Technical Report

Emerging and Adjunct Treatments for Common Mental Health Conditions Affecting Veterans:

A Rapid Evidence Assessment

Medicinal Cannabis Interventions

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GALLIPOLI
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Emerging and Adjunct Treatments for Common Mental Health Conditions Affecting Veterans: A Rapid Evidence Assessment – Medicinal Cannabis Interventions.

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List of Abbreviations

AE – Adverse Event

CBD – Cannabidiol

CBN – Cannabinol

CBT – Cognitive Behavioural Therapy

DCS – D-cycloserine

DVA – Department of Veterans' Affairs (Australian Government)

FDA – Food and Drug Administration (US Government)

GMRF – Gallipoli Medical Research Foundation

GRADE – Grading of Recommendations Assessment, Development, and Evaluation

LSD – Lysergic Acid Diethylamide

MA – Meta-analysis

MDMA – Methylenedioxymethamphetamine

NHMRC – National Health and Medical Research Council (Australian Government)

PICO – Population, Intervention, Comparison, Outcome

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PRISMA-S – Preferred Reporting Items for Systematic Reviews and Meta-Analyses – Search

PROSPERO – International Prospective Register of Systematic Reviews

PTSD – Posttraumatic Stress Disorder

RCT – Randomised Controlled Trial

REA – Rapid Evidence Assessment

RRMG – Rapid Reviews Methods Group

RoB 2 – The revised Cochrane Risk-of-Bias tool for randomised trials

SGB – Stellate Ganglion Block

SNRIs – Selective Norepinephrine Reuptake Inhibitors

SR – Systematic Review

SSRIs – Selective Serotonin Reuptake Inhibitors

TBS – Theta-Burst Stimulation

TGA – Therapeutic Goods Administration (Department of Health and Aged Care, Australian Government)

THC – Tetrahydrocannabinol

TMS – Transcranial Magnetic Stimulation

Assessments and Outcome Measures: Clinician-Administered and Self-Report

Name	Abbreviation
Alcohol, Smoking, and Substance Involvement Screening Test	ASSIST
Alcohol Use Disorders Identification Test	AUDIT
Beck Anxiety Inventory	BAI
Beck Depression Inventory	BDI
Cannabis Problems Questionnaire	CPQ
Cannabis Use Disorders Identification Test – Revised	CUDIT-R
Cannabis Withdrawal Scale	CWS
Cocaine Craving Questionnaire – Brief	CCQ-B
Columbia-Suicide Severity Rating Scale	C-SSRS
Fagerström Test for Nicotine Dependence	FTND
Fear of Negative Evaluation Questionnaire	FNE
Hamilton Anxiety Rating Scale	HAM-A
Heroin Craving Questionnaire	HCQ
Insomnia Severity Index	ISI
Inventory of Depression and Anxiety Symptoms	IDAS
Inventory of Psychosocial Functioning	IPF
Liebowitz Social Anxiety Scale	LSAS
Marijuana Craving Questionnaire	MCQ
Marijuana Rating Form	MRF
Minnesota Cocaine Craving Scale	MCCS
Mood and Physical Symptoms Scale	MPSS
Motivation To Stop Scale	MTSS
Opioid Treatment Index	OTI
Pleasantness Rating Task	PRT
Positive and Negative Affect Schedule	PANAS
Questionnaire of Smoking Urges – Brief	QSU-B
Severity of Dependence Scale	SDS
Short Form Survey, 36-item	SF-36
State Trait Anxiety Inventory	STAI
State Trait Anxiety Inventory – State Subscale	STAI-S
State Trait Anxiety Inventory – Trait Subscale	STAI-T
Structured Clinical Interview for DSM-IV	SCID
Structured Clinical Interview for DSM-IV Axis I Disorders	SCID-I
Structured Clinical Interview for DSM-IV Axis II Disorders	SCID-II
Structured Clinical Interview for DSM-5	SCID-5
Structured Clinical Interview for DSM-5 – Research Version	SCID-5-RV
Systematic Assessment for Treatment Emergent Events	SAFTEE
Timeline Followback	TLFB
Visual Analogue Scale – Anxiety	VAS-A
Visual Analogue Scale – Craving	VAS-C
UKU Side Effects Rating Scale	UKU-SERS
Yale-Brown Obsessive Compulsive Scale	Y-BOCS

Glossary of Terms

12-month prevalence

The proportion of a target population who have ever fulfilled diagnostic criteria for a codified health condition (e.g., ICD-10/ICD-11; DSM-IV/DSM-5) at some time in their life; and who have experienced symptoms of the health condition in the last 12 months.

Adjunct intervention

An adjunct intervention is added to a primary intervention. The aim of the adjunct intervention is to reduce symptom severity to a greater extent than the primary intervention is expected to achieve alone. When deciding whether an adjunct intervention is effective, one should compare the effectiveness of the primary intervention to the effectiveness of the combined intervention (i.e., primary plus adjunct intervention). Source: Adapted from Jones et al. (2020, p. 5).

Alternative intervention

Alternative interventions are not accepted as best-practice interventions, usually due to a lack of rigorous scientific evidence. These interventions may be popular, or widely used, but are not recommended by treatment guidelines. This does not mean that alternative interventions do not work; it just means that there is not enough evidence to know if they do work. Source: Adapted from Jones et al. (2020, p. 5).

Ayahuasca

See the glossary entry for "Dimethyltryptamine, DMT".

Cannabidiol (CBD)

Cannabidiol is one of the primary cannabinoids found in various concentrations within the cannabis plant. While it is structurally similar to tetrahydrocannabinol (THC), CBD has a diverse pharmacology, and does not cause intoxication or euphoria. CBD has increasingly been investigated in the literature after initially being overlooked in favour of THC (Russo & Marcu, 2017). While the exact mechanism of action is not fully understood, CBD elicits its pharmacological effects (e.g., antiepileptic, anxiolytic, antipsychotic, anti-inflammatory, and neuroprotective) without significant intrinsic activity on CB1 and CB2 receptors, thereby avoiding adverse psychoactive effects (Bridgeman & Abazia, 2017). While data on the long-term safety of CBD is lacking, a longitudinal study of children receiving CBD oil for epilepsy found the most common adverse effects were somnolence (30%) and diarrhoea (24%; Arnold, 2021).

Cannabinoids

Cannabinoids are compounds found in the cannabis plant (i.e., phytocannabinoids: primarily THC and CBD), or synthetic compounds that can interact with the endogenous or "endo-cannabinoid" system. Cannabinoids are usually taken orally (typically as oil or sublingual spray) or inhaled (i.e., smoked, or vaporised). Smoking of medicinal cannabis is generally not advised due to the associated health risks (see the glossary entry for "Vaped and smoked medicinal cannabis"). The endocannabinoid system plays a complex role in physiology, with widespread activity between the central nervous system and most bodily organs. The endocannabinoid system is usually described in relation to two major cannabinoid receptors (CB1 and CB2): cannabinoid receptor type 1 (CB1) is the most abundant receptor expressed primarily in the central nervous system; and cannabinoid receptor type 2 (CB2) is associated with immune function and limited activity in the central nervous system. Source: Adapted from Grinspoon (2021).

Cannabinol (CBN)

Cannabinol is a non-psychoactive cannabinoid found in trace amounts in cannabis. It is the non-enzymatic oxidation by-product of THC; most frequently detected after prolonged and/or inappropriate cannabis storage, especially at higher temperatures (Russo & Marcu, 2017). None of the studies included in this rapid evidence assessment (REA) examined the effects of CBN in isolation from other cannabis constituents.

Classic hallucinogens

"Classic" hallucinogenic or serotonergic tryptamines include lysergic acid diethylamide (LSD), psilocybin, N,N-dimethyltryptamine (DMT), and ayahuasca (the psychoactive compound in ayahuasca is DMT). These compounds belong to the indolamine subclass of monoamine neurotransmitters, which mimic the endogenous neurotransmitter serotonin, and act mainly through agonist activity on various serotonin (5-HT) receptors. Serotonin receptor activity has a wide range of functions including the maintenance of healthy sleep, mood, and behaviour. While 5-HT-receptor-mediated actions are thought to be primarily responsible for the therapeutic effects of serotonergic tryptamines, this mechanism is not sufficient to explain the drug-induced hallucinations associated with many compounds. The neuro-pharmacological evidence base is still developing. The dose and duration of effect for tryptamine derivatives can vary widely depending on their potency and route of administration. Source: Adapted from Frecska et al. (2016).

Clinical trial phases

There are four phases to clinical trials. "Phase 1 are first-in-human trials. These establish basic safety, usually in healthy volunteers who are paid for their participation. Phase 2 are first-in-patient trials. These establish feasibility of a new intervention in a patient population with a particular diagnosis. Phase 3 are efficacy trials. These are randomized, controlled trials, often in very large numbers of similar patients in numerous centers around the world. Phase 3 trials often cost hundreds of millions of dollars and take many years to complete. It is only phase 3 trials that are used to make licensing decisions, because only phase 3 trials have sufficiently robust designs to inform those decisions. Even after licensing, phase 4 trials investigate treatments further, often picking up rare side effects that phase 3 trials can't detect. Licenses are sometimes withdrawn on the basis of phase 4 trials. Even after this, drug safety monitoring is essentially endless, and drugs may be withdrawn for safety reasons after being on the market for many years" (Rucker & Young, 2021, p. 2).

Controversial intervention

Within the context of this report series, controversial interventions refer to healthcare treatments with access barriers (e.g., legislative, regulatory, ethical and/or social), which affect their use in research and clinical practice. Psychedelics and medicinal cannabis are the most controversial interventions examined by the REA. These compounds have a complicated socio-political history and controlled (illegal) status in most countries. In Australia, most psychedelic compounds are classified as Schedule 9 (prohibited) substances (i.e., use is limited to medical and scientific research and subject to regulatory controls); medicinal cannabis and ketamine are classified as Schedule 8 (controlled) substances (i.e., use in a medically controlled environment).

The resurgence of clinical trials examining psychedelic-assisted psychotherapy for various mental health conditions has demonstrated that some compounds (e.g., MDMA) are relatively safe and efficacious in highly controlled research settings (Sessa et al., 2019). Despite the legal barriers, widespread media coverage of these study findings may encourage individuals to seek out these compounds when accepted or conventional treatments fail. Clinicians have an ethical duty to minimise the potential risk of harm to consumers who are currently using (or interested in exploring) psychedelics, albeit within the current regulatory and legislative context (Pilecki et al., 2021). Harm minimisation strategies include education on safety; and the importance of set (i.e., preparation), setting (i.e., support during administration), and therapeutic follow-up (i.e., integration); to help consumers make informed choices about psychedelic use, avoid adverse events, and increase the probability of beneficial effects (Pilecki et al., 2021).

D-cycloserine (DCS)

D-cycloserine (DCS) is an antibiotic. It is traditionally prescribed at high doses as a second-line treatment for tuberculosis, but has increasingly been studied at lower doses in psychiatric conditions (e.g., PTSD, anxiety disorders, substance use disorders) and neurological conditions (e.g., dementia, autism). DCS acts as a partial agonist at the glycine-binding site of the N-methyl-D-aspartate (NMDA) receptor (in vivo, a partial agonist behaves like an agonist at low doses but has features of antagonists at high doses). The NMDA receptor plays a crucial role in cortical neuroplasticity through its influence on long-term potentiation (LTP): a neuronal mechanism thought to be relevant for learning. DCS is thought to enhance the efficacy of therapies that rely on learning processes (e.g., exposure therapy in PTSD and anxiety disorders; and cue-exposure therapy in

substance-related and addictive disorders) by improving fear extinction learning, and memory consolidation and retrieval.

In DCS studies with patients, drug interactions should be considered. There is evidence from animal studies that antidepressants (e.g., imipramine or citalopram) can offset the facilitating effect of DCS on extinction learning. Additionally, neuroleptics (e.g., olanzapine and clozapine) also seem to impair the effects of DCS, especially in patients with schizophrenia. In animal studies, chronic administration of DCS appears to reduce its efficacy; and a meta-analysis of exposure therapy in humans (Norberg et al., 2008) indicates that DCS efficacy is higher when administered a limited number of times, rather than repeatedly. Finally, animal studies indicate that the DCS mechanism of action may change (or even reverse) under conditions of high stress (due to different concentrations of surrounding neurotransmitters), which may be relevant to its efficacy in the treatment of mental health conditions that are characterised by sleep disturbance or fear (e.g., depression, schizophrenia, and anxiety disorders).

DCS is administered orally. At low doses, it is infrequently associated with mild side effects, including dizziness and fatigue. Other side effects on perception and cognition (including hyper-excitability, depression, anxiety, confusion, and memory loss) are mainly associated with high doses. At high doses, gastrointestinal upset, rash, allergy, fever, and cardiovascular problems (including cardiac arrhythmia) have been reported on rare occasions. Very rare reports of seizures have been associated with blood levels exceeding 35 µg/mL; therefore, most studies exclude participants with a history of seizures as a precautionary measure. Source: Adapted from Schade and Paulus (2015).

Diagnostic and Statistical Manual of Mental Disorders (DSM)

The Diagnostic and Statistical Manual of Mental Disorders (DSM) is published by the American Psychiatric Association (APA). It is an international system for classifying mental health disorders using a common language and standard criteria. It is used by clinicians, researchers, policy makers, drug regulation agencies, pharmaceutical companies, health insurance companies, and the legal system. The DSM evolved from systems for collecting census data, psychiatric hospital statistics, and from a United States Army manual. First published in 1952, each revision of the DSM has added psychiatric diagnoses, and removed those no longer considered to be mental health disorders. Criticisms of the DSM include: concerns about the reliability and validity of many diagnoses; the use of categorical distinctions between mental illness and 'normal' functioning; cultural biases; and the medicalisation of human distress. The DSM-IV was published in 1994. The APA collaborated with the WHO as it developed the ICD-10, increasing the alignment between the two classification systems. The DSM-5 was published in 2013, and the text revision (i.e., DSM-5-TR) was published in March 2022. The DSM-5-TR clarified certain diagnostic criteria, but no conceptual changes were made to the criteria sets. Source: Adapted from APA (2022).

Dimethyltryptamine (DMT) – constituent of ayahuasca

N,N-dimethyltryptamine (DMT) is a psychoactive compound that belongs to a class of drugs known as serotonergic (or hallucinogenic) tryptamines (see the glossary entry for "Classic hallucinogens"). DMT is the hallucinogenic component of the psychoactive beverage ayahuasca, which has traditionally been used in cultural and religious rituals in South America. DMT is also abundant in animal and plant organisms, including human blood and brain fluid. Oral consumption of ayahuasca is the most common route of administration and produces hallucinogenic effects within approximately one hour of ingestion, which can last approximately four hours (Fuentes et al. 2020). These effects include a modified state of consciousness and perception, which is thought to allow users to gain insight into maladaptive behavioural, emotional, or cognitive patterns, as well as to confront repressed memories and/or reveal ego defence mechanisms. Initial side effects may include dizziness, diarrhoea, nausea, and vomiting. These effects are common and are often considered an essential part of a process that is intended to bring a sense of "purge" and relief. The characteristic effects of ayahuasca make it difficult to study in a double-blind, placebo-controlled trial; therefore, the long-term risks and benefits are largely unknown. Source: Adapted from Frecska et al. (2016).

Disruptive intervention

Disruptive healthcare interventions are poorly defined in the literature, there is no specific health sector definition, and the term is frequently misapplied to healthcare innovations that may be better described as incremental or radical (Sounderajah et al., 2021). Within the context of this report series, disruptive interventions refer to healthcare innovations that have the potential to challenge established treatment paradigms in a market segment or patient population, leading to market upheaval (Sounderajah et al., 2021). For example, treatment protocols for psychedelic-assisted psychotherapy typically involve two therapists (i.e., a co-therapy team), and three phases of treatment sessions (i.e., preparatory; dosing; integrative), with dosing sessions lasting up to eight (8) hours. A further relevant example involves massed psychotherapy sessions for the treatment of anxiety disorders or PTSD (e.g., the Bergen 4-day treatment protocol for obsessive compulsive disorder; see Kvale et al., 2020). These types of treatment protocols have the potential to disrupt funding models for individual or group psychotherapy, which typically reimburse an individual practitioner for a series of treatment sessions lasting one (1) to two (2) hours. Disruptive interventions exist along a continuum that pose minor to substantial challenges to established treatment paradigms.

Emerging intervention

An intervention where research on treatment effectiveness has commenced, but is still in its infancy, and there is not enough evidence to support its use. These types of interventions may already be used by people with mental health conditions, and are often reported in the media as offering new hope. However, these media reports are typically based on anecdotal evidence or small preliminary studies. This does not mean that emerging interventions do not work; it just means that there is not enough evidence to know if they do work. Source: Adapted from Jones et al. (2020, p. 5).

Evidence-based intervention

Interventions that have been proven to be effective and are supported by rigorous scientific evidence. They are often recommended by treatment guidelines. Source: Adapted from Jones et al. (2020, p. 5).

Grading of Recommendations Assessment, Development, and Evaluation (GRADE)

A systematic approach for rating the certainty of a body of evidence in systematic reviews and other evidence syntheses (The GRADE Working Group, 2022).

Grey literature

Grey literature refers to a range of different document types (in print and electronic formats) produced across all levels of government, academia, business, and industry that: are protected by intellectual property rights; are of sufficient quality to be collected and preserved by library holdings or institutional repositories; and are not controlled by commercial publishers (Farace & Schopfel, 2010).

International Classification of Diseases (ICD)

The International Classification of Diseases (ICD) is published by the World Health Organisation (WHO). It is the international diagnostic classification standard for reporting morbidity (diseases, injuries, and symptoms), mortality (deaths), reasons for encounter, factors that influence health status, and external causes of disease. It is used by clinicians and researchers around the world to store, retrieve, and analyse health information. Specific uses include sharing and comparing health information from hospitals, regions, settings, and countries to: monitor the incidence and prevalence of diseases; track reimbursement and resource allocation trends; check compliance with safety and quality guidelines; and inform evidence-based decision making. The ICD-10 was published in 1992. It is used by more than 100 countries around the world, and cited in more than 20,000 scientific articles. The ICD-11 was published in 2019. Source: Adapted from WHO (2022).

Ketamine

Ketamine is referred to as a psychedelic or dissociative anaesthetic (Vollenweider, 2001). It is commonly used in surgical procedures by medical practitioners and veterinarians. When used for anaesthetic purposes, ketamine is usually administered via intravenous (IV) infusion or intramuscular (IM) injection. Dissociation, sedation, and patient comfort is achieved via its partial agonism on opiate mu-receptors. Due to its rapid onset, it is particularly

useful in emergency, disaster relief, and military situations. However, transient respiratory depression can result if improperly administered (i.e., excessive rate of delivery or excessive dose). Ketamine's antagonism on N-methyl-D-aspartate (NMDA) and glutamate receptors plays a significant role in controlling symptoms of depression and acute suicidal ideation. In 2019, the US Food and Drug Administration (FDA) approved esketamine (S-enantiomer of ketamine), in conjunction with an oral antidepressant, for treatment-resistant depression in adults. In 2020, the FDA approved esketamine, in conjunction with an oral antidepressant, to treat depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation. The drug is administered as an intranasal spray under the supervision of a healthcare provider. It is contraindicated in patients with schizophrenia due to its potential for exacerbating the underlying condition via short-term emergence phenomena or delirium, which can occur in up to 6-12% of patients, and last for up to 3 hours. Source: Adapted from Rosenbaum et al. (2022).

