legs)			*(103)*	*(56)*	6.010 (12.300)	2.150 (13.410)	**MD change from baseline**: 3.86(-0.06, 7.78) p-value=0.054	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		Spasticity: Ashworth			*(114)*	*(63)*	-0.64 (0.56)	-0.53 (0.58)	**MD change from baseline**: -0.11 (0.09) (-0.29, 0.07) p-value=0.218	
	Timing:6 weeks	**Spasticity:** Numerical rating scale (NRS spasticity score)	5.49	5.39	*(120)*	*(64)*	-1.18 (1.83)	-0.63 (1.62)	**MD at follow-up**: 0.52 (-1.029, -0.004) p-value=0.048	
Collin(2010)[5] **Study design:** Parallel group RCT	**Intervention:** Nabiximols (Sativex) **Comparator:** Placebo **Timing:**99 days **Analysis:** modified ITT; All patients who received at least one dose of study medication and had on treatment efficacy data	**QoL:** EQ-5D (Health state index) **Whole group:**							**MD change from baseline**: .02000 p-value=0.175	**Analysis Method:** ANCOVA; Treatment, center grouping, and patient-s ambulatory status as factors and baseline severity as covariate.
		Sleep: Fatigue (NRS (0-10)) **Whole group:**							**MD change from baseline**: .35000 p-value=0.185	
		Pain: NRS (0-10)							**MD change from baseline**: -0.08 p-value=0.763	
		Spasticity: Spasm severity (NRS (0-10))							**MD change from baseline**: -0.01 p-value=0.955	
		QoL: MSQoL (MSQoL-54 mental health composite)							**MD change from baseline**: -3.09 p-value=0.312	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		QoL: MSQoL (MSQoL-54 (physical health composite))							**MD change from baseline**: -1.51 p-value=0.549	
		QoL: EQ-5D (Health status VAS score)							**MD change from baseline**: 1.42 p-value=0.538	
		Mobility/ Disability: Barthel Index of activities of daily living (ADL)			*(162)*	*(165)*	-0.100(10.260)	.500(8.050)	**MD change from baseline**: -0.15 (-1.95, 1.64) p-value=0.867	
		Mobility/ Disability: Walk time (Timed 10m walk)			*(115)*	*(120)*	-2.100(17.370)	9.3(63.560)		
		Sleep: Numerical rating scale (0-10 NRS)			*(124)*	*(139)*	-0.70 (2.85)	-0.62 (2.37)	**MD change from baseline**: -0.07 (-0.55, .40) p-value=0.734	
		Spasticity: Ashworth (Modified Ashworth Scale; 20 muscle groups assessed for spasticity (1-5 scale) to give total score of 100.)			*(156)*	*(160)*	-3.3 (9.25)	-2.8 (7.81)	**MD change from baseline**: -0.16 (-1.94, 1.61) p-value=0.857	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		Spasticity: Numerical rating scale (0-10 point scale)	6.77	6.48	*(166)*	*(169)*	-1.22 (1.76)	-0.91 (1.72)	**MD change from baseline**: -0.23 (-0.59, .14) p-value=0.220	
Corey-Bloom(2012)[190] **Study design:** Cross-over RCT	**Intervention:** THC **Comparator:** Placebo **Timing:** 3 days **Analysis:** Per protocol	**Mobility/ Disability:** Walk time (Time range 0-66 s)	11.66 (8.90, 16.69) *(30)*	11.68 (8.87, 16.41) *(30)*	12.89 (9.55, 17.94) (*30*)	11.70 (8.81, 16.98) *(30)*	1.23 (0.33, 2.63)	0.03 (-0.95, 1.63)	**MD change from baseline**: 1.20 (0.15, 4.31)	**Analysis Method:** paired t-test; Bootstrap-based, bias-corrected accelerated CI
		General disease specific symptoms: (Perceived deficits PDQ score (0-80))	20.33 (15.73, 26.08) *(30)*	19.97 (16.12, 24.86) *(30)*	21.20 (17.47, 26.33) (*30*)	19.13 (14.73, 24.39) *(30)*			**MD change from baseline**: 1.70 (-3.23, 6.07)	
		General disease specific symptoms: (Brief symptom inventory (BSI) score (0-208))	19.13 (12.73, 26.29) *(30)*	17.43 (12.57, 22.06) *(30)*	14.00 (8.80, 20.86) (*30*)	9.43 (7.01, 11.97) *(30)*			**MD change from baseline**: -2.87 (-9.63, 4.58)	
		Spasticity: Modified Ashworth scale (Scores 0-30)	9.13 (8.21, 10.07) *(30)*	8.92 (8.03, 9.79) *(30)*	6.18 (5.13, 7.21) (*30*)	8.71 (7.57, 9.71) *(30)*	-2.95 (-3.38, -2.49)	-0.21 (-0.51, 0.09)	**MD change from baseline**: -2.74 (-3.14, -2.20)	
		Pain: Total pain score (VAS (0-100))	16.61 (10.79, 24.93) *(30)*	14.51 (9.16, 21.75) *(30)*	8.34 (4.89, 14.39) (*30*)	11.52 (7.21, 18.32) *(30)*	-8.27 (-13.49, -4.51))	-2.99 (-6.55, -0.04)	**MD change from baseline**: -5.28 (-10.01, -2.48)	
		Sleep: Fatigue (mFIS score (0-84))	34.27 (27.50, 39.67) *(30)*	32.83 (26.50, 38.78) *(30)*	34.63 (28.99, 40.36) (*30*)	35.00 (28.90, 39.87) *(30)*			**MD change from baseline**: -1.80 (-8.29, 3.56)	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
Dalzell(1986)[92] **Study design:** Cross-over RCT	**Intervention:** Nabilone (Cesamet) **Comparator:** Domperidone **Analysis:** Per protocol	**Nausea & vomiting:** Number of vomiting episodes	*(23)*	*(23)*	5.94 (*18*)	16.72 *(18)*			p-value <0.01	**Analysis Method:** Wilcoxen signed rank
		Nausea & vomiting: Nausea severity/intensity	*(23)*	*(23)*	1.5 (*18*)	2.5 *(18)*			p-value<0.01	
Einhorn(1981)[108] **Study design:** Cross-over RCT	**Intervention:** Nabilone (Cesamet) **Comparator:** Prochlorperazine **Timing:** 5 days **Analysis:** Per protocol	**Nausea & vomiting:** Nausea severity/intensity (Nausea rated from 0 (none) to 3 (severe).)					0.93	1.38	p-value=0.003	**Analysis Method:** ANOVA for 2 period crossover design
		Nausea & vomiting: Vomiting severity/intensity (Frequency of vomiting (number of episodes))					1.12	2.97	p-value=0.003	
Ellis(2009)[137] **Study design:** Cross-over RCT	**Intervention:** THC **Comparator:** Placebo **Timing:** 5 days **Analysis:** Per protocol	**Pain:** Total pain score (VAS (10 cm line))	*(28)*	*(28)*	(*28*)	*(28)*	-17 (-58, 52)	-4 (-56, 28)	p-value≤0.001	Median, range reported Wilcoxon's signed rank test
		Pain: Breakthrough analgesia use (Opioid use (morphine equivalent doses))	*(28)*	*(28)*	(*28*)	*(28)*	0.1	5.8		

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		Pain: Descriptor Differential Scale	11.1 (9.1, 13.7) *(28)*	11.1 (9.1, 13.7) *(28)*	*(28)*	*(28)*			**MD change from baseline**: 3.30 p-value=0.016	Wilcoxon's rank sum test
Frank (2008)[141] **Study design:** Cross-over RCT	**Intervention:** Nabilone (Cesamet) **Comparator:** Dihydrocodeine **Timing:**14 weeks **Analysis:** Modified ITT (available case analysis)	**Pain:** Descriptor Differential Scale (VAS (0-100mm))	69.6 (29.4, 95.2) *(96)*		59.93 (24.42) *(64)*	58.58 (24.08) *(64)*			**MD at follow-up**: 6.0 (1.40, 10.50) p-value=0.01	**Analysis Method:** assumed this is mean difference '(in the direction nabilone minus dihydrocodeine'. There is a concern that the analyses maybe by treatment pathway rather than by intervention.
		QoL: SF36 (Physical role)			*(69)*	*(69)*			**MD at follow-up**: 8.9 (1.1, 16.7) p-value=0.03	**Analysis Method:** Model with fixed patient effect, period effect, and treatment effect but no term for the carryover effect of treatment Positive values favour nabilone.
		QoL: SF36 (General health)			*(70)*	*(70)*			**MD at follow-up**: 0.8 (-3.1, 4.6) p-value=0.70	
		QoL: SF36 (Bodily pain)			*(71)*	*(71)*			**MD at follow-up**: -5.2 (-10.1, -0.4) p-value=0.03	
		QoL: SF36 (General pain)			*(70)*	*(70)*			**MD at follow-up**: 0.8(-3.1, 4.6) p-value=0.7	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		QoL: SF36 (Vitality)			*(71)*	*(71)*			**MD at follow-up**: -2.0 (-7.2, 3.3) p-value=0.46	
		QoL: SF36 (mental health)			*(71)*	*(71)*			**MD at follow-up**: 2.5 (-2.7, 7.6) p-value=0.35	
		QoL: SF36 (Role, emotional)			*(69)*	*(69)*			**MD at follow-up**: -1.2(-11.8, 9.5) p-value=0.83	
		QoL: SF36 (Physical functioning)			*(71)*	*(71)*			**MD at follow-up**: -1.2 (-4.5, 2.1) p-value=0.48	
		QoL: SF36 (Change in health)			*(70)*	*(70)*			**MD at follow-up**: 0.0 (-0.2, 0.2) p-value=0.88	
		Psychological Measurements: Depression (HAD score)			*(70)*	*(70)*			**MD at follow-up**: -0.2 (-1.2, 0.9) p-value=0.72	
		Sleep: Sleep time (number of hours slept per night)			*(71)*	*(71)*			**MD at follow-up**: 0.2 (-0.1, 0.5) p-value=0.2	
		Pain: Anxiety (HADS anxiety)			*(70)*	*(70)*			**MD at follow-up**: -0.6 (-1.4, 0.3) p-value=0.19	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		QoL: SF36 (Social functioning)			*(71)*	*(71)*			**MD at follow-up**: 3.4 (-4.1, 10.8) p-value=0.37	
George(1983)[104] **Study design:** Cross-over RCT	**Intervention:** Nabilone (Cesamet) **Comparator:** Chlorpromazine **Timing:** 24 hours **Analysis:** ITT	**Nausea & vomiting:** Number of vomiting episodes (per 24 hours)	*(20)*	*(20)*	9.5 (2.8) (*20*)	11.4 (2.2) *(20)*				
GW Pharma Ltd(2012)[79] **Study design:** Parallel group RCT	**Intervention:** Nabiximols (Sativex) **Comparator:** Placebo **Timing:** 3 weeks **Analysis:** modified ITT	**QoL:** MSQoL (Spitzer QoL index scores)	*(36)*	*(34)*	(*33*)	*(31)*	-0.2 (1.17)	-0.4 (1.54)	**MD at follow-up**: 0.28 (-0.36, 0.91) p-value=0.387	**Analysis Method:** ANCOVA; adjusted for baseline Spitzer QoL index score
		Pain: Brief pain inventory short form (BPI-SF)	*(36)*	*(34)*	(*34*)	*(34)*	-3.6 (5.12)	-1.9 (6.52)	**MD at follow-up**: -1.66 (-4.42, 1.10) p-value=0.233	**Analysis Method:** ANCOVA; adjusted for baseline BPI-SF
		Pain: Pain disability index (PDI) (total pain disability index score)	*(36)*	*(34)*	(*28*)	*(26)*	-5.9 (10.17)	-3.2 (9.77)	**MD at follow-up**: -2.79 (-8.14, 2.56) p-value=0.30	**Analysis Method:** ANCOVA; adjusted for baseline PDI
		Sleep: Sleep disturbance (sleep disturbance score (QoL))	*(36)*	*(34)*	(*36*)	*(34)*	-0.57 (0.85)	-0.34 (0.58)	**MD at follow-up**: -0.34 (-0.68, 0.0) p-value=0.052	**Analysis Method:** ANCOVA; adjusted for baseline sleep disturbance score

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
GW Pharma Ltd(2005)[77] **Study design:** Parallel group RCT	**Intervention:** Nabiximols (Sativex) **Comparator:** Placebo **Timing:** 14 weeks **Analysis:** modified ITT; all randomised participants who received at least one dose of study medication and yielded on treatment efficacy data	**QoL:** EQ-5D (Weighted Health State Index Score, 0-100)			*(138)*	*(135)*	3.30 (22.26)	7.80 (22.91)	**MD change from baseline**: -0.01 (0.021) (-0.06, 0.03) p-value=0.523	**Analysis Method:** ANCOVA; The model included treatment and centre group as factors and baseline symptom score as a covariate
		Pain: Brief pain inventory short form (BPI-SF) ('Pain Severity Composite Score')			*(137)*	*(135)*	-1.20 (1.92)	-1.20 (2.06)	**MD change from baseline**: -0.05 (-0.51, 0.42) p-value=0.841	
		Sleep: Sleep quality (0-10 NRS)			*(132)*	*(142)*	-2.00 (3.02)	-1.60 (2.76)	**MD change from baseline**: -0.45 (-1.04, 0.15) p-value=0.139	
		Pain: Neuropathic pain scale (0-100 NRS)			*(135)*	*(140)*	-13.70 (19.91)	-14.16 (17.42)	**MD change from baseline**: 0.37(2.153) (-3.87, 4.61) p-value=0.865	
		Pain: Diabetic Neuropathy Pain (0-10 NRS)			*(146)*	*(148)*	-1.67 (2.13)	-1.55 (2.09)	**MD change from baseline**: -0.12 (-0.60, 0.36) p-value=0.634	
		Pain: Breakthrough analgesia use (daily number of paracetamol tablets)			*(146)*	*(148)*	-0.53 (2.02)	-0.35 (1.94)	**MD change from baseline**: -0.17(-0.59, 0.24) p-value=0.410	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
Hagenbach(2003)[71] **Study design:** Parallel group RCT	**Intervention:** Dronabinol (Marinol) **Comparator:** Placebo **Timing:**6 weeks **Analysis:** Not specified	**Spasticity:** Ashworth (summed scores)	*(13)*	*(13)*	7.21	12.10			p-value=0.001	**Analysis Method:** NR (conference abstract only)
Johansson(1982)[106] **Study design:** Cross-over RCT	**Intervention:** Nabilone (Cesamet) **Comparator:** Prochlorperazine **Timing:** **Analysis:** Per protocol;	**Nausea & vomiting:** Vomiting severity/intensity (Total vomiting episodes (ejection and dry retching))			18.4 (*18*)	38.7*(18)*			p-value≤0.001	**Analysis Method:** ANOVA (no further details)
		Global impression: Physician global impression (Investigator grading of therapeutic effect from 1 to 5 (scale meaning unclear - 1 appears best))			2.4 (*18*)	3.6*(18)*			p-value≤0.001	
Johnson (2010)[82] **Study design:** Parallel group RCT	**Intervention:** Nabiximols (Sativex) **Comparator:** Placebo	**Nausea & vomiting:** Nausea severity/intensity (NRS (0-10))	2.44 *(54)*	1.98*(56)*			0.26	-0.22	**MD change from baseline**: 0.49 (-0.11, 1.09) p-value=0.11	**Analysis Method:** ANCOVA; adjusted for baseline values

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
	Timing: 2 weeks **Analysis:** modified ITT; All participants who were randomised, received at least one actuation of study medication and had on-treatment efficacy data	**Pain:** Brief pain inventory short form (BPI-SF) (Total interference by pain in last 24 hours (0-10))	46.63 *(15)*	51.05 *(18)*			-3.53	1.31	**MD change from baseline**: -1.04 (-5.23, 3.15) p-value=0.619	
		QoL: (EORTC QLQ-C30 global health status)	29.74 *(49)*	25.29 *(52)*			7.23	4.77	**MD change from baseline**: 2.47 (-3.87, 8.81) p-value=0.443	
		Appetite & weight: Appetite (NRS (0-10))	4.83 *(54)*	4.98 *(56)*			0.24	-0.59	**MD change from baseline**: 0.83 (0.16, 1.51) p-value=0.016	
		Sleep: Sleep quality (NRS (0-10))	4.33 *(54)*	4.17 *(56)*			-0.59 (1.88)	-0.26 (1.72)	**MD change from baseline**: -0.31 (-0.97, 0.34) p-value=0.346	
		Pain: NRS	5.68 (1.24) *(53)*	6.05 (1.32) *(56)*			-1.37 (1.64)	-0.67 (1.51)	**MD change from baseline**: -0.67 (-1.21, -0.14) p-value=0.0014	
	Intervention: THC **Comparator:** Placebo **Timing:** 2 weeks **Analysis:**	**QoL:** (EORTC QLQ-C30 global health status)	27.05 *(50)*	25.29 *(52)*			5.60	4.77	**MD change from baseline**: 0.84 (-5.46, 7.13) p-value=0.793	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
	modified ITT; All participants who were randomised, received at least one actuation of study medication and had on-treatment efficacy data	**Nausea & vomiting:** Nausea severity/intensity (NRS (0-10))	2.04 *(54)*	1.98*(56)*			0.24	-0.22	**MD change from baseline**: 0.46 (-0.13, 1.05) p-value=0.126	
		Appetite & weight: Appetite (NRS (0-10))	4.58 *(54)*	4.98*(56)*			0.06	-0.59	**MD change from baseline**: 0.66 (-0.02, 1.33) p-value=0.056	
		Pain: NRS	5.77 (1.33) *(52)*	6.05 (1.32) *(56)*			-1.01 (1.15)	-0.67 (1.51)	**MD change from baseline**: -0.32 (-0.86, 0.22) p-value=0.245	
		Pain: Brief pain inventory short form (BPI-SF) (Total interference by pain in last 24 hours (0-10))	39.39 *(17)*	51.05 *(18)*			-4.50	1.31	**MD change from baseline**: -4.07 (-8.10, -0.05) p-value=0.048	
		Sleep: Sleep quality (NRS (0-10))	4.46 *(54)*	4.17*(56)*			-0.24 (2.33)	-0.26 (1.72)	**MD change from baseline**: 0.02 (-0.64, .68) p-value=0.95	
Jones (1982) [90] **Study design:** Cross-over RCT	**Intervention:** Nabilone (Cesamet) **Comparator:**	**Nausea & vomiting:** Number of vomiting episodes			7.2 *(24)*	18.8 *(24)*			p-value<0.001	**Analysis Method:** NR

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
	Placebo **Timing:** 1 chemotherapy cycle **Analysis:** Per protocol	**Nausea & vomiting:** Nausea severity/intensity (Judged as none (0), mild (1), moderate (2), severe (3))			2.0 *(24)*	2.8 *(24)*			p-value<0.001	
Killestein(2002)[1] 93 **Study design:** Cross-over RCT	**Intervention:** Dronabinol (Marinol) **Comparator:** Placebo **Timing:** 4 weeks **Analysis:** ITT	**Spasticity:** Ashworth	1.08 (0.87, 1.3) *(16)*	1.08 (0.88, 1.3) *(16)*	0.91 (0.72, 1.11) *(16)*	0.98 (0.77, 1.16)*(16)*	-0.17	-0.10	p-value>0.05	”Mixed linear model”
		Global impression: Patient global impression (daily VAS scale score)	*(16)*	*(16)*	-104 (-235, 60) *(16)*	162 (-13, 326) *(16)*	NR	NR	p-value=0.01	**Analysis Method:** ”Mixed linear model” **Test statistic:** F statistic (9.2)
		Mobility/ Disability: Acitivities of daily living (VAS "walking score")	NR	NR	NR	NR	NR	NR	p-value=0.08	**Analysis Method:** ”Mixed linear model” **Test statistic:** F statistic (5.0)
	Intervention: THC/CBD **Comparator:** Placebo	**Spasticity:** Ashworth	1.13 (0.9, 1.34) *(16)*	1.08 (0.88, 1.3) *(16)*	0.91 (0.7, 1.11) *(16)*	0.98 (0.77, 1.16)*(16)*	-0.12	-0.10	p-value>0.05	”Mixed linear model”
		Global impression: Patient global impression (daily VAS scale score)	*(16)*	*(16)*	-76 (-224, 90) *(16)*	162 (-13, 326) *(16)*	NR	NR	p-value=0.02	**Analysis Method:** ”Mixed linear model” **Test statistic:** F statistic (7.1)

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
Lane(1991)[83] **Study design:** Parallel group RCT	**Intervention:** Dronabinol (Marinol) **Comparator:** Proclorperazine **Timing:**6 days **Analysis:** modified ITT; 54/62 patients - all patients who received chemotherapy	**Nausea & vomiting:** Nausea duration (mins)			10 (*20*)	15 (*17*)			p-value=0.09	Median, range reported **Analysis Method:** Mann-Whitney/ Wilcoxon test
		Nausea & vomiting: Nausea duration (Duration of nausea/vomiting (mins))			5 (*17*)	5 (*20*)				
		Nausea & vomiting: Vomiting duration (mins)			2 (*17*)	4 (*20*)				
	Intervention: Dronabinol (Marinol) **Comparator:** Dronabinol (Marinol) + prochlorperazine	**Nausea & vomiting:** Nausea duration (Duration of nausea/vomiting (mins))			5 (*17*)	2 (*17*)			p-value≤0.001	**Analysis Method:** Mann-Whitney/ Wilcoxon test
Langford (2013)[4] **Study design:** Parallel group RCT	**Intervention:** Nabiximols (Sativex) **Comparator:** Placebo **Timing:** 98 days **Analysis:** ITT	**QoL:** SF36 (Role physical)			(*167*)	*(172)*	5.62	6.51	**MD change from baseline**: -0.89 p-value=0.694	
		Pain: Neuropathic pain scale	*(167)*	*(172)*	(*167*)	*(172)*	-12.41	-10.58	**MD change from baseline**: 1.83 p-value=0.310	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		Pain: Brief pain inventory short form (BPI-SF)			(*167*)	*(172)*	-1.47	-1.35	**MD change from baseline**: -0.12 p-value=0.564	
		QoL: SF36 (Mental health)			(*167*)	*(172)*	3.17	3.73	**MD change from baseline**: -0.56 p-value=0.733	
		QoL: SF36 (Role emotion)			(*167*)	*(172)*	-0.18	3.15	**MD change from baseline**: -3.33 p-value=0.216	
		QoL: SF36 (Social functioning)			(*167*)	*(172)*	3.62	9.37	**MD change from baseline**: -5.75 p-value=0.020	
		QoL: SF36 (Vitality)			(*167*)	*(172)*	3.72	6.47	**MD change from baseline**: -2.75 p-value=0.095	
		QoL: SF36 (Bodily pain)			(*167*)	*(172)*	11.36	10.01	**MD change from baseline**: 1.35 p-value=0.494	
		Pain: Pain disability index (PDI)	*(167)*	*(172)*	(*167*)	*(172)*	-3.25	-6.04	**MD change from baseline**: 2.79 p-value=0.058	
		QoL: SF36 (Physical Functioning)			(*167*)	*(172)*	1.56	2.02	**MD change from baseline**: -0.45 p-value=0.785	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		QoL: EQ-5D (EQ-5D Health status VAS)			(*167*)	*(172)*	7.20	5.26	**MD change from baseline**: 1.94 p-value=0.383	
		QoL: EQ-5D (EQ-5D health status index)			(*167*)	*(172)*	0.05	0.07	**MD change from baseline**: -0.01 p-value=0.396	
		Sleep: Fatigue (NRS)			(*167*)	*(172)*	-0.96	-1.28	**MD change from baseline**: 0.32 p-value=0.176	
		Spasticity: Spasm severity (NRS)			(*167*)	*(172)*	-1.06	-0.92	**MD change from baseline**: -0.14 p-value=0.548	
		Spasticity: Numerical rating scale			(*167*)	*(172)*	-1.19	-1.09	**MD change from baseline**: -0.10 p-value=0.667	
		QoL: SF36 (General health)			(*167*)	*(172)*	2.32	4.02	**MD change from baseline**: -1.70 p-value=0.264	
		Pain: NRS (NRS 0-10 scale)	6.55 (1.35) *(167)*	6.61 (1.29) *(172)*	4.54 (2.24) (*167*)	4.73 (2.26) *(172)*	-1.93	-1.76	**MD change from baseline**: 0.17(-0.62, .29) p-value=0.47	
		Sleep: Sleep quality (NRS (0-10))			(*167*)	*(172)*	-1.960	-2.00	**MD change from baseline**: 0.05 p-value=0.833	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
Levitt(1982)[117] **Study design:** Cross-over RCT	**Intervention:** Nabilone (Cesamet) **Comparator:** Placebo	**Appetite & weight:** Caloric/food intake (Mean food intake - 0 (no food intake) to 3 (more than usual))			1.28 (*36*)	0.50 (*36*)			p-value=0.001	**Analysis Method:** NR
		Nausea & vomiting: Nausea severity/intensity (Severity of nausea rated from 0 (none) to 3 (severe))			1.03 (*36*)	2.25 (*36*)			p-value≤0.001	
		Nausea & vomiting: Number of vomits			2.97 (*36*)	7.47 (*36*)			p-value≤0.001	
Leweke(2008)[216] **Study design:** Parallel group RCT	**Intervention:** Cannabidiol (CBD) **Comparator:** Amisulpride **Timing:** 28 days	**Psychological Measurements:** Mental health (Brief Psychiatric Rating Scale)	58.1 (9.7) *(20)*	57.7 (10.3) *(19)*	(*17*)	*(18)*	20.5 (12.3)	19.4 (15.6)	**MD change from baseline**: -0.10(-9.20, 8.90) p-value=0.977	**Analysis Method:** Mixed model; A mixed effects repeated measures model (unstructured

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
	Analysis: modified ITT (39 out of 42 patients will efficacy results)	**Psychological Measurements:** Mood (Total PANSS (positive and negative syndrome scale))	91.2 (14.0) *(20)*	95.5 (17.1) *(19)*	(*17*)	*(18)*	30.5 (16.4)	30.1 (24.7)	**MD change from baseline**: 1(-12.60, 14.60) p-value=0.884	covariance matrix) for the change from baseline included baseline as a covariate with treatment, visit and treatment-by visit interaction as fixed effects (missing values were not imputed).
Lynch(2014)[148] **Study design:** Cross-over RCT	**Intervention:** Nabiximols (Sativex) **Comparator:** Placebo **Timing:**6 weeks **Analysis:** Per protocol; 16/18 patients	**Pain:** NRS (0-10 scale for pain intensity)	6.56 (1.24) *(16)*	7.0 (1.12) *(16)*	6.00 (5.02, 6.98) (*16*)	6.38 (5.67, 7.09) *(16)*				**Analysis Method:** ANOVA; Repeated measures ANOVA for crossover data with time as within participants factor and treatment as between participants factor.
		QoL: SF36 (Physical) **Whole group:**	32.68 (10.26) *(16)*	32.68 (10.26) *(16)*	35.50 (9.19) (*16*)	46.50 (8.50) *(16)*				
		QoL: SF36 (Mental) **Whole group:**	45.25 (10.21) *(16)*	45.25 (10.21) *(16)*	44.86 (9.98) (*16*)	33.90 (10.03) *(16)*				
Meiri(2007)[85] **Study design:** Parallel group RCT	**Intervention:** Dronabinol (Marinol) **Comparator:**	**Nausea & vomiting:** Nausea severity/intensity (VAS)	*(17)*	*(14)*	10.1 *(14)*	48.4 *(13)*			p-value<0.05	**Analysis Method:** Wilcoxon rank sum test

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
Comments: Favours dronabinol	Placebo **Timing:** 2-5 days (LOCF, values from a premature discontinuation visit included)	**Nausea & vomiting:** Number of vomiting episodes (episodes of vomiting and/or retching)	*(17)*	*(14)*	0.20 *(13)*	1.30 *(10)*				
		Global impression: ECOG assessment	*(17)*	*(14)*			0.058	0.077	p=0.036	ANOVA ("confounded by site differences")
	Intervention: Dronabinol + ondansetron **Comparator:** Placebo	**Nausea & vomiting:** Number of vomiting episodes (episodes of vomiting and/or retching)	*(17)*	*(14)*	0.7 *(15)*	1.3 *(10)*				
		Global impression: ECOG assessment	*(17)*	*(14)*			0.058	0.077		
		Nausea & vomiting: Nausea severity/intensity (VAS)	*(17)*	*(14)*	14.3 *(14)*	48.4 *(13)*			p-value<0.05	**Analysis Method:** Wilcoxon rank sum test
Melhem-Bertrandt(2014)[124] **Study design:** Parallel group RCT	**Intervention:** Dronabinol (Marinol) **Comparator:** Placebo **Timing:** 5 days	**Nausea & vomiting:** Frequency of nausea (average nausea episodes/day)			0.38 (0.41) *(29)*	0.62 (0.36) *(29)*			p-value=0.033	**Analysis Method:** Mann-Whitney/ Wilcoxon test

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
	Analysis: Modified ITT (58 out of 62, 3 withdrawals, 1 unclear)	**Nausea & vomiting:** Nausea duration (mean number of days)			1.86 (2.01) *(29)*	3.10 (1.80) *(29)*			p-value=0.027	
Müller-Vahl, (2001)[227] **Study design:** Cross-over RCT	**Intervention:** THC **Comparator:** Placebo **Timing:** 2 days **Analysis:** ITT	**Psychological Measurements:** Obsessive compulsive behaviours (OCB), (SCL-90-R checklist)	*(12)*	*(12)*	55.20 (9.40) *(12)*	50.80(12.60) *(12)*			p-value=0.041	**Analysis Method:** Mann-Whitney/ Wilcoxon test; Hill and Armitage method used to test for treatment, carry over and phase effects.
		Psychological Measurements: Tic severity (Tourette's syndrome symptoms list (TSSL) - Global score)	*(12)*	*(12)*	(*12*)	*(12)*	-14.00 (10.97)	-4.92 (6.69)	p-value=0.015	
		Psychological Measurements: Tic severity (Shapiro Tourette's syndrome severity scale)	3.60 (1.20) *(12)*	3.60 (1.20) *(12)*	(*12*)	*(12)*	-1.0 (1.0)	-0.33 (0.65)	p-value=0.132	
		Psychological Measurements: Tic severity (Tourette's syndrome global scale (TSGS))	22.60 (22) *(12)*	22.60 (22) *(12)*	(*12*)	*(12)*	-10 (8.61)	-3.50 (7.53)	p-value=0.132	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		Psychological Measurements: Tic severity (Yale global tic severtiy scale (YGTSS)- perfome d by an examiner)	45.8 (17.3) *(12)*	45.8 (17.3) *(12)*	*(12)*	*(12)*	-10.25 (12.95)	-3.75 (9.12)	p-value=0.132	
Müller-Vahl(2003)[225] **Study design:** Parallel group RCT	**Intervention:** THC **Comparator:** Placebo **Timing:**30 days **Analysis:** Per protocol; to 31	**General disease specific symptoms:** Tic severity (Shapiro Tourette Syndrome Severity Scale (STSSS))	3.29 (1.38)	3.40 (1.26)	*(7)*	*(10)*	-0.70	0.00	**MD change from baseline:** p-value=0.033	**Analysis Method:** Mann-Whitney/ Wilcoxon test
		General disease specific symptoms: Tic severity (Tourette syndrome symptom list (tic rating) TSSL)	28.29 (14.47)	23.50 (12.81)	*(7)*	*(10)*	-13.5	2.7	**MD change from baseline:** p-value<0.05	**Analysis Method:** Mann-Whitney/ Wilcoxon test
		General disease specific symptoms: Tic severity (Yale Global Tic Severity Scale (YGTSS))	44.71 (19.28)	38.60 (18.56)	*(7)*	*(11)*	-12.03	0.00	**MD change from baseline:** p-value=0.061	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		General disease specific symptoms: Tic severity (Tourette syndrome clinical global impression scale (TS-CGI))	2.57 (0.79)	2.40 (0.52)	*(7)*	*(10)*	-0.57	0.00	**MD change from baseline:** p-value=0.008	
Narang(2008)[139] **Study design:** Cross-over RCT	**Intervention:** Dronabinol (Marinol) (10mg) **Comparator:** Placebo **Timing:** 8 hours **Analysis:** per protocol	**Global impression:** Patient global impression					5.9	3.9	p-value<0.05	**Analysis Method:** Linear regression (fixed effects)
		Psychological: Anxiety (HADS).					-7.8	-5.2	not significant (no further details)	
		Pain: NRS (SPID)					-17.4	-6.4	p-value<0.01	
		Pain: NRS (pain intensity (0-10))	6.9 (1.3) *(30)*		5.7	6.6			p-value<0.001	
		Psychological Measurements: Depression (HADS)					-6.2	-2.0		
		Pain: Pain relief (Average relief scale (0-10))	3.9 (1.7) *(30)*		4.2	3.4			p-value<0.01	
		Pain: Pain relief ((integral relief scores))	*(30)*		39.7 *(29)*	31.1 *(29)*			p-value<0.05	
	Intervention: Dronabinol (Marinol) (20mg) **Comparator:**	**Psychological Measurements:** Depression (HADS)					-4	-2		

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
	Placebo	**Pain:** Pain relief ((integral relief scores)); 0-10 NRS	*(30)*		41.7	31.1			p-value<0.01	
		Pain: Pain relief (Average relief scale (0-10))	3.9 (1.7) *(30)*		4.3	3.4			p-value<0.01	
		Pain: NRS (pain intensity (0-10))	6.9 (1.3) *(30)*		5.1	6.6			p-value<0.001	
		Pain: NRS (pain intensity (0-10))	*(30)*				-19.7	-6.4	p-value<0.01	
		Psychological: Anxiety (HADS)					-1.5	-5.2	not significant (no further details)	
		Global impression: Patient global impression	*(30)*				5.9	3.9	p-value<0.05	
Niederle(1986)[100] **Study design:** Cross-over RCT	**Intervention:** Nabilone (Cesamet) **Comparator:** Alizapride **Timing:**5 days (average across all 5 days) **Analysis:** ITT	**Nausea & vomiting:** Nausea duration (hours)					1.3	5.1	p-value<0.01	**Analysis Method:** Wilcoxen signed rank

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
Niiranen (1985)[101] **Study design:** Cross-over RCT	**Intervention:** Nabilone (Cesamet) **Comparator:** Prochlorperazine **Timing:** 24h chemotherapy cycle **Analysis:** Modified ITT; 24 participants with full results repored (out of 32 randomised)	**Nausea and vomiting:** Number of vomiting episodes	*(24)*	*(24)*	6.5 *(24)*	11.0 *(24)*			p<0.05	**Analysis Method:** Method suggested by Hills and Armitage
Noyes (1975)[96] **Study design:** Cross-over RCT	**Intervention:** THC (5mg) **Comparator:** Placebo **Timing:**6 hours **Analysis:** ITT	**Pain:** NRS (Total Pain Reduction (Houde 1966, Keele 1948))					-2.60 (0.53) (*10*)	-0.90 (0.80) *(10)*		
		Pain: Pain relief (Houde 1966, Keele 1948)			4.70 (0.95) (*10*)	2.60 (0.61) *(10)*				
	Intervention: THC (10mg) **Comparator:** Placebo	**Pain:** NRS (Total Pain Reduction (Houde 1966, Keele 1948))					-1.40 (0.42) (*10*)	-0.90 (0.80) *(10)*		
		Pain: Pain relief (Houde 1966, Keele 1948)			4.4 (0.98) (*10*)	2.6 (0.61) *(10)*				
	Intervention: THC (15mg) **Comparator:** Placebo	**Pain:** NRS (Total Pain Reduction (Houde 1966, Keele 1948))					-3.60 (0.65) (*10*)	-0.90 (0.80) *(10)*		

