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Cannabis for the treatment of dementia

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Editorial group: Cochrane Dementia and Cognitive Improvement Group.


ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To determine the efficacy and safety of cannabis for the treatment of dementia.

BACKGROUND

Description of the condition

Dementia is a common chronic condition mainly affecting older adults and characterised by a progressive decline in cognitive and functional ability. The most common forms of dementia include Alzheimer’s disease (AD) (60% to 70% of cases), vascular dementia (VaD), dementia with Lewy bodies (DLB), dementia in Parkinson’s disease (PDD) and frontotemporal dementia (FTD). The boundaries between different subtypes of dementia are indistinct and mixed forms often co-exist (WHO 2013).

It has been estimated that there were 47 million people worldwide living with dementia in 2016, and the number was projected to increase to more than 131 million in 2050 due to population ageing (ADI 2016). This disabling condition brings with it a significant burden to the individuals and their carers, as well as a large financial burden for the health system (Standfield 2017), thus driving the need to identify effective therapeutic interventions. Medical treatments for dementia are limited. Licensed medications are available only for dementia due to AD and PDD and these have only modest benefits for cognitive symptoms. At least half of patients with dementia will also experience behavioural and psychological symptoms (BPSD) such as agitation, aggression, psychosis and circadian rhythm disturbances. These symptoms lead to significant caregiver stress (Rabins 1982), are distressing for the patient, and often precipitate placement in residential or nursing homes (Steele 1990). Antipsychotic drugs are widely used to treat BPSD but have only modest efficacy (Ballard 2006; Schneider 2006). Use of these drugs in dementia is also associated with serious side effects including an increased risk of cerebrovascular adverse events and death (FDA 2005; MHRA 2004; Schneider 2005). A range of pharmacological and non-pharmacological interventions is used for BPSD, but there are still continuing problems with their lack of efficacy, safety and feasibility. Accordingly, there is a
need for new, safe and more effective treatments for dementia and its associated symptoms.

**Description of the intervention**

The cannabinoids are one potential agent under investigation for the treatment of dementia. Multiple studies conducted among patients have indicated that they have positive attitudes towards medical cannabis (Banwell 2016; Gazibara 2017). There are three general classes of cannabinoids, including herbal cannabinoids (phytocannabinoids) that are derived from the cannabis plant (Cannabis sativa), endogenous cannabinoids that are produced in bodies of humans and animals, and synthetic cannabinoids that are produced in a laboratory. Cannabis, also known as marijuana, is preparation of the Cannabis plant. It is one of the most popular recreational drugs; an estimated 183 million annual users globally used cannabis in 2015, which roughly corresponds to 3.8 per cent of the global population (UNODC 2017). The use of cannabis is illegal in most countries. Although the general public may perceive cannabis as the least harmful illicit drug, there has been a noticeable increase in the number of patients seeking treatment for disorders related to cannabis use over the past decade (UNODC 2017).

Some countries have recently legalised medicinal-grade cannabis for chronically ill patients. Nausea and vomiting due to chemotherapy, appetite stimulation in HIV/AIDS, chronic pain, spasticity due to multiple sclerosis or paraplegia, depression, anxiety disorder, sleep disorder, psychosis, glaucoma, and Tourette syndrome are some indications for its legal use. Anxiety, drowsiness, euphoria, dry mouth, psychosis, dizziness and diarrhoea are known adverse effects (Whiting 2015). The first cannabinoids to be identified were the main psychoactive compound delta-9-tetrahydrocannabinol (THC) and the non-psychoactive compound cannabidiol (CBD), although there are thought to be numerous other cannabinoids, some of which may modulate the response to THC (Iversen 2000). Research for medical use of cannabinoids has resulted in development and marketing of synthetic cannabinoids dronabinol and nabilone. Dronabinol may be taken orally, or via local/topical, transdermal, sublingual or inhaled mode of administration. Nabilone is taken orally as a capsule. Daily dosage and route of administration depends on indication (Howard 2013). Nabilone and dronabinol are used as interventions for reducing vomiting associated with chemotherapy. A combination of cannabidiol and THC (Sativex) has been approved in several countries for treating spasticity in multiple sclerosis and it is being studies for cancer pain. The cannabidiol drug (Epidiols) has been studied for use in epilepsy. Many ongoing studies are exploring therapeutic targets for both cannabinoid receptor agonists and antagonists (Kaur 2016).

