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[Intervention Review]

The medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS

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ABSTRACT

Background

The use of cannabis (marijuana) or of its psychoactive ingredient delta-9-tetrahydrocannabinol (THC) as a medicine has been highly contested in many settings.There have been claims that smoked or ingested cannabis, either in its natural form or artificial form (pharmaceutically manufactured drug such as dronabinol), improves the appetites of people with AIDS, results in weight gain and lifts mood, thus improving the quality of life.

Objectives

The objectives of this review were to assess whether cannabis (in its natural or artificially produced form), either smoked or ingested, decreases the morbidity or mortality of patients infected with HIV.

Search methods

The search strategy was conducted to July 2012 and was based on that of the Cochrane HIV/AIDS Review Group. We searched the following databases: CENTRAL/CCTR, MEDLINE and EMBASE. In addition, searching was performed where necessary of journals, reference lists of articles, and conference proceedings.

Selection criteria

The review included randomised controlled trials (RCTs) of any cannabis intervention, in any form, and administered by any route, in adults with HIV or AIDS, compared with placebo or with a known effective treatment, and conducted in a hospital, outpatient clinic, or home care setting. Quasi-randomised studies using any form of cannabis as an intervention in patients with HIV or AIDS were also included.

Data collection and analysis

Data from the eligible studies were extracted and coded independently by two researchers, using a standardised data extraction form. Data were then analysed using RevMan 5.0. No meta-analyses were performed.

Main results

A total of seven relevant studies were included in the review, reported in eight publications. All were randomised controlled studies, with four utilising a parallel group design, two a within-subject randomisation and two a cross-over design. All of the studies were of a fairly short duration, ranging from 21 days to 84 days. In only four papers (in effect, three studies) were sequence generation and allocation

concealment judged to be adequate. The use of cannabis and rapidly acting cannabinoids posed considerable challenges for blinding, as the psychoactive effects are expected to be quickly discernible to study participants, particularly those who have been previous users of such products. Dronabinol was expected to be more easily blinded. The outcomes measured were variable, including change in weight, change in body fat (measured as a percentage of total body weight), change in appetite (measured on a visual analogue scale), change in caloric intake (measured in kcals/kg/24hr), change in nausea and vomiting (measured on a visual analogue scale), change in performance (measured by Karnofsky performance score or specific tests for memory and dexterity) and change in mood (measured on a visual analogue scale).The evidence for substantial effects on morbidity and mortality is currently limited. Data from only one relatively small study (n=139, of which only 88 were evaluable), conducted in the period before access to highly-active antiretroviral therapy (HAART), showed that patients administered dronabinol were twice as likely to gain 2kg or more in body weight (RR 2.09), but the confidence interval for this measure (95% CI 0.72 - 6.06) included unity. The mean weight gain in the dronabinol group was only 0.1kg, compared with a loss of 0.4kg in the placebo group. However, the quality of sequence generation and allocation concealment in this study, in which participants were randomised by centre, could not be assessed.

Authors' conclusions

Despite dronabinol being registered by at least some medicines regulatory authorities for the treatment of AIDS-associated anorexia, and some jurisdictions making allowances for the "medical" use of marijuana by patients with HIV/AIDS, evidence for the efficacy and safety of cannabis and cannabinoids in this setting is lacking. Such studies as have been performed have been of short duration, in small numbers of patients, and have focused on short-term measures of efficacy. Long-term data, showing a sustained effect on AIDS-related morbidity and mortality and safety in patients on effective antiretroviral therapy, has yet to be presented. Whether the available evidence is sufficient to justify a wide-ranging revisiting of medicines regulatory practice remains unclear.

PLAIN LANGUAGE SUMMARY

Medical use of cannabis in patients with HIV/AIDS.

The use of cannabis (marijuana), its active ingredient or synthetic forms such as dronabinol has been advocated in patients with HIV/AIDS, in order to improve the appetite, promote weight gain and lift mood. Dronabinol has been registered for the treatment of AIDS-associated anorexia in some countries. However, the evidence for positive effects in patients with HIV/AIDS is limited, and some of that which exists may be subject to the effects of bias. Those studies that have been performed have included small numbers of participants and have focused on short-term effects. Longer-term data, and data showing a benefit in terms of survival, are lacking. There are insufficient data available at present to justify wide-ranging changes to the current regulatory status of cannabis or synthetic cannabinoids.

BACKGROUND

The use of cannabis (marijuana) or of its psychoactive ingredient delta-9-tetrahydrocannabinol (THC) as a medicine is a hotly contested issue. Those in support of its medicinal use assert that marijuana is effective in the treatment of wasting syndrome in patients with AIDS and cancer; neurological disorders such as multiple sclerosis; and glaucoma (Aggarwal 2009). A counter argument might point to the existence of effective treatments for many, if not all, of these conditions. Not unlinked to this debate is the question of the legalisation or decriminalisation of marijuana as a recreational drug. A recent re-appraisal of the harms to individuals and others in the United Kingdom associated with various substances rated cannabis as less harmful than both alcohol and tobacco (Nutt 2010). Nonetheless, the current legal status of marijuana constitutes an important philosophical obstacle to the legitimacy of its use as a medicine (Cohen 2009).

There has been much anecdotal and some scientific evidence to suggest that smoked or ingested cannabis, either in its natural or artificial (pharmaceutically manufactured drug) form improves the appetites of people with AIDS; results in weight gain; and lifts mood (Beal 1995; Struwe 1993). In these studies, the overall effect of cannabis on patients' quality of life was claimed to be positive. Indeed, cannabis countered the adverse effects of antiretroviral drugs in certain cases (Kosel 2002). These effects, and the potential positive impact cannabis may make on the lives of people with HIV/AIDS, make it worthy of further investigation. Weighing the positive and negative effects of cannabis, such as immune suppression, psychic discomfort and respiratory changes (Bloom 1987), as well as calculating dosage in relation to effect, needs to be done in a logical and scientific way, avoiding the emotive issues that have dogged the debate to date. This review aims to objectively assess the studies that have examined the medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS.

Description of the condition

Acquired immune deficiency syndrome (AIDS) is a disease caused by the human immune deficiency virus (HIV) which has a complex life-cycle in the human body. The virus is spread by sexual contact, sharing of other body fluids particularly blood (for example during the birth process, through blood transfusions and through the sharing of needs for injection drug use), and breastfeeding. The HI virus infects CD4 lymphocytes, which are lysed (broken down) by cytotoxic T cells, or undergo apoptosis, resulting in significant losses of these cells. During the (often long) latent phase of the disease, the immune system remains functional, but during the end stages of the disease (classified as AIDS), the infected individual is vulnerable to developing various opportunistic infections as well as certain types of cancers (Abdool Karrim 2010).

Description of the intervention

Cannabis sativa is a plant species which contains, among 460 known chemicals (Ben Amar 2006), the psychoactive chemical delta-9-tetrahydrocannabinol (THC). THC and other cannabinoids, both natural and synthetic as well as endogenous, bind to G protein-coupled cannabinoid receptors in the terminals of both central and peripheral neurones (CB1) and in immune cells (CB2), thus mediating the release of various neurotransmitters as well as cytokines (Elphick 2001; Mechoulam 2001).

Due to its potent psychoactive properties and potential for abuse, cannabis was removed from the United States Pharmacopeoia in 1942 (Short communication 1999), and was banned for any use in Britain and most of Europe when they adopted the United Nations' 1971 Convention on Psychotropic Substances. However, there has been a trend towards the relaxation of these rules, particularly in Canada, some states in the United States, and some European countries such as the Netherlands, where the concept of "medical marijuana" has gained some acceptance (Ben Amar 2006).

While cannabis has been used for centuries for its psychoactive properties, THC and various cannabinoid receptor agonists have been investigated as medicines for a wide range of conditions, including for the relief of pain, gastrointestinal conditions, management of atherosclerosis, inhibition of angiogenesis, relief from symptoms of multiple sclerosis, Alzheimer's and amyotrophic lateral sclerosis, relief from symptoms of Tourette's syndrome, for anxiety disorders, attention-deficit hyperactivity disorder, depression, brain injury, management of neuroleptic-associated tardive dyskinaesia, management of glaucoma, cough and cholestatic pruritis (Pertwee 2010). However, the major applications of cannabinoid agonists have been as anti-emetics and appetite stimulants. Nabilone, a synthetic cannabinoid was the first registered in 1981 for the suppression of nausea and vomiting due to cancer chemotherapy. THC itself, in the synthetic form of dronabinol, was also registered as an anti-emetic (in 1985) and later (in 1992) as an appetite suppressant in AIDS patients experiencing excessive loss of body weight. Most recently (in 2005), a combination of THC and a non-psychoactive cannabinoid, cannabidiol, has been registered for the relief of neuropathic pain in patients with multiple sclerosis and as an aid to pain relief in patients with advanced cancer (Pertwee 2010). A cannabinoid antagonist, rimonabant, was initially registered as an anti-obesity agent, but subsequently withdrawn on safety grounds.

Efficacy in relation to nausea and vomiting, appetite stimulation, and pain relief are of particular relevance to patients with HIV/AIDS. Claims have been made regarding the efficacy of cannabinoids in managing cancer chemotherapy-associated nausea and vomiting (Machado Rocha 2008) and in pain relief (Ben Amar 2006). Oral THC has been shown to be effective in retarding weight loss in patients with advanced cancer, although it is less effective than megestrol acetate (Jatoi 2002).

How the intervention might work

Cannabinoid agonists can affect mood and neurology (including pain) by inhibiting the release of a wide range of neurotransmitters at central and peripheral neurones (including acetylcholine, noradrenaline, dopamine, 5-hydroxytryptamine, gamma-aminobutyric acid, glutamate, daspartate and cholecystokinin). However, the mechanism of their anti-emetic or appetite stimulant effects, and their effect on immunology, is still not completely understood (Mechoulam 2001).

Why it is important to do this review

Although a synthetic version of THC (dronabinol) has been registered by a number of medicines regulatory authorities for the management of HIV-associated appetite loss and weight loss, there are continued demands for the legalisation of "medical marijuana".Some of the effects of cannabis seem to directly address the symptoms of HIV disease, such as loss of appetite, loss

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

OBJECTIVES

To assess whether cannabis (in its natural or artificially produced form), either smoked or ingested, decreases the morbidity or mortality of patients infected with HIV.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) of any cannabis intervention, in any form, and administered by any route, in adults with HIV or AIDS, were included. Studies could compare cannabis with placebo or with a known effective treatment, or with different forms or routes of administration of THC. Trials with within-subject randomisation or cross-over designs using any form of cannabis as an intervention in patients with HIV or AIDS were included.

Types of participants

Adults with HIV-1 or HIV-2 infection in a hospital, outpatient clinic, or home care setting.

Types of interventions

Intervention:

- Smoked marijuana
- Ingested marijuana
- Smoked hashish
- Ingested hashish
- Ingested THC (dronabinol,or any other pharmaceutically produced form)

Comparison:

- Placebo
- No drug
- Other form of cannabis

Types of outcome measures

Primary outcomes

- Mortality (HIV-related; all-cause)
- Morbidity (frequency, type and duration of episodes of opportunistic infections; malignancies; incidence of AIDS (as defined by each study); hospital admissions; and other illness types as measured in the studies)

Secondary outcomes

- Subjective experience of appetite (using self-reported scoring system such as visual analogue scale)
- Subjective experience of nausea (also using self-reported scoring system such as visual analogue scale, for number, duration and severity of episodes)
- Subjective experience of mood (using standardised questionnaires and interviews etc. or self-reported scoring system)
- Subjective experience of pain (using self-reported scoring system such as visual analogue scale)
- Subjective experience of quality of life (using questionnaires and interviews etc. or self-reported scoring system)
- Objective evidence of appetite (using recall of dietary intake and/or analysis of caloric intake, using, for example, the Nutritionist III Dine Database)
- Anthropometry and measures of body composition (e.g. weight or change in weight, body mass index, percent body fat and lean body mass, the latter calculated using skinfold thickness)
- Haematological nutrition markers (Haemoglobin, serum albumin and pre-albumin, complete blood count, glucose)
- Indices of viral load (HIV RNA copies per ml plasma)
- Markers of effect on immune system (for example absolute CD4+ counts; CD4+ percent of total lymphocytes, CD8 count)
- Cognitive function (e.g. using mental state tests)
- Respiratory function (if cannabis is smoked) (e.g. using peak expiratory flow rate)
- Effect on pharmacokinetics of anti-retroviral treatment
- Development of dependence or adverse sociological effects (using standardised interviews and questionnaires)

Outcome measures were standardised where possible.

Adverse events

- Functional assessments of learning, memory, vigilance and psychomotor performance
- Incidence of cannabis-related effects, such as anxiety, hypertension, hypotension and tachycardia, euphoria, dizziness, altered thinking.

Search methods for identification of studies

See: Cochrane HIV/AIDS Group methods used in reviews.

Electronic searches

The search strategy was based on that of the Cochrane HIV/AIDS Collaborative Review Group. This includes searches of the CENTRAL/CCTR databases in the Cochrane Library (see Appendix 1, Appendix 2 and Appendix 3), PubMed (see Appendix 4, Appendix 5 and Appendix 6), EMBASE, (see Appendix 7, Appendix 8 and Appendix 9), ClinicalTrials.gov (see Appendix 10 and Appendix 11), AEGIS (see Appendix 12), AIDsearch (see Appendix 13), Gateway (see Appendix 14), WHO ICTRP (see Appendix 15 and Appendix 16). Three searches were performed, the first on 16 November 2007, covering the period from 1980 to 2007, the second on 15 December 2010, covering the period from 2006/7 to 2010 and the third on 30 July 2012, covering the period from 2010 to July 2012.

