Published in final edited form as:
Cochrane Database Syst Rev. ; (3): CD004837. doi:10.1002/14651858.CD004837.pub2.

Cannabis and schizophrenia

John Rathbone[1], **Hannele Variend**[2], and **Hetal Mehta**[3]

[1]HEDS, ScHARR, The University of Sheffield, Sheffield, UK

[2]CRHT, Becklin Centre, Leeds, UK

[3]Lancashire Care NHS Trust, Guild Lodge, Preston, UK

Abstract

Background—Many people with schizophrenia use cannabis and its effects on the illness are unclear.

Objectives—To evaluate the effects of cannabis use on people with schizophrenia and schizophrenia-like illnesses.

Search methods—We searched the Cochrane Schizophrenia Group Trials Register (April 2007) which is based on regular searches of BIOSIS, CENTRAL, CINAHL, EMBASE, MEDLINE and PsycINFO.

Selection criteria—We included all randomised trials involving cannabinoids and people with schizophrenia or schizophrenia-like illnesses.

Data collection and analysis—We extracted data independently. For dichotomous data we calculated relative risks (RR) and their 95% confidence intervals (CI) on an intention-to-treat basis, based on a fixed effects model. We calculated the numbers needed to treat/harm (NNT/NNH). For continuous data, we calculated weighted mean differences (WMD) again based on a fixed effects model.

Main results—We identified one randomised trial. No significant differences were found between the Cannabis and Psychosis Therapy (CAP) intervention group and the Psychoeducaton (PE) intervention for use of cannabis at three months assessment (n=47, RR 1.04 CI 0.6 to 1.7). BPRS-extended scale scores at three months assessment (n=47, WMD −3.60 CI −12.8 to 5.6) and nine months assessment (n=47, WMD 0.80 CI −7.5 to 9.1) were non-significant between CAP and PE. We found no significant improvement in social functioning in the CAP group compared with PE (at 3 months, n=47, WMD −0.80 CI −10 to 8.4) and (at 9 months, n=47, WMD −4.70 CI −14.5 to 5.1).

Contact address: John Rathbone, HEDS, ScHARR, The University of Sheffield, Regent Court, 30 Regent Street, Sheffield, S1 4DA, UK. J.Rathbone@sheffield.ac.uk. John.Rathbone@nottingham.ac.uk.

CONTRIBUTIONS OF AUTHORS John Rathbone - updated protocol, selected studies, data extracted, wrote final report.
Hannele Variend - selected studies, data extracted.
Hetal Mehta- selected studies.
Editorial group: Cochrane Schizophrenia Group.
Publication status and date: Edited (no change to conclusions), published in Issue 5, 2011.
Review content assessed as up-to-date: 21 August 2007.

DECLARATIONS OF INTEREST None.

Europe PMC Funders Author Manuscripts

Authors' conclusions—At present, there is insufficient evidence to support or refute the use of cannabis/cannabinoid compounds for people suffering with schizophrenia. This review highlights the need for well designed, conducted and reported clinical trials to address the potential effects of cannabis based compounds for people with schizophrenia.

Medical Subject Headings (MeSH)

Cannabis; Cannabinoids [therapeutic use]; Schizophrenia [* therapy]

MeSH check words

Humans

BACKGROUND

The cannabis plant (Cannabis sativa L.) grows in temperate and tropical areas. Herbal cannabis consists of the dried flowering tops and leaves. Cannabis resin is a compressed solid made from the resinous parts of the plant, and cannabis oil (hash) is a solvent extract of cannabis. Cannabis is usually smoked but occasionally ingested in foodstuffs.

Cannabinoids are present in the flowers, leaves, seeds and stalks of cannabis sativa, otherwise known as the hemp plant (Figure 1). Cannabinol was first isolated in 1895. An anonymous British physician working in British Guyana in 1893 (Tunving 1985) indicated that the use of cannabis might be a cause of mental illness. Dr Warnock in 1895, from his experience with inmates of the Cairo asylum in Egypt (Warnock 1903), also related abuse of hashish to mental illness and wondered how those outside the asylum could enjoy the drug without becoming ill. Concerns about its psychoactive properties date from 1928, when Egyptian and South African doctors stated that heavy use could cause mental disturbances (Berridge 2004).

Schizophrenia-like experiences have been described in cannabis smokers (Talbot 1969) and there have been anecdotal sporadic reports of cannabis-linked psychosis (Varma 1972, Chopra 1974) including the earliest reported British case of psychosis associated with cannabis abuse (Davison 1972). The diagnostic label of "cannabis psychosis" is less fashionable than it once was. It tended to be attached to young Afro-Caribbean patients (McGovern 1987), a practice which was rightly disputed (Carney 1984, Littlewood 1988). However, the relationship between cannabis and schizophrenia remains controversial.

In general, substance misuse has been reported to be the most prevalent comorbid condition associated with schizophrenia (Regier 1990) and cannabis is the most frequently used substance (Hall 1999, Farrell 1998). The reported rates of cannabis abuse among people with schizophrenia vary widely both within and between different countries, but are consistently higher than in other people with mental illnesses or in the general population (Smith 1994). The proportion of people with schizophrenia who use cannabis varies, but surveys commonly find prevalence rates to be about 40% (Table 1).

Europe PMC Funders Author Manuscripts

Cannabis contains the psychoactive constituent cannabinoid delta-9-tetrahydrocannabinol (THC). Concerns have been raised that THC concentrations in cannabis are higher than in the past, and therefore today cannabis usage poses a greater risk to health. Cannabis produced from intensive indoor cultivation methods has a higher concentration of THC than imported sources, which typically are not intensively cultivated. The higher concentrations have been attributed to the use of specific seed strains from the female plant which are grown in artificial light and prevented from undergoing fertilization or seed production. However, the majority of cannabis used in the UK originates from North Africa and the available data does not indicate an upward trend in potency from imported cannabis into Europe (EMCDDA 2004).

Cannabis as precipitant

A longitudinal follow-up study of Swedish conscripts Andreasson 1987 has shown that the relative risk for schizophrenia was up to six times greater in people who had reported high cannabis use (on more than 50 occasions) compared with non users, and cannabis was felt to be an independent risk factor for schizophrenia. Similar results were obtained in studies at five years post-conscription, to exclude the prodromal cases (Zammit 2002). This was replicated by Van Os 2002, and Arseneault 2002 in separate studies. A WHO study (Jablensky 1992) has shown that the use of cannabis early in the onset of schizophrenia is a predictor of a poor outcome. Another theory is that the continuous heavy use of cannabis can induce a psychotic illness, which is distinct from schizophrenia (Nunez 2002).

Cannabis as bidirectional perpetuant

In general cannabis use is felt to have a negative effect on the course and prognosis of the illness (Negrete 1986, Linszman 1994). A number of hypotheses have been put forward regarding the association between cannabis and schizophrenia. A recently published study (Hides 2006) examined the influence of cannabis use on psychotic relapse and the influence of psychotic symptom severity on relapse in cannabis use in the six months following hospital admission. They found that a higher frequency of cannabis use was predictive of psychotic relapse, after controlling for medication adherence, other substance use and duration of untreated psychosis. Also, an increase in psychotic symptoms was predictive of relapse to cannabis use. They concluded that the relationship between cannabis and psychosis might be “bidirectional”.

Self medication

An alternative theory is that cannabis is used by people with distressing psychotic symptoms as a form of self medication (Dixon 1990), or to reduce the unpleasant adverse effects caused by antipsychotic drug treatment. It has also been proposed that the negative symptoms of schizophrenia (affective flattening, poor volition, poverty of thought, social withdrawal) may be improved by use of cannabis.

Technical background

The major active principle in all cannabis products is delta-9-tetrahydrocannabinol (THC) (Figure 2) It was first identified in 1964 (Gaoni 1964) and this compound seems responsible

for most of the psychological effects of marijuana (Isbell 1967). As cannabis or the cannabinoids lead to dopamine release (Tanda 1997) it would seem plausible that its use could precipitate or exacerbate illness.

Cannabinoids are a group of terpenophenolic compounds present in cannabis. Cannabinoids exert their effect through specific endogenous cannabinoid receptors. THC exerts its effect by interaction with neuronal (CB1) receptors which are found in the cerebral cortex, limbic areas, basal ganglia, thalamus and brain stem. Within the brain, THC and other cannabinoids are differentially distributed with high concentrations in cortical, limbic, sensory and motor areas. CB2 receptors have also been identified in macrophages and other immune cells. The cannabinoid system of the brain is modulated by endogenous cannabinoids which include anandamide and palmitoylethanolamide. Concentrations of endogenous cannabinoids have been found to be significantly higher in the cerebrospinal fluid of people with schizophrenia than in non-schizophrenic controls (Leweke 1999).