Lifetime prevalence

The proportion of a target population who have ever fulfilled diagnostic criteria for a codified health condition (e.g., ICD-10/ICD-11; DSM-IV/DSM-5) at some time in their life.

Lysergic acid diethylamide (LSD)

Lysergic acid diethylamide (LSD) is an ergot derivative and "classic" hallucinogen (see the glossary entry for "Classic hallucinogens"), which was first synthesised for treating postpartum haemorrhage. After the accidental discovery of its psychoactive effects, it was marketed for psychological research from the 1950s. It was prohibited in 1967 in the USA due to increased recreational drug use through the early 1960s, and its association with counterculture movements. Oral administration of LSD is most common in scientific research, often as a single, one-off dose. LSD may produce variety of psychological and sensory effects including euphoria, hallucinations, and delusions, as well as distortions in the perception of time, depth, sound, colour, and touch. Due to these psychoactive effects, use in uncontrolled or unsupervised environments may lead to anxiety, dysphoria, confusion, and unpredictable behaviour, or the exacerbation of pre-existing psychotic disorders. Other possible adverse effects include increased blood pressure and heart rate, requiring precautions in patients with cardiovascular disease. Source: Adapted from Fuentes et al. (2020).

Methylenedioxymethamphetamine (MDMA)

3,4-Methylenedioxymethamphetamine (MDMA) belongs to a class of drugs termed "entactogens" (Vollenweider, 2001). MDMA induces a positive mood state, in conjunction with the activation of prefrontolimbic or paralimbic structures, and the deactivation of the amygdala and thalamus (Vollenweider, 2001). While entactogens (i.e., MDMA and related compounds) have a molecular structure that is similar to both stimulant amphetamines and hallucinogenic phenylethylamines (e.g., mescaline), entactogens' psychedelic-like effects are typically not accompanied by hallucinations (Vollenweider, 2001). Compared to LSD (see the glossary entry for "Lysergic acid diethylamide, LSD"), MDMA is shorter-acting and produces a more easily tolerated altered state of consciousness (Sessa et al., 2019). It enhances the user's feelings of empathy and bonding, and has been used as an adjunct to psychotherapy to access and process traumatic memories (Sessa et al., 2019).

MDMA was first synthesised in 1912 as one of a series of chemical compounds used to develop medications for managing abnormal bleeding. In 1953-54, the US Army conducted a brief series of toxicity studies in animals. In the late 1970s, psychiatrists and psychologists reported benefits of MDMA-assisted therapy in individuals and couples. Widespread recreational use followed thereafter, leading to criminalisation of the compound by the US Drug Enforcement Administration (DEA) in 1985. MDMA is notable for its ability to decrease fear responses, and increase empathy and interpersonal trust. For these reasons, it was expected to be especially useful in treating the emotional activation that accompanies access to traumatic memories in the treatment of PTSD. Source: Adapted from Williams (2017).

While recent clinical trials indicate that therapeutic doses of MDMA are generally well tolerated, adverse effects may include anxiety, restlessness, fatigue, jaw clenching, headache, and transient increases in blood pressure (Kisely et al., 2021). The long-term safety outcomes remain unknown.

Narrative synthesis

Narrative synthesis is an approach that relies primarily on the use of words and text to summarise and explain the findings from the studies included in a systematic literature review. The defining characteristic of a narrative synthesis is the textual approach used to 'tell the story' of the findings from the included studies, although it may involve the manipulation of statistical data. Source: Adapted from Popay et al. (2006, p. 5).

Psilocybin

Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) is a psychoactive compound that belongs to a class of drugs known as "classic" serotonergic (or hallucinogenic) tryptamines (see the glossary entry for "Classic hallucinogens"). Psilocybin can be derived from certain species of mushrooms. When orally administered, the body converts psilocybin to psilocin (4-hydroxy-N,N-dimethyltryptamine). Psilocin acts as a 5-HT agonist, primarily on the 5-HT2A receptor, which is thought to account for the psychotropic effects of the drug. Like ayahuasca, psilocybin has been used for centuries in cultural and religious rituals in Indigenous communities. It is also thought to have a similar mechanism of action to ayahuasca; with mystical-type experiences correlating with therapeutic outcomes, and the less acute adverse effects of the compound (e.g., nausea). Pharmacologically, psilocybin is closely related to LSD, but has been more widely studied in recent research for various mental health conditions, including treatment-resistant depression, anxiety, and substance use disorders. Source: Adapted from Araújo et al. (2015) and Johnson et al. (2017).

While recent clinical trials indicate that therapeutic doses of psilocybin are generally well tolerated, adverse effects may include anxiety, headache, and transient increases in blood pressure (Kisely et al., 2021).

Psychedelic-assisted psychotherapy

Professionally supervised use of novel and classic psychedelic medications (including ketamine, MDMA, psilocybin, ayahuasca, and LSD) as part of a structured psychotherapy protocol; typically including drug-free preparatory (pre-dosing) and integrative (post-dosing) therapy sessions, in addition to the psychedelic-assisted (dosing) therapy sessions (Schenberg, 2018).

Rapid evidence assessment (REA)

A rapid evidence assessment (REA), or rapid review, is "a form of knowledge synthesis that accelerates the process of conducting a traditional systematic review through streamlining or omitting various methods to produce evidence for stakeholders in a resource-efficient manner" (Hamel et al., 2021, p. 80).

Standalone intervention

The only intervention that an individual receives. The intervention is aimed at symptom reduction. A standalone intervention should be compared to a best-practice intervention/s to determine whether it is effective or not. Source: Adapted from Jones et al. (2020, p. 5).

Stellate ganglion block (SGB)

The stellate ganglion block (SGB) procedure is an injection of local anaesthetic (e.g., 0.5% bupivacaine) into a nerve bundle called the stellate ganglion. The stellate ganglion is located at the base of the neck in the cervical region of the spine (between vertebrae C6 and C7). The procedure is designed to temporally block the function of the stellate ganglion (i.e., interrupt the cervical sympathetic chain; Rae Olmsted et al., 2019). It is typically conducted under ultrasound or fluoroscopic guidance. Since the 1940s, SGB has been used to treat a wide range of neurological and neurovascular conditions (e.g., epilepsy, migraines, cerebral haemorrhage, embolisms, and thrombosis). The beneficial psychiatric effects associated with SGB treatment (e.g., reduced anxiety and depression; increased sleep quality) were first reported in 1947. The mechanism by which SGB may improve symptoms of mental health conditions is not well understood. Lipov et al. (2009) hypothesised that the stellate ganglion activates brain structures that increase levels of nerve growth factors and norepinephrine in the brain, leading to pathological brain states that underlie disorders such as PTSD and chronic pain. A right-sided SGB is usually performed, as the maintenance of chronic sympathetic responses is typically associated with the right central autonomic network. Although the procedure is invasive, it has an acceptable level of safety. The use of ultrasound or fluoroscopic guidance further decreases the risks of complication or adverse effects. The most

common serious adverse event reported from a 1992 survey of 45,000 SGBs, performed without fluoroscopic or ultrasonographic guidance, was generalised seizures due to inadvertent intravascular injection of the local anaesthetic. Temporary Horner syndrome is a common side effect of SGB that is caused by the disruption of the nerve pathway from the neck and head to the brain. Source: Adapted from Summers and Nevin (2017) and Rae Olmsted et al. (2019).

Horner Syndrome typically presents as a constricted pupil of the eye, a drooping eyelid, and decreased sweating on the affected side of the face (Khan & Bollu, 2022).

Tetrahydrocannabinol (THC)

Delta-9-tetrahydrocannabinol (THC) naturally occurs in variable concentrations within the cannabis plant. It is one of the primary psychoactive components of cannabis (see also the glossary entry for "Cannabidiol, CBD"). THC's mechanism of action is thought to be primarily mediated by CB1 receptors in the human central nervous system. CB1 receptors are thought to be responsible for the acute adverse effects of THC, ranging from dizziness and anxiety to mood disturbances and psychotic symptoms (Bridgeman & Abazia, 2017). For this reason, most clinical trials exclude participants with a personal or family history of psychosis. Evidence for the long-term safety of THC is mostly derived from recreational rather than medicinal use. Within the medical context, a 3-year randomised controlled trial (RCT) for participants with multiple sclerosis found that THC has an acceptable safety profile, with low-to-moderate toxicity, and a low incidence of serious adverse events (Arnold, 2021).

Theta burst stimulation (TBS)

Theta burst stimulation (TBS) refers to a type of transcranial magnetic stimulation (TMS) intervention that applies pulses of varying frequency to replicate the natural theta rhythm occurring in the hippocampus of the brain. TBS treatment sessions typically have a shorter duration of stimulation than standard repetitive TMS (rTMS) sessions (up to 5 minutes vs. up to 45 minutes, respectively), and fewer pulses are delivered overall. There are two commonly used TBS protocols: continuous (cTBS) and intermittent (iTBS). In cTBS, bursts of three (3) pulses at 50 Hz are delivered every second for either 20 seconds (100 bursts) or 40 seconds (200 bursts). In iTBS, bursts of three (3) pulses are delivered for 2 seconds then repeated every 10 seconds (i.e., cycles of 2 seconds of TBS followed by a pause of 8 seconds. Source: Adapted from Klomjai et al. (2015) and Oberman et al. (2011).

Transcranial magnetic stimulation (TMS)

Transcranial magnetic stimulation (TMS) is a neuro-stimulation and neuro-modulation technique. It aims to induce electric currents in the brain to inhibit at low frequency (i.e., 1 Hz), or excite at high frequency (i.e., 10 to 20 Hz), the neurons of a specific brain area. The medical device that delivers the stimulation is referred to as a coil. Repetitive TMS (rTMS) pulses (i.e., electromagnetic fields switched on and off at a very high rate) can modulate the neuronal response (or cortical excitability) beyond the duration of stimulation. These brain changes are proposed to lead to behavioural consequences with therapeutic potential. Inconsistencies in the findings from TMS intervention studies for different mental health conditions (e.g., OCD) have been attributed to varying treatment protocols (e.g., TMS frequency and intensity), which target different brain regions (e.g., the dorsolateral prefrontal cortex, DLPFC, the supplementary motor area, SMA, and the orbitofrontal cortex, OFC; Ziblak et al., 2021). In research settings, TMS intervention studies increasingly employ imaging (e.g., functional magnetic resonance imaging, fMRI) to target specific brain regions, which may improve the rigour and reproducibility of non-invasive brain stimulation studies over time (Rossi et al., 2021).

There is some evidence to suggest that the clinical response to TMS interventions may be affected by handedness and lateralisation of brain function (e.g., hemispheric variation in mood regulation; Fitzgerald et al., 2021). Consequently, some studies recruit participants or report findings based on handedness (i.e., right-handed, left-handed, or ambidextrous), as TMS interventions are typically hemisphere-specific, and handedness and hemispheric laterality may influence the treatment response (Fitzgerald et al., 2021).

TMS has been approved by several countries (including Australia, the US, the UK, Canada, and Israel) as an intervention for medication-resistant, treatment-refractory, depression in adults (Rossi et al., 2009). The US Food and Drug Administration (FDA) cleared the first TMS device for the treatment of Major Depressive Disorder

(MDD) in 2008. Since that time, the FDA has cleared various TMS devices for several additional treatment indications including: cortical mapping (in 2009); migraine headache with aura (in 2013); obsessive compulsive disorder (in 2017); a TBS protocol for treatment of medication-resistant MDD (in 2018); and short-term smoking cessation (in 2020; Cohen et al., 2022). In 2019, the FDA denied a *de novo* request for a TMS device for treatment of Alzheimer's disease (Cohen et al., 2022).

Common side effects of TMS include headache, drowsiness, and dizziness (Ziblak et al., 2021). Depending on the frequency and protocol of stimulation used, transient headache, localised pain, and discomfort range from possible to infrequent (Rossi et al., 2009). The most serious potential side effect of TMS is seizure. Since the late 1990s, the rTMS safety guidelines have been iteratively revised, which has greatly reduced the incidence of associated seizures. Recent estimates of seizure incidence are less than 1% (overall), which is comparable to most psychotropic medications (Stultz et al., 2020).

While TMS is non-invasive, reducing the number of stimuli (pulses), and selecting the minimum effective intensity, is desirable to avoid unnecessary discomfort for the patient (Temesi et al., 2014). This can be achieved by determining an individual's motor threshold, which is defined as the minimum amount of stimulation necessary to elicit a motor response (an involuntary muscle contraction also known as a motor evoked potential, MEP) in at least 50% of all attempts (as determined by visual inspection or electromyography). Motor thresholds are usually determined at rest (i.e., resting motor threshold, RMT), but can also be determined during weak voluntary muscular contraction such as holding a fist or ball (i.e., active motor threshold, AMT).

TMS: Period and carryover effects

Effective TMS interventions appear to require multiple weeks of sessions to achieve a sustained treatment effect. For example, the FDA-approved protocol for treatment of depression (Horvath et al., 2010) employs several weeks of high frequency (10 Hz) rTMS sessions to achieve a treatment effect that lasts several months beyond the period of active stimulation. Furthermore, the duration of the treatment effect may vary depending on: the mental health condition/s or symptom/s targeted by the TMS intervention; the frequency and intensity of stimulation; the brain region/s targeted by the treatment; and individual differences in treatment response. For example, after a 6-week course of deep TMS (dTMS) treatment, Carmi and colleagues (2019) found that approximately 45% of participants had reduced OCD symptoms at the one-month follow up. Liu and colleagues (2020) reported a longer treatment effect for a shorter treatment duration in participants with a heroin use disorder (i.e., after a 4-week course of rTMS targeting the DLPFC, craving severity was reduced for up to 60 days).

In contrast, it is unclear whether the effects of a single TMS session persist beyond the stimulation day. Several studies (Di Lazzaro et al., 2005; Huang et al., 2005; Huang et al., 2009) suggest that the maximum duration of the treatment effect for a single TMS session is a matter of hours (as evidenced by facilitation of motor evoked potentials in the brain). Thus, studies included in the REA that employed a crossover design were not penalised on the risk-of-bias assessments (Domain S: "bias arising from period and carryover effects") provided the study used a washout period that was longer than one day. Finally, it is not yet known whether superior treatment effects would be achieved with a bursting-pattern protocol (i.e., TBS) or a single-frequency protocol (i.e., rTMS).

Vaped and smoked medicinal cannabis

In Australia, a medical practitioner can prescribe numerous medicinal cannabis products (including dried flower formulations) via the Special Access Scheme (SAS) and Authorised Prescriber (AP) pathways (Therapeutic Goods Administration, 2022). Typically, these approvals are granted for the treatment of non-cancer pain and anxiety; however, some prescribers have used the same approval pathways for patients suffering from insomnia and PTSD (Arnold et al., 2020).

In respect of vaped cannabis, vaporising dried cannabis flower using an approved medical device differs from vaping using an electronic cigarette (e-cigarette) device. E-cigarette devices may expose patients to unsafe inhalation of constituent aerosolised "e-liquid" ingredients such as vitamin E acetate, which has been conclusively linked to an increased risk of a novel lung disease termed "e-cigarette or vaping product use-associated lung injury" (EVALI; Centers for Disease Control and Prevention, 2020). Currently, there is insufficient evidence to rule out other chemicals in (THC-containing) e-cigarette products as contributing to the development of EVALI (Centers for Disease Control and Prevention, 2020).

In Australia, prescribed medicinal cannabis products must conform to the Therapeutic Goods Administration (TGA) manufacturing standards, which do not permit formulations for e-cigarette delivery (Therapeutic Goods Administration, 2017). While evidence on the long-term effects of dried cannabis flower vaporisation is still emerging, many practitioners are likely to continue to recommend vaporised cannabis for rapid relief of breakthrough (pain) symptoms, with (daily) oral formulations preferred for maintenance of symptom control (Sihota et al., 2021).

In respect of smoked cannabis, several studies reported in the literature (and included in the REA) use smoking as a route of administration (e.g., Kayser et al., 2020; Bonn-Miller et al., 2021). The TGA explicitly recommends against the use of smoked cannabis due to the health risks associated with the inhalation of combusted plant matter (i.e., exposure to harmful compounds such as tar, carbon monoxide, and hydrocarbons; Therapeutic Goods Administration, 2017). In contrast, vaporisation heats the plant matter without igniting it, resulting in a vapour that is relatively free from the by-products of combustion. While this is an important harm-reduction strategy for cannabis smokers, the long-term health effects of dried cannabis vaporisation are unknown as it is a relatively new route of administration (Loflin & Earlywine, 2015). In the context of the REA, studies that use smoked cannabis as a route of administration (i.e., Kayser et al., 2020; Bonn-Miller et al., 2021) have been analysed in keeping with this serious limitation on the intervention's generalisability to the medical context (i.e., these studies have been penalised in the "directness" domain of the GRADE certainty of evidence summaries).

Veteran

A current- or former-serving member of the military having had one or more days of continuous, full-time military service in the Permanent or Reserve Forces (Australian definition). The definition of veteran varies by country. In the UK, the term refers to an individual who has served for at least one day in Her Majesty's Armed Forces (Regular or Reserve), or Merchant Mariners who have served on legally-defined military operations (UK Office for Veterans' Affairs, 2020). In Canada, the term applies to any former member of the Canadian Armed Forces with an honourable discharge, who successfully underwent basic training (Government of Canada, 2019). In the US, the term refers to an individual who has served full-time in the active military, naval, or air service (including service as a cadet at the United States Military, Air Force, or Coast Guard Academy, or as a midshipman at the United States Naval Academy), and who was discharged under conditions other than dishonourable (US Department of Veterans Affairs, 2019). In New Zealand, the term applies to an individual who has served in the New Zealand Armed Forces before 1 April 1974; and after that date, individuals with qualifying operational service (i.e., service at a time of war, or on deployments overseas where a ministerial declaration has confirmed a significant risk of harm; New Zealand Defence Force, 2018).

Executive Summary

Background

There are a number of treatments that have an emerging evidence base and could be considered in the management of common mental health conditions affecting veterans. Emerging and adjunct treatments are typically considered when an individual's adherence or response to accepted or conventional treatment/s is poor (i.e., chronic, treatment-resistant, or treatment-refractory mental health conditions).

Aim

The aim of the rapid evidence assessment (REA) was to identify and critically evaluate the current evidence on emerging and adjunct treatments for posttraumatic stress disorder (PTSD) and common mental health conditions affecting veterans.