Searching other resources

Hand searching was performed where necessary of journals, reference lists of articles, and conference proceedings (International AIDS Conference; International Conference on HIV/AIDS in Africa (ICASA); Consultative Group meetings; International Association of Physicians in AIDS Care (IAPAC); International Conference on Retroviruses and Opportunistic Infections). The

search strategy was iterative, in that references of included studies were searched for additional references. All languages were included.

Data collection and analysis

Selection of studies

Three reviewers (EL, AG and BM) independently reviewed the results of the searches to select articles for full test retrieval. These papers were assessed independently by EL, AG and BM for inclusion in the review. Any disagreements were discussed with a further reviewer (NS) and agreement reached by consensus. BM was an early reviewer but not an author of this review.

Data extraction and management

Data from the eligible studies were independently extracted and coded by EL and AG using a standardised data extraction form and entered into RevMan 5.0. Variables coded from each study included date of publication and location of study; details of study design; details of study population (e.g. age, socioeconomic status, type of HIV, antiretroviral therapy) and number of subjects; type, dosage and duration of intervention; details of which outcomes were assessed and how; duration of follow-up; and details of the analysis (adjusted or unadjusted, measures of effect).

Assessment of risk of bias in included studies

EL and AG independently examined the components of each included study for risk of bias using a standard form. This included information on the sequence generation, allocation concealment, blinding (participants, personnel and outcome assessor), incomplete outcome data, selective outcome reporting and other sources of bias. The methodological components of the studies were assessed and classified as adequate, inadequate or unclear as per the Cochrane Handbook of Systematic Reviews of Interventions (Higgins 2008). Where differences arose, these were resolved by discussions with a reviewer (NS).

Sequence generation

- Adequate: investigators described a random component in the sequence generation process such as the use of random number table, coin tossing, cards or envelops shuffling etc
- Inadequate: investigators described a non-random component in the sequence generation process such as the use of odd or even date of birth, algorithm based on the day/date of birth, hospital or clinic record number
- Unclear: insufficient information to permit judgment of the sequence generation process

Allocation concealment

- Adequate: participants and the investigators enrolling participants cannot foresee assignment, e.g. central allocation; or sequentially numbered, opaque, sealed envelopes.
- Inadequate: participants and investigators enrolling participants can foresee upcoming assignment, e.g. an open random allocation schedule (e.g. a list of random numbers); or envelopes were unsealed or nonopaque or not sequentially numbered
- Unclear: insufficient information to permit judgment of the allocation concealment or the method not described

Blinding

- Adequate: blinding of the participants, key study personnel and outcome assessor, and unlikely that the blinding could have been broken. Or lack of blinding unlikely to introduce bias. No blinding in the situation where non-blinding is not likely to introduce bias.
- Inadequate: no blinding, incomplete blinding and the outcome is likely to be influenced by lack of blinding
- Unclear: insufficient information to permit judgment of adequacy or otherwise of the blinding

Incomplete outcome data

- Adequate: no missing outcome data, reasons for missing outcome data unlikely to be related to true outcome, or missing outcome data balanced in number across groups
- Inadequate: reason for missing outcome data likely to be related to true outcome, with either imbalance in number across groups or reasons for missing data
- Unclear: insufficient reporting of attrition or exclusions

Selective Reporting

- Adequate: a protocol is available which clearly states the primary outcome as the same as in the final study report
- Inadequate: the primary outcome differs between the protocol and final study report
- Unclear: no study protocol is available or there is insufficient reporting to determine if selective reporting is present

Other forms of bias

- Adequate: there is no evidence of bias from other sources
- Inadequate: there is potential bias present from other sources (e.g. early stopping of study, fraudulent activity, extreme baseline imbalance or bias related to specific study design)
- Unclear: insufficient information to permit judgment of adequacy or otherwise of other forms of bias

Measures of treatment effect

Data analysis was conducted using Review Manager (RevMan) version 5.0.15 (2008). Outcome measures for dichotomous data (e.g. death, virologic suppression) were calculated as a relative risk with 95% confidence intervals. Where available, means were used as the unit for comparison for the following continuous outcomes. However, if the distribution of the data was not normal (for example in small studies), or medians were used for reporting, these could not be analysed in RevMan.

- Change in weight (measured in grams/kilograms/pounds/ounces)
- Change in body fat (measured as a percentage of total body weight)
- Change in appetite (measured on a visual analogue scale)
- Change in caloric intake (measured in kcals/kg/24hr)
- Change in nausea and vomiting (measured on a visual analogue scale)
- Change in performance (measured by Karnofsky performance score or specific tests for memory and dexterity)
- Change in mood (measured on a visual analogue scale).

Unit of analysis issues

As the included studies were small, with a range of 5 to 139 participants, and many did not report means but medians, most data were not analysable in RevMan. It was considered that those which did report means did so erroneously, since the sample sizes were small.

Assessment of heterogeneity

Although it was our original intention to do a meta-analysis on the included studies, this was not possible because the outcomes measured by the studies were too different, because insufficient data was supplied in the study articles and because measurements were often expressed in terms of medians, which could not be used in RevMan.

Data synthesis

Data could not be synthesized because of the different outcomes and different measurement of these outcomes used in the included studies.

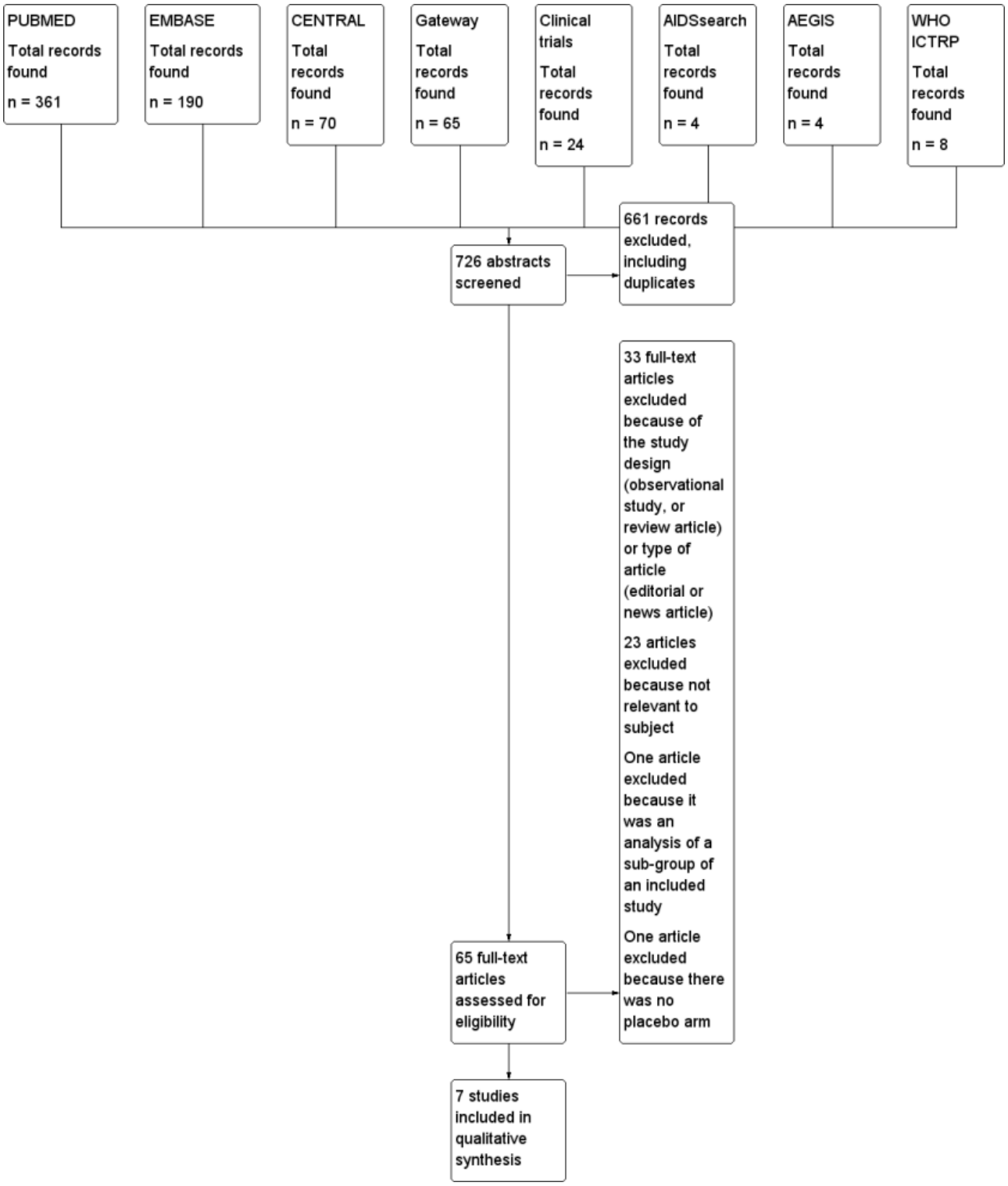
RESULTS

Description of studies

Results of the search

The search strategy found 726 potentially relevant references which were screened (see Figure 1). 661 of these abstracts (including duplicates) were excluded and 65 full text articles were retrieved; of those that we retrieved, 33 were excluded because they were not randomised controlled trials and 23 because they were not relevant to the subject. The reasons for exclusion of two possibly relevant reports of randomised controlled trials are summarised in the Characteristics of excluded studies table. The seven remaining randomised controlled trials met our inclusion criteria and are described in detail in the Characteristics of included studiestable.

Figure 1. Flow diagramme depicting screening process.



Included studies

Eight studies were included in this review, although one study (Kosel 2002) provided a subset of data from another included study (Abrams 2003). All were randomised controlled studies, but whereas four were parallel groups of individuals assigned to intervention or placebo groups, two (Haney 2007, Haney 2005) used within-subject randomisation, applying the same interventions in a staggered design to all participants and two (Ellis 2009, Struwe 1993) used a cross-over design. In all studies, participants were adults infected with HIV, but in some these

were healthy participants (Haney 2007, Abrams 2003, Kosel 2002) whilst in others participants were ill with AIDS (Haney 2005, Beal 1995, Struwe 1993). In two studies, patients had HIV-associated sensory neuropathy but no other symptoms or signs of AIDS (Ellis 2009, Abrams 2007). Whilst most studies compared both smoked marijuana and ingested dronabinol with placebo (Haney 2007, Haney 2005, Abrams 2003, Kosel 2002), four compared only one form of cannabis: Ellis 2009 and Abrams 2007 compared smoked marijuana with placebo, whilst Beal 1995 and Struwe 1993 compared ingested dronabinol with placebo. One study was conducted on an in-patient basis (Abrams 2003, Kosel 2002) but in others participants were outpatients who came into the hospital setting for interventions and measurements (Ellis 2009, Haney 2007, Haney 2005, Beal 1995, Struwe 1993) and in one there was both an inpatient and an outpatient phase (Abrams 2007). The duration of the studies ranged from 21 days (Abrams 2007, Abrams 2003, Kosel 2002), 28 days (Haney 2005) to 35 days (Ellis 2009) 42 days (Haney 2007, Beal 1995) and 84 days (Struwe 1993).

Excluded studies

Timpone 1997 investigated the safety and pharmacokinetics of dronabinol and megestrol acetate, alone and in combination, in patients with wasting due to AIDS. The effect of the drugs on weight gain was also investigated. Although this study originally seemed appropriate for inclusion in this review, it was ultimately excluded because there was no placebo arm.

Riggs 2012 was a sub-group analysis (7 patients) from Ellis's trial (Ellis 2009). The endpoints of the study were the hormones ghrelin, leptin, peptide YY and insulin, which are not measures of morbidity and mortality and so this study was excluded from this review.

Risk of bias in included studies

For a summary of the risk of bias across all included studies see Figure 2. For a summary of each of the risk items within individual studies see Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

