Systematic Reviews

PROTOCOL

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The safety and efficacy of cannabinoids for the treatment of mental health and substance use disorders: protocol for a systematic review and meta-analysis

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Abstract

There has been a global increase in the use of cannabinoids as a treatment for mental health (MH) and substance use disorders (SUD). In 2016, an Australian government-funded review found that although medicinal cannabinoids accounted for a small reduction in MH symptoms, the results varied according to study design. There has since been a rise in randomised controlled trials (RCTs) aiming to examine the efficacy of cannabinoids for the treatment of MH and SUD. Therefore, the current systematic review will (a) identify all RCTs examining the efficacy of cannabinoids in treating MH and SUD, (b) provide a quantitative or narrative synthesis of the evidence examining efficacy, and (c) synthesise adverse event data to examine evidence of harm. Electronic databases (Ovid MEDLINE, PsychINFO, Cochrane Central Register of Controlled Clinical Trials, Cochrane Database of Systematic Reviews, and Embase) were searched from 1980 to 24 May 2023. The study adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Guidelines. Articles will be screened to capture peer-reviewed RCTs evaluating the efficacy of plant-based and pharmaceutical cannabinoids in reducing or treating MH and SUD among people of any age. The Cochrane risk of bias tool 2.0 will be used to assess bias, while the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) tool will be used to assess the quality of evidence for each outcome. Study findings will be disseminated through published manuscripts, conferences, and health policy guidelines.

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Introduction

Mental health (MH) and substance use disorders (SUD) are among the greatest contributors to disability worldwide [1], yet traditional treatments are often inadequate and inaccessible [2, 3]. As an increasing number of countries adopt less restrictive regulatory approaches towards cannabis possession and use, there is growing interest in cannabinoids as a treatment for these conditions. Despite long-standing evidence that cannabinoids have anxiolytic effects and may precipitate psychosis in vulnerable individuals [4], MH and SUD are among the top reasons for accessing medicinal cannabis in countries such as the USA, Australia, and Canada [5, 6]. While most of the most recent clinical trial literature has focused on cannabinoids for treating chronic pain [7] and epilepsy [8], cannabinoids may also interact with brain regions that play a critical role in MH and SUD. A previous synthesis of the evidence found very little evidence for the efficacy of cannabinoids as a treatment for mental health [9]; however, given the growing interest in medicinal cannabinoids for MH and SUD, there has been a recent rise in higher-quality clinical trials.

The cannabis plant is made up of over 150 exogenous cannabinoids, which when consumed, interact with the human endocannabinoid system [10]. The endocannabinoid system plays a crucial role in brain development and intercellular communication while occupying a broad spatial range of our neural system [11]. Cannabinoid receptors are highly expressed in regions involved in stress, anxiety, mood, memory, learning, cognition, reward, addiction, appetite, sleep, and pain [12], which may partially explain their potential role as a treatment for psychopathologies. Exogenous cannabinoids can produce supraphysiological effects on cannabinoid receptors, interrupting normal endocannabinoid functioning [13], which may result in harmful or therapeutic effects.

There are more specific proposed mechanisms of action for cannabinoid treatments. One of the most abundant exogenous cannabinoids, delta-9-tetrahydrocannabinol (THC), is a partial agonist at cannabinoid type 1 receptor [14, 15] and has been shown to partially reduce inflammation, neuroinflammation, pain signalling, and nausea, symptoms directly or indirectly related to mental health and SUD [16]. The non-psychoactive cannabinoid, cannabidiol (CBD), may have antipsychotic effects via its upregulation of anandamide, an endocannabinoid shown to play a critical role in the onset of psychotic symptoms [17]. Experimental studies have also demonstrated that it may normalise brain regions typically impaired among those with psychosis [18]. CBD also acts on non-endocannabinoid receptors, such as those responsible for the modulation of serotonin and dopamine, potentially resulting in anxiolytic and antidepressant-like effects [19]. Furthermore, cannabinoid receptor activity has been shown to moderate substance-induced dopamine release, a reinforcing property of SUD [20].

In 2016, the Australian Therapeutic Goods Administration funded a review of the evidence examining cannabinoids for the treatment of mental health disorders [9]. A comprehensive search of the literature found that cannabinoids were commonly investigated for the treatment of depression, followed by anxiety, post-traumatic stress disorder (PTSD), psychosis, Tic/Tourette syndrome, and attention-deficit hyperactivity disorder (ADHD). There were small reductions in anxiety symptoms where it was secondary to another medical condition and improvements in global functioning among those with PTSD and psychosis. Otherwise, there was no significant benefit of cannabinoids for the treatment of mental health, and for every seven participants receiving these treatments, one would experience an adverse event.

Despite the overall lack of evidence for efficacy, the literature predominantly consisted of observational studies, with very few randomised controlled trials (RCTs). Furthermore, most of the included studies assessed mental health as secondary to a physical health condition. However, since the search was conducted (April 2018), there has been a substantial rise in RCTs aiming to examine the efficacy of cannabinoids for the treatment of MH and SUD [12]. Unlike other human studies, this gold standard method is a necessary step towards the development of new treatments. In addition to the mental health conditions explored in Black, Stockings [9], there is increasing interest in cannabinoids for the treatment of SUD [20], including cannabis use disorder (CUD) [21] and heroin use disorder [22].

Thus, the aims of this review are as follows:

1) Identify all RCTs examining the efficacy of cannabinoids in treating MH and SUD, including depression, anxiety, attention-deficit hyperactivity disorder (ADHD), tic/Tourette syndrome, post-traumatic stress disorder (PTSD), psychosis, bipolar disorder, other mental health disorders, cannabis use disorder (CUD), alcohol use disorder (AUD), opioid use disorder (OUD), tobacco use disorder (TUD), cocaine use disorder, and other substance use disorders.
2) Synthesise outcome data via quantitative and narrative synthesis to examine evidence of efficacy; and
3) Synthesise adverse event data to examine evidence of harm.