Rapid evidence assessment

A REA, or rapid review, is "a form of knowledge synthesis that accelerates the process of conducting a traditional systematic review through streamlining or omitting various methods to produce evidence for stakeholders in a resource-efficient manner" (Hamel et al., 2021, p. 80).

Current evidence

The REA examined the peer-reviewed literature published from 1 January 2017 to 8 February 2022.

Emerging and adjunct treatments

The REA examined five categories of interventions as follows:

9. Psychedelic compounds; specifically:
    a. Ketamine;
    b. Methylenedioxymethamphetamine (MDMA);
    c. Lysergic acid diethylamide (LSD);
    d. Psilocybin;
    e. Dimethyltryptamine (DMT) including ayahuasca.
10. Medicinal cannabis; specifically:
    a. Cannabidiol (CBD);
    b. Cannabinol (CBN);
    c. Tetrahydrocannabinol (THC).
11. D-cycloserine (DCS).
12. Stellate ganglion block (SGB).
13. Transcranial magnetic stimulation (TMS) including theta-burst stimulation (TBS).

Common mental health conditions affecting veterans

The REA examined four categories of mental health conditions as follows:

1. Anxiety disorder/s;
2. Mood or depressive disorder/s;
3. Substance-related and addictive disorder/s;
4. Trauma- and stressor-related disorder/s.

The REA included a specific focus on PTSD. Note that, in 2013, when the DSM-IV was revised to the DSM-5, PTSD was moved from the anxiety disorder/s category to the trauma- and stressor-related disorder/s category.

Search strategy

A comprehensive search strategy was developed in consultation with the review team, the GMRF Expert Panel, the DVA Emerging Treatments Project Team, and a liaison librarian (information specialist) with extensive experience developing search strategies for systematic reviews of health and medical research. In keeping with the best-practice guidelines (Garritty et al., 2020; Rethlefsen et al., 2021), the search strategy was peer-reviewed by a senior liaison librarian with an extensive background in health and medical research.

Four electronic databases (PubMed; APA PsycNet; Cochrane Library; PTSDpubs) were searched to identify peer-reviewed, English-language studies of human adults (18 years of age and over) that were published between 1 January 2017 and 8 February 2022. There was a specific emphasis on Level I and Level II evidence as defined by the National Health and Medical and Research Council (NHMRC, 2009). That is, the REA focused on the following three types of publications:

1. Systematic reviews (SRs);
2. Meta-analyses (MAs);
3. Randomised controlled trials (RCTs).

Results: Medicinal cannabis interventions

From the four databases that were searched, 42 studies met the inclusion criteria, including 35 secondary sources: 32 systematic reviews (SRs) and 3 SRs with accompanying meta-analyses (MAs). The studies within these secondary sources (i.e., those contained within SRs and MAs) were extracted to a database containing the primary sources (i.e., randomised controlled trials, RCTs). From this collated set of articles (320 in total), all studies that did not meet the inclusion criteria were excluded (e.g., cohort and case-control studies), and all duplicate studies were removed (i.e., often the same RCT would appear in multiple SRs and MAs; as well as being directly retrieved by the search strategy). The final set of articles included 12 RCTs (see Appendix 5). The findings from these studies were narratively synthesised, and risk of bias assessments were conducted for each RCT.

Risk of bias assessments: Medicinal cannabis interventions

The revised Cochrane risk-of-bias tool for randomised trials (RoB 2) was employed to conduct the risk-of-bias assessments (Sterne et al., 2019). The three categories of overall risk-of-bias judgements for the RoB 2 tool are: "low risk of bias"; "some concerns"; and "high risk of bias" (Sterne et al., 2019). Of the 12 RCTs of medicinal cannabis interventions included in the REA, one (1) study was judged to have a low risk of bias and eleven (11) studies were judged to have a high risk of bias (see Appendix 8).

GRADE certainty of evidence summaries: Medicinal cannabis interventions

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) is a structured, best-practice approach for assessing the certainty of a body of evidence. The REA used the approach recommended by Murad et al. (2017) for grading narrative summaries of a body of evidence where individual studies measure or report different outcomes. The interpretation of the four levels of evidence used in the GRADE profile are as follows:

GRADE	Definition
High ⊕⊕⊕⊕	High confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect.
Moderate ⊕⊕⊕	Moderate confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low ⊕⊕	Limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect.
Very Low ⊕	Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Source: Adapted from NHMRC (2019).

The GRADE certainty of evidence summaries for the medicinal cannabis interventions are as follows:

Intervention (no. of studies)	Design (no. of studies)	RoB Assessments (no. of studies)	Precision and Consistency	Directness	Publication Bias	GRADE Summary[1,2]
Natural or synthetic cannabidiol (CBD) (6)	Parallel arm RCT (5) Crossover RCT (1)	Serious (5 high risk; 0 some concerns; 1 low risk)	Serious	Not serious, borderline	Not suspected, pending further analysis	Very Low ⊕
Natural cannabis extract (THC+CBD) (2)	Parallel arm RCT (2)	Very serious (2 high risk; 0 some concerns; 0 low risk)	Serious	Not serious	Not suspected	Very Low ⊕
Dried cannabis (THC±CBD) (2)	Crossover RCT (2)	Serious (2 high risk; 0 some concerns; 0 low risk)	Not serious	Serious	Not suspected	Very Low ⊕
Synthetic cannabinoid (THC) (2)	Parallel arm RCT (1) Crossover RCT (1)	Serious (2 high risk; 0 some concerns; 0 low risk)	Serious	Not serious, borderline	Not suspected	Very Low ⊕

Notes. CBD = Cannabidiol. RCT = Randomised controlled trial. RoB = Risk of bias. THC = Tetrahydrocannabinol. 1. GRADE summary includes the risk of bias assessments, precision of the effect estimates, consistency of the individual study results, how directly the evidence answers the question of interest, and risk of publication or reporting biases (NHMRC, 2019). 2. Commonly used symbols to describe the certainty of evidence in evidence profiles: High ⊕⊕⊕⊕, Moderate ⊕⊕⊕, Low ⊕⊕, and Very Low ⊕.

Strengths and limitations

Strengths of the REA include the focus on peer-reviewed Level I and Level II evidence (NHMRC, 2009) from scientific journals in the fields of health, medicine, psychiatry, and psychology (including a specialist database developed by the US Department of Veterans' Affairs focusing on literature relevant to veterans with PTSD). Limitations of the REA include the exclusion of potentially relevant papers that were published prior to 2017 and the exclusion of non-English language papers.

The medicinal cannabis studies included in the REA employed various participant samples, various treatment regimens, and various outcome measures. Some studies were based on small participant samples, and there were concerns as to whether the studies were adequately powered to detect the effect/s of the intervention/s. Other studies had high rates of study dropout, which raised significant concerns about the risk of bias due to missing outcome data. Further methodologically robust research on medicinal cannabis interventions (conducted with larger cohorts over longer follow-up periods) is warranted.

Conclusions and recommendations for future research

It is difficult to draw conclusions and recommendations regarding medicinal cannabis interventions from the body of evidence considered by the REA. Two studies examined standalone medicinal cannabis interventions for participants with anxiety disorders: in one study, medicinal cannabis appeared to improve treatment outcomes; in the other study, the treatment effects were not significant. Both studies had a high risk of bias. No studies

included in the REA examined a combined medicinal cannabis intervention for anxiety disorders. Additionally, no studies examined medicinal cannabis interventions (either standalone or combined) for mood/depressive disorders. Three studies included in the REA examined a standalone medicinal cannabis intervention for substance-related and addictive disorders: all three studies had a high risk of bias. In two studies, medicinal cannabis appeared to improve treatment outcomes; in the third study, the treatment effects were not significant. Six studies examined a combined medicinal cannabis and psychotherapy intervention for participants with substance-related disorders. The findings from these studies were mixed: some studies showed an effect of the treatment, and other studies failed show a treatment effect. For example, there were two studies that examined a combined psychotherapy and medicinal cannabis (nabiximols oromucosal spray) intervention for the treatment of cannabis use disorder. One study reported that medicinal cannabis treatment was superior to placebo; the other study failed to demonstrate benefits of medicinal cannabis treatment over placebo. Both studies were judged to have a high risk of bias; primarily due to missing outcome data: approximately 50% of the participants dropped out before the end of the 12-week treatment.

There is a paucity of high-quality evidence examining medicinal cannabis interventions in anxiety disorders, mood/depressive disorders, substance-related and additive disorders, and trauma- and stressor-related disorders (including PTSD). The REA search strategy identified 12 clinical trial records for ongoing randomised controlled trials focusing on medicinal cannabis interventions (see Appendix 4 for details). Most of these studies are recruiting participants with a PTSD diagnosis (with or without comorbid conditions). The findings from these studies may be relevant to future reports.

A productive direction for future research efforts would be to focus on medicinal cannabis interventions for veterans with co-morbid PTSD, anxiety, depression, and chronic pain syndromes that are associated with premature (joint and soft tissue) injuries of weight-bearing joints. This is a clinical presentation where medicinal cannabis is currently being prescribed, and there would be considerable interest in the study findings. Studies that investigate both the psychoactive and pain-modulating effects of cannabinoids may be the most likely to yield positive outcomes. Additionally, future research could examine the efficacy of cannabinoids for addressing insomnia and sleep disturbance in veterans with formally diagnosed mental health conditions.

Finally, it is important for practitioners and consumers to note that the GRADE summaries in this report assess the certainty of the body of evidence for the randomised controlled trials included in the REA. These findings cannot be generalised beyond the specific interventions and mental health conditions that are the focus of the included studies.

Introduction

Background

There are a number of treatments that have an emerging evidence base and could be considered in the management of common mental health conditions affecting veterans. Emerging and adjunct treatments are typically considered when an individual's adherence or response to accepted or conventional treatment/s is poor (i.e., chronic, treatment-resistant, or treatment-refractory mental health conditions).

Aim

The aim of the rapid evidence assessment (REA) was to identify and critically evaluate the current evidence on emerging and adjunct treatments for posttraumatic stress disorder (PTSD) and common mental health conditions affecting veterans.

Common mental health conditions in veterans

Several sources of evidence were considered when selecting the four categories of mental health conditions that were the focus of the REA. This evidence is synthesised in Maguire (2020). Briefly, the data from the Transition and Wellbeing Research Programme (Department of Veterans' Affairs, 2020) – jointly commissioned by the Departments of Defence and Veterans' Affairs (Australian Government) – found that: alcohol disorders (47.5%), anxiety disorders (46.1%), and affective disorders (39.6%) were the most common classes of lifetime mental health disorders (ICD-10 criteria) in recently-transitioned (2010-2015) veterans; and one in four (24.9%) transitioned veterans met lifetime criteria for a diagnosis of PTSD (Van Hooff et al., 2018).

Chronic, treatment-resistant, or treatment-refractory mental health conditions

There are several reasons why an individual may have a poor treatment outcome (i.e., treatment is ineffective, partially effective, or the individual experiences a relapse or recurrence of the mental health condition/s targeted by the treatment/s). This can include factors that affect an individual's adherence to treatment and/or their response to treatment (e.g., characteristics of the treatment; characteristics of the mental health condition/s; an individual's personal circumstances; or characteristics of the health service environment). For example, factors intrinsic to the treatment/s (e.g., side effects of medications, or unpleasant emotions experienced during therapy) can affect an individual's decision to continue treatment. Similarly, factors extrinsic to the treatment/s (e.g., ongoing trauma exposure; relationship breakdown; financial hardship; stigma) can affect an individual's willingness and capacity to seek or continue treatment, or can influence their treatment progress. Finally, aspects of the health care system itself can create barriers to treatment access or treatment retention (e.g., geographical distance; long waitlists; high caseloads).

In the literature, there are various criteria employed to define treatment response and treatment resistance. The definition of treatment response varies considerably across studies and is often couched in terms of the health condition of interest and the most frequently employed outcome measure/s. For example, in studies of participants with a PTSD diagnosis, a 10-point reduction on the Clinician-Administered PTSD Scale for DSM-IV (CAPS) is a commonly used and validated benchmark for "treatment response" (Illingworth et al., 2021). Studies often define treatment resistance as a failure to respond to at least two evidence-based treatments (e.g., pharmacotherapy and/or psychotherapy).

Categories of intervention

Interventions can be classified as: (i) standalone treatments; or (ii) adjunct treatments (Jones et al. 2020). Interventions can also be classified according to the quality or amount of evidence supporting their use; that is: (iii) evidence-based; (iv) alternative; or (v) emerging treatments (Jones et al., 2020). The definitions employed by the Australian Department of Veterans' Affairs (DVA) are provided in Table 1.

Table 1. Definitions employed by DVA to classify interventions.

Type of intervention	Definition
Standalone	The only intervention that the individual receives. The intervention is aimed at symptom reduction. A standalone intervention should be compared to a best-practice intervention/s to determine whether it is effective or not.
Adjunct	An adjunct intervention is added to a primary intervention. The aim of the adjunct intervention is to reduce symptom severity to a greater extent than the primary intervention is expected to achieve alone. The combined intervention (i.e., adjunct plus primary intervention) should be compared to the primary intervention to determine whether an adjunct intervention is effective or not.
Evidence-based	Interventions that have been proven to be effective and are supported by rigorous scientific evidence. They are often recommended by treatment guidelines.
Alternative	Alternative interventions are not accepted as best-practice interventions, usually due to a lack of rigorous scientific evidence. These interventions may be popular, or widely used, but are not recommended by treatment guidelines. This does not mean that alternative interventions do not work; it just means that there is not enough evidence to know if they do work.
Emerging	An intervention where research on treatment effectiveness has commenced, but is still in its infancy, and there is not enough evidence to support its use. These types of interventions may already be used by people with mental health conditions, and are often reported in the media as offering new hope. However, these media reports are typically based on anecdotal evidence or small preliminary studies. This does not mean that emerging interventions do not work; it just means that there is not enough evidence to know if they do work.

Source: Adapted from Jones et al. (2020, p. 5).

Methods

Design

A REA was conducted to identify and critically evaluate the current literature on emerging and adjunct treatments for PTSD, and common mental health conditions affecting veterans. A REA, or rapid review, is "a form of knowledge synthesis that accelerates the process of conducting a traditional systematic review through streamlining or omitting various methods to produce evidence for stakeholders in a resource-efficient manner" (Hamel et al., 2021, p. 80).

National Health and Medical Research Council (NHMRC): Levels of evidence

The most appropriate study design to answer an intervention research question is Level II evidence (NHMRC, 2009). Level I studies are systematic reviews of appropriate Level II studies. Study designs that are progressively less robust are shown at Levels III and IV (see Table 2). Importantly, regardless of the quality of a systematic review (e.g., "exceptional"), an NHMRC "level of evidence" ranking is based on the risk of bias in the design of the studies contained within the review (NHMRC, 2009, p. 5). For example, a systematic review of cohort and case-control studies would be assigned a Level III-2 evidence ranking because the studies contained within the review likely have poorer internal validity and greater susceptibility to bias (NHMRC, 2009).

Table 2. NHMRC "level of evidence" hierarchy for intervention research questions.

Level of Evidence	Intervention Research Question
I	A systematic review of Level II studies
II	A randomised controlled trial
III-1	A pseudorandomised controlled trial (i.e., alternate allocation or some other method)
III-2	A comparative study with concurrent controls: • Non-randomised, experimental trial • Cohort study • Case-control study • Interrupted time series with a control group
III-3	A comparative study without concurrent controls: • Historical control study • Two or more single arm study • Interrupted time series without a parallel control group
IV	Case series with either post-test or pre-test/post-test outcomes

Source: NHMRC (2009, p. 15, Table 3); for explanatory notes see: NHMRC (2009, p. 16).

Protocol

The REA employed the best-practice guidelines (see Appendix 1) recommended by the Cochrane Rapid Reviews Methods Group (RRMG; Garritty et al., 2020); with reference to the guidelines specified by the Department of Veterans' Affairs (DVA; Varker et al., 2014). The REA protocol was submitted to the National Centre for Health Research (UK) – International prospective register of systematic reviews (PROSPERO; National Institute for Health Research, n.d.) to provide evidence of the methodological rigour of the project, and the independence of the review findings. The REA protocol can be accessed using the following link: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022307924.

Conditions being studied

The REA examined four categories of mental health conditions: anxiety disorders, mood/depressive disorders, substance-related and addictive disorders, and trauma- and stressor-related disorders. There was a specific focus on PTSD. The selection of the four disorder categories corresponding to "common mental health conditions affecting veterans" was informed by data from the Mental Health Prevalence Study (Van Hooff et al., 2018) conducted as part of the Transition and Wellbeing Research Programme (Department of Veterans' Affairs, 2020).

PICO framework

The Population, Intervention, Comparator, Outcome (PICO) framework for the REA is presented in Appendix 2.

Databases

The databases for the REA were selected in consultation with a liaison librarian (information specialist) with extensive experience developing search strategies for systematic reviews of health and medical research:

1. PubMed.
2. APA PsycNet (all databases: APA PsycINFO, APA PsycArticles, APA PsycBooks).
3. The Cochrane Library (all databases: Cochrane Database of Systematic Reviews; Cochrane Central Register of Controlled Trials, CENTRAL; Cochrane Clinical Answers).
4. PTSDpubs Database (formerly PILOTS) – US Department of Veterans' Affairs.

Search strategy

The search strategy was specified according to the best-practice guidelines (Rethlefsen et al., 2021). A PubMed (open-access database) search strategy was developed for the intervention of interest (see Appendix 3). The search strategy was developed in consultation with a liaison librarian (information specialist); and peer-reviewed by a senior liaison librarian as recommended by the best-practice guidelines (Garritty et al., 2020; Rethlefsen et al., 2021). Both liaison librarians had extensive experience developing search strategies for systematic reviews of health and medical research. The search strings exclude: (i) street names for drugs (e.g., ecstasy) as these terms retrieved a significant amount of irrelevant literature examining illicit drug use and mental health conditions; and all acronyms (except PTSD and rTMS) as the non-specific use of certain acronyms retrieved a significant amount of irrelevant literature during the development of the search strategy.

Types of studies

Inclusion criteria

1. Peer-reviewed, quantitative, or mixed-methods studies examining an intervention of interest.
2. Study inclusion was restricted to systematic reviews (SRs), meta-analyses (Mas), and randomised controlled trials (RCTs).
3. There was no restriction for study inclusion based on a concurrent treatment/s (i.e., a comparator) if the treatment included an intervention/s of interest (i.e., an adjunct treatment).

Exclusion criteria

1. Grey literature and certain publication types (e.g., comments, editorials, and letters).
2. Qualitative studies.
3. Epidemiological studies and observational studies (e.g., cohort and case-control studies).
4. Studies of human participants under 18 years of age.
5. Animal studies.

