Systematic review of cannabis for medical use

Protocol by Kleijnen Systematic Reviews Ltd

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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[1]

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.[2] 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.[3] 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.[4] 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).[4, 5] It was first isolated and synthesised in the 1960s.[1] 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.[6] A large number of other biologically active cannabinoids have been identified. These include Δ^8-THC, cannabidiol (CBD), tetrahydrocannabivarin (THCV), and THC-acid (THCA).[1, 7]

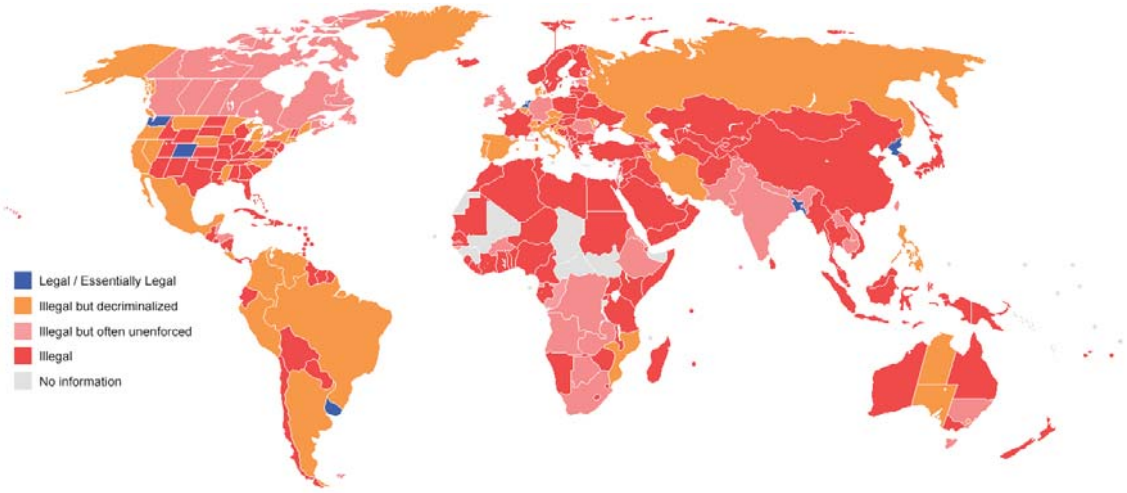
Cannabinoids act mainly via two different receptors: the prevalent CB-1 receptor and the CB-2 receptor. CB-1 is predominantly expressed on neurons, whilst CB-2 is predominantly expressed on cells of the immune system. The expression of these receptors is the biological basis for the medical use of cannabinoids 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.[8, 9]

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.[10] 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.[11] 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.[1, 3] Potential long term effects include developing cardiovascular or respiratory diseases or cancers, dependence and precipitating psychotic disorders including Schizophrenia.[3, 12, 13]

Cannabis was included as a controlled drug in the United Nations *Single Convention on Narcotic Drugs* in 1961[14], 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. The figure shows an overview of the legal status of cannabis throughout the world.

Figure. Legal status of cannabis in countries across the world[15]



In Switzerland, the production, culture, use and possession of cannabis is illegal and punishable by three years in prison or a fine.[16] 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.[17] 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.[18] The prevalence for cannabis consumption in Switzerland was estimated at 31% in 1998.[19]

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.[20] 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.[20] 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.[21] 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.[22]

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.[7] Prescribed CBMs include dronabinol gelatin capsules (brand name Marinol® since 1986, Abott 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).[7] 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.[23] 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.[23] Israel and the Czech Republic are setting up similar programmes and Italy, Finland and Germany are importing products from the Dutch programme. 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.[7]

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%).[7] 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%).[24] 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.[7, 24] 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®).[25]

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), symptoms associated with multiple sclerosis (spasticity and bladder dysfunction), nausea and vomiting (palliative care patients, cancer patients, chemotherapy patients, and mixed), Tourette's syndrome, epilepsy, dementia, HIV/AIDS patients post-traumatic stress disorder, and one general review of medicinal use of marijuana. There are also systematic reviews focussing specifically on the adverse effects of cannabis use – one on adverse effects in general and one on schizophrenia. None of these

reviews are up to date – the most recent search date was September 2013 in a review of cannabinoids for epilepsy. 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

Attempts will be made to identify relevant studies on the use of cannabis and cannabinoid derivatives as medical treatment for a number of indications. Search methods will meet best practice standards in systematic reviews.[50, 51] The search strategies will be developed specifically for each database and the keywords adapted according to the configuration of each database. Only studies conducted in humans will be sought. Searches will not be limited by language, date or publication status (unpublished or published). Searches will be undertaken in three phases to identify existing systematic reviews, protocols, health technology assessments (HTAs) and economic evaluations; clinical effectiveness of medicinal cannabis use; and to identify adverse events resulting from medicinal cannabis use.