Cannabinoids exert their effect by acting at two specific cannabinoid receptors, CB1 and CB2, in the endogenous cannabinoid system (Howlett 2002; Matsuda 1990). CB1 receptors are found throughout the central nervous system, particularly in the hippocampus, basal ganglia and cerebellum. In contrast, CB2 receptors are expressed in peripheral tissues, especially on white blood cells, and are much less widespread in the central nervous system (see Campbell 2007 for a review). Several studies have identified CB2 receptors on brainstem neurons (Van Sickle 2005) and cerebellar neurons (Onaivi 2006), but their role is not yet understood.

**How the intervention might work**

Several neurobiological effects of cannabinoids have been demonstrated which could be relevant in the treatment of dementia. The main function of the endogenous cannabinoid system (ECS) is thought to be the regulation of synaptic transmission (Baker 2003) and this process can be disordered in many neurological conditions including dementia. The ECS consists of endogenous cannabinoids (endocannabinoids), cannabinoid receptors, and enzymes responsible for synthesis and degradation of endocannabinoids (Lu 2016). The best characterised endogenous cannabinoids are anandamide (arachidonoyl ethanolamide) and 2-arachidonoyl glycerol (2-AG); there are also less characterised additional endogenous substances such as virodhamine and 2-arachidonoyl glycerol ether that also belong to the repertoire of endocannabinoids. Endocannabinoids exert their actions mainly by acting on cannabinoid receptors CB1 and CB2 (Gowran 2011); other receptors such as Peroxisome Proliferator Activated Receptors (PPARs) and Transient Receptor Potential (TRP) channels also mediate certain endocannabinoid actions, especially of the acylethanolamides. Relevant enzymes are fatty acid amino hydrolase (FAAH) involved in degradation of anandamide, monoacylglycerol lipase (MGL) and alpha/beta domain hydrolases 6 and 12 (ABHD6 and 12) involved in degradation of 2-AG (Lu 2016).

CB1 receptors are found mainly in the central and peripheral nervous system where they usually mediate inhibition of ongoing release of different neurotransmitters (Szabo 2005). Activation of CB1 affects cognition and memory, alters the control of motor function, and induces signs of analgesia (Pertwee 2010). They regulate processes such as excessive glutamate production and subsequent oxidative stress, which can damage neurons and lead to neurodegeneration (Grundy 2002). They are also found in peripheral tissues where they have a role in energy balance and metabolism (Silvestri 2013). CB2 receptors modulate immune cell migration and cytokine release, as they are located mostly in the immune cells (Pertwee 2005), while in the central nervous system, they are mainly located in the microglia (Cabral 2009), and in some neurons (Brusco 2008, Onaivi 2008), where they are connected with facilitation of neuronal survivor (Viscomi 2009).

There is also some evidence that CB2 receptors may be involved in neuroprotection by reducing neuroinflammation (Ehrhart 2005). Neurodegeneration is a feature common to the various types of...
dementia and the neuroprotective effects of cannabinoids may therefore be beneficial in slowing the progression of these diseases. Some authors have reported a significant reduction in the CB1 levels in cortical areas and neurons distant from senile plaques (Solas 2013), while others indicate that there are changes in the expression, distribution and availability of CB1 in AD (Ahmad 2014; Mulder 2011). According to Solas and colleagues, there is a significant increase of CB2 levels in the brains of people with AD, mainly on the microglia around the senile plaques (Solas 2013). Besides, CB1 and CB2, cannabinoids can bind to other types of receptors, such as GPR55, peroxisome proliferator-activated receptors PPARα and PPARγ, and transient receptor potential vanilloid-1 (TRPV1) channels (Maccarrone 2010; Pertwee 2010).