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		Pain: Pain relief (Houde 1966, Keele 1948)			5.8 (0.84) *(10)*	2.6 (0.610) *(10)*				
	Intervention: THC (20mg) **Comparator:** Placebo	**Pain:** NRS (Total Pain Reduction (Houde 1966, Keele 1948))					-4.60 (0.660) *(10)*	-0.90 (0.80) *(10)*		
		Pain: Pain relief (Houde 1966, Keele 1948)			10.80 (1.19) *(10)*	2.60 (0.61) *(10)*				
Nurmikko(2007) [80] **Study design:** Parallel group RCT	**Intervention:** Nabiximols (Sativex) **Comparator:** Placebo **Timing:** 4 weeks **Analysis:** ITT;	**Sleep:** Sleep disturbance (NRS)	3.0(0.8) *(63)*	3.0(0.9) *(62)*	*(63)*	*(62)*	-0.79	-0.36	**MD change from baseline**: -0.43 (-0.67, -0.19) p-value=0.001	**Analysis Method:** ANCOVA; model included treatment and trial centre as factors and baseline pain severity as a covariate.
		Pain: NRS (Dynamic allodynia)	5.4(2.7) *(63)*	5.0(3.4) *(62)*	*(63)*	*(62)*	-1.18	-0.37	**MD change from baseline**: -0.82 (-1.60, -0.03) p-value=0.042	
		Pain: Pain disability index (PDI)	40.9 (14.7) *(63)*	42.1 (13.4) *(62)*	*(63)*	*(62)*	-5.61	0.24	**MD change from baseline**: -5.85 (-9.62, -2.09) p-value=0.003	
		Pain: NRS (Punctate allodynia)	7.3 (1.8) *(63)*	7.4 (2.1) *(62)*	*(63)*	*(62)*	-0.87	-0.21	**MD change from baseline**: -0.87 (-1.62, -0.13) p-value=0.021	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		Pain: Patient global impression (pain at allodynic site))					46.77	17.74	**MD change from baseline**: 29.03 (13.79, 44.67) p-value=0.001	
		Pain: Patient global impression (PGIC (all neuropathic pain))					51.16	19.35	**MD change from baseline**: 29.03 (13.79, 44.67) p-value≤0.001	
		Pain: NRS (mean pain NRS score)	7.3(1.4) *(63)*	7.2(1.5)*(62)*	(*63)*	*(62)*	-1.48	-0.52	**MD change from baseline**: -0.96 (-1.59, -0.32) p-value=0.004	
		Global impression: General Health Questionnaire 12	17.2(7.3) *(63)*	17.6(6.5) *(62)*	(*63)*	*(62)*	-3.09	-2.34	**MD change from baseline**: -0.75 (-2.84, 1.35) p-value=0.483	
		Pain: Neuropathic pain scale (self assessed)	61.1(13) *(63)*	62.4 (13.7) *(62)*	(*63)*	*(62)*	-10.07	-2.04	**MD change from baseline**: -8.03 (-13.83, -2.23) p-value=0.007	
Pinsger(2006)[143] **Study design:** Cross-over RCT	**Intervention:** Nabilone (Cesamet) **Comparator:** Placebo	**Pain:** NRS (Reduction of mean spine pain intensitiy in last 4 weeks)			0.9(0.0, 2.0) (*30)*	0.50 (0.0, 1.7)*(30)*			p-value=0.196	Median, IQR reported **Analysis Method:** Wilcoxen signed

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
	Timing:4 weeks **Analysis:** ITT;	**Pain:** NRS (Reduction of current spine pain intensity)			0.6(0.0, 2.5) (*30*)	0.0 (-1.0, 1.0)*(30)*			p-value=0.006	rank; Non-parametric cross-over-analysis
		Pain: NRS (Reduction of mean headache intensity in last 4 weeks)			1.0 (-1.0, 2.4) (*25*)	0.2(-0.9, 1.0)*(25)*			p-value=0.241	
		Pain: NRS (Increase of number of headache-free days in last 4 weeks)			2.0 (0.0, 6.5) (*25*)	0.0 (-5.0, 4.0)*(25)*			p-value=0.093	
		QoL: Other (Score (Mezzich & Cohen, German translation 2003))			5.0(0.8, 10.8) (*30*)	2.0(-2.3, 8.0)*(30)*			p-value=0.902	
Pomeroy(1986)[9] **Study design:** Parallel group RCT	**Intervention:** Nabilone (Cesamet) **Comparator:** Domperidone **Timing:**1 cycle **Analysis:** Not specified	**Nausea & vomiting:** Number of vomiting episodes			4.53 (*32*)	10.81 *(33)*			p-value≤0.01	**Analysis Method:** t-test
		Nausea & vomiting: Nausea severity/intensity			1.50 (*32*)	2.00 *(33)*			p-value≥0.05	**Analysis Method:** Kolmagorov-Smirnov test
		Nausea & vomiting: Caloric/food intake (food intake			1.09 (*33*)	0.75 *(32)*			p-value=NR	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
Pooyania (2010)[128] **Study design:** Cross-over RCT	**Intervention:** Nabilone (Cesamet) **Comparator:** Placebo **Timing:**4 weeks **Analysis:** modified ITT; all treated patients	**Spasticity:** Spasm Frequency Scale	3.45 *(11)*		3.45 (*11*)	3.45 *(11)*			**MD at follow-up:** 0.0 (0.193) p-value=0.369	**Analysis Method:** Mann-Whitney/Wilcoxon test; Mean difference between treatment and placebo period in each participant, adjusted to the baseline (where available and a 1-sample sign rank tested that the mean difference equated to 0)
		Spasticity: Ashworth ("Ashworth in most involved muscle group")	7.63 *(11)*		6.54 (*11*)	7.45 *(11)*			**MD at follow-up:** -0.91 (0.85) p-value=0.003	
		Spasticity: Ashworth (Ashworth in 8 muscle groups (1964))	29.9 *(11)*		26.9 (*11*)	29.45 *(11)*			**MD at follow-up:** -2.55 (0.25) p-value=0.001	
		Spasticity: VAS scale (100-mm, 0= no spasticity, 100= most imaginable spasticity)	46.18 *(11)*		44.09 (*11*)	53.18 *(11)*			**MD at follow-up:** -9.09 (16.97) p-value=0.76	
		Global impression: Patient global impression	NR *(11)*		4.09 (*11*)	3.60 *(11)*			**MD at follow-up:** 0.49 (1.12) p-value=0.312	
		Global impression: Clinical global impression	NR *(11)*		3.72 (*11*)	*3.54 (11)*			**MD at follow-up:** 0.18 (1.16) p-value=0.789	
		Spasticity: Wartenberg Pendulum Test (Rotational damping ratio, sitting)	6.24 *(9)*		6.234 (*9*)	6.230 *(9)*			**MD at follow-up:**: 0.004 (0.31) p-value=0.6397	**Analysis Method:** t-test

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		Spasticity: Wartenberg Pendulum Test (Rotational natural frequency, sitting, pendulum variable)	0.15 *(9)*		0.051 (*9*)	0.549 *(9)*			**MD at follow-up:** 0.498 (0.802) p-value=0.018	
Portenoy (2012)[86] **Study design:** Parallel group RCT	**Intervention:** Nabiximols (Sativex) (1-4 sprays) **Comparator:** Placebo **Timing:** 5 weeks **Analysis:** modified ITT; All treated patients	**Pain:** NRS (Cumulative responder analysis; differences in proportions of patients who achieved various levels of response)			*(89)*	*(91)*	-20 (-48, -8)	-10 (-33, -5)	p-value=0.008	Pairwise Wilcoxon rank-sum test
		Pain: NRS (11 point NRS)	5.8 *(91)*	5.7 *(91)*	*(89)*	*(91)*	-1.6 (2.1)	-0.8 (1.8)	**MD change from baseline**: -0.75 (-1.28, -0.22) p-value=0.006	ANCOVA; Baseline value as a covariate and region and treatment group as factors
		QoL: Patient assessment of Consitpation quality of life	*(91)*	*(91)*	*(70)*	*(74)*	0 (0.6)	-0.1 (0.6)	p-value=0.226	NR
		Pain: Brief pain inventory short form (BPI-SF) (Interference composite score)	*(91)*	*(91)*					p-value=0.871	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		Pain: Brief pain inventory short form (BPI-SF) (Severity composite score)	*(91)*	*(91)*	*(69)*	*(74)*			p-value=0.236	
		Pain: NRS (Daily mean worst)	*(91)*	*(91)*	*(89)*	*(91)*	-1.6 (2.2)	-0.9 (2.0)	p-value=0.011	ANCOVA; Baseline value as a covariate and region and treatment group as factors
		Sleep: Sleep disturbance (Sleep disruption NRS)	*(91)*	*(91)*	*(89)*	*(91)*	-1.5 (2.1)	-0.8 (2.2)	p-value=0.003	
		Global impression: Patient global impression (Patient global assessment of change)	*(91)*	*(91)*					p-value=0.268	NR
		Psychological Measurements: Depression (MADRS)	*(91)*	*(66)*	*(91)*	*(69)*	-1.1 (7)	-2.9 (9)	p-value=0.480	
	Intervention: Nabiximols (Sativex) (6-10 sprays)	**QoL:** Patient assessment of Consitpation quality of life	*(91)*	*(91)*	*(69)*	*(74)*	-0.1 (0.5)	-0.1 (0.6)	-0.10 p-value=0.493	
	Comparator: Placebo	**Pain:** NRS (11 point NRS)	5.80 *(88)*	5.70 *(91)*	*(87)*	*(91)*	-1.2 (1.7)	-0.8 (1.8)	**MD change from baseline**: -0.36 (-0.89, 0.18) p-value=0.187	ANCOVA; Baseline value as a covariate and region and treatment group as factors

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		Psychological Measurements: Depression (MADRS)	*(88)*	*(66)*	*(91)*	*(69)*	-1 (8.5)	-2.9 (9)	p-value=0.151	NR
		Global impression: Patient global impression (Patient global assessment of change)	*(88)*	*(91)*					p-value=0.664	
		Pain: Brief pain inventory short form (BPI-SF) (Interference composite score)	*(91)*	*(91)*					p-value=0.088	
		Pain: Brief pain inventory short form (BPI-SF) (Severity composite score)	*(88)*	*(91)*	*(68)*	*(74)*			p-value=0.119	
		Pain: NRS (Cumulative responder analysis; differences in proportions of patients who achieved various levels of response)			*(87)*	*(91)*	-20 (-40, -6)	-10 (-33, -5)	p-value=0.038	Pairwise Wilcoxon rank-sum test
		Pain: NRS (Daily mean worst)	*(88)*	*(91)*	*(87)*	*(91)*	-1.2 (1.8)	-0.9 (2.0)	p-value=0.397	ANCOVA; Baseline value as a covariate

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		Sleep: Sleep disturbance (Sleep disruption NRS)	*(88)*	*(91)*	*(87)*	*(91)*	-0.9 (2.1)	-0.8 (2.2)	p-value=0.260	and region and treatment group as factors
	Intervention: Nabiximols (Sativex)(11-16 sprays) **Comparator:** Placebo	**Pain:** NRS (11 point NRS)	*(90)*	5.7 *(91)*	*(89)*	*(91)*	-0.9 (1.9)	-0.8 (1.8)	**MD change from baseline:** -0.09(-0.62, 0.44) p-value=0.75	
		QoL: Patient assessment of Consitpation quality of life	*(90)*	*(91)*	*(70)*	*(74)*	0 (0.7)	-0.1 (0.6)	p-value=0.139	NR
		Global impression: Patient global impression (Patient global assessment of change)	*(90)*	*(91)*					p-value=0.538	
		Pain: NRS (Cumulative responder analysis; differences in proportions of patients who achieved various levels of response)			*(89)*	*(91)*	-13 (-30, 6)	-10 (-33, 5)	p-value=0.675	Pairwise Wilcoxon rank-sum test

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		Pain: Brief pain inventory short form (BPI-SF) (Interference composite score)	*(91)*	*(91)*					p-value=0.956	NR
		Pain: Brief pain inventory short form (BPI-SF) (Severity composite score)	*(90)*	*(91)*	*(68)*	*(74)*			p-value=0.861	
		Pain: NRS (Daily mean worst)	*(90)*	*(91)*	*(89)*	*(91)*	-1.0 (1.9)	-0.9 (2.0)	p-value=0.14	ANCOVA; Baseline value as a covariate and region and treatment group as factors
		Sleep: Sleep disturbance (Sleep disruption NRS)	*(90)*	*(91)*	*(89)*	*(91)*	-0.7 (2.1)	-0.8 (2.2)	p-value=0.784	
		Psychological Measurements: Depression (MADRS)	*(90)*	*(67)*	*(91)*	*(69)*	-0.4 (8.6)	-2.9 (9)	p-value=0.083	NR
Prasad(2011)[72] **Study design:** Parallel group RCT	**Intervention:** Dronabinol (Marinol) **Comparator:** Placebo **Timing:**3 weeks **Analysis:** Not specified;	**Sleep:** Sleep Apnoea/hypopnea (AHI (apnea hypopnea index))	48.8 (24.9) *(17)*	30.5 (15.0) *(5)*	(*8*)	*(4)*	-13.27	6.37	p-value=0.018	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
Rohleder(2012)[75] **Study design:** Cross-over RCT	**Intervention:** Cannabidiol (CBD) **Comparator:** Placebo **Timing:**2 weeks **Analysis:** Modified ITT ('Drop-out patients were replaced per protocol')	**Psychological Measurements:** Mood (PANSS (positive and negative syndrome scale))	*(29)*						**MD at follow-up**: 2.40 (SE 3) In favour of CBM but not statistically significant.	**Analysis Method:** Mixed model; Mixed effects repeated measures model
Rog(2005)[144] **Study design:** Parallel group RCT	**Intervention:** Nabiximols (Sativex) **Comparator:** Placebo **Timing:** 5 weeks **Analysis:** modified ITT; All randomised and treated patients with outcome data (1 patient excluded)	**Sleep:** NRS (0-10)	5.26 (4.35, 6.18) *(33)*	4.47 (3.52, 5.42) *(32)*	2.69 (1.99, 3.39) (*33*)	3.64 (2.73, 4.55) *(32)*	-2.60 (2.35)	-0.80 (1.79)	**MD change from baseline**: -1.39 (-2.27, -0.50) p-value=0.003	**Analysis Method:** ANCOVA; Adjusted for baseline values
		Psychological Measurements: Brief Repeatable Battery of Neuopsychological Test Score ('Word Generation List')			(*33*)	*(32)*	5.10 (9.49) (-16, 22) (*22*)	2.90 (10.66) (-22, 29) (*29*)	**MD change from baseline**: 2.68(-2.01, 7.37) p-value=0.257	
		General disease specific symptoms: MS functional composite score			(*22*)	*(21)*	0.25 (0.364)	0.19 (0.174)	**MD change from baseline**: .06(-0.13, .24) p-value=0.535	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		General disease specific symptoms: Guys Neurological Disability Scale (GNDS)			(*33*)	*(32)*	-1.6 (4.5) (-11, 10) (*10*)	-0.5 (4.4) (-10, 11) (*11*)	**MD change from baseline**: -1.57(-3.73, 0.59) p-value=0.15	
		Psychological Measurements: Depression (HADS depression)			(*33*)	*(32)*	-0.10 (2.95) (-9, 4)(*4*)	-0.4 (2.01) (-4, 3)(*3*)	**MD change from baseline**: 0.15(-1, 1.31) p-value=0.795	
		Psychological Measurements: Anxiety (HADS anxiety)			(*33*)	*(32)*	-1 (2.09) (-5, 3)(*3*)	-0.50 (2.45) (-4, 5)(*5*)	**MD change from baseline**: -0.65(-1.78, .47) p-value=0.249	
		Pain: NRS	6.58 (6.00, 7.15) *(33)*	6.37 (5.77, 6.97) *(32)*	3.85 (3.13, 4.58) (*33*)	4.96 (4.19, 5.72) *(32)*	-2.7 (1.91)	-1.4 (1.65)	**MD change from baseline**: -1.25(-2.11, -0.39) p-value=0.005	
		Psychological Measurements: Brief Repeatable Battery of Neuopsychological Test Score ('Symbol Digit Modalities Test')			(*33*)	*(32)*	1.2 (6.28) (-12, 15) (*15*)	3.7 (4.64) (-4, 14) (*14*)	**MD change from baseline**: -2.53(-5.22, 0.15) p-value=0.064	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		Psychological Measurements: Brief Repeatable Battery of Neuopsychological Test Score ('10/36 Spatial Recall')			(*33*)	(*30*)	4.2 (10.84) (-28, 24) (*24*)	-1.5 (8.91) (-17, 23) (*23*)	**MD change from baseline**: 2.54(-1.64, 6.71) p-value=0.230	
		Pain: Neuropathic pain scale (0-10 NRS)	46.90 (41.74, 52.07) *(33)*	45.79 (40.23, 51.36) *(32)*	31.90 (26.56, 37.25) (*33*)	37.73 (31.40, 44.06) *(32)*	-15.3 (13.23)	-8.1 (14.6)	**MD change from baseline**: -6.58(-12.97, -0.19) p-value=0.044	
		Psychological Measurements: Brief Repeatable Battery of Neuopsychological Test Score ('Paced Autitory Serial Addition Test (2 second interval)')			(*29*)	(*29*)	5.2 (7.4) (-10, 24) (*24*)	3.6(7.2) (-20, 19) (*19*)	**MD change from baseline**: 1.85(-1.93, 5.63) p-value=0.33	
		Psychological Measurements: Brief Repeatable Battery of Neuopsychological Test Score ('Selective Reminding')			(*33*)	(*32*)	-0.9 (10.52) (-20, 23) (*23*)	5.7 (10.20) (-19, 26) (*26*)	**MD change from baseline**: -6.95(-12.12, -1.77) p-value=0.009	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
Selvarajah (2010)[136] **Study design:** Parallel group RCT	**Intervention:** Nabiximols (Sativex) **Comparator:** Placebo **Timing:** 12 weeks **Analysis:** modified ITT; 29/30 randomised patients - 1 placebo patient excluded due to protocol violations	**QoL:** EQ-5D (Health status index)	0.40 (0.21) *(15)*	0.43 (0.21) *(14)*	0.54 (0.22) *(15)*	0.60 (0.20) *(14)*			p-value=0.87	**Analysis Method:** Linear regression; Multiple linear regression was used for a normal distribution, while skewed distribution was initially transformed.
		QoL: EQ-5D (Health status VAS)	46.0 (20.4) *(15)*	44.6 (21.8) *(14)*	58.1 (20.5) *(15)*	56.4 (11.7) *(14)*			p-value=0.92	
		QoL: SF36 (Physical functioning)	26.9 (15.1) *(15)*	30.8 (22.7) *(14)*	30.5 (16.6) *(15)*	36.5 (27.9) *(14)*			p-value=0.63	
		QoL: SF36 (Role physical)	8.9 (27.1) *(15)*	12.5 (23.5) *(14)*	12.5 (32.1) *(15)*	39.3 (47.7) *(14)*			p-value=0.12	
		QoL: SF36 (Bodily pain)	22.4 (15.5) *(15)*	25.7 (11.3) *(14)*	35.6 (16.6) *(15)*	41.2 (24.6) *(14)*			p-value=0.64	
		QoL: SF36 (General health)	33.5 (18.7) *(15)*	28.4 (20.8) *(14)*	34.1 (18.2) *(15)*	29.6 (19.5) *(14)*			p-value=0.78	
		QoL: SF36 (Social functioning)	50.8 (32.5) *(15)*	48.2 (24.9) *(14)*	55.4 (25.3) *(15)*	67.0 (27.6) *(14)*			p-value=0.08	
		QoL: SF36 (Role emotional)	38.1 (41.1) *(15)*	33.3 (40.8) *(14)*	54.8 (46.4) *(15)*	47.6 (48.4) *(14)*			p-value=0.76	
		QoL: SF36 (Mental health)	57.9 (22.6) *(15)*	57.1 (19.9) *(14)*	64.4 (20.3) *(15)*	59.4 (20.6) *(14)*			p-value=0.76	
		Pain: McGill Pain rating (Affective scale)	4.6 (4.3) *(15)*	5.0 (3.8) *(14)*	3.1 (2.3) *(15)*	3.6 (3.8) *(14)*			**MD change from baseline**: -1.3(-3.0, 2.4) p-value=0.81	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		Pain: McGill Pain rating (VAS)	7.6 (1.8) *(15)*	6.9 (1.7) *(14)*	5.1 (2.2) (*15)*	3.8 (2.6) *(14)*			**MD change from baseline**: 1.0(-0.91, 3.40) p-value=0.24	
		QoL: SF36 (Vitality)	28.3 (23.2) *(15)*	30.8 (19.2) *(14)*	33.9 (22.4) (*15)*	39.6 (19.4) *(14)*			p-value=0.45	
		Pain: Muscular pain (100mm VAS scale)	52.0 (34.2) *(15)*	41.4 (28.3) *(14)*	37.9 (32.9) (*15)*	20.4 (29.9) *(14)*			**MD change from baseline**: 10.3 (-9.15, 33.00) p-value=0.26	
		Pain: McGill Pain rating (Sensory scale)	19.2 (6.9) *(15)*	16.3(6.3) *(14)*	14.7(7.2) (*15)*	12.5(8.7) *(14)*			**MD change from baseline**: 3.30(-5.39, 8.44) p-value=0.65	
		Pain: McGill Pain rating (Present pain intensity)	2.5 (1.1) *(15)*	2.0 (1.0) *(14)*	2.1 (1.1) (*15)*	1.4 (1.7) *(14)*			**MD change from baseline**: 0.53(-0.79, 1.40) p-value=0.57	
		Pain: Neuropathic pain scale	67.1 (19.4) *(15)*	63.6 (14) *(14)*	51.6 (21.9) (*15)*	51.9 (24.1) *(14)*			**MD change from baseline**: -7.80(-20.10, 12.10) p-value=0.62	
		Pain: Total pain score (Average of superficial, deep and muscular pain scores)	55.8 (26.7) *(15)*	44.9 (21.5) *(14)*	40.1 (28.5) (*15)*	25.2 (28.8) *(14)*			**MD change from baseline**: 9.50(-11.30, 27.80) p-value=0.40	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		Pain: Superficial pain (100mm VAS scale)	52.3 (33.0) *(15)*	45.9 (24.6) *(14)*	37.9 (32.1) *(15)*	30.2 (30.1) *(14)*			**MD change from baseline**: 9.10(-15.30, 21.93) p-value=0.72	
		Pain: Deep pain (100mm VAS scale)	63.1 (29.4) *(15)*	47.4 (21.4) *(14)*	44.5 (32.7) *(15)*	24.9 (29.5) *(14)*			**MD change from baseline**: 10.50(-12.20, 30.80) p-value=0.38	
Serpell (2014)[81] **Study design:** Parallel group RCT	**Intervention:** Nabiximols (Sativex) **Comparator:** Placebo **Timing:**15 weeks **Analysis:** modified ITT; 240/246 patients for whom on treatment efficacy data were available	**Pain:** Brief pain inventory short form (BPI-SF) (Pain severity composite score)			*(122)*	*(117)*			**MD change from baseline**: -0.25 (SE 0.236) (-0.72, 0.21) p-value=0.288	**Analysis Method:** ANCOVA; Models included treatment and centre group as factors and baseline values as a covariate
		Sleep: Numerical rating scale (0-10)			*(122)*	*(117)*			**MD change from baseline**: -0.83 (SE 0.306) (-1.43, -0.23) p-value=0.007	
		Pain: Neuropathic pain scale			*(122)*	*(117)*			**MD change from baseline**: -2.86 (SE 2.211) (-7.22, 1.50) p-value=0.198	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		Pain: (Peripheral neuropathic pain 0-10 NRS)			*(122)*	*(117)*			**MD change from baseline**: -0.34 (SE 0.23) (-0.79, 0.11) p-value=0.139	
		Pain: Brief pain inventory short form (BPI-SF) (Average pain)			*(122)*	*(117)*			**MD change from baseline**: -0.34 (SE 0.237) (-0.71, 0.12) p-value=0.148	
		Pain: Brief pain inventory short form (BPI-SF) (Pain interference composite score)			*(122)*	*(117)*			**MD change from baseline**: -0.32 (SE 0.241) (-0.80, 0.15) p-value=0.183	
		QoL: EQ-5D (Weighted health status index VAS)			*(122)*	*(117)*			**MD change from baseline**: -0.01 (SE 0.024) (-0.06, 0.04) p-value=0.617	
		QoL: EQ-5D (self-rated health status VAS)			*(122)*	*(117)*			**MD change from baseline**: -0.75 (SE 2.459) (-5.60, 4.09) p-value=0.760	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		Pain: Brief pain inventory short form (BPI-SF) (worst pain)			*(122)*	*(117)*			**MD change from baseline**: -0.30 (SE 0.265) (-0.82, 0.22) p-value=0.255	
Skrabek (2008)[140] **Study design:** Cross-over RCT	**Intervention:** Nabilone (Cesamet) **Comparator:** Placebo **Timing:**4 weeks **Analysis:** Not specified	**Pain:** Descriptor Differential Scale (VAS for pain (cm))	6.86 (2.14) *(20)*	6.20 (1.46) *(20)*	4.79 *(15)*	5.58 *(18)*	-2.04		p-value≤0.02	**Analysis Method:** Student's t-test
		Mobility/ Disability: Fibromyalgia impact questionnaire	66.45 (12.76) *(20)*	66.53 (16.21) *(20)*	54.4	65.4	-12.07		p-value≤0.02	
		Pain: Anxiety (FIQ subscale)	5.87 (1.72) *(20)*	5.39 (2.14) *(20)*	4.22	5.94	-1.67		p-value≤0.02	
Steele(1980)[110] **Study design:** Cross-over RCT	**Intervention:** Nabilone (Cesamet) **Comparator:** Prochlorperazine **Timing:** 1 chemotherapy cycle **Analysis:** Per protocol	**Nausea & vomiting:** Vomiting severity/intensity (Frequency (hours))			6.0 *(37)*	11.5 *(37)*				Median, range reported
		Nausea & vomiting: Vomiting duration (hours)			3.19 (0, 48) *(37)*	5.17 (0, 36) *(37)*				
		Nausea & vomiting: Nausea duration (days)			0.73 (0, 3) *(37)*	1.02 (0, 3) *(37)*				

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		Nausea & vomiting: Vomiting severity/intensity (0 (none) - 3 (severe))			1.53 *(37)*	1.86 *(37)*				
Struwe (1993)[130] **Study design:** Cross-over RCT	**Intervention:** Dronabinol (Marinol) **Comparator:** Placebo **Timing:**5 weeks **Analysis:** Per protocol	**Global impression:** (Symptoms/ functional limitations (out of 340))	*(12)*	*(12)*	(*5*)	(*5*)	-31 (-87, -7.5)	-3.50 (-32, 13.70)	**Median difference**: -33.5 p-value=0.04	Median, range reported **Analysis Method:** Wilcoxen signed rank
		Appetite & weight: Appetite (Score 0 (extremely hungry) - 100 (not hungry))	*(12)*	*(12)*	(*5*)	(*5*)	Median (range) -19.6 (-38.1, -6 .1)	Median (range) -5. 7 (-32.0, 13.7)	**Median difference**: -19.5 p-value=0.14	
		Appetite & weight: Caloric/food intake (kcal/kg/24h)	*(12)*	*(12)*	(*5*)	(*5*)	Median (range) 3.48 (-4.5, 32.9)	Median (range) 0.84 (-8.2, 13.6) (*13.600*)	**Median difference**: 4.2 p-value=0.50	
		Appetite & weight: Weight (KG)	*(12)*	*(12)*	(*5*)	(*5*)	Median (range) 0.5 (0.2, 0.98)	Median (range) -0. 7 (-1.1, 0.9)	**Median difference**: 1.0 p-value=0.13	
		Appetite & weight: (Body fat (%))	*(12)*	*(12)*	(*5*)	(*5*)	Median (range) 1.0 (-0.6, 1.9)	Median (range) 0.06 (-1.4, 1.6)	**Median difference**: 0.76 p-value=0.04	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
Svendsen(2004) [146] **Study design:** Cross-over RCT	**Intervention:** Dronabinol (Marinol) **Comparator:** Placebo **Timing:** 3 weeks **Analysis:** ITT	**Pain:** NRS (Spontaneous pain score.)			4.0 (2.3, 6.0) (*24*)	5.0 (4.0, 6.4) (*24*)			**Median difference (CI)**: -0.60 (-1.8, 0.0) p-value=0.02	Median, IQR reported **Analysis Method:** Hodges-Lehmann estimator
		QoL: SF36 (General health)			(*23*)	*(23)*			**Median difference (CI)**: 0.0 (-6, 5) p-value=0.95	
		QoL: SF36 (Bodily pain)			(*23*)	*(23)*			**Median difference (CI)**: 9.8 (0.0, 21.5) p-value=0.037	
		QoL: SF36 (Role physical)			(*23*)	*(23)*			**Median difference (CI)** 0.0 (-25.0, 12.5) p-value=0.73	
		QoL: SF36 (Physical functioning)			(*23*)	*(23)*			**Median difference (CI)**: 5.0 (0.0, 7.5) p-value=0.06	
		General disease specific symptoms: (EDSS)			(*24*)	*(24)*			p-value=1.00	
		Pain: Pain relief (NRS (0-10))			(*24*)	*(24)*			**Median difference (CI)**: 2.5 (0.5, 4.5) p-value=0.035	
		QoL: SF36 (Vitality)			(*23*)	*(23)*			**Median difference (CI)**: 2.5 (-5.0, 10.0) p-value=0.52	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		QoL: SF36 (Role emotional)			(*23*)	*(23)*			**Median difference (CI)**: 0 (-33, 0) p-value=0.46	
		QoL: SF36 (Mental health)			(*23*)	*(23)*			**Median difference (CI)**: 8(0, 12) p-value=0.023	
		QoL: SF36 (Social functioning)			(*23*)	*(23)*			**Median difference (CI)**: 6.3 (0.0, 12.5) p-value=0.17	
		Pain: (Radiating pain (NRS 0-10))			(*24*)	*(24)*			**Median difference (CI)**: -0.6 (-1.3, 0.0) p-value=0.039	
Timpone(1997)[8] [8]	**Intervention:** Dronabinol (Marinol) **Comparator:** Megestrol acetate 750 mg **Timing:** 12 weeks **Analysis:** modified ITT (Results for 34 out of 37 participants reported)	**Appetite & weight:** Weight (kg)	61.2 (9.0) *(12)*	60.7 (10.7) *(12)*	(*11*)	*(10)*	-2.0 (1.3)	6.5 (1.1)		

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
	Intervention: Dronabinol + megestrol acetate (5+750) **Comparator:** Megestrol acetate 750 mg		63.3 (12.8) *(13)*	60.7 (10.7) *(12)*	*(13)*	*(10)*	6.0 (1.0)	6.5 (1.1)		
Tomida (2006)[224] **Study design:** Cross-over RCT	**Intervention:** Cannabidiol (CBD) (20mg) **Comparator:** Placebo **Timing:** 12 hrs	**Physiological Measurements:** Intraocular pressure (Average of both eyes per patient)	28.08 (2.96) *(6)*	27.38 (4.40) *(6)*	22.33 (4.82) (*6*)	22.21 (4.38) *(6)*			NR	
	Intervention: Cannabidiol (CBD) (40mg) **Comparator:** Placebo		27.58 (3.22) *(6)*	27.38 (4.40) *(6)*	21.96 (4.43) (*6*)	22.21 (4.38) *(6)*				
	Intervention: THC **Comparator:** Placebo		27.38 (3.64) *(6)*	27.38 (4.40) *(6)*	21.63 (4.11) (*6*)	22.21 (4.38) *(6)*				
Ungerleider(1982)[91] **Study design:** Cross-over RCT	**Intervention:** THC **Comparator:** Prochlorperazine **Timing:**16 hours (evening of chemotherapy) **Analysis:** Modified ITT (reported for single/ multiple day regimen,	**Appetite & weight:** Caloric/food intake (Food intake) **Single day regimen**	1.61 *(98)*	1.50 *(98)*	1.29 (*98*)	1.31 *(98)*				**Analysis Method:** Repeated measures of ANOVA **Test statistic:** F
		Appetite & weight: Appetite **Single day regimen**	1.80 *(98)*	1.90 *(98)*	1.76 (*98*)	1.65 *(98)*				

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
	terminated)	**Nausea & vomiting:** Nausea severity/intensity (Nausea/vomiting scale (7 point scale)) **Single day regimen**	0.2 *(214)*		1.10 *(98)*	0.87 *(98)*				
		Appetite & weight: Caloric/food intake (Food intake) **Multiple day regimen**	1.38 *(41)*	1.38 *(41)*	1.27 *(41)*	1.19 *(41)*				
		Appetite & weight: Appetite **Multiple day regimen**	1.74 *(41)*	1.84 *(41)*	1.74 *(41)*	1.66 *(41)*				
		Nausea & vomiting: Vomiting severity/intensity (Nausea/ vomiting scale (7 point scale)) **Multiple day regimen**	0.2 *(214)*		0.18 *(41)*	0.29 *(41)*				
Vaney(2004)[192] **Study design:** Cross-over RCT	**Intervention:** THC/CBD **Comparator:** Placebo **Timing:** 9 days	**Spasticity:** Ashworth	12.2 (6.4) *(57)*	13.1 (6.3) *(57)*	11.6 (6.5) (*50*)	11.5 (6.1) *(50)*			**MD change from baseline**: -0.80 (0.66) (-2.1, 0.5) p-value=0.2379	**Analysis Method:** Linear regression; Mixed linear modelling or the generalised

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
	Analysis: modified ITT (7 withdrawals not included)	**Sleep:** Sleep disturbance ("Waking up again")	0.76 (0.43) *(57)*	0.76 (0.43) *(57)*	0.66 (0.48) *(50)*	0.74 (0.44) *(50)*			**MD change from baseline**: 1.69 (0.63, 4.59) p-value=0.308	estimating equations (GEE) within generalized linear models were used. Available baseline values were included in the model as covariables. Period and carry-over effects, initially included in the statistical model.
		Sleep: Sleep quality ("Falling asleep fast")	0.66 (0.48) *(57)*	0.62 (0.49) *(57)*	0.78 (0.42) *(50)*	0.64 (0.48) *(50)*			**MD change from baseline**: 2.13 (0.95, 4.74) p-value=0.073	
Wada (1982)[105] **Study design:** Cross-over RCT	**Intervention:** Nabilone (Cesamet) **Comparator:** Placebo **Timing:** 1 chemotherapy cycle **Analysis:** Modified ITT (Per protocol, 5 patients excluded from Placebo due to continous vomiting)	**Nausea & vomiting:** Vomiting severity/intensity (Number of vomiting episodes)	*(114)*	*(114)*	4.19 *(92)*	7.08 *(87)*			p-value≤0.001	**Analysis Method:** NR

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
	Analysis: Per protocol	**Nausea & vomiting:** Nausea severity/intensity (Severity rated as none (0), 1 (mild), moderate (2), severe (3).)	*(114)*	*(114)*	1.22 *(92)*	1.96 *(92)*			p-value≤0.001	**Analysis Method:** "Non-parametric test on ranks"
Wade (2004)[3] **Study design:** Parallel group RCT	**Intervention:** Nabiximols (Sativex) **Comparator:** Placebo **Timing:** 6 weeks **Analysis:** Not specified	**Spasticity:** Spasm Frequency Scale (Primary symptom VAS score)	*(80)*	*(80)*	(*77*)	*(77)*	-21.4	-20.1	**MD change from baseline**: -1.27(7.67)(-16.90, 14.30) p-value=0.869	**Analysis Method:** ANCOVA;
		Sleep: (VAS scale: Quality of sleep)	*(80)*	*(80)*	(*79*)	*(77)*	-16.7	-9.6	**MD at follow-up**: -7.10 (3.55) (-14.11, -0.08) p-value=0.047	
		General disease specific symptoms: Barthel Index of activities of daily living (ADL)	14.20 (6.1) *(79)*	15.70 (5.4) *(80)*	(*78*)	*(77)*	-0.38 (1.81)	0.09 (1.59)	**MD at follow-up**: -0.47 (0.27) (-1.01, 0.07) p-value=0.09	
		Mobility/ Disability: Acitivities of daily living (Nine-hole peg test of manual dexterity)	*(80)*	*(80)*	(*66*)	*(65)*	-0.47 (3.91)	0.38 (2.33)	**MD at follow-up**: -0.52 (0.54) (-1.58, 0.55) p-value=0.16	**Analysis Method:** Mann-Whitney/ Wilcoxon test;