The findings of this review will further our understanding of the efficacy and safety of cannabinoids for these health conditions, guiding clinicians and policy-makers on the use of medicinal cannabinoids.

Methods

This protocol adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) statement. The protocol has been registered with the PROSPERO International Prospective Register of Systematic Reviews of the University of York (CRD42023392718).

Search strategy

Electronic databases (Ovid MEDLINE, PsychINFO, Cochrane Central Register of Controlled Clinical Trials, Cochrane Database of Systematic Reviews, and Embase) were searched for peer-reviewed RCTs evaluating the efficacy of plant-based and pharmaceutical cannabinoids in reducing or treating MH and SUD. The search was limited to articles published from 1980 to 24 May 2023, with no restriction on language. The full search strategies are provided in Appendix. Ongoing or unpublished studies were searched on clinicaltrials.gov, EU Clinical Trials Register, and the Australian and New Zealand Clinical Trials Registry using keywords 'cannabis', 'cannabinoids', 'marijuana' and the mental health and substance use terms. A manual search of reference lists and relevant systematic reviews was also conducted. To ensure that the search captures up-to-date literature, an updated search will be conducted prior to publication.

The databases were searched for (1) cannabis terms, (2) clinical trial terms, and (3) mental health and substance use disorder terms. Specific search terms can be seen in the Appendix. These grouped terms will be combined with the following logic: 1 and 2 and 3. Search terms were adapted from the Black, Stockings [9] review, with the addition of other mental health disorders and the inclusion of SUD. Additional cannabinoid products were also identified in the literature (e.g. delta-8-tetrahydrocannabinol).

Eligibility criteria

RCTs evaluating the efficacy of plant-based and/or pharmaceutical cannabinoids in reducing or treating MH or SUD symptoms or disorders, published from 1980 to May 2023. Studies examining neurocognitive disorders such as dementia will be excluded, as this was outside the scope of the current review. Reviews, commentary articles, and clinical overviews will not be included.

Population

Articles will include participants of any age, with any of the mental health or substance use disorders listed in Table 1, where they are seeking treatment primarily for their mental health or SUD.

Intervention

The review will consider studies that evaluate plant-based and/or pharmaceutical cannabinoids administered with the intention of reducing or improving outcomes associated with mental health and substance use disorders. The review will consider studies of tetrahydrocannabinol; cannabidiol; combination tetrahydrocannabinol + cannabidiol; cannabis sativa; and where evidence exists, other cannabinoids and cannabinoid products (e.g. tetrahydrocannabinolic acid (thca), cannabidiolic acid, cannabidivarin, the synthetic delta-9-tetrahydrocannabinol formulations nabilone, dronabinol, and delta-8-tetrahydrocannabinol).

Comparator

Reference groups will be made to those administered placebo or active medications, waitlist controls, and other interventions.

Outcomes

As shown in Table 1, primary outcomes include remission from the primary MH or SUD and changes in symptoms. Secondary outcomes will include changes in related health outcomes, including global functioning, cardiovascular effects, weight, and sleep. All-cause, serious, and treatment-related adverse events, as well as study withdrawals, will be examined as secondary outcomes for all disorders.

Study design

We will include RCTs, including parallel, crossover, cluster, and factorial designs.

Study selection

Citations will be imported into, and deduplicated, in Endnote and exported and uploaded into the web-based screening platform Covidence [46] for screening. Each article will be double-screened based on titles and abstracts for relevance by numerous independent reviewers in the authorship team. An identical process will be conducted for full-text screening, and any inter-reviewer disagreement will be discussed to reach a consensus. Reviewers will nominate reasons for exclusion at the full-text stage. To identify the number of non-randomised studies, clinical trials without randomisation will be accepted at the title/abstract stage but excluded at the full-text stage. If consensus cannot be reached, a third reviewer will be consulted.

Data extraction

Data will be extracted independently by two reviewers using a pre-piloted data extraction form in Microsoft Excel. Study authors will be contacted if further data are needed. The following data details will be extracted: populations, interventions, comparisons, outcomes of significance to mental health and/or SUD (Table 1), study methods, cannabinoid dose and route of administration, placement in the therapeutic hierarchy, adverse events, and study

Table 1 Primary and secondary outcomes according to mental health and substance use disorders

Disorder Definition Global prevalence	Theoretical mechanism of effect	Primary outcomes	Secondary outcomes
Major depressive disorder Major depressive disorder (MDD), also known as clinical depression, is a mental health disorder characterised by persistently low mood, decreased interest in pleasurable activities, and physiological disturbances (e.g. lack of energy) [23] An estimated 3.4% of the global population reached diagnostic criteria for depression in 2019 [24]	Cannabinoid receptor type 1 (CB1) is highly expressed in regions of the brain associated with mood and reward. Cannabinoid receptor type 2 (CB2) is expressed by neurons that inhibit GABA, dopamine, and glutamate neurotransmitter release. Antidepressant effects may also be due to partial agonism at Dopamine D2 receptors, and the inhibition of inflammation [12]	• Remission—absence of a depressive disorder diagnosis based on ICD or DSM classification systems • Change in depressive symptoms using self-report or clinician-rated scales or items (e.g. The Beck Depression Inventory)	• Measures of global functioning—including quality of life, patient or caregiver global impression of change, and satisfaction with treatment
Anxiety Anxiety is a mental health condition characterised by excessive worry, fear, apprehension and vigilance. It can cause symptoms such as persistent distressing thoughts or sensations, restlessness and agitation, nausea, tachycardia, and avoidance behaviours among others [25]. The six sub-types of anxiety disorder are: 1. Generalised anxiety disorder (GAD): excessive worry about various aspects of life. 2. Panic disorder: recurrent sudden surges of intense fear or discomfort (panic attacks). 3. Social anxiety disorder (SAD): intense fear of social situations and negative evaluation. 4. Specific phobia: extreme fear of a specific object or situation. 5. Agoraphobia: fear of situations where escape may be challenging. 6. Separation anxiety disorder: excessive fear of separation from attachment figures. An estimated 3.8% of the global population met criteria for anxiety disorders in 2019 [24]	Cannabinoid receptor type 1 (CB1) is highly expressed in regions of the brain associated with stress and anxiety. Cannabinoid receptor type 2 (CB2) is expressed by neurons that inhibit GABA, dopamine, and glutamate neurotransmitter release. Anxiolytic effects may also be due to partial agonism at Dopamine D2 receptors, and the inhibition of inflammation [12]	• Remission—the absence of an anxiety disorder diagnosis based on ICD or DSM classification systems • Change in anxiety symptoms using self-report or clinician-rated scales or items	• Measures of global functioning—including quality of life, patient or caregiver global impression of change, and satisfaction with treatment
ADHD ADHD (Attention-Deficit/Hyperactivity Disorder) is a neurodevelopmental disorder marked by symptoms of inattention, hyperactivity, and impulsivity that interfere with daily functioning [26] An estimated 1.1% of the global population met criteria for ADHD in 2019 [24]	Consumption of cannabinoids may enhance dopaminergic transmission, ultimately reducing symptoms and enhancing cognitive performance [27]	• Remission—the absence of an ADHD diagnosis based on ICD or DSM classification systems • Change in ADHD symptoms using self-report or clinician-rated scales or items	• Measures of global functioning—including quality of life, patient or caregiver global impression of change, and satisfaction with treatment • Change in cardiovascular effects (e.g. blood pressure) • Weight changes