Cannabinoids may have more specific effects in Alzheimer's disease pathology, as they can reduce excitotoxicity, mitochondrial dysfunction, oxidative stress, neuroinflammation, and the formation of amyloid plaques and neurofibrillary tangles (Ahmed 2015; Aso 2014). Several studies have shown the protective effect of cannabinoids against amyloid-β peptide and tau phosphorylation (reviewed in: Aso 2014), which are the neuropathological hallmarks of AD. THC diminishes acetylcholinesterase-induced amyloid beta-peptide aggregation, the key pathological marker of AD (Ahmed 2015; Eubanks 2006). It has also been reported that THC competitively inhibits the enzyme acetylcholinesterase (AChE) - a similar action to the anti-dementia drugs like donepezil (Ahmed 2015). Another study investigated the effects of cannabinoids in rats injected with amyloid beta-peptide to model AD. Intracerebroventricular administration of a synthetic cannabinoid (WIN55,212-2) to these rats led to a prevention of their cognitive deficit and decreased neurotoxicity (Janefford 2014; Ramirez 2005). These studies suggest that cannabinoids could interrupt the disease process as well as treat symptoms in AD. Endocannabinoids (AEA, 2-AG, noladin ether) seem to increase the viability of neurons after exposure to toxic Aβ species (Chen 2011; Harvey 2012). Similar effect was reported with exogenous cannabinoids such as CBD (Janefford 2014), ACEA (Aso 2012), JWH-015, JWH-133 and HU-210 (Ramirez 2005). Several studies demonstrated positive results in prevention of memory deficits in Aβ-injected rats and mice for exogenous cannabinoids (Aso 2013; Martin-Moreno 2012; Wu 2013).

These studies indicate that the disease-modifying action of cannabinoids is most likely. However, there are also known symptomatic effects of cannabinoids which may be of benefit in dementia. The most common neuropsychiatric symptoms (NPS) in dementia, including depression, anxiety, agitation, aggression, wandering, pacing, sleep disorders, psychosis, and eating disorders, are associated with more rapid dementia progression and higher healthcare costs (Beeri 2002; Tschanz 2013). To this day, no drugs have been approved by the US Food and Drug Administration (FDA) for the treatment of the NPS associated with AD dementia (Ahmed 2015), while in the European Union and Australia, only the antipsychotic risperidone is indicated for the short-term management of severe aggression in patients with AD, with unsuccessful non-pharmacological methods (Panza 2015). A recent review indicated that findings from six studies showed significant benefits from synthetic cannabinoids dronabinol or nabilone on agitation and aggression; however conclusions were limited by small sample sizes, short trial duration, and lack of placebo control in some of these studies (Liu 2015). In another randomised controlled trial (van den Elsen 2015), oral THC 4.5 mg daily showed no benefit in the treatment of neuropsychiatric symptoms, but it was well-tolerated, which allows further study on whether higher doses would be more efficient. An open-label pilot study evaluated the effect of dronabinol in the treatment of NPS in dementia and showed that it significantly improved nocturnal motor activity and behaviour (Walther 2006). A recent retrospective systematic chart review suggested that administration of dronabinol improved sleep duration, food consumption and agitation (Woodward 2014).

**Why it is important to do this review**

Because of the increasing number of elderly people, the number of new cases of dementias is projected to rise. There is a growing need to offer effective and safe interventions to people with dementias. Since firm evidence of efficacy and safety of cannabinoids in this vulnerable patient group is lacking, a systematic review can help inform decisions of healthcare workers, researchers, politicians and other public health decision makers.

