PROTOCOL: Comparative effectiveness, safety and acceptability of pharmacological and psychosocial interventions for the treatment of cannabis use disorder

NIHR Bristol Evidence Synthesis Group

1 Document history

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2 Authors

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3 Protocol registration

This review will be registered on a platform such as Open Science Framework or Research Registry (PROSPERO does not accept registrations of reviews for which data extraction has already started).

4 Funding statement

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5 Plain English summary

5.1 What is the problem?

Cannabis is commonly used worldwide as a recreational drug. Cannabis use disorder is a condition characterized 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.

5.2 What are we trying to find out?

We will bring together the available evidence on medicines and psychosocial treatments for cannabis use disorder. We will compare the different types of treatments (or combination of treatments) to

identify which are the best approaches for the people with cannabis use disorder. The knowledge generated by this review will help policy makers in the UK.

6 Scientific abstract

Cannabis use disorder (CUD) is characterized 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 pharmacotherapies for CUD, none are yet approved. This project will involve a secondary analysis of data from two completed systematic reviews examining the effectiveness and safety of pharmacotherapies (NIHR165373) and psychosocial interventions (NIHR167862) for CUD in adults and young persons aged ≥16 years. The primary outcomes of interest are point and continuous abstinence from cannabis and level of cannabis use at the end of treatment, treatment completion, and (severe) adverse events. We will conduct network meta-analyses (NMA) to evaluate comparative effects of different pharmacotherapies, and different psychosocial interventions, within each treatment type. An additional NMA will evaluate comparative effects of both types of treatments, if pharmacotherapies and psychosocial interventions can be connected within the same network. This analysis approach overcomes limitations of pairwise meta-analysis and allows to make use of both direct and indirect evidence to estimate relative effectiveness, safety, and acceptability of different therapies for CUD.

7 Background and objectives

Cannabis is the most commonly used recreational drug worldwide, with an estimated 192 million users in 2018 (3.9% of the global population).[1] Recreational use of cannabis is higher in high-income countries and is increasing in low- and middle-income countries.[1] Cannabis use is higher among people who report psychiatric diagnoses, including psychotic symptoms,[2] mood disorder,[3] anxiety disorder,[4] conduct disorder, personality disorder or attention deficit hyperactivity disorder, as well as other substance use disorders.[5]

Cannabis use disorder (CUD) is characterized by habitual use, craving and inability to stop consuming cannabis even when it is causing physical and/or psychological harm, as well as 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. Between 1990 and 2019, estimates from the Global Burden of Disease study suggest that the incidence and prevalence of CUD increased by 32.3% and 38.6%, respectively, worldwide. CUD is more common among males than females, with incident and prevalent cases in males being nearly double those in females in 2019.[6]

The burden of cannabis use in terms of disability-adjusted life years is higher for young adults aged 20-24 years and adolescents with CUD, with serious problems including slower psychomotor speed, and poorer attention and memory.[7] Furthermore, neurocognitive deficits and functional impairment in adulthood are associated with heavy use of cannabis during adolescence.[6] CUD is also associated with increased risk of cardiovascular and respiratory diseases as well as overall mortality in adulthood.[8] From a societal perspective, evidence from longitudinal studies has shown that, in adolescents and young adults, cannabis use is associated with lower income, lower college degree

completion, a greater need for economic assistance, unemployment, as well as higher rates of juvenile offending.[8]

The increase in CUD prevalence has been accompanied by an increase in the number of people seeking treatment for CUD. While psychosocial interventions are the first choice of treatment,[9, 10] it is not clear which specific approaches should be used. A recent systematic review found that motivation enhancement and cognitive behavioural therapy (MET-CBT), dialectical behavioural/acceptance and commitment therapies (DBT/ACT), contingency management (CM) based on abstinence, as well as community reinforcement may improve some CUD outcomes, when compared with inactive/nonspecific controls or alternative psychosocial interventions. However, we judged the certainty of this evidence to be very low.[11, 12]

