Pharmacotherapies for cannabis withdrawal (Protocol)

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[Intervention Protocol]

Pharmacotherapies for cannabis withdrawal

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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 and safety of pharmacotherapies as compared with each other, placebo or no pharmacotherapy (supportive care) for reducing cannabis withdrawal and promoting cessation.

BACKGROUND

Description of the condition

Cannabis is the world's most widely produced, seized and consumed illicit drug (World Drug Report 2010).

The main active compound in all cannabis products is Δ^9- tetrahydrocannabinol (THC) (EMCDDA Cannabis Drug Profile). The number of cannabis users globally is estimated to range from between 129 to 191 million people or 2.9% to 4.3% of the world's population (World Drug Report 2010). Prevalence rates of cannabis use vary widely between regions, with the highest prevalence rates in Oceania, North America and sub-regions of Africa (World Drug Report 2010). Levels of cannabis use in Europe have generally stabilized, however rates of use are still increasing in some European countries (World Drug Report 2010). Cannabis use has declined in Oceania (World Drug Report 2010). In contrast, levels of cannabis use in South America, Africa and Asia appear to be rising (World Drug Report 2010). Cannabis use also appears to be increasing in the United States (SAMHSA 2010) although cannabis use in North America as a whole appears to be stabilizing or decreasing (World Drug Report 2010). Cannabis use within some indigenous communities in North America and Australia also appears to be more prevalent than their non-indigenous counterparts (Beauvais 2004, Clough 2004).

Cannabis use causes significant adverse effects (Budney 2007). Probable harmful consequences of cannabis use include cardiovascular disease, impaired respiratory function and an increased risk of involvement in motor vehicle accidents (Hall 2009). The use of cannabis has consistently been found to be associated with psychotic symptoms (Minozzi 2010).Intense long-term cannabis use has also been associated with impaired memory function, and these deficits are greater with the earlier age of initiation to cannabis use, and increased frequency, duration and dose of cannabis use (Solowij 2008). Memory deficits also appear to persist beyond the period of acute intoxication (Solowij 2008). Heavy users also report significantly lower levels of quality of life in terms of their physical and psychological health, the quality of their interpersonal relationships and work satisfaction (Gruber 2003). Cannabis use may also lead to dependence (Budney 2007). It has been estimated that some 10% of those who have used cannabis at least once, will develop cannabis dependence (Wagner 2002).

As with other drugs of dependence, the risk of developing dependency is influenced by multiple factors. However it is likely that intensive use of cannabis, that is daily or near daily use, is likely to increase the risk of cannabis dependence (EMCDDA 2004). It has been suggested that the earlier initiation of cannabis use, increased use of more potent forms of cannabis (e.g. the flowering heads of the female cannabis plant) and the greater use of waterpipes may have led to an increased amount of THC consumption by some cannabis users and therefore possibly greater rates of cannabis dependence (Hall 2001).

Estimates of the numbers of cannabis users experiencing withdrawal are variable (Agrawal 2008) (Hasin 2008) (Copersino 2006) (Chung 2008) (Cornelius 2008) (Budney 2006). Factors influencing the severity of cannabis withdrawal are yet to be identified, however it seems likely that the greater the intensity and duration of use, the greater the prevalence and severity of cannabis withdrawal symptoms, especially among those seeking treatment for cannabis dependence. More intensive cannabis users may therefore be more likely to experience withdrawal symptoms when the use of the drug is abruptly terminated, and they may therefore require assistance with the withdrawal and cessation process.

Support for a specific cannabis withdrawal syndrome has increased recently with the proposed inclusion of a cannabis withdrawal disorder in DSM-V (DSM-V). The signs and symptoms of the cannabis withdrawal syndrome include irritability, anger or increased aggression, nervousness or anxiety, sleep difficulty (insomnia), decreased appetite or weight loss, restlessness, depressed mood, and at least one of the following physical symptoms causing significant discomfort such as stomach pain, shakiness/tremors, sweating, fever, chills or headache (DSM-V). Symptoms of the cannabis withdrawal syndrome begin following cessation of heavy or prolonged cannabis use. Onset of symptoms is usually within 24 to 48 hours of abstinence, reaching peak intensity within the first week (Budney 2007). Symptoms may persist for up 3 to 4 weeks (Milin 2008), although there appears to be significant individual variability. The cannabis withdrawal syndrome is not life threatening nor is it associated with significant medical or psychiatric consequences (Budney 2003).