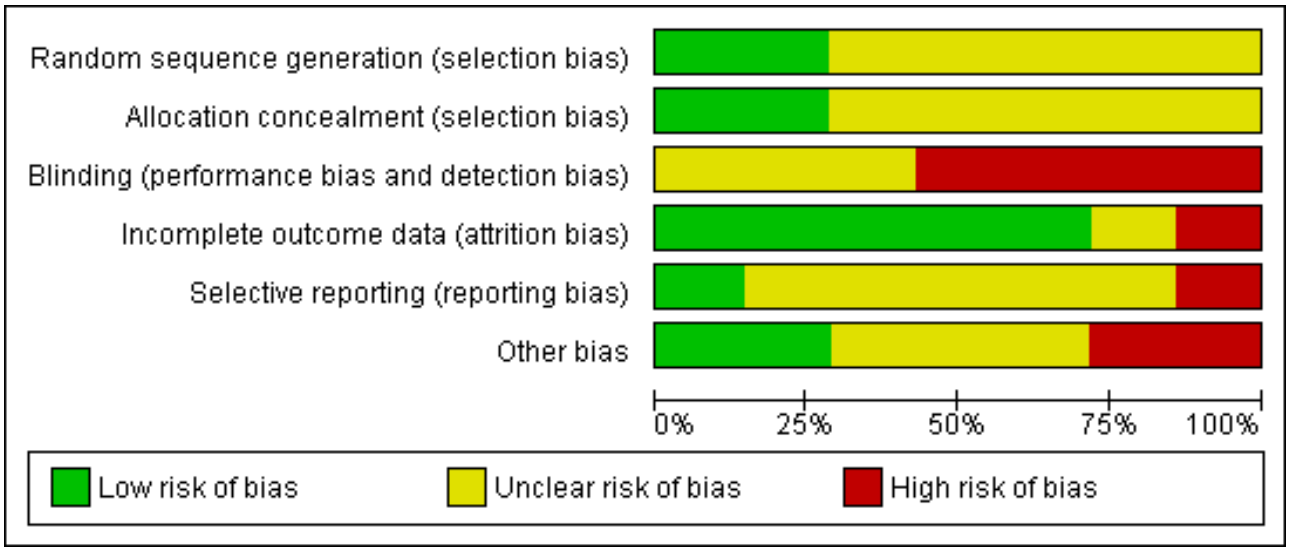
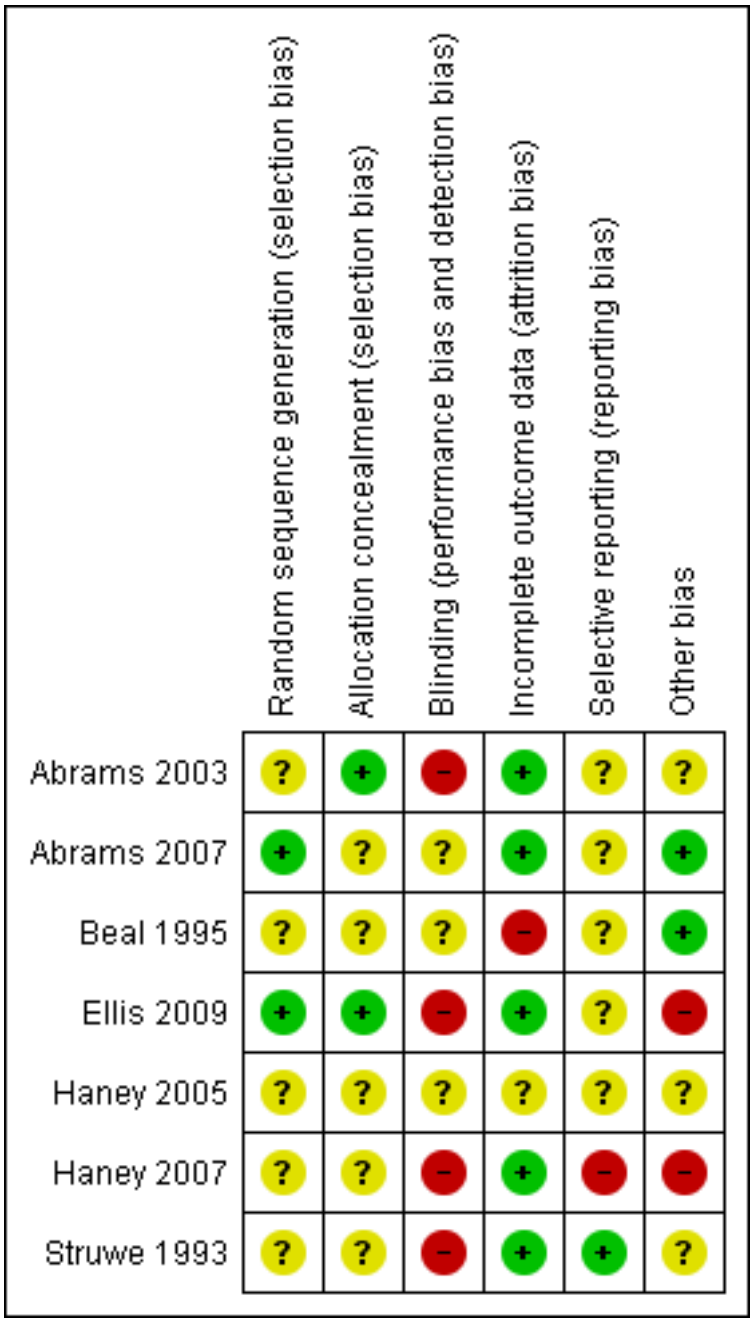


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Sequence generation was judged to be adequate in four studies (Ellis 2009, Abrams 2007, Abrams 2003, Kosel 2002) and unclear (because of insufficient description given) in four others (Haney 2007, Haney 2005, Beal 1995, Struwe 1993). In those where sequence generation was adequate, the randomisation procedure was generated by a study statistician.

Allocation concealment was again judged to be adequate in four studies (Ellis 2009, Abrams 2007, Abrams 2003, Kosel 2002) where the study pharmacist maintained the sequence in a secure location and where all participants were allocated to their groups on the same day of the study. In Haney 2007, Haney 2005, Beal 1995 and Struwe 1993, insufficient detail was given, leading to a judgement of "unclear".

Blinding

Blinding was well done in almost all the studies, with considerable effort undertaken to ensure that active and placebo cigarettes and capsules were identical. However, Struwe 1993 judged their own study to be incompletely blinded because of the "high" that patients were able to associate with active drug. Similarly, Ellis 2009 asked their participants to guess to which treatment they had been assigned, and the majority guessed correctly once they had passed through the active intervention stage. Since this is likely to have occurred in other studies, it is questionable whether the external

efforts at blinding in any of the studies (identical capsules and cigarettes for example) would have been sufficient to effectively blind participants to the recognisable drug effects.

Incomplete outcome data

In seven studies (Ellis 2009, Abrams 2007, Haney 2007, Haney 2005, Abrams 2003, Kosel 2002, Struwe 1993), attrition and exclusions were well described for all study arms and reasons for these unlikely to be related to study outcomes. However, in one study (Beal 1995), there was a significant number of exclusions from the study due to protocol violations (13 of 88 participants) and of these, 10 were the use of marijuana by participants in the placebo group. These participants were considered "inevaluable" and results for most study outcomes were presented separately for all and for "evaluable" patients. In this study, the reporting of outcomes data was considered to be inadequate.

Selective reporting

In all studies except one, this was considered to be adequate with all expected outcomes reported on. In Haney 2007, the ability of participants to identify placebo marijuana cigarettes was not reported on.

Other potential sources of bias

Three studies were considered to have a possible source of bias. In Haney 2007 and Haney 2005, this was because participants were allowed to use marijuana outside of study time (although in Haney 2005 use of both alcohol and marijuana were prohibited in the 24 hours prior to intervention and measurement, and biological tests (breath and urine tests) were performed to confirm this). However, the duration of the effects of cannabis in the body may extend beyond this 24 hour period and may have diluted the results of this study by reducing the effect size of the cannabinoids. In Struwe 1993 large numbers of eligible patients refused to participate in the study because they would have to forego marijuana for the 5 week placebo period. Having experienced beneficial effects of the drug, they were unwilling to do this. Thus this study may have selected out participants who would have shown a benefit from the cannabis intervention.

Effects of interventions

Only those outcomes are reported on for which data was available.

Change in weight (measured in grams/kilograms/pounds/ounces)

It was not possible to analyse results from two of the studies which reported on this outcome, because insufficient data was provided in the study articles. In Haney 2007, F values are given, and in Abrams 2003 and Struwe 1993, the medians were given but no standard deviations. Thus the results are presented as described by the individual study articles.

Haney 2007 found that the weights of participants on higher strength marijuana (3.9%) and higher doses of dronabinol (10mg) significantly increased (p<0.01) in comparison with those on lower doses.

Abrams 2003 found, as a secondary outcome of their study, that participants using dronabinol or marijuana gained significantly more weight than those in the placebo group. Those using marijuana gained a median of 3.0kg (range -0.75 to 0.86kg; p = 0.021), those using dronabinol gained a median of 3.2kg (range -1.4 to 7.6kg; p = 0.004) whilst those in the placebo group gained a median of 1.1kg (range -1.4 to 5.2kg). Most of the weight gained in all groups was characterised as fat mass, on the basis of dual-energy X-ray absorptiometry.

In Struwe's study (Struwe 1993), although all five participants gained weight whilst receiving dronabinol and 3 lost when receiving placebo, the differences were not statistically significant (median gain of 0.5kg versus median loss of 0.7kg from baseline).

In Beal 1995where change in weight was one of the primary outcomes of the study, there was no difference in weight gain between the intervention (dronabinol) and control groups. In this study, evaluable patients who remained in the study in the dronabinol arm gained a mean of 0.1kg, whilst those who remained in the study in the placebo arm lost a mean of 0.4kg (p = 0.14). In the same study, the proportion of patients who gained 2kg in the dronabinol group was not significantly different from the proportion in the placebo group (88 evaluable patients, one study, Analysis 1.3).

Change in body fat (measured as a percentage of total body weight)

Again, it was not possible to analyse the results from the study in which this outcome was studied (Struwe 1993), because only the median was reported on as a result of the very small sample size (5 patients). Thus the results as described by the study article are presented. Struwe 1993 found that patients receiving dronabinol gained 1.0% body fat (range -0.6 to 1.9), versus a 0.06% gain in patients receiving placebo (range -1.4 to 1.6) (p = 0.04).

Change in appetite (measured on a visual analogue scale)

Insufficient information from the relevant studies prevented analysis of this data. For example, Beal 1995 presented only the mean but no standard deviation, Struwe 1993 provided a median due to the small sample size, and Haney 2005 did not provide data on appetite per se but on related symptoms such as dry mouth. Although in Struwe 1993, participants experienced increased appetite whilst on dronabinol treatment compared to placebo, this difference was not statistically significant. On the other hand Beal 1995 reported that patients in the dronabinol arm of the study experienced significantly greater increases in appetite (37% on visual analogue scale) than those in the placebo arm (17% on visual analogue scale) (p = 0.05) (analysis on all patients). Although the measurement of difference in appetite was a stated objective of Haney 2005, it was reported on in the form of caloric intake rather than as appetite *per se*.

Change in food and caloric intake (measured in kcals/kg/24hr)

It was not possible to analyse data from the studies which reported on this outcome. Haney 2007 and Haney 2005 provided only F-values in the text and figures from which values could not be determined, and Struwe 1993 reported medians only with no standard deviations. Therefore results as reported by study articles are presented here. Haney 2007 reported that marijuana and higher doses of dronabinol significantly increased the number of daily eating occasions (p<0.005 and p<0.01 respectively), as well as the total calories consumed per day (p<0.005 for higher doses of marijuana and dronabinol and p<0.01 for lower doses). Haney

2005 reported that participants with significant weight loss due to HIV receiving marijuana or dronabinol consumed significantly more calories than those receiving placebo (p < 0.01 for both interventions). However, caloric consumption in participants with HIV who were of normal weight was not affected by cannabinoids. Similarly, although median daily caloric intake when participants received dronabinol was 3.48kcal/kg versus 0.84kcal/kg when they received placebo (Struwe 1993), this difference was not statistically significant.

Change in nausea and vomiting (measured on a visual analogue scale)

In the only study that reported on nausea and vomiting, Beal 1995 reported a significant decrease in nausea and vomiting in those participants receiving dronabinol compared to those receiving placebo (RR 4.96, 95% CI 1.51 to 16.27, 139 participants, one study, Analysis 1.2).

Change in performance (measured by Karnofsky performance score or specific tests for memory and dexterity)

Again, results as reported by individual study articles are presented because of insufficient information supplied for an independent analysis.

Haney 2007 reported that neither marijuana or dronabinol (of any strengths or concentrations) significantly affected performance on any tasks, which included measures of learning, memory, vigilance, psychomotor ability.

Haney 2005 reports that in the low Bioelectrical Impedance Analysis (BIA) group, 20mg dronabinol produced small but significant decreases in the number of digit symbol substitutes entered correctly (p < 0.01) and in the maximum speed attained in Divided Attention Task (p < 0.01). In the normal BIA group, dronabinol (30mg) decreased the number of 7 digit numbers entered correctly in digit recall task (p < 0.01). There were no changes in word recall or recognition for either group.

Beal 1995 reports that for all patients, the Karnofsky performance score decreased by 2.5 points in the dronabinol group vs no change in the placebo group (p = 0.18). In evaluable patients, the score decreased by a mean of 1 point in dronabinol patients and increased by 0.3 points in placebo patients (p = 0.07).

Change in mood (measured on a visual analogue scale)

Beal 1995 reports that, in the dronabinol group, mood improved by the end point in 7% of patients and in the placebo group in 2% (p = 0.14). for evaluable patients, mood improved by 10% in the dronabinol group and declined in the placebo group y 2% (p = 0.06). In the RevMan Analysis 2.1, 0f all 139 patients in this study, cannabinoids were associated with an improvement in mood but this was not statistically significant (p = 0.16) (RR4.96, 95% CI 1.51 to 16.27; 139 participants, one study, Analysis 1.1).

Subjective experience of drug effects

Haney 2007 reported that "Ratings of 'good drug effect', 'high', and ‘mellow’ were significantly increased by dronabinol (10 mg) and both active marijuana doses (2.0%, 3.9% THC; P , 0.005). Both active marijuana doses also increased ratings of 'stimulated', ‘friendly', and 'self-confident’ (P < 0.005). Only dronabinol (10 mg) increased ratings of ‘can’t concentrate' (P < 0.01), whereas only the lower strength marijuana cigarette (2.0%) increased ratings of ‘anxious'."

In Haney 2005, "active marijuana increased ratings of good drug effect (2.8, 3.9% THC), strength (2.8,3.9% THC), liking (3.9% THC), and desire to smoke again (3.9% THC) compared with placebo in the low BIA group (p<0.01; data not shown). These same ratings were increased by each active marijuana cigarette condition in the normal BIA group (p<0.001; data not shown). On the Capsule Rating Form, ratings of capsule strength were significantly increased by the highest dose of dronabinol in the low (p<0.01; data not shown) but not in the normal BIA group".

Effect on peripheral neuropathy

Abrams 2007 reported that 13/25 intervention participants had a greater than 30% reduction in pain from baseline to the end of treatment vs 6/25 placebo participants (52% vs 24%, p = 0.04). Median decrease in chronic neuropathic pain in daily diary VAS was 34% in the intervention group vs 17% in the placebo group (p = 0.03 (Mann-Whitney test).