Currently there are no specific drugs for the treatment of CUD[10] and the development of pharmacotherapies for substance misuse is a high priority.[13] Pharmacotherapies such as antidepressant, anticonvulsant and anxiolytic drugs, as well as medical preparations of THC, have been proposed as possible interventions to promote cessation of cannabis use and to alleviate the symptoms of cannabis withdrawal. A recent review update found that while some pharmacotherapies are promising, to date none have been demonstrated effectiveness in treating CUD[14, 15]

There are very few randomized controlled trials (RCTs) assessing the comparative effectiveness of psychosocial interventions or pharmacotherapies. Further, for many substance use disorders, optimal treatment combines psychosocial and pharmacological interventions. Although combinations of therapies have been evaluated in RCTs, where these studies have been included in previous evidence syntheses the focus of interest has been on their individual effects rather than potential additive, synergistic or antagonistic impacts on treatment outcomes. In part, this may be due to the use of standard, pairwise meta-analyses and therefore it is not clear which of the pharmacotherapies and psychosocial interventions are most effective, acceptable, and safest to use. A network meta-analysis (NMA) could overcome these limitations and enable the comparative effects of different psychosocial and pharmacological interventions to be estimated, including combination therapies, even if they have not been directly compared with each other in the primary studies. By capitalizing on all available data and strengthening intervention effect estimates by incorporating both direct and indirect evidence, a NMA could suggest which pharmacotherapies should be taken forward in further research.

7.1 Objectives

Using data from two recently conducted systematic reviews conducted by the NIHR Bristol Evidence Synthesis Group and external collaborators, the primary objective is to conduct a NMA to assess the comparative effectiveness, safety and acceptability of (*i*) all psychosocial interventions and (*ii*) all pharmacotherapies to treat CUD in adults and young people aged ≥16 years.

A secondary research objective is to conduct (*iii*) a combined NMA to evaluate the comparative effects of all psychosocial interventions and pharmacotherapies. However, this combined analysis will only be possible if psychosocial interventions and pharmacotherapies form a connected network.

7.2 Public involvement

As this project will bring together data from two existing systematic reviews, we are not planning to involve the public or patients in the initial stages. We will seek lived experience perspectives for interpretation of findings and dissemination.

8 Methods

This project will use data from two completed systematic reviews examining the effectiveness and safety of pharmacotherapies (NIHR165373) and psychosocial interventions (NIHR167862, CRD42024553382) for CUD. The review protocols were registered with PROSPERO or Cochrane.[12, 14-17] Review PICOs were closely aligned, and no substantial modifications are planned for analyses contributing to the primary objective of the present review (see Table 1). However, for our secondary objective of conducting a NMA combining both psychosocial interventions and pharmacotherapies, modifications to the intervention eligibility criteria will be necessary. Full details of which are outlined in section 8.2.1.

8.1 Eligibility criteria

Table 1. Inclusion and exclusion criteria for the planned network meta-analysis.

Participants	Inclusion criteria: • Adults and young people (≥16 years) diagnosed as having cannabis use disorder, who are cannabis dependent, or who are likely to be cannabis dependent based on reported dose, duration or frequency of use. Exclusion criteria: • Studies in which more than half of the participants are <16 years or the mean age at baseline is <16 years. • Studies in participants who are in remission from cannabis use disorder or dependence (e.g. studies aiming to prevent relapse in participants who are already detoxified/abstinent/ are in maintenance phase). • Studies in participants who have co-occurring schizophrenia, delirium, or psychosis. • Studies specifically focused on participants who did not voluntarily seek treatment (e.g. court-mandated treatment, including probation services; prison/detention settings in which treatment is mandatory; inpatient settings where patients are detained and treatment is not voluntary). • Studies of 'opportunistic' screening and treatment, e.g. where individuals attending university or a health care service unrelated to drug use are screened and recruited/offered treatment. • Studies specifically focused on participants with co-occurring substance use disorders (other than tobacco/nicotine).
Interventions	*Psychosocial interventions NMA* Inclusion criteria: • Any synchronous psychosocial intervention, or combination of two or more psychosocial interventions, lasting more than 4 sessions (or min. 4 weeks). • Combination therapies of psychosocial and pharmacological interventions, if an effect of a psychosocial intervention is assessed. • *Examples of identified psychosocial interventions:* cognitive-behavioural therapy, motivational interviewing/enhancement therapy, contingency management, dialectical behavioural therapy, acceptance and commitment therapy, community reinforcement. *Pharmacotherapies NMA* Inclusion criteria: • Any pharmacotherapy or combination of two or more pharmacotherapies, of any duration.