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		Mobility/ Disability: Walk time (Time in seconds to walk 10 meters)	*(80)*	*(80)*	(*38*)	*(47)*	-2.78 (4.75)	-0.74 (7.85)	**MD at follow-up**: -2.35 (1.41) (-5.16, 0.46) p-value=0.07	
		Psychological Measurements: Depression (Beck Depression Inventory (BDI))	*(80)*	*(80)*	(*78*)	*(77)*	-2.14 (5.59)	-2.83 (6.50)	**MD at follow-up**: 0.69 (0.91) (-1.11, 2.50) p-value=0.45	**Analysis Method:** ANCOVA; Baseline primary symptom score as the covariate
		Spasticity: (Primary symptom VAS score: Tremor)	*(80)*	*(80)*	(*77*)	*(77)*	-9.20	-5.10	**MD change from baseline**: -4.07 (16.79) (-42.1, 33.9) p-value=0.814	
		Pain: (Primary symptom VAS score)	*(80)*	*(80)*	(*77*)	*(77)*	-9.8	-19.9	**MD change from baseline**: 10.04 (8.45) (-7.14, 27.22) p-value=0.24	
		Spasticity: Spasm severity (Primary symptom VAS score)	*(80)*	*(80)*	(*77*)	*(77)*	-21.7	-21.6	**MD change from baseline**: -0.08 (8.42) (-17.28, 17.11) p-value=0.992	
		Sleep: Numerical rating scale (VAS scale: Feeling upon waking)	*(80)*	*(80)*	(*79*)	*(77)*	-9.56	-8.20	**MD at follow-up**: -1.36 (3.76) (-8.80, 6.07) p-value=0.717	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		Global impression: General Health Questionnaire 12 (General Health Questionnaire)	*(80)*	*(80)*	(*79)*	*(75)*	-2.02	-2.74	**MD at follow-up**: 0.72 (1.57) (-2.38, 3.82) p-value=0.65	
		Sleep: (VAS scale: How much sleep)	*(80)*	*(80)*	(*79)*	*(77)*	-13.9	-9.4	**MD at follow-up**: -4.53 (3.50) (-11.45, 2.40) p-value=0.198	
		Spasticity: NRS (Primary symptom VAS scores)	*(80)*	*(80)*	(*77)*	*(77)*	-17.00	1.42	**MD change from baseline**: -18.40 (6.59) (-31.80, -5.01) p-value=0.009	
		Spasticity: Fatigue (Fatigue Severity Scale)	*(80)*	*(80)*	(*78)*	*(76)*	-0.26	-0.14	**MD at follow-up**: -0.12 (0.15) (-0.43, 0.18) p-value=0.43	
		General disease specific symptoms: Guys Neurological Disability Scale (GNDS)	*(80)*	*(80)*	(*66)*	*(63)*	-0.93	-2.74	**MD at follow-up**: 1.81 (0.91) (0.02, 3.60) p-value=0.048	
		Spasticity: Ashworth (modified Ashworth Scale of Spasticity)	5.0 (3.7) *(76)*	4.60 (4.4) *(74)*	(*73)*	*(70)*	-0.37 (2.51)	-0.59 (2.04)	**MD at follow-up**: 0.22 (0.37) (-0.50, 0.94) p-value=0.55	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		Spasticity: Numerical rating scale (Primary Symptom: VAS: Tremor)	*(80)*	*(80)*	(*7*)	*(6)*	-21.4	-25.2	**MD at follow-up**: 3.75 (15.20) (-30.20, 37.70) p-value=0.81	
		Pain: NRS (Primary Symptom: VAS: Pain)	*(80)*	*(80)*	(*18*)	*(18)*	-11.4	-20.2	**MD at follow-up**: 8.73 (9.40) (-10.40, 27.80) p-value=0.360	
		General disease specific symptoms: (Primary Symptom Score (PSS): Sum of target symptoms (spasticity, spasm, bladder problems, tremor or pain) each measured on VAS scale.)	*(80)*	*(80)*	(*79*)	*(77)*	-25.2 (23.3)	-19.4 (27.0)	**MD at follow-up**: -5.93 (3.84) (-13.52, 1.65) p-value=0.124	
		Spasticity: Numerical rating scale (Primary Symptom: VAS: Spasms)	*(80)*	*(80)*	(*20*)	*(18)*	-26.5	-21.2	**MD at follow-up**: -5.30 (7.15) (-19.81, 9.22) p-value=0.464	
		Spasticity: Numerical rating scale (Primary Symptom: VAS spasticity)	*(80)*	*(80)*	(*19*)	*(18)*	-31.2 (21.6)	-8.4 (23.5)	**MD at follow-up**: -22.79 (6.26) (-35.52, -10.07) p-value=0.001	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
Wallace (2013)[76] **Study design:** Cross-over RCT **Comments:** Overall effect of cannabis dose on spontaneous pain, p=0.029.	**Intervention:** THC 7% **Comparator:** Placebo **Timing:** 4 hours **Analysis:** Not specified	**Pain:** Total pain score (Spontaneous pain Score (area under curve - vs time))							p-value=0.013	**Analysis Method:** Not specified.
		Pain: Descriptor Differential Scale (mean lowest achieved spontaneous pain score)							p-value=0.017	
	Intervention: THC (all concentrations) **Comparator:** Placebo **Timing:** 4 hours **Analysis:** Not specified	**Psychological Measurements:** Mental health								**Comments:** There was a significant difference in two of the three neuropsychological tests (Paced Auditory Serial Addition Test, p=0.005; Trail Making Test B, p=0.049; Trail Making Test A, p=0.362) -presume this is overall dose vs placebo.
Ware (2010)[133] **Study design:** Cross-over RCT	**Intervention:** Nabilone (Cesamet) **Comparator:** Amitriptyline **Timing:** 2 weeks	**Mobility/ Disability:** Fibromyalgia impact questionnaire (Total score)	62.6 (15.2) *(32)*						**MD change from baseline**: -0.7 (-7.3, 5.8)	**Analysis Method:** Linear regression; Within-participant comparison of sleep scores regression models included

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
	Analysis: Not specified; All participants who were randomised, received at least one actuation of study medication and had on-treatment efficacy data	**Psychological Measurements:** Mood (Profile of mood states score)	29.5 (16.6) *(32)*						**MD change from baseline**: 1.4 (-4.3, 7.20)	treatment, period and order
		Pain: McGill Pain rating (PPI)	2.3 (0.8) *(32)*						**MD change from baseline**: -0.1 (-0.3, 0.2)	
		Sleep: Leeds Sleep Evaluation Questionnaire (LSEQ) (Speed of getting to sleep (100 mm VAS))							**MD change from baseline**: -0.70 (-1.36, 0.03)	
		Sleep: Leeds Sleep Evaluation Questionnaire (LSEQ) (Ease of getting to sleep (100 mm VAS))							**MD change from baseline**: -0.70 (-1.40, 0.02)	
		Sleep: Leeds Sleep Evaluation Questionnaire (LSEQ) (Restfulness of sleep (100 mm VAS))							**MD change from baseline**: 0.48 (0.01, 0.95)	
		Sleep: Insomnia severity index (ISI)	18.3 (5.2) *(32)*						**MD change from baseline**: -3.25 (-5.26, -1.24)	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
Ware (2010)[135] **Study design:** Cross-over RCT	**Intervention:** THC (2.5%) **Comparator:** Placebo **Timing:** 5 days **Analysis:** Per protocol; Results for 21 or 22 patients reported (23 patients randomised)	**Psychological Measurements:** POMS (Total mood disturbance)			38.0 (24.5) (*22*)	39.1 (22.7) (*21*)				
		QoL: EQ-5D (State of Health, VAS)			48.6 (18.9) (*22*)	54.1 (19.5) (*21*)				
		Sleep: Leeds Sleep Evaluation Questionnaire (LSEQ) (Feeling now (tired - alert). Modified LSEQ (no further details)			1.3 (1.7) (*22*)	4.1 (1.5) (*21*)				
		Pain: McGill Pain rating (Total score)			30.4 (18.1) (*22*)	29.1 (17.0) (*21*)				
		Pain: NRS (Average daily pain (0-10 NRS))			5.9 (1.9) (*22*)	6.1 (1.6) (*21*)			**MD at follow-up**: -0.13 (-0.83, 0.56)	A generalized linear model including drug, period and first order carryover effects was fitted. If the arryover effect or period effect was not significant, then a reduced model was refitted.

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
	Intervention: THC (6%) **Comparator:** Placebo **Timing:**5 days	**Sleep:** Leeds Sleep Evaluation Questionnaire (LSEQ) (Feeling now (tired - alert). Modified LSEQ (no further details)			4.9 (2.0) (*21*)	4.1 (1.5) *(21)*				
		Psychological Measurements: POMS (Total mood disturbance)			36.9 (25.9) (*21*)	39.1 (22.7) *(21)*				
		QoL: EQ-5D (State of Health, VAS)			52.9 (22.0) (*21*)	54.1 (19.5) *(21)*				
		Pain: McGill Pain rating			25.8 (14.5) (*21*)	29.1 (17.0) *(21)*				
		Pain: NRS (Average daily pain (0-10 NRS))			6.0 (1.8) (*21*)	6.1 (1.6)*(21)*			**MD at follow-up**: -0.09 (-0.78, .60)	Generalized linear as above.
	Intervention: THC (9.4%) **Comparator:**	**QoL:** EQ-5D (State of Health, VAS)			56.3 (20.4) (*22*)	54.1 (19.5) *(21)*				

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
	Placebo	**Sleep:** Leeds Sleep Evaluation Questionnaire (LSEQ) (Feeling now (tired - alert). Modified LSEQ (no further details)			4.0 (1.7) (*22*)	4.1 (1.5) (*21*)				
		Psychological Measurements: POMS (Total mood disturbance)			31.2 (22.4) (*22*)	39.1 (22.7) (*21*)				
		Pain: McGill Pain rating (Total score)			24.8 (14.7) (*22*)	29.1 (17.0) (*21*)				
		Pain: NRS (Average daily pain (0-10 NRS))			5.4 (1.7) (*22*)	6.1 (1.6) (*21*)			**MD at follow-up**: -0.71 (-1.40, -0.02) p-value≤0.05	Generalized linear model as above
Wilsey (2013)[134] **Study design:** Cross-over RCT	**Intervention:** Cannabis (not specified) (3.53%) **Comparator:** Placebo **Timing:**5 hours	**Pain:** (Unpleasantness)							p-value<0.001	**Analysis Method:** Repeated measures model; Patients treated as random effect, takes into account repeated
		Pain: VAS score (Intensity; VAS scale (0-100)) **Whole group:**					42.3	52.3	p-value=0.0018	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
	Analysis: Per protocol;	**Global impression:** Patient global impression (Global impression of pain relief scale of -3 to +3) **Whole group:**			1.16	0.47			p-value=0.0001	measures aspect of the within-participants cross-over. Included dose, time, and dose x time interaction, and treatment sequence and timextime. P-value for overall model not individual treatment c
	Cannabis (not specified) (1.29%)	**Pain:** VAS score (Intensity; VAS scale (0-100)) **Whole group:**					41.3	52.3	p-value=0.0018	
		Global impression: Patient global impression (Global impression of pain relief scale of -3 to +3)			1.02	0.47			p-value=0.0001	
Wilsey (2011)[138] **Study design:** Cross-over RCT	**Intervention:** THC 3.5% **Comparator:** Placebo **Timing:** 4 hours **Analysis:** Per protocol	**Pain:** Descriptor Differential Scale (Global impression of change (pain relief))							**MD at follow-up**: 0.12 (0.029) (SE 0.065, 0.18) p-value<0.01	Linear mixed model **Test statistic:**
		Pain: Descriptor Differential Scale (VAS Pain intensity)							**MD at follow-up**: -0.00 36 (SE 0.0017) (-0.0069, 0.0003) p-value=0.03	

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		Pain: Descriptor Differential Scale (Pain unpleasantness (measure of the emotional dimension of pain by VAS)							**MD at follow-up**: -0.21 (SE 0.06) (-0.33, -0.09) p-value≤0.01	
	Intervention: THC 7% **Comparator:** Placebo **Timing:** 4 hours **Analysis:** Per protocol	**Pain:** Descriptor Differential Scale (Pain unpleasantness (measure of the emotional dimension of pain by VAS).							**MD at follow-up**: -0.21 (SE 0.06) (-0.33, -0.09) p-value≤0.01	
		Pain: Descriptor Differential Scale (Global impression of change (pain relief).							**MD at follow-up**: 0.12 (SE 0.029) (0.064, 0.18) p-value<0.01	
		Pain: Descriptor Differential Scale (VAS Pain intensity)							**MD at follow-up**: -0.0035 (SE 0.0017) (-0.0068, -0.0002) p-value=0.04	
Zajicek(2003)[89] **Study design:** Parallel group	**Intervention:** Dronabinol (Marinol)	**Global impression:** Questionaire 30	32.4 (11.61) *(185)*	31.84 (11.74) *(185)*	30.43 (13.28) *(185)*	29.68 (10.06) *(185)*	1.97 (13.10)	2.16 (11.99)		

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
RCT	**Comparator:** Placebo **Timing:** 13 weeks **Analysis:** modified ITT; 84/630 patients in ITT population not reported	**Spasticity:** Ashworth (scale 0-4)			(*197*)	(*207*)	-1.86 (7.95)	-0.92 (6.56)		
		Mobility/ Disability: Rivermead Mobility Index	6.33 (4.37) (*206*)	6.48 (4.590) (*213*)	6.55 (4.48) (*179*)	6.49 (4.75) (*197*)	0.22 (1.71)	0.03 (1.36)		
		Mobility/ Disability: Barthel Index of activities of daily living (ADL)	20.52 (7.32) (*168*)	21.48 (7.80) (*185*)	20.67 (7.24) (*168*)	21.4 (8.01) (*183*)	0.19 (2.62)	-0.04 (2.51)		
		Mobility/ Disability: 10 m walk time (s)	8.01	5.00	1.07	2.08	-6.94	-2.92		
		Mobility/ Disability: UK neurological disability score	22.0 (8.30) (*169*)	21.37 (8.16) (*185*)	20.71 (8.58) (*169*)	19.48 (8.28) (*185*)	-1.29 (6.04)	-1.90 (5.43)		
	Intervention: THC/CBD **Comparator:** Placebo **Timing:**13 weeks **Analysis:** modified ITT; Number of participants excluded varied by outcome	**Spasticity:** Ashworth (scale 0-4)			(*207*)	(*207*)	-1.24 (6.60)	-0.92 (6.56)		
		Mobility/ Disability: Rivermead Mobility Index	6.26 (4.36) (*211*)	6.48 (4.59) (*213*)	6.31 (4.51) (*197*)	6.49 (4.75) (*197*)	0.04 (1.78)	0.03 (1.36)		
		Mobility/ Disability: Barthel Index of activities of daily living (ADL)	20.91 (7.42) (*181*)	21.48 (7.80) (*185*)	20.78 (7.60) (*178*)	21.40 (8.01) (*183*)	-0.07 (2.86)	-0.040 (2.51)		

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		Mobility/ Disability: UK neurological disability score	22.24 (7.82) *(181)*	21.37 (8.16) *(185)*	19.99 (8.16) *(181)*	19.48 (8.28) *(185)*	-2.25 (5.940)	-1.90 (5.430)		
		Mobility/ Disability: 10 m walk time (s)	4.01	5.00	1.07	2.08	-2.94	-2.92		
		Global impression: General Health Questionaire 30	33.31 (12.92) *(185)*	31.84 (11.74) *(185)*	30.45 (13.35) *(185)*	29.68 (10.06) *(185)*	2.86(13.76)	2.16 (11.99)		
Zajicek (2012)[87] **Study design:** Parallel group RCT	**Intervention:** THC/CBD **Comparator:** Placebo **Timing:**12 weeks **Analysis:** modified ITT; All patients treated	**General disease specific symptoms:** Muscle stiffness (11 point category rating scale asking how muscle stiffness was compared to before study started.)			5.4 (2.6) *(143)*	6.4 (2.6) *(134)*	-1.8 (2.6)	-0.7 (2.4)		
		Pain: Bodily pain (11 point category rating scale asking how bodily pain compared to before study started.)			4.1 (2.9) *(143)*	4.7 (3.0) *(134)*	-1.2 (2.6)	-0.3 (2.4)		

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		General disease specific symptoms: Multiple Sclerosis Impact Scale (MSIS-29) (Psychological impact)			42.0 (27.5) *(143)*	40.4 (24.4) *(134)*	-6.3 (23.7)	-3.8 (22.8)		
		General disease specific symptoms: Multiple Sclerosis Impact Scale (MSIS-29) (Physical impact)			58.6 (25.7) *(143)*	62.4 (22.7) *(134)*	-10.1 (23.2)	-4.2 (18.5)		
		Spasticity: Multiple Sclerosis Spasticity Scale (MSSS-88) (Social functioning)			18.1 (7.6) *(143)*	17.6 (7.2) *(134)*	-1.2 (6.2)	-1.0 (5.6)		
		Spasticity: Multiple Sclerosis Spasticity Scale (MSSS-88) (Feelings)			30.9 (11.9) *(143)*	30.7 (12.2) *(134)*	-2.1 (8.9)	-1.8 (9.1)		
		Spasticity: Multiple Sclerosis Spasticity Scale (MSSS-88) (Body movement)			30.0 (10.0) *(143)*	31.2 (9) *(134)*	-3.9 (7.7)	-1.8 (7.9)		

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		Spasticity: Multiple Sclerosis Spasticity Scale (MSSS-88) (Ability to walk)			31.6 (7.9) *(143)*	34.2 (6.7) *(134)*	-3.0 (5.7)	-1.4 (4.2)		
		Spasticity: Multiple Sclerosis Spasticity Scale (MSSS-88) (Daily activities)			31.4 (10.1) *(143)*	31.4 (9.4) *(134)*	-1.3 (8.0)	-1.6 (8.2)		
		Spasticity: Multiple Sclerosis Spasticity Scale (MSSS-88) (Muscle spasms)			29.1 (11.0) *(143)*	30.5 (12.1) *(134)*	-5.2 (9.9)	-2.1 (9.2)		
		Spasticity: Multiple Sclerosis Spasticity Scale (MSSS-88) (Pain/discomfort)			21.7 (7.6) *(143)*	22.5 (7.6) *(134)*	-3.0 (6.4)	-1.6 (6.2)		
		Spasticity: Multiple Sclerosis Spasticity Scale (MSSS-88) (Muscle stiffness)			31.8 (9.6) *(143)*	34.2 (9.2) *(134)*	-5.0 (8.5)	-1.3 (7.9)		
		Sleep: Sleep quality (11 point category rating scale asking how sleep quality was compared to before study started.)			3.8 (2.9) *(143)*	4.3 (3.0) *(134)*	-1.4 (3.1)	-0.9 (2.6)		

Study details	Intervention, follow-up duration	Outcome	Baseline		Follow-up		Change from baseline		Effect estimate	Analysis details
			Into	Comp	Into	Comp	Into	Comp		
			Mean (sd) (CI) *(number of participants)**							
		Spasticity: Spasm severity (11 point category rating scale asking how muscle spasms were compared to before study started.)			4.7 (2.7) (*143)*	5.4 (2.8) *(134)*	-1.5 (2.7)	-0.7 (2.4)		
		Mobility/ Disability: Multiple sclerosis walking scale (MSWS-12) (Total score)			78.7 (26.2) (*143)*	89.6 (14.6) *(134)*	-9.0 (17.6)	-1.7 (12.4)		

*Some studies reported Median (range) or Median (IQR) rather than means; this is indicated in the analysis box

C. CATEGORICAL OUTCOMES

Study	Interventions	Outcome	Categories	Intervention		Comparator		Analysis
				Number of events	Number of participants	Number of events	Number of participants	
Frytak(1979)[111]	**Intervention** THC **Comparator** Placebo	*Nausea & vomiting;* Occurence of nausea and vomiting **Timing:** 24hrs **Analysis:** mITT (116 of 117 particpants)	None Nausea only Nausea and vomiting	16 2 20	38	7 6 24	37	
		Adverse events; Balance ("coordination problems") **Timing:** 24hrs **Analysis:** mITT (116 of 117 particpants)	None On questioning Volunteered Intolerable	11 9 6 12	38	30 5 1 1	37	
	Intervention THC **Comparator** Prochlorperazine	*Nausea & vomiting;* Occurence of nausea and vomiting **Timing:** 24hrs **Analysis:** mITT (116 of 117 particpants)	None Nausea only Nausea and vomiting	16 2 20	38	17 1 24	41	
		Adverse events; Balance ("coordination problems") **Timing:** 24hrs **Analysis:** mITT (116 of 117 particpants)	None On questioning Volunteered Intolerable	11 9 6 12	38	37 4 0 0	41	

Study	Interventions	Outcome	Categories	Intervention		Comparator		Analysis
				Number of events	Number of participants	Number of events	Number of participants	
GW Pharma Ltd(2005)[77] **Study design:** Parallel group RCT	**Intervention** Nabiximols (Sativex) **Comparator** Placebo	*Global impression;* Patient reported change in nerve pain due to diabetic neuropathy **Timing:** 14 Weeks **Analysis:** ITT	Very much improved Much improved Slightly improved No change Slightly worse Much worse Very much worse	13 40 48 30 6 2 1	140	14 36 35 45 9 2 0	141	OR: 1.30 (0.86, 1.98) p-value=0.219 **Analysis Method** Ordinal logistic regression The model incorporated centre group as a factor
Hutcheon(1983)[103] **Study design:** Parallel group RCT	**Intervention** Levonantradol (2mg) **Comparator** Placebo	*Appetite & weight;* Appetite (Self assessment) **Timing:** 24 Hours **Analysis:** ITT	Good Normal Fair Poor	2 14 6 5	27	4 6 7 10	27	
		Nausea & vomiting; Nausea severity/intensity (Self assessment) **Timing:** 24 Hours **Analysis:** ITT	None Mild Moderate Severe	14 6 7 0	27	9 13 4 1	27	
		Nausea & vomiting; Number of vomiting episodes **Timing:** 24 Hours **Analysis:** ITT	0 1-4 5-10 10	20 3 2 2	27	11 9 7 0	27	
	Intervention Levonantradol (3mg) **Comparator**	*Appetite & weight;* Appetite (Self assessment) **Timing:** 24 Hours **Analysis:** ITT	Good Normal Fair Poor	3 2 13 10	28	4 6 7 10	27	

Study	Interventions	Outcome	Categories	Intervention		Comparator		Analysis
				Number of events	Number of participants	Number of events	Number of participants	
	Placebo	*Nausea & vomiting;* Nausea severity/intensity (Self assessment) **Timing:** 24 Hours **Analysis:** ITT	None Mild Moderate Severe	8 14 5 1	28	9 13 4 1	27	
		Nausea & vomiting; Number of vomiting episodes **Timing:** 24 Hours **Analysis:** ITT	0 1-4 5-10 10	11 11 5 1	28	11 9 7 0	27	
	Intervention Levonantradol (4mg) **Comparator** Placebo	*Appetite & weight;* Appetite (Self assessment) **Timing:** 24 Hours **Analysis:** ITT	Good Normal Fair Poor	1 9 6 9	26	4 6 7 10	27	
		Nausea & vomiting; Nausea severity/intensity (Self assessment) **Timing:** 24 Hours **Analysis:** ITT	None Mild Moderate Severe	13 4 6 3	26	9 13 4 1	27	
		Nausea & vomiting; Number of vomiting episodes **Timing:** 24 Hours **Analysis:** ITT	0 1-4 5-10 10	14 4 8 0	26	11 9 7 0	27	
Johansson(1982)[1] 06 **Study design:** Cross-over RCT	**Intervention** Nabilone (Cesamet) **Comparator** Prochlorperazine	*Nausea & vomiting;* Nausea severity/intensity **Timing:** 1 chemotherapy cycle **Analysis:** Per protocol	None Mild Moderate Severe	3 6 7 2	18	0 3 11 4	18	p-value=0.027 **Analysis Method:** ANVOVA

Study	Interventions	Outcome	Categories	Intervention		Comparator		Analysis
				Number of events	Number of participants	Number of events	Number of participants	
		Nausea & vomiting; Number of vomiting episodes **Timing:** 1 chemotherapy cycle **Analysis:** Per protocol	0 1-5 6-10 11-20 >20	3 3 5 4 3	18	0 2 2 5 9	18	NR
Niederle(1986)[100] **Study design:** Cross-over RCT	**Intervention** Nabilone (Cesamet) **Comparator** Alizapride	*Nausea & vomiting;* Nausea severity/ intensity **Timing:** 5 Days **Analysis:** ITT	None Mild Moderate Severe	12 4 4 0	20	7 6 5 2	20	
Niiranen (1985)[101] **Study design:** Cross-over RCT	**Intervention** Nabilone (Cesamet) **Comparator** Prochlorperazine	*Appetite & weight;* Appetite (Patient assessment) **Timing:** After chemotherapy cycle **Analysis:** Modified ITT; 24 participants with full results repored (out of 32 randomised)	Not diminished Moderately diminished Markedly dimished	8 14 2 0	24	5 15 4 0	24	
		Global impression; Physician global impression of efficacy (very good = no nausea or vomiting after chemotherapy) **Timing:** After chemotherapy cycle **Analysis:** Modified ITT; 24 participants with full results repored (out of 32 randomised)	Very good Good Fair Poor very poor	3 9 5 6 1	24	5 3 6 3 7	24	

Study	Interventions	Outcome	Categories	Intervention		Comparator		Analysis
				Number of events	Number of participants	Number of events	Number of participants	
		Nausea & vomiting; Nausea severity/intensity (Patient assessment) **Timing:** After chemotherapy cycle **Analysis:** Modified ITT; 24 participants with full results repored (out of 32 randomised)	None Mild Moderate Severe	1 7 9 7	24	4 4 10 6	24	p-value= **Analysis Method**
Orr(1980)[109] **Study design:** Cross-over RCT	**Intervention** THC **Comparator** Prochlorperazine	*Nause & vomiting:* Nausea severity/intensity (Patient assessment) **Timing:** 24hrs **Analysis:** Per protocol	No nausea Mild nausea Severe nausea Emesis	40 7 5 3	55	5 8 13 29	55	
	Intervention THC **Comparator** Placebo		No nausea Mild nausea Severe nausea Emesis	40 7 5 3	55	8 11 18 18	55	
Rog(2005)[144] **Study design:** Parallel group RCT	**Intervention** Nabiximols (Sativex) **Comparator** Placebo	*Global impression;* Patient global impression **Timing:** 5 Weeks **Analysis:** ITT	Very much improved Much improved Slightly improved No change Slightly worse Much worse Very much worse	1 8 15 8 2 0 0	34	0 4 6 19 3 0 0	32	p-value=0.005 **Analysis Method** Logistic regression

Study	Interventions	Outcome	Categories	Intervention		Comparator		Analysis
				Number of events	Number of participants	Number of events	Number of participants	
Sallan(1980)[94] **Study design:** Cross-over RCT **Comments** N=number of courses not number of patients - patients received 2 doses of one of the interventions.	**Intervention** THC **Comparator** Prochlorperazine	*Nausea & vomiting;* Nausea and vomiting response **Timing:** Chemotherapy cycle **Analysis:** Results for 38 of 84 patients completing 3 courses (see comment)	Complete response Partial response No response	36 10 33	79	16 15 47	78	NR
Serpell(2014)[81] **Study design:** Parallel group RCT	**Intervention** Nabiximols (Sativex) **Comparator** Placebo	*Global impression;* Patient global impression **Timing:** 15 weeks **Analysis:** ITT	Very much improved Much improved Slightly improved No change Slightly worse Much worse	9 17 39 47 10 2	123	5 11 26 69 5 3	117	p-value=0.0003 **Analysis Method** Ordinal logistic regression and the proportional odds model, incorporating centre group.
Sheidler(1984)[113] **Study design:** Cross-over RCT	**Intervention** Levonantradol **Comparator** Prochlorperazine	*Nausea & vomiting;* Nausea (patient perception) **Timing:** 12hrs **Analysis:** Modified ITT (16 out of 20, 4 withdrawals)	Complete response Partial response No response	1 9 6	16	2 9 5	16	p-value=0.61 **Analysis Method** Mantel-Haenzel matched-pairs chi-square
Zajicek(2003)[89] **Study design:** Parallel group	**Intervention** THC/CBD **Comparator**	*Sleep:* Patient assessment **Timing:** 13 Weeks **Analysis:** ITT	Improvement Same Deterioration	82 62 20	164	59 79 25	163	

Study	Interventions	Outcome	Categories	Intervention		Comparator		Analysis
				Number of events	Number of participants	Number of events	Number of participants	
RCT	Placebo	*Spasticity*: patient assessment **Timing:** 13 Weeks **Analysis:** ITT	Improvement Same Deterioration	95 43 46	184	67 52 64	183	
	Intervention Dronabinol (Marinol) **Comparator** Placebo	*Sleep:* Patient assessment **Timing:** 13 Weeks **Analysis:** ITT	Improvement Same Deterioration	71 57 24	152	59 79 25	163	
		Spasticity: patient assessment **Timing:** 13 Weeks **Analysis:** ITT	Improvement Same Deterioration	89 40 47	176	67 52 64	183	

D. CROSS-OVER TRIALS THAT COMPARED TREATMENTS WITHIN PATIENTS

Study	Outcome	Categories	Intervention		Analysis
			Number of events	Number of participants	
Heim(1984)[102]	*Nausea & vomiting;* Intervention associated with greatest appetite **Timing:** 24 Hours **Analysis:** ITT	Dronabinol Metoclopramide Equal	22 2 21	45	p-value≤0.05 **Analysis Method** Chi-squared
	Nausea & vomiting; Intervention associated with least nausea **Timing:** 24 Hours **Analysis:** Per protocol	Dronabinol Metoclopramide Equal	28 5 12	45	≤≤
	Nausea & vomiting; Intervention associated with least vomiting **Timing:** 24 Hours **Analysis:** Per protocol	Dronabinol Metoclopramide Equal	25 8 12	45	
Johansson(1982)[106]	*Nausea & vomiting;* Intervention associated with least nausea **Analysis:** Per protocol	Nabilone Prochlorperazine Equal	9 1 8		
Jones(1982)[90]	*Nausea & vomiting;* Intervention associated with least nausea **Timing:** 1 chemotherapy cycle **Analysis:** Per protocol	Nabilone Placebo Equal	15 1 8	24	p-value≤0.001 **Analysis Method** NR
	Nausea & vomiting; Intervention associated with least vomiting **Timing:** 1 chemotherapy cycle **Analysis:** Per protocol	Nabilone Placebo Undecided (equal)	19 3 2	24	p-value≤0.001 **Analysis Method** NR
Levitt(1982)[117]	*Nausea & vomiting;* Intervention associated with least nausea **Timing:** 1 chemotherapy cycle **Analysis:** Per protocol	Nabilone Placebo No difference	26 2 8	36	p-value<0.001 **Analysis Method** NR
	Nausea & vomiting; Intervention associated with least vomiting **Timing:** 1 chemotherapy cycle **Analysis:** Per protocol	Nabilone Placebo No difference	29 4 3	36	
Wada(1982)[105]	*Nausea & vomiting;* Intervention associated with least nausea **Timing:** 1 chemotherapy cycle **Analysis:** Per protocol	Nabilone Placebo No difference	56 9 27	92	
	Nausea & vomiting; Intervention associated with least vomiting **Timing:** 1 chemotherapy cycle **Analysis:** Per protocol	Nabilone Placebo No difference	53 21 18	92	

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
Agrawal(2011)[229] **Study design** Case-control	Psychotic disease: Bipolar disorder	**Intervention** Cannabis **Details** lifetime history of cannabis use	Exposed: Ever Control: Never	OR= 6.80(5.41, 8.52)		
Aldington(2008)[230] **Study design** Case-control	Cancer: lung cancer	**Intervention** Cannabis **Details** >10.5 joint years vs never	Exposed: Regular Control: Never		OR= 5.70 (1.50, 21.60)	Logistic regression age, sex, ethnicity, family history of lung cancer and pack-yrs of cigarette smoking.
		Intervention Cannabis	Exposed: Ever Control: Never		OR= 1.20 (0.50, 2.60)	
		Intervention Cannabis **Details** up to 1.39 joint years vs never	Exposed: Regular Control: Never		OR= 0.30 (0.10, 1.70)	
		Intervention Cannabis **Details** 1.39 - 10.5 joint years vs never	Exposed: Regular Control: Never		OR= 0.50 (0.10, 2.00)	
Aldington(2008)[231] **Study design** Case-control	Cancer: head and neck cancer	**Intervention** Cannabis **Details**	Exposed: Ever Control: Never		OR= 1.00 (0.50, 2.30)	Logistic regression age, sex, ethnicity alcohol consumption, income, and pack years of cigarette smoking.
Barber(2013)[232]	Cardiovascular disease: ischemic	**Intervention** Cannabis	Exposed: Regular Control: Never		OR= 1.59 (0.71, 3.70)	age, sex, ethnicity, smoking

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
Study design Case-control	stroke / transient ischemic attack	**Details** regular defined as up to 72 hours after a single exposure and =< 10 weeks with daily use				
Beautrais(1999)[23] 3 **Study design** Case-control	Suicide: suicide attempt	**Intervention** Cannabis **Details** defined as dependent / abuse according to DSM3.	Exposed: Regular Control: Never	OR= 10.30(5.95, 17.80)	OR= 2.00 (0.97, 5.30)	Logistic regression age, sex, socio-economic status, education, poor parental relationship, childhood sexual abuse, in care during childhood, parental alcohol problems, psychiatric co-morbidity, other substance disorder
Berthiller(2009)[26] 0 **Study design** Case-control	Cancer: Head and neck	**Intervention** Marijuana **Details** Information on marijuana use was collected by questionnaire; questionnaire content differed between studies	Exposed: Duration >0-5 years Control: Never		OR= 0.81 (0.53, 1.23)	Logistic regression age; sex; race; education level; study; pack-year; alcohol duration; duration of smoking pipe; duration of smoking cigar
		Intervention Marijuana	Exposed: >3 times daily		OR= 0.87 (0.40, 1.89)	

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
		Details Information on marijuana use was collected by questionnaire; questionnaire content differed between studies	Control: Never			
		Intervention Marijuana **Details** Information on marijuana use was collected by questionnaire; questionnaire content differed between studies	Exposed: >1-3 times daily Control: Never		OR= 0.71 (0.35, 1.47)	
		Intervention Marijuana **Details** >3 times per day vs never	Exposed: Regular Control: Never		OR= 0.87 (0.40, 1.89)	Mixed/random effects models Adjusted for age (categorical), sex, race, education level, study, pack-year (continuous), alcohol duration (continuous), duration of smoking pipe (continuous), and duration of smoking
		Intervention Marijuana **Details** 1-3 times per day vs never	Exposed: Regular Control: Never		OR= 0.71 (0.35, 1.47)	

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
						cigar (continuous).
		Intervention Marijuana **Details** 0-1 time per day vs never	Exposed: Regular Control: Never		OR= 0.87 (0.61, 1.25)	
		Intervention Marijuana **Details**	Exposed: Ever Control: Never		OR= 0.88 (0.67, 1.16)	
Daling(2009)[235] **Study design** Case-control	Cancer: Testicular Germ Cell Tumors	**Intervention** Marijuana **Details** daily or more than once per week vs never	Exposed: Regular Control: Never		OR= 2.00 (1.30, 3.20)	Logistic regression age at reference date, reference year, alcohol use, current smoking, and history of cryptorchidism
		Intervention Marijuana **Details**	Exposed: Ever Control: Never		OR= 1.30 (1.00, 1.80)	
		Intervention Marijuana **Details** less than once per week vs never	Exposed: Occasional Control: Never		OR= 1.40 (0.90, 2.30)	
Davis(2013)[236] **Study design** Retrospective	Psychotic disease: schizotypical personality disorder	**Intervention** Cannabis **Details** regular defined as	Exposed: Regular Control: Never	OR= 2.88(2.38, 3.48)	OR= 2.83 (2.33, 3.43)	Logistic regression sex, age, and race

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
Cohort		"abuse"				
	Psychotic disease: schizotypical personality disorder	**Intervention** Cannabis **Details**	Exposed: Ever Control: Never	OR= 2.03(1.70, 2.42)	OR= 2.02 (1.69, 2.42)	
	Psychotic disease: schizofrenia or psychotic illness or episode	**Intervention** Cannabis **Details** regular defined as "dependence"	Exposed: Regular Control: Never	OR= 2.72(1.83, 4.05)	OR= 3.69 (2.49, 5.47)	
	Psychotic disease: schizofrenia or psychotic illness or episode	**Intervention** Cannabis **Details** regular defined as "abuse"	Exposed: Regular Control: Never	OR= 1.45(1.09, 1.92)	OR= 1.79 (1.35, 2.38)	
	Psychotic disease: schizofrenia or psychotic illness or episode	**Intervention** Cannabis **Details**	Exposed: Ever Control: Never	OR= 1.10(0.89, 1.35)	OR= 1.27 (1.03, 1.57)	
	Psychotic disease: schizotypical personality disorder	**Intervention** Cannabis **Details** regular defined as "dependence"	Exposed: Regular Control: Never	OR= 7.97(6.00, 10.60)	OR= 7.32 (5.51, 9.72)	
Di Forti(2009)[237]		**Intervention**	Exposed: Skunk	OR= 8.10(4.60,	OR= 6.80 (2.60,	Logistic regression

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
Study design Case-control	Psychotic disease: Psychosis using ICD10 criteria	Cannabis **Details** Skunk has higher THC levels	Control: Hash / Herbal	13.50)	25.40)	age, gender, ethnicity, other stimulant use, level of education achieved and employment status.
		Intervention Cannabis **Details** All participants were asked about their use of illicit drugs and those who reported ever using cannabis were interviewed using the Cannabis Experience Questionaire	Exposed: Ever Control: Never	OR= 0.80(0.60, 1.50)	Not done	
		Intervention Cannabis **Details** age at first use: under 17 vs 17 and over	Exposed: Occasional Control: Never	OR= 1.70(1.00, 4.70)	OR= 1.10 (0.80, 3.40)	Logistic regression age, gender, ethnicity, other stimulant use, level of education achieved and employment status.
		Intervention Cannabis **Details** daily vs less than daily	Exposed: Regular Control: Regular	OR= 6.70(2.00, 11.50)	OR= 6.40 (3.20, 28.60)	
		Intervention Cannabis **Details**	Exposed: Regular Control: Regular	OR= 2.40(1.20, 4.70)	OR= 2.10 (0.90, 8.40)	