Rapid appraisal of systematic reviews, protocols and health technology assessments

A full rapid appraisal will be undertaken to retrieve existing systematic reviews, protocols, HTAs, economics evaluations, guidance and guidelines relating to the used cannabis and cannabinoid derivatives in the therapeutic context.

The following databases will be searched from inception to present:

- Cochrane Database of Systematic Reviews (CDSR) (Wiley): up to 2014
- Database of Abstracts of Reviews of Effects (DARE) (Wiley): up to 2014
- Health Technology Assessment database (HTA) (Wiley): up to 2014
- NHS Economic Evaluations Database (NHS EED) (Wiley): up to 2014
- International Network of Agencies for Health Technology Assessment (INAHTA) (Internet): up to 2014 http://www.inahta.org/
- International Information Network on New and Emerging Health Technologies (EuroScan) (Internet): up to 2014 http://www.euroscan.org.uk/
- NIHR Project Portfolio (Internet): up to 2014 http://www.nets.nihr.ac.uk/projects/
- PROSPERO (International Prospective Register of Systematic Reviews) (Internet): up to 2014/03/17 http://www.crd.york.ac.uk/PROSPERO/
- International Guidelines Network Library (GIN) (Internet): up to 2014 http://www.g-i-n.net/
- National Guidelines Clearinghouse (Internet): up to 2014 http://www.guideline.gov/
- NICE Guidance (National Institute for Health and Care Excellence) (Internet): up to 2014 http://guidance.nice.org.uk/
- TRIPdatabase - Guidelines (Internet): up to 2014 http://www.tripdatabase.com/
- Canadian Agency for Drugs and Technologies in Health (CADTH) (Internet): up to 2014 http://www.cadth.ca/

Clinical effectiveness of medicinal cannabis

Where appropriate, database-specific objectively-derived randomised controlled trials filters,

such as Wong 2006, will be applied to limit the searches to retrieve trials.[52] If no randomised trials are found for an indication, additional searches for other types of studies will be carried out.

The following databases will be searched from inception to present:

- Embase (OvidSP): 1974-2014
- Medline (OvidSP): 1946-2014
- Medline In-Process Citations & Daily Update (OvidSP): up to 2014
- PsycINFO (OvidSP): 1806-2014
- BIOSIS Citation Index (Web of Science): 1926-2014
- CINAHL (Cumulative Index to Nursing and Allied Health Literature) (EBSCO): 1982-2014
- Science Citation Index (SCI) (Web of Science): 1900-2014
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): up to 2014

Supplementary searches will be undertaken to identify grey literature, completed and ongoing trials, in resources such as:

- International Association of Cannabis Medicines (IACM) (Internet): up to 2014 http://www.cannabis-med.org/index.php?tpl=def&id=241&lng=en
- IACM Database of Clinical Studies (Internet): up to 2014 http://www.cannabis-med.org/studies/study.php
- NIH ClinicalTrials.gov (Internet): up to 2014 http://www.clinicaltrials.gov
- metaRegister of Controlled Trials (Internet): up to 2014 http://www.controlled-trials.com
- WHO International Clinical Trials Registry Platform (ICTRP) (Internet): up to 2014 http://www.who.int/ictrp/en

A draft Embase search strategy for the RCT search is presented in Appendix 1.