**OBJECTIVES**

To determine the efficacy and safety of cannabinoids for the treatment of dementia.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

We will include all randomised controlled trials (RCTs) of cannabinoids for the treatment of dementia. Since dementia is a progressive disease, we will include only the data of the first period of cross-over RCTs.
Types of participants
We will include participants of any age and either sex diagnosed with dementia of any subtype or unspecified dementia of any severity and from any setting. The diagnosis should be made using internationally recognised criteria including Diagnostic and Statistical Manual of Mental Disorders V (DSM V) or previous editions of DSM (APA 2013), the International Classification of Diseases 10 (ICD 10) or previous editions of ICD (WHO 2010), NINDS-AIREN Criteria for the Diagnosis of Vascular Dementia (Roman 1993) or NINCDS-ADRDA Alzheimer’s criteria (McKhann 2011). Studies that include only a subset of relevant participants will be included only if data for the population of interest are reported separately.

Types of interventions
Experimental interventions: cannabinoids administered by any route, at any dose, for any duration.
Control interventions: placebo, no treatment, or any active control interventions.

Types of outcome measures

Primary outcomes
1. Changes in global and specific cognitive function, measured by any validated cognitive scale covering multiple cognitive domains or single cognitive domains (e.g. memory, executive function).
2. Overall behavioural and psychological symptoms of dementia (BPSD), measured with any validated instrument, e.g. the Neuropsychiatric Inventory (NPI) (Cummings 1994).
3. Adverse events.

Secondary outcomes
1. Changes in functional outcomes, such as activities in daily living (ADL), measured by validated tools such as:
   i) Alzheimer’s Disease Activities of Daily Living International Scale (ADCS-ADL) (Galasko 1997);
2. Overall dementia severity measured by validated tools such as:
   i) Clinical dementia rating scale-Sum of Boxes (CDR-SOB) (O’Bryant 2008);
   ii) Alzheimer’s Disease Cooperative Study-Clinical Global Impression of Change (CIBIC-Plus) (Schneider 1997).
3. Objective sleep outcomes measured with polysomnography or actigraphy:
   i) total nocturnal sleep time (TNST; i.e. total time spent asleep between 8.00 PM and 8.00 AM);
   ii) sleep efficiency (%; i.e. TNST/time in bed x 100);
   iii) nocturnal time awake (WASO; after sleep onset and before final awakening);
   iv) number of nocturnal awakenings;
   v) sleep latency;
   vi) ratio of daytime sleep to night-time sleep, or of night-time sleep to total sleep over 24 hours.
4. Changes in appetite:
   i) Change in body weight (kg);
   ii) Carer ratings of patient’s anorexia or change in appetite or both.
5. Agitated or aggressive behaviours:
   i) quantitative observational tools for measuring frequency of occurrence of wandering, agitation and general restlessness;
   ii) standardised tests such as Cohen-Mansfield Agitation Inventory (Cohen-Mansfield 1989).
6. Mood, measured with any validated tool.
7. Carer ratings of patient’s sleep using sleep diaries or validated observer scales.
8. Quality of life.
9. Any other symptoms associated with dementia (e.g. alterations in circadian rhythm, etc.).
10. Caregiver burden and caregiver quality of life.
11. Treatment or research discontinuation/dropout (as measures of acceptability).
12. Mortality.
We will not include biomarker outcomes.

