Effectiveness and safety of psychosocial and pharmacological interventions for the treatment of cannabis use disorder (Protocol)

Funding statement:

This review is funded by the NIHR Evidence Synthesis Programme (NIHR165373 and NIHR167862)

Review registration:

NIHR165373: PROSPERO registration is not applicable. This work is an update and expansion of a previous systematic review that has an ongoing registration with the Cochrane Library: CD008940 Original Cochrane protocol (Marshal 2011): https://doi.org/10.1002/14651858.CD008940. The most recent version of the full review, which will be updated (Nielsen 2019): https://doi.org/10.1002/14651858.CD008940.pub3

NIHR167862: PROSPERO registration CRD42024553382

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Plain English summary

What is the problem?

Cannabis is commonly used worldwide as a recreational drug. Cannabis use disorder is a condition characterised by frequent use, craving and inability to stop using cannabis even when it is causing physical or psychological problems for the user. This condition has become much more common during the past three decades and this has led to an increase in the number of people seeking treatment for it. While specific medicines are not widely available and none are approved for this purpose, psychosocial treatments (such as talking therapies, or giving people incentives like vouchers for staying in treatment) are currently the first choice of treatment.

What are we trying to find out?

We will systematically search the existing literature to find studies that have assessed either medicines or psychosocial treatments for cannabis use disorder. We will then assess what treatments (or combination of treatments) work better for the people with cannabis use disorder. We also want to know the costs of these treatments, and which ones provide the best value for money. The knowledge generated by this review will help policy makers in the UK.

Abstract

Cannabis use disorder (CUD) is characterised by habitual use, craving and inability to stop consuming cannabis even when it is causing physical or psychological harm. Psychosocial interventions are usually the first choice of treatment for CUD. While there is increasing interest in pharmacological treatments for CUD, none are yet approved. This project will evaluate current evidence on the effectiveness, safety and cost-effectiveness of (i) pharmacological and (ii) psychosocial interventions for the treatment of CUD in adults and young persons aged >16 years. To review the effect of

pharmacological treatments we will work with collaborators from Cochrane to update an existing Cochrane review of pharmacotherapies for cannabis dependence published in 2019. We will follow the review's published methods, with the addition of economic outcomes. We will apply the same eligibility criteria to review the evidence for psychosocial interventions, so that the two reviews are aligned. The primary outcomes of interest are abstinence from cannabis use, intensity of withdrawal, adverse events, and treatment completion. For the update of the pharmacological therapies review, we will search Cochrane CENTRAL, MEDLINE, Embase, PsycINFO and Web of Science from the date of the last search (March 2018), using the published search strategy. For the psychosocial interventions we will adapt the search strategy and search databases from their inception. We will assess risk of bias using the RoB 2 tool and use GRADE framework to assess the certainty of the evidence.

Background

Cannabis is the most commonly used recreational drug worldwide, with an estimated 192 million users in 2018 or 3.9% of the global population. [1] Cannabis preparations are usually obtained from the female *Cannabis sativa* plant and delta-9-tetrahydrocannabinol (THC) is the principal psychoactive component of all cannabis product. The Prevalence of recreational use of cannabis is higher in high-income countries and it is sharply increasing in low-income and middle-income countries.[1] Cannabis use is higher among individuals that report psychiatric disorders, including psychotic symptoms,[2] mood disorder[3] anxiety disorder,[4] conduct disorder, personality disorder or attention deficit hyperactivity disorder (ADHD), as well as other substance use disorders.[5]

Broadly, cannabis use disorder (CUD) is characterised by habitual use, craving and inability to stop consuming cannabis even when it is causing physical and/or psychological harm, as well as tolerance and withdrawal symptoms when the substance use is ceased or significantly decreased.
The global incidence and prevalence cases of CUD have been sharply increasing during the past three decades, and it has been estimated that nearly 3 out of 10 cannabis users developed CUD in 2012–2013. [6] Data from the 2019 Global Burden of Disease Study (GBD) show that the incidence and prevalence of CUD increased by 32.3% and 38.6%, respectively, from 1990 to 2019 worldwide. Incident and prevalent cases in males are nearly double than that of females in 2019. Incident cases were 2.42 million and 1.32 million for male and female, respectively; prevalence cases were 15.63 million and 8.21 million for males and females, respectively.[7]