Adverse events from medicinal cannabis use

Further focussed adverse events (AEs) searches may be necessary following screening of the clinical effectiveness search results. Where further information is required, a topic-specific search will be undertaken. Each strategy will be tailored to each resource searched, in combination with named adverse events and detrimental effects resulting from medicinal cannabis use. The adverse events (AE) component of each strategy will be developed following best practice guidance.[50, 51, 53] CRD guidance recommends that where searches have been limited by an RCT filter, additional searches may be necessary to ensure that adverse events that are long-term, rare or unanticipated are not missed.[49]

The following databases and resources may be included in any AEs searches:

- Embase (OvidSP): 1974-2014
- Medline (OvidSP): 1946-2014
- Medline In-Process Citations & Daily Update (OvidSP): up to 2014
- PsycINFO (OvidSP): 1806-2014
- BIOSIS Citation Index (Web of Science): 1926-2014
- CINAHL (Cumulative Index to Nursing and Allied Health Literature) (EBSCO): 1982-2014
- Science Citation Index (SCI) (Web of Science): 1900-2014
- IACM Database of Clinical Studies (Internet): up to 2014 http://www.cannabis-med.org/studies/study.php

Handling of citations

Identified references will be downloaded into Endnote X7 software for further assessment and handling. Rigorous records are maintained as part of the searching process. Individual records within the Endnote reference libraries are 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.

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 will be independently peer reviewed by a second Information Specialist, using the CADTH checklist.[54]

4.2 Inclusion Criteria

Studies that fulfil the following criteria will be eligible for inclusion:

a. Review of clinical effectiveness:

Population

People with any of the following conditions:

1) Nausea and vomiting due 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 will not be restricted based on outcome. We anticipate that the following outcomes will be reported:

1) Patient relevant outcomes e.g. symptoms of nausea and vomiting, pain, discomfort, spasticity, functional status
2) Activities of daily living
3) Quality of life
4) Mortality

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

Study designs
Randomised controlled trials (RCTs); if no RCTs are found then lower levels of evidence will be 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

If high quality systematic reviews (rated low on all ROBIS items, see section 4.3) are identified for any of the patient groups of interest that fulfil all inclusion criteria for the review then these will be eligible for inclusion. We will include the systematic review if it includes all relevant studies for a single population; if additional studies fulfil our inclusion criteria then the original review will be used only as a source of relevant studies.

b. Review of adverse events:

Population
Any population; we anticipate that studies will be conducted in the patient groups outlined in section 4.2 a.

Intervention
Any form of cannabis for medical use.

Comparators

Usual care, placebo or no treatment.

Outcomes

Serious adverse events (SAE) and drug-related adverse events (e.g. mood-related effects, effects on perception or cognitive function, impairment in psychomotor performance).

We anticipate that the following short term adverse events will be considered: dizziness, dysphoria (a state of feeling unwell or unhappy), depression, hallucinations, paranoia and impairment in psychomotor performance. Long term adverse events include developing cardiovascular or respiratory diseases or cancers, dependence, precipitating psychotic disorders including schizophrenia.

Study designs

We anticipate that data on short term adverse events will be reported in RCTs. If data on long term adverse events are not available in RCTs then we will include 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

If high quality systematic reviews (rated low on all ROBIS items, see section 4.3) are identified for any of the patient groups of interest that fulfil all inclusion criteria for the review then these will be eligible for inclusion. We will include the systematic review if it includes all relevant studies for a single population; if additional studies fulfil our inclusion criteria then the original review will be used only as a source of relevant studies.

4.3 Methods of Study Selection, Data Extraction and Quality Assessment

Study selection

Titles and abstracts identified through electronic database and web searching will be independently screened by two reviewers. During this initial phase of the screening process any references which obviously do not meet the inclusion criteria will be excluded. Full text copies will be obtained for all remaining references. These will then be independently examined in detail by two reviewers in order to determine whether they meet the criteria for inclusion in the review. All papers excluded at this second stage of the screening process will be documented along with the reasons for exclusion. With respect to both screening stages, any discrepancies between reviewers will be resolved through discussion or the intervention of a third reviewer.

Data extraction

Data will be extracted using standardised data extraction forms developed in Microsoft Access 2010 (Appendix 2). Data extraction forms will be piloted on a small sample of papers and adapted as necessary. In order to minimise bias and errors, data extraction will involve two reviewers. Disagreements will be resolved through discussion or referral to a third reviewer where necessary.