Table 1 (continued)

Disorder Definition Global prevalence	Theoretical mechanism of effect	Primary outcomes	Secondary outcomes
Tic/Tourette syndrome Tic disorders are neurological conditions characterised by involuntary and repetitive movements or vocalisations known as tics [28]. Tourette Syndrome is a specific type of tic disorder that involves both motor and vocal tics that last for at least one year. Tics can range from mild to severe and can significantly impact a person's daily functioning and social interactions An estimated 0.5% of the global population met criteria for Tourette Syndrome [29]	Disturbances to the endocannabinoid system can lead to dysfunctional dopaminergic neurotransmission, which in turn may be associated with the incidence of tics [30].	• Remission—the absence of a tic/tourette syndrome diagnosis based on ICD or DSM classification systems • Change in Tic/Tourette syndrome symptoms using self-report or clinician-rated scales or items	• Measures of global functioning—including quality of life, patient or caregiver global impression of change, and satisfaction with treatment • Change in cardiovascular effects • Weight changes
PTSD PTSD (post-traumatic stress disorder) is a mental health disorder triggered by experiencing or witnessing a traumatic event. Symptoms include flashbacks, nightmares, and heightened anxiety, leading to significant distress and impairment [31] The prevalence of PTSD varies depending on the population and the type of trauma experienced [31]. Epidemiological studies have reported lifetime prevalence rates of 13.0–20.4% for women and 6.2–8.2% for men [31], and during the COVID-19 pandemic it was estimated that the prevalence of PTSD in the general population was approximately 15% [32]	Reductions in the endocannabinoid, anandamide, may be associated with increased retention of aversive emotional memories. Therapeutic targets aim to restore levels of anandamide [33]	• Remission—the absence of PTSD diagnosis based on ICD or DSM classification systems • Change in PTSD symptoms using self-report or clinician-rated scales or items	• Measures of global functioning—including quality of life, patient or caregiver global impression of change, and satisfaction with treatment • Change in severity of depressive symptoms using a standardised measure • Change in severity of anxiety symptoms using a standardised measure • Change in sleep quality • Change in frequency of nightmares
Psychosis Psychosis is a mental health condition characterised by a loss of contact with reality. People experiencing psychosis may experience hallucinations, delusions, disorganised thoughts, disorganised or abnormal motor behaviour, and negative symptoms. These symptoms can severely impact a person's thoughts, emotions, and behaviour, making it difficult for them to distinguish between what is real and what is not [34] According to recent estimates, approximately 0.39% of the global population meets the criteria for psychotic disorders [35]	Cannabidiol (CBD), may have antipsychotic effects via its upregulation of anandamide, and an increase in CB1 receptor availability in certain brain areas may protect against psychotic symptoms [36]	• Remission—the absence of a psychosis diagnosis based on ICD or DSM classification systems • Change in positive and negative symptoms of psychosis using self-report or clinician-rated scales or items	• Measures of global functioning—including quality of life, patient or caregiver global impression of change, and satisfaction with treatment • Change in cognitive functioning • Measures of emotional functioning–—including depression, anxiety, mood, and social skills

Table 1 (continued)