	• Combination therapies of pharmacological and psychosocial interventions, if an effect of a pharmacotherapy is assessed. • *Examples of identified pharmacotherapies:* preparations containing THC, preparations containing CBD, antidepressants and anxiolytics, anticonvulsant and mood stabilizers, benzodiazepine and benzodiazepine-like medications. *Combined psychosocial and pharmacotherapies NMA* Inclusion criteria: • Any synchronous psychosocial intervention, or combination of two or more psychosocial interventions, lasting more than 4 sessions (or min. 4 weeks). • Any pharmacotherapy or combination of two or more pharmacotherapies, of any duration. • Combination therapies of psychosocial and pharmacological interventions, if psychosocial intervention component is synchronous and lasts more than 4 sessions (or min. 4 weeks).
Comparators	Inclusion criteria: • Any other eligible psychosocial intervention or pharmacotherapy, alone or in combination (as per intervention eligibility criteria for each NMA); or • Inactive control group (e.g. placebo, usual care/treatment as usual, no treatment, minimally treated control, delayed treatment control, supportive care).
Outcomes	Effectiveness outcomes: • Point abstinence at the end of treatment (based on urinalysis or self-report measures). • Continuous abstinence through to the end of treatment (based on urinalysis or self-report measures). • Level of cannabis use at the end of treatment (frequency or quantity of use). Safety outcomes: • Any adverse event. • Serious adverse events. Acceptability outcome: • Completion of scheduled treatment. • Adherence to treatment.
Study design	Inclusion criteria: • Randomized controlled trials, including individually randomized, cluster and cross-over designs (first period only).
Other considerations	Setting – inclusion criteria: • Outpatient and community-based treatment settings; or • Inpatient care settings. Setting – exclusion criteria: • Studies undertaken in purely research settings, such as residential research laboratories.

8.2 Rationale for eligibility modifications between separate and combined NMA

8.2.1 Interventions

For the primary objective to conduct separate NMA for (*i*) all psychosocial interventions and (*ii*) all pharmacotherapies, the intervention eligibility criteria are the same as those specified for each original review. However, as noted above, in order to conduct a combined NMA including all psychosocial interventions and pharmacotherapies, modifications to the original review intervention eligibility criteria are necessary so that psychosocial interventions are defined consistently when used as an adjunct to pharmacotherapies and as a standalone treatment (Table 1). Where a pharmacotherapy has been delivered alongside a psychosocial intervention, the study will only be eligible for inclusion in the combined NMA if the psychosocial intervention had a duration of ≥4 sessions or >4 weeks and was delivered synchronously. Although dose and duration thresholds for therapeutic effect will vary between psychosocial interventions and pharmacotherapies, the use of pharmacotherapies for managing CUD is an exploratory field of research. Most of the tested pharmacotherapies have been repurposed from other conditions or have different molecular targets (e.g. antidepressants, anxiolytics), and there are no established guidelines or recommendations for treatment of CUD. As such, setting a therapeutic duration threshold would not be appropriate.

8.2.2 Outcomes

This project will focus on a subset of outcomes that are considered of key importance or were consistently available across both source reviews (as listed in Table 1). For each of the three analyses, the primary effectiveness outcomes are point and continuous abstinence and level of cannabis use at the end of treatment, the primary safety outcomes are any adverse events and serious adverse events, and acceptability will be assessed by completion of scheduled treatment and adherence. While the original psychosocial interventions review included effectiveness outcomes assessed both the end of treatment and at later follow-up, the current project will only focus on outcomes assessed at the end of treatment (except for adverse events recorded at any time up to the end of the study period). Safety outcomes would be eligible for psychosocial interventions NMA, however, none of the studies included in the original review provided data suitable for synthesis. Based on stakeholder feedback, we will explore the feasibility of including adherence to treatment as an additional acceptability outcome that was not used in the source reviews.