Demand for treatment for cannabis related disorders has generally increased worldwide over the past decade, albeit with significant regional variation. The World Drug Report gives data on treatment demand in terms of the proportion of treatment services provided for the major drugs of dependence. Cannabis related disorders have dominated demand for drug treatment in Africa over the past 10 years with treatment rates consistently over 60%. Demand for cannabis treatment has grown significantly in some regions, more than doubling in Europe and South America, and more than trebling in Oceania (World Drug Report 2010). North America as a whole was the only region to see a decrease in the contribution of cannabis to treatment demand (World Drug Report 2010), but within the United States, cannabis admissions increased by 32% between 1996 and 2006 (SAMHSA 2008).

Description of the intervention

There are currently no accepted pharmacotherapies for the treatment of cannabis withdrawal or cessation (Nordstrom 2007). The identification and development of medications to fill this gap has become an increasing priority among researchers (Vandrey 2009). However a number of pharmacotherapies have been proposed as possible experimental interventions to attenuate the symptoms and signs of cannabis withdrawal and promote cessation.

These medications fall into two broad groups. The first group are medications that affect cannabinoid receptor systems including agonist (e.g. preparations of THC), and antagonist medication (e.g. rimonabant). The second group are medications that affect the specific symptoms of cannabis withdrawal. This group includes medications that have previously been used in the treatment of other drug withdrawal syndromes (e.g. bupropion), as well as medications that are known to alleviate specific withdrawal symptoms such as irritability, anxiety or sleep difficulty (e.g. benzodiazepines).

How the intervention might work

The proposed pharmacologic interventions may potentially lessen the symptoms and signs of cannabis withdrawal. The availability of effective pharmacotherapy for cannabis withdrawal may encourage people who are cannabis dependent to enter treatment, and may increase the rates of completion of withdrawal, cessation of cannabis use and entry into relapse prevention treatment.

It has been reported that the experience of cannabis withdrawal symptoms may be a significant obstacle to achieving abstinence in cannabis dependent individuals (Budney 2006; Copeland 2001; Hart 2005). Therefore the effective treatment of the cannabis withdrawal syndrome is an important component of cessation and the first step in the establishment of abstinence.

Why it is important to do this review

As discussed above, there is increasing recognition that cannabis use and dependence is an important public health issue.

Not all cannabis users will need pharmacotherapies to manage withdrawal or support cessation of their use. However it is important that effective pharmacotherapies are identified for the treatment of cannabis withdrawal, especially in intensive cannabis users who describe withdrawal symptoms on cessation.

Three reviews have previously been undertaken in the area of pharmacotherapies for cannabis use disorders (Benyamina 2008; Nordstrom 2007; Vandrey 2009). However none of these are systematic reviews and they do not focus specifically on treatments for cannabis withdrawal and cessation.

No Cochrane review to date examines the effectiveness of pharmacotherapies for the treatment of cannabis withdrawal. This review will contribute to the establishment of best practice in the management of cannabis withdrawal and cessation.

OBJECTIVES

To assess the effectiveness and safety of pharmacotherapies as compared with each other, placebo or no pharmacotherapy (supportive care) for reducing cannabis withdrawal and promoting cessation.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised and quasi-randomised controlled trials examining pharmacological interventions for cannabis withdrawal will be included. These studies will have to provide detailed information on the type and dose of intervention medication used and the characteristics of patients treated. Studies will also be required to provide information on the nature and severity of withdrawal symptoms and signs experienced, the occurrence of adverse effects and the rates of completion of the scheduled intervention.

