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Psychosocial interventions for cannabis abuse and/or dependence among persons with co-occurring cannabis use and psychotic disorders (Protocol)

Abayomi O, Adelufosi AO

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[Intervention Protocol]

Psychosocial interventions for cannabis abuse and/or dependence among persons with co-occurring cannabis use and psychotic disorders

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effectiveness of psychosocial interventions for treating cannabis abuse or dependence compared to no intervention or a different psychosocial intervention on reducing the use of cannabis in persons with co-occurring psychotic disorders.

BACKGROUND

Description of the condition

Cannabis contains the active ingredient delta-9-tetrahydrocannabinol which is available in the flowering tops, leaves and parts of the *Cannabis sativa* plant (UNODC 2007). According to the World Health Organization (WHO), the global 12-month prevalence of cannabis (2.5%) is higher than cocaine (0.2%) and opiates (0.2%) (WHO 2013). The highest rate of cannabis use is reported in North America (10.7%), followed by Oceania and Africa with a range of 3.8% to 10.4% of the population (UNODC 2012). Cannabis is the third most common type of drug dependence. In the United States, the annual prevalence of cannabis abuse and dependence is estimated at 1.8 %. Among cannabis users, dependence is as high as 9%. In persons with psychosis, higher prevalence rates (up to 22.5%) for cannabis misuse has been reported (Green 2005).

The two internationally recognised definitions of cannabis abuse or dependence, which are similar in most aspects, are the Diagnostic and Statistical Manual of Mental Disorders (DSM V) (APA 2013) and the International Classification of Diseases, tenth edition (ICD-10)(WHO 2009). DSM V defines cannabis use disorder as a problematic pattern of cannabis use leading to clinically significant impairment or distress. This is classified as mild, moderate or severe, depending on the number of symptoms involved. In ICD-10 (WHO 2009), the equivalent condition is described as harmful use or dependence according to severity of symptoms. Some of the clinical features include tolerance, withdrawal and loss of control. Cannabis use disorder was earlier classified as cannabis abuse and dependence by DSM IV (APA 1994).

Cannabis use may co-occur with psychotic disorders which include symptoms like delusions, hallucinations, and disorganised speech, abnormal psychomotor behaviour and negative symptoms. Persons with cannabis use disorders have been observed to have acute and chronic effects including perceptual distortions, psychosis, adverse social, legal and personal consequences (Hall 2009; NIDA 2010). High prevalence rates of co-occurring cannabis use and psychotic disorders have been reported in previous studies (Addington 2006; Barnett 2007; Moore 2007; Weich 2009).

In some individuals, cannabis may induce psychoses which remit following abstinence. This form of co-occurrence is transient and may be different from persons with co-occurring persistent psychotic disorders. Cannabis use impacts psychotic disorders in several ways. Its consumption has been reported to exacerbate positive and negative symptoms, trigger relapse and negatively influence the course and outcome of illness (Castle 2013). In view of this, it has been suggested that nonconsumption of cannabis may protect against relapse in persons with schizophrenia (San 2013). Cannabis use also impacts on cognitive functioning of persons with schizophrenia (Rabin 2013). Age of onset of cannabis use may predict age of onset of psychotic disorders (Galvez-Buccollini 2013). The most severe form of psychotic disorder is schizophrenia. This is a chronic disorder with a low incidence rate of 0.16 to 0.54/1000 and relatively high prevalence rate of 1.4 to 4.6/1000 depending on diagnostic criteria and population examined (Knapp 2004; Jablensky 2003). Schizophrenia-related psychosis has been associated with cannabis use. Studies have shown that persons with schizophrenia-related psychosis are more likely to use cannabis than the general population. According to a recent hospital-based study, 33.6% of persons with schizophrenia used cannabis and up to 88% of users were dependent (Lejoyeux 2014). This mirrors the global burden of disease (GBD 2010) study that found that cannabis use accounted for 7000 disability adjusted life years (DALYs) or 0.04% of schizophrenia (Degenhardt 2013). The possible contribution of cannabis to the development of schizophrenia-related psychosis has also been documented. For instance, a literature review concluded that cannabis use doubled the risk of schizophrenia onset in adolescence (Arsenault 2004). A clinically relevant feature of cannabis use in schizophrenia is cannabis withdrawal. This may contribute to relapse and impacts on persons with comorbidity (Boggs 2013). Although studies reveal that cannabis use is consistently associated with psychosis, more evidence on direction of causality and level of risk is needed in view of some conflicting findings (Minozzi 2010). The relationship between cannabis and psychosis may be modulated by some environmental and genetic factor (Parakh 2013). For example, in the genetics and psychosis study, the risk of psychosis was reported to be five times higher with high potency cannabis (Di Forti 2013). Also, significant interactions with AKT1 rs2494732 genetype with resultant deficits in task performance was reported when cannabis use preceded the onset of psychosis (Ozaita 2007; Van Winkel 2011). In another study, vulnerability to psychosis was found to be mediated by specific gene environment interactions including cannabis use (Smeets 2012).