8.3 Study identification

The source of studies for this project is the pair of completed systematic reviews (pharmacotherapies: NIHR165373; psychosocial interventions: NIHR167862).[12, 14] In both original reviews, we searched the following databases using relevant subject headings (controlled vocabularies), text-words and search syntax, appropriate to each resource:

- Ovid MEDLINE (1946 onwards);
- Ovid Embase (1974 onwards);
- Cochrane Central Register of Controlled Trials (CENTRAL) on the Cochrane Library (latest issue);
- Ovid PsycINFO (all available years).

We conducted the searches on the 12th June 2024 with no date or language restrictions. The publication date of included studies ranges between 1994 and 2024.

We do not plan to update the searches. However, we will screen randomized controlled trials (RCTs) previously identified as ongoing and potentially eligible to assess whether any have been completed and results published since.

8.4 Review strategy

8.4.1 Study selection and data extraction

The two source reviews followed the same study selection and data extraction processes. Two reviewers independently screened titles and abstracts for relevance and assessed full texts for eligibility. Data were extracted using pre-piloted standardized data extraction forms by one reviewer and checked by a second. Disagreements were resolved by consensus or discussion with a third reviewer. We collected the following data:

- study design (e.g. individual or cluster randomized trial);
- country, date and setting of study;
- inclusion/exclusion criteria;
- features of the participants, including the details of cannabis use disorder and pattern of use, co-occurring substance use disorders and dependence (e.g. cocaine, opioids, alcohol), and relevant PROGRESS+ characteristics (e.g. sex/gender, ethnicity, age, deprivation, socio-economic status);[18]
- details of the intervention, including intervention or drug name, dose(s), frequency of use, duration of intervention, mode and format of delivery, intervention setting;
- details of the comparator, including a description of 'usual care', if provided;
- detail of any co-intervention delivered to intervention and comparator groups;
- details of outcome measurement, time points for all outcomes;
- results;
- funding sources and conflict of interest.

In the source reviews, we extracted numerical outcome data at arm level. Dichotomous outcomes were extracted as number of participants with event (e.g. abstinence, treatment completion, adverse event) and total number of participants. For abstinence outcomes, the total was the number of participants in whom the outcome was assessed (i.e., those who completed the outcome assessment at the end of treatment); whereas for treatment completion and adverse events, this was the number of participants randomized. We extracted continuous outcomes as arm-level mean and standard deviation (SD) at baseline and at the end of treatment (e.g. mean number of days using cannabis), with preference for unadjusted estimates. We derived missing SDs from other within-study characteristics (e.g. standard errors [SE], 95% confidence intervals). Where such characteristics were not available, we imputed SDs from other studies in the dataset that used a comparable outcome measure. We used linear regression to impute missing SDs based on available means for frequency of cannabis use outcome in two studies in the psychosocial interventions dataset.

The review of pharmacotherapies included 37 studies, of which 36 were included in meta-analysis. The review of psychosocial interventions included 22 studies, of which 21 were included in meta-analysis at the end of treatment.

8.4.1.1 Additional data for separate network meta-analyses

For the current project, we do not plan to recheck the extracted data and will merge the datasets from the two original reviews. However, additional data will be extracted from the pharmacotherapies studies to classify the adjunct interventions used. To ensure intervention classifications across the two original review datasets are aligned, and to maximize network connectivity, we will revisit both the psychosocial and pharmacotherapy categorizations.

The original pharmacotherapy review focused on abstinence at the end of treatment, whereas the psychosocial review distinguished between point and continuous abstinence. To align the datasets we will re-categorize outcomes as either point or continuous abstinence at the end of treatment where necessary. We will also screen full texts of the included pharmacotherapies studies for any additional continuous abstinence outcome data and extract these data following the procedures described above. Following stakeholder's suggestion to consider additional acceptability outcomes, we will screen the included studies for adherence to treatment data and explore whether there is sufficient consistency in reporting this outcome to include it in the NMA. In such case we will extract the data as above.