Ellis 2009 found also that pain reduction with cannabis was significantly greater than that with placebo. During the active cannabis week, the proportion of subjects achieving pain reduction of 30% or more was 0.46 (95% CI 0.28, 0.65) whilst in the placebo week it was 0.18 (0.03, 0.32) (p=0.043). Using a different pain rating from that of Abrams 2007. Ellis 2009 also found that the median difference in pain reduction between active intervention and placebo was 3.3 DDS points, with an effect size of 0.60, p = 0.016.

It was not possible to combine data from these studies, as different pain scales were used.

Effect on pharmacokinetics of protease inhibitors

In Kosel 2002 (results from the same study as Abrams 2003) the primary end points were the steady-state pharmacokinetics of IDV, NFV and M8, including area under plasma concentration time curve to 8 hours (AUC8), maximum concentration (Cmax) and minimum concentration (Cmin). Cannabinoid pharmacokinetics were also investigated, to characterize differences in plasma concentrations between forms of administration. AUC6 hours was primary measurement for delta-9-THC; secondary measurements were Cmax and time to maximum concentration.

For IDV: most evident changes occurred in the marijuana arm: there was a significant decrease of -14% (p = 0.039) in Cmax. A similar decrease of -14.5% (p = 0.074) in AUC8 approached statistical significance. There was a modest decrease in Cmin of 33.7% (p = 0.65) perhaps because of large interpatient variability; this was not statistically significant. No significant changes detected for oral dronabinol arm.

NFV: There were similar decrease in Cmax, Cmin and AUC in the marijuana arm although these were not statistically significant. Cmax -17.4 (p = 0.46), AUC8 -10.2% (p = 0.15); Cmin -12.2% (p = 0.28). No changes detected for oral dronabinol arm.

The authors concluded that these minor changes in Cmax, Cmin and AUC8 were unlikely to be clinically significant for either IDV or NFV.

Effect on viral load and CD4 count

In Abrams 2003, there was no significant difference in viral load between the marijuana, dronabinol and placebo groups (adjusted mean difference of marijuana group from placebo group in log 10 copies per mL: -0.06 (-0.26 to 0.13) and adjusted mean difference of dronabinol group from placebo group in log 10 copies per mL: -0.07 (-0.24 to 0.06).There was however a significant difference in CD4 count between both the marijuana and dronabinol groups and placebo on day 21, based on repeated measures at four time points. For the marijuana group, the relative change in CD4 counts from baseline compared to placebo was 16 (2 to 33; p = 0.025) and for the dronabinol group, this was 14 (-1 to 32; p = 0.064). The relative change in CD8 counts, measured in the same way, for the marijuana group compared to placebo was 20 (4 to 42; p = 0.016) and for the dronabinol group was 10 (-3 to 32; p = 0.15).

Physiological measures (look at other studies for these)

Resting heart rate was significantly increased by both marijuana and dronabinol at all concentrations and doses (except for the lower dose of dronabinol which did not have a significant effect in the morning). Skin temperature was increased by high dose marijuana in the morning (p<0.01) and by both doses of marijuana in the afternoon (p<0.01) (Haney 2007).

Adverse events

In three studies, no participants were withdrawn due to adverse events (Abrams 2007: Haney 2005; Abrams 2003). In one study, adverse events were not reported on (Haney 2007). The following adverse events were described in the remaining studies:

Ellis 2009: One subject was withdrawn from the study due to an acute, cannabis-induced psychosis, and another was withdrawn due to an intractable, smoking-related cough. The authors note that more non-treatment limiting side effects were experienced with cannabis than with placebo. These included "concentration difficulties, fatigue, sleepiness or sedation, increased duration of sleep, reduced salivation and thirst."

Beal 1995: 43% of patients receiving dronabinol and 13% of those receiving placebo experienced adverse events (p<0.001). 8.3% of these were severe in the dronabinol group, compared to no severe adverse events in the placebo group. All resolved on reducing or stopping study medications. There was no difference in the drop out rate between the two arms (p=0.29).

Struwe 1993: Of the 12 patients eligible for this study, 2 withdrew early because of intolerance of cannabis (mood-altering effects and sedation). In the five patients who completed the study protocol, no treatment-limiting adverse events were reported.

DISCUSSION

Summary of main results

Despite the widespread popular acceptance of the efficacy of cannabis and cannabinoids as anti-emetics and appetite stimulants in patients with HIV/AIDS, the evidence for substantial effects on morbidity and mortality is slim. Data from only one study (Beal 1995) were amenable to further analysis in this review; the results of the remaining studies were only presented as they were reported in original articles. This relatively small study (n=139, of which only 88 were evaluable), conducted in the period before access to highly-active antiretroviral therapy (HAART), showed that patients administered dronabinol were twice as likely to gain 2kg or more in body weight (RR 2.09), but the confidence interval for this measure (95% CI 0.72 - 6.06) included unity. The mean weight gain in the dronabinol group was only 0.1kg, compared with a loss of 0.4kg in the placebo group. However, the quality of sequence generation and allocation concealment in this study, in which participants were randomised by centre, could not be assessed. Interestingly, this was the primary evidence used by the FDA when registering dronabinol for the treatment of AIDS-associated anorexia.

Overall completeness and applicability of evidence

All the studies included were of short duration and in populations that could be expected to vary considerably in HIV staging. Specifically, it is not clear to what extent the symptoms treated were reflective of the pre-HAART era, before access to effective triple antiretroviral therapy became more widely accessible. Where data on interactions with antiretrovirals (Kosel 2002) or the effect on HIV-related clinical parameters, such as CD4 counts or HIV RNA levels (Abrams 2003) were presented, these were of such short duration as to make interpretation of any effects uncertain. None of the studies included were able to measure such hard endpoints as progression to AIDS or AIDS-related mortality. The short duration of the studies also precluded extensive documentation of safety issues. The side effects noted were those expected of this class.

Quality of the evidence

Although all eight studies included (which represented seven separate studies) were randomised controlled studies, in only four papers (in effect, three studies) were sequence generation and allocation concealment judged to be adequate (Abrams 2003 , Kosel 2002, Abrams 2007, Ellis 2009). Cannabis and rapidly acting cannabinoids pose considerable challenges for blinding, as the psychoactive effects are expected to be quickly discernible to study participants, particularly those who have been previous users of such products. Dronabinol is expected to be more easily blinded, as peak effects are only seen after 120 minutes.

Potential biases in the review process

Comprehensive searches of journal and conference databases, including all languages, were conducted. Data extraction and the assessment of the methodological quality were done by at least two researchers, which minimised potential bias in the review. Extracting data from the report of the complex within-subject, staggered, double-dummy design used by Haney 2007 and Haney 2005 was very difficult and precluded the pooling of data from these studies. This limited the contribution of these trials to possible meta-analysis and the findings of this review. Many of the outcomes investigated in the trials were subjective in nature; given that blinding is unlikely to have been effective in these trials, our confidence in these subjective outcomes was low. This in itself is a subjective judgement however and another researcher may have felt differently.

Agreements and disagreements with other studies or reviews

As no head-to-head comparative studies with effective anti-emetics were included, this review could not confirm the "superiority" claimed by Machado Rocha 2008 in respect of the efficacy of

cannabinoids in chemotherapy-induced nausea and vomiting. In Machado Rocha's review, meta-analysis of five studies showed that dronabinol was significantly more efficacious than neuroleptic drugs, in terms of anti-emetic efficiency (n = 325; RR = 0.67; CI = 0.47–0.96). However, other meta-analyses of the same review showed no superiority of dronabinol over placebo, and no superiority of either nabilone or levonantradol over neuroleptics, in terms of anti-emetic efficiency. As in this review, the authors urged caution in the interpretation of their results, due to the small number of included trials and the small sample size of most trials (most trials had fewer than 50 patients). A further area of agreement with Machado Rocha's review and this review is that of the difficulty of blinding patients in trials involving cannabinoids. This, in combination with the fact that most patients in Machado Rocha's review preferred cannabinoid drugs to the controls, suggests that patients themselves might have been biased in their assessment of the efficacy of the drugs.

AUTHORS' CONCLUSIONS

Implications for practice

Despite dronabinol being registered by at least some medicines regulatory authorities for the treatment of AIDS-associated anorexia, and some jurisdictions making allowances for the "medical" use of marijuana by patients with HIV/AIDS, evidence for the efficacy and safety of cannabis and cannabinoids in this setting is lacking. Such studies as have been performed have been of short duration, in small numbers of patients, and have focused on short-term measures of efficacy. Long-term data, showing a sustained effect on AIDS-related morbidity and mortality and safety in patients on effective antiretroviral therapy, has yet to be presented. The available evidence is not sufficient to justify a wide-ranging revisiting of medicines regulatory practice.

Implications for research

The means to conduct larger, longer-duration, appropriately blinded and randomised studies of cannabis and cannabinoids in patients with HIV/AIDS are available and such studies should be conducted. However, as a source of data that is easier to collect, consideration should also be given to gathering observational data from cohorts of users of "medical marijuana" in settings where such use is allowed.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abrams 2003

Methods	Randomised, placebo controlled study comparing the short term effects of smoked marijuana and ingested dronabinol on HIV viral load (HIV RNA levels) CD4 and CD8 counts. Duration: 21 days. Second paper arising from this study (Kosel et al 2002):Investigated effects of cannabinoids on pharmacokinetics of IDV, NFV.
Participants	Number enrolled:62 participants eligible for primary end point. Inclusion criteria: Patients with documented HIV-1 infection, of 18 years and older on a stable ARV regimen of indinavir and nelfinavir for a minimum of 8 weeks prior to the study, Stable viral load (defined as a less than three fold (0.5 log 10) Exclusion criteria: active opportunistic infection, malignant condition requiring acute treatment, loss of 10% or more of body mass in the 6 months prior to the study, current substance dependence; history of serious pulmonary disease; pregnancy; stage II or higher AIDS dementia complex; haematocrit less than 0.25 or hepatic AST more than five times the upper limit of normal; concurrent use within 8 weeks prior to enrollment of anabolic hormones, prednisone, interleukin 2, or any other agents known to change immune function.
Interventions	3.95% THC marijuana cigarette or 2.5mg dronabinol capsule or placebo capsule, all taken three times per day before meals.
Outcomes	HIV RNA levels, CD4 and CD8 cell counts, and pharmacokinetic analyses of protease inhibitors (reported in Kosel et al) (see page 263 Table 2 and 264 Table 3). For Kosel (2002) Primary end points were the steady-state pharmacokinetics of IDV, NFV and M8, including area under plasma concentration time curve to 8 hours (AUC8), maximum concentration (Cmax) and minimum concentration (Cmin). Also looked at cannabinoid pharmacokinetics to characterize differences in plasma concentrations between forms of administration. AUC6 hours was primary measurement for delta-9-THC; secondary measurements were Cmax and time to maximum concentration.
Notes	Same study as reported on in Kosel (2002).. Limitation of study: study was of very short duration (21 days) and it is unlikely that changes in viral load and CD4 and CD8 counts would have occurred within this short time

Risk of bias

Abrams 2003 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were stratified by protease inhibitor then "allocated with equal probability in blocks of 12 to the study regimens (marijuana, dronabinol or placebo)." However, although the statistician generated the random allocation sequences: the mechanism of generating this sequence was not described.
Allocation concealment (selection bias)	Low risk	Pharmacists maintained the sequence in a secure location and distributed assignments to study co-ordinator on day 0 (all participants randomised on the same day so no need to keep allocation concealed from anyone for longer).
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was adequately done for those assigned to the oral regimens: participants were “randomly assigned in a double blind fashion to the oral regimens” and placebo and active drugs looked identical. However, it was not stated how blinding of staff was done, and marijuana smokers could not have been blinded as there was no placebo cigarette.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Flow of participants well described in Figure 1 page 261. Total of 603 assessed for eligibility; 67 randomly assigned; 5 patients dropped out or were excluded from analysis; attrition and exclusions well described for both arms and and unlikely to be related to outcomes.
Selective reporting (reporting bias)	Unclear risk	Protocol for study not available (although there is one protocol available at http://www.maps.org/mmj/abrams2.shtml, accessed on 03/08/2010, this is not the most recent protocol for the study because it describes a different methodology with different patient numbers).
Other bias	Unclear risk	Study very short - not necessarily enough time to cause clinically important changes. Need longer studies. For Kosel 2002: There was no smoking placebo. Smoking itself can induce the cytochrome p450 enzymes (thought to be mechanism for pharmacokinetic changes).

Abrams 2007

Methods	Randomised, placebo controlled study to determine the effect of smoked cannabis on the neuropathic pain of HIV-associated neuropathy and an experimental pain model. Duration: 7 day outpatient pre-intensive phase, 2 day inpatient lead in phase, 5 day inpatient intervention phase, 7 day outpatient post intervention phase. Participants smoked one study cigarette three times per day on study days.
Participants	Number enrolled: 50 participants. Inclusion criteria: Adults with HIV-1 infection and symptomatic HIV sensory neuropathy, with an average daily pain score of at least 30mm on 100mm visual analogue scale (VAS). Other inclusion criteria: stable health, without concurrent substance abuse, and following a stable medication regimen for HIV and for pain for at least 8 weeks prior to enrollment in the study. Also prior experience of smoking cannabis (defined as at least 6 times in a lifetime). Exclusion criteria: family history of polyneuropathy, neuropathy due to causes other than HIV or ddis; use of isoniazid, dapsone, or metronidazole, in the 8 weeks prior to enrollment in the study.