Various neurobiological and neurochemical findings suggest a causal link between cannabis and schizophrenia-related psychosis. For example, tetrahydrocannabinoids, the main metabolite of cannabis, promotes release of dopamine which has been linked to psychosis (Thompson 2013). Also, cannabinoids may have a direct effect on thalamic activity leading to psychosis (Vukadinovic 2013). Factors contributing to continued use of cannabis concomitantly with psychotic disordersinclude peer influence and its use to overcome positive and negative symptoms (e.g. amotivation) of psychotic disorders. Two common hypotheses explain this phenomenon of comorbidity between substance use and mental disorders, namely the self medication and shared vulnerability hypotheses (Kessler 1996).

Description of the intervention

Psychosocial interventions are a broad range of interventions that emphasise psychological or social factors (e.g. family therapy) rather than biological factors (e.g. medications) (Ruddy 2005). They may be delivered at the individual, family or group level (WHO 2009a). Only validated psychosocial interventions will be included in this study. All types of psychosocial interventions targeting persons with cannabis will be included in this review.

According to the literature (Danovitch 2012), such psychosocial interventions include:

1. Cognitive behavioural therapy

This form of treatment was proposed by Aaron Beck in the 1980s. It is based on the premise that disorders are attributable to a person's perception of events rather than the events themselves. These distortions in cognitive thinking are related to self, world and future. There is an emphasis on eliciting and restructuring illogical thinking processes. It involves both the therapists and patients and focuses on resolving current problems while acquiring new skills (Semple 2005). In achieving this aim, varying behavioural and cognitive techniques may be used. The behavioural techniques involve activity scheduling, exposure, graded assignments, response prevention, distraction, relaxation training and assertiveness training. The cognitive techniques involve automatic thought identification, thought rehearsal and psychoeducation.

2. Motivational therapy

This form of psychosocial intervention is aimed at helping the patient become motivated to stop using psychoactive substances (Miller 1991). This is often based on the stages of change model proposed by Prochaska and Diclemente (Prochaska 1983). It involves helping clients to negotiate different levels of change. This begins from the stage of precontemplation through contemplation, preparation, action, maintenance and termination. The techniques of motivational interviews includes empathy, nonjudgmental approach, and rolling with resistance. Motivational therapy

may be required in different phases of interactions with clients including recruitment, retention, progress, process, and outcomes. The key characteristics are best described by the acronym FRAMES (Miller 1993):

- Personalised feedback or assessment results detailing the target behaviour and associated effects and consequences on the individual
- Emphasising the individual's personal responsibility for change
- Giving advice on how to change
- Providing a menu of options for change
- Expressing empathy through behaviours conveying caring, understanding and warmth
- Emphasising self efficacy for change and instilling hope that change is not only possible but also within reach.