Disorder Definition Global prevalence	Theoretical mechanism of effect	Primary outcomes	Secondary outcomes
Bipolar Bipolar disorder (BD), (formerly known as manic-depressive illness), is a mood disorder characterised by alternating periods of depression and mania (elevated mood, increased energy, and impulsive behaviour). Bipolar I involves manic episodes, while Bipolar II involves hypomanic and depressive episodes [37] An estimated 0.5% of the global population met the criteria for BD in 2019 [24]	Cannabinoid receptor type 1 (CB1) is highly expressed in regions of the brain associated with mood and reward. Consumption of cannabinoids may enhance dopaminergic transmission. Increasing the uptake of anandamide may have anxiolytic effects	• Remission—the absence of a bipolar diagnosis based on ICD or DSM classification systems • Change in bipolar symptoms using self-report or clinician-rated scales or items	• Measures of global functioning—including quality of life, patient or caregiver global impression of change, and satisfaction with treatment • Change in severity of depressive symptoms using a standardised measure • Change in severity of manic symptoms using a standardised measure
Other mental health disorders (e.g. personality disorder, eating disorders)		• Remission—the absence of other mental health disorders based on ICD or DSM classification systems • Change in symptoms using self-report or clinician-rated scales or items	• Measures of global functioning—including quality of life, patient or caregiver global impression of change, and satisfaction with treatment
Cannabis use disorder (CUD) Cannabis use disorder is a problematic pattern of cannabis use leading to clinically significant impairment or distress. It includes symptoms like craving, tolerance, withdrawal, and difficulty controlling use as well as respiratory problems, deficiency in cognitive functioning and potential distress tolerance [38] An estimated 0.3% of the global population met criteria for cannabis use disorders in 2016 [39]	Reward saliency, motivation, and learned associations that maintain dependence may be modulated by the endocannabinoid system [40]	• Remission—the absence of a CUD diagnosis based on ICD or DSM classification systems • Change in CUD symptoms using self-report or clinician-rated scales or items • Changes in cannabis use or abstinence	• Measures of global functioning—including quality of life, patient or caregiver global impression of change, and satisfaction with treatment • Measure withdrawal symptoms using standardised measure • Quantitative levels of drug in urine drug screen, blood sample, or breath test
Alcohol use disorder (AUD) Alcohol Use Disorder is a chronic relapsing condition characterised by compulsive alcohol consumption, withdrawal, loss of control, and neglect of obligations and responsibilities. It ranges from mild to severe and can lead to physical and psychological dependence [41] An estimated 1.3% of the global population met the criteria for alcohol use disorder in 2016 [39]	Reward saliency, motivation, and learned associations that maintain dependence may be modulated by the endocannabinoid system [40]	• Remission—the absence of an AUD diagnosis based on ICD or DSM classification systems • Change in AUD symptoms using self-report or clinician-rated scales or items • Changes in alcohol use or abstinence	• Measures of global functioning—including quality of life, patient or caregiver global impression of change, and satisfaction with treatment • Measure withdrawal symptoms using standardised measure • Quantitative levels of alcohol in urine drug screen, blood sample, or breath test

Table 1 (continued)

Disorder Definition Global prevalence	Theoretical mechanism of effect	Primary outcomes	Secondary outcomes
Opioid use disorder (OUD) Opioid Use Disorder is a problematic pattern of opioid use leading to significant impairment or distress. It involves symptoms such as cravings, tolerance, withdrawal, difficulties in reducing or controlling use, aberrant behaviours and neglect of obligations and responsibilities [42] An estimated 0.4% of the global population met criteria for opioid use disorder in 2016 [39]	Reward saliency, motivation, and learned associations that maintain dependence may be modulated by the endocannabinoid system [40]	• Remission—the absence of an OUD diagnosis based on ICD or DSM classification systems • Change in OUD symptoms using self-report or clinician-rated scales or items • Changes in opioid use or abstinence	• Measures of global functioning—including quality of life, patient or caregiver global impression of change, and satisfaction with treatment • Measure withdrawal symptoms using standardised measure • Quantitative levels of drug in urine drug screen, blood sample, or breath test
Tobacco use disorder (TUD) Tobacco Use Disorder is a dependence on nicotine-containing products, primarily cigarettes. It is characterised by chronic use, withdrawal symptoms and unsuccessful attempts to quit, chronic cardiovascular and cerebral health issues and continued use despite health problems [43] Using daily smoking as an indicator of dependence, it is estimated that around 15.2% of the global population experience tobacco use disorder [44]	Reward saliency, motivation, and learned associations that maintain dependence may be modulated by the endocannabinoid system [40]	• Remission—the absence of a TUD diagnosis based on ICD or DSM classification systems • Change in TUD symptoms using self-report or clinician-rated scales or items • Changes in tobacco use or abstinence	• Measures of global functioning—including quality of life, patient or caregiver global impression of change, and satisfaction with treatment • Measure withdrawal symptoms using standardised measure • Quantitative levels of drug in urine drug screen, blood sample, or breath test
Cocaine use disorder Cocaine use disorder is a pattern of cocaine use leading to clinically significant impairment or distress. It includes symptoms such as craving, using larger amounts than anticipated, and withdrawal [45] An estimated 0.08% of the global population met criteria for cocaine use disorders in 2016 [39]	Reward saliency, motivation, and learned associations that maintain dependence may be modulated by the endocannabinoid system [40]	• Remission – the absence of a cocaine use disorder diagnosis based on ICD or DSM classification systems • Change in symptoms using self-report or clinician-rated scales or items • Changes in cocaine use or abstinence	• Measures of global functioning – including quality of life, patient or caregiver global impression of change, and satisfaction with treatment • Measure withdrawal symptoms using standardised measure • Quantitative levels of drug in urine drug screen, blood sample, or breath test
Other substance use disorder (e.g. amphetamine use disorder)		• Remission—the absence of a diagnosis based on ICD or DSM classification systems • Change in symptoms using self-report or clinician-rated scales or items • Changes in other substance use or abstinence	• Measures of global functioning—including quality of life, patient or caregiver global impression of change, and satisfaction with treatment • Measure withdrawal symptoms using standardised measure • Quantitative levels of drug in urine drug screen, blood sample, or breath test
All disorders			• Adverse events (AEs)—all-cause • Serious adverse events (SAEs; as defined by authors)—all-cause • Treatment-related adverse events (TAEs)—all-cause • Study withdrawals—all-cause • Study withdrawals—due to AEs

withdrawals. When multiple analyses were reported (e.g. intention to treat (ITT), available case, or per protocol), the most conservative figures were extracted with a preference for ITT analysis. AEs will be reported according to the high-level Medical Dictionary for Regulatory Activities (MedDRA; https://www.meddra.org/) categories.

Risk of bias and assessment of quality

Full-text studies considered eligible by two reviewers will be assessed for quality by one reviewer, with quality ratings checked by a second reviewer. The Cochrane risk of bias tool 2.0 [47] was used to assess indicators of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases in RCTs. The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) tool [48] will be used to assess the quality of evidence for each outcome. RCT evidence is initially rated as 'high quality' but can be downgraded due to (1) risk of bias, (2) indirectness of evidence, (3) inconsistency of results, (4) imprecision, and (5) publication bias.