Search methods for identification of studies

Electronic searches
We will search ALOIS (www.medicine.ox.ac.uk/alois), the Cochrane Dementia and Cognitive Improvement Group’s (CD-CIG) comprehensive register of trials. ALOIS is maintained by the Information Scientist of the CD-CIG. It contains RCTs on interventions in the area of dementia and cognitive impairment, as well as those about improvement of cognitive function, or prevention of its decline, in healthy people.
Records included in ALOIS are identified from:
1. monthly searches of multiple major healthcare databases: MEDLINE (Ovid SP), Embase (OVID SP), PsycINFO (OVID SP), CINAHL (EBSCOhost) and Lilacs (Bireme);
2. monthly searches of multiple national and international trial registers: CentreWatch Clinical Trials Listing Service, CENTRAL (the Cochrane Library), ClinicalTrials.gov, Current Controlled Trials (mRCT), IFPMA Clinical Trials Portal, ISRCTN Trials Register, National Research Register,
We will manage all references retrieved by the searches using the EndNote X5 software (EndNote 2011). The Systematic Review Assistant-Deduplication Module (SRA-DM) will be used to identify and remove duplications of the same references (Rathbone 2015).

Two review authors will independently screen titles and abstracts from all bibliographic records retrieved via the literature search to identify eligible studies. If it appears from the title and abstract that a study may be eligible, we will try to obtain a full text of the report to make a decision. If available, we will also obtain all errata and supplementary data for all full texts of studies eligible for inclusion. If necessary, we will translate full texts of reports that are not published in English, by employing a translation service. If we find multiple reports of the same study, we will link them together. Two review authors will independently evaluate the full texts of relevant articles according to the eligibility criteria. The review authors will not be blinded to the study data. We will resolve possible disagreement via discussion and, if necessary, by involving a third review author. We will list justifications for the exclusion of articles that were retrieved in full text. We will document the study selection process as suggested in the PRISMA statement (Liberati 2009).

Data extraction and management

Two review authors will independently extract the relevant data from the included studies. We will resolve potential discrepancies via discussion and involvement of a third author if necessary. In case of language ambiguity, we will contact researchers in the field familiar with the language in question. We will use an electronic data extraction form, including source, eligibility, methods, participants, interventions, comparators, outcomes, results and miscellaneous notes according to the Cochrane Handbook for Systematic Reviews of Interventions; Chapter 7.3 (Higgins 2011). We will also collect information on details of funding source, declaration of interests of the primary investigators and methods used to control possible conflicts of interests. Two review authors will independently pilot the form using two studies. The data extraction form will be adapted thereafter if necessary. For continuous data we will extract the mean value of the outcome measurement in each group at each time point (or, if this is not available, the mean change from baseline), the standard deviations (SDs) and the number of participants used to measure the outcome for each group.

For dichotomous outcomes we will extract the numbers of number of participants in each outcome group at each time point.

If we do not find the necessary data, we will try to complete them with the help of the primary study authors (see the section Dealing with missing data). Missing data will be derived from figures and statistics, where possible.

If the report contains only an estimate of effect size (such as a mean difference (MD) between the groups for continuous data or odds ratio (OR) or risk ratio (RR) for dichotomous data, as well as corresponding standard errors (SEs) or equivalent measures of uncertainty), then we will extract this instead. One author will enter the data into Review Manager 5 (RevMan 2014) and another author will check the data for accuracy. If we find published protocols of eligible studies, we will extract data from ongoing studies, including study name, methods, participants, interventions, outcomes, starting date, contact information and notes.

Data published only in figures/graphs will be requested from the corresponding authors. If we do not obtain original data then the
data from figures will be extracted using Plot Digitizer software (Jelicic Kadic 2016; Vucic 2015).

Assessment of risk of bias in included studies

Two review authors will independently assess the risk of bias for each study, using the Cochrane 'Risk of bias' tool according to the Cochrane Handbook for Systematic Reviews of Interventions; Chapter 8.5 (Higgins 2011). For all included studies, we will describe risk of bias both in tables and narratively in text. We will also provide an overall judgement about the included studies in the 'Risk of bias' tables and 'Risk of bias' charts. We will analyse whether there are any information addressing the appropriateness of methods used to prevent undue industry influence during the clinical trial process.