Types of participants

We will include studies that involve participants who are diagnosed according to DSM-IV or ICD-10 criteria as cannabis dependent or where dependence is likely based on reported dose, duration and frequency of use (daily or multiple days per week).

Studies involving participants dependent on, and withdrawing from, both cannabis and nicotine will be included. Subgroup analyses will be used to assess the impact of concurrent nicotine and cannabis withdrawal on the effectiveness of pharmacotherapies for cannabis withdrawal. Studies involving concurrent withdrawal from substances other than nicotine will be excluded.

Studies involving managed cannabis withdrawal within either an inpatient or outpatient setting will be included.

Types of interventions

Experimental interventions will involve the administration of medications with the aim of reducing the symptoms and signs of cannabis withdrawal or promoting cessation of cannabis use.

Comparison: Different pharmacotherapies, placebo or no pharmacotherapy (supportive care).

Types of outcome measures

Primary outcomes

1. Intensity of withdrawal; as measured via the use of visual analogue scales, peak withdrawal scores, the need for symptomatic medications in addition to the experimental intervention, and clinician and participant assessments of withdrawal.
2. Nature, incidence and frequency of adverse effects and whether the planned medication regime was modified in response to adverse effects.

3. Completion of withdrawal treatment; number of people who complete withdrawal treatment and the portion of the scheduled treatment episode that is completed on average.

4. Number of participants abstinent from cannabis at the end of treatment as determined by self-report and /or urine drug screens.

Secondary outcomes

1. Number of participants engaged in further treatment following completion of the withdrawal intervention. As discussed in the Background section, treatment of the cannabis withdrawal period may be considered as the first step in treatment, therefore engagement in further relapse prevention treatment may be considered to be a valid outcome of interest.

2. Level of cannabis use at the end of treatment; as measured via participant reported level of use and / or urine drug screens.

Search methods for identification of studies

All searches will include non-English language literature. We will assess studies with English abstracts on the basis of the abstract. If it is thought that the study is likely to meet inclusion criteria, it will be translated sufficiently to extract study methods and results.

Electronic searches

We will search:

1. Cochrane Central Register of Controlled Trials (*The Cochrane Library*, issue 10 2010) which includes the Cochrane Drugs and Alcohol Group' Register of Trials, via OVID Online

2. MEDLINE (1950 to Present with Daily Update) via Ovid Online

3. EMBASE (1980 to 2010 Week 28) via Ovid Online

4. PsycINFO (to 26 July 2010) via EBSCO Host

We developed a search strategy to retrieve references relating to the pharmacologic treatment of cannabis withdrawal. This strategy was adapted to each of the databases listed above.

For details see Appendix 1; Appendix 2; Appendix 3; Appendix 4.

We will also search some of the main electronic sources of ongoing trials:

- Current Controlled Trials (http://www.controlled-trials.com/)
- Clinical Trials.gov
- Osservatorio Nazionale sulla Sperimentazione Clinica dei Medicinali (https://oss-sper-clin.agenziafarmaco.it/)
- Trialsjournal.com

Searching other resources

We will check the reference lists of all relevant review articles and retrieved studies to identify any further studies of interest that were not retrieved by the electronic search. We will also contact selected researchers who are active in the area, seeking information about unpublished study reports. We will check conference proceedings likely to contain trials relevant to the review.

Data collection and analysis

Selection of studies

Two authors (KM and LG) will independently assess the titles and abstracts of records retrieved from the systematic search. Each author will assess potentially relevant studies for eligibility according to pre-defined inclusion and exclusion criteria. All authors agreed on the inclusion and exclusion criteria. The final selection of studies into the review will be undertaken by two authors. Disagreements about whether a study should be included or not will be resolved by discussion, or by referral to a third party if necessary (RA). No attempt will be made to blind the authors to the names of the study authors, institutions, journal of publication and results when eligibility criteria are applied.

Data extraction and management

Two authors (KM and LG) will independently extract data from the published reports using a data collection form. Disagreements will be resolved by discussion or by arbitration by a third party. Key findings of studies will be summarized descriptively in the first instance and the capacity for quantitative meta-analysis will be considered. We will contact study authors if we require additional information to include studies in meta-analyses.