Data synthesis

Key findings of studies will first be summarised descriptively before considering whether studies are appropriate for quantitative meta-analysis. Both clinical heterogeneity (variability in the participants, interventions, and outcomes studied) and methodological heterogeneity (variability in study design and risk of bias) will be considered, as well as whether studies are sufficiently homogeneous in terms of participants, interventions, and outcomes to provide a meaningful summary.

Meta-analysis

Where possible, data synthesis of efficacy will be stratified by mental disorder, type of cannabinoid, and comparator (active or placebo). Outcomes of studies suitable for meta-analysis will be combined where possible (depending on the comparability of interventions and outcomes between trials) with the use of a random-effects model, as some variability is expected in the included studies. Dichotomous outcomes (including disorder remission, adverse events, etc.) will be pooled as odds ratios (ORs), and continuous outcomes (including mean and standard deviation changes in symptom severity) will be pooled using standardised mean differences (SMDs). Where there is a sufficient number of studies, 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. Where publication bias is indicated by funnel plot asymmetry, we will use the trim and fill procedure to produce a bias-corrected estimate.

Assessment of heterogeneity and sensitivity analyses

We will conduct assessments of heterogeneity in the effect estimates by examining the I^2 statistic and associated p value, whereby a p value of the test lower than 0.10 or an I^2 statistic of at least 50% will indicate significant statistical heterogeneity. Sensitivity analyses (leave one out method) will be conducted to determine the degree of heterogeneity, and studies determined to be too heterogeneous (i.e. resulting in significantly different overall effect estimates) will be described separately. Where the effect of a decision on the outcome of the review is uncertain (for example, the decision to include or exclude a study remains unclear, or the impact of unavailable data on the findings is uncertain), sensitivity analysis will also be conducted, with the results described in a summary table (see Cochrane Handbook section 9.7 [49]). To incorporate the risk of bias assessment in the review process, we will first plot intervention effect estimates for different outcomes stratified for risk of bias for each item. If differences in results are present among studies at different risks of bias, we will perform sensitivity analysis, excluding studies deemed to be at a high risk of bias.

Subgroup analysis

If sufficient studies are included in the review, the following subgroups of participants will be examined and investigated for potential sources of heterogeneity:

- MH or SUD (e.g. depression, anxiety, psychosis, post-traumatic stress disorder, attention-deficit hyperactivity disorder (ADHD)/tic/Tourette syndrome, bipolar disorder, other mental health disorder, cannabis use disorder, opioid use disorder, tobacco use disorder, alcohol use disorder, cocaine use disorder, other substance use disorder)
- Cannabinoid product as treatment
- Age group (paediatric, adolescent, adult)

Ethics and dissemination

Ethical approval will not be required, as original data will not be collected. The findings of the review will be disseminated via publication, conferences, and seminars.

Discussion

This will form the most comprehensive review of gold-standard evidence for medicinal cannabinoids as a treatment for MH and SUD. Findings will be synthesised to provide a standard metric for the efficacy and safety of cannabinoids as a treatment for MH and SUD, while study limitations will be identified for future research to overcome. This review is particularly timely given the increasing access to cannabis for medicinal purposes globally.

Approximately one million applications have been approved for medicinal cannabis in Australia [5], similar to the USA and Canada [6], most of which have been approved for the treatment of chronic pain. Despite this, the evidence for cannabinoids as an effective treatment for non-cancer chronic pain is weak to moderate. A review of the evidence found that the number needed to achieve a 30% reduction in pain for one person using cannabis relative to a placebo was 24 [50]. While this highlights an alarming barrier between the evidence and practice, it is unclear whether this is the case for MH, which accounts for the second most common reason for which cannabis is prescribed in Australia. Clinical guidance is also necessary for the treatment of SUDs, an indication for which clinicians are now treating with cannabinoids but is in its infancy of evidence [51]. This review will allow clinicians to reflect on the most up-to-date synthesis of gold-standard evidence, ultimately informing best practices.

Appendix

Table 2 Search strategies for Embase Classic and Embase

Embase classic < 1947 to 1973 >		
Embase < 1974 to 2023 May 19 >		
Date of search	**23.05.23**	***N* results**
1	cannabis.mp. or exp Cannabis/	67322
2	marijuana.mp. or exp cannabis/	53760
3	cannabinoids.mp. or exp Cannabinoids/	88990
4	endocannabinoids.mp. or exp Endocannabinoids/	13490
5	endocannabinoid.mp	16068
6	dronabinol.mp. or exp Dronabinol/	9802
7	nabilone.mp	1691
8	marinol.mp	650
9	levonantradol.mp	270
10	tetrahydrocannabinol.mp. or exp tetrahydrocannabinol/	16170
11	cesamet.mp	321
12	delta-9-THC.mp	2120
13	delta-9-tetrahydrocannabinol.mp	5932
14	delta-8-THC.mp	332
15	delta-8-tetrahydrocannabinol.mp	300
16	nabiximols.mp	1092
17	sativex.mp	838
18	cannabidiol.mp. or exp Cannabidiol/	10129
19	medical marijuana.mp. or exp Medical Marijuana/	4688
20	medicinal marijuana.mp	125
21	medical cannabis.mp	4572
22	medicinal cannabis.mp	722
Embase classic < 1947 to 1973 >		
Embase < 1974 to 2023 May 19 >		
Date of search	**23.05.23**	***N* results**
23	randomized controlled trial.mp. or exp Randomized controlled Trial/	1062386
24	intervention.mp	1278433
25	clinical trial.mp. or Clinical Trial/	1804794
26	exp Mental Disorders/dt, pk, pc, tu, th [Drug Therapy, Pharmacokinetics, Prevention & Control, Therapeutic Use, Therapy]	440144
27	Substance-Related Disorders/de, dt, pc, rh, th, ur [Drug Effects, Drug Therapy, Prevention & Control, Rehabilitation, Therapy, Urine]	5352
28	Marijuana Abuse/	6926
29	cannabis use disorder.mp	1671
30	Substance Withdrawal Syndrome/	13206
31	cannabis dependent.mp	254
32	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	109099
33	23 or 24 or 25	3260015
34	26 or 27 or 28 or 29 or 30 or 31	457346
35	32 and 33 and 34	3429