Measures of treatment effect

We will use the mean differences (MDs) or standardised mean differences (SMDs) with 95% confidence intervals (CIs) for continuous outcomes and risk ratios (RRs) with 95% CI for the analysis of dichotomous outcomes. For binary outcome measures, we will summarise data using RRs. We will consider ordinal outcomes only if we can justifiably treat them as a continuous variable or if they can be sensibly dichotomised by combining adjacent categories. Considering that there are no definite guidelines for handling these measurements, we will report on our decision, which we will reach in discussion that will involve at least two review authors.

Unit of analysis issues

The unit of analysis will be a person with dementia. We will account for any unit of analysis errors originating from the study design. For studies with multiple treatment arms, we will combine comparable groups. If it is not possible to combine the groups, we will split the 'shared' group into two or more groups with smaller sample size, and include two or more (reasonably independent) comparisons according to the Cochrane Handbook for Systematic Reviews of Interventions; Chapter 16.5.4 (Higgins 2011).

Dealing with missing data

If data from a study are missing and can not be calculated using available data and statistics, we will try to contact the trial authors to complete the data. In order to contact the authors we will make at least two contact attempts via e-mail or other potential means of contact over six weeks, checking for alternate contact information if the first attempt should fail. In the case we are unable to retrieve the complete data, we will report this in the 'Risk of bias' assessment and address missing outcomes and summary data as a source of bias in data analysis.

We will carry out analyses on an intention-to-treat (ITT) basis for all outcomes, as far as possible. If the included studies do not provide ITT data, 'on-treatment' or the data for those who complete the trial will be sought and indicated as such.

Assessment of heterogeneity

We will evaluate clinical and statistical heterogeneity in the meta-analyses using the Chi² test and double check this graphically by using forest plots. We will quantify inconsistency using the I² statistics. For the assessment of clinical heterogeneity we will analyse the data extraction tables and consider the data for between-study variability with respect to participants, interventions and outcome measurements.

Assessment of reporting biases

To minimise reporting bias we will include both published and unpublished trials. For detecting possible reporting bias, we will use a funnel plot and Egger's test for asymmetry, if there are enough (more than 10) studies available (Egger 1997). If applicable, we will compare conference abstracts and available trial protocols of included studies with published data.

Data synthesis

We will use Review Manager 5 software to perform all statistical analyses (RevMan 2014). We will analyse effects of different substances separately. We will use meta-analysis for combining data if i) there are at least two studies with an estimated treatment effect, ii) the included studies appear to have similar characteristics, iii) the studies have the same outcome measures, and iv) each study reports the necessary data. For data synthesis, we will consider all primary and secondary outcomes listed. We will perform a meta-analysis using a random-effects model. If the type of participants, interventions, comparisons and outcome measures used are very different between the studies; we will use only narrative interpretative synthesis of data for individual studies separately.

Subgroup analysis and investigation of heterogeneity

We will conduct the following subgroup analyses, if data are available:
1. dose of intervention;
2. type of dementia;
3. stage of dementia, differentiating very mild, mild, moderate and severe dementia, as defined by validated tools such as the CDR-SOB (O’Bryant 2008).

We will perform tests for heterogeneity using the Chi² test and the I² statistics within each of these groups. For each of the subgroups, if sufficient data are available, we will perform a meta-analysis using
either a random-effects model or a fixed-effect model, depending on the presence of statistical heterogeneity.

**Presentation of results - GRADE and 'Summary of findings' tables**

We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Guyatt 2011) to assess the quality of the evidence behind each of our effect estimates (high, moderate, low or very low quality). This rating indicates our confidence that the effect estimate is close to the true effect size, taking account of risk of bias, inconsistency between the studies, imprecision in the effect estimate, indirectness with respect to our outcome of interest and publication bias.

Key findings for each comparison in this systematic review will be summarised in 'Summary of findings' tables. The ‘Summary of findings’ table will present a maximum of seven key results (Schünemann 2011).