Search dates and restrictions

1. Publication date: 1 January 2017 to 8 February 2022 (5-year period).
2. Language: English.
3. Full-text available.
4. Supplementary searching was limited to hand searching of systematic reviews (SRs) and meta-analyses (Mas) within the reference lists of extracted articles following full-text screening.

Context

There was no restriction for study inclusion based on location (e.g., country) or setting (e.g., inpatient; outpatient; community).

Risk of bias assessments

The revised Cochrane risk-of-bias tool for randomised trials (RoB 2; Sterne et al., 2019) was employed to conduct the risk-of-bias assessments for the REA. For individually randomised trials, the tool is structured into five domains that are based on theoretical and empirical research (Sterne et al., 2019):

1. Bias arising from the randomisation process (D1);
2. Bias due to deviations from intended interventions (D2);
3. Bias due to missing outcome data (D3);
4. Bias in measurement of the outcome (D4);
5. Bias in selection of the reported result (D5).

The five risk-of-bias domains (D1 to D5) are mandatory; and encompass all types of bias that can affect the results from randomised trials. For crossover designs, an additional risk-of-bias domain (DS) is employed to assess bias arising from period and carryover effects. No additional domains are required to assign an overall risk-of-bias judgment to a given study. The three categories of overall risk-of-bias judgements for the RoB 2 tool are presented in Table 3.

Table 3. Overall risk-of-bias judgements for the revised Cochrane risk-of-bias tool for randomised trials.

Overall risk-of-bias judgement	Criteria
Low risk of bias	The study is judged to be at low risk of bias for all domains.
Some concerns	The study is judged to raise some concerns in at least one domain, but not to be at high risk of bias for any domain.
High risk of bias	The study is judged to be at high risk of bias in at least one domain. OR The study is judged to have some concerns for multiple domains in a way that substantially lowers confidence in the result.

Source: Adapted from Sterne et al. (2019, p. 5, Table 3).

GRADE certainty of evidence assessments

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) is a structured, best-practice approach to assessing the certainty of a body of evidence. It is used by international organisations that develop clinical guidelines (e.g., Cochrane; World Health Organization, WHO; UK National Institute for Health and Care Excellence, NICE; and the Australian National Health and Medical Research Council, NHMRC). A GRADE assessment considers five factors that may affect confidence in the synthesised findings of a body of evidence (Guyatt et al., 2011; Murad et al., 2017). The five factors are as follows:

1. Risk of bias;
2. Precision of the effect estimates;
3. Consistency of the individual study results;
4. How directly the evidence answers the research question of interest;
5. Risk of publication or reporting biases.

These five factors are combined to provide an overall GRADE assessment for a body of evidence (see Table 4). The REA used the approach recommended by Murad et al. (2017) for grading narrative summaries of a body of evidence where individual studies measure or report different outcomes.

Table 4. Interpretation of the four levels of evidence used in the GRADE profile.

GRADE	Definition
High $\oplus\oplus\oplus\oplus$	High confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect.
Moderate $\oplus\oplus\oplus$	Moderate confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low $\oplus\oplus$	Limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect.
Very Low $\oplus$	Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Source: Adapted from NHMRC (2019).

Data extraction (selection and coding)

The study selection and coding process involved the following six phases:

1. The liaison librarian translated the PubMed search strategies for the other three databases; conducted the literature searches; generated the Endnote libraries; de-duplicated the retrieved citations in Endnote; and uploaded the citations to Covidence for screening.

2. A standardised title and abstract form was developed by three reviewers, and trialled by two reviewers, on the same 50 abstracts to calibrate and test the review form. Two reviewers independently screened all titles and abstracts, and a third reviewer resolved any conflicts.
3. A standardised full-text form was developed by three reviewers, and trialled by two reviewers, on the same 10 full-text articles to calibrate and test the review form. One reviewer screened all included full-text articles. Excluded full-text articles were screened by a second reviewer and any conflicts were resolved by a third reviewer.
4. One reviewer extracted data from the studies using a piloted form with a set of required data items (e.g., study characteristics, participant characteristics, main findings, and conclusions). A second reviewer checked the accuracy and completeness of the extracted data.
5. One reviewer performed the risk of bias appraisal. A second reviewer verified all judgements and support statements; a third reviewer resolved any conflicts.
6. One reviewer performed the GRADE certainty of evidence assessments. A second reviewer verified all judgements and support statements; a third reviewer resolved any conflicts.

Data synthesis

The review team synthesised and collated the data; and drafted, reviewed, and edited the draft report. The GMRF Expert Advisory Panel and the DVA Emerging Treatments Project Team reviewed the draft report. The report provides:

1. A PRISMA diagram (Results section).
2. A narrative synthesis of the findings (Summary of the Evidence section).
3. A list of the studies excluded during the full-text screening phase (Appendix 4: List of Excluded Studies).
4. A list of the included studies (Appendix 5: List of Included Studies).
5. A matrix of the included studies broken down by intervention type and disorder category (Appendix 6: Matrix of Included Studies).
6. Evidence summaries of the included studies (Appendix 7: Summary of Findings)
7. Risk of bias assessments (Appendix 8: Risk of Bias Assessments, RoB2).
8. GRADE certainty of evidence summaries (Appendix 9: GRADE Certainty of Evidence Summaries).

Review software

Software was used to facilitate review management and ensure a fully transparent review process. Specifically, EndNote X9/20 (Clarivate, 2022) was used for citation management, Covidence (Veritas Health Innovation, n.d.) was used for title/abstract and full-text screening, and Microsoft Excel 2016 (Microsoft Corporation, 2022) was used for data extraction, the risk of bias assessments (RoB 2), and for grading the certainty of the evidence (GRADE).

Results: Medicinal Cannabis Interventions

Figure 1 presents the number of records that were considered at each stage of the REA (i.e., identification, screening, eligibility, and included). The citations for the full-text articles that were excluded during the eligibility assessment are presented in Appendix 4 (based on the reason for exclusion).

From the four databases that were searched, 42 studies met the inclusion criteria, including 35 secondary sources: 32 systematic reviews (SRs) and 3 SRs with accompanying meta-analyses (MAs). The studies within these secondary sources (i.e., those contained within SRs and MAs) were extracted to a database containing the primary sources (i.e., randomised controlled trials, RCTs). From this collated set of articles (320 in total), all studies that did not meet the inclusion criteria were excluded (e.g., cohort and case-control studies), and all duplicate studies were removed (i.e., often the same RCT would appear in multiple SRs and MAs; as well as being directly retrieved by the search strategy).

The final set of articles included 12 RCTs (see Appendix 5). The findings from these studies were narratively synthesised, and risk of bias assessments were conducted for each RCT.

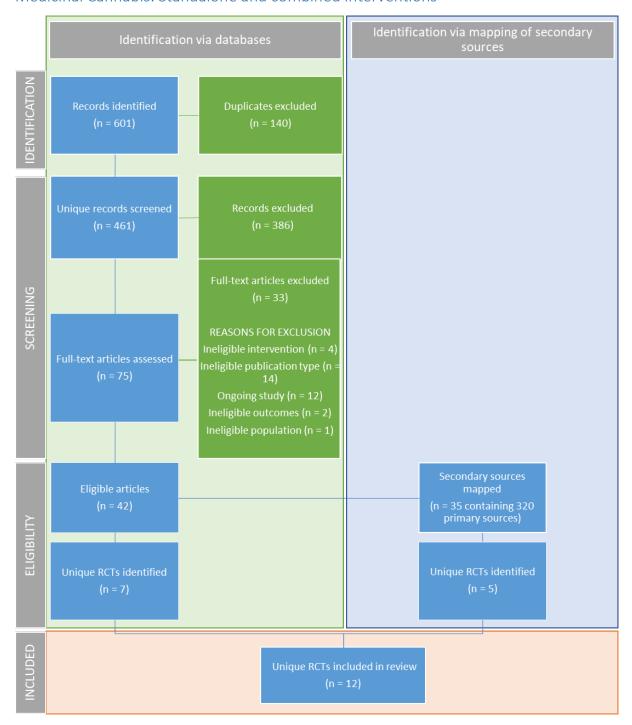## Medicinal Cannabis: Standalone and combined interventions

Figure 1. PRISMA diagram detailing the number of records under consideration at each stage of the REA for the medicinal cannabis interventions.

Summary of the Evidence: Medicinal Cannabis Interventions

This section of the report summarises the evidence relevant to the use of medicinal cannabis interventions for four categories of mental health conditions: anxiety disorders, mood/depressive disorders, substance-related and addictive disorders, and trauma- and stressor-related disorders.

Twelve (12) studies of medicinal cannabis interventions met the inclusion criteria for the REA. Six (6) studies examined standalone interventions, where the study focused on the effect of a medicinal cannabis intervention on the outcome/s of interest (e.g., improvements in mental health symptoms; safety/adverse effects). Six (6) studies examined combined interventions, where a medicinal cannabis intervention was used in conjunction with a psychotherapeutic intervention (e.g., cognitive behavioural therapy or motivational enhancement).

Appendix 6 provides a matrix of standalone and combined medicinal cannabis interventions for the 12 studies, broken down by the disorder categories of interest. Appendix 7 provides a detailed summary of the evidence from each of the 12 studies. The risk-of-bias assessments (Appendix 8) and the GRADE (certainty of evidence) summaries (Appendix 9) provide additional information that is relevant to the evidence summarised in this section of the report.

Anxiety disorders: Standalone interventions

Two studies examined a standalone medicinal cannabis intervention in participants with anxiety disorders (Masataka 2019; Kayser et al., 2020).

Masataka (2019; n = 40) recruited young adults (18 to 19 years of age) with a social anxiety disorder (SAD) and a comorbid diagnosis of avoidant personality disorder (DSM-IV criteria). Participants were randomised to receive an oral solution containing either cannabidiol (CBD) oil (300 mg; n = 20) or olive oil (placebo; n = 20) once per day for four (4) weeks. The outcome measures were the Fear of Negative Evaluation Questionnaire (FNE) and the Liebowitz Social Anxiety Scale (LSAS). Individuals were included in the study if their FNE scores were stable for a minimum of three (3) weeks prior to study entry. Assessments were conducted at multiple time-points: baseline (minimum of 3 weeks showing stable FNE scores) and post-treatment (end of the four-week intervention period). Clinical treatment response was not defined in the study. At post-treatment, self-reported social anxiety symptoms (as measured by the FNE and LSAS) were significantly lower for the CBD group compared with the placebo group (FNE: p = 0.0002; LSAS: p = 0.0018), but did not significantly differ between the two groups at baseline (FNE: p = 0.71; LSAS: p = 0.66). This study was judged to have a high risk of bias. No information on the method of randomisation was available; and (except for gender) baseline data was not reported. The study employed per-protocol analysis (rather than intention-to-treat analysis); excluding three participants who dropped out of the CBD group following randomisation (n = 3/20; 15%). These participants reportedly disliked the smell and taste of the CBD oil, indicating a potential failure of the study blind, which may have influenced responses to the self-reported outcome measures. This is contrary to the data reported for the post-intervention interview, which stated that the both the participants and psychologists involved in the study were not aware of the allocation to study conditions. Finally, the funding, ethics approval, and clinical trial record for the study could not be verified. Thus, the planned outcome measures and statistical analyses could not be compared with those reported in the published article.

Kayser and colleagues (2020; n = 14) recruited participants with a primary diagnosis of obsessive compulsive disorder (OCD; DSM-5 criteria) from the community (via flyers and online advertisements). All participants received three (smoked) cannabis cigarettes in a crossover design: (i) a cannabis cigarette high in THC content (7.0% THC; 0.18% CBD); (ii) a cannabis cigarette high in CBD content (0.4% THC; 10.4% CBD); and (iii) a placebo cannabis cigarette (0% THC; 0% CBD). The dose order was randomised across participants and there was a washout period between conditions (participants completed no more than one session per calendar week to control for potential carryover effects). All participants had severe, near-constant, OCD symptoms (with specific OCD symptoms covering all DSM-5 domains: contamination, harm, symmetry, taboo thoughts, and hoarding). Individuals were included in the study if they were taking serotonin reuptake inhibitors (SRIs), but not other psychotropic medications. The outcome measures were the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), the Obsessive Compulsive – Visual Analogue Scale (OCD-VAS), and the State-Trait Anxiety Inventory – State (STAI-S) subscale. Assessments were conducted at multiple time-points: baseline and post-treatment (minute

20, 40, 60, 90, 120, and 180). Clinical treatment response was not defined in the study. Self-reported OCD symptoms and anxiety symptoms significantly decreased over time (all p's < 0.001). There was a significant effect of cannabis varietal on anxiety symptoms (STAI-S: $p = 0.002$), but not on OCD symptoms (Y-BOCS: $p = 0.72$; OCD-VAS: $p = 0.90$). However, self-reported anxiety symptoms and OCD symptoms did not significantly differ between the three study conditions over time (STAI-S: $p = 0.740$; Y-BOCS: $p = 0.577$; OCD-VAS: $p = 0.818$). Post-hoc analyses suggested the placebo treatment was superior to the active treatments in reducing self-reported anxiety symptoms: anxiety symptoms (as measured by the STAI-S) were significantly lower immediately following administration of the placebo cigarette (i.e., at the 20-minute time-point) compared with both the high THC ($p = 0.002$) and high CBD ($p = 0.039$) cigarette. This difference between the placebo and high THC cigarette on anxiety symptoms persisted for at least 40 minutes ($p = 0.033$). This study was judged to have a high risk of bias. The study employed per-protocol analysis (rather than intention-to-treat analysis); excluding two participants who dropped out of the study following the first of three study sessions ($n = 2/14$; 14.3%), reporting that the time commitment was "too great". The baseline severity of OCD symptoms was not reported for these participants, which further reduced confidence in the study findings due to the small sample size. Finally, the efficacy of the study blind was not assessed, and the differences in psychoactive effects across the study conditions were potentially discernible (e.g., high THC vs. placebo), which may have influenced participant's responses to the self-reported outcome measures.

Anxiety disorders: Combined intervention

No studies included in the REA examined a combined medicinal cannabis intervention for anxiety disorders.

Mood or depressive disorders: Standalone and combined interventions

No studies included in the REA examined a standalone or combined medicinal cannabis intervention for mood/depressive disorders.

Substance-related and addictive disorders: Standalone interventions

Three studies examined a standalone medicinal cannabis intervention in participants with substance-related disorders (Schlienz et al., 2018; Hurd et al., 2019; Hindocha et al., 2018).

Schlienz and colleagues (2018; $n = 16$) recruited participants with a cannabis use disorder (defined as self-reported cannabis use for a minimum of 25 days per month in the past year) from the community (via flyers and newspaper advertisements). Ten participants met DSM-IV criteria for cannabis dependence. Participants were not treatment seeking (or otherwise motivated to abstain from cannabis use except for the behavioural or monetary costs incurred as part of the study). Once the maximum dronabinol dose was determined; all participants received three oral capsules per day for three (12-day) dronabinol maintenance conditions in a crossover design (with dose order counterbalanced across participants): (i) low-dose dronabinol (120 mg/day; 40 mg three times per day); (ii) high-dose dronabinol (180 to 240 mg/day; 60 to 80 mg three times per day); and (iii) matched placebo (three times per day). The authors did not employ washout periods between the three study conditions stating: "the behavioral effects of dronabinol tend to abate after approximately four to six hours and withdrawal effects begin to onset within 24 hours of abstinence" (Schlienz et al., 2018, p. 255). Participants who were undergoing treatment with psychoactive medications were not included in the study. During each of the three (12-day) study conditions, participants could self-administer cannabis under four access conditions: (i) progressive-ratio access to smoked, active (5.7% THC) cannabis (3 days); (ii) progressive-ratio access to smoked, placebo (< 1% THC) cannabis (3 days); (iii) forced-choice between smoked, active (5.7% THC) cannabis or receiving money (3 days); and (iv) forced-choice between smoked, placebo (< 1% THC) cannabis or receiving money (3 days). Cannabis type (active vs. placebo) and access condition (progressive-ratio vs. forced-choice) were randomly assigned for each day, as was the order in which they occurred over each (12-day) study condition. On the morning of each study day (one hour after dronabinol dosing), participants were informed of the type of cannabis available for the day (i.e., Drug A or Drug B), and the condition under which it could be accessed (i.e., progressive-ratio or forced-choice). Importantly, participants were not explicitly advised whether the cannabis cigarettes (available on a given day) were active or placebo; rather they were advised that either Drug A or Drug B was available (i.e., their choices were dependent on the experiential knowledge they derived during the initial exposure and discrimination training phase of the study). The primary outcome measure was the number of cannabis cigarettes self-administered during the progressive-ratio and forced-choice access

conditions (money vs. cannabis). Secondary outcome measures included self-reported measures of drug effects, cannabis withdrawal, sleep, and vital signs. Assessments were conducted every day during the study (i.e., day 1 to day 12 for each of the three, 12-day, study conditions). Clinical treatment response was not defined in the study. In the progressive-ratio access conditions, participants self-administered significantly fewer placebo (< 1% THC) cannabis cigarettes compared with active (5.7% THC) cannabis cigarettes ($p < 0.001$). Compared with placebo dronabinol maintenance under progressive-ratio access, maintenance on both low-dose (120 mg) and high-dose (180 to 240 mg) dronabinol significantly reduced self-administration of active (5.7% THC) cannabis cigarettes (both p's ≥ 0.05). There was no significant difference between low-dose and high-dose dronabinol maintenance on self-administration of active (5.7% THC) cannabis cigarettes ($p = 0.63$). In the forced-choice access conditions, participants self-administered a greater number of active (5.7% THC) cannabis cigarettes compared with placebo (< 1% THC) cannabis cigarettes (all p's < 0.001). Compared with placebo dronabinol maintenance under forced-choice access (cannabis vs. money): in the USD 0.25 choice condition, high-dose but not low-dose dronabinol maintenance reduced self-administration of active (5.7% THC) cannabis cigarettes ($p = 0.05$); in the USD 1.00 choice condition, both low-dose and high-dose dronabinol maintenance significantly reduced self-administration of active (5.7% THC) cannabis cigarettes ($p = 0.01$ and $p = 0.03$, respectively); and in USD 2.00 choice condition, low-dose but not high-dose dronabinol maintenance significantly reduced self-administration of active (5.7% THC) cannabis cigarettes ($p = 0.03$ and $p = 0.23$, respectively). There were no differences between low-dose and high-dose dronabinol maintenance on self-administration of active (5.7% THC) cannabis cigarettes at any monetary value in the forced-choice access conditions (all p's > 0.25). This study was judged to have a high risk of bias. Carryover effects were not assessed. The analysis did not control for period effects, and baseline values between groups may not have been comparable at different time-points. Additionally, follow-up analyses were not reported for the study conditions in which participants could access placebo (< 1% THC) cannabis cigarettes (i.e., only the follow-up analyses for self-administration of active, 5.7% THC, cannabis cigarettes were reported). Finally, the study employed per-protocol analysis (rather than intention-to-treat analysis); excluding three participants following study enrolment ($n = 3/16$; 18.8%). Two of the participants were excluded from the study because they expressed a preference for placebo (< 1% THC) cannabis cigarettes (during initial exposure and discrimination training), which may have biased the results. A third participant voluntarily withdrew from the study for personal reasons, reducing the sample size to 13 participants.