3. Contingency management
This is based on the principle of operant conditioning which suggests that substance use is maintained partly by a chemical (dopamine relapse) and behavioural reward system (e.g. social relationships) (Stitzer 2006). This treatment reorganises the patient's environment to increase reinforcement for abstinence and reduce reinforcement for drug use. In order to unlearn drug-related behaviours, contingency management uses reinforcement techniques whereby substance use may lead to a loss of reinforcement, while reduction or abstinence leads to positive reinforcement i.e. payment of money or tokens to individuals.
4. Counselling
This involves providing information and advice to substance abusers. It may include elements of cognitive behavioural, psychodynamic and person-centred approaches. In non-directive counselling, the patient plays an active role in deciding themes and exploring emotional and cognitive conflicts, while the therapist is passive and does not provide feedback nor advice (Puri 2009).
5. Social network behaviour therapy
This is founded on the recognition of the impact of one's social environment on substance use (UKATT 2001). The therapist offers advice and feedback with a view to helping the patient maximise positive social support. The involvement of significant others (e.g. family members) may positively influence the patient's level of substance use (Puri 2009).
6. Twelve step approach
In this approach, persons with substance use disorders meet regularly to discuss and apply the principles of a twelve step ideology in order to achieve and maintain drug-free lifestyles. Although originally conceived as a self help scheme, it may also be facilitated by a therapist as part of comprehensive drug treatment available for patients at drug rehabilitation centres. Twelve step facilitation is a manual driven, structured programme delivered to individuals over a period of 12 to 26 weeks (Nowinski 1992). The use of twelve step programmes by groups such as Narcotics Anonymous has been identified as effective as other approaches (e.g. cognitive behavioural therapy) in meeting the goal of abstinence among persons with substance abuse problems (Ouimette 1997).
7. Family oriented therapy
This is based on the recognition of the role of family members in encouraging or discouraging the initiation and/or maintenance of substance use in individuals (Stanton 1997). For example, close parental relationships have been associated with reduced rates of risky substance use in some persons (Padila-Walker 2008). This has led to the involvement of family members in treatment. Approaches used vary widely. These include family psychoeducation, family or behavioural couples therapy, parenting education, parent-child therapy and reunification therapy (McGillicuddy 2001).
8. Brief intervention
This is a time bound intervention delivered in different settings with the aim of reducing risky substance use or increasing motivation for treatment. It involves providing counsel or advice or teaching behavioural skills during interactions between healthcare professionals and patients. It has been reported to be time efficient and cost effective in persons at low to moderate risk (Babor 2007).
9. Relapse prevention
In relapse prevention, people who abuse drugs are helped to develop skills to identify and avoid drug taking cues or triggers in the individual's internal or external environments. They may be trained to use a range of cognitive and behavioural strategies to cope effectively with these situations (Carroll 1996). It deals with factors influencing relapse such as craving, outcome expectancies, self efficacy, motivation, and emotional states. Several models of relapse prevention exist.
10. Community reinforcement approach
In this approach, the emphasis is placed on adjustments to environmental factors (e.g. work, recreation) in order to develop a more satisfying and rewarding lifestyle that is better than substance use (Miller 1991).

How the intervention might work

Psychosocial interventions are grounded in various theoretical models e.g. theory of change which may apply to both psychotic and non-psychotic substance using populations. In contrast to pharmacological treatments, psychotherapeutic interventions are not specific to psychoactive substances. Varying reasons have been provided for the potentially positive outcomes resulting from the use of psychosocial interventions in persons with substance use. These include shaping, operant conditioning and modelling. For example, behaviours may be modified by use of rewards (Dutra 2008; Semple 2005). Some of the techniques include information giving, client focused discussions and use of problem solving approaches. According to the transtheoretical model, motivational counselling may be a basis for relapse prevention strategies and facilitate treatment retention (Prochaska 1992) which are major challenges in persons with comorbid psychotic disorders (Hunt

2002). These strategies are particularly relevant to persons with co-occurring psychotic disorders who may require prolonged and intensive treatments. In persons with psychotic disorders, psychosocial interventions also play an important role in resolving intrapsychic conflicts, changing abnormal thought and behaviour patterns, and improving coping styles (Semple 2005). These could facilitate abstinence and prevent relapse in persons with cannabis and co-occurring psychotic disorders.

Why it is important to do this review

Treatment outcomes for persons with co-occurring cannabis use and psychotic disorders depend on certain factors e.g. perception and attitude to substance use and expectancies which may differ from persons without psychotic disorders (Hides 2009; Thornton 2012).In addition, poor insight, cognitive deficits, negative symptoms and stigma associated with mental illness may significantly influence the effectiveness and range of psychotherapeutic interventions available for persons with co-occurring disorders. In view of these, the effective treatment for cannabis use in persons with comorbid psychotic disorders may differ from those without similar comorbidity. Therefore a review of specific interventions targeting this special population is required (Hjorthoj 2009).
The Cochrane Drugs and Alcohol Group has conducted several reviews of psychosocial interventions on a range of substances, such as opioids (Amato 2011; Mayet 2005), alcohol (Kaner 2007; Mcqueen 2011), cocaine (Knapp 2007) and in special groups including, for example, pregnant women (Lui 2008). Although there is a recent review exploring psychosocial interventions for broad groups of substances in persons with severe mental illness (Hunt 2013), the use of varying psychosocial interventions for specific substances made comparisons difficult. Also, the Hunt 2013 review did not include some forms of clinically relevant psychotic disorders associated with Cannabis use e.g. affective disorders and substance induced psychosis. Clinically important subgroups, for example, cannabis abuse versus dependence, and first episode psychosis versus others are also needed (Hunt 2013). In view of these, it is important to undertake a review of evidence for psychosocial interventions in the treatment of cannabis abuse and/or dependence among persons with co-occurring psychotic disorders.