Table 3 Evidence-based medicine (EBM) review set search strategy

EBM Reviews-Cochrane Methodology Register < 3rd Quarter 2012 >		
EBM Reviews-Database of Abstracts of Reviews of Effects < 1st Quarter 2016 >		
EBM Reviews-Health Technology Assessment < 4th Quarter 2016 >		
EBM Reviews-NHS Economic Evaluation Database < 1st Quarter 2016 >		
EBM Reviews-Cochrane Database of Systematic Reviews < 2005 to May 16, 2023 >		
EBM Reviews-ACP Journal Club < 1991 to April 2023 >		
EBM Reviews-Cochrane Clinical Answers < May 2023 >		
EBM Reviews-Cochrane Central Register of Controlled Trials < April 2023 >		
Date of search	23.05.23	*N* results
1	cannabis.mp. or exp Cannabis/	3198
2	marijuana.mp. or exp cannabis/	2494
3	cannabinoids.mp. or exp Cannabinoids/	1544
4	endocannabinoids.mp. or exp Endocannabinoids/	205
5	endocannabinoid.mp	362
6	dronabinol.mp. or exp Dronabinol/	1055
7	nabilone.mp	198
8	marinol.mp	51
9	levonantradol.mp	23
10	tetrahydrocannabinol.mp. or exp tetrahydrocannabinol/	1516
11	cesamet.mp	15
12	delta-9-THC.mp	107
13	delta-9-tetrahydrocannabinol.mp	570

14	delta-8-THC.mp	4
15	delta-8-tetrahydrocannabinol.mp	0
16	nabiximols.mp	105
17	sativex.mp	178
18	cannabidiol.mp. or exp Cannabidiol/	1062
19	medical marijuana.mp. or exp Medical Marijuana/	84
20	medicinal marijuana.mp	5
21	medical cannabis.mp	130
22	medicinal cannabis.mp	68
23	randomized controlled trial.mp. or exp Randomized controlled Trial/	600984
24	intervention.mp	514469
25	clinical trial.mp. or Clinical Trial/	450820
26	exp Mental Disorders/dt, pk, pc, tu, th [Drug Therapy, Pharmacokinetics, Prevention & Control, Therapeutic Use, Therapy]	1190
27	Substance-Related Disorders/de, dt, pc, rh, th, ur [Drug Effects, Drug Therapy, Prevention & Control, Rehabilitation, Therapy, Urine]	52
28	Marijuana Abuse/	763
29	cannabis use disorder.mp	273
30	Substance Withdrawal Syndrome/	2270
31	cannabis dependent.mp	79
32	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	5753
33	23 or 24 or 25	1085307
34	26 or 27 or 28 or 29 or 30 or 31	4359
35	32 and 33 and 34	542

Table 4 MEDLINE search strategy

Ovid MEDLINE(R) ALL < 1946 to May 18, 2023 >		
Date of search	**23.05.23**	***N* results**
1	cannabis.mp. or exp Cannabis/	31328
2	marijuana.mp. or exp cannabis/	32662
3	cannabinoids.mp. or exp Cannabinoids/	22794
4	endocannabinoids.mp. or exp Endocannabinoids/	8916
5	endocannabinoid.mp	9176
6	dronabinol.mp. or exp Dronabinol/	8514
7	nabilone.mp	398
8	marinol.mp	94
9	levonantradol.mp	72
10	tetrahydrocannabinol.mp. or exp tetrahydrocannabinol/	11689
11	cesamet.mp	24
12	delta-9-THC.mp	1344
13	delta-9-tetrahydrocannabinol.mp	4061
14	delta-8-THC.mp	209
15	delta-8-tetrahydrocannabinol.mp	251
Ovid MEDLINE(R) ALL < 1946 to May 18, 2023 >		
Date of search	**23.05.23**	***N* results**
16	nabiximols.mp	341
17	sativex.mp	236
18	cannabidiol.mp. or exp Cannabidiol/	5697
19	medical marijuana.mp. or exp Medical Marijuana/	2832
20	medicinal marijuana.mp	95
21	medical cannabis.mp	1511
22	medicinal cannabis.mp	502
23	randomized controlled trial.mp. or exp Randomized controlled Trial/	637864
24	intervention.mp	809239
25	clinical trial.mp. or Clinical Trial/	791054
26	exp Mental Disorders/dt, pk, pc, tu, th [Drug Therapy, Pharmacokinetics, Prevention & Control, Therapeutic Use, Therapy]	416918
27	Substance-Related Disorders/de, dt, pc, rh, th, ur [Drug Effects, Drug Therapy, Prevention & Control, Rehabilitation, Therapy, Urine]	34281
28	Marijuana Abuse/	7027
29	cannabis use disorder.mp	1176
30	Substance Withdrawal Syndrome/	22624
31	cannabis dependent.mp	172
32	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	65199
33	23 or 24 or 25	1776100
34	26 or 27 or 28 or 29 or 30 or 31	446129
35	32 and 33 and 34	1802

Table 5 PsycInfo search strategy

APA PsycInfo < 1806 to May Week 3 2023 >		
Date of search	**23.05.23**	***N* results**
1	cannabis.mp. or exp Cannabis/	24596
2	marijuana.mp. or exp cannabis/	24805
3	cannabinoids.mp. or exp Cannabinoids/	7624
4	endocannabinoids.mp. or exp Endocannabinoids/	2037
5	endocannabinoid.mp	2696
6	dronabinol.mp. or exp Dronabinol/	1829
7	nabilone.mp	100
8	marinol.mp	16
9	levonantradol.mp	17
10	tetrahydrocannabinol.mp. or exp tetrahydrocannabinol/	2947
11	cesamet.mp	9