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
		0-5 years vs over 5 years				
Dutta(2014)[238] **Study design** Case-control	Cardiovascular disease: Ischemic stroke	**Intervention** Marijuana or hashish **Details** Exposure determined by self-report	Exposed: non-frequent use (<1.88 times per month Control: no use in previous year		OR= 0.55 (0.26, 1.20)	Logistic regression age; gender; current smoking
		Intervention Marijuana or hashish **Details** Exposure determined by self-report	Exposed: frequent use (1.88 times per month) Control: no use in previous year		OR= 1.56 (0.79, 3.06)	
Giordano(2014)[239] **Study design** Case-control	Psychotic disease: Schizophrenia **Follow-up:** Case-control At baseline	**Intervention** Cannabis **Details** Registered cannabis abuse as distinct from any use of cannabis	Exposed: Control: General population	OR= 10.44(8.99, 12.11)	OR= 5.07 (4.17, 6.16)	Other method of survival analysis Adjusted to full sibling pairs.
	Psychotic disease: Schizophrenia **Follow-up:** Case-control 7 years between exposure and disease	**Intervention** Cannabis **Details** Registered cannabis abuse as distinct from any use of cannabis	Exposed: Control: Never	OR= 4.24(3.54, 5.07)	OR= 1.98 (1.59, 2.48)	
Hashibe(2006)[240] **Study design**	Cancer: Laryngeal cancer: 30 to <60 joint-years	**Intervention** Marijuana **Details**	Exposed: 30 to <60 joint-years Control: Never	OR= 2.60(0.96, 7.40)	OR= 0.71 (0.19, 2.70)	Logistic regression

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
Case-control						
	Cancer: Laryngeal cancer: =>60 joint-years	**Intervention** Marijuana **Details**	Exposed: =>60 joint-years Control: Never	OR= 2.40(1.00, 5.80)	OR= 0.84 (0.28, 2.50)	
	Cancer: Esophageal (Oesophageal) Cancer: 1 to <10 joint-years	**Intervention** Marijuana **Details**	Exposed: 1 to <10 joint-years Control: Never	OR= 0.99(0.52, 1.90)	OR= 0.77 (0.36, 1.60)	
	Cancer: Laryngeal cancer: 1 to <10 joint-years	**Intervention** Marijuana **Details**	Exposed: 1 to <10 joint-years Control: Never	OR= 0.69(0.30, 1.60)	OR= 0.42 (0.15, 1.20)	
	Cancer: Esophageal (Oesophageal) Cancer: =>30 joint-years	**Intervention** Marijuana **Details**	Exposed: =>30 joint-years Control: Never	OR= 1.50(0.69, 3.10)	OR= 0.53 (0.22, 1.30)	
	Cancer: Pharyngeal cancer: =>30 joint-years	**Intervention** Marijuana **Details**	Exposed: =>30 joint-years Control: Never	OR= 0.82(0.34, 2.00)	OR= 0.57 (0.20, 1.60)	
	Cancer: Lung cancer: 1 to <10 joint-years	**Intervention** Marijuana **Details**	Exposed: 1 to <10 joint-years Control: Never	OR= 0.82(0.59, 1.20)	OR= 0.71 (0.46, 1.10)	
	Cancer: Lung cancer: 10 to <30 joint-years	**Intervention** Marijuana **Details**	Exposed: 10 to <30 joint-years Control: Never	OR= 0.88(0.56, 1.40)	OR= 0.56 (0.31, 1.00)	
	Cancer: Lung cancer: 30 to <60 joint-years	**Intervention** Marijuana	Exposed: 30 to <60 joint-years	OR= 1.40(0.74, 2.50)	OR= 0.82 (0.38, 1.70)	

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
		Details	Control: Never			
	Cancer: Lung cancer: =>60 joint-years	**Intervention** Marijuana **Details**	Exposed: =>60 joint-years Control: Never	OR= 1.50(0.90, 2.40)	OR= 0.62 (0.32, 1.20)	
	Cancer: Esophageal (Oesophageal) Cancer: 10 to <30 joint-years	**Intervention** Marijuana **Details**	Exposed: 10 to <30 joint-years Control: Never	OR= 0.83(0.32, 2.20)	OR= 0.44 (0.15, 1.30)	
	Cancer: Oral cancer: 1 to <10 joint years	**Intervention** Marijuana **Details**	Exposed: 1 to <10 joint years Control: Never	OR= 1.30(0.88, 2.00)	OR= 1.10 (0.65, 1.70)	
	Cancer: laryngeal cancer	**Intervention** Marijuana **Details** 0-1 joint-years	Exposed: Occasional Control: Never	OR= 0.91(0.54, 1.50)	OR= 0.81 (0.42, 1.60)	Logistic regression age (15 categories), gender, race/ethnicity (4 categories), education (5 categories), drink-years, tobacco use (ever/never), and pack-years.
	Cancer: esophageal cancer	**Intervention** Marijuana **Details** 0-1 joint-years	Exposed: Occasional Control: Never	OR= 0.89(0.55, 1.40)	OR= 0.71 (0.41, 1.20)	
	Cancer: lung cancer	**Intervention** Marijuana **Details** 0-1 joint-years	Exposed: Occasional Control: Never	OR= 0.80(0.63, 1.00)	OR= 0.63 (0.46, .87)	
	Cancer: Laryngeal cancer: 10 to <30	**Intervention** Marijuana	Exposed: 10 to <30 joint-years	OR= 1.70(0.76, 3.80)	OR= 0.91 (0.33, 2.50)	Logistic regression

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
	joint-years	**Details**	Control: Never			
	Cancer: oral cancer	**Intervention** Marijuana **Details** 0-1 joint-years	Exposed: Occasional Control: Never	OR= 1.20(0.86, 1.60)	OR= 1.10 (0.74, 1.50)	Logistic regression age (15 categories), gender, race/ethnicity (4 categories), education (5 categories), drink-years, tobacco use (ever/never), and pack-years.
	Cancer: pharyngeal cancer	**Intervention** Marijuana **Details** 0-1 joint-years	Exposed: Occasional Control: Never	OR= 0.52(0.31, .87)	OR= 0.67 (0.37, 1.20)	
	Cancer: Oral cancer: 10 to <30 joint-years	**Intervention** Marijuana **Details**	Exposed: 10 to <30 joint-years Control: Never	OR= 1.40(0.83, 2.50)	OR= 0.92 (0.48, 1.70)	Logistic regression
	Cancer: Oral cancer: 30 to <60 joint-years	**Intervention** Marijuana **Details**	Exposed: 30 to <60 joint-years Control: Never	OR= 2.10(1.00, 4.40)	OR= 0.88 (0.38, 2.00)	
	Cancer: Oral cancer: =>60 joint-years	**Intervention** Marijuana **Details**	Exposed: =>60 joint-years Control: Never	OR= 2.80(1.60, 4.90)	OR= 1.10 (0.56, 2.10)	
	Cancer: Pharyngeal cancer: 1 to <10 joint-years	**Intervention** Marijuana **Details**	Exposed: 1 to <10 joint-years Control: Never	OR= 0.51(0.24, 1.10)	OR= 0.71 (0.30, 1.70)	
	Cancer: Pharyngeal cancer: 10 to <30	**Intervention** Marijuana	Exposed: 10 to <30 joint-years	OR= 0.69(0.27, 1.80)	OR= 0.39 (0.10, 1.50)	

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
	joint-years	**Details**	Control: Never			
Lacson(2012)[241] **Study design** Case-control	Cancer: Testicular Germ Cell Tumour (TGCT) **Follow-up:** Reference period of 1 year	**Intervention** Marijuana **Details** Exposure details were obtained by trained interviews, using structured questionnaires, administered at the participants' homes. Information was requested for the period of 1 year before the diagnosis of TGCT	Exposed: User for <10 years Control: Never	OR= 1.42(0.82, 2.45)	OR= 2.09 (1.09, 3.98)	Logistic regression cocaine use; amyl nitrate use; cryptorchidism; religiosity; education
			Exposed: <1 per week Control: Never	OR= 1.41(0.83, 2.41)	OR= 2.10 (1.09, 4.03)	
			Exposed: Ever Control: Never	OR= 1.32(0.79, 2.22)	OR= 1.94 (1.02, 3.68)	
			Exposed: Former user Control: Never	OR= 1.58(0.91, 2.76)	OR= 2.28 (1.17, 4.43)	
			Exposed: User for at least 10 years Control: Never	OR= 1.20(0.67, 2.15)	OR= 1.51 (0.66, 3.47)	
			Exposed: at least 1 per week Control: Never	OR= 1.14(0.60, 2.17)	OR= 1.53 (0.73, 3.24)	
			Exposed: Current user Control: Never use	OR= 1.06(0.59, 1.89)	OR= 1.38 (0.67, 2.87)	
Liang(2009)[242]	Cancer: head and neck squamous cell	**Intervention** Marijuana	Exposed: Weekly Control: Never		OR= 0.62 (0.34, 1.12)	Logistic regression age, gender,

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
Study design Case-control	carcinoma	**Details** 1.5-4.5 times per week vs never				education, race, smoking (pack-year), and average drinks of alcohol.
		Intervention Marijuana **Details** Former use	Exposed: Occasional Control: Never		OR= 0.65 (0.36, 1.16)	
		Intervention Marijuana **Details** 0.5-1.5 times per week vs never (<0.5 / week has same numbers in table as never group)	Exposed: Weekly Control: Never		OR= 0.52 (0.32, .85)	
		Intervention Marijuana **Details** >4.5 times per week vs never	Exposed: Weekly Control: Never	= 0.00(0.00, .00)	OR= 0.55 (0.31, .99)	
		Intervention Marijuana **Details** Current	Exposed: Regular Control: Never	= 0.00(0.00, .00)	OR= 0.52 (0.34, .80)	
Llewellyn(2004)[24] [4]	Cancer: oral squamous cell carcinoma	**Intervention** Cannabis **Details**	Exposed: Ever Control: Never	OR= 1.20(0.60, 2.50)	OR= 1.00 (0.50, 2.20)	Conditional logistic regression alcohol and tobacco

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
Study design Case-control						consumption.
		Intervention Cannabis **Details**	Exposed: Ever Control: Never	OR= 0.50(0.10, 1.70)	OR= 0.30 (0.10, 1.80)	
Manrique-Garcia(2012)[245] **Study design** Prospective Cohort	Psychotic disease: other non-affective psychoses **Follow-up:** 35.00 Years	**Intervention** Cannabis **Details** 11-50 times	Exposed: Regular Control: Never	OR= 2.70(1.10, 6.80)	OR= 1.80 (0.70, 4.90)	Logistic regression psychiatric diagnosis at conscription; IQ score; disturbed behaviour; smoking status; brought up in a city
		Intervention Cannabis **Details** Exposure during late adolescence (before conscription) assessed by questionnaire (at conscription)	Exposed: 2-4 times Control: Never	OR= 0.50(0.10, 2.10)	OR= 0.40 (0.10, 2.00)	
	Suicide: Suicide or possible suicide **Follow-up:** 33.00 Years	**Intervention** Cannabis **Details** Exposure during late adolescence (before conscription) assessed by questionnaire (at conscription)	Exposed: 1-10 Control: Never	OR= 1.35(0.95, 1.90)	OR= 0.89 (0.61, 1.29)	Logistic regression problematic behaviour during childhood; psychological adjustment; social relations; parental psychotropic medication; alcohol; smoking; psychiatric diagnosis
		Intervention Cannabis **Details**	Exposed: >50 times Control: Never	OR= 3.45(2.21, 5.39)	OR= 1.04 (0.57, 1.91)	

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
		Exposure during late adolescence (before conscription) assessed by questionnaire (at conscription)				
	Psychotic disease: schizophrenia **Follow-up:** 35.00 Years	**Intervention** Cannabis **Details** once	Exposed: Occasional Control: Never	OR= 0.50(0.20, 1.40)	OR= 0.60 (0.30, 1.80)	Logistic regression Psychiatric diagnosis at conscription, IQ score, disturbed behaviour, smoking, brought up in a city
		Intervention Cannabis **Details** 2-4 times	Exposed: Occasional Control: Never	OR= 1.30(0.70, 2.30)	OR= 1.30 (0.70, 2.40)	
		Intervention Cannabis **Details** 5-10 times	Exposed: Occasional Control: Never	OR= 1.40(0.70, 2.90)	OR= 1.30 (0.60, 2.60)	
		Intervention Cannabis **Details** 11-50 times	Exposed: Regular Control: Never	OR= 2.50(1.30, 4.50)	OR= 1.90 (1.00, 3.60)	
	Psychotic disease: Other non-affective psychosis **Follow-up:**	**Intervention** Cannabis **Details** Exposure during late adolescence (before	Exposed: >50 times Control: Never	OR= 3.30(1.50, 7.20)	OR= 2.00 (0.80, 4.70)	Logistic regression psychiatric diagnosis at conscription; IQ score; disturbed behaviour; smoking

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
	35.00 Years	conscription) assessed by questionnaire (at conscription)				status; brought up in a city
	Cancer: Lung cancer **Follow-up:** 40.00 Years	**Intervention** Cannabis **Details** Exposure during late adolescence (before conscription) assessed by questionnaire (at conscription)	Exposed: 2-4 times Control: Never	HR= 0.95(0.39, 2.33)	HR= 0.66 (0.27, 1.62)	Cox proportional hazards regression level of tobacco smoking; level of alcohol consumption; respiratory conditions diagnosed at conscription; socio-economic status in 1970
		Intervention Cannabis **Details** Exposure during late adolescence (before conscription) assessed by questionnaire (at conscription)	Exposed: Ever Control: Never	HR= 1.90(1.30, 2.75)	HR= 1.25 (0.84, 1.87)	
		Intervention Cannabis **Details** Exposure during late adolescence (before conscription) assessed by questionnaire (at conscription)	Exposed: Once Control: Never	HR= 2.07(1.06, 4.06)	HR= 1.52 (0.77, 3.01)	

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
	Psychotic disease: other non-affective psychoses **Follow-up:** 35.00 Years	**Intervention** Cannabis **Details** 5-10 times	Exposed: Occasional Control: Never	OR= 1.30(0.40, 4.20)	OR= 1.10 (0.30, 3.70)	Psychiatric diagnosis at conscription, IQ score, disturbed behaviour, smoking, brought up in a city Logistic regression
		Intervention Cannabis **Details** 2-4 times	Exposed: Occasional Control: Never	OR= 0.50(0.10, 2.10)	OR= 0.40 (0.10, 2.00)	
		Intervention Cannabis **Details** once	Exposed: Occasional Control: Never	OR= 1.60(0.60, 4.10)	OR= 1.80 (0.70, 4.70)	
		Intervention Cannabis **Details** >50 times	Exposed: Regular Control: Never	OR= 4.20(2.20, 8.20)	OR= 2.20 (1.00, 4.70)	
		Intervention Cannabis **Details** 11-50 times	Exposed: Regular Control: Never	OR= 3.40(1.50, 7.30)	OR= 2.50 (1.10, 5.50)	
		Intervention Cannabis **Details** >50 times	Exposed: Regular Control: Never	OR= 6.30(4.30, 9.20)	OR= 3.70 (2.30, 5.80)	
		Intervention	Exposed: Occasional	OR= 1.20(0.40,	OR= 1.10 (0.40,	

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
		Cannabis **Details** once	Control: Never	3.20)	3.00)	
		Intervention Cannabis **Details** 2-4 times	Exposed: Occasional Control: Never	OR= 1.20(0.50, 2.80)	OR= 1.20 (0.50, 3.10)	
		Intervention Cannabis **Details** 5-10 times	Exposed: Occasional Control: Never	OR= 1.20(0.40, 3.70)	OR= 0.90 (0.30, 2.90)	
		Intervention Cannabis **Details** >50 times	Exposed: Regular Control: Never	OR= 3.30(1.50, 7.20)	OR= 2.00 (0.80, 4.70)	
	Cancer: Lung cancer **Follow-up:** 40.00 Years	**Intervention** Cannabis **Details** Exposure during late adolescence (before conscription) assessed by questionnaire (at conscription)	Exposed: 11-50 Control: Never	HR= 2.69(1.26, 5.74)	HR= 1.68 (0.77, 3.66)	Cox proportional hazards regression level of tobacco smoking; level of alcohol consumption; respiratory conditions diagnosed at conscription; socio-economic status in 1970.
	Psychotic disease: Other non-affective	**Intervention** Cannabis	Exposed: Once Control: Never	OR= 1.60(0.60, 4.10)	OR= 1.80 (0.70, 4.70)	Logistic regression psychiatric diagnosis

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
	psychosis **Follow-up:** 35.00 Years	**Details** Exposure during late adolescence (before conscription) assessed by questionnaire (at conscription)				at conscription; IQ score; disturbed behaviour; smoking status; brought up in a city.
	Psychotic disease: Brief psychosis **Follow-up:** 35.00 Years	**Intervention** Cannabis **Details** Exposure during late adolescence (before conscription) assessed by questionnaire (at conscription)	Exposed: >50 times Control: Never	OR= 4.20(2.20, 8.20)	OR= 2.20 (1.00, 4.70)	Logistic regression psychiatric diagnosis at conscription; IQ score; disturbed behaviour; smoking status; brought up in a city.
		Intervention Cannabis **Details** Exposure during late adolescence (before conscription) assessed by questionnaire (at conscription)	Exposed: 11-50 times Control: Never	OR= 3.40(1.50, 7.30)	OR= 2.50 (1.10, 5.50)	
		Intervention Cannabis **Details** Exposure during late adolescence (before conscription) assessed	Exposed: 5-10 Control: Never	OR= 1.20(0.40, 3.70)	OR= 0.90 (0.30, 2.90)	

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
		by questionnaire (at conscription)				
		Intervention Cannabis **Details** Exposure during late adolescence (before conscription) assessed by questionnaire (at conscription)	Exposed: 2-4 times Control: Never	OR= 1.20(0.50, 2.80)	OR= 1.20 (0.50, 3.10)	
		Intervention Cannabis **Details** Exposure during late adolescence (before conscription) assessed by questionnaire (at conscription)	Exposed: Once Control: Never	OR= 1.20(0.40, 3.20)	OR= 1.10 (0.40, 3.00)	
	Psychotic disease: Schizophrenia **Follow-up:** 35.00 Years	**Intervention** Cannabis **Details** Exposure during late adolescence (before conscription) assessed by questionnaire (at conscription)	Exposed: >50 times Control: Never	OR= 6.30(4.30, 9.20)	OR= 3.70 (2.30, 5.80)	Logistic regression psychiatric diagnosis at conscription; IQ score; disturbed behaviour; smoking status; brought up in a city.
		Intervention	Exposed: 11-50	OR= 2.50(1.30,	OR= 1.89 (1.00,	

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
		Cannabis **Details** Exposure during late adolescence (before conscription) assessed by questionnaire (at conscription)	times Control: Never	4.50)	3.60)	
		Intervention Cannabis **Details** Exposure during late adolescence (before conscription) assessed by questionnaire (at conscription)	Exposed: 5-10 times Control: Never	OR= 1.40(0.70, 2.90)	OR= 1.30 (0.60, 2.60)	
		Intervention Cannabis **Details** Exposure during late adolescence (before conscription) assessed by questionnaire (at conscription)	Exposed: 2-4 times Control: Never	OR= 1.30(0.70, 2.30)	OR= 1.30 (0.70, 2.40)	
		Intervention Cannabis **Details** Exposure during late adolescence (before	Exposed: Once Control: Never	OR= 0.50(0.20, 1.40)	OR= 0.60 (0.30, 1.80)	

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
		conscription) assessed by questionnaire (at conscription)				
	Suicide: Suicide or possible suicide **Follow-up:** 33.00 Years	**Intervention** Cannabis **Details** Exposure during late adolescence (before conscription) assessed by questionnaire (at conscription)	Exposed: 11-50 times Control: Never	OR= 1.27(0.63, 2.57)	OR= 0.55 (0.26, 1.20)	Logistic regression problematic behaviour during childhood; psychological adjustment; social relations; parental psychotropic medication; alcohol; smoking; psychiatric diagnosis
	Respiratory disease: Lung cancer **Follow-up:** 40.00 Years	**Intervention** Cannabis **Details** Exposure during late adolescence (before conscription) assessed by questionnaire (at conscription)	Exposed: 5-10 Control: Never	HR= 1.02(0.32, 3.20)	HR= 0.68 (0.21, 2.16)	Cox proportional hazards regression level of tobacco smoking; level of alcohol consumption; respiratory conditions diagnosed at conscription; socio-economic status in 1970.
	Psychotic disease: Other non-affective psychosis **Follow-up:** 35.00 Years	**Intervention** Cannabis **Details** Exposure during late adolescence (before conscription) assessed by questionnaire (at	Exposed: 5-10 times Control: Never	OR= 1.30(0.40, 4.20)	OR= 1.10 (0.30, 3.70)	Logistic regression psychiatric diagnosis at conscription; IQ score; disturbed behaviour; smoking status; brought up in a city.

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
		conscription)				
		Intervention Cannabis **Details** Exposure during late adolescence (before conscription) assessed by questionnaire (at conscription)	Exposed: 11-50 times Control: Never	OR= 2.70(1.10, 6.80)	OR= 1.80 (0.70, 4.90)	
	Cancer: Lung cancer **Follow-up:** 40.00 Years	**Intervention** Cannabis **Details** Exposure during late adolescence (before conscription) assessed by questionnaire (at conscription)	Exposed: >50 times Control: Never	HR= 3.72(1.96, 7.06)	HR= 2.12 (1.08, 4.14)	Cox proportional hazards regression level of tobacco smoking; level of alcohol consumption; respiratory conditions diagnosed at conscription; socio-economic status in 1970.
	Psychotic disease: Schizophrenia **Follow-up:** 35.00 Years	**Intervention** Cannabis **Details** Exposure during late adolescence (before conscription) assessed by questionnaire (at conscription)	Exposed: Ever Control: Never use	OR= 2.10(1.60, 2.80)	OR= 1.80 (1.30, 2.50)	Logistic regression psychiatric diagnosis at conscription; IQ score; disturbed behaviour; smoking status; brought up in a city.
	Suicide: Suicide or	**Intervention**	Exposed: Ever	OR= 1.63(1.28,	OR= 0.88 (0.65,	Logistic regression

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
	possible suicide **Follow-up:** 33.00 Years	Cannabis **Details** Exposure during late adolescence (before conscription) assessed by questionnaire (at conscription)	Control: Never	2.07)	1.20)	problematic behaviour during childhood; psychological adjustment; social relations; parental psychotropic medication; alcohol; smoking; psychiatric diagnosis.
Marks(2014)[246] **Study design** Case-control	Cancer: Oral tongue	**Intervention** Marijuana **Details**	Exposed: Ever Control: Never	OR= 0.63(0.41, .98)	OR= 0.47 (0.29, .75)	Logistic regression Adjusted for age (continuous), sex, race, education level, ever use of tobacco, ever use of cigar/pipes, pack-years of tobacco smoking, and alcohol-year.
	Cancer: Oropharyngeal	**Intervention** Marijuana **Details**	Exposed: Ever Control: Never	OR= 1.76(1.52, 2.03)	OR= 1.24 (1.06, 1.47)	Logistic regression Adjusted for age (continuous), sex, race, education level, ever use of tobacco, ever use of cigar/pipes, pack-years of tobacco smoking, and alcohol-year.
McGrath(2010)[247]	Psychotic disease: schizophrenia (ICD-10	**Intervention** Cannabis	Exposed: Regular Control: Never		OR= 1.50 (0.80, 2.90)	Logistic regression age, sex, early

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
Study design Prospective Cohort	code F20) / persistent delusional disorder (ICD-10 code F22) / acute and transient psychotic disorders (ICD-10 code F23) **Follow-up:** 21.00 Years	**Details** =<3 years since start of usage				psychotic-like experiences and specific parental mental illnesses (maternal or paternal history of schizophrenia, alcohol abuse/dependence, and depression or anxiety disorders)
		Intervention Cannabis **Details** 4-5 years since first usage of cannabis	Exposed: Regular Control: Never		OR= 1.60 (0.80, 3.20)	
		Intervention Cannabis **Details** >6 years since first usage	Exposed: Regular Control: Never		OR= 2.10 (1.00, 4.30)	
Pederson(2008)[24] **Study design** Prospective Cohort	Suicide: suicide ideation **Follow-up:** 13.00 Years	**Intervention** Cannabis **Details** 1-10 times	Exposed: Occasional Control: Never		OR= 2.40 (1.30, 4.30)	Logistic regression full list visible in review information.
		Intervention Cannabis **Details** >10 times	Exposed: Regular Control: Never		OR= 2.70 (2.80, 6.40)	
		Intervention Cannabis **Details** 1-10 times	Exposed: Occasional Control: Never		OR= 0.70 (0.40, 1.50)	

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
		Intervention Cannabis **Details** >11 times	Exposed: Regular Control: Never		OR= 2.90 (1.30, 6.10)	
		Intervention Cannabis **Details** 1-10 times	Exposed: Occasional Control: Never		OR= 1.40 (0.80, 2.10)	
		Intervention Cannabis **Details** >11 times	Exposed: Regular Control: Never		OR= 0.90 (0.40, 2.50)	
Rolfe(1993)[249] **Study design** Case-control	Psychotic disease: Psychotic illness	**Intervention** Cannabis **Details** Cannabinoids urine test	Exposed: Ever detected or used Control: Never detected or used	OR= 4.00(0.00, .00)	OR= 4.50 (2.10, 9.90)	Logistic regression Adjusted for variables of psychotic illness
Rosenblatt(2004)[250] **Study design** Case-control	Cancer: Oral Squamous Cell Carcinoma (OSCC): Times used/week :<1yr of use (numbers of patients calculated from reported percentages)	**Intervention** Marijuana **Details** <1yr of use	Exposed: Ever Control: Never		OR= 1.00 (0.60, 1.80)	Logistic regression
		Intervention Marijuana **Details** Marijuana use <1 times/week	Exposed: <1 times/week Control: Never		OR= 0.80 (0.50, 1.40)	

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
	Cancer: Oral Squamous Cell Carcinoma (OSCC):6-15yrs of use (numbers of patients calculated from reported percentages)	**Intervention** Marijuana **Details** 6-15yrs of marijuana use	Exposed: 6-15yrs Control: Never		OR= 0.70 (0.40, 1.40)	Logistic regression
	Cancer: Oral Squamous Cell Carcinoma (OSCC): Years since first use: >25yrs (numbers of patients calculated from reported percentages)	**Intervention** Marijuana **Details** >25 yrs since first use	Exposed: >25 yrs since first use Control: Never		OR= 0.90 (0.40, 2.00)	
	Cancer: Oral Squamous Cell Carcinoma (OSCC): Years since first use: 21-25yrs (numbers of patients calculated from reported percentages)	**Intervention** Marijuana **Details** 21-25 yrs since first use	Exposed: 21-25 yrs since first use Control: Never		OR= 0.90 (0.50, 1.70)	
	Cancer: Oral Squamous Cell Carcinoma (OSCC): Years since first use 16-20yrs (numbers of	**Intervention** Marijuana **Details** 16-20 yrs since first use	Exposed: 16-20 yrs since first use Control: Never		OR= 0.70 (0.30, 1.40)	

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
	patients calculated from reported percentages)					
	Cancer: Oral Squamous Cell Carcinoma (OSCC): Years since first use <15 yrs (numbers of patients calculated from reported percentages)	**Intervention** Marijuana **Details** <15 yrs since first use	Exposed: <15 yrs since first use Control: Never		OR= 0.70 (0.30, 1.60)	
	Cancer: Oral Squamous Cell Carcinoma (OSCC): Times used/week :1-7 times/week (numbers of patients calculated from reported percentages)	**Intervention** Marijuana **Details** Marijuana use 1-7 times/week	Exposed: 1-7 times/week Control: Never		OR= 0.80 (0.40, 1.60)	
	Cancer: Oral Squamous Cell Carcinoma (OSCC): >15yrs of use (numbers of patients calculated from reported percentages)	**Intervention** Marijuana **Details** >15 yrs of marijuana use	Exposed: >15yrs Control: Never		OR= 1.20 (0.60, 2.20)	
	Cancer: Oral	**Intervention**	Exposed: 2-5 yrs of		OR= 1.30 (0.60,	

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
	Squamous Cell Carcinoma (OSCC): 2-5 yrs of use (numbers of patients calculated from reported percentages)	Marijuana **Details** 2-5 yrs of marijuana use	use Control: Never		2.60)	
	Cancer: Oral Squamous Cell Carcinoma (OSCC): 1 yr of use (numbers of patients calculated from reported percentages)	**Intervention** Marijuana **Details** 1 yr of marijuana use	Exposed: 1 yr of use Control: Never		OR= 0.20 (0.10, .70)	
	Cancer: Oral Squamous Cell Carcinoma (OSCC): <1yr of use (numbers of patients calculated from reported percentages)	**Intervention** Marijuana **Details** <1yr of marijuana use	Exposed: <1yr of use Control: Never		OR= 0.80 (0.40, 1.20)	
	Cancer: oral squamous cell carcinoma	**Intervention** Marijuana **Details** more than 7 times per week	Exposed: Regular Control: Never		OR= 0.50 (0.20, 1.60)	Logistic regression sex, education, birth year (continuous), alcohol consumption (continuous average drinks/week), cigarette smoking (continuous pack-
		Intervention Marijuana	Exposed: Regular Control: Never		OR= 0.80 (0.40, 1.60)	

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
		Details 1-7 times per week				years), and study (first or second).
		Intervention Marijuana **Details** <1 times per week	Exposed: Occasional Control: Never		OR= 0.80 (0.50, 1.40)	
		Intervention Marijuana **Details**	Exposed: Ever Control: Never		OR= 0.90 (0.60, 1.30)	
	Cancer: Oral Squamous Cell Carcinoma (OSCC): Times used/week :>7 times/week (numbers of patients calculated from reported percentages)	**Intervention** Marijuana **Details** Marijuana use >7 times/week	Exposed: >7 times/week Control: Never		OR= 0.50 (0.20, 1.60)	Logistic regression
Sasco(2002)[251] **Study design** Case-control	Cancer: lung cancer	**Intervention** Cannabis **Details**	Exposed: Ever Control: Never		OR= 1.93 (0.57, 6.58)	Conditional logistic regression smoking, history of chronic bronchitis, passive smoking, occupational exposure, cooking and heat source, lighting source, ventilation of kitchen

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
Tan(2009)[252] **Study design** Retrospective Cohort	Respiratory disease: COPD defined by spirometric testing	**Intervention** Marijuana **Details** Exposure was determined using standardised questionnaires, administered by interviewers	Exposed: At least 50 marijuana cigarettes smoked Control: Nonsmokers		OR= 1.66 (0.52, 5.26)	Logistic regression age; sex; ethnic background; BMI; education; asthma and other co-morbidities (i.e. heart disease, hypertension, stroke, diabetes and tuberculosis); interaction terms for concurrent smoking of marijuana and tobacco
	Respiratory disease: COPD defined by self-report of physician diagnosis	**Intervention** Marijuana **Details** Exposure was determined using standardised questionnaires, administered by interviewers	Exposed: At least 50 marijuana cigarettes smoked Control: Nonsmokers		OR= 0.67 (0.09, 5.29)	
	Respiratory disease: COPD defined by self-report of symptoms	**Intervention** Marijuana **Details** Exposure was determined using standardised questionnaires, administered by interviewers	Exposed: At least 50 marijuana cigarettes smoked Control: Nonsmokers		OR= 0.62 (0.31, 1.27)	
Trabert(2011)[253]	Cancer: Testicular	**Intervention**	Exposed: Ever		OR= 0.70 (0.40,	Logistic regression

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
Study design Case-control	germ cell tumors	Marijuana **Details**	Control: Never		1.10)	age, race, history of cryptorchidism, cigarette smoking and alcohol consumption.
		Intervention Marijuana **Details** >10 y	Exposed: Regular Control: Never		OR= 1.20 (0.60, 2.80)	
		Intervention Marijuana **Details** <10 y	Exposed: Regular Control: Never		OR= 0.60 (0.30, 1.00)	
		Intervention Marijuana **Details** daily or more	Exposed: Regular Control: Never		OR= 2.20 (1.00, 5.10)	
		Intervention Marijuana **Details** <1 / day	Exposed: Weekly Control: Never		OR= 0.50 (0.30, .90)	
van Os(2002)[254] **Study design** Prospective Cohort	Psychotic disease: psychosis **Follow-up:** 3.00 Years	**Intervention** Cannabis **Details** at baseline	Exposed: Ever Control: Never	OR= 3.25(1.48, 7.15)	OR= 2.11 (0.78, 5.71)	Logistic regression age, sex, ethnic group, single marital status, level of education, urbanicity, level of discrimination AND OTHER DRUGS. (Table 4)

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
Veling(2008)[255] **Study design** Case-control	Psychotic disease: Schizophrenia	**Intervention** Cannabis **Details** Lifetime use of cannabis was assessed with the section on drugs of the Comprehensive Assessment of Symptoms and History (CASH)	Exposed: More than five times Control: Five times or less	OR= 6.40(2.90, 14.30)	OR= 7.80 (2.70, 22.60)	Logistic regression use of psychostimulants and cocaine; use of opiates and psychedelic drugs; sex; marital status; level of education; employment status.
		Intervention Cannabis **Details** Lifetime use of cannabis was assessed with the section on drugs of the Comprehensive Assessment of Symptoms and History (CASH)	Exposed: More than five times Control: Five times or less	OR= 30.00(4.10, 220.00)	OR= 15.90 (1.50, 167.10)	
Voirin(2006)[256] **Study design** Case-control	Cancer: lung cancer	**Intervention** Cannabis **Details**	Exposed: Ever Control: Never		OR= 4.10 (1.90, 9.00)	Logistic regression age, occupational exposure, duration of tobacco smoking
Weller(1985)[257] **Study design** Prospective	Psychotic disease: Schizophrenia/schizoaffective disorder	**Intervention** Marijuana **Details** Minimum 50 times in a	Exposed: Regular Control: Never or 'experimental'			no analysis

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
Cohort	**Follow-up:** 6.50 Years 6-7	6 month period				
	Psychotic disease: Schizophrenia/ Psychotic disorder **Follow-up:** 6.50 Years 6 to 7 years	**Intervention** Marijuana **Details**	Exposed: Weekly Control: Never			
Zhang(2014)[259] **Study design** Case-control	Cancer: Lung cancer	**Intervention** Cannabis **Details** 1+ joints per day	Exposed: Regular Control: Never		OR= 0.88 (0.63, 1.24)	Other method of survival analysis age,sex,race, educn, smoking status, tobacco smoking years.
		Intervention Cannabis **Details** Non habitual those with cumulative cannabis consumprion of less than 1-joint/year	Exposed: Habitual Control: Non habitual		OR= 0.96 (0.66, 1.38)	
		Intervention Cannabis **Details** < 1 joint per day	Exposed: Occasional Control: Non habitual		OR= 0.77 (0.51, 1.16)	
Zhang(1999)[258] **Study design** Case-control	Cancer: Head and neck cancer	**Intervention** Marijuana **Details**	Exposed: Ever Control: Never	OR= 2.40(1.10, 5.60)	OR= 3.10 (0.99, 9.70)	Logistic regression Adjusted for age (continuous variable), gender; race; education; heavy

Study Details	Outcome	Intervention	Exposure levels	Crude OR (95% CI)	Adjusted OR (95% CI)	Adjusted analysis and variables adjusted for
						alcohol use; passive smoking and missing data were replaced by median.
		Intervention Marijuana **Details**	Exposed: Ever Control: Never	OR= 1.50(0.80, 2.90)	OR= 2.60 (1.10, 6.60)	

APPENDIX 8: RESULTS OF THE RISK OF BIAS ASSESSMENT

A. COCHRANE RISK OF BIAS TOOL FOR RCTS

Study	Domain	Support for judgement	Risk of bias
Abrams(2003)[129]	Random sequence generation	The statistician generated the random allocation sequences	**Low**
	Allocation concealment	The pharmacists maintained the sequences in a secure location and distributed the assignments to the study coordinator on day 0.	**Low**
	Participant/ Personnel blinding	Arm 1 (Int 1) used smoked marijuana (unblinded). Arms 2 and 3 (Int 2 and placebo) used capsules in a "double-blind fashion". However no detail given whether capsules were matched/identical.	**High/ unclear**
	Outcome assessor blinding		**High/ unclear**
	Incomplete outcome data	Results for treated patients reported (n=62 out of 67, mITT).	**Low**
	Selective outcome reporting	Study described as safety study but adverse events were not reported (other pre-specified outcomes were reported).	**High**
Abrams(2007)[142]	Random sequence generation	Randomisation (1:1) was computer-generated by the study statistician and managed by an independent research pharmacist.	**Low**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	'Treatment was double-blind' and 'identical-appearing placebo cannabis cigarettes'	**Low**
	Outcome assessor blinding	'Treatment was double-blind'. No further details given.	**Unclear**
	Incomplete outcome data	'Statistical analyses were conducted on a modified intent-to-treat (ITT) sample.'	**High**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**
Ahmedzai(1983)[112]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study reported as double-blind but no details on blinding or placebo provided (active comparison but given at different times to CBM; state that "double dummy" design used).	**Low**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	8/34 patients withdrew; efficacy data only reported for 26 patients	**High**
	Selective outcome reporting	All outcomes described in methods were reported in the results	**Low**