OBJECTIVES

To assess the effectiveness of psychosocial interventions for treating cannabis abuse or dependence compared to no intervention or a different psychosocial intervention on reducing the use of cannabis in persons with co-occurring psychotic disorders.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials or quasi-randomised controlled trials (these include trials where randomisation cannot be ruled out, and where allocation is known but is not considered strictly random).

Types of participants

Inclusion criteria:

- Persons with co-occurring cannabis abuse/dependence and psychotic disorders. This refers to persons with cannabis abuse or dependence meeting criteria for psychosis in the context of DSM V or ICD 10 disorders, including brief psychotic disorder, schizophrenia, schizophreniform disorders, schizoaffective disorders, delusional disorder and psychotic disorder, not otherwise specified.
- Setting: residential and outpatient facilities in primary, secondary, and tertiary care settings.

Exclusion criteria:

- Persons without psychotic disorders.

Types of interventions

Psychosocial interventions include "any non-pharmacological intervention carried out in a therapeutic context at an individual, family or group level" (WHO 2009a). It may include motivational enhancement therapy, twelve step facilitation, community reinforcement, self help groups, cognitive behaviour therapy, contingency management, social skills training, family involvement, peer support/counselling, or vocational/educational counselling. Comparisons will include no intervention, treatment as usual, or different psychosocial interventions.

Types of outcome measures

Primary outcomes

1. Use of cannabis at the end of treatment, as measured by:

- any biological marker of cannabis metabolites provided in original studies (e.g. urine drug screen or hair analysis);
- self reported use of cannabis.

Secondary outcomes

- Related to cannabis use

i) Severity of cannabis dependence, as measured by any validated scale such as the Addiction Severity Index etc.
ii) Motivation/confidence to change cannabis use

- Related to co-occurring psychotic disorder

i) Severity of psychotic symptoms measured with instruments, e.g. Brief Psychiatric Rating Scale

- Others

i) Adverse outcomes, as measured by:
a) perceptual distortions (time distortion, and impaired short-term memory and attention)
b) increase in anxiety or sleep disturbance
ii) Adherence, as measured by:
a) attendance at sessions
iii) Retention in treatment, as measured by:
a) number of participants who dropped out

Search methods for identification of studies

Electronic searches

The search will incorporate a number of methods to identify completed or ongoing studies.
We will obtain relevant trials from the following sources.

- Electronic Bibliographic Databases

- i) The Cochrane Central Register of Controlled Trials (CENTRAL- *The Cochrane Library*, most recent) which includes the Cochrane Drugs and Alcohol Groups Specialised Register
ii) PubMed (from 1966 to present)
iii) EMBASE (from 1988 to present)
iv) CINAHL Cumulative Index to Nursing and Allied Health Literature (1982 to present)
v) PsychINFO (1872 to present)
vi) ERIC (Education Resources Information Centre, (January 1966 to present)
vii) All EBM Reviews (1991 to present, Ovid Interface)
viii) AMED (Allied & Alternative Medicine) 1985 to present)
ix) ASSIA (Applied Social Sciences Index & Abstracts (1960 to present)
x) LILACS (Jan 1982 to present)
xi) National Register
xii) Web of Science (1900 to present)
- Electronic Grey Literature Databases

i) Dissertation Abstract
ii) Index to Theses

We will search databases using a strategy developed incorporating the filter for the identification of RCTs (Higgins 2011), combined with selected MeSH terms and free text terms relating to cannabis abuse/dependence. We will translate the PubMed search strategy into the other databases using the appropriate controlled vocabulary, as applicable. The search strategy for PubMed is shown in Appendix 1.

We will search for ongoing clinical trials and unpublished studies via Internet searches on the following websites.

1. www.controlled-trials.com
2. www.clinicalstudyresults.org
3. www.centrewatch.com

Searching other resources

We will also:

1. search references of the articles obtained;
2. search conference proceedings likely to contain studies relevant to the review; and
3. contact investigators and relevant study authors to seek information about unpublished or incomplete trials.