THC produces a euphoric effect, but it can cause perceptual alterations, impaired short term memory and attention, anxiety and panic attacks (Ashton 2001, Thomas 1996), and may lead to a withdrawal (Kouri 1999) or dependence syndrome (Stephens 1993). In high doses, visual and auditory hallucinations, delusions and thought disorder may result (Lishman 1998).

OBJECTIVES

To review the effects of cannabis use or cannabis withdrawal/antagonists on people with schizophrenia and schizophrenia-like illnesses.

METHODS

Criteria for considering studies for this review

Types of studies—We included randomised controlled trials. Where a trial was described as ‘double-blind’ but it was implied that the study was randomised we included these trials in a sensitivity analysis. If there was no substantive difference within primary outcomes (see types of outcome measures) when these ‘implied randomisation’ studies were added, then we included these in the final analysis. If there was a substantive difference only clearly randomised trials were utilised and the results of the sensitivity analysis were described in the text. We excluded quasi-randomised studies, such as those allocating by using alternate days of the week.

Types of participants—We included people with schizophrenia and other types of schizophrenia-like psychosis (e.g. schizophreniform and schizoaffective disorders), irrespective of the diagnostic criteria used. There is no clear evidence that the schizophrenia-like psychoses are caused by fundamentally different disease processes or require different treatment approaches (Carpenter 1994).

Types of interventions—

1. Cannabinoids: instigation of any dose or form of application.

Europe PMC Funders Author Manuscripts

2. Cannabinoids: withdrawal of any dose or form of application.
3. Cannabinoid antagonists.
4. Placebo or no treatment.
5. Any other treatments or interventions.

Types of outcome measures—

1. Death (suicide or natural causes)
2. Mental state
    - 2.1 No clinically important change in general mental state*
    - 2.2 Not any change in general mental state
    - 2.3 Average endpoint general mental state score
    - 2.4 Average change in general mental state scores
    - 2.5 No clinically important change in specific symptoms (Positive symptoms, negative symptoms, depression, mania)
    - 2.6 Not any change in specific symptoms
    - 2.7 Average endpoint specific symptom score
    - 2.8 Average change in specific symptom scores
3. General functioning
    - 3.1 No clinically important change in general functioning
    - 3.2 Not any change in general functioning
    - 3.3 Average endpoint general functioning score
    - 3.4 Average change in general functioning scores
    - 3.5 No clinically important change in specific aspects of functioning, such as social or life skills
    - 3.6 Not any change in specific aspects of functioning, such as social or life skills
    - 3.7 Average endpoint specific aspects of functioning, such as social or life skills
    - 3.8 Average change in specific aspects of functioning, such as social or life skills
4. Global state
    - 4.1 Relapse*
    - 4.2 Time to relapse
    - 4.3 No clinically important change in global state

Europe PMC Funders Author Manuscripts

4.4 Not any change in global state

4.5 Average endpoint global state score

4.6 Average change in global state scores

5. Behaviour

5.1 No clinically important change in general behaviour*

5.2 Not any change in general behaviour

5.3 Average endpoint general behaviour score

5.4 Average change in general behaviour scores

5.5 No clinically important change in specific aspects of behaviour

5.6 Not any change in specific aspects of behaviour

5.7 Average endpoint specific aspects of behaviour

5.8 Average change in specific aspects of behaviour

6. Adverse effects

6.1 Clinically important general adverse effects

6.2 Any general adverse effects

6.3 Average endpoint general adverse effect score

6.4 Average change in general adverse effect scores

6.5 No clinically important change in specific adverse effects

6.6 Not any change in specific adverse effects

6.7 Average endpoint specific adverse effects

6.8 Average change in specific adverse effects

7. Leaving the study early

7.1 For specific reasons

7.2 For general reasons

8. Engagement with services

8.1 No clinically important engagement

8.2 Not any engagement

8.3 Average endpoint engagement score

8.4 Average change in engagement scores

9. Satisfaction with treatment

9.1 Recipient of care not satisfied with treatment

9.2 Recipient of care average satisfaction score

9.3 Recipient of care average change in satisfaction scores

9.4 Carer not satisfied with treatment

9.5 Carer average satisfaction score

9.6 Carer average change in satisfaction scores

10. Quality of life

10.1 No clinically important change in quality of life

10.2 Not any change in quality of life

10.3 Average endpoint quality of life score

10.4 Average change in quality of life scores

10.5 No clinically important change in specific aspects of quality of life

10.6 Not any change in specific aspects of quality of life

10.7 Average endpoint specific aspects of quality of life

10.8 Average change in specific aspects of quality of life

11. Service outcomes

11.1 Hospitalisation

11.2 Time to hospitalisation

11.3 Days in hospital

11.4 Change in hospital status

12. Economic outcomes

12.1 Direct costs

12.2 Indirect costs

* Primary outcomes of interest

We grouped outcomes into the short term (up to 12 weeks), medium term (13 to 26 weeks), and long term (more than 26 weeks).

Search methods for identification of studies

1. Electronic searching—We searched the Cochrane Schizophrenia Group register (April 2007) with the phrase:

[canna* or marijuana* or marihuana* in title, abstract and index terms of REFERENCE] or [cana* or marijuana* or marihuana* in interventions of STUDY]

This register is compiled by systematic searches of major databases, hand searches and conference proceedings (see Group Module).

2. Reference searching—We inspected reference lists of identified studies for more trials.

3. Personal contact—We contacted authors of relevant studies to enquire about other sources of relevant information.

Data collection and analysis

1. Study selection—We (JR, HV) independently inspected all identified citations for relevance independently. Citations were checked again by HM. Where disagreement occurred we attempted to resolve this by discussion, where doubt still remained we acquired the full article for further inspection. We independently decided whether the selected studies met the review criteria. Again, where disagreement occurred attempts were made to resolve this through discussion; if doubt still remained we added these trials to the list of those awaiting assessment pending acquisition of further information.

2. Assessment of quality—We assessed the methodological quality of included studies using the criteria described in the Cochrane Handbook (Higgins 2006), which is based on the degree of allocation concealment. Poor concealment has been associated with overestimation of treatment effect (Schulz 1995). Category A includes studies in which allocation has been randomised and concealment is explicit. Category B studies are those which have randomised allocation but in which concealment is not explicit. Category C studies are those in which allocation has neither been randomised nor concealed. Only trials that are stated to be randomised (categories A or B of the handbook) will be included in this review. The categories are defined below:

- **A.** Low risk of bias (adequate allocation concealment)
- **B.** Moderate risk of bias (some doubt about the results)
- **C.** High risk of bias (inadequate allocation concealment).

When disputes arose as to which category a trial should be allocated, again we attempted resolution by discussion. When this was not possible we did not enter the data and the trial was added to the list of those awaiting assessment until further information could be obtained.

3. Data collection We—(JR, HV) independently extracted data from selected trials. When disputes arose we attempted to resolve these by discussion. When this was not possible and further information was necessary to resolve the dilemma, we did not enter data and added the trial to the list of those awaiting assessment.

4. Data synthesis

4.1 Intention to treat analysis: We excluded data from studies where more than 50% of participants in any group were lost to follow up (this did not include the outcome of ‘leaving the study early’). In studies with less than 50% dropout rate, we assumed that participants had had a poor outcome and were included in the analysis (intention-to-treat / ITT analysis); except for the event of death, or adverse events in studies using a placebo comparator group.

We analysed the impact of including studies with high attrition rates (30-50%) in a sensitivity analysis. If inclusion of data from this latter group resulted in a substantive change in the estimate of effect, we did not add their data to trials with less attrition, but presented them separately.

4.2 Binary data: For binary outcomes (improved/not improved etc.) we calculated the relative risk (RR) and its 95% confidence interval (CI) based on a fixed effects model. Relative Risk is more intuitive (Boissel 1999) than odds ratios, and odds ratios tend to be interpreted as RR by clinicians (Deeks 2000). This misinterpretation then leads to an overestimate of the impression of the effect. When the overall results were significant and homogeneous we calculated the number needed to treat (NNT) and the number needed to harm (NNH).

Where possible, efforts were made to convert outcome measures to binary data. This can be done by identifying cut off points on rating scales and dividing participants accordingly into “clinically improved” or “not clinically improved”. It was generally assumed that if there had been a 50% reduction in a scale-derived score such as the Brief Psychiatric Rating Scale (BPRS, Overall 1962) or the Positive and Negative Syndrome Scale (PANSS, Kay 1986), this could be considered as a clinically significant response (Leucht 2005a, Leucht 2005b). It was recognised that for many people, especially those with chronic or severe illness, a less rigorous definition of important improvement (e.g. 25% on the BPRS) would be equally valid. If individual patient data were available, the 50% cut-off was used for the definition in the case of non-chronically ill people and 25% for those with chronic illness. If data based on these thresholds were not available, we used the primary cut-off presented by the original authors.