Abrams 2007 *(Continued)*

Interventions	Placebo and cannabis cigarettes, identical in appearance, weighing on average 0.9g. Active cannabis cigarettes contained 3.56% delta-9-THC. Cigarettes were kept in a locked and alarmed freezer, and re-hydrated overnight in a humidifier.
Outcomes	Ratings of chronic pain and percentage of participants achieving more than 30% reduction in pain intensity. Primary outcome: Daily diary pain visual analogue scale, started in OPD pre-intervention phase, continued through post-intervention phase. Secondary outcomes: Ratings of chronic neuropathic pain: visual analogue scale Other assessments of effect of cannabis on pain: Long thermal stimulation (LTS) procedure Heat/capsaicin heat sensitization model Safety
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“Randomisation (1:1) was computer-generated by study statistician and managed by independent research pharmacist”. Both arms were similar in terms of demographics, suggesting that randomisation had been successful.
Allocation concealment (selection bias)	Unclear risk	Although all patients were allocated to their groups on the same day, therefore lower risk of investigators changing pattern of allocation, there was no description of how this allocation was done.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	It was stated that the study was double-blind, and the appearance of cigarettes was identical, with the active cigarettes containing 3.56% delta-9-THC, and the placebos containing 0%. Although it is assumed that the patients and the staff administering the cigarettes were the ones who were blinded, this is not clearly said. Also, because the "high" associated with smoking marijuana is impossible to disguise, it is likely that participants were aware of their allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	“Modified, intent-to-treat sample”. 223 participants were assessed for eligibility, 55 randomised (Table 2 page 517). Attrition fully explained for both arms, unlikely to be related to outcomes with equal numbers and equal reasons for attrition on both sides.
Selective reporting (reporting bias)	Unclear risk	No full version of the protocol was found, although short summaries are available at http://clinicaltrials.gov/show/NCT00046722. Therefore a complete judgement on this criterion could not be made.
Other bias	Low risk	Study is free of other sources of bias.

Beal 1995

Methods	Multi-centre, double blind, placebo controlled parallel group study.

Beal 1995 *(Continued)*

	Duration: 6 weeks.
Participants	Number enrolled: 139 participants. Inclusion criteria: HIV infected adults with at least one AIDS defining event according to 1987 CDC definition; loss of at least 2.3kg of normal body weight; ability to feed oneself and consume a normal diet. Participants were allowed to take their ARVs if they had tolerated them for at least 4 weeks prior to enrollment and had been on the same dose for at least 2 weeks before the start of the study. Exclusion criteria: acute infections, diabetes mellitus, candida oesophagitis, ascites, pleural effusion, oedema, uncontrolled diarrhoea, dementia and/or biliary or pancreatic or GI obstruction. Megesterol acetate, tube feeding and corticosteroids were not allowed during the study. Patients who had used marijuana within the 30 days prior to the study were not eligible. Patients agreed not to use marijuana throughout the course of the study.
Interventions	Treatment arm: capsules containing 2.5mg dronabinol (marinol) bd one hour before lunch and one hour before supper. Placebo: identical capsules containing no dronabinol, taken according to t he same schedule. If participant could not tolerate 2.5mg bd, could take 2.5mg daily.
Outcomes	Change in appetite as measured by visual analogue scale 100mm with 0 = no appetite and 100 = opposite. Measured at baseline and 3 days weekly at home throughout the study. Mood, nausea and vomiting measured the same way. Changes in Karnofsky performance status score also measured. Adherence assessed by testing urinary cannabinoids. Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Although one arm of the study was allocated to an identical placebo capsule, blinding per se was not described. Also, 10 of 13 patients allocated to placebo used marijuana outside the study, presumably because they no longer experienced the beneficial effects of the drug while on placebo. This implies that the drug effects made patients aware of whether they were receiving the active intervention or placebo.
Incomplete outcome data (attrition bias) All outcomes	High risk	There were difference in reasons for exclusion in dronabinol vs placebo arms. 404 patients assessed for eligibility, 221 considered eligible and 139 enrolled. 72 assigned to dronabinol group and 67 to placebo group. No statistically significant difference between groups. However, only 88 of 139 patients enrolled were evaluable. The single most common reason for this was presence of cannabinoids in urine of placebo group - this accounted for 10 of 13 protocol violations. 6 patients on dronabinol and 3 on placebo discontinued because of drug toxicity. There were 50 evaluable patients in the dronabinol group and 30 in the placebo group and 13 protocol violations in the placebo group and one in the dronabinol group.

Beal 1995 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Study protocol not available.
Other bias	Low risk	

Ellis 2009

Methods	Single group, double blind, placebo controlled, crossover study. Duration: 7 weeks. There were 5 study periods over the 7 week study duration: a one week wash-out followed by 5 days of intervention or placebo, a further 2 weeks wash out followed again by 5 days of intervention or placebo administration. There were 4 daily smoking sessions during each intervention week; smoking sessions were separated by intervals of 90 - 120 minutes.
Participants	Number enrolled: 34 Inclusion criteria: Adults "with documented HIV infection, neuropathic pain refractory to at least two previous analgesics, and an average score of 5 or higher on the pain intensity sub-scale of the Descriptor Differential Scale (DDS)." Exclusion criteria: Current substance use disorders, "lifetime history of dependence on cannabis, ...previous psychosis with or intolerance to cannabinoids,...concurrent use of approved cannabinoid medications,...positive urine toxicology screen for cannabinoids,... and serious medical conditions that might affect participant safety or the conduct of the study." Also evidence of alcohol or other drug dependence in the 12 months prior to the study, and evidence of ongoing use of non-prescribed recreational drugs.
Interventions	Cannabis cigarettes with strengths ranging from 1% to 8% delta-9-THC concentration by weight. Placebo cigarettes were made from whole plant material with cannabinoids removed. Patients followed the smoking cues of the study nurse.
Outcomes	Change in self reported pain magnitude assessed by the Descriptor Differential Scale; subjective assessment of pain experience on visual analogue scale; clinical assessments including disability, mood and quality of life, safety assessments including chest x rays, ECG, blood chemistry, viral load, CD4 counts, urine toxicology.
Notes	The study was conducted on an outpatient basis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was done by a research pharmacist using a random number generator.
Allocation concealment (selection bias)	Low risk	"The key to study assignment was withheld from investigators until completion (of) statistical analysis."
Blinding (performance bias and detection bias) All outcomes	High risk	Great efforts were made to ensure that both study participants and investigators were blinded. Placebo cigarettes were "made from whole plant material with cannabinoids removed and were identical in appearance to active cigarettes." However, study participants were able to guess accurately their allocation, thus nullifying the attempts at blinding.
Incomplete outcome data (attrition bias)	Low risk	The drop out rate of 18% was higher than expected but the study authors accounted for all participants who left the study. Intention to treat analysis.

Ellis 2009 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Study protocol not available.
Other bias	High risk	Overall there was a high risk of bias in this study. The fact that a high percentage of participants had used marijuana in the past, means that their expectations of the intervention were that it would be beneficial. Added to the fact that the majority of participants correctly guessed their study assignments, it is very difficult to objectively assess the benefit of cannabis in this study.

Haney 2005

Methods	Within-subject randomisation; staggered, double-dummy design. Aimed to compare dronabinol (0, 10, 20 30mg per os) and marijuana (0.0, 1.8, 2.9 and 3.9% delta-9-THC) in two samples of HIV positive marijuana smokers - those with (n = 15) and those without (n = 15) a clinically significant loss of muscle mass. Duration: Participants completed 8 sessions of 7 hours duration over a period of 3 to 4 weeks.
Participants	Number enrolled: 30 participants. Inclusion criteria: HIV positive adults of 21 to 50 years, prescribed at least 2 anti-retroviral medicines, under care of physician for HIV management at time of study. Had to be smoking marijuana at least twice per week, for two weeks prior to the study. Had to be medically and psychiatrically stable. Exclusion criteria: nutritional malabsorption, major depression, dementia, chronic diarrhoea, weakness, fever, significant pulmonary disease, opportunistic infection within the 3 months prior to the study, obesity, use of steroids in the 3 months prior to the study, drug dependence (excluding nicotine and marijuana). Participants were divided into low BIA and high BIA (BIA = bio-electrical impedance analysis) to assess clinically significant muscle mass loss.
Interventions	Dronabinol of varying doses (0, 10, 20 30mg per os) and marijuana of varying strengths (0.0, 1.8, 2.9 and 3.9% delta-9-THC). Strictly supervised smoking routine, placebo identical to intervention (both capsules and cigarettes).
Outcomes	Outcomes: 1. Food intake 2. Tolerability and efficacy 3. Hunger-satiety measured on VAS and by food intake Performance measured by a number of tests Moods measured by VAS Physical symptoms, e.g. blood pressure and heart rate Psychological symptoms e.g. forgetfulness, withdrawal, dreaming, energetic, social, talkative. Drug effects: measured marijuana rating form and capsule rating form. For all the above, it was measured whether effects vary as function of lean muscle mass.
Notes	Is is unclear whether all patients were adequately treated, as the inclusion criteria were that participants has been prescribed at least 2 antiretroviral medications. It was noted, however, that viral suppression was 53% in the low BIA group and 47% in normal BIA group, CD4 counts were 428 +/- 321 and 449 +/- 301, respectively.

Haney 2005 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description.
Allocation concealment (selection bias)	Unclear risk	No description.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	“Participants and research assistants were blind to capsule and marijuana strength” pg 172. Placebo and active cigarettes and capsules were identical. However, because the effect of the "high" inherent in smoked marijuana cannot be disguised, it is likely that patients in smoking arms knew their treatment allocations.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	36 participants were enrolled; 5 started but discontinued due to personal reasons or non-compliance with protocol (no further details given) (2 in low BIA group, 3 in normal BIA group). One completed the study but revealed he had not taken his HIV medications so data was not included.
Selective reporting (reporting bias)	Unclear risk	Study protocol not available.
Other bias	Unclear risk	Patients were allowed to use marijuana at home throughout the study! Marijuana use on the morning of testing was prohibited, and alcohol use was not allowed for 24 hours before a session. Both confirmed biologically with urine and breath tests respectively.

Haney 2007

Methods	Study design: Within-subject placebo controlled double blind randomised study of placebo, dronabinol (5 and 10mg) and smoked marijuana (2.0% and 3.9%) THC), each administered 4 times daily for 4 day (two sixteen day in-patient phases separated by a 5 to 10 day outpatient phase with no illicit drug use, but marijuana allowed). Duration: 37 to 42 days in total.
Participants	Number enrolled: 10 participants inclusion criteria: HIV positive adults of 21 to 50 years, prescribed at least 2 anti-retroviral medicines, under care of physician for HIV management at time of study. Had to be smoking marijuana at least twice per week, for four weeks prior to the study. Had to be medically and psychiatrically stable. Exclusion criteria: nutritional malabsorption, major depression, dementia, chronic diarrhoea, weakness, fever, significant pulmonary disease, opportunistic infection within the three months prior to the study, obesity, use of steroids in the three months prior to the study, drug dependence (excluding nicotine and marijunana).
Interventions	Dronabinol of varying doses (0, 5 and 10mg per os) and marijuana of varying strengths (0.0, 2.0 and 3.9% delta-9-THC). Strictly supervised smoking routine, placebo identical to intervention (both capsules and cigarettes).
Outcomes	Frequency of food intake from provided snack boxes and beverages Hunger-satiety 6-item VAS (including hunger, fullness, nausea, thirst and desire to eat form)

Haney 2007 *(Continued)*

	Marijuana and capsule rating form using 6-item VAS, measuring strength of marijuana effect, marijuana liking, desire to smoke marijuana again, whether a good or bad marijuana effect was experienced, whether the marijuana was active or placebo (done 45 minutes after each cigarette); measuring strength of capsule, good or bad effects, liking, whether the capsule was like a stimulant, sedative or placebo, and willingness to take capsule again (measured 45 minutes after each capsule administration). Cognitive test battery, consisting of three minute digital-symbol substitution task, three minute repeated acquisition task, ten minute divided attention task, ten minute rapid information task, immediate and delayed digit-recall tasks, 50 item VAS. Number of tobacco cigarettes smoked Sleep latency, total sleep time and percentage of time spent in rapid eye movement sleep Six-item VAS modified St Mary's Hospital Sleep Questionnaire Heart rate and skin temperature at 10 minute intervals between 8.30am and 11.30pm.
Notes	Although the methods used and food availability was similar to Haney 2005, mean total caloric intake was markedly higher. Even on placebo, mean calorie intake exceeded that reported in any groups in Haney 2005.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding (performance bias and detection bias) All outcomes	High risk	Marijuana cigarettes, both active and placebo, were identical and smoked through hollow plastic cigarette holders so that marijuana was not visible. Marijuana administration was performed one hour after dronabinol dosing in order to match the expected onset of action and therefore make it difficult for participants to determine whether marijuana or dronabinol was active. Dronabinol capsules were over-encapsulated in opaque capsules with lactose filler. However, all participants were experienced marijuana users and would therefore have been able to identify double placebo administration.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data resulting from technical problems was reported (three participants in terms of sleep measures, and one participant in terms of physiological measurements.
Selective reporting (reporting bias)	High risk	Abilty of participants to identify placebo (a stated objective of the study) was not reported on.
Other bias	High risk	The fact that all participants were allowed to use marijuana at home may have diluted the drug effects during the study.

Struwe 1993

Methods	Prospective, randomised, double-blind, placebo-controlled study, cross-over design. Duration:70 days (35 days intervention, 35 days placebo, in random order).