We will include non-English language literature searches and we will assess studies with English abstracts for inclusion. When considered likely to meet inclusion criteria, we will translate such studies.

Data collection and analysis

Selection of studies

Authors AO and AOA will independently inspect the study citations identified from the search. We will identify potentially relevant abstracts, order full papers and reassess these for inclusion and methodological quality. Where the authors disagree, the final decision will be made by consensus with the involvement of another member of the review team (EE).

Data extraction and management

Two authors (OA, AOA) will independently extract data from included studies. We will contact the authors of studies for any necessary clarification.
We will extract data onto standard, simple forms. We will use a data collection form template as used by the Cochrane Drugs and Alcohol Group (as shown in Appendix 2). One author will collate and enter data into Review Manager (RevMan 2014).

Assessment of risk of bias in included studies

The authors will independently assess risk of bias in accordance with the Cochrane Collaboration's recommendation for evaluating the risk of bias in included studies (Higgins 2011). The recommended approach for assessing risk of bias in studies included in Cochrane Reviews is a two-part tool, addressing seven specific

domains, namely sequence generation and allocation concealment (selection bias), blinding of participants and providers (performance bias), blinding of outcome assessor (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias. The first part of the tool involves describing what was reported to have happened in the study. The second part of the tool involves assigning a judgement relating to the risk of bias for that entry. To make these judgments we will use the criteria indicated by the *Cochrane Handbook for Systematic Reviews of Interventions*, adapted to the addiction field (Higgins 2011).

We will consider blinding of participants, personnel and outcome assessor (avoidance of performance bias and detection bias) separately for objective outcomes (e.g. drop out, use of substance of abuse measured by urine-analysis, subjects relapsed at the end of follow up, subjects engaged in further treatments) and subjective outcomes (e.g. duration and severity of signs and symptoms of withdrawal, patient self reported use of substance, side effects). We will assess the risk of bias, in each domain and overall, and categorise each domain as either:

1. low risk of bias: plausible bias unlikely to seriously alter the results;
2. high risk of bias: plausible bias that seriously weakens confidence in the results; or
3. unclear risk of bias.

If the raters disagree, the final rating will be made by consensus with the involvement of another member of the review team. Where inadequate details of randomisation and other characteristics of trials are provided, we will contact the authors of the studies in order to obtain further information.

We will consider incomplete outcome data (avoidance of attrition bias) for all outcomes. The 'Risk of bias' tool from the Cochrane Drug and Alcohol Group is shown in Appendix 3.

Measures of treatment effect

Binary data

For binary outcomes we will calculate the risk ratio (RR) and its 95% confidence interval (CI). For statistically significant results we will calculate the number needed to treat/harm statistic (NNT/NNH) and its 95% CI, taking account of the event rate in the control group.

Continuous data

Summary statistic

For continuous outcomes we will estimate a weighted mean difference (WMD) between groups. We will calculate WMDs and 95% CIs comparing the mean score differences from the end of treatment to baseline for each group. We will also use the standardised mean difference (SMD) when different scales or way to measure the same outcomes (e.g. quality of life) are used in different studies.

Endpoint versus change data

Where both final endpoint data and change data are available for the same outcome category, we will only present final endpoint data, as it is more clinically relevant. Where studies report only change data, we will contact authors for endpoint figures, but if endpoint data are unavailable, we will report change data.

Skewed data

Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we will apply the following standards to all data before inclusion: (a) standard deviations and means are reported in the paper or obtainable from the authors; (b) when a scale starts from the finite number zero, the standard deviation, when multiplied by two, is less than the mean (as otherwise the mean is unlikely to be an appropriate measure of the centre of the distribution; (c) if a scale starts from a positive value (such as PANSS which can have values from 30 to 210) the calculation described above will be modified to take the scale starting point into account. In these cases skew is present if 2SD > (S - S min), where S is the mean score and S min is the minimum score. Endpoint scores on scales often have a finite start and end point and these rules can be applied. When continuous data are presented on a scale which includes a possibility of negative values (such as change data), it is difficult to tell whether data are skewed or not. Skewed data from studies of less than 200 participants will be entered in additional tables rather than into an analysis. Skewed data pose less of a problem when looking at means if the sample size is large and will be entered into syntheses.