The following outcomes will be included in the ‘Summary of findings’ table:

2. Global cognitive function assessed with Mini-Mental State Exam (MMSE) (Folstein 1975).
3. Overall behavioural and psychological symptoms of dementia assessed with: NPI.
4. Any adverse event (combined).

For each outcome the ‘Summary of findings’ table, we will include the estimate of the treatment effect, the quantity of supporting evidence, and the quality of that evidence assessed using the GRADE approach (Guyatt 2011).

**Sensitivity analysis**

If appropriate, we will conduct sensitivity analyses to explore the robustness of the analyses. For meta-analyses, we will explore the differences between the fixed-effect and random-effects models. We will not impute any data in the data synthesis, therefore we will use imputation methods in the sensitivity analysis to check for possible bias from missing data. Thus we will explore any possible bias where studies were excluded from meta-analysis because of missing summary data or where data necessary for ITT analysis were missing.

**ACKNOWLEDGEMENTS**

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ADI 2016

Ahmad 2014

Ahmed 2015

APA 2013

Aso 2012

Aso 2013

Aso 2014

Baker 2003

Ballard 2006

Banwell 2016
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Beeri 2002

Brane 2001

Brusco 2008

Cabral 2009

Campbell 2007

Chen 2011

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Cummings 1994

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Folstein 1975

Galasko 1997

Gazibara 2017

Gowran 2011

Grundy 2002

Guyatt 2011

Harvey 2012

Higgins 2011

Howard 2013

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McKhann 2011

MHRA 2004

Mulder 2011

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Pertwee RG. The therapeutic potential of drugs that target cannabinoid receptors or modulate the tissue levels or actions of endocannabinoids. *The AAPS Journal* 2005;7(3):e625–54.

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Rabins 1982

Ramirez 2005
Rathbone 2015

RevMan 2014 [Computer program]

Roman 1993

Rosen 1984

Schneider 1997

Schneider 2005

Schneider 2006

Schünemann 2011

Silvestri 2013

Solas 2013

Standfield 2017

Sze 2005

Tschanz 2013

UNODC 2017

van den Elsen 2015

Van Sickle 2005

Viscomi 2009

Vucic 2015

Walther 2006

Whiting 2015

WHO 2010

WHO 2013

Woodward 2014

Wu 2013

* Indicates the major publication for the study

APPENDICES

Appendix 1. Search strategies
MEDLINE
1. "alzheimer disease"/
2. "creutzfeldt jakob syndrome"/
3. exp Dementia/
4. "dementia vascular"/
5. "kluver bucy syndrome"/
6. "lewy body disease"/
7. "pick disease of the brain"/
8. "huntington disease"/
9. "delirium"/
10. "wernicke encephalopathy"/
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. (dement* or neuroprotect*).mp.
13. alzheimer*.mp.
14. (lewy* and bod*).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
15. deliri*.mp.
16. ((cognit* or memory* or mental*) and (declin* or impair* or los* or deteriorat*)). mp
17. (chronic and cerebrovascular).mp.
18. ("organic brain syndrome" or "organic brain disease").mp
19. "supra nuclear palsy".mp.
20. ("normal pressure hydrocephalus" and shunt*).mp.
22. (cerebr* and deteriorat*).mp.
23. (cerebr* and insufficien*).mp.
24. (confusion* or confused).mp.
25. (Pick* and disease).mp.
26. (creutzfeldt or JCD or CJD).mp. 27. Huntington*.mp.
29. korsako*.mp.
30. "korsakoff syndrome"/
31. (Wernicke* and (syndrome or encephalopathy)).mp.
CONTRIBUTIONS OF AUTHORS

All authors contributed to searching the relevant literature, intellectual content, writing of the updated version of the protocol, and approved the final version of the protocol.

DECLARATIONS OF INTEREST

The review authors have no conflict of interest to declare.
SOURCES OF SUPPORT

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• No sources of support supplied

External sources

• NIHR, UK.

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