4.3 Continuous data

4.3.1 Normal distribution: Continuous data on outcomes in trials relevant to mental health issues are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data we applied the following standards to continuous final value endpoint data before inclusion: (a) standard deviations and means were reported in the paper or were obtainable from the authors; (b) when a scale started from zero, the standard deviation, when multiplied by two, should be less than the mean (otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution - Altman 1996); In cases with data that are greater than the mean they were entered into ‘Other data’ table as skewed data. If a scale starts from a positive value (such as PANSS, which can have values from 30 to 210) the calculation described above in (b) should be modified to take the scale starting point into account. In these cases skewness is present if 2SD>(S-Smin), where S is the mean score and Smin is the minimum score. We reported non-normally distributed data (skewed) in the ‘other data types’ tables.

For change data (mean change from baseline on a rating scale) it is impossible to tell whether data are non-normally distributed (skewed) or not, unless individual patient data are available. After consulting the ALLSTAT electronic statistics mailing list, we presented change data in RevMan graphs to summarise available information. In doing this, we

assumed either that data were not skewed or that the analysis could cope with the unknown degree of skew.

4.3.2 Final endpoint value versus change data: Where both final endpoint data and change data were available for the same outcome category, we only presented final endpoint data . We acknowledge that by doing this much of the published change data may be excluded, but argue that endpoint data is more clinically relevant and that if change data were to be presented along with endpoint data, it would be given undeserved equal prominence. Where studies reported only change data we contacted authors for endpoint figures.

4.3.3 Summary statistic: For continuous outcomes we estimated a weighted mean difference (WMD) between groups based on a fixed effects model. Continuous data presented without use of summary statistics (i.e. mean, SD, SE) were not considered good evidence, though the existence of these data were noted in the text.

4.3.4 Conversion to a common metric: To facilitate comparison between trials, we converted variables (such as days in hospital) that could be reported in different metrics (mean days per year, per week or per month) to a common metric (e.g. mean days per month).

4.4 Rating scales: A wide range of instruments are available to measure mental health outcomes. These instruments vary in quality and many are not valid, and are known to be subject to bias in trials of treatments for schizophrenia (Marshall 2000). Therefore continuous data from rating scales were included only if the measuring instrument had been described in a peer-reviewed journal.

4.5 Cluster trials: Studies increasingly employ cluster randomisation (such as randomisation by clinician or practice) but analysis and pooling of clustered data poses problems. Firstly, authors often fail to account for intra class correlation in clustered studies, leading to a unit-of-analysis error (Divine 1992) whereby p values are spuriously low, confidence intervals unduly narrow and statistical significance overestimated. This causes Type I errors (Bland 1997, Gulliford 1999).

Where clustering was not accounted for in primary studies, we presented the data in a table, with a (*) symbol to indicate the presence of a probable unit of analysis error. In subsequent versions of this review we will seek to contact first authors of studies to obtain intra-class correlation co-efficients of their clustered data and to adjust for this using accepted methods (Gulliford 1999). Where clustering has been incorporated into the analysis of primary studies, we will also present these data as if from a non-cluster randomised study, but adjusted for the clustering effect.

We have sought statistical advice and have been advised that the binary data as presented in a report should be divided by a design effect. This is calculated using the mean number of participants per cluster (m) and the intraclass correlation co-efficient (ICC) [Design effect=1+(m-1)*ICC] (Donner 2002). If the ICC was not reported it was assumed to be 0.1 (Ukoumunne 1999). If cluster studies had been appropriately analysed taking into account

intra-class correlation coefficients and relevant data documented in the report, we synthesised these with other studies using the generic inverse variance technique.

5. Investigation for heterogeneity—Firstly, we considered all the included studies within any comparison to judge for clinical heterogeneity. Then we visually inspected graphs to investigate the possibility of statistical heterogeneity. We supplemented this by using primarily the I-squared statistic. This provides an estimate of the percentage of variability due to heterogeneity rather than chance alone. Where the I-squared estimate was greater than or equal to 50%, we interpreted this as indicating the presence of considerable levels of heterogeneity (Higgins 2003). Where heterogeneity was present, reasons for this were investigated. If it substantially altered the results, data were not summated, but presented separately and reasons for heterogeneity investigated.

6. Addressing publication bias—We entered data from all included studies into a funnel graph (trial effect against trial size) in an attempt to investigate the likelihood of overt publication bias (Egger 1997).

7. Sensitivity analyses—We analysed the effect of including studies with high attrition rates in a sensitivity analysis.

8. General—Where possible, we entered data in such a way that the area to the left of the line of no effect indicated a favourable outcome for cannabis/cannabinoids.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

1. Excluded studies—We excluded one study. Meltzer 2004 used four novel antagonists (neurokinin, serotonin, cannabinoid and neurotensin) and a placebo, but the length of treatment intervention varied and we were unable to extract any usable data.

2. Awaiting assessment—Three studies are awaiting assessment. D'Souza 2005 is a randomised, double blind trial comparing placebo with 2.5 mg and 5 mg of Delta-9-tetrahydrocannabinol in people with schizophrenia, and we are seeking further data from this trial. Leweke 2000 is a double blind study comparing cannabidiol antagonist with amisulpiride in people with schizophrenia, and we are seeking the results from this trial. Leweke 2004 is a randomised, double blind, placebo controlled, crossover study involving people with schizophrenia; it compares cannabidiol antagonist with no treatment, and we are seeking further information.

3. Ongoing studies—We are not aware of any ongoing trials.

4. Included studies—We were able to include just one study Edwards 2006. This study randomised people diagnosed with first episode psychosis that were using cannabis. Participants were randomised to two intervention groups.

4.1 Length of trial: The study involved three months of intervention and a follow up period of six months.

4.2 Participants: Participants included in the study all had first episode psychosis and were diagnosed using the DSM-IV schedule. The inclusion criteria specified a DSM IV diagnosis of psychotic disorder i.e. schizophrenia, schizophreniform, schizoaffective, delusional disorder, bipolar disorder, major depressive disorder with psychotic features, psychosis not otherwise stated, and brief reactive psychosis.

4.3 Setting: The study was undertaken at The Early Psychosis Prevention and Intervention Centre (EPPIC) which is a youth orientated mental health service centre in Melbourne, Australia.

4.4 Study size: Forty seven people were randomised to Cannabis and Psychosis Therapy (CAP) or Psychoeducaton (PE) interventions.

4.5 Interventions: The main study group (n=23) of interest were given a behavioural modification intervention, Cannabis and Psychosis Therapy (CAP). This consisted of a individually delivered cognitive behavioural orientated programme provided as weekly sessions by trained clinicians over three months, and did not involve giving cannabis to participants. The aim of the CAP intervention is to reduce cannabis intake and to improve clinical and psychosocial functioning. CAP involves an assessment of engagement, followed by education about cannabis and psychosis and developing motivation to change. The focus of the therapy is determined by the phase of commitment to change and may include further educational sessions, motivational interviewing, goal setting, and discussion about relapse prevention. An active control group (n=24) was used which consisted of Psychoeducaton (PE), provided in ten individual sessions which explained psychosis, medication and other treatments, and relapse prevention, but did not discuss cannabis.

4.6 Outcomes

4.6.1 Rating scales

4.6.1.1.1 Cannabis and Substance Use Assessment Schedule - CASUAS (Wing 1990): This scale measures the percentage of days using cannabis in the past four weeks and includes an index of severity of cannabis use. The scale is modified from the Schedule for Clinical Assessment on Neuropsychiatry and includes similar information to the Addiction Severity Index.

4.6.1.2.1 Knowledge About Psychosis Questionnaire - KAPQ (Birchwood 1992): This questionnaire tests the patients understanding about psychosis and treatments.

4.6.1.3.1 Brief Psychiatric Rating Scale-E - BPRS-E (Overall 1962): The BPRS is an 18-item scale measuring positive symptoms, general psychopathology and affective symptoms. The original scale has sixteen items, but a revised eighteen-item scale is commonly used. Scores can range from 0-126. Each item is rated on a seven-point scale varying from ‘not present’ to ‘extremely severe’, with high scores indicating more severe symptoms. The BPRS-E is an expanded positive symptom subscale formed by summing conceptual

disorganisation, hallucinations, unusual thought content and suspiciousness items. Higher scores indicate worse outcome.