The burden of cannabis use in terms of disability-adjusted life years (DALY) is higher for young adults aged 20-24 and adolescents with CUD, with serious deficits including slower psychomotor speed, poorer attention and memory, and disability.[8] Furthermore, neurocognitive deficits and functional impairment in adulthood are associated with heavy usage of cannabis during adolescence. [9] Cannabis use disorder is also associated with increased risk of cardiovascular and respiratory diseases as well as overall mortality in adulthood.[10]

From a societal perspective, evidence from longitudinal studies have shown that, in adolescent and young adults, cannabis use is associated with lower income, lower college degree completion, a greater need for economic assistance, unemployment, use of other drugs, as well as higher rates of juvenile offending and affiliations with delinquent and substance-using peers.[10]

The increase in CUD prevalence is accompanied by an increase in the number of persons seeking treatment for CUD and its associated conditions. For most substance use disorders, the optimal treatments combine psychosocial and pharmacological interventions. However, for CUD, while psychosocial interventions are the first choice of treatment, pharmacological treatments are not commonly available. Various psychosocial interventions which identify the importance of the

individual or the social environment including motivational enhancement therapy (MET) and cognitive behavioural therapy (CBT), as well as abstinence-based contingency management strategies have been shown to be effective alone or in combination in reducing cannabis use frequency and quantity, abstinence rates, severity of CUD and cannabis-related problems.[11]

Currently there are no specific drugs for the treatment of CUD and their development is a high priority. A number of pharmacotherapies that are currently prescribed for the treatment of other mental health disorders have been proposed as possible interventions to promote cessation of cannabis use and to alleviate the symptoms of cannabis withdrawal. These include antidepressant, anticonvulsant and anxiolytic drugs, as well as medical preparations of THC. To date, evidence show that none of these drugs are effective in treating CUD, but the evidence on the effectiveness is limited.[12]

Aims and Objectives

In this review we aim to assess the effectiveness, safety and cost-effectiveness of:

1) pharmacological interventions (research question 1) and
2) psychosocial interventions (research question 2)

for the treatment of cannabis use disorder.

Methods

This review will follow the methods described in the published Cochrane protocol (Marshal 2011)[13] and in the most recent version for the full review of pharmacotherapies for cannabis dependance by Nielsen 2019.[12] The review will be expanded to include also psychosocial interventions, applying the same methods, as described below. We will carry out some additional components that were not included in the Nielsen 2019 review, these are outlined below.

Eligibility criteria

Eligibility criteria for population and study designs are as described in Nielsen 2019,[12] as follows:

Population:

- Adults and young people (≥16 years) diagnosed as cannabis dependent, undergoing withdrawal, or who were likely to be dependent based on reported dose, duration and frequency of use (daily or multiple days per week).
- For research question 2 only: Adults in remission from CUD or dependence (e.g., who are in maintenance phase of treatment)

Settings:

- Outpatient and community-based treatment settings.
- Inpatient care settings.

Exclusions:

- Adolescents and children (<16 years)
- Studies in participants who have co-occurring schizophrenia, delirium, or psychosis will be excluded.
- Studies of participants with co-occurring substance use disorders (other than tobacco/nicotine).
- Studies undertaken in purely research settings, such as residential research laboratories.

Study designs: randomised controlled trials.

Interventions

Research question 1 (pharmacological interventions)

We will include studies examining one or more pharmacological interventions for the management of cannabis use disorder, as described in Nielsen 2019.[12]

Research question 2 (psychosocial interventions)

We will include studies examining one or more psychosocial interventions for the management of CUD. We will include, but will not be limited to, the following psychosocial interventions delivered in group or individual format synchronously:

- Cognitive-behavioural therapy (CBT).
- Motivational interviewing/motivational enhancement therapy (MET).
- Components of cognitive and motivational approaches delivered with focus on the importance of obtaining social support (SS).
- Drug counselling and/or education (DC).
- Contingency management (CM).
- Mindfulness-based meditation (MM).
- Relapse prevention (RP).
- Combinations of the above and combinations of psychosocial and pharmacological therapies.