Quality assessment

Systematic reviews will be assessed for methodological quality using the ROBIS tool, currently being developed by the authors.[55] This tool aims to assess the risk of bias in systematic reviews and includes domains covering study eligibility criteria, identification and selection of studies, data collection and study appraisal, synthesis and findings, and interpretation (Appendix 3a). Trials will be assessed for methodological quality using the Cochrane Risk of Bias tool (Appendix 3b).[56] 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). There is also an additional field for other sources of bias. We believe that all important concerns about bias are included in the other domains in the tool and so no further domains will be added. We hope to use the new Cochrane risk of bias tool for non-randomised studies to assess the risk of bias in observational studies.[57] This is currently under development. If a version of the tool is available on time then we will use this tool and contribute to the piloting process. It is expected include 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. If a version of the Cochrane non-randomised tool is not available within the required time frame for this review then we will adapt the Down and Black's tool to focus on risk of bias with ratings of high and low risk of bias similar to the ROBIS and Cochrane Risk of Bias tool.[56] For all tools, if at least one of the domains is rated as "high" the study will be considered at high risk of bias, if all domains are judged as "low" the trial will be considered at low risk of bias, otherwise the trial will be considered at "unclear" risk of bias. The risk of bias assessment will be conducted as part of the data extraction process.

4.4 ANALYSIS

Narrative synthesis methods

A narrative summary of the included studies will be presented. This will include a summary of the characteristics (e.g. study aim, study design, population size, geographical location, year, baseline population characteristics, outcome definition and assessments). If data are considered too heterogeneous to pool, or not reported in a format suitable for pooling (e.g. data reported as medians) then we will employ a narrative synthesis. This will involve 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. This involves organising the studies by (as appropriate) population or outcomes assessed, summarising the results of the studies, summarising the range and size of the associations these studies report, and describing the most important characteristics of the included studies. A detailed commentary on the major methodological problems or biases that affected the studies will also be included, together with a description of how this has affected the individual study results.

Quantitative analysis and meta-analysis methods

If sufficient studies assessing similar populations and outcomes are found then a formal meta-analysis will be used to estimate summary measures of effect.

For dichotomous data we will calculate the relative risk (RR) for each trial with the associated 95% confidence intervals (CIs). Continuous data will be analysed as the mean difference between groups and associated 95% CIs. For multi-arm studies, we will analyse each intervention arm compared to the control group separately. For cross-over trials, data for the first period of the trial only will be extracted and included in the meta-analysis.

We anticipate that systematic differences between studies (heterogeneity) will be likely. Therefore, the random-effects model will be used to calculate summary estimates. Heterogeneity will be investigated visually using forest plots and statistically using the I^2 and Q statistics.[58]

Heterogeneity will be formally investigated using meta-regression analyses, where sufficient data are available. We anticipate that the effects of the following variables will be investigated: methodological quality of the primary studies, route of cannabis administration (e.g. smoking, vaporiser, tea, food/tincture, medical oral use, medical oromucosal administration), forms of cannabis (e.g. pure cannabinoids, herbal cannabis (marijuana), dronabinol, nabilone, THC vaporiser, nabiximols), daily dose, population/condition, previous drug use, age, sex and comorbidities. Other variables considered relevant on further examination of the literature or input from clinical experts may also be considered. The coefficient describing the effect of each variable on the outcome will be modelled, using a random effects model.

Small study effects (publication bias) will be assessed using a modified linear regression test for funnel plot asymmetry as recommended by Harbord et al (2005) where there are sufficient numbers of trials (i.e. six trials).[59]

A detailed analysis plan will be produced before the analysis is conducted. Statistical analyses will be performed using Stata (version 10), the MetaXL add on for Microsoft Excel, and RevMan (version 5).

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.[60-62] It rates the quality of a complete body of evidence for a specific outcome in a specific population. The quality of evidence will be 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.[63] 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 will draft specific questions based on the research questions outlined above. For each question, we will develop GRADE evidence profiles and summary of findings tables to summarise the evidence and rate the quality of evidence (See Appendix 4c for an example of an evidence profile).

5. TIMETABLE

The proposed time line for the project is summarised in Table 1.

Table 1: Project Timetable

Deadline	Project stage
20 March	Project start date
20-31 March	Protocol development
31 March	**Submit protocol**
31 March – 6 April	Kick-off meeting, feedback on protocol, agreement of protocol
7 April – 20 April	Searches for studies
14 April – 13 July	Inclusion assessment of full papers, data extraction, creation of structured tables
30 June	**Interim report**
14 July – 3 August	Analyses
4 August – 7 September	Preparing GRADE profiles, drafting of report
7 September	**Submit draft report to sponsor**
22 September	Sponsor submits comments to KSR
22 September – 30 September	Incorporate comments from sponsor
30 September	**Submit final report**

6. TEAM MEMBERS

Robert Wolff and Penny Whiting will act as the primary contacts on behalf of KSR during the period of the project. In case of annual leave or other absence Shona Lang will act as secondary contact or alternatively the general KSR phone and email contact details can be used (Tel: +44 (0)1904 727980; email: enquiries@systematic-reviews.com).