Study	Domain	Support for judgement	Risk of bias
Beal(1995)[84]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	31% of CBM and 43% of placebo group excluded from some analyses; high risk for per-protocol outcomes, low risk for ITT analyses	**High/Low**
	Selective outcome reporting	All outcomes described in methods were reported in the results. Assessment of adverse events not specified in methods but included in results.	**Low**
Bergamaschi(2011)[95]	Random sequence generation	Patients were randomly assigned to the two groups. The first participant had his treatment blindly chosen between the two treatment options available; the next participant (whose characteristics were matched to the first one's) had his treatment drawn from the remaining option. Groups were matched according to gender, age, years of education, and socioeconomic status.	**High**
	Allocation concealment	Method not reported. Matching of patients, described in randomisation indicates a high risk of bias.	**High**
	Participant/ Personnel blinding	Double blind trial. Blinding not reported, but placebo and CBD prepared in same manner, therefore blinded to patient.	**Low**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	24 patients were randomised and 24 patients were included in analysis. No statement of missing data in methods.	**Low**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**
Berman(2004)[145]	Random sequence generation	"Patients were randomly allocated by a computer generated list to the six possible sequences of receiving the three study medications."	**Low**
	Allocation concealment	Use of sealed code break envelopes which are not considered to be a safe option for allocation concealment.	**High**
	Participant/ Personnel blinding	"Blinding was maintained throughout the study."	**Low**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	Results for all treated patients reported (46 out of 48 randomised).	**Low**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**

Study	Domain	Support for judgement	Risk of bias
Berman(2007)[1]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study described as double blind (Participant, Caregiver, Investigator, Outcomes Assessor). Placebo contains no active drug but colourants and excipients, therfore likely to be blinded to patient.	**Low**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	Primary outcome analysed by mITT, 'all randomised patients who received at least one dose of test treatment and have on-treatment efficacy data were included in the analysis' (Results for up to 38 out of 116 participants not reported).	**High**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**
Blake(2006)[78]	Random sequence generation	"…randomized treatment allocation using permuted blocks of four"	**Low**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	"...randomized, double-blind, parallel group study…". Study reported as double-blind but no details on blinding.	**Unclear**
	Outcome assessor blinding	"...randomized, double-blind, parallel group study…". Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	1 withdrawal in CBM group and 3 in placebo. All contributed to AE analysis, unclear if all were included in efficacy analysis.	**Unclear**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**
Broder(1982)[74]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	35/44 (79.5%) completed.	**Unclear**
	Selective outcome reporting	No outcomes specified.	**Unclear**

Study	Domain	Support for judgement	Risk of bias
Chan(1987)[93]	Random sequence generation	"The antiemetic agent for cycle 1 of chemotherapy in each registered patient was supplied according to a sequence randomly assigned, and the second antiemetic agent for cycle 2 of chemotherapy was automatically the other drug." No details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	"The study was double-blinded in that neither the medical personnel nor the patients and their parents were aware of the order in which the antiemetic drugs were supplied." "Prochlorperazine was supplied in 5-mg capsules identical in appearance with those containing nabilone. The drugs were packaged in identical containers marked only by a number code."	**Low**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	10 (out of 40) withdrawals not included for efficacy outcomes. 4 withdrawals not included for detailed safety outcomes.	**High**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**
Collin(2010)[5]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Placebo vehicle combined excipients and colourants.	**Low**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	A modified ITT analysis was conducted based on all patients who received at least one dose of study medication. ITT set contained 335 patients comapred to 337 randomised.	**Low**
	Selective outcome reporting	Primary outcome was the same as that specified in the trial registry entry. Secondary outcomes pre-specified in the trial registry entry were also reported in the paper.	**Low**
Collin (2007)[2]	Random sequence generation	Participants were randomised to CBM or placebo in a 2:1 ratio by a balanced schedule design for each centre.	**Low**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Not reported. Study is however described as double blind and placebo was identically flavoured incipient to reduce the risk of unblinding.	**Low**
	Outcome assessor blinding	Outcome assessors blinded.	**Low**
	Incomplete outcome data	The primary analysis was performed on the intention-to-treat (ITT) population, defined as all randomised participants receiving at least one dose of study medication with recorded post-baseline efficacy data.	**Low**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**

Study	Domain	Support for judgement	Risk of bias
Corey-Bloom(2012)[190]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	7/37 participants apear to have been excluded form the analyses	**High**
	Selective outcome reporting	According to clinicaltrials.gov, there are 3 primary outcomes; according to the main trial there only is one primary outcome (Ashworth score).	**Low**
Dalzell(1986)[92]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	The study was described as double blind but there were no detailed methods. Identical looking capsules were given, but no further details.	**Low**
	Outcome assessor blinding	Study reported as double-blind but no details on outcome assessor blinding.	**Unclear**
	Incomplete outcome data	5 patients out of 23 were excluded from the analysis, therefore likely to be per protocol anlaysis. Safety results reported for 22 out of 23 participants.	**High**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**
Duran(2010)[97]	Random sequence generation	Randomisation was stratified by sex and hospital. Treatment allocation was made using randomised permuted blocks of four (two active drug, two placebo), with treatments sequentially assigned to either a CBM containing THC and CBD, administered as an oromucosal spray,or placebo.	**Low**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Trial described as double blind. Placebo was designed to match the appearance, smell and taste of the active formulation, but contained no active components.	**Low**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	ITT	**Low**
	Selective outcome reporting	Some of the secondary outcomes (absence of emesis, no signficiant nausea, proportion of patients with reduced frequency, duration and severity of CINV, impact of CINV on daily life and patient/dr satisfaction with treatment) do not match the secondary outcomes reported in the results.	**High**

Study	Domain	Support for judgement	Risk of bias
Einhorn(1981)[108]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	"Identically prepared capsules".	**Low**
	Outcome assessor blinding	No details on blinding.	**Unclear**
	Incomplete outcome data	20/100 patients excluded from analysis	**High**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**
Ellis(2009)[137]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	The primary analyses excluded 6 participants (out of 34, 18%) who did not complete the study. Results of an ITT analysis, using multiple mputation for missing data, were reported as p values only.	**High**
	Selective outcome reporting	Full data were not reported for all listed pain oucome measures (no data for POMS, SIP and BSI)	**High**
Frank(2008)[141]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	The study was described as double blind but there were no detailed methods. The medication was given in identical tablets.	**Low**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	Two analyses were presented. The available case analysis used the fullest dataset—all patients randomised who provided data in each treatment period (modified ITT = 73/96). The per protocol analysis excluded patients who did not comply with the trial drugs, as assessed by their pain diary (64/96).	**High**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**

Study	Domain	Support for judgement	Risk of bias
Frytak(1979)[111]	Random sequence generation	Treatment assignments determined by sequential entry on a list of antiemetic treatments arranged in random order and ifentified only by code number.	**Low**
	Allocation concealment	Treatment assignments determined by sequential entry on a list of antiemetic treatments arranged in random order and ifentified only by code number.	**High**
	Participant/ Personnel blinding	Each antiemetic drug or placebo was prepared in identical opaque gelatin capsules. The drugs were dispensed in idvidual packets identified only by code number.	**Low**
	Outcome assessor blinding	Study reported as double-blind but no details on outcome assessor blinding.	**Unclear**
	Incomplete outcome data	1 patient excluded on day 1. 18 patients on days 2-4. Any patient who vomited more than 2 times was judged a treatment failure and withdrawn from the study. However, efficacy data extracted for 1 day time point and AE data only had 1 patient missing so unlikely to have been impacted by missing data.	**Low**
	Selective outcome reporting	All outcomes described in methods were reported in the results	**Low**
George(1983)[104]	Random sequence generation	The study was described as randomised by drawing lots.	**Low**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Matched placebo to each intervention given together with intervention	**Low**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	All patient results were included in the analysis.	**Low**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**
GW Pharma Ltd(2005)[77]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	Full-analysis set reported which included all randomised participants who received at least one dose of study medication and yielded on-treatment efficacy data but 23% of patients did not have complete outcome data.	**High**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**

Study	Domain	Support for judgement	Risk of bias
GW Pharma NCT01606176(2012)[79]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Outcome assessor blinding	Outcome assessor reported as blinded	**Low**
	Incomplete outcome data	Modified ITT ("All patients who were randomised, received at least one actuation of study medication and completed at least one set of efficacy assessments were included in the analysis."), results not reported for up to 27 (out of 70) participants.	**High**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**
Hagenbach(2003)[71]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	It is unclear if all 13 participants randomised were included in the analysis	**Unclear**
	Selective outcome reporting	Outcomes are not specified in the methods and no protocol is available.	**Unclear**
Heim(1984)[102]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	No details on blinding but no placebo drug for alternative medication or details on comparability of the two interventions.	**High**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	It appears that 57 patients were randomised but only 45 received two chemotherapy cycles and had results data	**High**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**

Study	Domain	Support for judgement	Risk of bias
Herman(1979)[123]	Random sequence generation	"The drugs were packaged in identical containers marked only with a number code. The first antiemetic that the patient received was randomly assigned to be nabilone or prochlorperazine by the pharmaceutical company, and the second was automatically the other agent. " Methods used to generate randomisation sequence not reported.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	"Prochlorperazine was supplied in capsules identical in appearances to those containing Nabilone." "Neither the medical personnel nor the patients knew in which order the drugs were supplied".	**Low**
	Outcome assessor blinding	"Neither the medical personnel nor the patients knew in which order the drugs were supplied".	**Low**
	Incomplete outcome data	39/152 patients excluded from the efficacy analysis	**High**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**
Hutcheon(1983)[103]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Identically coded ampoules were prepared for drug and control, but no further details given. It would appear the patients are blind.	**Low**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	All randomised patients included in analysis.	**Low**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**
Johansson(1982)[106]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	No details on blinding.	**Unclear**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	27 patients enrolled but only 18 included in efficacy analyses and 26 and 23 in safety analysis.	**High**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**

Study	Domain	Support for judgement	Risk of bias
Johnson(2010)[82]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	19% (33 out of 177) of patients did not have complete outcome evaluation due to withdrawals.	**High**
	Selective outcome reporting	All outcomes described in trial registry entry were reported in the results.	**Low**
Jones(1982)[90]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	30/54 patients withdrew from the study and were excluded from the analysis.	**High**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**
Karst(2003)[147]	Random sequence generation	Computer based randomisation	**Low**
	Allocation concealment	Randomisation, labeling, and packaging in high-density polyethylene bottles were performed at Creapharm.	**Low**
	Participant/ Personnel blinding	Study investigators were blinded to the randomisation method. All study bottles were labeled with numbers from 1 to 21 pertaining to each of the 21 patients. Each study day (14 in all) was indicated on the bottles, each of which contained either 4 or 8 capsules.	**Low**
	Outcome assessor blinding	Study investigators were blinded to the randomisation method. cians. Treatment assignment codes were not available to investigators until all patients completed the study and the data had been entered.	**Low**
	Incomplete outcome data	Modified ITT carried out due to 1 patient dropping out of each arm, this is approx 10% of each arm and therefore could infleunce the results	**High**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**
Killestein 2002(2002)[193]	Random sequence generation	Described as randomised but no details on how random sequence was generated	**Unclear**
	Allocation concealment	No detail of allocation method/concealment given	**Unclear**
	Participant/ Personnel blinding	Study reported as double-blind using “identical-appearing capsules”	**Low**
	Outcome assessor blinding	Outcomes assessed by a different physician to the treating physician "to avoid unmasking"	**Low**
	Incomplete outcome data	Data were available for all participants	**Low**
	Selective outcome reporting	Full data were not reported for all outcomes listed in the methods scetion	**High**

Study	Domain	Support for judgement	Risk of bias
Lane(1991)[83]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study reported as double-blind but no specific details on blinding. Placebo used for each of the two intervention drugs suggesting the study was blinded.	**Low**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	54/62(87%) included in evaluation of primary outcome	**High**
	Selective outcome reporting	Data reported for all outcomes specified in the methods	**Low**
Langford(2013)[4]	Random sequence generation	Randomisation occurred using a pre-determined computergenerated randomisation code in which treatment allocation was stratified by center, and used randomly permuted blocks of variable sizes	**Low**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Placebo reported to be coloured but no further details. "Patients, investigators, and those assessing the data were therefore blinded to the patients' treatment allocation."	**Low**
	Outcome assessor blinding	"Patients, investigators, and those assessing the data were therefore blinded to the patients' treatment allocation."	**Low**
	Incomplete outcome data	ITT analysis based on all patients randomised performed.	**Low**
	Selective outcome reporting	Additional outcomes to those specified as secondary efficacy outcomes in the methods section reported. Primary effecicacy outcome remained the same. Reporting of outcomes not related to statistical significance.	**Low**
Levitt(1982)[117]	Random sequence generation	Described as randomised but no details on how random sequence was generated. Randomisation stratified on prior chemotherapy.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	Only 36/58 patients included in efficacy analysis	**High**
	Selective outcome reporting	No outcomes pre-specified	**Unclear**

Study	Domain	Support for judgement	Risk of bias
Leweke(2008)[216]	Random sequence generation	'The hospital pharmacy provided individual medication kits according to a randomization sequence prepared by a person otherwise not involved in the study (drawing paper lots out of a bowl).'	**Low**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	In all, 39 patients were evaluated according to modified intention-to-treat (primary outcomes), 33 were observed and treated per protocol and all 42 were valid for safety evaluation.	**Low**
	Selective outcome reporting	According to clinicaltrials.gov, BPRS was the primary outcome and PANSS was secondary outcome. In the main report, both are primary outcomes.	**High**
Long(1982)[73]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	42 patients in the trial; 36/42 (86%) completed and 34/42 (81%) evaluated for all reported outcomes. Analysis type not reported.	**High**
	Selective outcome reporting	Not all outcomes were detailed in the results, e.g. degree of nausea.	**High**
Lynch(2014)[148]	Random sequence generation	Participants who met the study criteria were given a study number. The study numbers were assigned consecutively. A computer generated randomisation schedule determined the order of treatment (placebo-nabiximols or nabiximols-placebo) and was used at the manufacturing site where study numbers were assigned to each participant's supply of study medication. Participants and study staff were blinded to the randomisation code, which was not broken until the completion of the study.	**Low**
	Allocation concealment		**Low**
	Participant/ Personnel blinding	Participants and study staff were blinded to the randomisation code, which was not broken until the completion of the study. Placebo packaged in exactly the same way as CBM, with a similar yellowish color and peppermint flavor.	**Low**
	Outcome assessor blinding	Participants and study staff were blinded to the randomisation code, which was not broken until the completion of the study.	**Low**
	Incomplete outcome data	2/18 patients excluded; no ITT analysis	**High**
	Selective outcome reporting	All outcomes described in methods were reported in the results	**Low**

Study	Domain	Support for judgement	Risk of bias
McCabe 1988(1988)[98]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Assumed open label - no detail of blinding given	**High**
	Outcome assessor blinding	Assumed open label - no detail of blinding given	**High**
	Incomplete outcome data	Complete outcome data reported	**Low**
	Selective outcome reporting	Pre-specified outcomes were reported.	**Low**
Meiri(2007)[85]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study reported as double-blind, treatments and placebo were matched.	**Low**
	Outcome assessor blinding	Study reported as double-blind but no details on outcome assessor blinding.	**Unclear**
	Incomplete outcome data	Modified ITT was used; patients randomised into the trial who took at least one capsule of study medication, had a baseline (day 1) efficacy evaluation, and had at least one postbaseline efficacy evaluation (any type). This led to the loss of 3/17 patients in the dronabonol arm which could be influential. Appear to have used LOCF or last observation at baseline for missing data.	**High**
	Selective outcome reporting	QoL results only reported for one comparison (dronabinol vs. combination, not extracted). All other outcomes described in methods were reported in the results.	**Low**
Melhem-Bertrandt(2014)[124]	Random sequence generation	'according to a computer-generated random assignment schedule'.	**Low**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study reported as double blind. 'The nature of the capsules (dronabinol or placebo) was not indicated on the vial'. Therefore the patients were blinded.	**Low**
	Outcome assessor blinding	Study reported as double-blind but no details on outcome assessor blinding.	**Unclear**
	Incomplete outcome data	Study diagram shows total of 59 patients (30 intervention 1, 29 control), efficacy outcome (number of vomiting /nausea episodes shows only 58 patients. (29 intervention 1, 29 control). Study describes 3 drop outs, 4 patients missing for efficacy. Modifiede ITT analysis included 58/59 patients	**Low**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**

Study	Domain	Support for judgement	Risk of bias
Müller-Vahl(2001)[227]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study reported as double-blind, use of visually identical placebo.	**Low**
	Outcome assessor blinding	Study reported as double-blind but no details on outcome assessor blinding.	**Unclear**
	Incomplete outcome data	No patients withdrawals, therefore it is assumed that all patients completed the trial and were analysed -ITT.	**Low**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**
Müller-Vahl(2003)[225]	Random sequence generation	Study described as randomised. 'Randomisation was done by a psychiatrist who was not involved in the study and kept the codes until completion of the study'. No details on how random sequence was generated or on whether allocation was concealed.	**Unclear**
	Allocation concealment		**Unclear**
	Participant/ Personnel blinding	Study reported as double-blind, placebo 'identical in taste and appearance'. 'None of the investigators or patients had access to the randomization codes during the study'.	**Low**
	Outcome assessor blinding	Study reported as double-blind, 'all examiner ratings were done under blind conditions by one of the authors'	**Low**
	Incomplete outcome data	Modified ITT analyses excluded results of 7 out of 24 randomised participants. Per protocol analyses included 20 of the 24 participants.	**High**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**
Narang(2008)[139]	Random sequence generation	"The Investigational Drug Service (IDS) Pharmacy of the hospital generated the randomization scheme (www.randomization.com)."	**Low**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study reported as double-blind. "Study personnel and participants were blinded until all the participants had completed the Phase I trial."	**Low**
	Outcome assessor blinding	Study reported as double-blind but no details on outcome assessor blinding.	**Unclear**
	Incomplete outcome data	1 out of 30 participants dropped out.	**Low**
	Selective outcome reporting	Not all secondary outcomes were reported, e.g. patient blinding	**High**
Niederle(1986)[100]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	All patients completed the trial and data were reported for all patients	**Low**
	Selective outcome reporting	Data for most outcomes reported in methods reported in results; no data for vomiting.	**High**

Study	Domain	Support for judgement	Risk of bias
Niiranen(1985)[101]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study reported as double-blind, identical capsules were used.	**Low**
	Outcome assessor blinding	Study reported as double-blind but no details on outcome assessor blinding.	**Unclear**
	Incomplete outcome data	8 of the 32 randomised patients were excluded from the analyses	**High**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**
Noyes(1976)[323]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study described as double blind. All drugs and placebo were identical in appearance, but no further details.	**Low**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	2 patients (out of 46 patients) were not included in the analysis but there was no mention of how this was accounted for.	**Low**
	Selective outcome reporting	Severity of pain was listed as an outcome, but was not included in the results in any defined form.	**High**
Nurmikko(2007)[80]	Random sequence generation	The randomisation schedule had a 1:1 treatment allocation ratio with randomly permuted blocks stratified by centre and was generated using a computer based pseudo-random number algorithm.	**Low**
	Allocation concealment	'The randomisation schedule was held by the sponsor with a copy in patient-specific sealed envelopes sent to the pharmacy in each centre.' Sealed envelopes are usually not considered effective for allocation concealment.	**High**
	Participant/ Personnel blinding	The study was described as double blind. The placebo medication was identical in composition, appearance, odour and taste with the study medication but without cannabis extract. That the smell and taste of the cannabinoid preparation might lead to unblinding was averted by disguising them with addition of peppermint oil to both preparations. All medication was provided in identical amber vials, packaged and labelled by the sponsor.	**Low**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	ITT was perfromed for the primary analysis (all patients who remained in the study at each time point were included in the analyses). Per protocol was used for some outcomes.	**High**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**

Study	Domain	Support for judgement	Risk of bias
Orr(1980)[109]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study described as double-blind. Study drugs administered in identical capsule forms and at the same time (1hr before chemotherapy).	**Low**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	24 patients (30%) withdrew from the study. Results only reported for 55 remaining participants.	**High**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**
Pinsger(2006)[143]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	PP and ITT reported.	**Low**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**
Pomeroy(1986)[99]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study described as double-blind. Study drugs "in white capsules of identical appearance". No other detail given	**Low**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	Efficacy analyses based on 29 up to 36 out of 38 patients (i.e. those who completed the study). Adverse events analyses reported on all patients.	**High**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**
Pooyania(2010)[128]	Random sequence generation	"…computerized randomization system…"	**Low**
	Allocation concealment	"…subjects were randomly assigned by the pharmacist…" (no further details)	**Unclear**
	Participant/ Personnel blinding	"…in order to keep both subject and clinician blind of the randomization"	**Low**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	Primary and secondary outcome reported for all treated participants (11 out of 12 participants)	**Low**
	Selective outcome reporting	All outcomes described in the trial registry entry were reported in the results.	**Low**

Study	Domain	Support for judgement	Risk of bias
Portenoy(2012)[86]	Random sequence generation	Participants were randomly assigned by computer using a block approach, first to 1 of 3 dose groups, and then within each group, to either active drug or placebo. The allocation to active drug or placebo was in a 3:1 ratio. The randomisation was stratified by region (North America/Rest of the World).	**Low**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Described as "double-blind". "…each placebo dose contained only excipients plus colorants."	**Low**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	ITT analysis performed for all participants who entered the trial and received at least one dose of study medication. 1 participant who was randomised did not contribute to ITT population.	**Low**
	Selective outcome reporting	Primary outcome same as that specified in trial registry entry. All outcomes specified in methods reported in results	**Low**
Prasad(2011)[72]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	No withdrawals reported. However, results stratified according to dose and so data were only usable for those who titrated to 10mg dose (8/17).	**High**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**
Rohleder(2012)[75]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	'Drop-out patients were replaced per protocol to gain a total of 18 patients treated'.	**High**
	Selective outcome reporting	Primary outcome measure (BPRS) and several secondary outcomes that were reported in the trial register were not presented in the available conference abstract.	**High**

Study	Domain	Support for judgement	Risk of bias
Rog(2005)[144]	Random sequence generation	Patients were randomised using a predetermined randomisation code drawn up by a statistician who remained unknown to study personnel throughout the duration of the trial. Treatment allocation was made using randomised permuted blocks of four (two active drug, two placebo)	**Low**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Placebo was designed to match the appearance, smell, and taste of the active formulation but contained no active components. To facilitate blinding, participants completed pain and sleep assessments at home, the physician examined participants, gave dosing advice, and assessed them for adverse events (AEs); trials nurses completed all other secondary outcome assessments; and a trials pharmacist dispensed the study medication. The identity of study medication assigned to participants, to which all study personnel remained blinded, was contained in individually sealed envelopes retained in the hospital 24-hour pharmacy and with the sponsor's Pharmacovigilance Department.	**Low**
	Outcome assessor blinding	See above.	**Low**
	Incomplete outcome data	Only 2 withdrawals during study. Both included in ITT analysis for safety, one excluded from ITT analysis for efficacy. For some secondary outcomes ITT population excluded larger number of participants. Overall not judged to have impacted on results of the study.	**Low**
	Selective outcome reporting	All outcomes described in trial registry entry were reported in the results.	**Low**
Sallan(1980)[94]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	"Opaque capsules identical in appearance"	**Low**
	Outcome assessor blinding	"Neither the person administering the drug nor the one recording the participant's response knew which drug the participant received"	**Low**
	Incomplete outcome data	Full data for all outcomes only available for 38/84 participants	**High**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**

Study	Domain	Support for judgement	Risk of bias
Selvarajah(2010)[136]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	Modified ITT analysis conducted that included 29/30 randomised participants; 1 placebo participant excluded due to protcol violations.	**Low**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**
Serpell(2014)[81]	Random sequence generation	"Randomization was carried out using a predetermined computer-generated randomization code, produced by the GW Biometrics Department, in which treatment allocation was made using permuted blocks of four.	**Low**
	Allocation concealment	"Study medication was pre-packed by the GW Clinical Trial Supplies Department and dispatched to the investigator centres labelled with patient numbers. The randomization scheme involved patient numbers being assigned sequentially by the investigator staff." Unclear whether the allocation schedule was concealed.	**Unclear**
	Participant/ Personnel blinding	"each spray of placebo delivered the excipients plus colorants. Both THC/CBD spray and placebo contained peppermint oil to blind the smell and taste". "As such, participants, investigators are caregivers were all blinded to the treatment allocation."	**Low**
	Outcome assessor blinding	"As such, participants, investigators are caregivers were all blinded to the treatment allocation."	**Low**
	Incomplete outcome data	6/246 participants did not contribute to ITT analysis as no on-treatment efficacy data available. All contributed to safety analysis. Very small proportion so unlikely to have affected results	**Low**
	Selective outcome reporting	All outcomes described in methods were reported in the results	**Low**
Sheidler(1984)[113]	Random sequence generation	Randomised by Pfizer Central Research. No details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study reported as double-blind '…, if a patient preferred one drug over the other, the double blind code was broken by contacting Pfizer.'	**High**
	Outcome assessor blinding	Study reported as double-blind '…, if a patient preferred one drug over the other, the double blind code was broken by contacting Pfizer.'	**High**
	Incomplete outcome data	Four participants who did not complete the crossove were excluded from the analyses (total study population n=20)	**High**
	Selective outcome reporting	All relevant outcomes described in methods were reported in the results (pulse and blood pressure not reported).	**Low**

Study	Domain	Support for judgement	Risk of bias
Skrabek(2008)[140]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whetherallocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Physicians and participants were blinded and placebo was identical to treatment	**Low**
	Outcome assessor blinding	Outcomes reported by blinded participants.	**Low**
	Incomplete outcome data	No methods were reported for incomplete data analysis and 7 participants ou of 40 dropped out.	**High**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**
Steele(1980)[110]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	No details on blinding.	**Unclear**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	Results only available for 37/55 randomised participants	**High**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**
Struwe(1993)[130]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	12 participants enrolled but only 5 completed the study and were included in the analysis.	**High**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**
Svendsen(2004)[146]	Random sequence generation	Participants were assigned to treatment using a computer generated randomisation code.	**Low**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Both investigators and participants were blinded to treatment allocation, and we maintained blinding until the data analysis was completed. Placebo capsules were identical to the dronabinal capsules in appearance, taste, and smell.	**Low**
	Outcome assessor blinding		**Low**
	Incomplete outcome data	All enrolled participants completed the study protocol. QoL data missing for one participant.	**Low**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**

Study	Domain	Support for judgement	Risk of bias
Timpone(1997)[88]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation concealed.	**Unclear**
	Participant/ Personnel blinding	Open label trial (unblinded)	**High**
	Outcome assessor blinding	Open label trial (unblinded)	**High**
	Incomplete outcome data	ITT reported but appears to be modified ITT, since there are very few participants per arm this may cause bias. Owing to a pharmacy dispensing error, one participant who was randomised to M750 was incorrectly issued M250+D for the entire duration of study participation. This participant's results are analyzed as treated, in an otherwise intention to treat analysis. Two participants who completed baseline evaluations did not initiate study therapy owing to development of a contraindicating condition by one participant and refusal to accept arm assignment by another (note no indication of which treatment arm this was).	**High**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**
Tomida(2006)[224]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	Data reported for all participants	**Low**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**
Ungerleider(1982)[91]	Random sequence generation	'Participants were assigned by the pharmacist, using a table of random numbers, to a paired trial.' (no further information)	**Low**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	Appears to be ITT. All participants analysed for N/V although by subgroup: single treatment (n=98), multiple regimen (n-41) and termintated (n=75).	**Low**
	Selective outcome reporting	All outcomes described in methods were reported in the results	**Low**

Study	Domain	Support for judgement	Risk of bias
Vaney(2004)[192]	Random sequence generation	Randomisation was by a randomisation list established by the trial statistician using SAS† version 8.2 (SAS Inc., Cary, NC), and held by the principal investigator (CV).	**Low**
	Allocation concealment	Allocating sequentially to the next randomisation code to the next participant who had successfully passed screening measurements.	**Low**
	Participant/ Personnel blinding	Unblinded study nurse knew the participant's group and status "but this information was not disclosed to any other person". Placebo capsules were identical in shape, taste and colour.	**Low**
	Outcome assessor blinding	Assessing physiotherapist blinded to treatment	**Low**
	Incomplete outcome data	Reported as ITT but only 50/57 participants analysed (7 withdrawals not analysed). Analysis statistics vary by results.	**High**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**
Wada(1982)[105]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Reported to be double blind; nabilone 2 mg and placebo was supplied by the Eli Lilly Company in identical capsules.	**Low**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	92/114 participants were evaluable for efficacy and 104/114 evaluable for safety - reason not given (30 pts withdrew). Type of analysis not clearly stated.	**High**
	Selective outcome reporting	All outcomes described in methods were reported in the results. NB: AEs reported for both study drugs combined, i.e. not extractable.	**Low**
Wade(2004)[3]	Random sequence generation	Participants were randomised by permuted blocks of size four, stratified by nominated primary symptom and centre.	**Low**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Reporting slightly inconsistent."We failed to assess the degree of blinding of our patients and outcome assessors, but we did make every effort to ensure blinding." "All preparations incorporated a peppermint flavour and colouring to disguise the taste and appearance of CBME."	**Low**
	Outcome assessor blinding	"After the six-week double-blind parallel group trial, participants returned to the study centre for a repeat of the full assessment battery. This was undertaken by a research nurse who was not involved in dosing advice and home contact with that participant, to ensure blinding".	**Low**
	Incomplete outcome data	6 out of 160 participants did not have information on outcomes (4%) Analysis method unclear in main paper.	**High**
	Selective outcome reporting	All outcomes described in methods and clinicaltrials.gov were reported in the results.	**Low**

Study	Domain	Support for judgement	Risk of bias
Wallace(2013)[76]	Random sequence generation	Described as randomised but no details on how random sequence was generated.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study reported as double-blind but no details on blinding. Placebo was administered by the same method as active treatments.	**Low**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	Analysis type not specified. Limited outcomes reported (only trial register entry and abstract available).	**High**
	Selective outcome reporting	The trial registry outlines outcomes, e.g. AEs, which were not reported in the abstract.	**High**
Ware(2010)[135]	Random sequence generation	Eligible participants were randomised to a sequence of treatment periods based on a Latin square design, no further details reported.	**Unclear**
	Allocation concealment	No details on whether allocation was concealed.	**Unclear**
	Participant/ Personnel blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Outcome assessor blinding	Study reported as double-blind but no details on blinding.	**Unclear**
	Incomplete outcome data	2 participants withdrew, one of which had "increased pain" under 6%-THC. Appears that per-protocol analyses reported although authors stated that "Data from all randomized participants were included in all safety and efficacy analyses." which doesn't seem correct, e.g. AEs for up to 22 of 23 randomised participants reported.	**High**
	Selective outcome reporting	Reported ouctomes are the ones reported in the trial register.	**Low**
Ware(2010)[133]	Random sequence generation	Computerised block randomisation (using Stata), prepared by the study pharnacist independently of the investigators	**Low**
	Allocation concealment	Randomisation schedule was kept separate from the investigators	**Low**
	Participant/ Personnel blinding	Physician, nurses and participants were blinded	**Low**
	Outcome assessor blinding	Outcomes were participant reported	**Low**
	Incomplete outcome data	3 out 32 (9%) of the participants withdrew and did not have outcome information.	**Low**
	Selective outcome reporting	All outcomes described in methods and trial register were reported in the results.	**Low**

Study	Domain	Support for judgement	Risk of bias
Wilsey(2013)[134]	Random sequence generation	Random order (using a web-based random numbergenerating program, ‘‘Research Randomizer’’ (http://www.randomizer.org/).	**Low**
	Allocation concealment	The allocation schedule was kept in the pharmacy and concealed from other study personnel. Participants were assigned to treatment after they signed a consent form.	**Low**
	Participant/ Personnel blinding	Participants and assessors were blinded to group assignments. Placebo cannabis was made from whole plant with extraction of cannabinoids.	**Low**
	Outcome assessor blinding	Participants and assessors were blinded to group assignments.	**Low**
	Incomplete outcome data	1 participant did not participate in placebo phase, 3 in low dose phase, and 3 in medium dose phase. Per-protocol rather than ITT analysis performed. As numbers low unlikely to have affected results.	**Low**
	Selective outcome reporting	All outcomes described in methods were reported in the results.	**Low**
Wilsey(2011)[138]	Random sequence generation	Web-based random number– generating program, ”Research Randomizer”	**Low**
	Allocation concealment	The allocation schedule was kept in the pharmacy and concealed from other study personnel.	**Low**
	Participant/ Personnel blinding	Participants and assessors were blinded to group assignments.	**Low**
	Outcome assessor blinding	Participants and assessors were blinded to group assignments.	**Low**
	Incomplete outcome data	Appears to be per protocol analysis (38 randomised, 33-36 analysed)	**High**
	Selective outcome reporting	Adverse events not fully reported.	**High**
Zaijcek(2012)[87]	Random sequence generation	Computer generated permuted block randomisation was used, stratified by centre, ambulatory status (able to walk or not) and concurrent use of antispasticity medication (yes or no).	**Low**
	Allocation concealment	Participants were evenly allocated to CBM or placebo by means of an interactive voice response system.	**Low**
	Participant/ Personnel blinding	Matched placebo capsules contained the same partial glyceride vehicle as active treatment. The study coordinating team, all investigators and participants were blinded to treatment allocation throughout.	**Low**
	Outcome assessor blinding	The study coordinating team, all investigators and participants were blinded to treatment allocation throughout. All decisions regarding primary outcome data were finalised by a blind data review panel before unblinding.	**Low**
	Incomplete outcome data	1 participant in each arm was not included in ITT population unlikely to have had substantial influence on results. Additional 34 withdrawals in CBM and 19 withdrawals in placebo arm but appropriate ITT analysis performed.	**Low**
	Selective outcome reporting	Primary outcome same as specified on trial registration, however, more outcomes reported than pre-specified in the trial register. Results for all outcomes specified in methods reported.	**Low**

Study	Domain	Support for judgement	Risk of bias
Zajicek(2003)[89]	Random sequence generation	Participants were randomly assigned by adaptive randomisation to minimise imbalance between centres and ambulatory status.	**Low**
	Allocation concealment	Once written informed consent had been obtained from an eligible participant, the investigator contacted the coordinating centre by telephone. The coordinating centre allocated the participant a trial number and then forwarded relevant details to the central trial pharmacy, where randomisation took place, using a dedicated stand-alone computer. Matching of active and placebo capsules was assessed by an independent panel before the start of the study to ensure there was no obvious difference between them.	**Low**
	Participant/ Personnel blinding	Throughout the study, the list of treatment allocation codes was kept at the central trial pharmacy, located separately from the coordinating office. The study coordinating team, all investigators, the data monitoring committee, and participants were unaware of the treatment allocation for the duration of the study.	**Low**
	Outcome assessor blinding	Throughout the study, the list of treatment allocation codes was kept at the central trial pharmacy, located separately from the coordinating office. The study coordinating team, all investigators, the data monitoring committee, and participants were unaware of the treatment allocation for the duration of the study. "...blinding was maintained in the assessing individuals…"	**Low**
	Incomplete outcome data	"Of the 630 participants included in the intention-to-treat analysis, follow-up data on the primary outcome was obtained for 611 (97%)" ["lack of efficacy" and "intolerable side-effects" reported by more than half]. "Completion and return of data for the secondary outcome measures was also generally high, with data available for analysis from 84–91% of participants."	**Low**
	Selective outcome reporting	All outcomes described in trial registry entry were reported in the results.	**Low**

B. ACROBAT NRS TOOL FOR NON-RANDOMISED STUDIES

Study	Domain	Risk of bias	
		Support for judgement	**Judgement**
Agrawal(2011)[229] Case-control study **Outcome:** Bipolar disorder	**Confounding**	No data were reported for the adjusted effect size for the outcome of interest (psychosis)	Critical
	Selection of participants	Controls were selected from a similar population to cases	Moderate
	Measurement of interventions	Exposure was assessed as lifetime history of cannabis abuse (likely to be subject to recall bias)	Critical
	Departures from intended interventions		No information
	Missing data		No information
	Measurement of outcomes	Case-control study	Not applicable
	Selection of reported result	Adjusted effect estimates were not reported where not statistically significant	Serious
	Overall	Study rated as critical risk of bias for confounding and measurement of interventions	Critical
Aldington(2008)[231] Case-control study **Outcome:** Cancer Head and neck	**Confounding**	Critically important confounders adjusted for in logistic regression analysis. Some subjectivity in measurement of confounders, but measures appropriate for data.	Moderate
	Selection of participants	Controls were people with no respiratory tract cancer, head and neck cancer, or lung cancer who were randomly selected from the electoral roll in the same geographic areas as cases; matched in five-year age groups.	Low
	Measurement of interventions	Information on exposure was collected by face-to-face interview. Information related to historical exposure (possible recall bias)	Critical
	Departures from intended interventions		No information
	Missing data	Outcome status data appeared complete	Low
	Measurement of outcomes	Case-control study	Not applicable
	Selection of reported result	Results appear to be reported for all outcomes specified	Low
	Overall	Study rated as critical risk of bias for measurement of interventions	Critical
Aldington(2008)[230] Case-control study **Outcome:** Cancer Lung	**Confounding**	All critical confounders were adjusted for in logistic regression analysis	Low
	Selection of participants	Controls selected form the same population as cases (electoral role) and matched in 5 year age groups	Low
	Measurement of interventions	Lifetime exposure assessed by interview, susceptible to recall bias	Critical
	Departures from intended interventions		No information
	Missing data	Outcome status determination appears to be complete	Low