4.6.1.3.2 Beck Depression Inventory - BDI-SF (Beck 1961): This is a 21-item self-rating scale for depression. Each item comprises four statements (rated 0-4) describing increasing severity of the abnormality concerned. The person completing the scale is required to read each group of statements and identify the one that best describes the way they have felt over the preceding week. A total of 12/13 is an indicative score for presence of significant depression.

4.6.1.3.3 Scale for the Assessment of Negative Symptoms - SANS (Andreasen 1983): This scale allows a global rating of the following negative symptoms: alogia (impoverished thinking), affective blunting, avolition-apathy, anhedonia-asociality and attention impairment. Assessments are made on a six-point scale (0=not at all to 5=severe). Higher scores indicate more symptoms.

4.6.1.4.1 Social and Occupational Functioning Assessment Scale - SOFAS (Goldman 1992): The SOFAS focuses on the individual's level of social and occupational functioning while excluding severity of symptoms. It is a 100 point scale, with higher scores indicating better functioning.

Risk of bias in included studies

1. Randomisation—Participants were randomised in the Edwards 2006 study using computer generated numbers table, and sealed envelopes were used to conceal treatment allocation. This method of randomisation is important to exclude selection biases (Jüni 2001) and falls into quality category A (adequate concealment of allocation).

2. Blinding to interventions and outcomes—The Edwards 2006 study was single blind and attempts were made to maintain rater blindness by the use of separate rooms and administration procedures for staff. The success of blinding was not tested.

3. Follow-up—The last observation carried forward method was used by Edwards 2006 and all 47 participants were utilised in the reporting of outcome data. Attrition data were not reported.

4. Data reporting—Outcome data were reported with means and standard deviations, although some outcomes contained considerable skew (wide confidence intervals) and those are reported in 'other data' tables.

Effects of interventions

1. The search—The initial search of the Cochrane Schizophrenia Group's register of trials identified 55 references to 51 studies. After a careful examination of the abstracts, two were thought to be suitable for further examination. One study Meltzer 2004 was excluded as we were unable to extract any usable data. One study Edwards 2006 was included (n=47), comparing Cannabis and Psychosis Therapy (CAP) with an active comparator group given

Europe PMC Funders Author Manuscripts

psychoeducaton (PE). In addition, three trials were added to awaiting assessment until further information is obtained.

1.2 Cannabis usage: We found no significant difference between the CAP intervention group and PE for use of cannabis at three months assessment (n=47, RR 1.04 CI 0.6 to 1.7). Nine months data were also not significantly different (n=47, RR 1.30 CI 0.8 to 2.2). The percentage of days using cannabis and the severity of cannabis usage were also reported by Edwards 2006 but data were skewed and are reported in 'other data' tables. Both outcomes were however non-significant.

1.3 Global state - KAPQ: We found no significant difference in the knowledge of psychosis and treatments between intervention groups at three months (n=47, WMD 0.80 CI −1.8 to 3.4) and again no differences were found at nine months assessment (n=47, WMD 0.90 −1.4 to 3.2).

1.4 Mental state

1.4.1 BPRS: Average endpoint BPRS-extended scale scores at three months assessment (n=47, WMD −3.60 CI −12.8 to 5.6) and nine months assessment time point (n=47, WMD 0.80 CI −7.5 to 9.1) were not significantly different between the cannabis and psychosis therapy group, and those given psychoeducation. BPRS positive symptom scores were evaluated by Edwards 2006, but data were skewed and are reported in 'other data' tables.

1.4.2 SANS: Outcome data from the scale for the assessment of negative symptoms were skewed, although the authors reported no significant differences in negative symptom scores between groups.

1.4.3 BDI: Beck Depression Inventory scores were reported but these contained wide confidence intervals (skewed data) and are not reported here.

1.5 Social functioning - SOFAS: We found no significant improvement in social functioning in the CAP group compared with PE at three months assessment period (n=47, WMD −0.80 CI −10 to 8.4) and also at nine months (n=47, WMD −4.70 CI −14.5 to 5.1).

DISCUSSION

1. The search

The Cochrane Schizophrenia Group's register of trials is the most comprehensive register of its kind. It is compiled by searching mainstream and less well known bibliographic databases and from manual searches of key journals and conference proceedings. We were able to include only one study Edwards 2006 and found three additional studies (D'Souza 2005, Leweke 2000, Leweke 2004) which were added to awaiting assessment whilst further information is sought. Trials published in languages other than English, and those with equivocal results are often difficult to find, and our search relied heavily on English phrases. However, it seems unlikely that well designed and reported randomised trials went unnoticed.

2. COMPARISON 1. CANNABIS and PSYCHOSIS THERAPY versus PSYCHOEDUCATION

2.1 Cannabis usage—The key aim of this study was to minimise the usage of cannabis in people with first episode psychosis. None of the outcomes revealed any significant difference between groups. Had the study been larger, differences may have emerged. Given the lack of trial based data in this area this study provides a welcome appraisal, and hopefully more studies will shed light on the impact of cannabis in people with psychoses.

2.2 Global state—The KAPQ questionnaire was used to inform participants about psychosis, but did not reveal any differences in the groups understanding at the three and nine month assessment points. It is possible that the lack of significant differences to emerge may, in part, have been due to using an active control group.

2.3 Mental state—From the available data on the positive symptoms of psychosis measured with the BPRS scale, no differences emerged that demonstrated an overall benefit for CAP therapy compared with PE. Other scales were used but these reported skewed data which we had pre-stated we would not use due to too much inconsistency.

2.4 Social functioning—The participants' social functioning did not improve in either group during the trial whilst interventions were given for three months, or at the follow up stage six months later.

AUTHORS' CONCLUSIONS

Implications for practice

1. For people with schizophrenia—At present, the data is too limited to support, or refute, the use of cannabis/cannabinoid compounds for people suffering with schizophrenia.

2. For clinicians—There is insufficient trial-based evidence to support or refute the use of cannabis based interventions. Clearly the clinician cannot be sure that treating patients with cannabis/cannabinoid compounds is desirable practice. It is understandable if clinicians, and people with schizophrenia, felt that treatment outside of a randomised controlled trial would be difficult to justify.

3. For policy makers—There is an absence of robust data regarding the clinical implications of using cannabis based compounds in schizophrenia.

Implications for research

1. General—Public registration of a study before subjects are randomised would ensure that participants could be confident that people would know that the study had at least taken place. Compliance with CONSORT (Moher 2001), both on the part of authors and editors, would help to clarify methodology and ensure outcomes are reported in a manner that is accessible and usable to others. Failure to comply with CONSORT guidelines results in loss of data and confusion in results, neither of which helps clinicians, patients or managers.

2. Methods—Future trials should ensure that a clear description of the interventions are given. Such a study would only be meaningful if undertaken within usual resources available to routine care and measured outcomes of relevance to clinicians and recipients of care as well as researchers. Study samples should include people with schizophrenia and closely related disorders, or at least allow data on this group of people to be extracted from the paper.

Acknowledgments

We would like to thank Wendel Abel, Sean Dornan and David Wong for their valuable contribution to the development of the protocol.

We would like to thank Judy Wright for performing the trials search, Clive Adams for his advice and Tessa Grant for final stage editing.

SOURCES OF SUPPORT

Internal sources

- Leeds Community and Mental Health Services, NHS Teaching Trust, UK.
- University of the West Indies, Jamaica.

External sources

- No sources of support supplied

CHARACTERISTICS OF STUDIES

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

Edwards 2006

Methods	Allocation: randomised, computer generated, placed in sealed envelopes. Blinding: single; attempts to maintain rater blindness included use of separate rooms and admin procedures for staff. Duration: 3 months intervention phase followed by 6 months of follow up. Country: Melbourne, Australia. Setting: youth mental health service; early psychosis, prevention and intervention centre (EPPIC). Analyses: ITT analyses were used and last observation carried forward
Participants	Diagnosis: first episode psychosis (DSM-IV). N=47. History: patients continuing to use cannabis after initial treatment for FEP. Sex: male and female. Age: 15-29 years. Inclusion criteria: DSM-IV diagnosis of a psychotic disorder (i.e. schizophrenia, schizophreniform, schizoaffective, delusional disorder, bipolar disorder, major depressive disorder with psychotic features, psychosis not otherwise stated, brief reactive psychosis; Exclusion criteria: only participants with at least 10 weeks continuous cannabis usage prior to study were eligible for study inclusion
Interventions	1. Cannabis and Psychosis Therapy: mean no. of CAP sessions 8. N=23 2. Psychoeducation: mean no. of sessions 8. N=24. CAP therapy consisted of a cognitive-behavioural-orientated program delivered in weekly sessions by trained clinicians over 3 months Psychoeducation was an active control.
Outcomes	Behavioural: CASUAS. Mental state: BPRS, SANS, BDI-SF. Social functioning: SOFAS. Global state: KAPQ.