For continuous outcomes, both reviews extracted end-of-treatment mean values. For the NMA, we will assess if mean difference in change-from-baseline values are reported or could be estimated from available data. If baseline and end-of-treatment means and SDs are available, we will use these to estimate change from baseline, assuming empirically derived estimate of pre-post correlation.[19] However, if a substantial proportion of baseline data are missing (e.g. >20%), we will use mean end-of-treatment values as per the original reviews. For the purpose of fitting NMA models, we will also compute SEs as SD/√n (where n is the number of participants).

8.4.1.2 Additional data for combined network meta-analysis

We anticipate challenges when integrating the psychosocial and pharmacological intervention datasets to form a connected network of treatment comparisons. For example, there are no head-to-head trials between psychosocial and pharmacological interventions and the trials of psychosocial interventions and pharmacotherapies used different comparator types (e.g. waitlist/nonspecific therapy or placebo). However, the pharmacotherapy trials often included a psychosocial intervention, either as a background therapy or an adjunct, and this may provide a route through which a combined network can be formed. Where the network remains disconnected, we will consider a sensitivity analysis that incorporates a supplementary set of brief and asynchronous psychosocial interventions. However, this sensitivity analysis would require re-screening records and extracting additional data from studies that had not been eligible for the original review of psychosocial interventions.

8.5 Risk-of-bias assessment

The risk of bias (RoB) was assessed in the two original systematic reviews using the RoB 2 tool for randomized trials.[20] Assessment was done in duplicate by two reviewers independently, or, for a proportion of studies by one reviewer and checked in detail by another reviewer. We will double check that the approach to assessment aligns across both reviews. If any discrepancies are identified, we will seek consensus on the decision rules and amend the relevant judgements. However, we do not plan to conduct new RoB assessments for the NMA.

8.6 Synthesis methods

8.6.1 Analysis assumptions

In advance of statistical synthesis, we will examine transitivity by assessing the distribution of potential effect modifiers across treatment contrasts. We will prepare visual and/or descriptive summaries across the body of evidence, considering the following characteristics (if consistently reported across most studies): treatment setting, intervention duration, intensity and duration of cannabis use at baseline, mean age of participants, proportion of males, or specifically recruiting individuals with co-occurring mental health conditions.

We will examine network connectedness by drawing network plots in R using the multiNMA package.[21-23] Where networks are disconnected, we will firstly re-examine categorization of interventions and whether it is appropriate to group some intervention nodes. If there are individual comparisons disconnected from a network, these will be excluded from the analysis (and their study-level effect estimates reported separately). For disconnected comparisons including at least two studies, we will present pooled effect estimates from pairwise random effects meta-analysis. Where separate psychosocial interventions and pharmacotherapies networks are sparse or disconnected, we will explore the use of informative priors on treatment effects and heterogeneity parameters, as this might facilitate more robust estimation when direct evidence is limited. For combined network, we will consider sensitivity NMA including supplementary interventions to improve the network connectedness (see section 8.6.3).

8.6.2 Analytical approach to network meta-analysis

Arm-level data, which are available for all studies reporting numerical outcome data, will be used for analysis. For dichotomous outcomes, relative effects will be summarized as odd ratios (OR) with 95% credible intervals (CrI). For continuous outcomes, relative effects will be summarized using the mean difference (MD) in change from baseline (reported with 95% CrIs). However, where a substantial proportion of baseline data are missing (e.g. >20%), we will use mean difference between final values (as per the two original reviews). Standardized mean difference (SMD) will be used where different measures of the same outcome cannot be aligned.

We will fit all NMA models in a Bayesian framework, using the multiNMA package in R.[21-23] We will specify vague prior distributions for model parameters such as intercept (baseline), intervention effect, and between-study variance (heterogeneity). We will also use package-defaults for specifying the sampling parameters such as number of chains, warmups (burn-ins), and post burn-in iterations. However, we will consider alternative prior distributions and/or different sampling parameters during model fitting in case of problems with convergence. We will use R-hat rank-based diagnostics (comparing the between- and within-chain estimates for model parameters) to assess convergence. R-hat values close to 1 and below 1.1 indicate good convergence. Our primary analyses will use a random effects model (assuming common between-study variance) and fixed-effect NMA will be reported as a sensitivity analysis.