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APPENDIX 1: SEARCH STRATEGIES

Randomised controlled trials (RCT) search

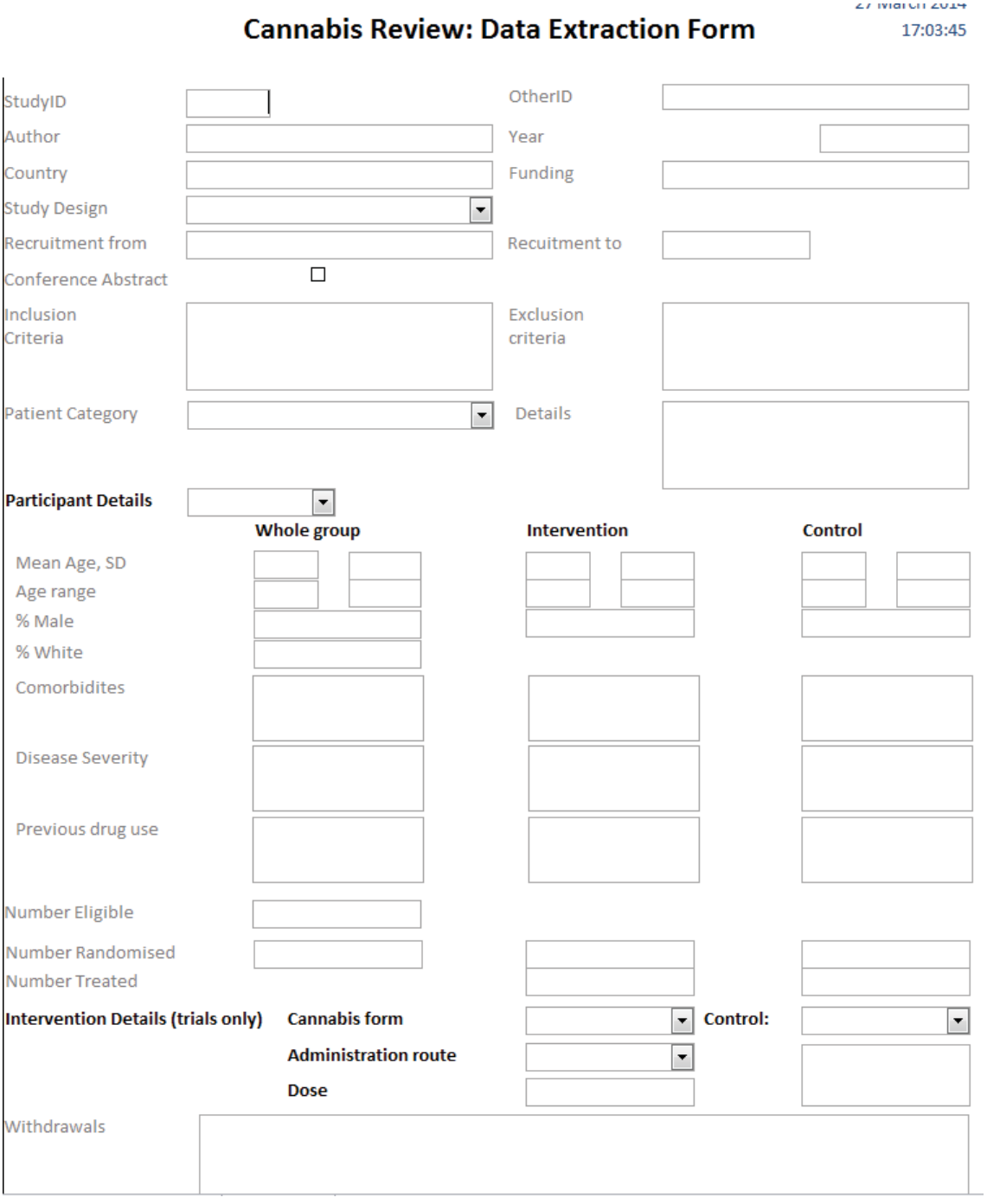
Embase (OvidSP): 1974-2013/12/10
Searched 11.12.13