Struwe 1993 *(Continued)*

Participants	Number enrolled: 5 participants. Inclusion criteria: HIV positive men who had lost at least 2.25kg of usual body weight but who were at least 70% of their ideal body weight, and were able to feed themselves and tolerate a regular diet. Exclusion criteria: Patients were excluded if they were experiencing acute concomitant medical complications, had a history of HIV dementia or substance abuse, were using steroids, were experiencing frequent changes of medications due to gastro-intestinal symptoms, or who were receiving tube-feeding or parenteral nutrition.
Interventions	Dronabinol 5mg bd (half an hour before lunch and dinner) for 5 weeks, followed by a two week wash out period and 5 weeks of placebo in the same schedule. Intervention and placebo were administered in random order.
Outcomes	Nutritional status, measured by: dietary intake (24 hour recall measured one day per week), anthropometrics (height, weight, body mass index, percent body fat and lean body mass), laboratory parameters (serum chemistries, complete blood count, CD4 lymphocyte count, serum albumin and prealbumin), appetite (measure on 100mm visual analogue scale) and "symptom distress" (a score calculated from ratings of 40 separate parameters, including mood and physical symptoms).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description.
Allocation concealment (selection bias)	Unclear risk	No description.
Blinding (performance bias and detection bias) All outcomes	High risk	"It is unlikely that the study was truly blind, as a number of participants (when asked after the study) were able to associate a "high" with one of the treatment arms, which may have influenced the caloric data" (page 830).
Incomplete outcome data (attrition bias) All outcomes	Low risk	All drop outs from the study identified with reasons. Only two dropped out for reasons that might have been related to study outcome (i.e. inability to tolerate dronabinol).
Selective reporting (reporting bias)	Low risk	All expected outcomes were reported on.
Other bias	Unclear risk	A large number of patients refused to participate in the study because they were unwilling to go without marijuana for 5 weeks (the placebo period), since they felt they were benefiting from it. Thus the study could have selected out many of those patients who experienced positive effects from cannabinoids.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Riggs 2012	This was a sub-group analysis (7 patients) from Ellis's trial (Ellis 2009). The endpoints of the study were the hormones ghrelin, leptin, peptide YY and insulin, which are not measures of morbidity and mortality and so this study was excluded from this review.

Study	Reason for exclusion
Timpone 1997	No placebo arm to which cannabis interventions could be compared.

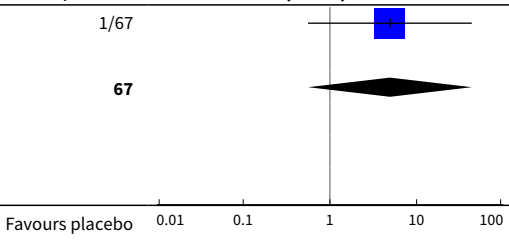
DATA AND ANALYSES

Comparison 1. Cannabinoids versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in mood	1	139	Odds Ratio (M-H, Fixed, 95% CI)	4.93 [0.56, 43.30]
2 Decrease in nausea and vomiting	1	139	Odds Ratio (M-H, Fixed, 95% CI)	6.10 [1.69, 22.01]
3 Weight gain (evaluable patients)	1	88	Odds Ratio (M-H, Fixed, 95% CI)	2.40 [0.70, 8.23]

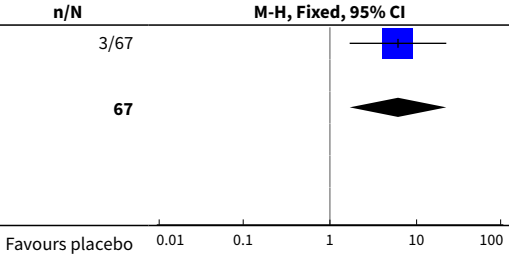
Analysis 1.1. Comparison 1 Cannabinoids versus placebo, Outcome 1 Change in mood.

Study or subgroup	Cannabinoids n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Beal 1995	5/72	1/67		100%	4.93[0.56,43.3]
Total (95% CI)	**72**	**67**		**100%**	**4.93[0.56,43.3]**
Total events: 5 (Cannabinoids), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.44(P=0.15)					

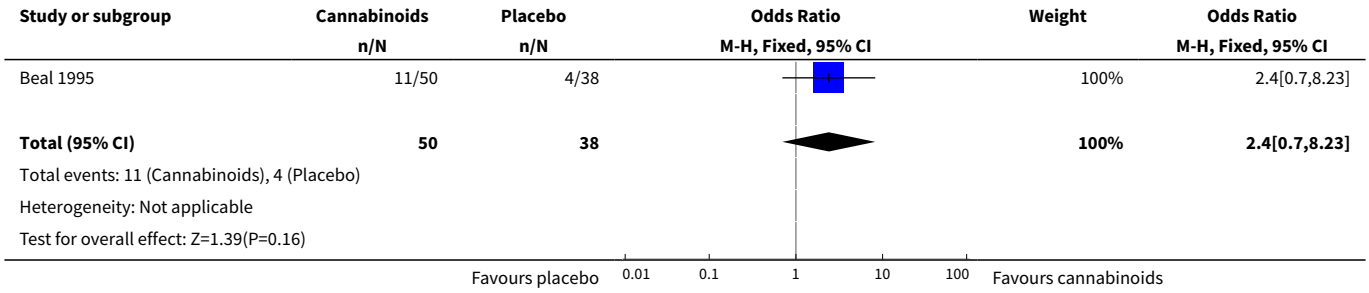


Analysis 1.2. Comparison 1 Cannabinoids versus placebo, Outcome 2 Decrease in nausea and vomiting.

Study or subgroup	Cannabinoids n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Beal 1995	16/72	3/67		100%	6.1[1.69,22.01]
Total (95% CI)	**72**	**67**		**100%**	**6.1[1.69,22.01]**
Total events: 16 (Cannabinoids), 3 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.76(P=0.01)					



Analysis 1.3. Comparison 1 Cannabinoids versus placebo, Outcome 3 Weight gain (evaluable patients).



APPENDICES

Appendix 1. CLIB search strategy 2010

Date: 15 December 2010

ID	Search	Hits
#1	MeSH descriptor HIV Infections explode all trees	6327
#2	MeSH descriptor HIV explode all trees	2008
#3	hiv OR hiv-1* OR hiv-2* OR hiv1 OR hiv2 OR HIV INFECT* OR HUMAN IMMUNODEFICIENCY VIRUS OR HUMAN IMMUNEDEFICIENCY VIRUS OR HUMAN IMMUNE-DEFICIENCY VIRUS OR HUMAN IMMUNO-DEFICIENCY VIRUS OR HUMAN IMMUN* DEFICIENCY VIRUS OR ACQUIRED IMMUNODEFICIENCY SYNDROME OR ACQUIRED IMMUNEDEFICIENCY SYNDROME OR ACQUIRED IMMUNO-DEFICIENCY SYNDROME OR ACQUIRED IMMUNE-DEFICIENCY SYNDROME OR ACQUIRED IMMUN* DEFICIENCY SYNDROME	9653
#4	MeSH descriptor Lymphoma, AIDS-Related, this term only	21
#5	MeSH descriptor Sexually Transmitted Diseases, Viral, this term only	18
#6	(#1 OR #2 OR #3 OR #4 OR #5)	9740
#7	MeSH descriptor Cannabis, this term only	233
#8	MeSH descriptor Cannabinoids explode all trees	386
#9	cannabis:kw,ti,ab OR hemp:kw,ti,ab OR marijuana:kw,ti,ab OR ganja:kw,ti,ab OR hashish:kw,ti,ab OR marihuana:kw,ti,ab OR bhang:kw,ti,ab OR cannibinoid:kw.ti.ab OR cannabinoids:kw,ti,ab OR marinol:kw,ti,ab OR dronabinol:kw,ti,ab OR nabilone:kw,ti,ab OR cesamet:kw,ti,ab OR dexanabinol:kw,ti,ab OR sativex:kw,ti,ab OR tetrahydrocannabinol:kw,ti,ab	1283
#10	(#7 OR #8 OR #9)	1284
#11	(#6 AND #10)	43
#12	(#6 AND #10), from 2006 to 2010	18

Appendix 2. CLIB search strategy 2007

Date: **16 November 2007**

ID	Search	Hits
#1	"HIV Infections" OR HIV OR hiv OR "hiv-1*" OR "hiv-2*" OR hiv1 OR hiv2 OR "hiv infect*" OR "human immunodeficiency virus" OR "human immunedeficiency virus" OR "human immuno-deficiency virus" OR "human immune-deficiency virus" OR ("human immun*" AND "deficiency virus") OR "acquired immunodeficiency syndrome" OR "acquired immunedeficiency syndrome" OR "acquired immuno-deficiency syndrome" OR "acquired immune-deficiency syndrome" OR ("acquired immun*" AND "deficiency syndrome") OR "viral sexually transmitted diseases"	7229
#2	CANNABIS OR MARIJUANA OR DRONABINOL OR MARINOL OR SATIVEX OR NABILONE OR CESAMET OR DEXANABINOL	1015
#3	(#1 AND #2), from 1980 to 2007	53

Appendix 3. CLIB search strategy 2012

Date: 30 July 2012

ID	Search	Hits
#1	MeSH descriptor HIV Infections explode all trees	6712
#2	MeSH descriptor HIV explode all trees	2245
#3	hiv OR hiv-1* OR hiv-2* OR hiv1 OR hiv2 OR HIV INFECT* OR HUMAN IMMUNODEFICIENCY VIRUS OR HUMAN IMMUNEDEFICIENCY VIRUS OR HUMAN IMMUNE-DEFICIENCY VIRUS OR HUMAN IMMUNO-DEFICIENCY VIRUS OR HUMAN IMMUN* DEFICIENCY VIRUS OR ACQUIRED IMMUNODEFICIENCY SYNDROME OR ACQUIRED IMMUNEDEFICIENCY SYNDROME OR ACQUIRED IMMUNO-DEFICIENCY SYNDROME OR ACQUIRED IMMUNE-DEFICIENCY SYNDROME OR ACQUIRED IMMUN* DEFICIENCY SYNDROME	10952
#4	MeSH descriptor Lymphoma, AIDS-Related, this term only	21
#5	MeSH descriptor Sexually Transmitted Diseases, Viral, this term only	22
#6	(#1 OR #2 OR #3 OR #4 OR #5)	11029
#7	MeSH descriptor Cannabis, this term only	242
#8	MeSH descriptor Cannabinoids explode all trees	427
#9	cannabis:kw,ti,ab OR hemp:kw,ti,ab OR marijuana:kw,ti,ab OR ganja:kw,ti,ab OR hashish:kw,ti,ab OR marihuana:kw,ti,ab OR bhang:kw,ti,ab OR cannibinoid:kw.ti.ab OR cannabinoids:kw,ti,ab OR marinol:kw,ti,ab OR dronabinol:kw,ti,ab OR	1397

(Continued)

	nabilone:kw,ti,ab OR cesamet:kw,ti,ab OR dexanabinol:kw,ti,ab OR sativex:kw,ti,ab OR tetrahydrocannabinol:kw,ti,ab	
#10	(#7 OR #8 OR #9)	1399
#11	(#6 AND #10)	52
#12	(#6 AND #10), from 2010 to 2012	3

Appendix 4. PubMed search strategy 2010

Database: **PubMed 2007 - 2010**

Date: **15 December 2010**

Search	Most Recent Queries	Time	Result
#6	Search #1 AND #2 AND #3 Limits: Publication Date from 2007/11/01 to 2010/12/15	05:41:33	36
#4	Search #1 AND #2 AND #3	05:37:49	239
#3	Search cannabis[mh] OR cannabis[tiab] OR hemp[tiab] OR marijuana[tiab] OR ganja[tiab] OR hashish[tiab] OR marihuana[tiab] OR bhang[tiab] OR cannabinoids[mh] OR cannibinoids[tiab] OR cannibinoid[tiab] OR marinol[tiab] OR dronabinol[tiab] OR nabilone[tiab] OR cesamet[tiab] OR dexanabinol[tiab] OR sativex[tiab] OR tetrahydrocannabinol[tiab]	05:25:13	21091
#2	Search (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])	05:12:54	2324958
#1	Search HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) OR "sexually transmitted diseases, viral"[MESH:NoExp]	05:12:17	265967

Appendix 5. PubMed search strategy 2007

Database: **PubMed 1980 – 2007**

Date: **16 November 2007**

Search	Most Recent Queries	Time	Result

(Continued)

#5	Search **#1 AND #2 AND #3** Limits: Publication Date from 1980 to 2007	03:43:31	279
#4	Search **#1 AND #2 AND #3**	03:42:42	279
#3	Search **CANNABIS OR MARIJUANA OR DRONABINOL OR MARINOL OR SATIVEX OR NABILONE OR CESAMET OR DEXANABINOL**	03:42:23	15268
#2	Search **randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animals [mh] NOT human [mh])**	03:40:45	3033621
#1	Search **HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) OR "sexually transmitted diseases, viral"[MESH:NoExp]**	03:40:19	224143

Appendix 6. PubMed search strategy 2012

Date: **30 July 2012**

Search	Query	Items found
#5	Search (#1 AND #2 AND #3) AND ("2010/12/01"[Date - Publication] : "2012/07/30"[Date - Publication])	23
#4	Search #1 AND #2 AND #3	256
#3	Search cannabis[mh] OR cannabis[tiab] OR hemp[tiab] OR marijuana[tiab] OR ganja[tiab] OR hashish[tiab] OR marihuana[tiab] OR bhang[tiab] OR cannabinoids[mh] OR cannibinoids[tiab] OR cannibinoid[tiab] OR marinol[tiab] OR dronabinol[tiab] OR nabilone[tiab] OR cesamet[tiab] OR dexanabinol[tiab] OR sativex[tiab] OR tetrahydrocannabinol[tiab]	22817
#2	Search randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT humans[mh])	2581088
#1	Search HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tiab] OR hiv-1*[tiab] OR hiv-2*[tiab] OR hiv1[tiab] OR hiv2[tiab] OR hiv infect*[tiab] OR human immunodeficiency virus[tiab] OR human immunedeficiency virus[tiab] OR human im-	284957

(Continued)

muno-deficiency virus[tiab] OR human immune-deficiency virus[tiab] OR ((human immun*[tiab]) AND (deficiency virus[tiab])) OR acquired immunodeficiency syndrome[tiab] OR acquired immunedeficiency syndrome[tiab] OR acquired immuno-deficiency syndrome[tiab] OR acquired immune-deficiency syndrome[tiab] OR ((acquired immun*[tiab]) AND (deficiency syndrome[tiab])) OR "sexually transmitted diseases, Viral"[MeSH:NoExp]

Appendix 7. Embase search strategy 2007

Date: 16 November 2007

EMBASE.com Session Results

No.