APA PsycInfo < 1806 to May Week 3 2023 >		
Date of search	**23.05.23**	***N* results**
12	delta-9-THC.mp	139
13	delta-9-tetrahydrocannabinol.mp	1077
14	delta-8-THC.mp	19
15	delta-8-tetrahydrocannabinol.mp	29
16	nabiximols.mp	54
17	sativex.mp	76
18	cannabidiol.mp. or exp Cannabidiol/	1102
19	medical marijuana.mp. or exp Medical Marijuana/	872
20	medicinal marijuana.mp	41
21	medical cannabis.mp	534
22	medicinal cannabis.mp	142
23	randomized controlled trial.mp. or exp Randomized controlled Trial/	25065
24	intervention.mp	335967
25	clinical trial.mp. or Clinical Trial/	27215
26	exp Mental Disorders/dt, pk, pc, tu, th [Drug Therapy, Pharmacokinetics, Prevention & Control, Therapeutic Use, Therapy]	0
27	Substance-Related Disorders/de, dt, pc, rh, th, ur [Drug Effects, Drug Therapy, Prevention & Control, Rehabilitation, Therapy, Urine]	0
28	Marijuana Abuse/	0
29	cannabis use disorder.mp	1483
30	Substance Withdrawal Syndrome/	0
31	cannabis dependent.mp	170
32	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	31574
33	23 or 24 or 25	363914
34	26 or 27 or 28 or 29 or 30 or 31	1633
35	32 and 33 and 34	245

Authors' contributions
JW and ES contributed to the conceptualisation and writing of the manuscript. All other authors contributed to the editing. All authors read and approved the final manuscript.

Declarations

Ethics approval and consent to participate
Ethics and consent were not required.

Consent for publication
All authors consented to the publication of this manuscript.

Competing interests
The authors declare that they have no conflicts of interest.

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References

1. Rehm J, Shield KD. Global burden of disease and the impact of mental and addictive disorders. Curr Psychiatry Rep. 2019;21(2):10.
2. Degenhardt L, Glantz M, Evans-Lacko S, Sadikova E, Sampson N, Thornicroft G, et al. Estimating treatment coverage for people with substance use disorders: an analysis of data from the World Mental Health Surveys. World Psychiatry. 2017;16(3):299–307.
3. Kilbourne AM, Beck K, Spaeth-Rublee B, Ramanuj P, O'Brien RW, Tomoyasu N, et al. Measuring and improving the quality of mental health care: a global perspective. World Psychiatry. 2018;17(1):30–8.
4. Wilson J, Freeman TP, Mackie CJ. Effects of increasing cannabis potency on adolescent health. Lancet Child Adolesc Health. 2018;3:121–218.
5. Therapeutic Goods Administration. Medicinal Cannabis authorised prescriber patient data 2023. Available from: https://dashboard-data.health.gov.au/single/?appid=f330a1c6-d805-4c64-a6ef-76a69d32d8b7&sheet=a7cdc199-1658-4c94-87d0-9a3b76c520eb&select=clearall.
6. Leung J, Chan G, Stjepanović D, Chung JYC, Hall W, Hammond D. Prevalence and self-reported reasons of cannabis use for medical purposes in USA and Canada. Psychopharmacology. 2022;239(5):1509–19.
7. Amin MR, Ali DW. Pharmacology of medical cannabis. Adv Exp Med Biol. 2019;1162:151–65.
8. Stockings E, Zagic D, Campbell G, Weier M, Hall WD, Nielsen S, et al. Evidence for cannabis and cannabinoids for epilepsy: a systematic review of controlled and observational evidence. J Neurol Neurosurg Psychiatry. 2018;89(7):741–53.
9. Black N, Stockings E, Campbell G, Tran LT, Zagic D, Hall WD, et al. Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis. Lancet Psychiatry. 2019;6(12):995–1010.
10. Bonini SA, Premoli M, Tambaro S, Kumar A, Maccarinelli G, Memo M, et al. Cannabis sativa: a comprehensive ethnopharmacological review of a medicinal plant with a long history. J Ethnopharmacol. 2018;227:300–15.
11. Chadwick B, Miller ML, Hurd YL. Cannabis use during adolescent development: susceptibility to psychiatric illness. Front Psychiatry. 2013;4:1–8.
12. Henson JD, Vitetta L, Hall S. Tetrahydrocannabinol and cannabidiol medicines for chronic pain and mental health conditions. Inflammopharmacology. 2022;30(4):1167–78.
13. Keimpema E, Mackie K, Harkany T. Molecular model of cannabis sensitivity in developing neuronal circuits. Trends Pharmacol Sci. 2011;32(9):551–61.
14. Hanuš LO, Meyer SM, Muñoz E, Taglialatela-Scafati O, Appendino G. Phytocannabinoids: a unified critical inventory. Nat Prod Rep. 2016;33(12):1357–92.
15. Bhattacharyya S, Morrison PD, Fusar-Poli P, Martin-Santos R, Borgwardt S, Winton-Brown T, et al. Opposite Effects of Δ-9-tetrahydrocannabinol and Cannabidiol on human brain function and psychopathology. Neuropsychopharmacology. 2010;35(3):764–74.
16. de Almeida DL, Devi LA. Diversity of molecular targets and signaling pathways for CBD. Pharmacol Res Perspect. 2020;8(6):e00682.
17. Davies C, Bhattacharyya S. Cannabidiol as a potential treatment for psychosis. Ther Adv Psychopharmacol. 2019;9:2045125319881916.
18. Bhattacharyya S, Wilson R, Appiah-Kusi E, O'Neill A, Brammer M, Perez J, et al. Effect of cannabidiol on medial temporal, midbrain, and striatal dysfunction in people at clinical high risk of psychosis: a randomized clinical trial. JAMA Psychiat. 2018;75(11):1107–17.
19. Melas PA, Scherma M, Fratta W, Cifani C, Fadda P. Cannabidiol as a potential treatment for anxiety and mood disorders: molecular targets and epigenetic insights from preclinical research. Int J Mol Sci. 2021;22(4):1863.
20. Sloan ME, Gowin JL, Ramchandani VA, Hurd YL, Le Foll B. The endocannabinoid system as a target for addiction treatment: trials and tribulations. Neuropharmacology. 2017;124:73–83.
21. Freeman TP, Hindocha C, Baio G, Shaban NDC, Thomas EM, Astbury D, et al. Cannabidiol for the treatment of cannabis use disorder: a phase 2a,