Study	Domain	Risk of bias	
		Support for judgement	**Judgement**
	Measurement of outcomes	Case-control study	Not applicable
	Selection of reported result	Multiple analyses presented	Low
	Overall	Study was rated as critical risk of bias for measurement of interventions	Critical
Barber(2013)[232] Case-control study **Outcome:** cardiovascular disease Ischemic stroke and TIA	**Confounding**	All specified critical confounders adjusted for in logistic regression modelling	Low
	Selection of participants	Controls selected from the same population as cases	Low
	Measurement of interventions	Objective measure (urine screen), but will only give information on a narrow time window	Serious
	Departures from intended interventions		No information
	Missing data	Outcome determination appeared reasonably complete	Moderate
	Measurement of outcomes	Case-control study	Not applicable
	Selection of reported result	All outcomes appear to have been reported	Low
	Overall	Study rated as serious risk of bias for measurement of interventions, but most other domains were rated as low risk of bias or NI/NA	Serious
Beautrais(1999)[233] Case-control study **Outcome:** Suicide Serious suicide attempts	**Confounding**	All specified critical confounders were adjusted for in logistic regression analyses	Low
	Selection of participants	Controls were selected form the electoral roll and matched on age and gender	Low
	Measurement of interventions	Exposure was assessed as cannabis abuse/dependence (DSM-III-R) in the previous month (some potential for recall bias).	Moderate
	Departures from intended interventions		No information
	Missing data	5% of cases and 15% controls were not included (did not provide exposure data). Missing data was not included in analysis	Moderate
	Measurement of outcomes	Case-control study	Not applicable
	Selection of reported result	Results were reported for all specified analyses	Low
	Overall	Possibility of recall bias and some missing exposeure data	Moderate
Berthiller(2009)[260] Case-control study **Outcome:** Cancer Head and neck	**Confounding**	All specified critical confounders adjusted for in logistic regression analysis	Low
	Selection of participants	IPD analysis of data from five studies. Controls matched for age and gender and, additionally, for neighbourhood of residence in one study	Low
	Measurement of interventions	Exposure data were for historical marijuana smoking (likely to be susceptible to recall bias)	Critical
	Departures from intended interventions		No information

Study	Domain	Risk of bias	
		Support for judgement	**Judgement**
	Missing data	No evidence of missing data	Low
	Measurement of outcomes	Case-control studies	Not applicable
	Selection of reported result	Results were reported for all specified analyses	Low
	Overall	Study rated as critical risk of bias for measurement of interventions	Critical
Daling(2009)[235] Case-control study **Outcome:** Cancer TGCT	**Confounding**	All specified critical confounders were adjusted for in logistic regression analyses	Low
	Selection of participants	Controls were selected from the same geographical area as cases, using random number dialling, and matched on 5 year age group	Low
	Measurement of interventions	Exposure information was determined by interview and related to a period before diagnosis/study entry (likely to be subject to recall bias)	Critical
	Departures from intended interventions		No information
	Missing data	67.5% cases interviewed but only 52.2% of controls	Moderate
	Measurement of outcomes	Case-control study	Not applicable
	Selection of reported result	Results were reported for all specified analyses	Low
	Overall	Study rated as critical risk of bias for measurement of interventions	Critical
Davis(2013)[236] Historical cohort **Outcome:** schizophrenia or psychotic illness or episode / schizotypal personality disorder	**Confounding**	No adjustment for susceptibility to psychiatric disease, or other illicit drug use/abuse	Critical
	Selection of participants	Retrospective analysis of data from a national survey	Moderate
	Measurement of interventions	Measuring the exposure retrospectively is les likely to cause recall bias in this specific case (alcohol and drug use disorders assessed by structured interview and DSM IV criteria	Moderate
	Departures from intended interventions		No information
	Missing data	Data appear to be reasonably complete	Low
	Measurement of outcomes	Outcome assessment was subjective and asessors may have been aware of the exposure	Moderate
	Selection of reported result	All outcomes appear to have been reported	Low
	Overall	Study assessed as critical risk of bias for confounding	Critical
Di Forti(2009)[237] Case-control study **Outcome:** psychosis	**Confounding**	All specified critical confounders adjusted for in logistic regression analysis	Low
	Selection of participants	Controls were recruited from the same local area as cases and were matched for age, gender, ethnicity, educational qualifications and employment status	Low
	Measurement of interventions	Exposure was determined by questionnaire and included historical use (likely to be susceptible to recall bias)	Critical

Study	Domain	Risk of bias	
		Support for judgement	**Judgement**
	Departures from intended interventions		No information
	Missing data	40% of cases refused to participate	Serious
	Measurement of outcomes	Case-control study	Not applicable
	Selection of reported result	Results were reported for all specified analyses	Low
	Overall	Study rated as critical risk of bias for measurement of interventions	Critical
Dutta (2014)[238] Case-control study **Outcome:** Cardiovascular Ischemic stroke	**Confounding**	All specified critical confounders were adjusted for in logistic regression analysis	Low
	Selection of participants	Controls were recruited form the same geographic area as controls. Matching not reported	Moderate
	Measurement of interventions	Exposure was assessed by interview as history of illicit drug use (likely to be susceptible to recall bias)	Criticall
	Departures from intended interventions		No information
	Missing data		No information
	Measurement of outcomes	Case-control study	Not applicable
	Selection of reported result	Abstract only, analyses not clearly pre-specified	No information
	Overall	Study rated as critical risk of bias for measurement of interventions	Critical
Giordano(2014)[239] Case-control study **Outcome:** Psychosis Schizophrenia	**Confounding**	No adjustment for confounders	Critical
	Selection of participants	Participants were matched as closely as possible to account for environmental/familial issues and multiple drug use was also tested for.	Low
	Measurement of interventions	Exposure defined as registered cannabis user before diagnosis of schizophrenia. Objective measure, but some users may not be classified as having exposure	Serious
	Departures from intended interventions	No information about de-registration possibilities	No information
	Missing data		No information
	Measurement of outcomes	Case-control study	Not applicable
	Selection of reported result	Unclear definitions throughout	Serious
	Overall	No adjustment for confounders. Registered cannabis abuse is not the same as cannabis use and may be a feature unique to Sweden. Abuse is suggestive of a "problem" and so linking to scizophrenia may be a self-fulfilling prophesy	Critical
Hashibe(2006)[240]	**Confounding**	All specified critical confounders were adjusted for in logistic regression modelling	Low

Study	Domain	Risk of bias	
		Support for judgement	**Judgement**
Case-control study **Outcome:** Cancer Lung and upper aerodigestive tract	**Selection of participants**	Controls were selected from the same geographical area as cases and matched on age, gender and residential neighbourhood	Low
	Measurement of interventions	Exposure was assessed as lifetime exposure, determined by face-to-face interview using a structured questionnaire (likely to be subject to recall bias)	Critical
	Departures from intended interventions		No information
	Missing data	Data appeared reasonably complete, but not clear whether all participants provided information on exposure. Participation rate was low	Moderate
	Measurement of outcomes	Cade control study	Not applicable
	Selection of reported result	Results were reported for all specified analyses	Low
	Overall	Study rated critical risk of bias for measurement of interventions	Critical
Lacson(2012)[241] Case-control study **Outcome:** cancer TGCT	**Confounding**	Unadjusted analyses show no effect. Some of the adjusted analyses showed a statistically significant effect, and some of the confounders adjusted for may not have been relevant.	Moderate
	Selection of participants	Controls were sampled from the same population, but some cases were not included because no matched control was identified and some were matched using 'relaxed' criteria	Serious
	Measurement of interventions	Intervention assessment may be subject to recall bias	Critical
	Departures from intended interventions	Balance of smoking status between cannabis exposure categories unclear	No information
	Missing data	Outcome data appear complete	Low
	Measurement of outcomes	Case-control study	Not applicable
	Selection of reported result	Many analyses are reported, most significant are stressed.	Serious
	Overall	Study rated as critical risk of bias for measurement of interventions	Critical
Liang(2009)[242] Case-control study **Outcome:** Cancer (HNSCC)	**Confounding**	All specified critical confounders adjusted for in logistic regression analysis	Low
	Selection of participants	Controls selected form the same population as controls; matched for age, gender and area of residence	Low
	Measurement of interventions	Exposure status (current and former) was assessed by self-reported questionnaire (likely to be subject to recall bias)	Critical
	Departures from intended interventions	Unclear whether smoking and alcohol use were similar across exposure groups, but both were adjusted for in the analysis	Low

Study	Domain	Risk of bias	
		Support for judgement	**Judgement**
	Missing data	About 299 of approximately 1000 participants were excluded due to unavailable HPV 16 detection (n =248), or missing information regarding marijuana use (n =51)	Serious
	Measurement of outcomes	Case-control study	Not applicable
	Selection of reported result	Results were reported for all specified analyses	Low
	Overall	Study rated critical risk of bias for measurement of interventions and some data missing for a high proportiopn of participants	Critical
Llewellyn(2004)[243] Case-control study **Outcome:** Cancer Oral	**Confounding**	Adjustment for alcohol and tobacco consumption only	Serious
	Selection of participants	Controls were selected from the same geographic area as cases and were matched for sex, age and area of residence	Low
	Measurement of interventions	Exposure was assessed by structured questionnaire, but it was not clear whether questions on cannabis use related to the time of diagnosis/study entry, or to a historical time period	Moderate
	Departures from intended interventions		No information
	Missing data	Information on number of patients, for which exposure data is missing is unclear	Serious
	Measurement of outcomes	Case-control studies	Not applicable
	Selection of reported result	Results reported for all specified outcomes	Low
	Overall	Some specified confounders (age, gender) were not included in the model, unclear how much exposure data is missing.	Serious
Llewellyn(2004)[244] Case-control study **Outcome:** Cancer Oral	**Confounding**	Some confounders not included in the model (age, gender)	Moderate
	Selection of participants	Controls selected from the same geographic area. Matched for age, sex and area of residence	Low
	Measurement of interventions	Exposure information collected by self-report questionnaire. Unclear whether questions on cannabis use related to current or historical time period (possibility of recall bias)	Moderate
	Departures from intended interventions		No information
	Missing data	Some cannabis exposure data missing	Serious
	Measurement of outcomes	Case-control study	Not applicable
	Selection of reported result	Results reported for all specified analyses	Low
	Overall	Unknown amount of missing exposure data, some confounders not adressed and some potential for recall bias.	Serious
Manrique-Garcia(2012)[2]	**Confounding**	All critical confounders adjusted for in logistic regression analyses	Low

Study	Domain	Risk of bias	
		Support for judgement	**Judgement**
[45] Prospective cohort study **Outcome:** Cancer Lung Psychosis Schizophrenia, brief psychosis, other non-affective psychosis Suicide and possible suicide	**Selection of participants**	Un-selected cohort of male conscripts, exposure occurred before study entry	Low
	Measurement of interventions	Information collected was on previous cannabis use (during early adolescence) and therefore likely to be susceptible to recall bias	Critical
	Departures from intended interventions		No information
	Missing data	8144 participants had missing information, including 3381 who did not respond to the question on drug use	critical
	Measurement of outcomes	Hospital discharge data and ICD classifications used, diagnoses were not made as part of this study	Low
	Selection of reported result	Results were reported for all specified analyses	
	Overall	Study rated as critical risk of bias for measurement of interventions and missing data	Critical
Marks (2014)[246] Case-control study **Outcome:** Cancer Oropharyngeal and oral tongue	**Confounding**	All critical confounders adjusted for in logistic regression analyses	Low
	Selection of participants	IPD analysis 9 studies. All studies matched controls for age and sex, some studies additionally matched on race and ethnicity or area of residence	Low
	Measurement of interventions	Information collected was on previous cannabis use (lifetime exposure) and therefore likely to be susceptible to recall bias	Critical
	Departures from intended interventions		No information
	Missing data	Missing data for 3% of cases and 2% of controls	Low
	Measurement of outcomes	Case-control study	Not applicable
	Selection of reported result	Results were reported for all specified analyses	
	Overall	Study rated as critical risk of bias for measurement of interventions	Critical
McGrath(2010)[247] Prospective cohort study **Outcome:** psychosis	**Confounding**	All specified critical confounders adjusted for in logistic regression analysis	Low
	Selection of participants	Selection was unrelated to exposure (determined for follow-up period)	Moderate
	Measurement of interventions	Exposure was determined at 21 year follow-up, using a self-report questionnaire (likely to be susceptible to recall bias)	Critical
	Departures from intended interventions	Illicit drug use and alcohol use during 14 year follow-up were strongly related to duration of cannabis use	Critical
	Missing data	No evidence of missing data	Low
	Measurement of outcomes	Subjective outcome measures which may not have been assessed blind to exposure information	Serious
	Selection of reported result	Data appear to have been reported for all analyses specified	Low

Study	Domain	Risk of bias	
		Support for judgement	**Judgement**
	Overall	Study rated as critical risk of bias for measurement of interventions and departure from intended interventions	Critical
Pederson(2008)[248] Prospective cohort **Outcome:** Suicide	**Confounding**	Most of the specified critical confounders were adjusted for in the analysis; psychiatric co-morbidity, in-care during childhood and childhood sexual abuse were not considered in this study	Moderate
	Selection of participants	School cohort, selection un-related to exposure	Low
	Measurement of interventions	Exposure status assessed was based on lifetime ever cannabis use and cannabis use in the previous 12 months (likely to be subject to recall bias)	Critical
	Departures from intended interventions		No intervention
	Missing data	Cumulative response rate over all follow-up points 70%	Moderate
	Measurement of outcomes	Outcome suicide and suicidal ideation	Low
	Selection of reported result	Results reported for all specified analyses	Low
	Overall	Study rated as critical risk of bias for measurement of interventions	Critical
Rolfe(1993)[249] Case-control study **Outcome:** Psychotic disease	**Confounding**	All specified critical confounders were included in the logictic regression analysis, but the authors stated that ascertainment of confounders may have been unreliable	Serious
	Selection of participants	Family and friend controls, matched for age, sex and place of residence	Low
	Measurement of interventions	Exposure determined by urine toxicology screen. This is an objective measure but only provides information on a very narrow time window	Serious
	Departures from intended interventions		No infromation
	Missing data	No information	No information
	Measurement of outcomes	Case-control study	Not applicable
	Selection of reported result	All outcomes appear in the results	Low
	Overall	Study rated as serious risk of bias for confounding and measurement of interventions	Serious
Rosenblatt(2004)[250] Case-control study **Outcome:** Cancer Oral squamous cell	**Confounding**	All specified critical confounders were adjusted for in logistic regression analysis	Low
	Selection of participants	Controls were selected from the same geographic area, by random digit dialling. Matched on age group and gender	Low
	Measurement of interventions	Exposure was assessed by structured questionnaire, as history of use (likely to be subject to recall bias)	Critical
	Departures from intended interventions		No information

Study	Domain	Risk of bias	
		Support for judgement	**Judgement**
	Missing data	Some missing data, low participation rate	Moderate
	Measurement of outcomes	Case-control study	Not applicable
	Selection of reported result	Results were reported for all specified analyses	Low
	Overall	Study rated as critical risk of bias for measurement of interventions	Critical
Sasco(2002)[251] Case-control study **Outcome:** Cancer Lung	**Confounding**	Age and gender not adjusted for in the analyses	Serious
	Selection of participants	Controls selected from non-cancer patients in the same hospital; matched on age and gender	Moderate
	Measurement of interventions	Information on exposure was obtained using a standardise questionnaire, administered by a physician; unclear whether questions related to current or past exposure	Moderate
	Departures from intended interventions		No information
	Missing data	No evidence of missing data	Low
	Measurement of outcomes	Case-control study	Not applicable
	Selection of reported result	Results reported for all specified analyses	Low
	Overall	Residual confounding and possible limitations in selection of controls and measurement of interventions	Moderate
Tan(2009)[252] Retrospective cohort study **Outcome:** Respiratory disease COPD	**Confounding**	All specified critical confounders adjusted for in logistic regression analysis	Low
	Selection of participants	Population based cohort, historical exposure	low
	Measurement of interventions	Exposure information related to history of use (likely to be susceptible to recall bias)	Critical
	Departures from intended interventions		No information
	Missing data	Full protocol completed by 856 of 1786 eligible participants	Serious
	Measurement of outcomes	Separate analyses for subjective and objective outcomes definitions	Low
	Selection of reported result	Results reported for all specified analyses	Low
	Overall	Study rated as critical risk of bias for measurement of interventions. Low proportion of completers	Critical
Trabert(2011)[253] Case-control study **Outcome:** Cancer	**Confounding**	All specified critical confounders were adjusted for in logistic regression analysis	Low
	Selection of participants	Friend controls of similar age and race to cases, but tended to be older and have higher income	Moderate
	Measurement of interventions	Unclear whether detailed information on exposure related to current or historical use. Categorisation of intervention frequency was poor (daily use vs. <daily use)	Moderate

Study	Domain	Risk of bias	
		Support for judgement	Judgement
TGCT	**Departures from intended interventions**		No information
	Missing data	Data appeared reasonably complete	Low
	Measurement of outcomes	Case-control	Not applicable
	Selection of reported result	All specified analyses appear to be reported	Low
	Overall	Study rated as moderate risk of bias for selection of participants and measurement of intervention	Moderate
van Os(2002)[254] Prospective cohort study **Outcome:** Psychosis	**Confounding**	All specified critical confounders adjusted for in logistic regression analysis	Low
	Selection of participants	Longitudinal population cohort, outcomes appear to have been determined by experienced clinicians, separate to exposure interviews	Low
	Measurement of interventions	Exposure determined by structured interview and included some current and some historical information (may be susceptible to recall bias)	Moderate
	Departures from intended interventions		No information
	Missing data	No evidence of missing data	Low
	Measurement of outcomes	Outcomes determined by experienced clinician (psychiatrist or psychologist), DSM-III-R criteria, exposure appears to have been determined at separate interview	Low
	Selection of reported result	Results reported for all specified analyses	Low
	Overall	Some data may be at risk of recall bias	Moderate
Veling (2008)[255] Case-control study **Outcome:** Psychosis Schizophrenia	**Confounding**	All specified critical confounders were adjusted for in logistic regression analysis	Low
	Selection of participants	Two control groups: siblings and non-psychiatric hospital population of same ethnicity. Matched for 5 year age group, gender and ethnicity	Low
	Measurement of interventions	Exposure assessed, by structured diagnostic interview, as lifetime history of cannabis use (likely to be subject to recall bias)	Critical
	Departures from intended interventions		No information
	Missing data	No evidence of missing data, all cases and controls included in the analysis	Low
	Measurement of outcomes	Case-control study	Not applicable
	Selection of reported result	Results reported for all specified analyses	Low
	Overall	Study rated as critical risk of bias for measurement of intervention	Critical
Voirin(2006)[256] Case-control	**Confounding**	All critical confounders were adjusted for in logistic regression analysis	Low
	Selection of participants	Controls were men hospitalised at the same institution as cases	Low

Study	Domain	Risk of bias	
		Support for judgement	**Judgement**
study **Outcome:** Cancer Lung	**Measurement of interventions**	Exposure status was determined retrospectively by self-report questionnaire (likely to be susceptible to recall bias)	Critical
	Departures from intended interventions	Unclear whether tobacco use was similar between users and non-users of cannabis, but tobacco use was adjusted for in the model	Low
	Missing data	No evidence of missing data	Low
	Measurement of outcomes	Case-control study	Not applicable
	Selection of reported result	Results reported for all specified analyses	Low
	Overall	Study rated as critical risk of bias for measurement of intervention	Critical
Weller(1985)[257] Prospective cohort study **Outcome:** Schizophrenia / Psychotic disorder	**Confounding**	No adjustment for confounding factors	Critical
	Selection of participants	Participants were selected on the basis of marijuana use status 6-7 years before the start of follow-up	Critical
	Measurement of interventions	Exposure status was determined retrospectively (risk of recall bias)	Critical
	Departures from intended interventions	Not enough reported to allow judgement	No information
	Missing data	Participants missing from follow-up, which could be related to adverse outcomes, but only 3 out of 100 missing	Moderate
	Measurement of outcomes	Some subjectivity in outcome determination, but appropriate for clinical area (structured interview and DSM-III criteria)	Moderate
	Selection of reported result	Results appeared to be reported for all outcomes specified	Low
	Overall	Study rated as critical risk of bias for confounding, participant selection and measurement of intervention	Critical
Zhang(1999)[258] Case-control study **Outcome:** Cancer (HNSCC)	**Confounding**	All specified critical confounders adjusted for in logistic regression analysis	low
	Selection of participants	Blood donor controls, matched for age and sex	Moderate
	Measurement of interventions	Exposure information assessed by questionnaire and participants asked about historical use (likely to be susceptible to recall bias)	Critical
	Departures from intended interventions		No information
	Missing data	No evidence of missing data. Proximately 90% participation rate (cases and controls)	Low
	Measurement of outcomes	Case-control study	Not applicable
	Selection of reported result	All the outcomes listed in methods were reported.	Low
	Overall	Study rated as critical risk of bias measurement of intervention	Critical

Study	Domain	Risk of bias	
		Support for judgement	**Judgement**
Zhang(2014)[25] 9 Case-control study **Outcome:** Lung cancer	**Confounding**	Nalyses adjusted for age, sex, race and education. Separate analyses conducdted for whole population and never tobacco smokers	Moderate
	Selection of participants	Poorly matched controls.	Serious
	Measurement of interventions	Exposure assessed by self-reported questionnaire and related to lifetime use (likely to be susceptible to recall bias)	Critical
	Departures from intended interventions		No information
	Missing data		No information
	Measurement of outcomes	Case-control study	Not applicable
	Selection of reported result	Results reported for all specified analyses	Low
	Overall	Study rated as critical risk of bias measurement of intervention	Critical

APPENDIX 9: OUTCOME MEASURES EVALUATED IN INCLUDED STUDIES

Category	Outcome	Description	Scale	Treat-ment arm favoured by positive mean difference (MD)
Depression	Montgomery–Åsberg Depression Rating Scale	See Williams 2008. [324] The Montgomery-Asberg depression scale (abbreviated MADRS) is a10-item diagnostic questionnaire which is used by psychiatrists to measure the severity of depressive episodes in patients with mood disorders. The questionnaire includes questions on the following symptoms 1. Apparent sadness 2. Reported sadness 3. Inner tension 4. Reduced sleep 5. Reduced appetite 6. Concentration difficulties 7. Lassitude 8. Inability to feel 9. Pessimistic thoughts 10. Suicidal thoughts A self-rating version of this scale (MADRS-S) is often used in clinical practice and correlates reasonably well with expert ratings. The MADRS-S instrument has nine questions, with an overall score ranging from 0 to 54 points.	Cut-off points: 0-6: Normal, symptom absent, 7-19 Mild Depression, 20-34 Moderate Depression, >34 Severe depression. Higher scores indicate worse outcomes	Favours control (lower scores indicate better outcomes)
General	Numerical rating scale	See Hartrick 2003. [325] Usually refers to an 11-point Pain Rating Scale. Can also be known as the NRS-11.	11 point scale (0- 10) with 0 = no pain , 1-3=mild pain, 4-6 = moderate pain and and 7-10= “severe pain”	Favours control (lower scores indicate better outcomes)
General	Visual analogue scale	See Huskisson 1982. [326]Operationally, a VAS is usually a horizontal line, 100mm in length, anchored by word descriptors at each end. The patient marks on the line the point that they feel represents	Can be represented in different ways (i.e. 0-10, 0-100) but generally the high points on the scale represent worse outcomes.	Favours control (lower scores indicate better outcomes)

Category	Outcome	Description	Scale	Treat-ment arm favoured by positive mean difference (MD)
		their perception of their current state. The VAS score is determined by measuring in millimetres from the left hand end of the line to the point that the patient marks. There are other ways to present a VAS, including by vertical line and lines with extra descriptors.		
General disease specific symptoms	Tourettes syndrome clinical global impression scale (TS-CGI)	See Cath 2011.[327] Tourettes Syndrome – Clinical Global Impressions Scale (TS-CGI-S) The CGI-S assesses change in global daily functioning. The CGI-S has shown good face validity and is extremely easy to use, although inter-rater reliability is somewhat low.	A 7-point scale (0-6) is used.; (between 0 = much deteriorated and, via 3 = no change, to 6 = very much improved). Lower scores indicate worse outcomes.	Favours CBM (Higher scores indicate better outcomes)
General disease specific symptoms	28-joint disease activity score (DAS28)	See van der Heijde 1990. [328]The DAS28 is a measure of disease activity in rheumatoid arthritis (RA). DAS stands for 'disease activity score' and the number 28 refers to the 28 joints that are examined in this assessment. The DAS28 is a composite score derived from 4 of the following measures: Joint swelling and tenderness, global scores of pain and overall status, blood markers of inflammation (e.g. ESR and CRP), questionnaires assessing function and X-rays/ultrasound/MRI.	A composite score derived from the following: Number of swollen joints (out of 28), Number of tender joints (out of 28), blood measurements of ESR or CRP, and a “global assessment of health” by the patient on a 10cm line. A “complex mathematical formula” produces the overall DAS score. A DAS28 of >5.1 implies active disease, <3.2 = low disease activity and <2.6 = remission. Higher scores indicate worse outcomes.	Favours control (lower scores indicate better outcomes)
General disease specific symptoms	Multiple Sclerosis Impact Scale (MSIS-29)	See Hobart 2001. [329] Multiple Sclerosis Impact Scale (MSIS-29)	29-item questionnaire which asks how MS symptoms are limiting ability/bothering the	Favours control (lower scores indicate better

Category	Outcome	Description	Scale	Treat-ment arm favoured by positive mean difference (MD)
		A 29-item questionnaire designed as an outcome measure for clinical trials that is disease specific and combines patient perspective with rigorous psychometric methods that complement existing instruments.	patients. 5-point scale (1-5) with 1= "Not at all" to 5 = "Extremely". Higher scores indicate worse outcomes.	outcomes)
General disease specific symptoms	MS functional composite score	See Rudick 2002. [330] Multiple Sclerosis Functional Composite (MSFC). The score is based on a combination of timed tests of walking, arm function, and cognitive ability and was developed by the MS society. MSFC components should be administered in the following order: 1.Trial 1, Timed 25-Foot Walk 2.Trial 2, Timed 25-Foot Walk 3.Trial 1, Dominant Hand, 9-HPT 4.Trial 2, Dominant Hand, 9-HPT 5.Trial 1, Non-Dominant Hand, 9-HPT 6.Trial 2, Non-Dominant Hand, 9-HPT 7.PASAT-3'' (Paced-Auditory Serial Addition Test) Scoring appears to be complex, and is based on the composite score of: 1) the average scores from the four trials on the 9-HPT (the two trials for each hand are averaged, converted to the reciprocals of the mean times for each hand and then the two reciprocals are averaged); (2) the average	MSFC is based on the concept that scores for these three dimensions—arm, leg, and cognitive function are combined to create a single score (the MSFC) that can be used to detect change over time in a group of multiple sclerosis patients. This is done by creating Z-scores for each component of the MSFC: the MSFC score represents he MSFC represents the average change in the three tests. MSFC Score={ (Average (1/9-HPT) - Baseline Mean (1/9-HPT) / Baseline Std Dev (1/9-HPT) + { - (Average 25-Foot Walk - Baseline Mean 25-Foot Walk) /Baseline Std-Dev 25-Foot Walk} + (PASAT-3 - Baseline Mean PASAT-3) /Baseline Std Dev PASAT-3} / 3.0 A minus Z- score indicates a better outcome	Favours CBM (higher scores on the BRB indicate better outcomes)

Category	Outcome	Description	Scale	Treat-ment arm favoured by positive mean difference (MD)
		scores of two 25-Foot Timed Walk trials; (3) the number correct from the PASAT-3 (Paced-Auditory Serial Addition Test).		
Global impression	General Health Questionnaire 12	See Sanchez-Lopez 2008. [331] GHQ-12 – a measure of current mental health. The questionnaire was originally developed as a 60-item instrument but at present a range of shortened versions of the questionnaire including the GHQ-30, the GHQ-28, the GHQ-20, and the GHQ-12 is available. The scale asks whether the respondent has experienced a particular symptom or behaviour recently. Each item is rated on a four-point scale (less than usual, no more than usual, rather more than usual, or much more than usual); and for example when using the GHQ-12 it gives a total score of 36 or 12 based on the selected scoring methods.	The 12-Item General Health Questionnaire (GHQ-12) (Goldberg & Williams, 1988) consists of 12 items, each one assessing the severity of a mental problem over the past few weeks using a 4-point Likert-type scale (from 0 to 3). The score was used to generate a total score ranging from 0 to 36. The positive items were corrected from 0 (always) to 3 (never) and the negative ones from 3 (always) to 0 (never). High scores indicate worse health.	Favours control (lower scores indicate better health/outcomes)
Global impression	Karnofsky performance status	See Karnofsky 1949. [131] Performance status is an attempt to quantify cancer patients' general well-being and activities of daily life. This measure is used to determine whether they can receive chemotherapy, whether dose adjustment is necessary, and as a measure for the required intensity of palliative care.	The Karnofsky score runs from 100 to 0, where 100 is "perfect" health” and 0 is death. Lower scores indicate worse outcomes.	Favours CBM (higher scores = better outcomes)
Mobility/Disability	Barthel Index of activities of daily living	See Mahoney 1965. [213]The Barthel scale or Barthel ADL index is an ordinal scale	Individuals are scored on 10 activities which are summed to give a score of 0 (totally	Favours CBM (higher scores = better outcomes)

Category	Outcome	Description	Scale	Treat-ment arm favoured by positive mean difference (MD)
	(ADL)	used to measure performance in activities of daily living (ADL). The scale covers the following dimensions: Feeding, mobility from bed to wheelchair, personal toilet (washing etc), getting on and off the toilet, Bathing, Walking on a level surface, going up/downstairs stairs/dressing/incontinence (bladder and bowel).	dependent) to 100 (fully independent) Lower scores indicate worse outcomes. A modified scoring gives a maximum score of 20 to patients who are continent, able to wash feed and dress themselves and are independently mobile.	
Mobility/Disability	Rivermead Mobility Index	See Collen 1991. [332]. 15 questions about mobility	Score 0 points (each question) for "No" answer and 1 point (each question) for "Yes" answer. Score ranges from 0-15. Higher scores = better mobility, so better outcomes.	Favours CBM (higher scores = better outcomes)
Mobility/Disability	Tremor Activities of Daily Living Scale	See Tremor Research Group 2008. [333] and Elble 2008.[334] This refers to the TRG essential Tremor Rating Assessment Scale (TETRAS) Activities of Daily Living Scale.	The impact of tremor is rated on 12 daily living activities. 5 point scale (0-4). 0= Normal, 5= Severe impairment. There is also a more descriptive performance subscale, again with 0-4 scores 0= no tremor and 4 = tremor is severely affecting functioning. Higher scores = worse outcome.	Favours control (lower scores indicate better outcomes/ less impact of tremor)
Mobility/Disability	Nine-hole peg test of manual dexterity	See Mathiowetz 1985. [335]	This is scored on a continuous scale of male norms and female norms for manual dexterity according to age.	Favours control (lower time scores = better manual dexterity)

Category	Outcome	Description	Scale	Treat-ment arm favoured by positive mean difference (MD)
			Lower time in seconds = better dexterity.	
Mobility/Disability	Walk time (10m)	See Tilson 2010.[336] "Timed 10 meter walk test" The individual walks without assistance 10 meters (32.8 feet) and the time is measured for the intermediate 6 meters (19.7 feet) to allow for acceleration and deceleration.	Scored on a continuous scale. Patient is timed in seconds. Faster time in seconds = better outcome.	Favours control (lower time scores = better mobility)
Mobility/Disability	UK neurological disability score (UKNDS) also known as the Guys Neurological Disability Scale (GNDS).	See Sharrack 1999[337] and Pearson 2004.[338]. This is the UK neurological disability SCALE also formerly known as "Guys Neurological Disability Scale (UKNDS/GNDS)" The Guy's Neurological Disability Scale (GNDS) was devised as a simple and user-friendly clinical disability scale capable of embracing the whole range of disabilities which could be encountered in the course of multiple sclerosis. It has 12 separate categories which include cognition, mood, vision, speech, swallowing, upper limb function, lower limb function, bladder function, bowel function, sexual function, fatigue, and `others'.	A multiple sclerosis (MS) specific measure. Patient-based questionnaire composed of twelve subsections including mobility, scored 0–5 based on use of aids. Walking is considered 'not affected' or affected but independent (no assistance) for scores of 0 and 1, respectively, while scores 2–5 represent increasing degrees of support (aids, person, wheelchair). 5= restricted to wheelchair. Lower scores indicate better outcomes.	Favours control (lower scores indicate better outcomes)
Mobility/Disability	Fibromyalgia impact	See Burckhardt 1991.[339]. Self-reported	20 questions on various aspects of	Favours control (lower

Category	Outcome	Description	Scale	Treat-ment arm favoured by positive mean difference (MD)
	questionnaire (FIQ) – *already described above in "Anxiety /psychological "section*	questionnaire measuring health related QoL, physical functioning and signs and symptoms.	functioning with fibromyalgia (including anxiety). Higher scores indicate poorer outcomes.	scores indicate better outcomes)
Mobility/Disability	Multiple sclerosis walking scale (MSWS-12)	See Holland 2006. [340] The Multiple Sclerosis Walking Scale (MSWS-12) was originally developed to measure the impact of multiple sclerosis on walking. However, as other disabling neurological conditions affect a person's ability to walk, it was adapted to become a generic measure of walking and mobility and renamed the Walk-12. The Walk-12 contains twelve items describing the impact of MS on walking which were generated from 30 MS patient interviews, expert opinion, and literature review. Any reference to MS was removed to produce a generic tool.	12 questions on a 5-point scale (1-5). Questions test limitations on mobility 1= Never, 5= Extremely. Gives a total score out of 60. Higher scores indicate poorer outcomes.	Favours control (lower scores indicate better outcomes)
Nausea & vomiting	ECOG assessment	See Oken 1982. [341]	A 6-point "performance scale rated from 0 (Fully active, able to carry on all pre-disease performance without restriction) to 5. Higher scores indicate worse outcomes.	Favours control (lower scores indicate better outcomes
Pain	Descriptor differential scale	The scale included 12 words (faint, moderate, barely strong, intense, weak, strong, very mild, extremely intense, very weak, slightly intense, very intense, and mild). For each item, participants indicate if their pain either is equal in magnitude to that implied by the descriptor, or how much greater or lesser on a 10-point graphic scale.		