Unit of analysis issues

If all arms in a multi-arm trial are to be included in the meta-analysis and one treatment arm is to be included in more than one of the treatment comparisons, we will then divide the number of events and the number of participants in that arm by the number of treatment comparisons made. This method avoids the multiple use of participants in the pooled estimate of treatment effect, while retaining information from each arm of the trial. It does, however, compromise the precision of the pooled estimate slightly.

Dealing with missing data

Whenever possible, we would contact original investigators to request missing data. We will make explicit the assumptions of any methods used to cope with missing data. We will use sensitivity

analysis to assess how sensitive results are to reasonable changes in assumptions made. The potential impact of missing data on findings of the review will be treated in the Discussion.

Assessment of heterogeneity

We will test the presence of heterogeneity between the trials using the I^2 statistic and Chi^2 test. A P value of the Chi^2 test less than 0.10 indicates significant heterogeneity (Higgins 2011).

Assessment of reporting biases

We will use a funnel plot (plot of the effect estimate from each study against the sample size or effect standard error) to assess the potential for bias related to the size of the trials, which could indicate possible publication bias.

Data synthesis

We will assess the effectiveness of psychosocial interventions, first considering all types of interventions together (any type) - provided that this make any sense from a theoretical and practical perspective - and then we will assess them separately for different types of therapy (i.e. contingency management, psychodynamic approach, counselling, etc). This will include psychosocial interventions versus treatment as usual and psychosocial intervention A versus psychosocial intervention B.

We will combine the outcomes from the individual trials through meta-analysis, where possible (comparability of intervention and outcomes between trials). Based on the preliminary assumption of heterogeneity, we would apply a random-effects model.

Subgroup analysis and investigation of heterogeneity

If possible, subgroup analyses will include comparisons between men and women; residential versus outpatient facility; younger versus older persons; cannabis abuse versus cannabis dependence; first episode psychosis versus others; brief psychotic disorders versus others; trained people delivering the intervention versus non-trained people; and duration of contact between patient and deliverer of intervention. In order to minimise the likelihood of heterogeneity, either as a result of methodological diversity (e.g. studies with markedly different durations of follow-up timelines) or clinical diversity (e.g. patient characteristics), we will utilise the strategies stated in section 9.5.3 of the *Cochrane Handbook Systematic Reviews of Interventions* for addressing heterogeneity (Higgins 2011). This includes checking again that data are correct and exploring heterogeneity.

Sensitivity analysis

To incorporate assessment in the review process we will plot the intervention effects estimates stratified for risk of bias for each relevant domain. If differences in results are present among studies at different risk of bias, we will perform a sensitivity analysis, excluding from the analysis studies with high risk of bias (defined as at least three out of five domains being categorised as 'high risk'). We will also perform a subgroup analysis for studies with low and unclear risks of bias.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. PubMed search strategy

1. "Marijuana Abuse"[Mesh]
2. "Marijuana Smoking"[Mesh]
3. Cannabis[Mesh] OR canna*[tiab] OR marijuana*[tiab] OR marihuana*[tiab] OR hashish[tiab]
4. abstain*[tiab] OR abstin*[tiab] OR abuse*[tiab] OR dependen*[tiab] OR disorder*[tiab] OR intoxicat*[tiab] OR misuse[tiab] OR use*[tiab] OR withdrawal*[tiab]
5. #3 AND #4
6. #1 OR #2 OR #3 OR #5
7. Psychotic Disorders[Mesh]
8. Schizophrenia[Mesh]
9. schizo*[tiab] OR psychotic*[tiab] OR psychosis*[tiab] OR psychoses*[tiab]

10. ((chronic*[tiab] OR sever*[tiab]) AND mental*[tiab] AND (ill[tiab] OR illness[tiab] OR disorder*[tiab]))
11. #7 OR #8 OR #9 OR #10
12. psychotherapy [MeSH]
13. Counseling[Mesh]
14. incentive*[tiab] OR voucher[tiab] OR psychotherap*[tiab] OR psychosocial*[tiab] OR behaviour therapy[tiab] OR behavior therapy[tiab] OR reinforcement[tiab] OR motivation*[tiab] OR contingent*[tiab] OR advice[tiab] OR biofeedback[tiab] OR community[tiab] OR stimulation[tiab] OR education*[tiab] OR counsel*[tiab] OR 'cognitive therapy [tiab] OR CBT[tiab] OR 'family therapy [tiab] OR social skill [tiab] OR stress management training [tiab] OR supportive expressive therapy [tiab] OR neurobehavioral* [tiab] OR coping skill[tiab] OR self-control training[tiab]
15. #12 OR #13 OR #14
16. randomized controlled trial [pt]
17. controlled clinical trial [pt]
18. randomized [tiab]
19. placebo [tiab]
20. drug therapy [sh]
21. randomly [tiab]
22. trial [tiab]
23. groups [tiab]
24. #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
25. animals [mh] NOT humans [mh]
26. #24 NOT #25
27. #6 AND #11 AND #15 AND #26