Assessment of risk of bias in included studies

The Cochrane Handbook for Systematic Reviews of Interventions (Version 5.0.2 updated September 2009) recommends the use of a two-part tool to assess the risk of bias in studies included in Cochrane reviews. This tool addresses the specific domains of sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and 'other issues'. Each included study will be analysed and described according to these domains and a judgement of the likelihood of bias will be provided. A judgement of 'Yes' indicates low risk of bias, 'No' indicates high risk of bias and 'Unclear' indicates an unknown or unclear risk of bias. An assessment of the risk of bias for each eligible study will be included in the 'Characteristics of Included Studies' section. See Appendix 5 for the detailed description of the criteria used.

Measures of treatment effect

Where possible, the treatment effect for each dichotomous outcome will be expressed as a relative risk (RR) with 95% confidence intervals (CI). Where there is a comparable outcome measure (e.g.

time in treatment) the treatment effect for each continuous outcome will be expressed as a mean difference (MD) with 95% CIs. Where there is variability in outcome measure (e.g. withdrawal assessment scales) the treatment effect for each continuous outcome will be expressed as a standardized mean difference (SMD) with 95% CIs.

Unit of analysis issues

If there are trials with multiple treatment arms that may be included in a meta-analysis, then we will either combine groups to allow single-pair wise comparisons or we will set up separate analyses or perform subgroup analyses and suppress the calculation of overall totals to avoid the unit of analysis error of double-counting participants. Also if Urine Drug Screens are reported in studies, then the unit of analysis will be the number of study participants not the number of tests performed.

Dealing with missing data

When possible, attempts will be made to contact the original investigators to request missing data. If sufficient studies meet the inclusion criteria, a sensitivity analysis may be performed to assess the impact of different approaches to handling missing data. In addition the potential impact of missing data on review findings will be addressed in the discussion section.

Assessment of heterogeneity

Clinical and methodological heterogeneity will be assessed by reviewing the variations between studies in terms of the characteristics of participants included, the interventions and the reported outcomes. Meta-analysis will only be undertaken if sufficient studies are located that are clinically and methodologically suitable to combine.

In order to identify heterogeneity, results will be inspected graphically in the first instance. Where there is statistical heterogeneity as indicated by a Chi-squared test (p-value <0.05) or an I-squared statistic of at least 50%, then a random effects model will be used for meta-analyses.

Assessment of reporting biases

If a meta-analysis is conducted, funnel plots (plots of the effect estimate from each study against the standard error) will be used to assess the potential for bias related to the size of the trials, which could indicate possible publication bias.

Data synthesis

Statistical analysis will be undertaken using Review Manager 5. Dichotomous data (e.g. number completing treatment) will be used to calculate relative risks. For continuous data (e.g. withdrawal scores) either mean differences or standardized mean differences will be calculated. If significant statistical heterogeneity is detected, then a random effects model will be applied.

Subgroup analysis and investigation of heterogeneity

This review will consider the following potential sources of heterogeneity through subgroup analyses:

1. Patterns of cannabis use and the estimated level of THC intake (as indicated by duration and level of use, number of days of use, number of uses per day [frequency], modality of use / route of administration, age of initiation of use)
2. Concurrent tobacco smoking
3. Concurrent psychiatric illness +/- current treatment for a psychiatric illness
4. The nature of the treatment setting
5. The nature of adjunct treatment

Sensitivity analysis

Methodological quality will not be used as a criterion for inclusion in this review. We intend to perform a sensitivity analysis to judge methodological quality. If differences in results are present among studies at different risks of bias, then a sensitivity analysis will be undertaken. Studies with a higher risk of bias will be excluded from analysis at this stage.