double-blind, placebo-controlled, randomised, adaptive Bayesian trial. Lancet Psychiatry. 2020;7(10):865–74.
22. Hurd YL, Spriggs S, Alishayev J, Winkel G, Gurgov K, Kudrich C, et al. Cannabidiol for the reduction of cue-induced craving and anxiety in drug-abstinent individuals with heroin use disorder: a double-blind randomized placebo-controlled trial. Am J Psychiatry. 2019;176(11):911–22.
23. Uher R, Payne JL, Pavlova B, Perlis RH. Major depressive disorder in DSM-5: implications for clinical practice and research of changes from DSM-IV. Depress Anxiety. 2014;31(6):459–71.
24. GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Psychiatry. 2022;9(2):137–50.
25. Perrotta G. Anxiety disorders: definitions, contexts, neural correlates and strategic therapy. J Neur Neurosci. 2019;6(1):042.
26. Weibel S, Menard O, Ionita A, Boumendjel M, Cabelguen C, Kraemer C, et al. Practical considerations for the evaluation and management of Attention Deficit Hyperactivity Disorder (ADHD) in adults. Encéphale. 2020;46(1):30–40.
27. Cooper RE, Williams E, Seegobin S, Tye C, Kuntsi J, Asherson P. Cannabinoids in attention-deficit/hyperactivity disorder: a randomised-controlled trial. Eur Neuropsychopharmacol. 2017;27(8):795–808.
28. Perrotta G. Tic disorder: definition, clinical contexts, differential diagnosis, neural correlates and therapeutic approaches. J Neurosci Rehab. 2019;2019:1–6.
29. Jafari F, Abbasi P, Rahmati M, Hodhodi T, Kazeminia M. Systematic review and meta-analysis of tourette syndrome prevalence; 1986 to 2022. Pediatr Neurol. 2022;137:6–16.
30. Müller-Vahl KR, Bindila L, Lutz B, Musshoff F, Skripuletz T, Baumgaertel C, et al. Cerebrospinal fluid endocannabinoid levels in Gilles de la Tourette syndrome. Neuropsychopharmacology. 2020;45(8):1323–9.
31. Bryant RA. Post-traumatic stress disorder: a state-of-the-art review of evidence and challenges. World Psychiatry. 2019;18(3):259–69.
32. Zhang L, Pan R, Cai Y, Pan J. The prevalence of post-traumatic stress disorder in the general population during the COVID-19 pandemic: a systematic review and single-arm meta-analysis. Psychiatry Investig. 2021;18(5):426–33.
33. Sbarski B, Akirav I. Cannabinoids as therapeutics for PTSD. Pharmacol Ther. 2020;211:107551.
34. Fusar-Poli P, Estradé A, Stanghellini G, Venables J, Onwumere J, Messas G, et al. The lived experience of psychosis: a bottom-up review co-written by experts by experience and academics. World Psychiatry. 2022;21(2):168–88.
35. Moreno-Küstner B, Martín C, Pastor L. Prevalence of psychotic disorders and its association with methodological issues. A systematic review and meta-analyses. PLoS One. 2018;13(4):e0195687.
36. Leweke FM, Mueller JK, Lange B, Rohleder C. Therapeutic potential of cannabinoids in psychosis. Biol Psychiat. 2016;79(7):604–12.
37. Perrotta G. Bipolar disorder: definition, differential diagnosis, clinical contexts and therapeutic approaches. J Neurosci Neurol Surg. 2019;5(1):1–6. https://doi.org/10.31579/2578-8868/097.
38. Kroon E, Kuhns L, Hoch E, Cousijn J. Heavy cannabis use, dependence and the brain: a clinical perspective. Addiction. 2020;115(3):559–72.
39. Degenhardt L, Charlson F, Ferrari A, Santomauro D, Erskine H, Mantilla-Herrara A, et al. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Psychiatry. 2018;5(12):987–1012.
40. Chye Y, Christensen E, Solowij N, Yücel M. The endocannabinoid system and Cannabidiol's promise for the treatment of substance use disorder. Front Psychiatry. 2019;10:63.
41. Witkiewitz K, Litten RZ, Leggio L. Advances in the science and treatment of alcohol use disorder. Sci Adv. 2019;5(9):eaax4043.
42. Kosten TR, Baxter LE. Review article: effective management of opioid withdrawal symptoms: a gateway to opioid dependence treatment. Am J Addict. 2019;28(2):55–62.
43. Benowitz NL, Liakoni E. Tobacco use disorder and cardiovascular health. Addiction. 2022;117(4):1128–38.
44. Peacock A, Leung J, Larney S, Colledge S, Hickman M, Rehm J, et al. Global statistics on alcohol, tobacco and illicit drug use: 2017 status report. Addiction. 2018;113(10):1905–26.
45. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Washington, DC: Author; 2013.
46. Covidence systematic review software VHI, Melbourne, Australia. Available from: www.covidence.org. Accessed 16 Sep 2023.
47. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
48. Brozek JL, Akl EA, Alonso-Coello P, Lang D, Jaeschke R, Williams JW, et al. Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. Allergy. 2009;64(5):669–77.
49. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. 2011;343:d5928.
50. Stockings E, Campbell G, Hall WD, Nielsen S, Zagic D, Rahman R, et al. Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. Pain. 2018;159(10):1932–54.
51. Fernandes JAB, Filev R, Fidalgo TM. Cannabinoids for substance use disorder treatment: what does the current evidence say? Cannabis Cannabinoid Res. 2023;8:703–15.

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