For the primary analyses, we will assess global consistency by comparing the goodness of fit of a model assuming consistency with a model allowing for inconsistency. If the global assessment suggests potential inconsistency, we will examine it further using loop-based (local) approaches, such as node-splitting. Studies contributing to any implicated loops will be re-checked for potential data extraction errors and study characteristics re-reviewed for potential effect modifiers. We will use the CINeMA framework to assess the impact of inconsistency on the certainty of findings.

The analysis will be based on an iterative model fitting process. We will explore whether alternative statistical models, for example assuming additive or interactive intervention effects, improve network connectivity and model fit. Modelling assumptions will be discussed with topic experts to ensure that they are justifiable, and model fit statistics will be reported for all models explored. We will assess model fit using the posterior mean of the residual deviance. We will also estimate the deviance information criterion (DIC), which considers model fit in the context of model complexity. For model selection, a difference of ≥5 points in the posterior mean residual deviance and DIC will be considered meaningful, with lower values indicating better model fit.

8.6.3 Sensitivity analyses

In addition to random effects NMAs, we will also report results of fixed effects NMAs as sensitivity analyses.

If the psychosocial interventions and pharmacotherapies cannot be connected in a combined network through re-categorizing interventions and relaxing additivity/interaction assumptions, we will consider including brief and/or asynchronous psychosocial interventions in the network. Such supplementary interventions may be added if they can improve the network connectivity, and if they had been directly compared against an eligible psychosocial intervention or pharmacotherapy, and/or combined with an eligible psychosocial intervention of psychotherapy. Note that we will not make inferences about the effectiveness, safety, or acceptability of those brief or asynchronous psychosocial interventions.

8.6.4 Subgroup analyses

Subgroup analyses were planned in the two original reviews but were not possible due to insufficient data. As such, we do not plan subgroup analyses for the NMA.

8.7 Certainty of the evidence

Where NMA is feasible, we will also assess the certainty of the evidence using CINeMA[24] for the primary analyses (i.e. separate psychosocial interventions and pharmacotherapies networks). GRADE[25] assessments were completed in the two original reviews based on pairwise meta-analyses. We will double-check that the approach to assessing specific domains aligns across both reviews (e.g. that the same reasons were considered for indirectness). For CINeMA, assessments will be re-considered by one reviewer and checked by a second, based on results from the NMA. We will resolve any disagreements by consensus, or through discussion with a third reviewer.

The source pharmacotherapies review, at the level of each pairwise meta-analysis, assessed risk of bias due to missing evidence (RoB-ME)[26] to inform the GRADE judgements regarding publication bias. The original psychosocial interventions review did not include RoB-ME assessment. For the purpose of this NMA project, we will assess RoB-ME for direct comparisons in the psychosocial interventions dataset. These assessments will inform our judgements of across-studies bias domain in CINeMA.

9 Study Within A Review (SWAR)

Systematic reviews with network meta-analyses are often considered to be more time-consuming and resource intensive to conduct than those with standard, pairwise meta-analyses. Alongside this NMA, we plan to conduct a SWAR to identify the resource implications and length of time taken. We will follow the outline proposed in SWAR 24: Time and resource implications of a systematic review with network meta-analysis. SWAR 24 is registered with the Northern Ireland Network for Trials Research, at Queen's University, Belfast. It is available from: https://www.qub.ac.uk/sites/TheNorthernIrelandNetworkforTrialsMethodologyResearch/SWATSWARInformation/Repositories/SWARStore

10 Competing interests of authors

None to declare.

11 Proposed timetable/milestones

Milestone	Date to be completed
Proposed start	01/03/2025
Draft protocol	31/03/2025
Final protocol	02/05/2025
Draft report	30/06/2025
Journal submission	14/07/2025

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