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	A - Adequate

CASUAS - Cannabis and Substance Use Assessment Schedule

BPRS-E - Brief Psychiatric Rating Scale-E

BDI - Beck Depression Inventory

SANS - Scale for the Assessment of Negative Symptoms

SOFAS - Social and Occupational Functioning Assessment Scale

KAPQ - Knowledge About Psychosis Questionnaire

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

Study	Reason for exclusion
Meltzer 2004	Allocation: randomised. Participants: people with schizophrenia. Interventions: neurokinin antagonist versus serotonin antagonist versus central cannabinoid antagonist versus neurotensin antagonist. Outcomes: no usable data.

DATA AND ANALYSES

Comparison 1

CANNABIS AND PSYCHOSIS THERAPY vs PSYCHOEDUCATION

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cannabis use: 1. Used cannabis in last 4 weeks	1	94	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.82, 1.67]
1.1 by 3 months - end of treatment	1	47	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.62, 1.74]
1.2 by 9 months - 6 months after end of treatment	1	47	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.79, 2.15]
2 Cannabis use: 2. Percentage days used cannabis in last 4 weeks (skewed data)			Other data	No numeric data
2.1 by 3 months - end of treatment			Other data	No numeric data
2.2 by 9 months - 6 months after end of treatment			Other data	No numeric data
3 Cannabis use: 3. Severity of cannabis use (skewed data)			Other data	No numeric data
3.1 by 3 months - end of treatment			Other data	No numeric data
3.2 by 9 months - 6 months after end of treatment			Other data	No numeric data

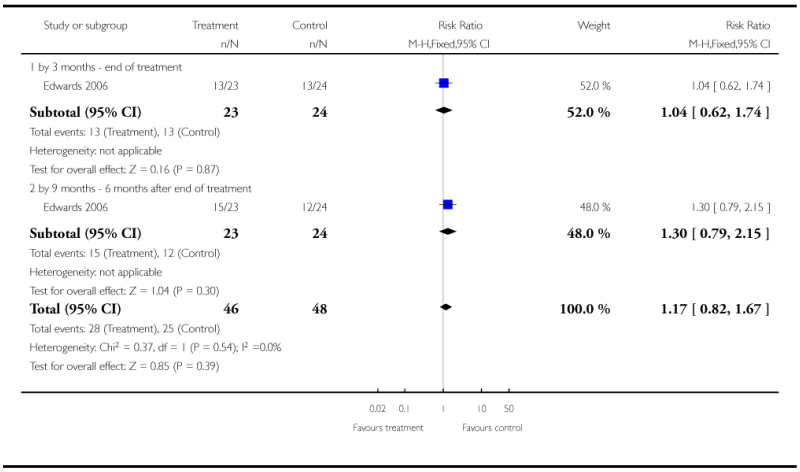
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Global state: Average score (KAPQ total endpoint, higher = good)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 by 3 months - end of treatment	1	47	Mean Difference (IV, Fixed, 95% CI)	0.80 [−1.78, 3.38]
4.2 by 9 months - 6 months after end of treatment	1	47	Mean Difference (IV, Fixed, 95% CI)	0.90 [−1.42, 3.22]
5 Mental state: 1. Average score (BPRS-E total endpoint, higher scores=poor)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 by 3 months - end of treatment	1	47	Mean Difference (IV, Fixed, 95% CI)	−3.60 [−12.81, 5.61]
5.2 by 9 months - 6 months after end of treatment	1	47	Mean Difference (IV, Fixed, 95% CI)	0.80 [−7.47, 9.07]
6 Mental state: 2. Average score (BPRS-PS total endpoint, higher scores=poor) (skewed data)			Other data	No numeric data
6.1 by 3 months - end of treatment			Other data	No numeric data
6.2 by 9 months - 6 months after end of treatment			Other data	No numeric data
7 Mental state: 3. Average negative symptom score (SANS endpoint, higher scores=poor) (skewed data)			Other data	No numeric data
7.1 by 3 months - end of treatment			Other data	No numeric data
7.2 by 9 months - 6 months after end of treatment			Other data	No numeric data
8 Mental state: 4. Average score (BDI-SF total endpoint , higher scores =poor) (skewed data)			Other data	No numeric data
8.1 by 3 months - end of treatment			Other data	No numeric data
8.2 by 9 months - 6 months after end of treatment			Other data	No numeric data
9 Social functioning: Average score (SOFAS total endpoint, higher scores =good)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 by 3 months - end of treatment	1	47	Mean Difference (IV, Fixed, 95% CI)	−0.80 [−9.95, 8.35]
9.2 by 9 months - 6 months after end of treatment	1	47	Mean Difference (IV, Fixed, 95% CI)	−4.70 [−14.52, 5.12]

Analysis 1.1. Comparison 1 CANNABIS AND PSYCHOSIS THERAPY vs PSYCHOEDUCATION, Outcome 1 Cannabis use: 1. Used cannabis in last 4 weeks

Review: Cannabis and schizophrenia

Comparison: 1 CANNABIS AND PSYCHOSIS THERAPY vs PSYCHOEDUCATION

Outcome: 1 Cannabis use: 1. Used cannabis in last 4 weeks



Analysis 1.2. Comparison 1 CANNABIS AND PSYCHOSIS THERAPY vs PSYCHOEDUCATION, Outcome 2 Cannabis use: 2. Percentage days used cannabis in last 4 weeks (skewed data)

Cannabis use: 2. Percentage days used cannabis in last 4 weeks (skewed data)

Study	Intervention	Mean	SD	N
by 3 months - end of treatment				
Edwards 2006	CAP	30.4	41.8	23
Edwards 2006	PE	18.8	30.6	24
by 9 months - 6 months after end of treatment				
Edwards 2006	CAP	32.4	44.9	23
Edwards 2006	PE	19.3	30.4	24

Analysis 1.3. Comparison 1 CANNABIS AND PSYCHOSIS THERAPY vs PSYCHOEDUCATION, Outcome 3 Cannabis use: 3. Severity of cannabis use (skewed data)

Cannabis use: 3. Severity of cannabis use (skewed data)

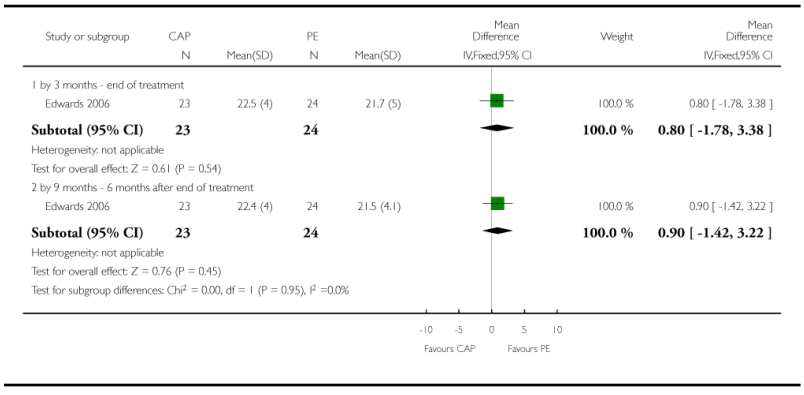
Study	Intervention	Mean	SD	N
by 3 months - end of treatment				
Edwards 2006	CAP	1.4	1.4	23
Edwards 2006	PE	1.3	1.4	24
by 9 months - 6 months after end of treatment				
Edwards 2006	CAP	1.4	1.4	23
Edwards 2006	PE	1.3	1.5	24

Analysis 1.4. Comparison 1 CANNABIS AND PSYCHOSIS THERAPY vs PSYCHOEDUCATION, Outcome 4 Global state: Average score (KAPQ total endpoint, higher = good)

Review: Cannabis and schizophrenia

Comparison: 1 CANNABIS AND PSYCHOSIS THERAPY vs PSYCHOEDUCATION

Outcome: 4 Global state: Average score (KAPQ total endpoint, higher = good)