Query

Results

Date

#1

(((((**'human immunodeficiency virus infection'**/exp OR **'human immunodeficiency virus infection'**) OR (**'human immunodeficiency virus infection'**/exp OR **'human immunodeficiency virus infection'**)) OR ((**'human immunodeficiency virus infection'**/exp OR **'human immunodeficiency virus infection'**) OR (**'human immunodeficiency virus infection'**/exp OR **'human immunodeficiency virus infection'**))) OR (((**'human immunodeficiency virus infection'**/exp OR **'human immunodeficiency virus infection'**) OR (**'human immunodeficiency virus infection'**/exp OR **'human immunodeficiency virus infection'**)) OR ((**'human immunodeficiency virus infection'**/exp OR **'human immunodeficiency virus infection'**) OR (**'human immunodeficiency virus infection'**/exp OR **'human immunodeficiency virus infection'**)))) OR ((((**'human immunodeficiency virus infection'**/exp OR **'human immunodeficiency virus infection'**) OR (**'human immunodeficiency virus infection'**/exp OR **'human immunodeficiency virus infection'**)) OR ((**'human immunodeficiency virus infection'**/exp OR **'human immunodeficiency virus infection'**) OR (**'human immunodeficiency virus infection'**/exp OR **'human immunodeficiency virus infection'**))) OR (((**'human immunodeficiency virus infection'**/exp OR **'human immunodeficiency virus infection'**) OR (**'human immunodeficiency virus infection'**/exp OR **'human immunodeficiency virus infection'**)) OR ((**'human immunodeficiency virus infection'**/exp OR **'human immunodeficiency virus infection'**) OR (**'human immunodeficiency virus infection'**/exp OR **'human immunodeficiency virus infection'**))))) OR ((((((**'human immunodeficiency virus'**/exp OR **'human immunodeficiency virus'**) OR (**'human immunodeficiency virus'**/exp OR **'human immunodeficiency virus'**)) OR ((**'human immunodeficiency virus'**/exp OR **'human immunodeficiency virus'**) OR (**'human immunodeficiency virus'**/exp OR **'human immunodeficiency virus'**))) OR (((**'human immunodeficiency virus'**/exp OR **'human immunodeficiency virus'**) OR (**'human immunodeficiency virus'**/exp OR **'human immunodeficiency virus'**)) OR ((**'human immunodeficiency virus'**/exp OR **'human immunodeficiency virus'**) OR (**'human immunodeficiency virus'**/exp OR **'human immunodeficiency virus'**)))) OR ((((**'human immunodeficiency virus'**/exp OR **'human immunodeficiency virus'**) OR (**'human immunodeficiency virus'**/exp OR **'human immunodeficiency virus'**)) OR ((**'human immunodeficiency virus'**/exp OR **'human immunodeficiency virus'**) OR (**'human immunodeficiency virus'**/exp OR **'human immunodeficiency virus'**))) OR (((**'human immunodeficiency virus'**/exp OR **'human immunodeficiency virus'**) OR (**'human immunodeficiency virus'**/exp OR **'human immunodeficiency virus'**)) OR ((**'human immunodeficiency virus'**/exp OR **'human immunodeficiency virus'**) OR (**'human immunodeficiency virus'**/exp OR **'human immunodeficiency virus'**))))))) OR (**hiv**:ti OR **hiv**:ab) OR (**'hiv-1'**:ti OR **'hiv-1'**:ab) OR (**'hiv-2'**:ti OR **'hiv-2'**:ab) OR (**'human immunodeficiency virus'**:ti OR **'human immunodeficiency virus'**:ab) OR (**'human immuno-deficiency virus'**:ti OR **'human immuno-deficiency virus'**:ab) OR (**'human immunedeficiency virus'**:ti OR **'human immunedeficiency virus'**:ab) OR (**'human immune-deficiency virus'**:ti OR **'human immune-deficiency virus'**:ab) OR (**'acquired immune-deficiency syndrome'**:ti OR **'acquired immune-deficiency syndrome'**:ab) OR (**'acquired immunedeficiency syndrome'**:ti OR **'acquired immunedeficiency syndrome'**:ab) OR (**'ac-**

(Continued)

quired immunodeficiency syndrome':ti OR **'acquired immunodeficiency syndrome**':ab) OR (**'acquired immuno-deficiency syndrome**':ti OR **'acquired immuno-deficiency syndrome**':ab)

266,873

16 Nov 2007

#2

(**random***:ti OR **random***:ab) OR (**factorial***:ti OR **factorial***:ab) OR (**cross?over***:ti OR **cross?over**:ab OR **crossover***:ti OR **crossover***:ab) OR (**placebo***:ti OR **placebo***:ab) OR (((**doubl***:ti AND **blind***:ti) OR (**doubl***:ab AND **blind***:ab))) OR (((**singl***:ti AND **blind***:ti) OR (**singl***:ab AND **blind***:ab))) OR (**assign***:ti OR **assign***:ab) OR (**volunteer***:ti OR **volunteer***:ab) OR ((((((**'crossover procedure**'/exp OR **'crossover procedure**') OR (**'crossover procedure**'/exp OR **'crossover procedure**')) OR ((**'crossover procedure**'/exp OR **'crossover procedure**') OR (**'crossover procedure**'/exp OR **'crossover procedure**'))) OR (((**'crossover procedure**'/exp OR **'crossover procedure**') OR (**'crossover procedure**'/exp OR **'crossover procedure**')) OR ((**'crossover procedure**'/exp OR **'crossover procedure**') OR (**'crossover procedure**'/exp OR **'crossover procedure**')))) OR ((((**'crossover procedure**'/exp OR **'crossover procedure**') OR (**'crossover procedure**'/exp OR **'crossover procedure**')) OR ((**'crossover procedure**'/exp OR **'crossover procedure**') OR (**'crossover procedure**'/exp OR **'crossover procedure**'))) OR (((**'crossover procedure**'/exp OR **'crossover procedure**') OR (**'crossover procedure**'/exp OR **'crossover procedure**')) OR ((**'crossover procedure**'/exp OR **'crossover procedure**') OR (**'crossover procedure**'/exp OR **'crossover procedure**'))))))) OR ((((((**'double-blind procedure**'/exp OR **'double-blind procedure**') OR (**'double-blind procedure**'/exp OR **'double-blind procedure**')) OR ((**'double-blind procedure**'/exp OR **'double-blind procedure**') OR (**'double-blind procedure**'/exp OR **'double-blind procedure**'))) OR (((**'double-blind procedure**'/exp OR **'double-blind procedure**') OR (**'double-blind procedure**'/exp OR **'double-blind procedure**')) OR ((**'double-blind procedure**'/exp OR **'double-blind procedure**') OR (**'double-blind procedure**'/exp OR **'double-blind procedure**')))) OR ((((**'double-blind procedure**'/exp OR **'double-blind procedure**') OR (**'double-blind procedure**'/exp OR **'double-blind procedure**')) OR ((**'double-blind procedure**'/exp OR **'double-blind procedure**') OR (**'double-blind procedure**'/exp OR **'double-blind procedure**'))) OR (((**'double-blind procedure**'/exp OR **'double-blind procedure**') OR (**'double-blind procedure**'/exp OR **'double-blind procedure**')) OR ((**'double-blind procedure**'/exp OR **'double-blind procedure**') OR (**'double-blind procedure**'/exp OR **'double-blind procedure**'))))))) OR ((((((**'single-blind procedure**'/exp OR **'single-blind procedure**') OR (**'single-blind procedure**'/exp OR **'single-blind procedure**')) OR ((**'single-blind procedure**'/exp OR **'single-blind procedure**') OR (**'single-blind procedure**'/exp OR **'single-blind procedure**'))) OR (((**'single-blind procedure**'/exp OR **'single-blind procedure**') OR (**'single-blind procedure**'/exp OR **'single-blind procedure**')) OR ((**'single-blind procedure**'/exp OR **'single-blind procedure**') OR (**'single-blind procedure**'/exp OR **'single-blind procedure**')))) OR ((((**'single-blind procedure**'/exp OR **'single-blind procedure**') OR (**'single-blind procedure**'/exp OR **'single-blind procedure**')) OR ((**'single-blind procedure**'/exp OR **'single-blind procedure**') OR (**'single-blind procedure**'/exp OR **'single-blind procedure**'))) OR (((**'single-blind procedure**'/exp OR **'single-blind procedure**') OR (**'single-blind procedure**'/exp OR **'single-blind procedure**')) OR ((**'single-blind procedure**'/exp OR **'single-blind procedure**') OR (**'single-blind procedure**'/exp OR **'single-blind procedure**'))))))) OR ((((((**'randomized controlled trial**'/exp OR **'randomized controlled trial**') OR (**'randomized controlled trial**'/exp OR **'randomized controlled trial**')) OR ((**'randomized controlled trial**'/exp OR **'randomized controlled trial**') OR (**'randomized controlled trial**'/exp OR **'randomized controlled trial**'))) OR (((**'randomized controlled trial**'/exp OR **'randomized controlled trial**') OR (**'randomized controlled trial**'/exp OR **'randomized controlled trial**')) OR ((**'randomized controlled trial**'/exp OR **'randomized controlled trial**') OR (**'randomized controlled trial**'/exp OR **'randomized controlled trial**')))) OR ((((**'randomized controlled trial**'/exp OR **'randomized controlled trial**') OR (**'randomized controlled trial**'/exp OR **'randomized controlled trial**')) OR ((**'randomized controlled trial**'/exp OR **'randomized controlled trial**') OR (**'randomized controlled trial**'/exp OR **'randomized controlled trial**'))) OR (((**'randomized controlled trial**'/exp OR **'randomized controlled trial**') OR (**'randomized controlled trial**'/exp OR **'randomized controlled trial**')) OR ((**'randomized controlled trial**'/exp OR **'randomized controlled trial**') OR (**'randomized controlled trial**'/exp OR **'randomized controlled trial**'))))))) OR (**allocat***:ti OR **allocat***:ab)

764,639

16 Nov 2007

#3

(**'cannabis**'/exp OR **'cannabis**') OR (**'marijuana**'/exp OR **'marijuana**') OR (**'dronabinol**'/exp OR **'dronabinol**') OR (**'marinol**'/exp OR **'marinol**') OR (**'sativex**'/exp OR **'sativex**') OR (**'nabilone**'/exp OR **'nabilone**') OR (**'cesamet**'/exp OR **'cesamet**') OR (**'dexanabinol**'/exp OR **'dexanabinol**')

22,595

16 Nov 2007

#4

(Continued)

#1 AND **#2** AND **#3**

72

16 Nov 2007

Appendix 8. Embase search strategy 2010

Date: **15 December 2010**

No.	Query	Results	Date
#7	#1 AND #2 AND #5 AND [embase]/lim AND [1-3-2006]/sd NOT [15-12-2010]/sd	56	15 Dec 2010
#6	#1 AND #2 AND #5	113	15 Dec 2010
#5	'cannabis'/syn OR 'marijuana'/syn OR 'marihuana'/syn OR 'bhang'/syn OR 'ganja'/syn OR 'ganjah'/syn OR 'hashish'/syn OR 'hemp'/syn OR 'sativex'/syn OR 'cannabinoid'/syn OR 'marinol'/syn OR 'dronabinol'/syn OR 'nabilone'/syn OR 'cesamet'/syn OR 'dexanabinol'/syn OR 'tetrahydrocannabinol'/syn	42730	15 Dec 2010
#2	random*:ti OR random*:ab OR factorial*:ti OR factorial*:ab OR cross?over*:ti OR cross?over*:ab OR crossover*:ti OR crossover*:ab OR placebo*:ti OR placebo*:ab OR (doubl*:ti AND blind*:ti) OR (doubl*:ab AND blind*:ab) OR (singl*:ti AND blind*:ti) OR (singl*:ab AND blind*:ab) OR assign*:ti OR assign*:ab OR allocat*:ti OR allocat*:ab OR volunteer*:ti OR volunteer*:ab OR 'crossover procedure'/exp OR 'crossover procedure'/de OR 'crossover procedure' OR 'double-blind procedure'/exp OR 'double-blind procedure'/de OR 'double-blind procedure' OR 'single-blind procedure'/exp OR 'single-blind procedure'/de OR 'single-blind procedure' OR 'randomized controlled trial'/exp OR 'randomized controlled trial'/de OR 'randomized controlled trial'	1040811	15 Dec 2010
#1	'human immunodeficiency virus infection'/exp OR 'human immunodeficiency virus infection'/de OR 'human immunodeficiency virus infection' OR 'human immunodeficiency virus'/exp OR 'human immunodeficiency virus'/de OR 'human immunodeficiency virus' OR hiv:ti OR hiv:ab OR 'hiv-1':ti OR 'hiv-1':ab OR 'hiv-2':ti OR 'hiv-2':ab OR 'human immunodeficiency virus':ti OR 'human immunodeficiency virus':ab OR 'human immuno-deficiency virus':ti OR 'human immuno-deficiency virus':ab OR 'human immunedeficiency virus':ti OR 'human immunedeficiency virus':ab OR 'human immune-deficiency virus':ti OR 'human immune-deficiency virus':ab OR 'acquired immune-deficiency syndrome':ti OR 'acquired immune-deficiency syndrome':ab OR 'acquired immunedeficiency syndrome':ti OR 'acquired immunedeficiency syndrome':ab OR 'acquired immunodeficiency syndrome':ti OR 'acquired immunodeficiency syndrome':ab OR 'acquired immuno-deficiency syndrome':ti OR 'acquired immuno-deficiency syndrome':ab	338399	15 Dec 2010