ACKNOWLEDGEMENTS

None

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. CENTRAL Search strategy via OVID online

1. exp Cannabis/
2. cannabis.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
3. mari#uana.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
4. exp Marijuana abuse
5. exp Substance Withdrawal Syndrome/
6. exp Metabolic Detoxication, Drug/
7. (detoxifi$ or desintoxi$ or disintoxi$ or disintossi$ or withdrawal).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
8. 1 or 2 or 3 or 4
9. 5 or 6 or 7
10. 8 and 9

Appendix 2. MEDLINE Search Strategy via Ovid Online

1. (cannabis or mari#uana).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
2. exp Cannabis/
3. exp Marijuana Abuse/
4. withdrawal.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
5. exp Substance Withdrawal Syndrome/
6. (detoxifi$ or desintoxi$ or disintoxi$ or disintossi$).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]
7. exp Metabolic Detoxication, Drug/
8. 1 or 2 or 3
9. 4 or 5 or 6 or 7
10. 8 and 9
11. limit 10 to human

Appendix 3. EMBASE Search Strategy via Ovid Online

1. cannabis.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
2. mari#uana.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
3. *cannabis/
4. *cannabis addiction/ or *cannabis smoking/
5. *drug withdrawal/ or *withdrawal syndrome/
6. *drug detoxification/ or *detoxification/
7. (detoxifi$ or desintoxi$ or disintoxi$ or disintossi$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
8. 1 or 2 or 3 or 4
9. 5 or 6 or 7
10. 8 and 9
11. limit 10 to human

Appendix 4. PsycINFO Search Strategy via EBSCO Host

1. MM “Cannabis”
2. MM “Marijuana”
3. cannabis
4. mari#uana
5. MM “Marijuana Usage”
6. MM “Drug Withdrawal”
7. MM “Detoxification”
8. detoxification or detoxify or detoxified
9. S1 or S2 or S3 or S4 or S5
10. S6 or S7 or S8
11. S9 and S10
12. limit 11 to human

Appendix 5. Criteria for risk of bias assessment in RCTs and CCTs

	Item	Judgment	Description
1	Was the method of randomization adequate?	Yes	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; minimization
		No	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 the intervention
		Unclear	Insufficient information about the sequence generation process to permit judgement of Yes or No
2	Was the treatment allocation concealed?	Yes	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, randomization); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes
		No	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 non opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure
		Unclear	Insufficient information to permit judgement of Yes or No. 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	Was knowledge of the allocated interventions adequately prevented during the study? (blinding of patients, provider, outcome assessor) Objective outcomes	Yes	Blinding of participants, providers and outcome assessor and unlikely that the blinding could have been broken; Either participants or providers were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias No blinding, but the objective outcome measurement are not likely to be influenced by lack of blinding
		No	No blinding or incomplete blinding, and the outcome or outcome measurement 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;

(*Continued*)

			Either participants or outcome assessor were not blinded, and the non-blinding of others likely to introduce bias
		Unclear	Insufficient information to permit judgement of Yes or No;
4	Was knowledge of the allocated interventions adequately prevented during the study? (blinding of patients, provider, outcome assessor) Subjective outcomes	Yes	Blinding of participants, providers and outcome assessor and unlikely that the blinding could have been broken; Either participants or providers were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias
		No	No blinding or incomplete blinding, and the outcome or outcome measurement 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; Either participants or outcome assessor were not blinded, and the non-blinding of others likely to introduce bias
		Unclear	Insufficient information to permit judgement of Yes or No;
5	Were incomplete outcome data adequately addressed? For all outcomes except retention in treatment or drop out	Yes	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 standardized 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 randomized patients are reported/analyzed in the group they were allocated to by randomization irrespective of non-compliance and co-interventions (intention to treat)
		No	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 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 randomization;

(*Continued*)

		Unclear	Insufficient reporting of attrition/exclusions to permit judgement of Yes or No (e.g. number randomized not stated, no reasons for missing data provided; number of drop out not reported for each group);

HISTORY

Protocol first published: Issue 1, 2011

CONTRIBUTIONS OF AUTHORS

All authors contributed to the review concept and design. Kushani Marshall was responsible for the text of the protocol in consultation with Linda Gowing.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- WHO Collaborating Centre in the Treatment of Drug and Alcohol Problems, Australia.

External sources

- No sources of support supplied