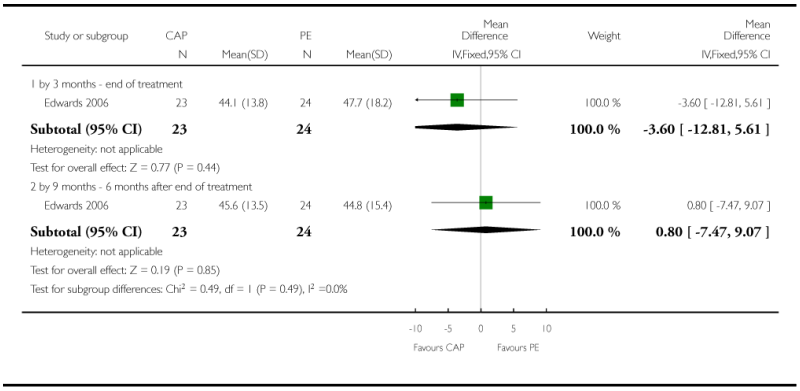


Analysis 1.5. Comparison 1 CANNABIS AND PSYCHOSIS THERAPY vs PSYCHOEDUCATION, Outcome 5 Mental state: 1. Average score (BPRS-E total endpoint, higher scores=poor)

Review: Cannabis and schizophrenia

Comparison: 1 CANNABIS AND PSYCHOSIS THERAPY vs PSYCHOEDUCATION

Outcome: 5 Mental state: 1. Average score (BPRS-E total endpoint, higher scores=poor)



Analysis 1.6. Comparison 1 CANNABIS AND PSYCHOSIS THERAPY vs PSYCHOEDUCATION, Outcome 6 Mental state: 2. Average score (BPRS-PS total endpoint, higher scores=poor) (skewed data)

Mental state: 2. Average score (BPRS-PS total endpoint, higher scores=poor) (skewed data)

Study	Intervention	Mean	SD	N
by 3 months - end of treatment				
Edwards 2006	CAP	8.9	4.8	23
Edwards 2006	PE	9.5	5.4	24
by 9 months - 6 months after end of treatment				
Edwards 2006	CAP	9.4	4.6	23
Edwards 2006	PE	8.8	4.8	24

Analysis 1.7. Comparison 1 CANNABIS AND PSYCHOSIS THERAPY vs PSYCHOEDUCATION, Outcome 7 Mental state: 3. Average negative symptom score (SANS endpoint, higher scores=poor) (skewed data)

Mental state: 3. Average negative symptom score (SANS endpoint, higher scores=poor) (skewed data)

Study	Intervention	Mean	SD	N
by 3 months - end of treatment				

Europe PMC Funders Author Manuscripts

Study	Intervention	Mean	SD	N
Edwards 2006	CAP	21.8	14.9	23
Edwards 2006	PE	23.5	14.0	24
by 9 months - 6 months after end of treatment				
Edwards 2006	CAP	23.7	17.2	23
Edwards 2006	PE	19.4	13.5	24

Analysis 1.8. Comparison 1 CANNABIS AND PSYCHOSIS THERAPY vs PSYCHOEDUCATION, Outcome 8 Mental state: 4. Average score (BDI-SF total endpoint , higher scores =poor) (skewed data)

Mental state: 4. Average score (BDI-SF total endpoint , higher scores =poor) (skewed data)

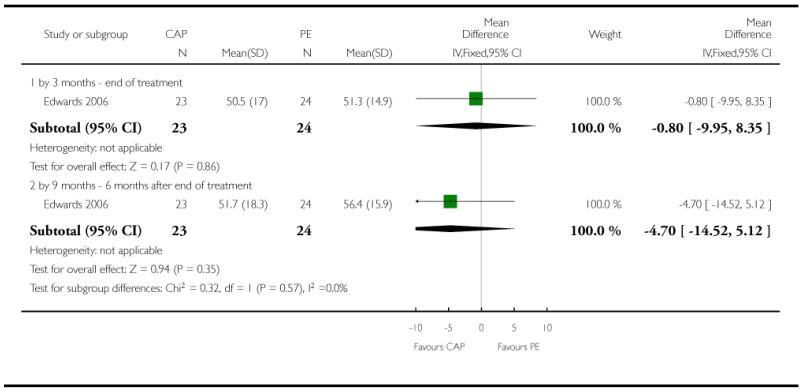
Study	Intervention	Mean	SD	N
by 3 months - end of treatment				
Edwards 2006	CAP	6.2	5.9	23
Edwards 2006	PE	7.8	8.1	24
by 9 months - 6 months after end of treatment				
Edwards 2006	CAP	7.5	6.3	23
Edwards 2006	PE	6.3	7.2	24

Analysis 1.9. Comparison 1 CANNABIS AND PSYCHOSIS THERAPY vs PSYCHOEDUCATION, Outcome 9 Social functioning: Average score (SOFAS total endpoint, higher scores =good)

Review: Cannabis and schizophrenia

Comparison: 1 CANNABIS AND PSYCHOSIS THERAPY vs PSYCHOEDUCATION

Outcome: 9 Social functioning: Average score (SOFAS total endpoint, higher scores =good)



HISTORY

Protocol first published: Issue 3, 2004

Review first published: Issue 3, 2008

Date	Event	Description
18 December 2008	Amended	plain language summary added
14 May 2008	New citation required and conclusions have changed	Full review published
19 March 2008	Amended	Converted to new review format.
22 August 2007	New citation required and conclusions have changed	Substantive amendment

WHAT'S NEW

Last assessed as up-to-date: 21 August 2007.

Date	Event	Description
13 April 2011	Amended	Contact details updated.

References to studies included in this review

Edwards 2006 {published data only} . Edwards, J. Early psychosis service developments: becoming real. 3rd International Conference on Early Psychosis; Copenhagen, Denmark. 2002 Sep 25-28; 2002. [: KA03]Edwards J, Elkins K, Hinton M, Harrigan SM, Donovan K, Athanasopoulos O, McGorry PD. Randomized controlled trial of a cannabis-focused intervention for young people with first-episode psychosis. Acta Psychiatrica Scandinavica. 2006; 114(2): 109–17. [MEDLINE: 16836598]. [PubMed: 16836598] Edwards J, Elkins KS, Hinton MF, Harrigan SM, Donovan KD, Athanasopoulos O. Randomized controlled trial of a cannabis-focused intervention versus psychoeducation for young people continuing to use cannabis in the 12 months following entry to treatment for first-episode psychosis. Schizophrenia Research. 2004; 70(1):61. [: ISI: 000224551100164].

Europe PMC Funders Author Manuscripts

References to studies excluded from this review

Meltzer 2004 {published data only} . Arvanitis L, Bauer D, Rein W. Results of the metatrial project: efficacy and tolerability of four novel compounds in schizophrenia and schizoaffective disorder. International Journal of Neuropsychopharmacology. 2002; 5(Suppl 1):S188. [: P.4.E. 039]. Meltzer HY, Arvanitis L, Bauer D, Rein W, Meta-Trial Study Group. Placebo-controlled evaluation of four novel compounds for the treatment of schizophrenia and schizoaffective disorder. American Journal of Psychiatry. 2004; 161(6):975–84. [MEDLINE: 15169685; : EMBASE 2004245661]. [PubMed: 15169685] Rein W, Arvanitis L. Antipsychotic effect of four different compounds - results of the metatrial. Journal of the European College of Neuropsychopharmacology. 2003; 13(4):S95. [: S.01.01].

References to studies awaiting assessment

D'Souza 2005 {published data only} . D'Souza DC. Pharmacological studies with delta-9-thc in schizophrenic patients versus controls. International Journal of Neuropsychopharmacology. 2002; 5(Suppl 1):S47. [: S.49.3]. D'Souza DC, Abi-Saab W, Madonick S, Wray Y, Forselius K, macDougall L, Brush L, Cassello K, Krystal J. Cannabinoids and psychosis: evidence from studies with IV THC in schizophrenic patients and controls. Schizophrenia Research. 2000; 41(1):33. [MEDLINE: 97202599]. D'Souza DC, Abi-Saab WM, Madonick S, Forselius-Bielen K, Doersch A, Braley G, Gueorguieva R, Cooper TB, Krystal JH. Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. Biological Psychiatry. 2005; 57(6):594–608. [MEDLINE: 15780846; : EMBASE 2005138690]. [PubMed: 15780846] D'Souza DC, Gil R, Zuzarte E, Zimmerman L, Abi-Saab D, Damon D, White J, Sernyak M, Krystal J. Tetrahydrocannabinol effects in schizophrenic subjects & healthy controls. Schizophrenia Research. 1997; 24(1,2):213. [MEDLINE: 97202599]. D'Souza, DCyril; Abi-Saab, Walid; Belger, Aysenil; Adams, Steve; Madonick, Steve; Larvey, Kristine; Cassello, Karyn; Sernyak, Michael; Krystal, John. Cannabinoid sensitivity in schizophrenia: evidence from a study with intravenous tetrahydrocannabinol in schizophrenics and controls. 21st Collegium Internationale Neuro-Psychopharmacologicum Congress; Glasgow, UK. 1998 Jul 12-16; 1998. [: APA2006L1.4102]D'Souza DD, Abi-Saab W, Madonic S, Belger A, Larvey K, Cassello K, Forselius K, Sernyak M, Krystal. Cannabinoids and psychosis: evidence from studies with IV THC in schizophrenics and controls. Schizophrenia Research. 1999; 1, 2 & 3:104. [MEDLINE: 97202599].