1 Cannabaceae/ (50)
2 exp cannabinoid/ (42913)
3 (marijuana or marihuana or cannabis or canabis).ti,ab,ot,hw. (31904)
4 (Hashish or hash or bhang or ganja or ganjah or hemp or charas).ti,ab,ot,hw. (1723)
5 (cannador or eucannabinolide or 8001-45-4 or 8063-14-7 or 38458-58-1).ti,ab,ot,hw,rn. (21217)
6 (9tetrahydrocannabinol$ or delta3-thc or sp-104 or sp104 or 1972-08-3).ti,ab,ot,hw,rn. (5408)
7 (Dronabinol or Marinol or ea-1477 or ea1477 or tetranabinex or qcd-84924 or qcd84924 or 7663-50-5).ti,ab,ot,hw,rn. (5397)
8 (delta-9-THC or 5957-75-5 or 1972-08-3).ti,ab,ot,hw,rn. (5709)
9 delta9?11?tetrahydrocannabinol.ti,ab,ot,hw. (0)
10 (THC or CBD or AEA).ti,ab,ot. (13297)
11 (nabidiolex or 13956-29-1).ti,ab,ot,hw,rn. (1875)
12 (dexanabinol or Hu-210 or Hu-211 or hu210 or hu211 or 112924-45-5).ti,ab,ot,hw,rn. (1113)
13 (Cannabichromene or 521-35-7).ti,ab,ot,hw,rn. (965)
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. (959)
15 (Nabiximols or Sativex or Gw-1000 or gw1000 or sab-378 or sab378 or 56575-23-6).ti,ab,ot,hw,rn. (240)
16 (Anandamide or N-arachidonoylethanolamine).ti,ab,ot,hw. (5037)
17 (canabinoid$ or canabidiol$ or cannabinoid$ or Tetrahydrocannabinol$ or tetra-hydrocannabinol$ or endocannabinoid$ or Cannabidiol or cannabinol).ti,ab,ot. (21640)
18 (nantradol or cp-44001 or cp-44001-1 or cp440011 or cp44001-1 or 72028-54-7).ti,ab,ot,hw,rn. (104)
19 or/1-18 (60699)
20 Random$.tw. or clinical trial$.mp. or exp health care quality/ (3251060)
21 animal/ (1895159)
22 animal experiment/ (1733216)
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. (5862963)
24 or/21-23 (5862963)
25 exp human/ (15173832)
26 human experiment/ (319069)
27 or/25-26 (15175273)
28 24 not (24 and 27) (4666990)
29 20 not 28 (3095760)
30 19 and 29 (8549)

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.

APPENDIX 2: EXAMPLE DATA EXTRACTION FORMS

2A BASELINE DATA FORM



Cannabis Review: Data Extraction Form

27 March 2014
17:03:45

StudyID | OtherID
Author | Year
Country | Funding
Study Design
Recruitment from | Recuitment to
Conference Abstract ☐
Inclusion Criteria | Exclusion criteria
Patient Category | Details