Hurd and colleagues (2019, $n = 50$) recruited participants with a diagnosis of heroin use disorder (DSM-IV criteria) from addiction treatment sites and the community. Participants were randomised to one of three study conditions (oral solution every day for three days): (i) 400 mg CBD ($n = 14$); (ii) 800 mg CBD ($n = 13$); or (iii) matched placebo ($n = 15$). Participants were not included in the study if they were undergoing pharmacological treatment for heroin cessation (i.e., methadone, buprenorphine, or an opioid antagonist). The outcome measures were the Visual Analogue Scale for Craving (VAS-C; primary outcome), Visual Analogue Scale for Anxiety (VAS-A), Heroin Craving Questionnaire, and the Positive and Negative Affect Schedule (PANAS). Assessments were conducted at multiple time-points: baseline (session 1), during treatment (session 1: 1 to 2 hours after first oral solution; session 2: 24 hours after first oral solution), and follow-up (session 4: 7 days after third oral solution). Clinical treatment response was not defined in the study. Baseline craving scores did not differ between the dose groups (p-values not reported). Gender was a significant factor in baseline craving ($p = 0.0476$), with women reporting nearly twofold greater craving than men. A significant difference in craving (as measured by the VAS-C; adjusted for baseline craving) was observed for the cue condition (drug-related vs. neutral cue: $p < 0.0001$). Across participants, craving was significantly higher following exposure to drug-related cues [M(diff) = 1.09] than following exposure to neutral cues [M(diff) = -0.02]. Additionally, a significant difference in craving (as measured by the VAS-C; adjusted for baseline craving) was observed for the CBD dose condition (placebo vs. 400 mg vs. 800 mg; $p = 0.0047$). Across sessions, participants receiving placebo CBD reported significantly greater craving after the drug-related cues [M(diff) = 0.93) compared with participants in the active CBD groups (400mg CBD: M(diff) = 0.44; 800mg CBD: M(diff) = 0.23). No significant difference in craving scores was observed between the active CBD groups (p-value not reported), indicating that both CBD doses (400mg; 800mg) equally reduced craving. This study was judged to have a high risk of bias. The study employed per-protocol analysis (rather than intention-to-treat analysis); excluding eight participants who dropped out of the study following randomisation ($n = 8/50$; 16%) for various reasons (e.g., voluntary

withdrawal, lost to follow-up). Baseline data for these participants was not reported; and the reasons for dropout were not reported by study condition. Thus, the differences in missing outcome data for the CBD and placebo groups could not be assessed. Additionally, abstinence was required for study participation, and the participants who dropped out of the study may have had more severe symptoms of addiction. Finally, the efficacy of the study blind was not assessed, which may have influenced responses to the self-reported outcome measures if participants discerned the allocation to study conditions.

Hindocha and colleagues (2018; n = 44) recruited participants with a nicotine dependence, who were not treatment seeking, from the community. Nicotine dependence was defined as smoking at least (≥) 10 cigarettes per day (for a minimum of one year); and a score of at least (≥) 4 (moderate dependence) on the Fagerström Test for Nicotine Dependence (FTND). All participants received three (3) sessions: one (75-minute) "satiated" session (baseline; smoking "as normal" prior to the session), and two (3.5-hour) "abstinence" sessions (intervention; overnight abstinence prior to the sessions). For the two "abstinence" (intervention) sessions, participants received oral capsules in a crossover design: (i) 800 mg CBD; and (ii) matched placebo (lactose powder). The intervention order was randomised, and counterbalanced across participant gender, and there was a washout period of at least one week between sessions. Individuals who were undergoing nicotine replacement or cessation pharmacotherapy were not included in the study. The outcome measures were the Questionnaire of Smoking Urges – Brief (QSU-B; primary outcome: self-reported craving), the Mood and Physical Symptoms Scale (MPSS; primary outcome: self-reported withdrawal), a visual probe task, a pleasantness rating task, and a Visual Analogue Scale (VAS; self-reported side effects). Assessments were conducted at multiple time-points for each session: baseline (satiated) session (minute 12: T1; minute 35: T2; and minute 75: T3) and intervention (abstinence) sessions (minute 5: T1; minute 70: T2; minute 130: T3; and minute 200: T4). Clinical treatment response was not defined in the study. Prior to drug administration, craving (as measured by the QSU-B) and withdrawal (as measured by the MPSS) was greater under the abstinence (intervention) sessions than under the satiation (baseline) session (both p's < 0.001), indicating that abstinence increased self-reported craving and withdrawal. Prior to drug administration, craving and withdrawal symptoms did not significantly differ for the CBD and placebo conditions in the abstinence (intervention) sessions (p = 0.99 and p = 0.85, respectively). Following drug administration in the abstinence (intervention) sessions, craving and withdrawal significantly differed over time (both p's < 0.001). However, there was no significant effect of drug condition (CBD vs. placebo) on craving (p = 0.81) or withdrawal (p = 0.64), and craving and withdrawal did not significantly differ for the CBD and placebo (intervention) conditions over time (p-values not reported). This study was judged to have a high risk of bias. The study employed per-protocol analysis (rather than intention-to-treat analysis), excluding 14 participants following randomisation (n = 14/44; 31.8%) for various reasons: five (5) participants were excluded due to low carbon monoxide readings; two (2) participants were excluded due to positive drug urine screens; and seven (7) participants voluntarily dropped out of the study. Additionally, a pre-specified analysis plan was not available; therefore, the planned outcome measures and statistical analyses could not be compared with those reported in the published article.

Substance-related and addictive disorders: Combined interventions

There were six studies that examined a combined medicinal cannabis and psychotherapy intervention in participants with substance-related disorders. The findings from these studies are synthesised based on the substance-related disorder.

Cannabis Use Disorder

Four studies examined a combined medicinal cannabis and psychotherapy intervention in participants with a cannabis use disorder (Freeman et al., 2020; Lintzeris et al., 2019; Trigo et al., 2018; Hill et al., 2017).

Freeman and colleagues (2020, n = 82) recruited participants with a diagnosis of cannabis use disorder (DSM-5 criteria) from the community (via flyers and online advertisements). All participants received six (30-minute) sessions of motivational interviewing. Participants were randomised to one of four study conditions (two oral capsules twice per day for four weeks to achieve daily doses of): (i) 200 mg CBD (n = 12); (ii) 400 mg CBD (n = 24); (iii) 800 mg CBD (n = 23); or (iv) placebo (n = 23). Individuals were not included in the study if they were taking psychotropic medications. The outcome measures were cannabis use (as measured by urine concentrations of THC-COOH:creatinine), and self-reported cannabis abstinence (number of days per week).

Assessments were conducted at five (5) time-points: baseline (week 0) and during intervention (week 1 to 4). Clinical treatment response was defined as lower cannabis use, or increased cannabis abstinence, as evidenced by posterior probabilities exceeding 0.9 (i.e., Pr > 0.9) for CBD compared with placebo. The interim Bayesian analysis (n = 48) indicated that the 200 mg CBD treatment was ineffective, and the participants that were subsequently recruited to the study (n = 34) were not randomised to this condition. The final Bayesian analysis (n = 70) indicated that the CBD groups exceeded the defined posterior probabilities (Pr > .9) for both cannabis use (400 mg CBD: Pr = 0.9995; 800 mg CBD: Pr = 0.9965) and self-reported cannabis abstinence (400 mg CBD: Pr = 0.9966; 800 mg CBD: Pr = 0.9247) compared with the placebo group. Urine THC concentrations were significantly lower for the 400mg CBD group (M = -94.21 ng/ml; 95% CI = -161.83 to -35.56) and the 800 mg CBD group (M = -72.02 ng/ml; 95% CI = -135.47 to -19.52) compared with the placebo group. Similarly, self-reported cannabis abstinence increased for the CBD groups compared with the placebo group; however, the increase in cannabis abstinence was significant for the 400 mg CBD group (M = 0.48 days per week, 95% CI = 0.15 to 0.82 days), but not for the 800 mg CBD group (M = 0.27 days per week, 95% CI = -0.09 to 0.64 days). This study was judged to have a low risk of bias. The study employed an intention-to-treat, Bayesian analysis. While the effectiveness of the study blind was not assessed, there was no evidence to suggest that the participants were aware of the allocation to study conditions (i.e., the CBD was administered in capsules; CBD does not cause intoxication or euphoria; and there was a high level of concordance between the objective and self-reported findings within the 400 mg and 800 mg CBD conditions).

Lintzeris and colleagues (2019, n = 137) recruited participants with a diagnosis of cannabis use disorder (ICD-10 criteria) from four (4) outpatient specialist alcohol and drug treatment services. All participants were offered six sessions of individual (CBT-based) counselling, and weekly clinical reviews to titrate the dose of medication (i.e., optimise efficacy and safety). Participants were randomised to receive an oromucosal spray (daily for 12 weeks) of either self-titrated nabiximols (n = 64; natural cannabis extract containing a maximum of 86.4 mg of THC and 80 mg of CBD per day) or placebo (n = 73; using the same carrier and flavouring). Participants who did not attend clinical sessions for more than two consecutive weeks were excluded from the study. The outcome measures were self-reported total days of illicit cannabis use (week 1 to 12; maximum of 84 days; using the Timeline Followback method), treatment retention (number of participants who completed the 12-week treatment protocol), the Cannabis Problems Questionnaire (CPQ), the Cannabis Withdrawal Scale (CWS), the Marijuana Craving Questionnaire (MCQ), the Fagerström Test for Nicotine Dependence (FTND), the Alcohol Use Disorders Identification Test (AUDIT), the 36-item Short Form Survey (SF-36), and the Opioid Treatment Index (OTI). Assessments were conducted at four (4) time-points: baseline (week 0), during intervention (week 4 and 8), and post-intervention (week 12). Clinical treatment response was not defined in the study. In a modified intention-to-treat (ITT) analysis (defined as participants who attended all four assessment time-points across the 84-day trial; placebo: n = 36; nabiximols: n = 31), the number of self-reported days of illicit cannabis use was higher in the placebo group (M = 53.1 days; SD = 33.0 days) compared with the nabiximols group (M = 35.0 days; SD = 32.4 days); a significant difference of 18.6 days (95% CI = 3.5 to 33.7 days) after adjusting for baseline cannabis use (p = 0.02). There were no significant between-group differences in treatment retention (p-value not reported): a total of 60 participants (n = 60/128; 46.9%) completed the 12-week treatment protocol; 30 participants (n = 30/67; 44.8%) in the placebo group, and 30 participants (n = 30/61; 49.2%) in the nabiximols group. Note that these reported findings exclude nine participants (n = 9/137): six (6) participants in the placebo group, and three (3) participants in the nabiximols group, who did not receive their allocated intervention following randomisation. No significant between-group differences were observed in the remaining outcome measures (e.g., 4-week abstinence rate, cannabis-related problems, cannabis craving, cannabis withdrawal, alcohol use, nicotine use, general health status and psychosocial functioning, aberrant medication use, or adverse events). This study was judged to have a high risk of bias; primarily due to missing outcome data. Prior to the end of the 12-week trial protocol, 77 participants (n = 77/137; 56.2%) dropped out of the study following randomisation for various reasons (e.g., protocol deviations, unknown reasons, unable to attend). Additionally, the criteria employed for the modified ITT analysis excluded data for over half the randomised participants (n = 70/137; 51.1%), which is likely to have introduced a significant risk of bias. Finally, participants were more likely to correctly guess their allocation to study condition in the nabiximols group (82.4%) than in the placebo group (49.1%), which may have influenced their responses to the self-reported outcome measures.

Trigo and colleagues (2018, *n* = 50) recruited participants with a diagnosis of cannabis use disorder (DSM-IV criteria) from the community (via flyers and media advertisements). All participants received 12 (1-hour) sessions (one session per week) of motivational enhancement therapy and cognitive behavioural therapy (MET/CBT). Participants were randomised to receive an oromucosal spray (daily for 12 weeks) of either nabiximols (natural cannabis extract; maximum of 42 sprays equal to 113.4 mg THC/105 mg CBD per day; *n* = 20) or matched placebo (*n* = 20). Individuals were not included in the study if they were taking psychotropic medications (other than treatment for insomnia). The outcome measures were the tolerability of the self-titrated medication (self-reported number of sprays per day); and self-reported cannabis abstinence, use (quantity and frequency), craving, and withdrawal. Assessments were conducted at multiple time-points: baseline (week 0) and during treatment (week 1 to 12). Clinical treatment response was defined as at least (≥) 50% reduction in cannabis use from baseline to post-treatment. The medication was well tolerated by all participants and no serious adverse events were reported. The study participants displayed high variability in their use of the self-titrated medication, which prompted the investigators to perform a sub-group analysis of "low" medication users (less than 20 sprays on all days; *n* = 8 and *n* = 11 for nabiximols and placebo, respectively) and "high" medication users (at least 20 sprays on any day; *n* = 5 and *n* = 3 for nabiximols and placebo, respectively). The rate of cannabis abstinence (seven-day point prevalence) measured one week after the treatment phase was 30.8% (*n* = 4) for the nabiximols group and 42.9% (*n* = 6) for the placebo group. There was no significant difference in abstinence rates for the two groups (*p* < 0.05). Quantity of cannabis use (grams) decreased over time (*p* < 0.001). However, no significant between-group differences in cannabis use (grams) were observed (*p* = 0.179), and cannabis use (grams) did not significantly differ between the nabiximols and placebo groups over time (*p* = 0.664). Frequency of cannabis use (% days per week) decreased over time (*p* < 0.001). However, no significant between-group differences in cannabis use (% days per week) were observed (*p* = 0.298), and cannabis use (% days per week) did not significantly differ between the nabiximols and placebo groups over time (*p* = 0.221). Cannabis craving decreased over time (*p* < 0.001). No significant between-group difference in craving was observed (*p* = 0.438). However, there was a significant difference in craving between the nabiximols and placebo groups over time (*p* < 0.05). A follow-up analysis indicated this difference appeared to be primarily driven by higher craving scores in the placebo condition (relative to the nabiximols condition) at the week-7 timepoint. Cannabis withdrawal decreased over time (*p* < 0.001). However, no significant between-group difference in cannabis withdrawal was observed (*p* = 0.593), and cannabis withdrawal did not significantly differ for the nabiximols and placebo groups over time (*p* = 0.601). The study findings suggested that the MET/CBT intervention, which was offered to all participants, may have improved cannabis outcomes (i.e., abstinence; quantity and frequency of cannabis use; cannabis craving and withdrawal). This study was judged to have a high risk of bias; primarily due to missing outcome data. Prior to the end of the 12-week trial protocol, study participation was terminated for 23 participants (*n* = 23/50; 46%) for "one or more" of the following reasons: "severe adverse effects; major protocol violations; loss to follow-up; pregnancy; or withdrawal of consent" (p. 3). The authors reported that all analyses were conducted on an intention-to-treat basis, and missing data were handled by maximum likelihood estimation; however, it is unclear whether the data were missing at random. While participants were unable to differentiate the subjective effects of the nabiximols and placebo treatments during a nurse-supervised (2-hour) intake session, the effectiveness of the study blind was not assessed at the end of the 12-week trial. If participants were aware of the allocation to study conditions, this may have influenced their responses to the self-reported outcome measures.

Hill and colleagues (2017; *n* = 18) recruited participants with a diagnosis of cannabis use disorder (DSM-IV criteria) from the community (via newspaper and online advertisements). All participants were offered weekly physician-guided medical management (MM) sessions, which included monitoring of medication side effects and strategies to increase medication adherence and support abstinence. Participants were randomised to receive oral capsules (daily for 10 weeks) of either 2 mg nabilone (*n* = 10; synthetic THC) or placebo (*n* = 8; agent not specified). The outcome measures were the participants' urine concentrations of THC (as measured by THC-COOH:creatinine; primary outcome), the number of cannabis use sessions per day (as measured by the Timeline Followback, TLFB, method; primary outcome), the Marijuana Craving Questionnaire (MCQ), the Beck Anxiety Inventory (BAI), and the Quick Inventory for Depressive Symptoms (QIDS). Assessments were conducted at multiple time-points: baseline, during treatment (week 1 to 10), and follow-up (four weeks post-treatment). Clinical treatment response was not defined in the study. During the 10-week treatment period, the nabilone

group reported an average of 2.55 cannabis use sessions per day, and the placebo group reported 3.14 cannabis use sessions per day. There was no significant effect of the treatment on changes in cannabis use sessions for the nabilone group compared with the placebo group at the end of treatment ($p = 0.29$), or at the 4-week follow-up ($p = 0.53$). There was no significant effect of the treatment on changes in urine cannabinoid levels for the nabilone group compared with the placebo group at the end of treatment ($p = 0.17$), or at the 4-week follow-up ($p = 0.34$). This study was judged to have a high risk of bias. No information on the method of randomisation was available. Additionally, six participants ($n = 6/18$; 33.3%) did not complete the 10-week trial protocol: 40% ($n = 4/10$) of participants in the nabilone group, and 25% ($n = 2/8$) of participants in the placebo group. There was a higher dropout rate in the nabilone group, which could be correlated with baseline severity of cannabis dependence (not reported). The effectiveness of the study blind was not assessed, which may have biased the results if the participants discerned their allocation to study conditions.

Cocaine Use Disorder

Two studies recruited participants with a cocaine use disorder (Meneses-Gaya, et al., 2021; Mongeau-Pérusse, et al., 2021).

Meneses-Gaya and colleagues (2021; $n = 31$) recruited participants with a diagnosis of cocaine use disorder (DSM-IV criteria) from a specialised therapeutic community unit, which received referrals from the public health system. All participants were routinely offered weekly sessions of group psychotherapy within the treatment setting. Participants were randomised to receive oral capsules (two 150 mg capsules per day for 10 days) of either CBD (300 mg; $n = 14$) or matched placebo ($n = 17$). The outcome measures were the Cocaine Craving Questionnaire – Brief (CCQ-Brief; primary outcome), Minnesota Cocaine Craving Scale (MCCS; primary outcome), Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), and Visual Analog Sleep Scales (VAS). Assessments were conducted at multiple time-points: baseline, during treatment (day 1 to day 10), and post-treatment (day 10). Clinical treatment response was not defined in the study. The study employed a modified intention-to-treat analysis (defined as all participants with at least one post-baseline craving assessment). Cocaine craving significantly decreased over the 10-day trial (CCQ-Brief: $p < 0.001$; MCCS: $p < 0.001$). However, no between-group difference in craving was observed (CCQ-Brief: $p = 0.116$; MCCS: $p = 0.130$), and craving did not significantly differ for the CBD and placebo groups over time (CCQ-Brief: $p = 0.897$; MCCS: $p = 0.113$). This study was judged to have a high risk of bias. No information on the method of randomisation was available. Additionally, six participants ($n = 6/31$; 19.3%) dropped out of the study and left the specialised therapeutic community unit: 21% ($n = 3/14$) of participants in the CBD group, and 18% ($n = 3/17$) of participants in the placebo group. Finally, the clinical trial record and a pre-specified analysis plan were not available; therefore, the planned outcome measures and statistical analyses could not be compared with those reported in the published article.