Leweke 2000 {published data only} . Leweke, M., et al. Cannabidiol versus amisulpiride for schizophrenia. Stanley Foundation Research Programs; 2000.

Leweke 2004 {published data only} . Leweke, FM. A 31-day, double-blind, randomized, placebo-controlled cross-over study of cannabidiol as monotherapy in 16 patients with schizophrenia. Stanley Foundation Research Programs; 2004. [: 05T–678]

Additional references

Altman 1996 . Altman DG, Bland JM. Detecting skewness from summary information. BMJ. 1996; 313:1200. [PubMed: 8916759]

Andreasen 1983 . Andreasen NC. Negative symptoms in schizophrenia. Archives of General Psychiatry. 1983; 39:784–8. [PubMed: 7165477]

Andreasson 1987 . Andreasson S, Allebeck P, Engstrom A, Rydberg U. Cannabis and schizophrenia: a longitudinal study of Swedish conscripts. Lancet. 1987; 2:1483–6. [PubMed: 2892048]

Arseneault 2002 . Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffit TE. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. BMJ. 2002; 325:1212–213. [PubMed: 12446537]

Ashton 2001 . Ashton CH. Pharmacology and effects of cannabis: a brief review. British Journal of Psychiatry. 2001; 178:101–6. [PubMed: 11157422]

Beck 1961 . Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Archives of General Psychiatry. 1961; 4:53–63.

Berridge 2004 . Berridge V. Cannabis Britannica: Empire, trade and prohibition. English Historical Review. 2004; 483:1075–11075.

Birchwood 1992 . Birchwood M, Smith J, Cochrane R. Specific and nonspecific effects of educational intervention for families living with schizophrenia. A comparison of three methods. The British Journal of Psychiatry. 1992; 160:806–14. [PubMed: 1617364]

Bland 1997 . Bland JM, Kerry SM. Statistics notes. Trials randomised in clusters. BMJ. 1997; 315:600. [PubMed: 9302962]

Boissel 1999 . Boissel JP, Cucherat M, Li W, Chatellier G, Gueyffier F, Buyse M, Boutitie F, Nony P, Haugh M, Mignot G. The problem of therapeutic efficacy indices. 3. Comparison of the indices and their use. Therapie. 1999; 54(4):405–11. [PubMed: 10667106]

Carney 1984 . Carney M, Bacelle L, Robinson B. Psychosis after cannabis use. BMJ. 1984; 288:1047. [PubMed: 6423193]

Carpenter 1994 . Carpenter WT Jr, Buchanan RW. Schizophrenia. New England Journal of Medicine. 1994; 330:681–90. [PubMed: 8107719]

Chopra 1974 . Chopra GS, Smith JW. Psychotic reactions following cannabis use in East Indians. Archives of General Psychiatry. 1974; 30:24–7. [PubMed: 4808733]

Davison 1972 . Davison K, Wilson H. Psychosis Associated with Cannabis Smoking. Addiction. 1972; 67(3):225–28.

Deeks 2000 . Deeks, J. Issues in the selection for meta-analyses of binary data. Abstracts of 8th International Cochrane Colloquium; Cape Town, South Africa. 2000 Oct 25-28th; 2000.

Divine 1992 . Divine GW, Brown JT, Frazer LM. The unit of analysis error in studies about physicians' patient care behavior. Journal of General Internal Medicine. 1992; 7:623–9. [PubMed: 1453246]

Dixon 1990 . Dixon L, Haas G, Wedien PJ, Sweeney J, Frances AJ. Acute effects of drug abuse in schizophrenic patients: clinical observations and patients' self-reports. Schizophrenia Bulletin. 1990; 16:69–79. [PubMed: 2185536]

Donner 2002 . Donner A, Klar N. Issues in the meta-analysis of cluster randomized trials. Statistics in Medicine. 2002; 21:2971–80. [PubMed: 12325113]

Egger 1997 . Egger M, Davey G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315:629–34. [PubMed: 9310563]

EMCDDA 2004 . An overview of drug potency in Europe. European Monitoring Centre for Drugs and Drug Addiction;

Farrell 1998 . Farrell M, Howes C, Taylor C. Substance misuse of psychiatric co-morbidity: an overview of the OPCS National Psychiatric Morbidity Survey. Addictive Behavior. 1998; 23:908–18.

Gaoni 1964 . Gaoni Y, Mechoulam R. Isolation, structure, and partial synthesis of an active constituent of hashish. Journal of the American Chemical Society. 1964; 86:1646–7.

Goldman 1992 . Goldman HH, Skodol AE, Lave TR. Revising axis V for DSM-IV: a review of measures of social functioning. American Journal of Pschiatry. 1992; 149:1148–56.

Gulliford 1999 . Gulliford MC, Ukoumunne OC, Chinn S. Components of variance and intraclass correlations for the design of community-based surveys and intervention studies: data from the Health Survey for England 1994. American Journal of Epidemiology. 1999; 149:876–83. [PubMed: 10221325]

Hall 1999 . Hall, W.; Johnston, L.; Donnelly, N. The Health Effects of Cannabis. 1st Edition. Toronto:Additction Research Foundation; Toronto: 1999.

Hides 2006 . Hides L, Dawe S, Kavanagh DJ, Young RM. Psychotic symptom and cannabis relapse in recent-onset psychosis. Prospective study. British Journal of Psychiatry. 2006; 189:137–43. [PubMed: 16880483]

Higgins 2003 . Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003; 327:557–60. [PubMed: 12958120]

Higgins 2006 . Higgins, JPT. Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006]. In: Higgins, JPT.; Green, S., editors. The Cochrane Library. John Wiley & Sons, Ltd.; Chichester, UK: 2006.

Isbell 1967 . Isbell H, Gorodetsky CW, Jasinski D, Claussen U, Spulak F, Korte F. Effects of 9-trans-tetrahydrocannabinol in man. Psychophormacologia. 1967; 11:184.

Jablensky 1992 . Jablensky A, Sartorius N, Ernberg G, Anker M. Schizophrenia: manifestations, incidence and course in different cultures: A World Health Organization ten-country study. Psychological Medicine. 1992; (Suppl 20):97.

Jüni 2001 . Jüni P, Altman DG, Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. BMJ. 2001; 323:42–6. [PubMed: 11440947]

Kay 1986 . Kay, SR.; Opler, LA.; Fiszbein, A. Positive and negative syndrome scale (PANSS) manual. Multi-Health Systems; North Tonawanda (NY): 1986.

Kouri 1999 . Kouri EM, Harrison G, Pope G Jnr. Changes in aggressive behavior during withdrawal from long term marijuana use. Psychopharmacology. 1999; 143:302–8. [PubMed: 10353434]

Leucht 2005a . Leucht S, Kane JM, Kissling W, Hamann J, Etschel E, Engel R. Clinical implications of Brief Psychiatric Rating Scale Scores. British Journal of Psychiatry. 2005; 187:366–71. [PubMed: 16199797]

Leucht 2005b . Leucht S, Kane JM, Kissling W, Hamann J, Etschel E, Engel R. What does the PANSS mean? Schizophrenia Research. 2005; 79:231–8. [PubMed: 15982856]

Leweke 1999 . Leweke FM, Guiffrida A, Wurster U, Emrich HM, Piomelli D. Elevated endogenous cannabinoids in schizophrenia. Neuroreport. 1999; 10:1665–69. [PubMed: 10501554]

Linszman 1994 . Linszman DH, Dingemans PM, Lenoir ME. Cannabis abuse and the course of recent onset schizophrenic disorders. Archives of General Adult Psychiatry. 1994; 51:273–9.

Lishman 1998 . Lishman, WA. Organic Psychiatry: The Psychological Consequences of Cerebral Disorder. 3rd Edition. Blackwell; Oxford: 1998.

Littlewood 1988 . Littlewood R. Ideology, Camouflage or Contingency? Racism in British Psychiatry. Transcultural Psychiatry. 1988; 30(3):243–90.

Marshall 2000 . Marshall M, Lockwood A, Adams C, Bradley C, Joy C, Fenton M. Unpublished rating scales - a major source of bias in randomised controlled trials of treatments for schizophrenia? British Journal of Psychiatry. 2000; 176:249–52. [PubMed: 10755072]

McGovern 1987 . McGovern D, Cope R. First admission rates of first and second generation Afro-Caribbeans. Journal of Social Distress and the Homeless. 1987; 22:139–48.