Category	Outcome	Description	Scale	Treat-ment arm favoured by positive mean difference (MD)
		From Gracely RH, Kwilosz DM. The descriptor differential scale: applying psychophysical principals to clinical pain assessment. *Pain*. 1988; 35:279-288. Reprinted with permission from the International Association for the Study of Pain.		
Pain	SPID (sum of pain intensity difference).	See Max 2003 [342] on clinical trials in pain. To account for differences in baseline pain intensity among patients in the study, pain intensity category and VAS scores are converted into "pain intensity difference (PID) scores by subtracting them from the pain score taken at baseline. Positive scores indicate reduction in pain, making the PID scores analogous to pain relief scores. (An alternative method is to use analysis of covariance). PID or relief scores are commonly summed over the observation period, weighted for the time between observations, and the summed scores respectively termed SPID (summed pain intensity difference) or TOTPAR (total pain relief). These summary variables are estimates of the area under the time-effect curve (AUC)	Positive scores indicate reduction in pain, making the PID scores analogous to pain relief scores	Favours CBM (higher SPID = better outcomes)
Pain	McGill Pain rating	See Melzack 1975 [184] The McGill Pain Questionnaire can be used to evaluate a person experiencing significant pain. It can be used to	The scale has 20 sections measuring different aspects of pain: Temporal, spatial, punctuate pressure, incisive pressure, constrictive pressure, traction pressure, thermal,	Favours control (lower scores = better outcomes)

Category	Outcome	Description	Scale	Treat-ment arm favoured by positive mean difference (MD)
		monitor the pain over time and to determine the effectiveness of any intervention. See here for description.	brightness, dullness, sensory miscellaneous, tension, autonomic, fear, punishment, affective-evaluative-sensory: miscellaneous, evaluative, sensory: miscellaneous (2 separate scales), sensory and affective-evaluative: miscellaneous. On each scale from 1-3, 1-4, 1-5 or 1-6, the lowest score (1) indicates a better outcome.	
Pain	Neuropathic pain scale	See Galer 1997 [343] The NPS consists of 10 individual items. Nine of these provide a total of ten 0–10 NRS responses and there is a multi-part free text question. The NPS score to be used for the analysis was the sum of the ten 0–10 NRS responses. If up to three individual items were missing, then an NPS score was imputed by multiplying the mean of the completed items by 10. If more than three individual items were missing, then the whole score was missing.	Various subscales on 0-10. 0 being the best outcome (i.e. “No pain” or “not sharp” to 10 being the worst outcome i.e. “the most intense pain imaginable” or “the most sharp sensation imaginable”).	Favours control (lower scores = better outcomes)
Pain	Pain disability index (PDI)	See Chibnall 1994. [344] A “simple and rapid” instrument for measuring the impact that pain has on the ability of a person to participate in essential life activities. This can be used to evaluate patients initially to monitor them over time and to judge the effectiveness of the interventions.	0-10 point scale for 7 outcomes – family and home responsibilities, recreation, social activity, occupation, sexual behaviour, self-care and life-support activity (Minimal index: 0 – Maximal index 70). The higher the index, the greater a person’s disability due to pain.	Favours control (lower scores = better outcomes and less disability due to pain)

Category	Outcome	Description	Scale	Treat-ment arm favoured by positive mean difference (MD)
Pain	Bodily pain	This is a subscale on the SF-36 QOL scale. See Ware 1992 [187]	SF-36 “Bodily pain” Lowest possible score = very severe and extremely limiting pain”. Highest possible score “ No pain or limitations due to pain”	Outcome favours CBM (lower scores = worse outcomes)
Pain	Pain on movement	This was measured on a 0-10 NRS scale. See McCaffery 1993. [345] The Numeric Rating Scale (NRS-11) is an 11–point scale for patient self-reporting of pain. It is for adults and children 10 years old or older.	0 = no pain. 1-3 = Mild pain, (nagging, annoying, interfering little with Activities of Daily Living (ADLs), 4-6 = Moderate pain (interferes significantly with ADLs), 7-10 = Severe pain (disabling, unable to perform ADLs)	Favours control (lower scores = less pain)
Pain	Pain relief	See The British Pain Society Pain Rating Scale [346]	British Pain Rating Scale (PRS). 0= no pain, 10= extreme pain	Favours control (lower scores = better outcomes)
Pain	Pain relief: Houde 1966, Keele 1948 (TOTPAR – Total Pain Relief at 8 hours – integral relief scores.)	See Beaver 1966[347] and Keele 1948 [348]. PID or relief scores are commonly summed over the observation period, weighted for the time between observations, and the summed scores respectively termed SPID (summed pain intensity difference) or TOTPAR (total pain relief). These summary variables are estimates of the area under the time-effect curve (AUC)	Positive scores indicate reduction in pain, making the PID scores analogous to pain relief scores	Favours CBM (higher TOTPAR/PID= better outcomes)
Pain	Pain Box Scale-11	This is a reference to the Numerical 11-point Box (BS-11) – see Jensen 1989.[349]	A standard eleven point ordinal pain severity scale ranging from zero (0) ‘Best Imaginable’ to 10 ‘Worst Imaginable’, recorded in the daily diary.	Favours control (lower scores= less pain)

Category	Outcome	Description	Scale	Treat-ment arm favoured by positive mean difference (MD)
Pain	NRS	See McCaffery 1993. [345] The Numeric Rating Scale (NRS-11) is an 11–point scale for patient self-reporting of pain. It is for adults and children 10 years old or older.	0 = no pain. 1-3 = Mild pain, (nagging, annoying, interfering little with Activities of Daily Living (ADLs), 4-6 = Moderate pain (interferes significantly with ADLs), 7-10 = Severe pain (disabling, unable to perform ADLs)	Favours control (lower scores= less pain)
Pain	Brief pain inventory short form (BPI-SF)	See Cleeland 1994.[182] The Brief Pain Inventory (Short Form) is a 14-item questionnaire that asks patients to rate pain over the prior week and the degree to which it interferes with activities on a 0 to 10 scale, where 0=no pain and 10=pain as bad as you can imagine. Severity is measured as worst pain, least pain, average pain, and pain right now. The severity composite score was calculated as the arithmetic mean of the four severity items (range 0-10). The minimum value is zero and maximum is 10. A reduction in score from baseline indicates an improvement.	11 point scale (0-10) on various domains of pain based on “what number describes your pain at its worst over the last 24 hours/on average/right now” and also” pain interference with general activity/mood/walking ability/normal work/relations with other people/sleep/enjoyment of life.) = No pain, 10= Worst pain imaginable. 0=no interference with activities, 10 = completely interferes with activities.	Favour control (lower scores = less pain/interference with activities)
Psychological Measurements	SSPS-N scores	See Hofmann 2000. [350]This is the 5-item “the Negative Self-Statements Subscale (SSPS-N) and is linked to the The Self-Statements During Public Speaking (SSPS) scale which also has a “Positive Self-Statements” (SSPS-P) subscale.	This questionnaire uses negative-self statements. A high SSPS-N score appears to be correlated with lower expectations for success, compared with a lower score.	Favours control (lower scores appear to be correlated with better expectations for success).
Psychological Measurements	Obsessive compulsive behaviours (OCB),	See Derogatis 1973 [351] and Derogatis 1977.[352] This self-rating test is used to	The SCL 90-R consists of 90 items and takes 12–15 minutes to administer, yielding nine	Favours control (lower scores indicate better

Category	Outcome	Description	Scale	Treat-ment arm favoured by positive mean difference (MD)
	measured by the Symptom Checklist 90-R (SCL 90-R)	identify and rate the following symptoms: somatisation, OCB (obsessive compulsive behaviours, depression, anxiety, anger-hostility, phobic anxiety, paranoid ideation, and psychoticism.	scores along primary symptom dimensions and three scores among global distress indices. A higher score for OCB indicates more obsessive compulsive behaviours.	outcomes)
Psychological Measurements	Anxiety: FIQ subscale	See Burckhardt 1991. [339] FIQ stands for Fibromyalgia Impact Questionnaire. Self-reported questionnaire measuring health related QoL, physical functioning and signs and symptoms.	20 questions on various aspects of functioning with fibromyalgia (including anxiety). Higher scores indicate poorer outcomes.	Favours control (lower scores indicate better outcomes).
Psychological Measurements	HADS anxiety	See Zigmond 1983. [353] HADS is the Hospital Anxiety and Depression Scale - a scale used to determine the level of anxiety and depression that a patient may be experiencing.	Asks 14 anxiety and depression-related questions on a 4-point scale (0-3) Higher scores indicate worse outcomes.	Favours control (lower scores indicate better outcomes)
Psychological Measurements	Beck Depression Inventory (BDI)	See Beck 1972[354] and Beck 1996. [355]. The Beck Depression Inventory is one of the most widely used instruments for measuring the severity of depression. A 21-question multiple-choice self-report inventory.	Rated on a 4-point Likert-type scale ranging from 0 to 3, based on severity of each item. Higher scores indicate worse outcomes.	Favours control (lower scores indicate better outcomes)
Psychological Measurements	HADS depression	See Zigmond 1983. [353]. This is part of the HADS scale (see “HADS anxiety”)	Asks 14 anxiety and depression-related questions on a 4-point scale (0-3). Higher scores indicate worse outcomes.	Favours control (lower scores indicate better outcomes)
Psychological Measurements	Profile of mood states (POMS)(depression-dejection subscale)	See McNair 1971[356] and Curran 1995. [357] Short form of the Profile of Mood States (POMS-SF). POMS contains 65 self-report items	7 scales: Anger-Hostility, Confusion-Bewilderment, Depression-Dejection, Fatigue-Inertia, Tension-Anxiety, Vigo-Activity, Friendliness.	Favours control (lower scores indicate better outcomes)

Category	Outcome	Description	Scale	Treat-ment arm favoured by positive mean difference (MD)
		using the 5-point Likert Scale (there is also a shorter version, with 37 items).	Lower scores on POMS indicate "People with more stable mood profiles"	
Psychological Measurements	Visual analogue mood scale	See Folstein 1973. [358] The scales have a "neutral" schematic face (and accompanying word) at the top of a 100 mm vertical line and a specific "mood" face (and word) at the bottom of the line. Respondents indicate the point along the vertical line that best describes how they are currently feeling.	The VAMS measures 8 specific mood states - Afraid, Confused, Sad, Angry, Energetic, Tired, Happy, and Tense. The score for each mood ranges from 0 to 100, with 100 representing a maximal level of that mood and zero representing a minimal level (or absence) of that mood.	Favours control (lower scores indicate absence of mood disorder and better outcomes)
Psychological Measurements	PANSS (positive and negative syndrome scale)	See Kay 1987. [359] A medical scale used for measuring symptom severity of patients with schizophrenia.	Three scales: positive scale (7 items – score 7-49)), negative scale (7 items – score 7-49) and general psychopathology scale (16 items – score 16-112). As 1 rather than 0 is given as the lowest score for each item, a patient can not score lower than 30 for the total PANSS score. Higher mean scores indicate more psycho-pathological outcomes.	Favours control (lower scores are indicated with more positive outcomes)
Psychological Measurements	Brief Psychiatric Rating Scale	See Overall 1962. [360]. A scale assessing the positive, negative, and affective symptoms of individuals who have psychotic disorders, especially schizophrenia. It has proven particularly valuable for documenting the efficacy of treatment in patients who have moderate to severe disease.	There are 20 items (psychiatric symptoms e.g. depression, emotional withdrawal, hallucinations) – each item is rated 1-7 and depending on the version between a total of 18-24 symptoms are scored. Overall higher scores indicate more symptoms and worse outcomes.	Favours control (lower scores indicate better outcomes)
Psychological Measurements	Shapiro Tourette's syndrome severity	See Shapiro 1984[361] and Shapiro 1988.[362]	7 point scale from 0 (no tics) to 6 (very severe tics).	Favours control (lower scores indicate better

Category	Outcome	Description	Scale	Treat-ment arm favoured by positive mean difference (MD)
	scale -performed by an examiner	The Shapiro Tourette Syndrome Severity Scale (STSSS) as developed to measure changes in symptoms of Tourettes in a clinical trial of pimozide. The clinician rated scale assess five factors about tics and item scores can be summed to produce total ratings.	Higher scores indicate worse outcomes.	outcomes)
Psychological Measurements	Tourette's syndrome global scale (TSGS) - performed by an examiner	See Harcherik 1984. [363] The scale rates the frequency of different types of tics.	Tics are rated on a scale of 1-5 (1 is 1 or fewer tics in 5 minutes, 5 is virtually uncountable) and degree of disruption (1 is easy to camouflage, 5 is disruptive to the point of making it impossible to hide). Higher score indicates worse outcomes.	Favours control (lower scores indicate better outcomes).
Psychological Measurements	Tourette's syndrome symptoms list (TSSL) - Global score - self rating.	See Leckman 1988. [364]Tourette's syndrome symptoms list (TSSL)	Appears to be a symptom checklist on a 1-5 scale with scores for whether symptoms have been observed and the intensity/severity. Higher scores APPEAR to indicate worse outcomes.	Favours control (lower scores indicate better outcomes)
Psychological Measurements	Yale global tic severity scale (YGTSS)- perfomed by an examiner	See Leckman 1989. [365] Yale global tic severity scale (YGTSS)	A combined descriptive symptom checklist alongside a severity checklist “scale”. Items are marked on a 6 point scale (0-5) according to severity. Scores are totalled to a maximum of 100. Higher scores indicate worse outcomes.	Favours control (lower scores indicate better outcomes)
Psychological Measurements	Brief Repeatable Battery (BRB) of Neuropsychological	See Boringa 2001. [366] Brief Repeatable Battery of Neuropsychological Test Score (BRB-N). Used almost exclusively	A higher score on the battery test appears to indicate a better outcome on the tests.	Favours CBM (higher scores on the BRB indicate better outcomes)

Category	Outcome	Description	Scale	Treat-ment arm favoured by positive mean difference (MD)
	Test Score	in MS. This consists of the Selective Reminding Test, the 10/36 Spatial Recall Test, the Symbol Digit Modalities Test, the Paced Auditory Serial Addition Test and the Word List Generation Test.		
QoL	SF36	See Ware 1992. [187] Developed in 1990 (SF-36v1®) - Modified in 1998 (SF-36v2® - version currently used) SF-36 scales measure physical and mental components of health. Domains: Physical function, Role physical, Bodily Pain, General Health, Mental Health, Role Emotional, Social Function and Vitality. The SF-36 was constructed to satisfy minimum psychometric standards necessary for group comparisons.	Lowest scores on all domains = worst possible outcomes. Highest scores= best possible outcomes (Number of variables/items assessable differ for each outcome from 2 outcomes/items for Social Functioning up to 35 items for the "Physical Component Summary" and "Mental Component Summary" .	All outcomes on SF-36 scale favour CBM (lower scores = worse outcomes)
QoL	EQ-5D	See EuroQoL group 1990 [186] and EuroQol 2013 [211] The EQ-5D-3L (latest version) essentially consists of 2 pages - the EQ-5D descriptive system (page 2) and the EQ visual analogue scale (EQ VAS). For the descriptive system: The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. The EQ VAS records the respondent's self-rated health on a vertical, visual	On the EQ-VAS : 0=the worst imaginable health state, 100= the best imaginable health state. EQ5D dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, Anxiety/Depression	All outcomes on EQ-5D scale favour CBM (lower scores = worse outcomes)

Category	Outcome	Description	Scale	Treat-ment arm favoured by positive mean difference (MD)
		analogue scale where the endpoints are labelled 'Best imaginable health state' and 'worst imaginable health state'. This information can be used as a quantitative measure of health outcome as judged by the individual respondents.		
QoL	Patient assessment of Constipation quality of life (PAC-QOL)	See Marquis 2005[367] and Cook 2007 [368] The28- question PAC-QOL has four subscales–physical discomfort, psychosocial discomfort, worries and concerns, and dissatisfaction–and assesses the impact of patients' symptoms during the previous 2 weeks.	Scale of 0-4 (on a scale of 0–4, 0=excellent constipation-related QoL; 4=poor constipation- related QoL)	Outcomes favour control (lower score = better outcome)
QoL	MSQoL	See Vickrey 1995. [188] Scores for each domain (health distress, overall quality of life, Emotional wellbeing, role limitations – emotional and cognitive function) are weighted with Emotional Wellbeing carrying the most weight and Health Distress the least weight).	The scale comprises 54 items on numerical scales. Higher scores are linked to worse outcomes. A final score is then calculated using a Scale of 0-100 - The total number of items in each scale is listed as the divisor for each subtotal.	Favours control (lower scores appear to be linked to better outcomes)
Sleep	mFIS score (0-84)	See Fisk 1994. [369]The Modified Fatigue Impact Scale (MFIS). This is a modified form of the Fatigue Impact Scale (FIS) and a component of the Multiple Sclerosis Quality of Life inventory (MSQLI). The MFIS is a structured, self-report	The total score for the MFIS is the sum of the scores for the 21 items. Individual subscale scores for physical, cognitive, and psychosocial functioning can also be generated by calculating the sum of specific sets of items. 5 point scale on (0-4) with O being "Never"	Favours control (lower scores indicate better outcomes)

Category	Outcome	Description	Scale	Treat-ment arm favoured by positive mean difference (MD)
		questionnaire that the patient can generally complete with little or no intervention from an interviewer. However, patients with visual or upper extremity impairments may need to have the MFIS administered as an interview.	and 4 being “Almost always” e.g. “I have been less alert, I have been forgetful”. A higher score indicates poorer outcomes.	
Sleep	Sleep disturbance score (QoL)	See Yu 2011.[370] This refers to the PROMIS (Patient –Reported Outcomes Measurement Information System) Sleep Disturbance instrument There are two main types. The short form and the Computerised Adaptive Test (CAT) using algorithms to adapt the test to the patient’s responses.	Items are scaled on a 5 point scale 1-5 from “not at all” to “very much” and are scaled accordingly to positive or negative statements. E.g. “My sleep was restless” would carry 1 for “not at all” and 5 for “very much” whereas “I got enough sleep” would score 5 for “Never” and 1 for “Always”. Higher scores indicate more negative outcomes.	Favours control (lower scores indicate better outcomes)
Sleep	Sleep Quality BS-11	See Jensen 1989. [349] The sleep quality BS-11 score is also termed the “11-point box scale” and is linked to a wider pain questionnaire (already detailed earlier in the table).	A standard eleven point ordinal pain severity scale ranging from zero (0) ‘Best Imaginable’ to 10 ‘Worst Imaginable’, recorded in the daily diary.	Favours control (lower scores indicate better outcomes)
Sleep	Insomnia severity index (ISI)	See Morin 2011. [371] An instrument to detect cases of insomnia in the population and which is sensitive to treatment response in clinical patients.	Seven questions –score is totalled from these questions. 5 point scale (0-4) with 0 being the lowest denominator (e.g. “None”) and 4 being the highest (e.g. “Very Severe”). Higher scores indicate poorer outcomes.	Favours control (lower scores indicate better outcomes)
Sleep	Leeds Sleep Evaluation Questionnaire (LSEQ)	See Parrott 1978[214] and Parrott 1980. [372] 10-item, subjective, self-report measure, the LSEQ was designed to assess	A visual-analogue-scale (VAS), respondents place marks on 10cm lines representing changes they have experienced in sleep	Favours CBM (higher scores indicate better sleep outcomes)

Category	Outcome	Description	Scale	Treat-ment arm favoured by positive mean difference (MD)
		changes in sleep quality over the course of a psychopharmacological treatment intervention. The scale evaluates four domains: ease of initiating sleep, quality of sleep, ease of waking, and behavior following wakefulness.	symptoms since starting treatment. Lines extend between extremes like “more difficult than usual” and “easier than usual”. Responses are measured using a 100-mm scale and are then averaged to provide a score for each domain. Higher scores indicate improved sleep parameters.	
Sleep	AHI (apnea hypopnea index)	See Manser 2001. [373]The apnea–hypopnea index or apnoea–hypopnoea index (AHI) is an index of sleep apnea severity that combines apneas and hypopneas. The apneas (pauses in breathing) must last for at least 10 seconds and are associated with a decrease in blood oxygenation. Combining these gives an overall sleep apnea severity score that evaluates both number of sleep disruptions and degree of oxygen desaturation (low blood level).	An average score that represents the combined numbers of apnoeas and hypopnoeas that occur per hour of sleep. In general, the AHI can be used to classify the severity of disease (mild 5-15, moderate 15-30, and severe greater than 30). Higher scores indicate worse outcomes	Favours control (lower scores indicate better outcomes)
Spasticity	Ashworth	See Ashworth 1964 [374]cited in Bohannon 1987[210] a five-point ordinal scale for grading the resistance encountered during passive muscle stretching in patients with spasticity.	0 = normal muscle tone; 1 = slight increase in muscle tone, "catch" when limb moved; 2 = more marked increase in muscle tone, but limb easily flexed; 3 = considerable increase in muscle tone; and 4 = limb rigid in flexion or extension	Favours control (as 0 = normal muscle tone)
Spasticity	Modified Ashworth	See Bohannon 1987 [210] - a modified version of a five-point ordinal scale for grading the resistance encountered during passive muscle stretching in	0 = no increase in muscle tone; 1= slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end of the range of motion (ROM)when	Favours control (as 0 = no increase in muscle tone)

Category	Outcome	Description	Scale	Treat-ment arm favoured by positive mean difference (MD)
		patients with spasticity.	the affected part(s) is moved in flexion or extension; 1+ = slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM. 2 = more marked increase in muscle tone through most of the ROM, but affected part(s) easily moved. 3= considerable increase in muscle tone, passive movement difficult. 4= affected part(s) rigid in flexion or extension.	
Spasticity	Wartenberg Pendulum Test	See Valle 2006.[375] The pendulum test of Wartenberg is a technique commonly used to measure passive knee motion with the aim to assess spasticity. To perform the test, the clinician extends the knee and releases the limb, allowing the leg to swing passively - The trajectory of the oscillating leg provides a set of kinematic parameters such as peak angular values, useful to monitor the changes in the range of knee motion.	The numbers in the scale indicate location of skin reference markers in the pendulum test. : 1= 2/3 thigh; 2= lateral femoral condyle; 3=head of fibula; 4=lateral malleolus.	Favours control (as 1= Able to perform usual self care, vocational and avocational activity)
Spasticity	Spasm Frequency Scale	Penn Spasm Frequency Scale - see Adams 2007 [376] Composed of 2-parts; the first is a self report measure with items on 5-point scales developed to augment clinical ratings of spasticity and provides a more comprehensive assessment of spasticity.	Spasm Frequency: 0 = no spasm, 1=mild spasms induced by stimulation, 2= Infrequent full spasms occurring less than once per hour, 3= Spasms occurring more than once per hour, 4= Spasms occurring more than 10 times per hour.	Favours control (as 0=no spasm)
Spasticity	Numerical rating scale (Spasticity)	See Anwar 2009[377] and Farrar 2008. [378]	A 0-10 numeric rating scale (NRS) as a patient-rated measure of the perceived severity of spasticity.	Favours control (as lower numbers in the NRS scale indicate better outcomes)

Category	Outcome	Description	Scale	Treat-ment arm favoured by positive mean difference (MD)
			Higher scores = worse outcomes	
Spasticity	Multiple Sclerosis Spasticity Scale (MSSS-88)	See Hobart 2006. [379] An 88- item instrument with eight subscales to measure of the impact of spasticity in multiple sclerosis.	Various scales (Muscle stiffness: 1=stiffness when walking to 12= whole body feeling rigid. Pain and discomfort: 1=Restricted and uncomfortable to 9=Constant pain in muscles. Muscle spasms: 1= Spasms start unpredictably to 14 = Spasms pushing patient out of chair or wheelchair. Activities of Daily Living (ADL): 1 = putting on socks or shoes to 11 = drying self with a towel. Walking: 1 = Difficulties walking smoothly to 10 = Feeling embarrassed to walk. Body movement: 1 = Difficulties moving freely to 11 = No control over one's body. Emotional health: 1 = Feeling frustrated to 13 = Feeling nervous. Social functioning: 1= Difficulties going out to 8 = Difficulties interacting with people.	Favours control (as lower numbers in the scales appear to indicate better outcomes)
Spasticity	Motricity Index Score	See Collin 1990. [380] This test gives a rapid overall indication of a patient's limb impairment. The test consists of various measures to assess limb function on a varied points scale. Scores are based on Medical Research Council (MRC) Grades.	More points = better outcomes. Minimum score = 0, Maximum score = 100. Example (this does not explain the complete scale/test): MRC score 0= no movement, 1= palpable flicker but no movement, 2= movement but not against gravity, 3=movement against gravity, 4=movement against resistance, 5=normal.	Favours CBM (higher scores = better outcomes)

APPENDIX 10: OVERVIEW OF RELEVANT SYSTEMATIC REVIEWS

Author (year)	Population	Date of searches	Number of studies	Review conclusions
Abouqal (2014) [381]	AE: Lung cancer	Ongoing	Ongoing	Ongoing
Calabria (2010)[382]	AE: All- cause mortality; road accidents; cancer and suicidal behaviours	January 2008	Observational studies (n=19)	There is a need for long-term cohort studies that follow cannabis using individuals into old age, when the likelihood of any detrimental effects of cannabis use are more likely to emerge among those who persist in using cannabis into middle age and older. Case–control studies of cannabis use and various causes of mortality are also needed.
Crippa (2009)[383]	AE: Anxiety	August 2008	Observational studies (n=8)	The precise relationship between cannabis use and anxiety has yet to be established. Research is needed to fully clarify the mechanisms of such the association.
Degenhardt (2003)[384]	AE: Depression	NR	NR	Heavy cannabis use and depression are associated and evidence from longitudinal studies suggests that heavy cannabis use may increase depressive symptoms among some users. It is still too early, however, to rule out the hypothesis that the association is due to common social, family and contextual factors that increase risks of both heavy cannabis use and depression. Longitudinal studies and studies of twins discordant for heavy cannabis use and depression are needed to rule out common causes. If the relationship is causal, then on current patterns of cannabis use in the most developed societies cannabis use makes, at most, a modest contribution to the population prevalence of depression.

Author (year)	Population	Date of searches	Number of studies	Review conclusions
Grant (2003)[385]	AE: Neurocognitive effects	NR	Observational studies (n=11)	NR
Semple (2005)[386]	AE: Psychosis	January 2004	Observational studies (n=11)	The available evidence supports the hypothesis that cannabis is an independent risk factor, both for psychosis and the development of psychotic symptoms. Addressing cannabis use, particularly in vulnerable populations, is likely to have beneficial effects on psychiatric morbidity.
Tetrault (2007)[387]	AE: Respiratory disease	October 2005	Observational studies (n=34)	Short-term exposure to marijuana is associated with bronchodilation. Physiologic data were inconclusive regarding an association between long-term marijuana smoking and airflow obstruction measures. Long-term marijuana smoking is associated with increased respiratory symptoms suggestive of obstructive lung disease.
Wang (2008)[54]	AE: Medical cannabinoids	October 2007	RCTs (n=23); Observational studies (n=8)	Short-term use of existing medical cannabinoids appeared to increase the risk of non-serious adverse events. The risks associated with long-term use were poorly characterized in published clinical trials and observational studies. High-quality trials of long-term exposure are required to further characterize safety issues related to the use of medical cannabinoids.
Institut fur Qualitaet und Wirtschaftlichkeit im Gesundheitswesen[388]	MS	NA	NA	Critique of a dossier submitted to the Federal Joint Committee (G-BA)

Author (year)	Population	Date of searches	Number of studies	Review conclusions
Lakhan (2009)[42]	MS: Multiple sclerosis	April 2009	RCTs (n=6)	We found evidence that combined THC and CBD extracts may provide therapeutic benefit for MS spasticity symptoms. Although some objective measures of spasticity noted improvement trends, there were no changes found to be significant in post-treatment assessments. However, subjective assessment of symptom relief did often show significant improvement post treatment. Differences in assessment measures, reports of adverse events, and dosage levels are discussed.
Sevilla (2012)[43]	MS: MS-related blader dysfucntion	November 2010	RCTs (n=2)	Both studies compared the effectiveness of cannabinoids in decreasing MS-related bladder dysfunction compared with placebo; however, they used different protocols, different active treatments from cannabis and a different number of subjects.
Shakespeare (2003)[389]	MS: Spasticity	June 2003	RCTs (n=26)	The absolute and comparative efficacy and tolerability of anti-spasticity agents in multiple sclerosis is poorly documented and no recommendations can be made to guide prescribing. The rationale for treating features of the upper motor neurone syndrome must be better understood and sensitive, validated spasticity measures need to be developed.
Wade (2010)[390]	MS: Spasticity	NR	RCTs (n=3)	The meta-analysis demonstrates that nabiximols is well tolerated and reduces spasticity.
Benze (2012)[44]	N&V: Palliative cancer	August 2011	n=75 (several study types,	Cannabinoids rather have a status as a second line antiemetic.

Author (year)	Population	Date of searches	Number of studies	Review conclusions
			including RCTs and case reports)	
Cotter (2009)[391]	N&V: Chemotherapy-Induced Nausea and Vomiting	Present (2009)	RCTs (n=10)	This synthesis shows that cannabinoids are more effective than placebo and comparable to antiemetics such as prochlorperazine and ondansetron for CINV.
Machado Rocha (2008)[45]	N&V: Chemotherapy-Induced Nausea and Vomiting	December 2006	RCTs (n=30)	The superiority of the anti-emetic efficacy of cannabinoids was demonstrated through meta-analysis.
Phillips (2010)[392, 393]	N&V: Chemotherapy-Induced Nausea and Vomiting	February 2008	RCTs (n=27)	Our overall knowledge of the most effective antiemetic's to prevent chemotherapy-induced nausea and vomiting in childhood is incomplete. Future research should be undertaken in consultation with children, young people and families that have experienced chemotherapy and should make use of validated, age-appropriate measures. This review suggests that 5-HT3 antagonists with dexamethasone added are effective in patients who are to receive highly emetogenic chemotherapy although the risk benefit profile of additional steroid remains uncertain.
Tramer (2001)[47]	N&V: Chemotherapy-	August 2010	RCTs (n=30)	In selected patients, the cannabinoids tested in these trials may be useful as mood enhancing adjuvants for controlling chemotherapy

Author (year)	Population	Date of searches	Number of studies	Review conclusions
	Induced Nausea and Vomiting			related sickness. Potentially serious adverse effects, even when taken short term orally or intramuscularly, are likely to limit their widespread use.
Van den Elsen (2014)[394]	N&V: Chemotherapy-Induced Nausea and Vomiting	October 2013	RCTs (n=5)	The studies showed no efficacy on dyskinesia, breathlessness and chemotherapy induced nausea and vomiting. Two studies showed that THC might be useful in treatment of anorexia and behavioral symptoms in dementia. Adverse events were more common during cannabinoid treatment compared to the control treatment, and were most frequently sedation like symptoms. Although trials studying medical cannabinoids included older subjects, there is a lack of evidence of its use specifically in older patients. Adequately powered trials are needed to assess the efficacy and safety of cannabinoids in older subjects, as the potential symptomatic benefit is especially attractive in this age group.
Alberta Heritage Foundation for Medical Research ((2004)[32]	Pain	NR	Observational studies(n=2)	NR
Burns (2006)[395]	Pain	August 2005		Cannabinoids provide a potential approach to pain management with a novel therapeutic target and mechanism. Chronic pain often requires a polypharmaceutical approach to management, and cannabinoids are a potential addition to the arsenal of treatment options. NB: Studies or reviews using animal models of pain were also included.

Author (year)	Population	Date of searches	Number of studies	Review conclusions
Campbell, F.A.T., M. R. Carroll, D. Reynolds, D. J(2001)[38]	Pain	October 1999	RCTs (n=9)	Cannabinoids are no more effective than codeine in controlling pain and have depressant effects on the central nervous system that limit their use. Their widespread introduction into clinical practice for pain management is therefore undesirable. In acute postoperative pain they should not be used. Before cannabinoids can be considered for treating spasticity and neuropathic pain, further valid randomised controlled studies are needed.
Canadian Agency for Drugs and Technologies in Heal(2010)[35]	Pain	June 2010	RCTs (n=3); Observational studies (n=1)	In conclusion, the four identified studies suggest that the use of cannabinoids as co-analgesia in patients with non-neuropathic pain is effective. The patient populations included in the studies varied and included patients with cancer pain, non-cancer pain, rheumatoid arthritis, and acute postherpetic neuralgia. The studies also varied with type of cannabinoid used, the agents used for co-analgesia, and the outcome measurements.
Canadian Agency for Drugs and Technologies in Heal(2010)[36]	Pain	June 2010	RCTs (n=7)	Overall, the limited evidence suggests that cannabinoids may provide pain relief in patients with HIV or MS who have neuropathic pain when used as add on therapy. It is not clear if this benefit would be maintained longer-term. No benefit was observed in diabetic neuropathy and pain relief with nabilone was inferior to a narcotic analgesic. These points may be considered when making formulary decisions about the use of cannabinoids in neuropathic pain.
Canadian Agency for Drugs and Technologies in	Pain MS	October 2011	Systematic reviews (n=4); RCTs	The majority of the studies were conducted in Canada, which may be more helpful in guiding the use of nabilone in chronic pain management in the Canadian population. Additional well-designed,

Author (year)	Population	Date of searches	Number of studies	Review conclusions
Heal(2011)[37]			(n=2); Observational studies (n=2); Clinical practice guidelines (n=3)	large-scale randomized trials with longer-term follow-up are required to evaluate the clinical effectiveness and safety of nabilone in patients with chronic pain.
Davis (2008)[396]	Pain N&V	NR	RCTs (n=30)	Nabilone is superior to placebo, domperidone and prochlorperazine but not metoclopramide or chlorpromazine.
De Souza Nascimento (2013)[397]	Pain Sleep	January 2013	RCTs (n=8)	Based on the current review, it is unclear whether MP or RNP is effective in treating fibromyalgia. However, it was noted that these therapies are promising in the treatment of rheumatic conditions as chronic fibromyalgia. More studies with adequate methodological quality in order to investigate the efficacy and safety of MP or RNP for fibromyalgia are needed.
Iskedjian (2007)[39]	Pain MS	June 2006	RCTs (n=7)	Cannabinoids including the cannabidiol/THC buccal spray are effective in treating neuropathic pain in MS.
Jawahar (2013)[398, 399]	Pain MS	December 2012	RCTs (n=11); Observational studies (n=4)	More trials with rigorous design and reporting are needed to determine effective treatments for specific pain types presenting in people living with MS.
Kung (2011)[400, 401]	Pain	NR	RCTs (n=4)	Cannabinoids appear to be efficacious for treatment of pain in the

Author (year)	Population	Date of searches	Number of studies	Review conclusions
				musculoskeletal diseases RA, FM and back pain.
Lynch (2011)[40]	Pain	October 2010	RCTs (n=15)	In conclusion this systematic review of 18 recent good quality randomized trials demonstrates that cannabinoids are a modestly effective and safe treatment option for chronic non-cancer (predominantly neuropathic) pain. Given the prevalence of chronic pain, its impact on function and the paucity of effective therapeutic interventions, additional treatment options are urgently needed. More large scale trials of longer duration reporting on pain and level of function are required.
Martín-Sánchez (2009)[402]	Pain	February 2008	RCTs (n=18)	Currently available evidence suggests that cannabis treatment is moderately efficacious for treatment of chronic pain, but beneficial effects may be partially (or completely) offset by potentially serious harms. More evidence from larger, well-designed trials is needed to clarify the true balance of benefits to harm.
Phillips (2010)[403]	Pain	February 2010	RCTs (n=14)	Evidence of efficacy exists only for capsaicin 8%, smoked cannabis and rhNGF. However,rhNGF is clinically unavailable and smoked cannabis cannot be recommended as routine therapy. Evaluation of novel management strategies for painful HIV-SN is urgently needed.
Pittler (2008)[404]	Pain	March 2006	Systematic reviews (n=5); RCTs (n=15)	On the basis of our findings, the evidence is not fully convincing for most complementary and alternative medicine modalities in relieving neuropathic or neuralgic pain. However, for topically applied capsaicin there is evidence of effectiveness beyond placebo. The evidence can be classified as encouraging and warrants further study

Author (year)	Population	Date of searches	Number of studies	Review conclusions
				for cannabis extract, magnets, carnitine, and electrostimulation.
Richards (2012)[405]	Pain	November 2010	RCTs (n=4)	There is currently weak evidence that oral nefopam, topical capsaicin and oromucosal cannabis are all superior to placebo in reducing pain in patients with RA. However, each agent is associated with a significant side effect profile. The confidence in our estimates is not strong given the difficulties with blinding, the small numbers of participants evaluated and the lack of adverse event data. In some patients, however, even a small degree of pain relief may be considered worthwhile. Until further research is available, given the relatively mild nature of the adverse events, capsaicin could be considered as an add-on therapy for patients with persistent local pain and inadequate response or intolerance to other treatments. Oral nefopam and oromucosal cannabis have more significant side effect profiles however and the potential harms seem to outweigh any modest benefit achieved.
Snedecor (2014)[406]	Pain	June 2011	RCTs (n=58)	Selecting an appropriate pDPN therapy is key given the large number of available treatments. Comparative results revealed relative equivalence among many of the studied interventions having the largest overall sample sizes and highlight the importance of standardization of methods to effectively assess pain.
Rathbone (2008)[55]	Psychosis: Schizophrenia	April 2007	RCTs (n=1)	At present, there is insufficient evidence to support or refute the use of cannabis/cannabinoid compounds for people suffering with schizophrenia. This review highlights the need for well designed, conducted and reported clinical trials to address the potential effects

Author (year)	Population	Date of searches	Number of studies	Review conclusions
				of cannabis based compounds for people with schizophrenia.
Schoeler (2013)[407]	Psychosis: Psychotic disorder	NR	RCTs (n=66)	The present results suggest that memory as global construct appears to be impaired in healthy users without the diagnosis of a psychotic disorder but not in those suffering from the illness. Latter users seem to perform better in certain domains such as long-term memory and working memory, indicating that individual characteristics related to psychopathology are likely to explain the distinct outcome between the two cannabis using groups.
Zammit (2008)[408]	Psychosis: Psychotic disorder	November 2006	Observational studies (n=13)	Confidence that most associations reported were specifically due to cannabis is low. Despite clinical opinion, it remains important to establish whether cannabis is harmful, what outcomes are particularly susceptible, and how such effects are mediated. Studies to examine this further are eminently feasible.
Curtis (2007)[48]	Tourette's	Present (2007)	RCTs (n=2)	Not enough evidence to support the use of cannabinoids in treating tics and obsessive compulsive behaviour in people with Tourette's syndrome.
Waldon (2013)[409]	Tourette's	NR	RCTs (n=33)	Our results are in line with the findings of uncontrolled open-label studies. However, most trials have low statistical power due to the small sample sizes, and newer agents, such as Aripiprazole, have not been formally tested in double-blind randomised controlled trials. Further research should focus on better outcome measures, including

Author (year)	Population	Date of searches	Number of studies	Review conclusions
				Quality of Life instruments.