Mongeau-Pérusse and colleagues (2021; $n = 78$) recruited participants with a diagnosis of cocaine use disorder (DSM-5 criteria) from a hospital research centre, clinical programs, and the community (via newspaper, online advertising, and word of mouth). All participants were offered psychotherapy. During Phase I (10-day inpatient detoxification), nurse-administered medication was provided every day with group psychoeducation sessions and standard medical care. During Phase II (12-week outpatient follow-up), self-administered medication was provided every week with group relapse prevention sessions and standard medical follow-up. Participants were randomised to receive an oral solution (once per day for 92 days) of either 800 mg CBD ($n = 40$) or matched placebo ($n = 38$). Randomisation to the study conditions was stratified by gender and baseline severity of cocaine dependence (as determined by the Severity of Dependence Scale, SDS). The outcome measures were the Visual Analogue Scale for Craving (VAS-C), and the time-to-relapse cocaine use. Assessments were conducted at multiple time-points: baseline, every two (2) days during Phase I (day 2, 4, 6, and 8), and every two (2) weeks during Phase II (week 2, 4, 6, 8, 10, and 12). Clinical treatment response was not defined in the study. At day 8 (Phase I end-point), no significant change from baseline craving scores (as measured by the VAS-C; adjusted for gender and baseline SDS score) was observed for the CBD group ($n = 36$) compared with the placebo group ($n = 28$) following exposure to the drug-related cues ($p = 0.069$), stress-related cues ($p = 0.887$), or neutral cues ($p = 0.222$), during the guided-imagery session. The median time-to-relapse cocaine use (during the Phase II outpatient follow-up) was four (4) days for the CBD group and seven (7) days for the placebo group. Participants who were lost to follow-up were considered to have relapsed. By week 12 (Phase II end-point), all but three

participants had relapsed to cocaine use (CBD group: $n = 33/34$; placebo group: $n = 25/27$). The risk of cocaine relapse was similar for the CBD and placebo groups ($p = 0.51$). This study was judged to have a high risk of bias. The study employed per-protocol analysis (rather than intention-to-treat analysis); excluding 14 participants ($n = 14/78$; 17.9%) from the Phase I (cocaine craving) analysis due to missing outcome data: 10% ($n = 4/40$) of participants in the CBD group, and 26% ($n = 28/38$) of participants in the placebo group. Of the randomised participants, 36% ($n = 28/78$) of participants did not complete Phase II of the study for various reasons (i.e., treatment refusal; investigator decision; lost to follow-up; study withdrawal). Of the participants who did complete the study ($n = 50$), 48.1% ($n = 13/27$) of the CBD group, and 39.1% ($n = 9/23$) of the placebo group, correctly guessed their allocation to study condition.

Trauma- and stressor-related disorders: Standalone or combined interventions

One study examined a standalone medicinal cannabis intervention in participants with trauma- and stressor-related disorders (Bonn-Miller et al., 2021).

Bonn-Miller and colleagues (2021; $n = 80$) recruited military veterans with a diagnosis of posttraumatic stress disorder (PTSD; DSM-5 criteria) from the community (via advertisements, presentations, and websites). The study employed a two-stage crossover design. In Stage I, participants were randomised to one of four treatment conditions (self-administration of smoked dried cannabis): (i) high THC (12% THC and < 0.05% CBD; $n = 19$), (ii) high CBD (0.5% THC and 11% CBD; $n = 19$), (iii) combined THC+CBD (7.9% THC and 8.1% CBD; $n = 18$), or (iv) placebo (< 0.03% THC and < 0.01% CBD; $n = 20$). In Stage II, the placebo condition was discontinued, and participants from all four Stage I groups were re-randomised into three conditions: (1) high THC ($n = 29$), (ii) high CBD ($n = 27$), or (iii) combined THC+CBD ($n = 18$). Each stage included a three-week period of *ad libitum* (i.e., "as you please") self-administration of the assigned treatment (to provide a more naturalistic comparison to the real-world setting), followed by a two-week cessation period. Participants were provided a total of 37.8 grams (1.8 grams/day) of dried cannabis for each three-week study period, and a metal pipe for smoked self-administration. Participants were included in the study if they were currently taking medications or engaged in psychotherapy, but only if the treatment regimen remained stable prior to study commencement. The outcome measures were the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5; primary outcome measure), PTSD Checklist for DSM-5 (PCL-5), Inventory of Depression and Anxiety Symptoms (IDAS), Inventory of Psychosocial Functioning (IPF), and Insomnia Severity Index (ISI). Assessments were conducted at multiple time-points: baseline, every week during the three-week treatment periods (Stage I; Stage II), and before and after the two-week cessation periods (Stage I; Stage II). Clinical treatment response was not defined in the study. In Stage I, no significant between-group differences in change scores (baseline to end of treatment: visit 0 to visit 7) were observed for PTSD severity (as measured by the CAPS-5; $p = 0.15$). However, significant within-participant reductions in PTSD severity were observed for all four treatment groups from baseline to end of treatment (visit 0 to visit 5; all p's < 0.05). Specifically, in Stage I, participants who received placebo reported a mean reduction of 13.1 points ($p = 0.0002$), participants who received high THC reported a mean reduction of 15.2 points ($p < 0.0001$), participants who received high CBD reported a mean reduction of 8.4 points ($p = 0.0181$), and participants who received THC+CBD reported a mean reduction of 8.5 points ($p = 0.0143$). Additionally, in Stage I, no significant between-group differences in change scores (visit 0 to visit 6) were observed for self-reported (past week) PTSD symptoms, depression and anxiety symptoms, psychosocial functioning, and insomnia severity (as measured by the PCL-5, IDAS, ISI, and IPF, respectively). In Stage II, significant between-group differences in change scores (baseline to end of treatment: visit 7 to visit 12) were observed for PTSD severity (as measured by CAPS-5; $p = 0.0019$). The authors reported that the follow-up contrasts indicated significant differences in change scores between participants in the high THC and THC+CBD groups (95% CI: 3.82 to 18.88), and between participants in the high CBD and THC+CBD groups (95% CI: 1.19 to 15.86). Notably, in Stage II, a significant within-participant reduction in PTSD symptoms (from baseline to end of treatment: visit 7 to visit 12) was observed for the combined THC+CBD group ($p = .0027$), but not for the high THC ($p = 0.25$) or high CBD ($p = 0.99$) groups. This study was judged to have a high risk of bias. There were concerns about period and carryover effects in relation to the two-stage crossover design, concerns about failure of the study blind, and concerns about missing outcome data. When the placebo condition was dropped following Stage I, and participants were re-randomised to the three active treatment conditions in Stage II, the number of participants in the THC+CBD condition ($n = 18$) was significantly lower than the number of participants in the other two conditions (high THC: $n = 29$; high

CBD: *n* = 27). The authors acknowledged that the Stage II study findings should be interpreted cautiously, given the possible carryover effects, and the unbalanced randomisation to groups. Additionally, the study blind failed in both the high THC and combined THC+CBD groups (i.e., 100% of the participants and clinicians guessed the allocation to an active treatment group). Importantly, the authors noted a major study limitation: in Stage I, the participants who were randomised to receive high THC had a risk of cannabis use disorder that was nearly two times higher than the participants who were assigned to the other active treatment conditions (as measured by the Cannabis Use Disorders Identification Test – Revised, CUDIT-R). Finally, by the end of Stage II, a significant proportion of participants (16.3%; *n* = 13/80) had dropped out of the study due to adverse events (8) and voluntary withdrawal (5). The authors noted that the self-administration of cannabis was lower than expected (based on a comparative analysis to other studies), which they attributed to the lower perceived quality of the cannabis available for the study, relative to the quality of cannabis sold commercially.

Strengths and Limitations

Strengths of the REA include the focus on peer-reviewed Level I and Level II evidence (NHMRC, 2009) from scientific journals in the fields of health, medicine, psychiatry, and psychology (including a specialist database developed by the US Department of Veterans' Affairs focusing on literature relevant to veterans with PTSD). Limitations of the REA include the exclusion of potentially relevant papers that were published prior to 2017 and the exclusion of non-English language papers.

The medicinal cannabis studies included in the REA employed various participant samples, various treatment regimens, and various outcome measures. Some studies were based on small participant samples, and there were concerns as to whether the studies were adequately powered to detect the effect/s of the intervention/s. Other studies had high rates of study dropout, which raised significant concerns about the risk of bias due to missing outcome data. Further methodologically robust research on medicinal cannabis interventions (conducted with larger cohorts over longer follow-up periods) is warranted.

Conclusions and Recommendations for Future Research

It is difficult to draw conclusions and recommendations regarding medicinal cannabis interventions from the body of evidence considered by the REA. Two studies examined standalone medicinal cannabis interventions for participants with anxiety disorders: in one study, medicinal cannabis appeared to improve treatment outcomes; in the other study, the treatment effects were not significant. Both studies had a high risk of bias. No studies included in the REA examined a combined medicinal cannabis intervention for anxiety disorders. Additionally, no studies examined medicinal cannabis interventions (either standalone or combined) for mood/depressive disorders. Three studies included in the REA examined a standalone medicinal cannabis intervention for substance-related and addictive disorders: all three studies had a high risk of bias. In two studies, medicinal cannabis appeared to improve treatment outcomes; in the third study, the treatment effects were not significant. Six studies examined a combined medicinal cannabis and psychotherapy intervention for participants with substance-related disorders. The findings from these studies were mixed: some studies showed an effect of the treatment, and other studies failed show a treatment effect. For example, there were two studies that examined a combined psychotherapy and medicinal cannabis (oromucosal spray) intervention for the treatment of cannabis use disorder. One study reported that cannabis treatment was superior to placebo; the other study failed to demonstrate benefits of cannabis treatment over placebo. Both studies were judged to have a high risk of bias; primarily due to missing outcome data: approximately 50% of the participants dropped out before the end of the 12-week treatment.

There is a paucity of high-quality evidence examining medicinal cannabis interventions in anxiety disorders, mood/depressive disorders, substance-related and additive disorders, and trauma- and stressor-related disorders (including PTSD). The REA search strategy identified 12 clinical trial records for ongoing randomised controlled trials focusing on medicinal cannabis interventions (see Appendix 4 for details). Most of these studies are recruiting participants with a PTSD diagnosis (with or without comorbid conditions). The findings from these studies may be relevant to future reports.

A productive direction for future research efforts would be to focus on medicinal cannabis interventions for veterans with co-morbid PTSD, anxiety, depression, and chronic pain syndromes that are associated with premature (joint and soft tissue) injuries of weight-bearing joints. This is a clinical presentation where medicinal cannabis is currently being prescribed, and there would be considerable interest in the study findings. Studies that investigate both the psychoactive and pain-modulating effects of cannabinoids may be the most likely to yield positive outcomes. Additionally, future research could examine the efficacy of cannabinoids for addressing insomnia and sleep disturbance in veterans with formally diagnosed mental health conditions.

Finally, it is important for practitioners and consumers to note that the GRADE summaries in this report assess the certainty of the body of evidence for the randomised controlled trials included in the REA. These findings cannot be generalised beyond the specific interventions and mental health conditions that are the focus of the included studies.

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Appendix 1: Best-Practice Guidelines for Rapid Reviews

Cochrane Rapid Reviews Methods Group (RRMG) Recommendations (Garritty et al., 2021)

Setting the research question – topic refinement

- Involve key stakeholders (e.g., review users such as consumers, health professionals, policymakers, decision-makers) to set and refine the review question, eligibility criteria, and the outcomes of interest. Consult with stakeholders throughout the process to ensure the research question is fit for purpose, and regarding any ad-hoc changes that may occur as the review progresses. (R1)
- Develop a protocol that includes review questions, PICOS, and inclusion and exclusion criteria.

Setting eligibility criteria

Together with key stakeholders:
- Clearly define the population, intervention, comparator, and outcomes.
    - Limit the number of interventions (R2) and comparators (R3).
    - Limit the number of outcomes, with a focus on those most important for decision-making. (R4)
- Consider date restrictions with a clinical or methodological justification. (R5)
- Setting restrictions are appropriate with justification provided. (R6)
- Limit the publication language to English; add other languages only if justified. (R7)
- Systematic reviews (SRs)[1] should be considered a relevant study design for inclusion. (R8)
- Place emphasis on higher quality study designs (e.g., SRs or RCTs); consider a stepwise approach to study design inclusion. (R9)

Searching

- Involve an information specialist.
- Limit main database searching to CENTRAL, MEDLINE (e.g., via PubMed), and Embase (if available access). (R10)
- Searching of specialized databases (e.g., PsycINFO and CINAHL) is recommended for certain topics but should be restricted to 1–2 additional sources or omitted if time and resources are limited. (R11)
- Consider peer review of at least one search strategy (e.g., MEDLINE). (R12)
- Limit grey literature and supplemental searching (R13). If justified, search study registries and scan the reference lists of other SRs or included studies after screening of the abstracts and full texts.

Study selection

- Title and abstract screening
    - Using a standardized title and abstract form, conduct a pilot exercise using the same 30-50 abstracts for the entire screening team to calibrate and test the review form.
    - Use two reviewers for dual screen of at least 20% (ideally more) of abstracts, with conflict resolution.
    - Use one reviewer to screen the remaining abstracts and a second reviewer to screen all excluded abstracts, and if needed resolve conflicts. (R14)
- Full-text screening
    - Using a standardized full-text form, conduct a pilot exercise using the same 5-10 full-text articles for the entire screening team to calibrate, and test the review form.
    - Use one reviewer to screen all included full-text articles and a second reviewer to screen all excluded full-text articles. (R15)

Data extraction

- Use a single reviewer to extract data using a piloted form. Use a second reviewer to check for correctness and completeness of extracted data. (R16)
- Limit data extraction to a minimal set of required data items. (R17)
- Consider using data from existing SRs to reduce time spent on data extraction. (R18)

Risk of bias assessment

- Use a valid risk of bias tool, if available for the included study designs.
- Use a single reviewer to rate risk of bias, with full verification of all judgments (and support statements) by a second reviewer. (R19)

Cochrane Rapid Reviews Methods Group (RRMG) Recommendations (Garritty et al., 2021)
• Limit risk of bias ratings to the most important outcomes, with a focus on those most important for decision-making. (R20)
Synthesis
• Synthesize evidence narratively. • Consider a meta-analysis only if appropriate (i.e., studies are similar enough to pool). (R21) Standards for conducting a meta-analysis for an SR equally apply to an RR. • Use a single reviewer to grade the certainty of evidence, with verification of all judgments (and footnoted rationales) by a second reviewer. (R22)
Other considerations for Cochrane RRs
• RRs should be preceded by a protocol submitted to and approved by Cochrane (R23). • The protocol should be published (e.g., PROSPERO or Open Science Framework) (R24). • Allow for post hoc changes to the protocol (eligibility criteria etc.) as part of an efficient and iterative process (R25). • Document all post hoc changes; and incorporate use of online SR software (e.g., Covidence, DistillerSR, and EPPI-Reviewer) to streamline the process (R26).

Source: Garritty et al. (2021, p. 17; Table 1). Notes: 1. To be considered a systematic review (SR) for screening purposes, studies need to: clearly report inclusion/exclusion criteria; search at least two databases; conduct a risk of bias assessment; and provide a list and synthesis of included studies.

Appendix 2: Population, Intervention, Comparator, Outcome (PICO) Framework

Review Question	What is the current evidence for emerging treatments for Posttraumatic Stress Disorder (PTSD) and common mental health conditions affecting veterans, including adjunct treatments?
Population (P)	INCLUSION CRITERIA: (i) Human studies. (ii) Adults (18 years of age and over). (iii) Diagnosed with: anxiety disorder/s; mood or depressive disorder/s; substance-related and addictive disorder/s; or trauma- and stressor-related disorder/s. (iv) Majority of the intervention sample has been diagnosed using the following classification systems: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), or Fifth Edition (DSM-5); or the International Classification of Diseases, 10th Revision (ICD-10), or 11th Revision (ICD-11). EXCLUSION CRITERIA: (i) Studies of human participants under 18 years of age. (ii) Animal studies.
Intervention/s (I)	1. Stellate ganglion block (SGB). 2. Psychedelic-assisted therapies; specifically: (i) ketamine; (ii) methylenedioxymethamphetamine (MDMA); (iii) lysergic acid diethylamide (LSD); (iv) psilocybin; (v) dimethyltryptamine (DMT). 3. Medicinal cannabis; specifically: (i) cannabidiol (CBD); (ii) cannabinol (CBN); (iii) tetrahydrocannabinol (THC). 4. D-cycloserine (DCS). 5. Repeated transcranial magnetic stimulation (rTMS); including theta-burst stimulation (TBS).
Comparator/s (C)	Interventions considered to be the most effective in treating the mental health condition/s of interest; including those listed as having Level I and Level II evidence (National Health and Medical Research Council, Australian Government) in extant clinical guidelines (e.g., the Australian Psychological Society, 2018).
Outcome/s (O)	MAIN OUTCOMES: (i) Symptom severity using a standardised clinician-rated or self-report instrument for the mental health condition/s of interest including generalisation/maintenance of gains/outcomes (i.e., pre-treatment/during/post-treatment and follow-up measures; as available). (ii) Global Assessment of Functioning (GAF). (iii) Quality of Life (QoL) or Health-Related Quality of Life (HR-QoL). ADDITIONAL OUTCOMES: (i) Rates of response (i.e., non-response or partial-response) to intervention/s. (ii) Rates of remission (i.e., partial or full remission) of mental health condition/s. (iii) Rates of relapse (i.e., return of symptoms) or recurrence (i.e., new episode) of mental health condition/s. (iv) Serious adverse events. (v) Retention/dropout rates. (vi) Cost-effectiveness of intervention/s (as available).