Moher 2001 . Moher D, Schulz KF, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA. 2001; 285:1987–91. [PubMed: 11308435]

Negrete 1986 . Negrete JC, Knapp WP, Douglas DE, Smith WB. Cannabis affects the severity of schizophrenic symptoms: results of a clinical survey. Psychological Medicine. 1986; 16:515–20. [PubMed: 3489951]

Nunez 2002 . Nunez LA, Gurpegui M. Cannabis-induced psychosis: a cross-sectional comparison with acute schizophrenia. Acta Psychiatrica Scandinavica. 2002; 105:173–8. [PubMed: 11939970]

Overall 1962 . Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. Psychological Reports. 1962; 10:799–812.

Regier 1990 . Regier DA, Farmer ME, Rae DS. Co-morbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiologic Catchment Area (ECA) study. Journal of the American Medical Association. 1990; 264:2511–8. [PubMed: 2232018]

Schulz 1995 . Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA. 1995; 273:408–12. [PubMed: 7823387]

Smith 1994 . Smith J, Hucker S. Schizophrenia and substance abuse. British Journal of Psychiatry. 1994; 165:13–21. [PubMed: 7953023]

Stephens 1993 . Stephens RS, Roffman RA, Simpson EE. Adult marijuana users seeking treatment. Journal of Consulting and Clinical Psychology. 1993; 62:1100–4. [PubMed: 8113490]

Talbot 1969 . Talbot JA, Teague JW. Marihuana, Psychosis: Acute Toxic Psychosis Associated With the Use of Cannabis Derivatives. Journal of the American Medical Association. 1969; 210:299–302. [PubMed: 5394365]

Tanda 1997 . Tanda G, Pontiere FE, DiChiara G. Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common mu1 opioid receptor mechanism. Science. 1997; 276:2048–50. [PubMed: 9197269]

Thomas 1996 . Thomas H. A community survey of adverse effects of cannabis use. Drug and Alcohol Dependence. 1996; 42:201–7. [PubMed: 8912803]

Tunving 1985 . Tunving K. Psychiatric effects of cannabis use. Acta Psychiatrica Scandinavica. 1985; 72:209–17. [PubMed: 3000137]

Ukoumunne 1999 . Ukoumunne OC, Gulliford MC, Chinn S, Sterne JAC, Burney PGJ. Methods for evaluating area-wide and organisation-based intervention in health and health care: a systematic review. Health Technology Assessment. 1999; 3(5):1–75.

Van Os 2002 . Van Os J, Bak M, Hanssen M, Bijl RV, de Graaf R, Verdoux H. Cannabis use and psychosis: A longitudinal population-based study. American Journal of Epidemiology. 2002; 156:319–27. [PubMed: 12181101]

Varma 1972 . Varma LP, Varma LP. Cannabis psychosis. Indian Journal of Psychiatry. 1972; 14:241–55.

Warnock 1903 . Warnock J. Insanity from Hasheesh. Journal of Mental Sciences. 1903; 49:96–110.

Wing 1990 . Wing, Jk; Barbo, T.; Brugha, T.; Burke, J.; Cooper, J.; Giel, R.; Jablenski, A.; Regier, D.; Sartorius, N. Schedules for Clinical Assessment in Neuropsychiatry. Archives of General Psychiatry. 1990; 47:589–93. [PubMed: 2190539]

Zammit 2002 . Zammit S, Allebeck P, Andreasson S, Lundberg I, Lewis G. Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. BMJ. 2002; 325:1199–201. [PubMed: 12446534]

* *Indicates the major publication for the study*

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

PLAIN LANGUAGE SUMMARY

Cannabis for schizophrenia

Schizophrenia is a mental illness characterised mainly by hallucinations and delusions (psychosis) which for the majority of people has an onset in late adolescence or early adulthood. Many people across many cultures, especially the young, use cannabis, a plant containing the psychoactive component delta-9-tetrahydrocannabinol. This plant, which is usually smoked or eaten, gives a feeling of well-being, but in high doses it may also cause psychosis and those who have schizophrenia may have a worse overall outcome from using it. There are some people with schizophrenia however, who claim that using cannabis helps their symptoms and reduces the adverse effects of antipsychotic medication. This review aims to look at the effects of cannabis, both its use and withdrawal, in people who have schizophrenia.

Four relevant studies were identified but three of these are awaiting assessment because further information is being sought from the trial authors. The last trial was based in a youth mental health service centre in Australia. It looked at whether a specific intervention using education on cannabis and psychosis and trying to motivate change (Cannabis and Psychosis Therapy CAP) or a series of general lectures explaining psychosis, treatments and relapse prevention (psychoeducation PE) was more likely to reduce the use of cannabis. The trial contained 47 people, 23 in the CAP group and 24 in the PE group. There were no significant differences between these two groups in the mental state of the people concerned after three months and nine months. There was also no significant difference in the use of cannabis, and knowledge on mental health and cannabis was the same in both groups. The main problem with this trial was the small number of people studied, and perhaps differences between the treatments would emerge with a larger number of people taking part. Overall, at present, it is still not possible to say whether using cannabis causes an improvement or a deterioration of the mental health of people with schizophrenia.

(Plain language summary prepared for this review by Janey Antoniou of RETHINK, UK www.rethink.org).

Figure 1.
Cannabis sativa

Europe PMC Funders Author Manuscripts

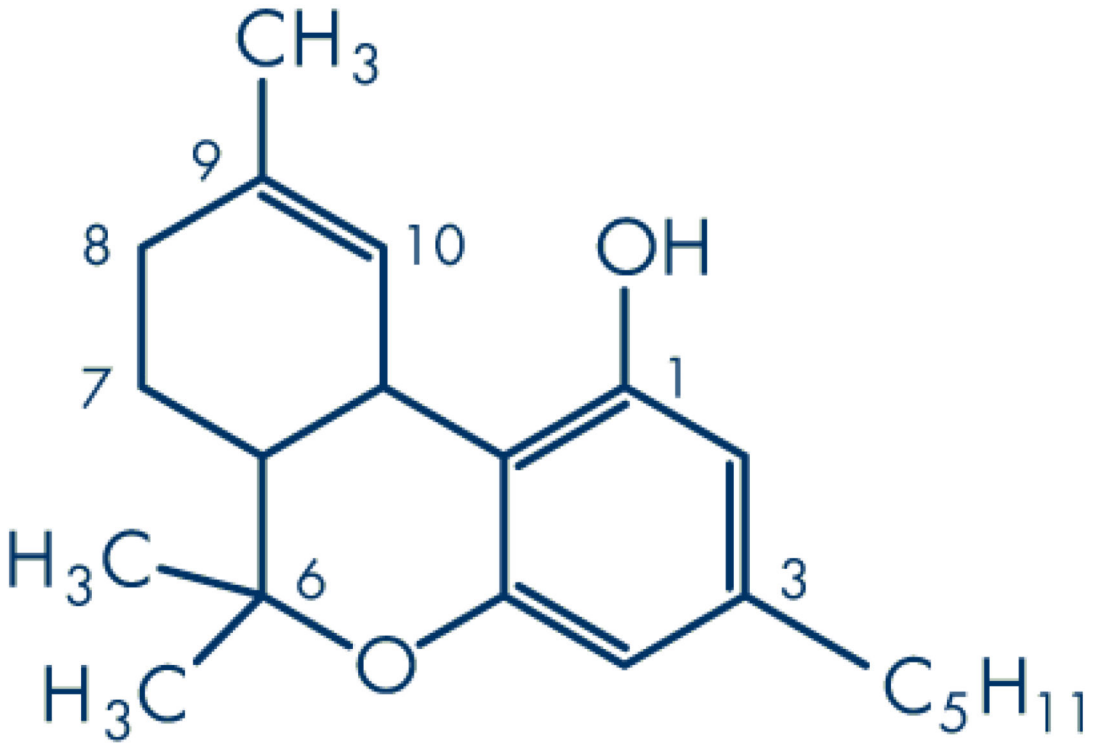


Figure 2.
delta-9-tetrahydrocannabinol (THC)

Europe PMC Funders Author Manuscripts

Table 1

Prevalence of cannabis use in people with schizophrenia

Proportion	Country	Study
5%	Germany	Soyka 1993
13%	Germany	Hambrecht 2000
18.9%	UK	Duke 2001
23%	USA	Regier 1990
40%	UK	Virgo 1998
40%	Australia	Baigent 1995
41.8%	USA	Warner 1994
42%	Ireland	Condren 2001
43%	Italy	Bersani 2002
69%	Sweden	Allebeck 1993