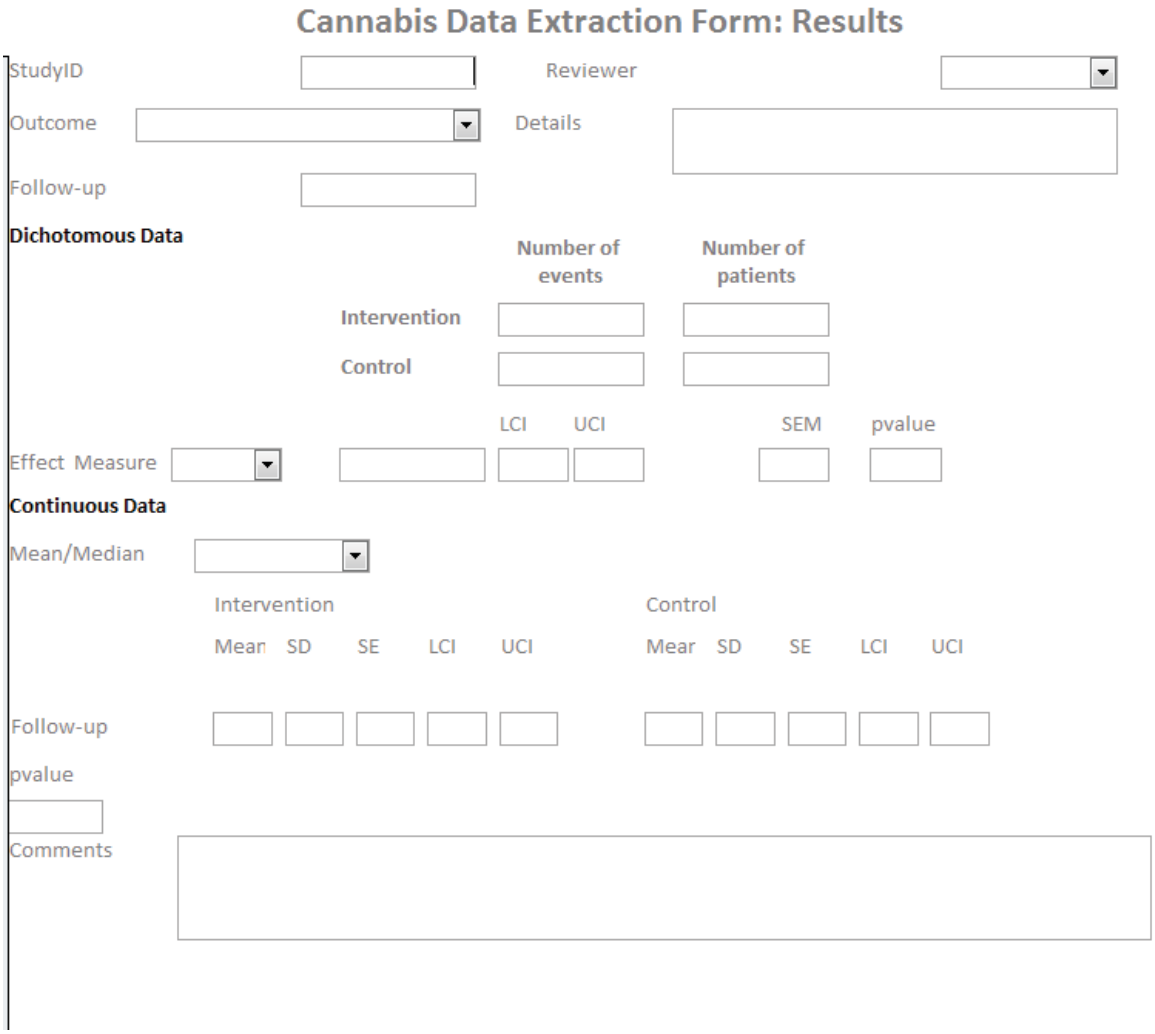
Participant Details

	Whole group	Intervention	Control
Mean Age, SD			
Age range			
% Male			
% White			
Comorbidites			
Disease Severity			
Previous drug use			
Number Eligible			
Number Randomised			
Number Treated			

Intervention Details (trials only) — **Cannabis form** | **Control:**
Administration route
Dose

Withdrawals

2B RESULTS FORM



APPENDIX 3: EXAMPLE RISK OF BIAS ASSESSMENT FORMS

3A ROBIS

Cannabis ROBIS FORM

ID (New) Author Year

State your overview/guideline question and the question being addressed in the review being assessed:

Patients/Population		
Intervention		
Comparator		
OutcomeReview		

Does the question addressed by the review match the question you are trying to answer (e.g. in your overview or guideline)?

DOMAIN 1: STUDY ELIGIBILITY CRITERIA

Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives an eligibility criteria were pre-specified:

- Did the review adhere to pre-defined objectives and eligibility criteria?
- Were the eligibility criteria appropriate for the review question?
- Were eligibility criteria unambiguous?
- Were any restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?
- Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?

Risk of bias introduced by specification of study eligibility criteria

DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES

Describe methods of study identification and selection (e.g. number of reviewers involved):

- Did the review search an appropriate range of databases/electronic sources for published and unpublished reports?
- Were methods additional to database searching used to identify relevant reports?
- Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?
- Did the search methods avoid restrictions based on date, publication format, or languages
- Were efforts made to minimise error in selection of studies?

Risk of bias introduced by methods used to identify and/or select studies

DOMAIN 3: DATA COLLECTION AND STUDY APPRAISAL

Describe methods of data collection, what data were extracted from studies or collected through other means, how risk of bias was assessed (e.g. number of reviewers involved) and the tool used to assess risk of bias:

- Were efforts made to minimise error in data collection?
- Were sufficient study characteristics considered for both review authors and readers to be able to interpret the results?
- Were all relevant study results collected for use in the synthesis?
- Was risk of bias (or methodological quality) formally assessed using an appropriate tool?