Appendix 3: Search Strategy (PubMed)

Search string: Medicinal cannabis interventions

("Medical Marijuana"[Mesh] OR "Cannabinoids"[Mesh] OR "medical cannabis"[tiab] OR "medicinal cannabis"[tiab] OR "medical marijuana"[tiab] OR "medicinal marijuana"[tiab] OR "synthetic cannabis"[tiab] OR "cannabinoids"[tiab] OR "cannabinoid"[tiab] OR "cannabidiol"[tiab] OR "cannabinol"[tiab] OR "tetrahydrocannabinol"[tiab])

Search string: Common mental health conditions affecting veterans

AND ("Trauma and Stressor Related Disorders"[Mesh] OR "Anxiety Disorders"[Mesh] OR "Mood Disorders"[Mesh] OR "Substance-Related Disorders"[Mesh] OR "Behavior, Addictive"[Mesh] OR "trauma and stress related disorders"[tiab] OR "trauma and stress related disorder"[tiab] OR "traumatic stress disorder"[tiab] OR "traumatic stress disorders"[tiab] OR "post traumatic stress"[tiab] OR "posttraumatic stress"[tiab] OR "PTSD"[tiab] OR "post traumatic neuroses"[tiab] OR "posttraumatic neuroses"[tiab] OR "acute stress disorder"[tiab] OR "acute stress disorders"[tiab] OR "reactive attachment disorder"[tiab] OR "reactive attachment disorders"[tiab] OR "disinhibited social engagement disorder"[tiab] OR "disinhibited social engagement disorders"[tiab] OR "anxiety disorder"[tiab] OR "anxiety disorders"[tiab] OR "depressive disorder"[tiab] OR "depressive disorders"[tiab] OR "depression"[tiab] OR "depressions"[tiab] OR "substance related disorder"[tiab] OR "substance related disorders"[tiab] OR "addictive disorder"[tiab] OR "addictive disorders"[tiab] OR "substance addiction"[tiab] OR "substance dependence"[tiab] OR "substance abuse"[tiab])

Search string: Study type

AND ("Clinical Trials as Topic"[Mesh] OR "Clinical Trial" [Publication Type] OR "Systematic Reviews as Topic"[Mesh] OR "Systematic Review" [Publication Type] OR "Meta-Analysis as Topic"[Mesh] OR "Meta-Analysis" [Publication Type] OR "trial"[tiab] OR "randomized"[tiab] OR "randomised"[tiab] OR "randomly"[tiab] OR "systematic review"[ti] OR "systematic reviews"[ti] OR "systematic literature review"[ti] OR "systematic scoping review"[ti] OR "systematic narrative review"[ti] OR "systematic evidence review"[ti] OR "systematic quantitative review"[ti] OR "systematic critical review"[ti] OR "systematic mixed studies review"[ti] OR "systematic mapping review"[ti] OR "Cochrane review"[ti] OR "Cochrane reviews"[ti] OR "systematic search and review"[ti] OR "systematic integrative review"[ti] OR "systematically"[tiab] OR "meta analysis"[ti] OR "meta analyses"[ti] OR "metanalysis"[ti] OR "metanalyses"[ti] OR "metaanalysis"[ti] OR "metaanalyses"[ti] OR "meta review"[ti] OR "meta reviews"[ti] OR "metareview"[ti] OR "metareviews"[ti] OR "umbrella review"[ti] OR "umbrella reviews"[ti])

Search string: Search limits

NOT ("Comment" [Publication Type] OR "Editorial" [Publication Type] OR "Letter" [Publication Type]) NOT ("Animals"[Mesh] NOT "Humans"[Mesh]) AND (eng[la] OR und[la]) AND (2017:2022[dp])

Appendix 4: List of Excluded Studies

List of excluded studies (*n* = 33) by reason for exclusion in Figure 1 PRISMA diagram (Medicinal cannabis: Standalone and combined interventions).

Ongoing study (n = 12)

#	Registry ID	Mental Health Condition	Experimental intervention	Principal Investigator(s)	Location	Date of Registration	Expected Completion Date
1	NCT03549819	Anxiety Disorders	CBD (oil)	Van Ameringen, M.	Canada	2018 (Jun 8)	2023 (Feb 28)
2	EUCTR2020-003739-62-NL	Anxiety (and/or PTSD) among military personnel or veterans	CBD (capsule)	Geuze, E.	The Netherlands	2021 (Apr 21)	Not listed - last update June 2021
3	NCT04880278	OCD	THC (nabilone capsules)	Kayser, R.	United States	2021 (May 10)	2026 (Jul 1)
4	NCT05041647	Depression/Insomnia	CBD/THC (oil)	Frey, B. N.	Canada	2021 (Sep 13)	2023 (Jul 31)
5	NCT04205682	Alcohol Use Disorder (AUD)	CBD (capsule)	Haber, P., Lintzeris, N., McGregor, I., & Morley K.	Australia	2019 (Dec 19)	2021 (Jan 31)
6	NCT03787628	Opioid Use Disorder	CBD (capsule)	London, E. & De La Garza, R.	United States	2018 (Dec 26)	2023 (Nov 15)
7	NCT03248167	AUD comorbid PTSD	CBD (capsule)	Marmar, C. R.	United States	2017 (Aug 14)	2022 (Apr 20)
8	NCT03518801	PTSD (military veterans)	CBD (oral) + Prolonged Exposure	Ayers, C. R. & Martis, B.	United States	2018 (May 18)	2024 (Sep 30)
9	NCT04550377	PTSD (comorbid mild traumatic brain injury)	CBD (oral)	Blessing, E. M. & Marmar, C. R.	United States	2020 (Sep 16)	2023 (Jul 31)
10	NCT04080427	PTSD	THC (dronabinol capsules)	Rabinak, C. A.	United States	2019 (Sep 6)	2025 (Dec 31)
11	NCT05132699	PTSD	CBD (oral) + Prolonged Exposure	Straud, C.	United States	2021 (Nov 24)	2023 (June 30)
12	NCT04197102	PTSD	CBD (oil)	Telch, M. J.	United States	2019 (Dec 12)	2024 (May 31)

Ineligible publication type (n = 14)

#	YEAR	Reference	Exclusion reason
1	2022	Kirkland, A. E., Fadus, M. C., Gruber, S. A., Gray, K. M., Wilens, T. E., & Squeglia, L. M. (2022). A scoping review of the use of cannabidiol in psychiatric disorders. *Psychiatry Research*, *30*, Article 8114347. https://doi.org/10.1016/j.psychres.2021.114347	Narrative review
2	2022	Hill, K. P., Gold, M. S., Nemeroff, C. B., McDonald, W., Grzenda, A., Widge, A. S., Rodriguez, C., Kraguljac, N. V., Krystal, J. H., & Carpenter, L. L. (2022). Risks and benefits of cannabis and cannabinoids in psychiatry. *American Journal of Psychiatry, 179*(2), 98-109. https://doi.org/10.1176/appi.ajp.2021.21030320	Narrative review
3	2021	Kwee, C., Baas, J., Moerbeek, M., van der Veen, D., Batelaan, N., van Balkom, T., & Cath, D. (2021). Cannabidiol enhancement of exposure therapy in treatment refractory patients with phobias: A randomized controlled trial. *Biological Psychiatry, 89*(9), S230-S231. https://doi.org/110.1016/j.biopsych.2021.02.580	Poster abstract
4	2021	Gilman, J., Schmitt, W., Wheeler, G., Tervo-Clemmens, B., Hickey, S., Potter, K., Schuster, R., Cooke, M., Pachas, G., & Evins, A. E. (2021). A twelve-week trial of medical marijuana cards in adults with complaint of pain, insomnia, anxiety or depressive symptoms: A randomized, pragmatic clinical trial. *Neuropsychopharmacology, 46*, 399-400. https://doi.org/10.1038/s41386-021-01238-5	Poster abstract
5	2020	Kayser, R. R., Raskin, M., Snorrason, I., Hezel, D. M., Haney, M., & Simpson, H. B. (2020). Cannabinoid augmentation of exposure-based psychotherapy for obsessive-compulsive disorder. *Journal of Clinical Psychopharmacology*, *40*(2), 207-210. https://doi.org/10.1097/JCP.0000000000001179	Letter to the editor
6	2020	Bonn-Miller, M. O., Brunstetter, M., Simonian, A., Loflin, M. J., Vandrey, R., Babson, K. A., & Wortzel, H. (2020). The long-term, prospective, therapeutic impact of cannabis on post-traumatic stress disorder. *Cannabis Cannabinoid Research*. Online ahead of print. https://doi.org/10.1089/can.2020.0056	Observational study; Cannabis use as a variable of interest rather than intervention
7	2020	Van Ameringen, M., Zhang, J., Patterson, B., & Turna, J. (2020). The role of cannabis in treating anxiety: An update. *Current Opinion in Psychiatry, 33*(1), 1-7. https://doi.org/10.1097/YCO.0000000000000566	Narrative review
8	2020	Urits, I., Gress, K., Charipova, K., Li, N., Berger, A. A., Cornett, E. M., Hasoon, J., Kassem, H., Kaye, A. D., & Viswanath, O. (2020). Cannabis use and its association with psychological disorders. *Psychopharmacology Bulletin, 50*(2), 56-67. PMID: 32508368.	Narrative review
9	2020	Chadwick, V. L., Rohleder, C., Koethe, D., & Leweke, F. M. (2020). Cannabinoids and the endocannabinoid system in anxiety, depression, and dysregulation of emotion in humans. *Current Opinions in Psychiatry, 33*(1), 20-42. https://doi.org/10.1097/yco.0000000000000562	Not systematic
10	2020	Garakani, A., Murrough, J. W., Freire, R. C., Thom, R. P., Larkin, K., Buono, F. D., & Iosifescu, D. V. (2020). Pharmacotherapy of anxiety disorders: Current and emerging treatment options. *Frontiers in Psychiatry, 11*, Article 595584. https://doi.org/10.3389/fpsyt.2020.595584	Narrative review
11	2020	Kwee, C., Baas, J. M. P., Van Balkom, A. J. L. M., Batelaan, N. M., Van der Veen, D. C., Moerkbeek, M., & Cath, D. C. (2020). P.102 Cannabidiol enhancement of exposure therapy in treatment refractory patients with phobias: First results	Poster abstract

#	YEAR	Reference	Exclusion reason
		after augmented in vivo exposure therapy. *European Neuropsychopharmacology, 40*, S66. https://doi.org/10.1016/j.euroneuro.2020.09.089	
12	2019	van der Flier, F. E., Kwee, C. M. B., Cath, D. C., Batelaan, N. M., Groenink, L., Duits, P., van der Veen, D. C., van Balkom, A. J. L. M., & Baas, J. M. P. (2019). Cannabidiol enhancement of exposure therapy in treatment refractory patients with phobias: Study protocol of a randomized controlled trial. *BMC Psychiatry, 19*(1), 69. https://doi.org/10.1186/s12888-019-2022-x	Protocol only
13	2018	El-Solh, A. A. (2018). Management of nightmares in patients with posttraumatic stress disorder: Current perspectives. *Nature and Science of Sleep, 10*, 409-420. https://doi.org/10.2147/NSS.S166089	Narrative review
14	2018	Rabinak, C., Peters, C., Elrahal, F., Milad, M., Rauch, S., Phan, K. L., & Greenwald, M. (2018). Cannabinoid facilitation of fear extinction in posttraumatic stress disorder. *Biological Psychiatry, 83*(9), S21. https://doi.org/10.1016/j.biopsych.2018.02.069	Poster abstract

Ineligible intervention (n = 4)

#	YEAR	Reference	Exclusion reason
1	2020	Prajapati, S. K., Bhaseen, S., Krishnamurthy, S., & Sahu, A. N. (2020). Neurochemical evidence of preclinical and clinical reports on target-based therapy in alcohol use disorder. *Neurochemical Research, 45*(2), 491-507. https://doi.org/10.1007/s11064-019-02944-9	No cannabis related studies - only "Cannabinoid modulating treatments" e.g., rimonabant; an anti-obesity anorectic
2	2020	Varker, T., Watson, L., Gibson, K., Forbes, D., & O'Donnell, M. (2020). Efficacy of psychoactive drugs for the treatment of posttraumatic stress disorder: A systematic review of MDMA, ketamine, LSD and psilocybin. *Journal of Psychoactive Drugs, 53*(1), 85-95. https://doi.org/10.1080/02791072.2020.1817639	No cannabis related studies
3	2019	Yang, B., Lin, L., Bazinet, R. P., Chien, Y-C., Chang, J. P-C., Satyanarayanan, S. K., Su, H., & Su, K-P. (2019). Clinical efficacy and biological regulations of ω-3 PUFA-derived endocannabinoids in major depressive disorder. *Psychotherapy and Psychosomatics, 88*(4), 215-224. https://doi.org/10.1159/000501158	Endocannabinoids – endogenously produced from polyunsaturated fatty acids
4	2018	Bahorik, A. L., Sterling, S. A., Campbell, C. I., Weisner, C., Ramo, D., & Satre, D. D. (2018). Medical and non-medical marijuana use in depression: Longitudinal associations with suicidal ideation, everyday functioning, and psychiatry service utilization. *Journal of Affective Disorders, 241*, 8-14. https://doi.org/10.1016/j.jad.2018.05.065	Medical and non-medical marijuana use is a predictor of effect of motivational interviewing rather than intervention of interest.

Ineligible population (n = 1)

#	YEAR	Reference	Exclusion reason
1	2022	Oppong-Damoah, A., Gannon, B. M., Murnane, K. S. (2022). The endocannabinoid system and alcohol dependence: Will cannabinoid receptor 2 agonism be more fruitful than cannabinoid receptor 1 antagonism? *CNS & Neurological Disorders – Drug Targets, 21*(1), 3-13. https://doi.org/10.2174/1871527320666210211115007	Animal studies only

Ineligible outcomes (n = 2)

#	YEAR	Reference	Exclusion reason
1	2020	Rabinak, C. A., Blanchette, A., Zabik, N. L., Peters, C., Marusak, H. A., Iadipaolo, A., & Elrahal, F. (2020). Cannabinoid modulation of corticolimbic activation to threat in trauma-exposed adults: A preliminary study. *Psychopharmacology, 237*(6), 1813-1826. https://doi.org/10.1007/s00213-020-05499-8	No clinical outcomes: Reaction time to threatening versus non-threatening faces.
2	2022	Bolsoni, L. M., Crippa, J. A. S., Hallak, J. E. C., Guimarães, F. S., Zuardi, A. W. (2022). Effects of cannabidiol on symptoms induced by the recall of traumatic events in patients with posttraumatic stress disorder. *Psychopharmacology, 239*, 1499-1507. https://doi.org/10.1007/s00213-021-06043-y	Outcome measures do not measure change in symptoms for the condition of interest (PTSD).

Appendix 5: List of Included Studies

Medicinal cannabis: Standalone and combined interventions (n = 12)

#	Study	Experimental intervention	Target condition	Combined intervention details (if applicable)
1	Masataka (2019)	Cannabidiol (CBD) – oral solution	SAD	N/A
2	Kayser et al. (2020)	Dried cannabis (THC±CBD) – smoked (cigarettes)	OCD	N/A
3	Schlienz et al. (2018)	Dronabinol (THC) – oral capsules	CUD	N/A
4	Hurd et al. (2019)	Cannabidiol (CBD) – oral solution	HUD	N/A
5	Hindocha et al. (2018)	Cannabidiol (CBD) – oral capsules	TUD	N/A
6	Freeman et al. (2020)	Cannabidiol (CBD) – oral capsules	CUD	Motivational interviewing
7	Lintzeris et al. (2019)	Nabiximols (THC+CBD) – oromucosal spray	CUD	CBT-based counselling (individual)
8	Trigo et al. (2018)	Nabiximols (THC+CBD) – oromucosal spray	CUD	Motivational enhancement therapy and cognitive behavioural therapy (MET/CBT)
9	Hill et al. (2017)	Nabilone (THC) – oral capsules	CUD	Physician-guided medical management (MM)
10	Meneses-Gaya et al. (2021)	Cannabidiol (CBD) – oral capsules	CocUD	Psychotherapy (group)
11	Mongeau-Pérusse et al. (2021)	Cannabidiol (CBD) – oral solution	CocUD	Psychoeducation (group)
12	Bonn-Miller et al. (2021)	Dried cannabis (THC±CBD) – smoked (metal pipe)	PTSD	N/A

Notes: N/A = Not applicable. CBD = Cannabidiol; CBT = Cognitive Behavioural Therapy; CocUD = Cocaine Use Disorder; CUD = Cannabis Use Disorder; HUD = Heroin Use Disorder; MET = Motivational Enhancement Therapy; OCD = Obsessive Compulsive Disorder; PTSD = Post Traumatic Stress Disorder; SAD = Social Anxiety Disorder; TUD = Tobacco Use Disorder.

Appendix 6: Matrix of Included Studies

Medicinal cannabis: Standalone and combined interventions (n = 12)

	Anxiety Disorders	Mood/Depressive Disorders	Substance-Related and Addictive Disorders	Trauma and Stressor-Related Disorders
Natural or synthetic cannabidiol (CBD)	X	1 x standalone Tx (SAD)	2 x combined Tx (CocUD) 1 x combined Tx (CUD) 1 x standalone Tx (HUD) 1 x standalone Tx (TUD)	X
Natural cannabis extract (THC&CBD)	X	X	2 x combined Tx (CUD)	X
Natural dried cannabis (THC±CBD)	1 x standalone Tx (OCD)	X	X	1 x standalone Tx (PTSD)
Synthetic cannabinoids (THC)	X	X	1 x standalone Tx (CUD) 1 x combined Tx (CUD)	X

Notes: Standalone Tx refers to interventions that were not combined with other psychotherapy or pharmacological intervention/s (e.g., antidepressants; mood stabilisers; anti-psychotics). Combined Tx refers to interventions that were combined with other psychotherapy or pharmacological intervention/s. X indicates there were no studies included in the analysis for the medicinal cannabis compound of interest (i.e., CBD; CBN; THC) and the mental health condition/s of interest. CocUD = Cocaine Use Disorder. CUD = Cannabis Use Disorder. HUD = Heroin Use Disorder. OCD = Obsessive Compulsive Disorder. PTSD = Posttraumatic Stress Disorder. SAD = Social Anxiety Disorder. TUD = Tobacco Use Disorder.

Appendix 7: Summary of Findings

1. Natural Cannabidiol (CBD) for Social Anxiety Disorder and Comorbid Avoidant Personality Disorder: Standalone intervention

Citation	Masataka (2019)
Study Design	• Double-blind, randomised, placebo-controlled, trial.
Sample Size	• 37 participants (per-protocol sample). • 40 participants enrolled. • 3 participants dropped out of the CBD study condition as they disliked the smell and taste of the CBD oil.
Population	• Japan. • Social anxiety disorder and comorbid avoidant personality disorder (DSM-IV criteria). • Older teenagers (aged 18 to 19 years). • I (CBD): 70.6% male. • C (placebo): 70.0% male.
Intervention/s (I) and Comparator/s (C)	• All participants received an oral solution once daily for four (4) weeks. • I (n = 17): CBD oil (300 mg) in solution • C (n = 20): olive oil (placebo) in solution.
Outcome Measure/s	• Fear of Negative Evaluation Questionnaire (FNE). • Liebowitz Social Anxiety Scale (LSAS).
General	• All participants were diagnosed by a psychiatrist using the Structured Clinical Interview for DSM-IV Axis I and Axis II Disorders (SCID-I and SCID-II). • Period study was conducted: not reported.
Inclusion Criteria	• 18 to 19 years old. • Naïve to cannabis. • Social anxiety disorder (SAD; DSM-IV criteria). • Symptoms of SAD for at least 6 months at study commencement.
Exclusion Criteria	• Previous or concurrent pharmacological or psychological treatment. • Any form of psychotic or organic illness. • Diagnosis of cluster A or cluster B personality disorder, acute suicidality, or substance dependence. • Comorbid diagnosis of other anxiety or mood disorders.
Assessment Time-Point/s	• Baseline: minimum of 3 weeks showing stable FNE scores. • Post-treatment: end of the four-week intervention period. • Follow-up: brief home check-ins (once a week) by clinical psychologist for up to 6 months post-treatment.