We will exclude asynchronous treatments, such as those delivered entirely by mail, mobile phone and computer-based treatments (e.g. web or mobile applications); pharmacological interventions, unless they are combined with psychosocial interventions.

Comparators

Eligible comparators are, as described in Nielsen 2019:

- Inactive interventions (including untreated/minimally treated control or delayed treatment control).
- Any other active intervention or a combination of active interventions (e.g., pharmacological interventions, psychosocial interventions and combinations of psychosocial interventions with pharmacological interventions).

Outcomes of interest

Outcomes are the same as those included in Nielsen 2019 with the addition of economic outcomes, as follows:

Primary outcomes

- Effectiveness*:*
    - Number of participants abstinent from cannabis at the end of treatment as determined by self-report or urine drug screens, or both.
    - Intensity of withdrawal as determined by scores on withdrawal scales, the need for symptomatic medications in addition to the experimental intervention or overall assessments by clinicians and participants.
    - Completion of scheduled treatment
- Safety*:*

- Nature, incidence and frequency of adverse effects and whether the planned intervention was modified in response to adverse effects.
- Dropout due to adverse events.

Secondary outcomes

- Effectiveness*:*
  - Level of cannabis use at the end of treatment as measured via participant-reported level of use or urine drug screens, or both.
  - Number of participants engaged in further treatment following completion of the withdrawal intervention.
- Economic outcomes:
  - Incremental effectiveness and cost measures (e.g. incremental cost-effectiveness ratio).

Study identification

For research question 1 (pharmacological interventions) the search strategy will be these same as that used in Nielsen 2019. The bibliographic databases will be searched from the date of the previous search, March 2018. To identify economic evaluations associated with trials already included in the Nielsen 2019 we will check all primary and associated articles for relevant references.

For research question 2 (psychosocial interventions) a new search strategy using relevant subject headings (controlled vocabularies), text-words and search syntax will be designed for Cochrane CENTRAL, MEDLINE, and PsycINFO databases. We will not apply any language restrictions to the search. To identify further published or unpublished research, we will scan the reference lists of included studies and any relevant systematic reviews.

For both research questions an additional search applying a health economic study-specific filter will be conducted to identify trial-based full economic evaluations.

Review strategy

The review strategy will follow those described in Nielsen 2019.

In addition to the data collected by Nielsen 2029, we will extract the following data (for both research questions):

- population equity characteristics described by the PROGRESS+ acronym.[14]
- characteristics and results of economic evaluations/cost-effectiveness analyses (e.g., type of economic analysis, outcomes measured, discount rate, cost year, currency, and perspective).

Risk of bias assessment

For studies reporting clinical effectiveness and safety, risk of bias assessments will be conducted using the risk-of-bias 2 tool (RoB 2) for randomized trials. This differs from the methods used in Nielsen 2019, which used the original Cochrane Risk of Bias Tool.[15] For studies reporting economic outcomes we will use the Drummond and Jefferson 36-item critical appraisal checklist.[16] Assessments will be conducted independently by two reviewers. Any disagreements will be resolved by consensus or discussion with a third reviewer.

Synthesis methods

The synthesis strategy will follow methods described in Nielsen 2019 for both research questions. However, for research question 2, we will use odds ratios to summarise treatment effects alongside risk ratios.

Subgroup analyses

In addition to the subgroup analyses described in Nielsen 2019, we will consider population equity, following characteristics described by the PROGRESS+ acronym,[14] for both research questions.

For psychosocial interventions we will additionally consider treatment intensity (e.g., duration, number of sessions, use of booster sessions).

Public and patient involvement

We will work with the Bristol Drugs Project to identify members of the public with history of cannabis use to shape this project.

Declaration of author interests

Authors declare no conflicts of interest.

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