Risk of bias introduced by methods used to collect data and appraise studies

DOMAIN 4: SYNTHESIS AND FINDINGS

Describe synthesis methods:

- Did the synthesis include all studies that it should, or use techniques to account for missing studies?
- Were all pre-defined analyses reported or their absence explained?
- Was the synthesis appropriate given the degree of similarity in the research questions, study designs and outcomes across included studies?
- Was heterogeneity in results minimal, or addressed in the synthesis?
- Was robustness of the finding(s) assessed e.g. through sensitivity analysis?
- Were biases in primary studies minimal or addressed in the synthesis?
- Was a complete account provided of results including variation and uncertainty?

Risk of bias introduced by the synthesis

DOMAIN 5: INTERPRETATION

Describe whether conclusions were supported by the evidence:

- Was the quality of the evidence considered when interpreting the results and drawing conclusions?
- Was the relevance of identified studies to the review's research question appropriately considered?
- Did the reviewers avoid selecting or emphasising results on the basis of their statistical significance?

Risk of bias introduced by the interpretation of results

3B COCHRANE RISK OF BIAS TOOL

Cannabis: Risk of Bias Assessment

Author		StudyID
	Support for judgement	**Risk of bias**
Random Sequence Generation		
Allocation Concealment		
Participant/Personnel blinding		
Outcome assessor blinding		
Incomplete Outcome Data		
Selective outcome reporting		
Comments		

APPENDIX 4: GRADE FRAMEWORK AND PROFILES

4A DEFINITION, CATEGORIES, AND FACTORS AFFECTING THE QUALITY OF EVIDENCE

Definition: The extent of our confidence that the estimate of an effect is adequate to support a particular decision or recommendation

Categories:

- **High**: we are very confident in the effect estimate: the true effect lies close to that of the estimate of the effect.
- **Moderate**: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low**: we have limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect.
- **Very low**: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Factors affecting quality of evidence

Study design	Initial grade	Grade lowered if	Grade raised if	Final grade
Randomized trial →	High	Limitations of design Inconsistency Indirectness Imprecision Publication bias	Large effect Dose response All plausible confounding would reduce a demonstrated effect	High
	Moderate			Moderate
Observational study →	Low			Low
	Very low			Very low

4B EXAMPLE OF AN EVIDENCE PROFILE

Evidence Profile – Community-based care for chronic wound management

Quality Assessment							Summary of Findings				
							No of Patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Wound Care Team	Usual Care	Relative (95% CI)	Absolute	Quality
Proportion of Wounds Healed (follow-up 6 months; Proportion of wounds healed)											
1[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	112/180 (62.2%)	85/162 (52.5%)	RR 1.19 (0.99 to 1.43)	100 fewer per 1000 (from 5 fewer to 226 more)	⊕OOO VERY LOW
Proportion of Persons with wounds healed (follow-up mean 3 months)											
1	observational studies[5]	serious[6]	no serious inconsistency	no serious indirectness	serious[7]	strong association[8]	100/180 (55.6%)	18/78 (23.1%)	OR 4.17 (2.28 to 7.62)	325 more per 1000 (from 175 more to 465 more)	⊕OOO VERY LOW
Persons with BPI score=0 (follow-up mean 6 months; Brief Pain Inventory9)											
1	randomised trials[1]	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	49/127 (38.6%)	29/119 (24.4%)	RR 1.58 (1.08 to 2.33)	141 more per 1000 (from 19 more to 324 more)	⊕OOO VERY LOW
Proportion of Persons needing daily treatments (follow-up mean 3 months)											
1	randomised trials[1]	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	49/127 (38.6%)	29/119 (24.4%)	RR 1.58 (1.08 to 2.33)	141 more per 1000 (from 19 more to 324 more)	⊕OOO VERY LOW

[1] One Study by Vu et al. 2007
[2] Alternating randomization, lack of allocation concealment
[3] Nursing Home setting not a community-based study
[4] Sparse data, one small study
[5] One study by Harrison et al. 2005
[6] Outcome measure not assessed independent of the exposure status
[7] One study contributing to body of evidence therefore considered sparse data
[8] Relative odds reduction of 76%
[9] 11-point scale (0-10) to assess wound-associated pain

From: Medical Advisory Secretariat. Community-based care for chronic wound management: an evidence-based analysis. Ontario Health Technology Assessment Series 2009; 9(18).