Appendix 9. Embase search strategy 2012

Date: **30 July 2012**

No.	Query	Results
#10	#1 AND #7 AND #8 AND [embase]/lim AND [1-12-2010]/sd NOT [30-7-2012]/sd	62
#9	#1 AND #7 AND #8	276
#8	'cannabis'/syn OR 'marijuana'/syn OR 'marihuana'/syn OR 'bhang'/syn OR 'ganja'/syn OR 'ganjah'/syn OR 'hashish'/syn OR 'hemp'/syn OR 'sativex'/syn OR 'cannabinoid'/syn OR 'marinol'/syn OR 'dronabinol'/syn OR 'nabilone'/syn OR 'cesamet'/syn OR 'dexanabinol'/syn OR 'tetrahydrocannabinol'/syn	50257
#7	#2 NOT #6	1594505
#6	#3 NOT #5	2090713
#5	#3 AND #4	16882850
#4	'human'/de OR 'human'	17258863
#3	'animal'/de OR 'animal' OR 'nonhuman'/de OR 'nonhuman' OR 'animal experiment'/de OR 'animal experiment'	18973563
#2	'randomized controlled trial'/de OR 'randomized controlled trial' OR random*:ab,ti OR trial:ti OR allocat*:ab,ti OR factorial*:ab,ti OR placebo*:ab,ti OR assign*:ab,ti OR volunteer*:ab,ti OR 'crossover procedure'/de OR 'crossover procedure' OR 'double-blind procedure'/de OR 'double-blind procedure' OR 'single-blind procedure'/de OR 'single-blind procedure' OR (doubl* NEAR/3 blind*):ab,ti OR (singl*:ab,ti AND blind*:ab,ti) OR crossover*:ab,ti OR cross+over*:ab,ti OR (cross NEXT/1 over*):ab,ti	1671248
#1	'human immunodeficiency virus infection'/exp OR 'human immunodeficiency virus infection'/de OR 'human immunodeficiency virus infection' OR 'human immunodeficiency virus'/exp OR 'human immunodeficiency virus'/de OR 'human immunodeficiency virus' OR 'human immunodeficiency virus:ab,ti' OR hiv:ab,ti OR 'hiv-1':ab,ti OR 'hiv-2':ab,ti OR 'human immunodeficiency virus':ab,ti OR 'human immunedeficiency virus':ab,ti OR 'human immune-deficiency virus':ab,ti OR 'human immuno-deficiency virus':ab,ti OR 'acquired immunodeficiency syndrome':ab,ti OR 'acquired immuno-deficiency syndrome':ab,ti OR 'acquired immune-deficiency syndrome':ab,ti OR 'acquired immunedeficiency syndrome':ab,ti	382957

Appendix 10. Clinical Trials search strategy 2010

Date: 15 December 2010

Found 17 studies with search of: HIV AND (cannabis OR marijuana OR cannabinoids OR dronabinol OR nabilone OR dexanabinol)

Appendix 11. Clinical trials search strategy 2012

Date: 30 July 2012

Found 7 studies with search of: HIV AND (marijuana OR cannabinoids OR dronabinol OR nabilone OR dexanabinol)

Appendix 12. AEGIS search strategy 2010

Date: 15 December 2010

Your Search for (cannabis OR marijuana OR cannabinoids OR dronabinol OR nabilone OR dexanabinol) matched 487 Documents

358 abstracts searched on 10/01/2011, 4 abstracts downloaded.

Appendix 13. AIDsearch search strategy 2007

Date: **16 November 2007**

Set #	Search Strategy	Matches
#1	(HIV INFECTIONS) OR HIV OR HIV OR HIV-1* OR HIV-2* OR HIV1 OR HIV2 OR (HIV INFECT*) OR (HUMAN IMMUNODEFICIENCY VIRUS) OR (HUMAN IMMUNEDEFICIENCY VIRUS) OR (HUMAN IMMUNO-DEFICIENCY VIRUS) OR (HUMAN IMMUNE-DEFICIENCY VIRUS) OR ((HUMAN IMMUN*) AND (DEFICIENCY VIRUS)) OR (ACQUIRED IMMUNODEFICIENCY SYNDROME) OR (ACQUIRED IMMUNEDEFICIENCY SYNDROME) OR (ACQUIRED IMMUNO-DEFICIENCY SYNDROME) OR (ACQUIRED IMMUNE-DEFICIENCY SYNDROME) OR ((ACQUIRED IMMUN*) AND (DEFICIENCY SYNDROME)) OR (SEXUALLY TRANSMITTED DISEASES, VIRAL)	269,827
#2	((RANDOMIZED CONTROLLED TRIAL) OR (CONTROLLED CLINICAL TRIAL) OR (RANDOMIZED CONTROLLED TRIALS) OR (RANDOM ALLOCATION) OR (DOUBLE-BLIND METHOD) OR (SINGLE-BLIND METHOD) OR (CLINICAL TRIAL) OR (CLINICAL TRIALS) OR ("CLINICAL TRIAL") OR ((SINGL* OR DOUBL* OR TREBL* OR TRIPL* AND (MASK* OR BLIND*)) OR PLACEBOS OR PLACEBO* OR RANDOM* OR (COMPARATIVE STUDY) OR (EVALUATION STUDIES) OR (FOLLOW-UP STUDIES) OR (PROSPECTIVE STUDIES) OR CONTROL* OR PROSPECTIV* OR VOLUNTEER*)) NOT (ANIMALS NOT HUMAN)	153,716
#3	#1 AND #2	109,587
#4	CANNABIS OR MARIJUANA OR DRONABINOL OR MARINOL OR SATIVEX OR NABILONE OR CESAMET OR DEXANABINOL	782
#5	(#3 AND #4) AND PY>=1980	4

Appendix 14. Gateway search strategy 2007

Date: **16 November 2007**

Search Number	**Search**	**Items Found**
#8	Search: (CANNABIS OR MARIJUANA OR DRONABINOL OR MARINOL OR SATIVEX OR NABILONE OR CESAMET OR DEXANABINOL) AND (((ACQUIRED IMMUNEDEFICIENCY SYNDROME) OR (ACQUIRED IMMUNO-DEFICIENCY SYNDROME) OR (ACQUIRED IMMUNE-DEFICIENCY SYNDROME) OR ((ACQUIRED IMMUN*) AND (DEFICIENCY SYNDROME)) OR (SEXUALLY TRANSMITTED DISEASES, VIRAL)) OR ((HIV INFECTIONS) OR HIV OR HIV OR HIV-1* OR HIV-2* OR HIV1 OR HIV2 OR (HIV INFECT*) OR (HUMAN IMMUNODEFICIENCY VIRUS) OR (HUMAN IMMUNEDEFICIENCY VIRUS) OR (HUMAN IMMUNO-DEFICIENCY VIRUS) OR (HUMAN IMMUNE-DEFICIENCY VIRUS) OR ((HUMAN IMMUN*) AND (DEFICIENCY VIRUS)) OR (ACQUIRED IMMUNODEFICIENCY SYNDROME))) AND ((((RANDOMIZED CONTROLLED TRIAL) OR (CONTROLLED CLINICAL TRIAL) OR (RANDOMIZED CONTROLLED TRIALS) OR (RANDOM ALLOCATION) OR (DOUBLE-BLIND METHOD) OR (SINGLE-BLIND METHOD) OR (CLINICAL TRIAL) OR (CLINICAL TRIALS) OR (CLINICAL TRIAL) OR ((SINGL* OR DOUBL* OR TREBL* OR TRIPL*) AND (MASK* OR BLIND*))) OR (PLACEBOS OR PLACEBO* OR RANDOM* OR	392

(Continued)

	(COMPARATIVE STUDY) OR (EVALUATION STUDIES) OR (FOLLOW-UP STUDIES) OR (PROSPECTIVE STUDIES) OR CONTROL* OR PROSPECTIV* OR VOLUNTEER*)) NOT (ANIMALS NOT HUMAN)) Limit: 1980:2007	
#7	Search: (((RANDOMIZED CONTROLLED TRIAL) OR (CONTROLLED CLINICAL TRIAL) OR (RANDOMIZED CONTROLLED TRIALS) OR (RANDOM ALLOCATION) OR (DOUBLE-BLIND METHOD) OR (SINGLE-BLIND METHOD) OR (CLINICAL TRIAL) OR (CLINICAL TRIALS) OR (CLINICAL TRIAL) OR ((SINGL* OR DOUBL* OR TREBL* OR TRIPL*) AND (MASK* OR BLIND*))) OR (PLACEBOS OR PLACEBO* OR RANDOM* OR (COMPARATIVE STUDY) OR (EVALUATION STUDIES) OR (FOLLOW-UP STUDIES) OR (PROSPECTIVE STUDIES) OR CONTROL* OR PROSPECTIV* OR VOLUNTEER*)) NOT (ANIMALS NOT HUMAN)	3849793
#6	Search: PLACEBOS OR PLACEBO* OR RANDOM* OR (COMPARATIVE STUDY) OR (EVALUATION STUDIES) OR (FOLLOW-UP STUDIES) OR (PROSPECTIVE STUDIES) OR CONTROL* OR PROSPECTIV* OR VOLUNTEER*	4714290
#5	Search: (RANDOMIZED CONTROLLED TRIAL) OR (CONTROLLED CLINICAL TRIAL) OR (RANDOMIZED CONTROLLED TRIALS) OR (RANDOM ALLOCATION) OR (DOUBLE-BLIND METHOD) OR (SINGLE-BLIND METHOD) OR (CLINICAL TRIAL) OR (CLINICAL TRIALS) OR (CLINICAL TRIAL) OR ((SINGL* OR DOUBL* OR TREBL* OR TRIPL*) AND (MASK* OR BLIND*))	796308
#4	Search: ((ACQUIRED IMMUNEDEFICIENCY SYNDROME) OR (ACQUIRED IMMUNO-DEFICIENCY SYNDROME) OR (ACQUIRED IMMUNE-DEFICIENCY SYNDROME) OR ((ACQUIRED IMMUN*) AND (DEFICIENCY SYNDROME)) OR (SEXUALLY TRANSMITTED DISEASES, VIRAL)) OR ((HIV INFECTIONS) OR HIV OR HIV OR HIV-1* OR HIV-2* OR HIV1 OR HIV2 OR (HIV INFECT*) OR (HUMAN IMMUNODEFICIENCY VIRUS) OR (HUMAN IMMUNEDEFICIENCY VIRUS) OR (HUMAN IMMUNO-DEFICIENCY VIRUS) OR (HUMAN IMMUNE-DEFICIENCY VIRUS) OR ((HUMAN IMMUN*) AND (DEFICIENCY VIRUS)) OR (ACQUIRED IMMUNODEFICIENCY SYNDROME))	331296
#3	Search: (HIV INFECTIONS) OR HIV OR HIV OR HIV-1* OR HIV-2* OR HIV1 OR HIV2 OR (HIV INFECT*) OR (HUMAN IMMUNODEFICIENCY VIRUS) OR (HUMAN IMMUNEDEFICIENCY VIRUS) OR (HUMAN IMMUNO-DEFICIENCY VIRUS) OR (HUMAN IMMUNE-DEFICIENCY VIRUS) OR ((HUMAN IMMUN*) AND (DEFICIENCY VIRUS)) OR (ACQUIRED IMMUNODEFICIENCY SYNDROME)	91318
#2	Search: (ACQUIRED IMMUNEDEFICIENCY SYNDROME) OR (ACQUIRED IMMUNO-DEFICIENCY SYNDROME) OR (ACQUIRED IMMUNE-DEFICIENCY SYNDROME) OR ((ACQUIRED IMMUN*) AND (DEFICIENCY SYNDROME)) OR (SEXUALLY TRANSMITTED DISEASES, VIRAL)	246413
#1	Search: CANNABIS OR MARIJUANA OR DRONABINOL OR MARINOL OR SATIVEX OR NABILONE OR CESAMET OR DEXANABINOL	20458

Appendix 15. WHO ICTRP search strategy 2010

Date: **15 December 2010**

6 records for 6 trials retrieved with search of: hiv AND cannabis OR hiv AND cannibinoids OR hiv AND marijuana OR hiv AND dronabinol OR hiv AND nabilone OR hiv AND dexanabinol OR hiv AND sativex

Appendix 16. WHO ICTRP search strategy 2012

Date: **31 July 2012**

2 records for 2 trials retrieved with search of: hiv AND cannabis OR hiv AND cannibinoids OR hiv AND marijuana OR hiv AND dronabinol OR hiv AND nabilone OR hiv AND dexanabinol OR hiv AND sativex

CONTRIBUTIONS OF AUTHORS

EL, AG and BM selected articles for inclusion in the review. EL and AG interrogated articles in terms of quality of evidence and utility of data for further analysis and conducted data extraction. NS provided mentorship and assisted with all stages of the review process with advice and review as well as data extraction when necessary.

DECLARATIONS OF INTEREST

None declared.

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INDEX TERMS

Medical Subject Headings (MeSH)

*Cannabis; Acquired Immunodeficiency Syndrome [complications] [mortality]; Cannabinoids [*therapeutic use]; Dronabinol [*therapeutic use]; HIV Infections [*complications] [*mortality]; Morbidity; Phytotherapy [*methods]; Randomized Controlled Trials as Topic; Weight Gain

MeSH check words

Adult; Humans