Appendix 2. Data collection sheet

Study
Study title:
Authors:
Contact author address etc:
Source:
Year: Volume: Part: Pages:
Other references to this study? Yes/No Details:
1. Eligibility Verification
Randomised: Yes No Unclear
General eligibility criteria specific to the review:
Participants:
Interventions:
Control group:
Outcomes:
2. Study Characteristics
a) Methods
Patient blinding: Yes No Unclear
Outcome assessor blinding: Yes No Unclear
Cointerventions:
Other potential confounders:
b) Participants
Group 1 2 3 4
Number of patients:
Age:
Sex:
Concurrent conditions:
Other

characteristics:
Exclusion criteria:
Setting
Location:
Diagnostic criteria:
c) Interventions
Group 1 2 3 4
Intervention
Timing:
Duration:
Person delivering intervention
trained in that
specific intervention?:
d) Outcomes
Outcomes
Assessed:
Method of assessment:
Timing of assessment:
Length of follow-
up:
e) Results
Continuous Data
Treatment Group Control Group
Outcomes Time N Mean/Mean
Change
Standard Devi-
ation
N Mean/Mean
Change
Standard Devi-
ation
Dichotomous Data
Treatment Group Control Group
Outcome Time Observed Total Observed Total

Appendix 3. Criteria for risk of bias assessment for randomised controlled trials and clinical controlled trials

Item	Judgement	Description
1. Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process such as: random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimisation
	High risk	The investigators describe a non-random component in the sequence generation process such as: odd or even date of birth; date (or day) of admission; hospital or clinic record number; alternation; judgement of the clinician; results of a laboratory test or a series of tests; availability of

(*Continued*)

		the intervention
	Unclear risk	Insufficient information about the sequence generation process to permit judgement of low or high risk
2. Allocation concealment (selection bias)	Low risk	Investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based, and pharmacy-controlled, randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes
	High risk	Investigators enrolling participants could possibly foresee assignments because one of the following method was used: open random allocation schedule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure
	Unclear risk	Insufficient information to permit judgement of low or high risk This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement
3. Blinding of participants and providers (performance bias) Objective outcomes	Low risk	No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
	High risk	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
	Unclear risk	Insufficient information to permit judgement of low or high risk
4. Blinding of participants and providers (performance bias) Subjective outcomes	Low risk	Blinding of participants and providers and unlikely that the blinding could have been broken
	High risk	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding
	Unclear risk	Insufficient information to permit judgement of low or high risk

(*Continued*)

5. Blinding of outcome assessor (detection bias) Objective outcomes	Low risk	No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
	High risk	No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	Unclear risk	Insufficient information to permit judgement of low or high risk
6. Blinding of outcome assessor (detection bias) Subjective outcomes	Low risk	Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
	High risk	No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding
	Unclear risk	Insufficient information to permit judgement of low or high risk
7. Incomplete outcome data (attrition bias) for all outcomes except retention in treatment or drop out	Low risk	No missing outcome data; Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; Missing data have been imputed using appropriate methods; All randomised patients are reported/analysed in the group they were allocated to by randomisation irrespective of non-compliance and cointerventions (intention to treat)
	High risk	Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; For continuous outcome data, plausible effect size (difference in means

(*Continued*)

		or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation
	Unclear risk	Insufficient information to permit judgement of low or high risk (e.g. number randomised not stated, no reasons for missing data provided; number of drop out not reported for each group)
8. Selective reporting (reporting bias)	Low risk	The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way; The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon)
	High risk	Not all of the study's prespecified primary outcomes have been reported; One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not prespecified; One or more reported primary outcomes were not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; The study report fails to include results for a key outcome that would be expected to have been reported for such a study
	Unclear risk	Insufficient information to permit judgement of low or high risk
9. Other bias	Low risk	
	High risk	
	Unclear risk	

CONTRIBUTIONS OF AUTHORS

Abayomi Olukayode developed the protocol.

Adelufosi Adegoke assisted in writing the protocol.

DECLARATIONS OF INTEREST

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