APPENDIX 11: GRADE EVIDENCE PROFILES

TABLE 55: GRADE EVIDENCE PROFILE: NAUSEA AND VOMITING DUE TO CHEMOTHERAPY

Author(s): Kleijnen Systematic Reviews Ltd
Date: 2014-09-09
Question: Should CBM be used for nause and vomiting due to chemotherapy?
Settings: Not specified
Bibliography: Systematic review for Swiss Federal Office of Public Health

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBM	Control	Relative (95% CI)	Absolute		
Complete response for nausea and vomiting (follow-up 5 days; assessed with: no vomiting and no or very little nausea)												
3[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	24/51 (47.1%)	10/51 (19.6%)	OR 3.44 (1.45 to 8.15)	260 more per 1000 (from 65 more to 469 more)	⊕OOO VERY LOW	
Any adverse events (follow-up 6 days[4])												
10[5]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	294/389 (75.6%)	197/395 (49.9%)	OR 3.51 (2.21 to 5.56)[7]	279 more per 1000 (from 189 more to 348 more)	⊕⊕⊕O MODERATE	

[1] Duran 2010, Meiri 2007, Melham-Bertrandt 2014
[2] Risk of bias: Insufficient details on randomisation (Meiri 2007), concealment of allocation (all studies) and outcome assessor blinding (all studies); high risk of bias for incomplete outcome data (Meiri 2007) and selective outcome reporting (Duran 2010).
[3] Imprecision: 3 studies including 102 patients (34 events).
[4] Chan 1987, George 1983, Heim 1984, Johansson 1982, Pomeroy 1986, Ungerleider 1982: 1 chemotherapy cycle; Hutcheon 1983: 1 day; Duran 2010, Meiri 2004: 5 days; Lane 1991: 6 days
[5] Chan 1987, Duran 2010, George 1983, Heim 1984, Hutcheon 1983, Johansson 1982, Lane 1991, Meiri 2004, Pomeroy 1986, Ungerleider 1982
[6] Risk of bias: Insufficient details on randomisation (Chan 1987, Heim 1984, Hutcheon 1983, Johansson 1982, Lane 1991, Meiri 2007, Pomeroy 1986), concealment of allocation (all studies) and blinding (all studies); high risk of bias for incomplete outcome data (Duran 1987, Heim 1984, Johansson 1982, Meiri 2007, Pomeroy 1986).
[7] OR across all patient populations (29 studies): 3.03, 95%-CI 2.42 to 3.80 (see section 5.3 for details)

TABLE 56: GRADE EVIDENCE PROFILE: HIV/AIDS

Author(s): Kleijnen Systematic Reviews Ltd
Date: 2014-09-09
Question: Should CBM be used for HIV/AIDS?
Settings: Not specified
Bibliography: Systematic review for Swiss Federal Office of Public Health

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBM	Control	Relative (95% CI)	Absolute		
Weight gain (follow-up 6 weeks; assessed with: Number of patients who gained ≥2kg)												
1[1]	randomised trials	serious[2]	no serious inconsistency[3]	no serious indirectness	serious[4]	none	11/50 (22%)	4/38 (10.5%)	OR 2.2 (0.68 to 7.27)	100 more per 1000 (from 31 fewer to 356 more)	⊕⊕OO LOW	
Weight[5] (follow-up 3-12 weeks[6]; measured with: kg; Better indicated by lower values)												
3[7]	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[9]	none	142	99	-[5]	not pooled[5]	⊕⊕OO LOW	
Appetite (measured with: VAS scale; range of scores: 0-100; Better indicated by higher values)												
1[1]	randomised trials	serious[2]	no serious inconsistency[3]	no serious indirectness	serious[4]	none	50	38	-	MD 20 higher (0 to 0 higher)[10]	⊕⊕OO LOW	
Nausea severity/intensity (measured with: VAS scale; range of scores: 0-100; Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency[3]	no serious indirectness	serious[4]	none	50	38	-	MD 18 lower (0 to 0 higher)[11]	⊕⊕OO LOW	
Karnofsky Performance Status (range of scores: 0-100; Better indicated by higher values)												
1[1]	randomised trials	serious[2]	no serious inconsistency[3]	no serious indirectness	serious[4]	none	50	38	-	MD 0.70 higher (0 to 0 higher)[12]	⊕⊕OO LOW	
Any adverse events (follow-up 6-12 weeks[13])												

2[14]	randomised trials	very serious[15]	serious[16]	no serious indirectness	serious[17]	none	38/83 (45.8%)	17/77 (22.1%)	OR 1.73 (0.17 to 18.0)[18]	108 more per 1000 (from 175 fewer to 615 more)	⊕OOO VERY LOW	

[1] Beal 1995
[2] Risk of bias: Insufficient details on randomisation, concealment of allocation and blinding; high risk of bias for selective outcome reporting.
[3] Inconsistency: Not applicable (single study)
[4] Imprecision: Study included only 139 patients
[5] Abrams 2003: p-value (Dronabinol vs. Placebo)=0.004, p-value (Marijuana vs. Placebo)=0.021; Beal 1995 (Dronabinol vs. Placebo): MD change from baseline 0.5 (p-value=0.14); Timpone 1997: MD change from baseline (Dronabinol vs. Placebo)=-8.5, -9.18, -.7.82); MD change from baseline (Dronabinol + megestrol acetate vs. Placebo)=-0.5, -1.10, 0.10);
[6] Abrams 2003: 3 weeks, Beal 1995: 6 weeks, Timpone 1997: 12 weeks
[7] Abrams 2003, Beal 1995, Timpone 1997
[8] Risk of bias: Insufficient details on randomisation (Beal 1995, Timpone 1997), concealment of allocation (Beal 1995, Timpone 1997) and blinding (Abrams 2003-D, Beal 1995); high risk of bias for blinding (Abrams 2003-M) and selective outcome reporting (Beal 1995, Timpone 1997).
[9] Imprecision: 3 studies including only 243 patients
[10] No 95 %-CI reported, p-value=0.05
[11] No 95 %-CI reported, p-value=0.26
[12] No 95 %-CI reported, p-value=0.07
[13] Beal 1995: 6 weeks; Timpone 1997: 12 weeks
[14] Beal 1995, Timpone 1997
[15] Risk of bias: Insufficient details on randomisation (both studies), concealment of allocation (both studies) and blinding (Beal 1995); high risk of bias for blinding (Timpone 1997) and incomplete data reporting (Timpone 1997)
[16] Inconsistency: I2=79%
[17] Imprecision: Two studies including 160 patients (55 events)
[18] OR across all patient populations (29 studies): 3.03, 95%-CI 2.42 to 3.80 (see section 5.3 for details)

TABLE 57: GRADE EVIDENCE PROFILE: CHRONIC PAIN

Author(s): Kleijnen Systematic Reviews Ltd
Date: 2014-09-09
Question: Should CBM be used for chronic pain?
Settings: Not specified
Bibliography: Systematic review for Swiss Federal Office of Public Health

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBM	Control	Relative (95% CI)	Absolute		
30% reduction in pain (follow-up 2-15 weeks[1]; assessed with: NRS or VAS)												
8[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none[4]	254/685 (37.1%)	215/685 (31.4%)	OR 1.35 (0.95 to 1.93)	68 more per 1000 (from 11 fewer to 155 more)	⊕⊕⊕O MODERATE	
Improvement with Nabiximols (follow-up 3-14 weeks[5]; assessed with: Patient global impression of change)												
5[6]	randomised trials	serious[7]	serious[8]	no serious indirectness	no serious imprecision	none	63/126 (50%)[9]	31/126 (24.6%)[9]	OR 1.94 (1.15 to 3.28)	142 more per 1000 (from 27 more to 271 more)	⊕⊕OO LOW	
Pain (follow-up 2-14 weeks[10]; measured with: Numerical rating scale; range of scores: 0-10; Better indicated by lower values)												
6[11]	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	no serious imprecision	none	472	476	-	WMD 0.46 lower (0.8 to 0.11 lower)	⊕⊕⊕O MODERATE	
Pain (follow-up 3-15 weeks[13]; measured with: Brief Pain Inventory-Short Form (BPI-SF); range of scores: 0-10; Better indicated by lower values)												
3[14]	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	no serious imprecision	none	313	300	-	WMD 0.17 lower (0.5 lower to 0.16 higher)	⊕⊕⊕O MODERATE	
Neuropathic pain (follow-up 5-15 weeks[15]; measured with: Neuropathic Pain Scale; range of scores: 0-100; Better indicated by lower values)												
5[16]	randomised trials	serious[17]	no serious inconsistency	no serious indirectness	no serious imprecision	none	389	375	-	WMD 3.89 lower (7.32 to 0.47 lower)	⊕⊕⊕O MODERATE	
Quality of life (follow-up 12-15 weeks[18]; measured with: EQ-5D; range of scores: 0-100; Better indicated by higher values)												

3[19]	randomised trials	serious[20]	no serious inconsistency	no serious indirectness	no serious imprecision	none	292	281	-	WMD 0.01 lower (0.05 lower to 0.02 higher)	⊕⊕⊕O MODERATE	
Any adverse events (follow-up 1-15 weeks[21])												
9[22]	randomised trials	serious[23]	no serious inconsistency	no serious indirectness	no serious imprecision	none	515/599 (86%)	396/588 (67.3%)	OR 3.17 (2.19 to 4.58)[24]	194 more per 1000 (from 145 more to 231 more)	⊕⊕⊕O MODERATE	

[1] Abrams 2007, Johnson 2010: 2 weeks; Nurmikko 2007: 5 weeks; Portenoy 2012: 9 weeks; Selvarajah 2010: 12 weeks; GW Pharma Ltd 2005, Langford 2013: 14 weeks; Serpell 2014: 15 weeks
[2] Abrams 2007, GW Pharma Ltd 2005, Johnson 2010, Langford 2013, Nurmikko 2007, Portenoy 2012, Selvarajah 2010, Serpell 2014
[3] Risk of bias: Insufficient details on randomisation (GW Pharma Ltd 2005, Johnson 2010, Selvarajah 2010), concealment of allocation (Abrams 2007, GW Pharma Ltd 2005, Johnson 2010, Langford 2013, Portenoy 2012, Selvarajah 2010, Serpell 2014) and blinding (Abrams 2007, GW Pharma Ltd 2005, Johnson 2010, Nurmikko 2007, Portenoy 2012, Selvarajah 2010); high risk of bias for concealment of allocation (Nurmikko 2007) and incomplete outcome data (Abrams 2007, GW Pharma Ltd 2005, Johnson 2010)
[4] No evidence of small study effects (Egger test, p=0.304)
[5] Berman 2007, GW Pharma Ltd 2012: 3 weeks; Rog 2005: 5 weeks; GW Pharma Ltd 2005, Langford 2013: 14 weeks
[6] Berman 2007, GW Pharma Ltd 2005, GW Pharma Ltd 2012, Langford 2013, Rog 2005
[7] Risk of bias: Insufficient details on randomisation (Berman 2007, GW Pharma Ltd 2005, GW Pharma Ltd 2012), concealment of allocation (all studies) and blinding (Berman 2007, GW Pharma Ltd 2005, GW Pharma Ltd 2012); high risk of bias for incomplete outcome data (Berman 2007, GW Pharma Ltd 2005, GW Pharma Ltd 2012)
[8] Inconsistency: I2=69%
[9] Numbers not reported for GW Pharma Ltd 2005 and Langford 2013
[10] Johnson 2010: 2 weeks; Berman 2007: 3 weeks; Nurmikko 2007, Rog 2005: 5 weeks; Portenoy 2012: 9 weeks; Langford 2013: 14 weeks
[11] Berman 2007, Johnson 2010, Langford 2013, Nurmikko 2007, Portenoy 2012, Rog 2005
[12] Risk of bias: Insufficient details on randomisation (Berman 2007, Johnson 2010), concealment of allocation (all but Nurmikko 2007) and blinding (Berman 2007, Johnson 2010, Nurmikko 2007, Portenoy 2012); high risk of bias for concealment of allocation (Nurmikko 2007) and incomplete outcome data (Berman 2007, Johnson 2010)
[13] GW Pharma Ltd 2012: 3 weeks; GW Pharma Ltd 2005: 14 weeks; Serpell 2014: 15 weeks
[14] GW Pharma Ltd 2005, GW Pharma Ltd 2012, Serpell 2012
[15] Nurmikko 2007, Rog 2005: 5 weeks; Selvarajah 2010: 12 weeks; GW Pharma Ltd: 14 weeks; Serpell 2014: 15 weeks
[16] GW Pharma Ltd, Nurmikko 2007, Rog 2005, Selvarajah 2010, Serpell 2014
[17] Risk of bias: Insufficient details on randomisation (GW Pharma Ltd 2005, Selvarajah 2010), concealment of allocation (all but Nurmikko 2007) and blinding (GW Pharma Ltd 2005, Nurmikko 2007, Selvarajah 2010); high risk of bias for concealment of allocation (Nurmikko 2007) and incomplete outcome data (GW Pharma Ltd 2005)
[18] Selvarajah 2010: 12 weeks; GW Pharma Ltd 2005: 14 weeks; Serpell 2014: 15 weeks
[19] GW Pharma Ltd 2005, Serpell 2014, Selvarajah 2010
[20] Risk of bias: Insufficient details on randomisation (GW Pharma Ltd 2005, Selvarajah 2010), concealment of allocation (all studies) and blinding (GW Pharma Ltd 2005, Selvarajah 2010); high risk of bias for incomplete outcome data (GW Pharma Ltd 2005)
[21] Karst 2003: 1 week; Berman 2007, GW Pharma Ltd 2012, Svendsen 2004: 3 weeks; Nurmikko 2007, Rog 2005: 5 weeks; Portenoy 2012: 9 weeks; GW Pharma Ltd 2005: 12 weeks; Serpell 2014: 15 weeks
[22] Berman 2007, GW Pharma Ltd 2005, GW Pharma Ltd 2012, Karst 2003, Nurmikko 2007, Portenoy 2012, Rog 2005, Serpell 2014, Svendsen 2004
[23] Risk of bias: Insufficient details on randomisation (Berman 2007, GW Pharma Ltd 2005, GW Pharma Ltd 2012), concealment of allocation (Berman 2007, GW Pharma Ltd 2005, GW Pharma Ltd 2012, Portenoy 2012, Rog 2005, Serpell 2014, Svendsen 2004) and blinding (all but Karst 2003 and Nurmikko 2007; high risk of bias for concealment of allocation (Nurmikko 2007), incomplete outcome data (Berman 2007, GW Pharma Ltd 2005, GW Pharma Ltd 2012, Karst 2003), selective outcome reporting.
[24] OR across all patient populations (29 studies): 3.03, 95%-CI 2.42 to 3.80 (see section 5.3 for details)

TABLE 58: GRADE EVIDENCE PROFILE: SPASTICITY DUE TO MULTIPLE SCLEROSIS OR PARAPLEGIA

Author(s): Kleijnen Systematic Reviews Ltd
Date: 2014-09-09
Question: Should CBM be used for spasticity due to multiple sclerosis or paraplegia?
Settings: Not specified
Bibliography: Systematic review for Swiss Federal Office of Public Health

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBM	Control	Relative (95% CI)	Absolute		
30% reduction in spasticity symptoms (follow-up 6-14 weeks[1]; assessed with: 0-10 Numerical rating scale (NRS))												
2[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious	none	99/286 (34.6%)	56/233 (24%)	OR 1.40 (0.81 to 2.41)	67 more per 1000 (from 36 fewer to 192 more)	⊕⊕OO LOW	
50% reduction in spasticity symptoms (follow-up 6-14 weeks[1]; assessed with: 0-10 Numerical rating scale (NRS))												
2[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	42/286 (14.7%)	24/233 (10.3%)	OR 1.64 (0.95 to 2.83)	55 more per 1000 (from 5 fewer to 142 more)	⊕⊕OO LOW	
Spasticity (follow-up 3-15 weeks[5]; measured with: Ashworth score; Better indicated by lower values)												
5[6]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none[8]	647	597	-	WMD 0.14 lower (0.27 to 0.01 lower)	⊕⊕⊕O MODERATE	
Spasticity: Treatment benefit (THC/CBD) (follow-up 15 weeks; assessed with: Patient assessment of whether there was a treatment benefit)												
1[9]	randomised trials	no serious risk of bias	no serious inconsistency[10]	no serious indirectness	serious[11]	none	121/197 (61.4%)	91/198 (46%)	OR 1.8 (1.25 to 2.78)	145 more per 1000 (from 56 more to 243 more)	⊕⊕⊕O MODERATE	
Spasticity: Treatment benefit (Dronabinol) (follow-up 15 weeks; assessed with: Patient assessment of whether there was a treatment benefit)												
1[9]	randomised trials	no serious risk of bias	no serious inconsistency[10]	no serious indirectness	serious[11]	none	108/181 (59.7%)	91/198 (46%)	OR 1.7 (1.15 to 2.6)	132 more per 1000 (from 35 more to 229 more)	⊕⊕⊕O MODERATE	

Global impression of change in symptoms (follow-up 3-14 weeks[12]; assessed with: Patient assessment)												
4[9]	randomised trials	serious[13]	no serious inconsistency	no serious indirectness	serious[14]	none	128/259 (49.4%)[15]	64/202 (31.7%)[15]	OR 1.78 (1.12 to 2.82)	135 more per 1000 (from 25 more to 250 more)	⊕⊕OO LOW	
Any adverse events (follow-up 6-15 weeks[16])												
5[17]	randomised trials	serious[18]	no serious inconsistency	no serious indirectness	no serious imprecision	none	578/681 (84.9%)	441/619 (71.2%)	OR 2.48 (1.61 to 3.83)[19]	148 more per 1000 (from 87 more to 192 more)	⊕⊕⊕O MODERATE	

[1] Collin 2007: 6 weeks, Collin 2010: 14 weeks
[2] Collin 2007, Collin 2010
[3] Risk of bias: Insufficient details on randomisation (Collin 2007), concealment of allocation (both studies) and blinding (Collin 2007)
[4] Imprecision: 2 studies including only 519 patients (<300 events)
[5] Berman 2007: 3 weeks; Collin 2007, Wade 2004: 6 weeks; Collin 2010: 14 weeks; Zajicek 2003: 15 weeks
[6] Berman 2007, Collin 2007, Collin 2010, Wade 2004, Zajicek 2003
[7] Risk of bias: Insufficient details on randomisation (Berman 2003, Collin 2007), concealment of allocation (all but Zajicek 2003) and blinding (Berman 2003, Collin 2007); high risk of incomplete outcome data (Berman 2007, Wade 2004)
[8] No evidence of small study effects (Egger test, p=0.437)
[9] Zajicek 2003
[10] Inconsistency: Not applicable (single study)
[11] Imprecision: Study included 657 patients (<300 events)
[12] Berman 2007: 3 weeks; Collin 2007, Wade 2004: 6 weeks; Langford 2013: 14 weeks
[13] Risk of bias: Insufficient details on randomisation (Berman 2003, Collin 2007), concealment of allocation (all studies) and blinding (Berman 2003, Collin 2007); high risk of incomplete outcome data (Berman 2007, Wade 2004)
[14] Imprecision: 4 studies including only 461 patients (<300 events)
[15] Numbers of events and patients not reported for Langford 2013. Study reported an OR which is included in the pooled estimate.
[16] Collin 2007, Wade 2004: 6 weeks; Collin 2010, Langford 2013: 14 weeks; Zajicek 2012: 15 weeks
[17] Collin 2007, Collin 2010, Langford 2013. Wade 2004, Zajicek 2012
[18] Risk of bias: Insufficient details on randomisation (Collin 2007), concealment of allocation (all but Zajicek 2003) and outcome assessor blinding (Collin 2007); high risk of bias for incomplete outcome data.
[19] OR across all patient populations (29 studies): 3.03, 95%-CI 2.42 to 3.80 (see section 5.3 for details)

TABLE 59: GRADE EVIDENCE PROFILE: DEPRESSION

Author(s): Kleijnen Systematic Reviews Ltd
Date: 2014-09-09
Question: Should CBM be used for depression?
Settings: Not specified
Bibliography: Systematic review for Swiss Federal Office of Public Health

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBM	Control	Relative (95% CI)	Absolute		
Depression (follow-up 9 weeks; measured with: Montgomery–Åsberg depression scale (MADRS); range of scores: 0-54; Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency[3]	serious[4]	serious[5]	none	91	91	-	MD 1.80 higher (0.32 lower to 3.92 higher)[6]	⊕OOO VERY LOW	
Depression (follow-up 6 weeks; measured with: Beck Depression Inventory (BDI); range of scores: 0-63; Better indicated by lower values)												
1[7]	randomised trials	serious[8]	no serious inconsistency[3]	serious[9]	serious[10]	none	80	80	-	MD 0.69 higher (0.76 lower to 2.14 higher)	⊕OOO VERY LOW	
Depression (follow-up 5 weeks; measured with: Hospital Anxiety and Depression Scale (HADS); range of scores: 0-52; Better indicated by lower values)												
1[11]	randomised trials	serious[12]	no serious inconsistency[3]	serious[9]	serious[13]	none	34	32	-	MD 0.15 higher (1 lower to 1.31 higher)	⊕OOO VERY LOW	
Any adverse events (follow-up 1-105 days[14])												
29[15]	randomised trials	serious[16]	no serious inconsistency	serious[17]	no serious imprecision	none	1438/1779 (80.8%)	1058/1710 (61.9%)	OR 3.03 (2.42 to 3.80)	212 more per 1000 (from 178 more to 242 more)	⊕⊕OO LOW	

[1] Portenoy 2012
[2] Risk of bias: Insufficient details on concealment of allocation and blinding
[3] Inconsistency: Not applicable (single study)
[4] Indirectness: Study included pain patients
[5] Imprecision: Study included only 182 patients

[6] Results for 1-4 sprays nabiximols vs. placebo. Two more groups reported: 6-10 sprays vs. placebo (1.90 (-0.22 to 4.02)) and 11-14 sprays vs. placebo (2.50 (0.38 to 4.62))
[7] Wade 2004
[8] Risk of bias: Insufficient details on concealment of allocation; high risk for incomplete outcome data.
[9] Indirectness: Study included MS/ paraplegia patients
[10] Imprecision: Study included only 160 patients
[11] Rog 2005
[12] Risk of bias: Insufficient details on concealment of allocation.
[13] Imprecision: Study included only 66 patients
[14] See Appendix 5 (Baseline details of included studies)
[15] Beal, 1995, Berman 2007, Chan 1987, Collin 2007, Collin 2010, Duran 2010, George 1983, GW Pharma Ltd 2005, GW Pharma Ltd 2012, Heim 1984, Hutcheon 1983, Johansson 1982, Karst 2003, Lane 1991, Langford 2013. Meiri 2004, Müller-Vahl 2001, Müller-Vahl 2003, Nurmikko 2007, Pomeroy 1986, Portenoy 2012, Rog 2005, Serpell 2014, Svendsen 2004, Timpone 1997, Tomida 2006, Ungerleider 1982, Wade 2004, Zajicek 2012
[16] See Appendix 8 (Results of the risk of bias assessment)
[17] Indirectness: Analysis of AEs across all patient populations, excluding anxiety, depression, psychosis and sleep disorders

TABLE 60: GRADE EVIDENCE PROFILE: ANXIETY

Author(s): Kleijnen Systematic Reviews Ltd
Date: 2014-09-09
Question: Should CBM (cannabidiol, single dose of 600mg) be used for generalized Social Anxiety Disorder (SAD); ≥ 6 points on self-assessed short version of the Social Phobia Inventory named MINISPIN.?
Settings: Not specified
Bibliography: Systematic review for Swiss Federal Office of Public Health

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**CBM (cannabidiol, single dose of 600mg)**	**Control**	**Relative (95% CI)**	**Absolute**		
Anxiety (follow-up 107 minutes; measured with: Visual analogue mood scale (VAMS): anxiety factor[1]; range of scores: 0-100; Better indicated by lower values)												
1[2]	randomised trials	serious[3]	no serious inconsistency[4]	no serious indirectness	serious[5]	none	12	12	-	MD 16.52 lower (0 to 0 higher)[6]	⊕⊕OO LOW	
Any adverse events (follow-up 1-105 days[7])												
29[8]	randomised trials	serious[9]	no serious inconsistency	serious[10]	no serious imprecision	none	1438/1779 (80.8%)	1058/1710 (61.9%)	OR 3.03 (2.42 to 3.80)	212 more per 1000 (from 178 more to 242 more)	⊕⊕OO LOW	

[1] Assessed during public speaking event
[2] Bergamaschi 2011
[3] Risk of bias: High risk of bias for randomisation and allocation concealment
[4] Inconsistency: Not applicable (single study)
[5] Imprecision: Study included only 24 patients
[6] Change from pre-test. No 95%-CI reported, p-value=0.012
[7] See Appendix 5 (Baseline details of included studies)
[8] Beal, 1995, Berman 2007, Chan 1987, Collin 2007, Collin 2010, Duran 2010, George 1983, GW Pharma Ltd 2005, GW Pharma Ltd 2012, Heim 1984, Hutcheon 1983, Johansson 1982, Karst 2003, Lane 1991, Langford 2013. Meiri 2004, Müller-Vahl 2001, Müller-Vahl 2003, Nurmikko 2007, Pomeroy 1986, Portenoy 2012, Rog 2005, Serpell 2014, Svendsen 2004, Timpone 1997, Tomida 2006, Ungerleider 1982, Wade 2004, Zajicek 2012
[9] See Appendix 8 (Results of the risk of bias assessment)
[10] Indirectness: Analysis of AEs across all patient populations, excluding anxiety, depression, psychosis and sleep disorders

TABLE 61: GRADE EVIDENCE PROFILE: SLEEP DISORDER

Author(s): Kleijnen Systematic Reviews Ltd
Date: 2014-09-09
Question: Should CBM be used for sleep disorder?
Settings: Not specified
Bibliography: Systematic review for Swiss Federal Office of Public Health

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBM	Control	Relative (95% CI)	Absolute		
Sleep Apnoea/ hypopnea (follow-up 3 weeks; measured with: Apnea hypopnea index (AHI); Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency[3]	no serious indirectness	serious[4]	none	17	5	-	MD 19.64 lower (0 to 0 higher)[5]	⊕⊕OO LOW	
Sleep quality (follow-up 2-15 weeks[6]; measured with: Numerical rating scale[7]; range of scores: 0-10; Better indicated by lower values)												
8[8]	randomised trials	serious[9]	no serious inconsistency	serious[10]	no serious imprecision	reporting bias[11]	269	270	-	WMD 0.58 lower (0.87 to 0.29 lower)	⊕OOO VERY LOW	
Sleep disturbance (follow-up 2-15 weeks[12]; measured with: Numerical rating scale; range of scores: 0-10; Better indicated by lower values)												
3[13]	randomised trials	serious[9]	serious[14]	serious[15]	no serious imprecision	none	868	769	-	WMD 0.26 lower (0.52 lower to 0 higher)	⊕OOO VERY LOW	
Any adverse events (follow-up 1-105 days[16])												
29[17]	randomised trials	serious[18]	no serious inconsistency	serious[19]	no serious imprecision	none	1438/1779 (80.8%)	1058/1710 (61.9%)	OR 3.03 (2.42 to 3.80)	212 more per 1000 (from 178 more to 242 more)	⊕⊕OO LOW	

[1] Prasad 2011
[2] Risk of bias: Insufficient details on randomisation, concealment of allocation and blinding; high risk of bias for incomplete outcome data
[3] Inconsistency: Not applicable (single study)
[4] Imprecision: Study included only 22 patients
[5] No 95 %-CI reported, p-value=0.018
[6] Johnson 2010: 2 weeks; Blake 2006, Rog 2005: 5 weeks; Wade 2004: 6 weeks; Zajicek 2012: 12 weeks; Collin 2010, GW Pharma Ltd 2005: 14 weeks; Serpell 2014: 15 weeks

[7] 0-10 or 0-100. 0-100 VAS results were transformed to a 0-10 scale by dividing by 10
[8] Blake 2006, Collin 2010, GW Pharma Ltd 2005, Johnson 2010, Rog 2005, Serpell 2014, Wade 2004, Zajicek 2012
[9] Risk of bias: Insufficient details on randomisation (Berman 2007, GW Pharma Ltd 2005), concealment of allocation (Berman 2007, GW Pharma Ltd 2005) and blinding (all three); high risk for allocation concealment (Nurmikko 2007) and incomplete outcome data (Berman 2007, GW Pharma Ltd 2005)
[10] Indirectness: Studies were conducted in patients with chronic pain (GW Pharma Ltd 2005, Nurmikko 2007) and chronic pain as well as MS/ paraplegia (Berman 2007)
[11] Evidence of small study effects (Egger test, p=0.012)
[12] Berman 2007: 3 weeks; Nurmikko 2007: 5 weeks; GW Pharma Ltd 2005: 14 weeks
[13] Berman 2007, GW Pharma Ltd 2012, Nurmikko 2007
[14] Inconsistency: I2=64%
[15] Indirectness: Studies were conducted in patients with chronic pain (Blake 2006, GW Pharma Ltd 2005, Johnson 2010, Rog 2005, Serpell 2014) and MS/ paraplegia (Collin 2010, Wade 2004, Zajicek 2012)
[16] See Appendix 5 (Baseline details of included studies)
[17] Beal, 1995, Berman 2007, Chan 1987, Collin 2007, Collin 2010, Duran 2010, George 1983, GW Pharma Ltd 2005, GW Pharma Ltd 2012, Heim 1984, Hutcheon 1983, Johansson 1982, Karst 2003, Lane 1991, Langford 2013. Meiri 2004, Müller-Vahl 2001, Müller-Vahl 2003, Nurmikko 2007, Pomeroy 1986, Portenoy 2012, Rog 2005, Serpell 2014, Svendsen 2004, Timpone 1997, Tomida 2006, Ungerleider 1982, Wade 2004, Zajicek 2012
[18] See Appendix 8 (Results of the risk of bias assessment)
[19] Indirectness: Analysis of AEs across all patient populations, excluding anxiety, depression, psychosis and sleep disorders

TABLE 62: GRADE EVIDENCE PROFILE: PSYCHOSIS

Author(s): Kleijnen Systematic Reviews Ltd
Date: 2014-09-09
Question: Should CBM (cannabidiol, max. 800 mg/day) vs Amisulpride (max. 800 mg/day) be used for psychosis?
Settings: Not specified
Bibliography: Systematic review for Swiss Federal Office of Public Health

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBM (cannabidiol, max. 800 mg/day)	Amisulpride (max. 800 mg/day)	Relative (95% CI)	Absolute		
Mental health (follow-up 4 weeks; measured with: Brief Psychiatric Rating Scale; Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency[3]	no serious indirectness	serious[4]	none	17	18	-	MD 0.10 lower (9.2 lower to 8.9 higher)[5]	⊕⊕OO LOW	
Mood (follow-up 4 weeks; measured with: Positive and negative syndrome scale (PANSS); range of scores: 30-210; Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency[3]	no serious indirectness	serious[4]	none	17	18	-	MD 1.0 higher (12.6 lower to 14.6 higher)[6]	⊕⊕OO LOW	
Any adverse events (follow-up 1-105 days[7])												
29[8]	randomised trials	serious[9]	no serious inconsistency	serious[10]	no serious imprecision	none	1438/1779 (80.8%)	1058/1710 (61.9%)	OR 3.03 (2.42 to 3.80)	212 more per 1000 (from 178 more to 242 more)	⊕⊕OO LOW	

[1] Leweke 2012
[2] Risk of bias: Insufficient details on concealment of allocation and blinding; high risk of bias for selective outcome reporting.
[3] Inconsistency: Not applicable (single study)
[4] Imprecision: Study included only 42 patients
[5] p-value=0.977
[6] p-value=0.884
[7] See Appendix 5 (Baseline details of included studies)
[8] Beal, 1995, Berman 2007, Chan 1987, Collin 2007, Collin 2010, Duran 2010, George 1983, GW Pharma Ltd 2005, GW Pharma Ltd 2012, Heim 1984, Hutcheon 1983, Johansson 1982, Karst 2003, Lane 1991, Langford 2013. Meiri 2004, Müller-Vahl 2001, Müller-Vahl 2003, Nurmikko 2007, Pomeroy 1986, Portenoy 2012, Rog 2005, Serpell 2014, Svendsen 2004, Timpone 1997, Tomida

2006, Ungerleider 1982, Wade 2004, Zajicek 2012

[9] See Appendix 8 (Results of the risk of bias assessment)

[10] Indirectness: Analysis of AEs across all patient populations, excluding anxiety, depression, psychosis and sleep disorders

TABLE 63: GRADE EVIDENCE PROFILE: GLAUCOMA

Author(s): Kleijnen Systematic Reviews Ltd
Date: 2014-09-09
Question: Should CBM be used for glaucoma?
Settings: Not specified
Bibliography: Systematic review for Swiss Federal Office of Public Health

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBM	Control	Relative (95% CI)	Absolute		
Any adverse events (follow-up 12 hours)												
1	randomised trials	serious[1]	no serious inconsistency[2]	no serious indirectness	very serious[3]	none	3/6 (50%)	2/6 (33.3%)	OR 2.00 (0.19 to 20.61)[4]	167 more per 1000 (from 247 fewer to 578 more)	⊕OOO VERY LOW	

[1] Risk of bias: Insufficient details on randomisation, concealment of allocation and blinding
[2] Inconsistency: Not applicable (single study)
[3] Imprecision: Study included only 42 patients (cross-over design)
[4] OR across all patient populations (29 studies): 3.03, 95%-CI 2.42 to 3.80 (see section 5.3 for details)

TABLE 64: GRADE EVIDENCE PROFILE: MOVEMENT DISORDERS DUE TO TOURETTE SYNDROME

Author(s): Kleijnen Systematic Reviews Ltd
Date: 2014-09-09
Question: Should CBM be used for Movement disorders due to Tourette syndrome?
Settings: Not specified
Bibliography: Systematic review for Swiss Federal Office of Public Health

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CBM	Control	Relative (95% CI)	Absolute		
Tic severity (follow-up 6 weeks; measured with: Shapiro Tourette Syndrome Severity Scale (STSSS); range of scores: 0-6; Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency[3]	no serious indirectness	serious[4]	none	7	10	-	MD 0.70 lower (0 to 0 higher)[5]	⊕⊕OO LOW	
Tic severity (follow-up 6 weeks; measured with: Tourette syndrome symptom list (TSSL) - tic rating; Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency[3]	no serious indirectness	serious[4]	none	7	10	-	MD 16.2 lower (0 to 0 higher)[6]	⊕⊕OO LOW	
Tic severity (follow-up 6 weeks; measured with: Yale Global Tic Severity Scale (YGTSS); range of scores: 0-100; Better indicated by lower values)												
1[1]	randomised trials	serious[2]	no serious inconsistency[3]	no serious indirectness	serious[4]	none	7	11	-	MD 12.03 lower (0 to 0 higher)[7]	⊕⊕OO LOW	
Tic severity (follow-up 6 weeks; measured with: Tourettes syndrome clinical global impression scale (TS CGI); range of scores: 0-6; Better indicated by higher values)												
1[1]	randomised trials	serious[2]	no serious inconsistency[3]	no serious indirectness	serious[4]	none	7	10	-	MD 0.57 lower (0 to 0 higher)[8]	⊕⊕OO LOW	
Any adverse events (follow-up 2-42 days[9])												
2[10]	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	very serious[12]	none	10/21 (47.6%)	5/23 (21.7%)	OR 3.45 (0.91 to 13.08)[13]	272 more per 1000 (from 16 fewer to 567 more)	⊕OOO VERY LOW	

[1] Müller-Vahl 2003
[2] Risk of bias: Insuficient information on randomisation and allocation concealment; high rsk for incomplete outcome data

[3] Inconsistency: Not applicable (single study)
[4] Imprecision: Study included only 24 patients
[5] No 95 %-CI reported, p-value=0.033
[6] No 95 %-CI reported, p-value<0.05
[7] No 95 %-CI reported, p-value=0.061
[8] No 95 %-CI reported, p-value=0.008
[9] Müller-Vahl 2001: 2 days; Müller-Vahl 2003: 6 weeks
[10] Müller-Vahl 2001, Müller-Vahl 2003
[11] Risk of bias: Insufficient details on randomisation (both studies), concealment of allocation (both studies) and blinding (Müller-Vahl 2001); high risk of bias for incomplete outcome data (Müller-Vahl 2003)
[12] Imprecision: 2 studies including 44 patients (16 events)
[13] OR across all patient populations (29 studies): 3.03, 95%-CI 2.42 to 3.80 (see section 5.3 for details)