Main Findings	• FNE scores:
	  o CBD group: M = 24.4 (SD = 2.7) in the pre-intervention measurement and M = 19.1 (SD = 2.1) in the post-intervention measurement.
	  o Placebo group: 23.5 (2.1) in the pre-intervention measurement and 23.3 (2.9) in the post-intervention measurement.
	  o At post-treatment (week 4) social anxiety symptoms (as measured by the FNE) were significantly lower for the CBD group compared with the placebo group (p = 0.0002), but the groups did not significantly differ at baseline (p = 0.71).
	• LSAS scores
	  o CBD group: M = 74.2 (SD = 7.5) in the pre-intervention measurement and M = 62.1 (SD = 8.7) in the post-intervention measurement.

Citation	Masataka (2019)
	o Placebo group: M = 69.9 (SD = 10.3) in the pre-intervention measurement and M = 66.8 (SD = 11.2) in the post-intervention measurement. o At post-treatment (week 4) social anxiety symptoms (as measured by the LSAS) were significantly lower for the CBD group compared with the placebo group at post-intervention (p = 0.0018), but the groups did not significantly differ at baseline (p = 0.66).
Safety and Adverse Events	• No assessments of safety or adverse events were reported.

2. Natural Dried Cannabis (THC±CBD) for Obsessive Compulsive Disorder (OCD): Standalone intervention

Citation	Kayser et al. (2020)
Study Design	• Double-blind, randomised, placebo-controlled, trial. • Crossover design.
Sample Size	• 12 participants (per-protocol sample). • 14 participants enrolled. • 2 participants dropped out of the study following randomisation (after the first session) reporting that the time commitment was "too great".
Population	• United States. • OCD (primary diagnosis; DSM-5 criteria). • Total sample: M = 26.8 years (SD = 7.4); 67% male.
Intervention/s (I) and Comparator/s (C)	• All participants received three dried cannabis cigarettes (smoked) in a randomised order with a washout period between conditions. • Participants completed no more than one session per calendar week to control for potential carryover effects (mean days between sessions = 12.5; standard deviation = 11.7; range = 5 to 56). • I (n = 12): THC dominant (7.0% THC; 0.18% CBD). • I (n = 12): CBD dominant (0.4% THC; 10.4% CBD). • C (n = 12): placebo with no active cannabinoids (0% THC; 0% CBD).
Outcome Measure/s	• Primary: o Yale-Brown Obsessive Compulsive Scale (Y-BOCS). o Obsessive Compulsive – Visual Analog Scale (OCD-VAS). o State-Trait Anxiety Inventory – State (STAI-S) subscale. • Secondary: o Subjective drug-related effects measured using a modified version of the Marijuana Rating Form (MRF). o Cardiovascular measures.
General	• Period study was conducted: October 2017 to October 2020.
Inclusion Criteria	• 21 to 55 years of age. • Physically healthy. • Primary diagnosis of OCD (DSM-5 criteria) with illness duration of at least (≥) one (1) year and near-constant symptoms (i.e., greater than 8 hours per day or maximum symptom-free interval less than 1 hour per day). • Y-BOCS score of at least (≥) 16. • No psychotropic medication in last 6 weeks other than SRIs, and no change to SRI dose in past 6 weeks. • Prior experience using cannabis without significant adverse effects.

Citation	Kayser et al. (2020)
	• Capable of providing informed consent.
Exclusion Criteria	• Not pregnant or breastfeeding. • Lifetime history of bipolar disorder or psychosis, or first-degree relative with these conditions. • HDRS-17 score greater than (>) 25 or current suicidal ideation. • History of significant medical condition that could increase risk of cannabis side effects. • Currently enrolled in, or planning to commence, exposure and response/ritual prevention (ERP) therapy. • Substance use disorder in the last year (including cannabis use disorder) or positive urine toxicology (for substances other than cannabis) at screening. • Seeking treatment for substance use.

Assessment Time-Point/s	• Three lab-based sessions conducted no more than once per calendar week; schedule as follows:
	  o Minute -50: carbon monoxide, breathalyser (alcohol), urine toxicology, and pregnancy test (female participants only).
	  o Minute -30: balance, TLFB, vitals (BP/HR), self-report scales (OCD-VAS, Y-BOCS, STAI-S, and MRF).
	  o Minute 0: cannabis administration.
	  o Minute 20, 40, 60, 90, and 120: vitals, self-report scales.
	  o Minute 180: vitals, self-report scales, field sobriety test, and participant discharge.

Main Findings	• There was a significant effect of time on all three symptom self-report measures, with significant decreases in OCD symptoms (as measured by the Y-BOCS: $F_{(6, 10)} = 10.50$; $p < 0.001$; and the OCD-VAS: $F_{(6, 10)} = 8.93$; $p < 0.001$), and significant decreases in anxiety symptoms (as measured by the STAI-S: $F_{(6, 10)} = 7.00$; $p < 0.001$).
	• There was a significant effect of cannabis varietal on anxiety symptoms (as measured by the STAI-S: $F_{(2, 10)} = 6.26$; $p = 0.002$), but not on OCD symptoms (as measured by the Y-BOCS: $F_{(2, 10)} = 0.33$; $p = 0.72$; or the OCD-VAS: $F_{(2, 10)} = 0.10$; $p = 0.90$).
	• There was no significant cannabis varietal by time interaction (Y-BOCS: $p = 0.577$; OCD-VAS: $p = 0.818$; STAI-S: $p = 0.740$).
	• Though mean STAI-S scores decreased in all three conditions, they were significantly lower for placebo compared with both THC [M(diff) = -4.31, SE = 1.34, $p = 0.001$] and CBD [M(diff) = -3.85, SE = 1.34, $p = 0.004$].
	• Post-hoc analyses:
	  o At the 20-minute time-point, participants had significantly lower anxiety symptoms (as measured by the STAI-S) after placebo administration compared with both THC [M(diff) = -11.25, SE = 3.54, $p = 0.002$] and CBD cannabis [M(diff) = -7.33, SE = 3.54, $p = 0.039$].
	  o At the 40-minute timepoint, anxiety symptoms (as measured by the STAI-S) remained significantly lower for placebo compared with THC [M(diff) = -7.58, SE = 3.54, $p = 0.033$), but not for placebo compared with CBD [M(diff) = -6.33, SE = 3.54, $p = 0.075$].
	  o At the 60-minute and subsequent time-points, there were no between-group differences in anxiety symptoms (as measured by the STAI-S; p-values not reported).

Safety and Adverse Events	• No serious adverse events were reported. • THC increased heart rate, blood pressure, and intoxication compared with CBD and placebo.

Citation	Kayser et al. (2020)
	• Across all conditions, the most common self-reported side effects were nervousness and dry mouth.

3. Synthetic Cannabinoid (THC) for Cannabis Use Disorder (CUD): Standalone intervention

Citation	Schlienz et al. (2018)
Study Design	• Double-blind, randomised, placebo-controlled, trial. • Crossover design.
Sample Size	• 13 participants (per-protocol sample). • 16 participants enrolled. • 3 participants were excluded due to protocol deviations; 2 were discharged from the study following initial exposure and discrimination training (prior to dronabinol dosing) because they indicated a preference for placebo cannabis over active cannabis; 1 participant voluntarily withdrew from the study for personal reasons.
Population	• United States. • Daily cannabis users (defined as self-reported cannabis use for a minimum of 25 days per month in the past year). • 10 of 13 participants met DSM-IV criteria for cannabis dependence. • Not treatment-seeking. • Total sample: M = 25 years (SD = 5); 77% male.
Intervention/s (I) and Comparator/s (C)	• Once the maximum dronabinol dose was determined; all participants received three (3) oral capsules per day for three, sequential (12-day) dronabinol maintenance periods (with dose order counterbalanced across participants). • I (n = 13): low-dose dronabinol (120 mg/day: 40 mg three times per day). • I (n = 13): high-dose dronabinol (180 to 240 mg/day: 60 to 80 mg three times per day). • C (n = 13): placebo dronabinol (three times per day).

Outcome Measure/s	• Primary:
	  a. Number of self-administered cannabis cigarettes (active vs. placebo) under two access conditions:
	    2. progressive-ratio; and
	    3. forced-choice (cannabis vs. money).
	• Secondary (past 24 hours)
	  o Marijuana Withdrawal Checklist: cannabis withdrawal symptoms.
	  o Sleep diary: self-reported latency to sleep onset, total sleep, number of nocturnal awakenings, time awake after sleep onset, and 100 mm visual analogue scale (VAS) ratings of sleep quality, mood on awakening, and alertness on awakening.
	  o Self-reported adverse event form (4-point Likert scale: none, mild, moderate, severe): medication side effects for dronabinol.
	  o Vital signs (as measured by an automated monitor): three times per day (09:00, 14:00, and 19:00).

General	• Participants were not treatment-seeking or otherwise motivated to abstain from cannabis use (except for the behavioural or monetary costs incurred as part of the study). • During each of the three (12-day) study conditions, participants could self-administer cannabis under four access conditions: (i) progressive-ratio access to smoked, active (5.7% THC) cannabis (3 days); (ii) progressive-ratio access to

Citation	Schlienz et al. (2018)
	smoked, placebo (< 1% THC) cannabis (3 days); (iii) forced-choice between smoked, active (5.7% THC) cannabis or receiving money (3 days); and (iv) forced-choice between smoked, placebo (< 1% THC) cannabis or receiving money (3 days).
Inclusion Criteria	• 18 years of age and older. • Cannabis use for a minimum of 25 days per month in the past year (self-report). • Urine specimen > 50 ng/mL THCCOOH. • Not currently taking psychoactive medication. • Does not meet DSM-IV-TR criteria for an Axis I psychiatric disorder other than nicotine or cannabis dependence. • Negative urine toxicology test for illicit drugs other than cannabis at study admission.
Exclusion Criteria	• Pregnant, breastfeeding, or planning to become pregnant in the next three months. • Treatment-seeking for cannabis-related problems or otherwise trying to reduce use. • Using cannabis under the guidance of a physician for a medical disorder. • Unstable or uncontrolled cardiovascular disease (e.g., hypertension, angina). • Allergic to the study medication.
Assessment Time-Point/s	• Every day (day 1 to day 12) for each of the three (12-day) study conditions (placebo, low-dose, and high-dose dronabinol maintenance).

Main Findings	• Progressive-ratio access conditions:
	  o Significant main effects of cannabis-type [$F_{(1,12)} = 391.5$, $p < 0.001$] and dronabinol dose [$F_{(2,24)} = 9.1$, $p = 0.001$] were observed on days in which cannabis was available under the two progressive-ratio access conditions.
	  o Participants self-administered significantly fewer placebo (< 1% THC) cannabis cigarettes compared with active (5.7% THC) cannabis cigarettes on progressive-ratio study days.
	  o Compared with placebo dronabinol maintenance, maintenance on both low-dose (120 mg) and high-dose (180 to 240 mg) dronabinol significantly reduced self-administration of active (5.7% THC) cannabis cigarettes under progressive-ratio access (both p's ≥ 0.05).
	  o There was no difference between low-dose and high-dose dronabinol maintenance on self-administration of active (5.7% THC) cannabis cigarettes under progressive-ratio access (p = 0.63).
	• Forced-choice access conditions:
	  o Significant main effects of cannabis-type were observed for self-administration of cannabis cigarettes at all three monetary choice values (USD 0.25, 1.00, or 2.00; F's$_{(1,12)}$ = 52.2 to 117.3; all p's < 0.001). Main effects for dronabinol dose: findings not reported.
	  o In keeping with the progressive-ratio access conditions, participants self-administered a greater number of active (5.7% THC) cannabis cigarettes compared with placebo (< 1% THC) cannabis cigarettes under the forced-choice access conditions.
	  o Compared with placebo dronabinol maintenance:
	    ▪ In the cannabis versus USD 0.25 choice condition, high-dose but not low-dose dronabinol maintenance reduced self-administration of active (5.7% THC) cannabis cigarettes (p = 0.05).
	    ▪ In the cannabis versus USD 1.00 choice condition, both low-dose and high-dose dronabinol maintenance significantly reduced self-administration of active (5.7% THC) cannabis cigarettes (p = 0.01 and p = 0.03, respectively).

Citation	Schlienz et al. (2018)
	▪ In the cannabis versus USD 2.00 choice condition, low-dose but not high-dose dronabinol maintenance significantly reduced self-administration of active (5.7% THC) cannabis cigarettes (p = 0.03 and p = 0.23, respectively). ○ There were no differences between low-dose and high-dose dronabinol maintenance on self-administration of active (5.7% THC) cannabis cigarettes at any monetary value in the forced-choice access conditions (all p's > 0.25).
Safety and Adverse Events	• Self-administration of placebo (< 1% THC) cannabis cigarettes: ○ Low-dose dronabinol significantly reduced both systolic and diastolic blood pressure (BP) compared with placebo but did not affect heart rate. ○ High-dose dronabinol significantly reduced systolic and diastolic blood pressure and increased heart rate (statistically but not clinically significant). ○ No significant differences in blood pressure or heart rate were observed between the low-dose and high-dose dronabinol conditions. • Self-administration of active (5.7% THC) cannabis cigarettes: ○ Findings not reported.

4. Natural Cannabidiol (CBD) for Heroin Use Disorder: Standalone intervention

Citation	Hurd et al. (2019)
Study Design	• Double-blind, randomised, placebo-controlled, trial.
Sample Size	• 42 participants (per-protocol sample). • 50 participants enrolled. • 8 participants were excluded from analyses following randomisation for various reasons (not reported by study condition): voluntary withdrawal (2); health measures unrelated to study drug (2); positive toxicology result in session where a test drug would be administered (1); weather precluded receiving daily test drug (1); and lost to follow-up (2). Baseline characteristics were not reported for excluded participants.
Population	• United States. • Heroin Use Disorder (DSM-IV criteria); abstinence required for study participation. • I [400 mg CBD]: 51.9 years (7.9); 86% male. • I [800 mg CBD]: 50.5 years (11.6); 85% male. • C [placebo]: 47.3 years (8.0); 80% male.
Intervention/s (I) and Comparator/s (C)	• All participants received an oral solution. • I (n = 14): 400 mg oral CBD (*Epidiolex* natural cannabis extract: pure CBD). • I (n = 13): 800 mg oral CBD (*Epidiolex* natural cannabis extract: pure CBD). • C (n = 15): matched placebo (excipients alone).
Outcome Measure/s	Primary: • Visual Analogue Scale – Craving (VAS-C). • Visual Analogue Scale – Anxiety (VAS-A). Secondary: • Heroin Craving Questionnaire (HCQ). • Positive and Negative Affect Schedule (PANAS). • Vital signs (skin temperature, blood pressure, heart rate, respiratory rate, oxygen saturation, and salivary cortisol levels).

Citation	Hurd et al. (2019)
	• Cognitive tasks (Session 3 only).
General	• The study focused on self-reported craving in a laboratory setting with no attempt to measure actual opioid use. • Recruitment targeted individuals who were abstinent and not taking psychoactive medications, who are at greater risk of relapse than participants on agonist maintenance treatment (i.e., methadone). • Most participants (78.6%) indicated a preference for intranasal heroin use and, on average, 83.3% reported currently using more than 10 bags of heroin daily (one bag = 1 g), and had been using heroin for approximately 13.2 years. • Most participants (64.3%) had been abstinent from heroin use for less than 1 month, 14.3% for 1 to 2 months, and 21.4% for 2 to 3 months. • In addition to heroin use disorder, most participants had a history of alcohol use disorder or cannabis use disorder but were not currently diagnosed with those disorders. The majority were also tobacco smokers. • Period study was conducted: September 2015 to May 2017. • Secondary analyses in other papers. o Epstein (2019) – editorial.
Inclusion Criteria	• 21 to 65 years old. • Opiate dependence over the last 3 months as determined by the Structured Clinical Interview for DSM-IV (SCID). • No opioid use in the past 7 days (verified by urine drug screen and opiate metabolite test).
Exclusion Criteria	• Using any psychoactive drug (other than nicotine) at any time up to Session 3. • Diagnosis of drug dependence (except for heroin or nicotine) in the past 3 months (DSM-IV criteria). • Heroin maintenance therapy (e.g., methadone or buprenorphine, or taking opioid antagonists such as naltrexone). • Observable symptoms of acute heroin withdrawal. • Medical conditions, including DSM-IV Axis I psychiatric conditions as determined by the Mini International Neuropsychiatric Interview (MINI). • History of cardiac disease, arrhythmias, head trauma, and seizures. • History of hypersensitivity to cannabinoids. • Arriving to the study site visibly intoxicated, as determined by a clinical evaluation for signs and symptoms of intoxication, and as verified by a drug screen. • Participation in another pharmacotherapy trial in the last 3 months. • Pregnant or breastfeeding. • Not using, or irregular use of, appropriate methods of contraception.

Assessment Time-Point/s	• Baseline: Session 1 (before the first oral solution).
	• During treatment:
	   o Session 1 (1 to 2 hours after first oral solution).
	   o Session 2 (24 hours after first oral solution).
	   o Session 3 (day 3).
	• Follow-up: Session 4 (7 days after third oral solution).

Main Findings	• Cue condition (drug-related vs. neutral cue):
	   o A significant difference in craving (as measured by the VAS-C; adjusted for baseline craving) was observed for the cue condition (drug-related vs. neutral cue: $p < 0.0001$).
	   o Across participants, craving was significantly higher following exposure to drug-related cues [M(diff) = 1.09] than following exposure to neutral cues [M(diff) = -0.02].

Citation	Hurd et al. (2019)

	• CBD dose condition (placebo vs. 400 mg vs. 800 mg):
	   o A significant difference in craving (as measured by the VAS-C; adjusted for baseline craving) was observed for the CBD dose condition (placebo vs. 400 mg vs. 800 mg; p = 0.0047).
	   o Across sessions, participants receiving placebo CBD reported significantly greater craving after the drug-related cues [M(diff) = 0.93] compared with participants in the active CBD groups [400mg CBD: M(diff) = 0.44; 800mg CBD: M(diff) = 0.23].
	   o No significant difference in craving scores was observed between the active CBD groups (p-value not reported), indicating that both CBD doses (400mg; 800mg) equally reduced craving.

Safety and Adverse Events	• No serious adverse events were noted in association with CBD administration throughout the duration of the trial. • Mild diarrhoea was reported in three participants, headache in three participants (two of whom had received placebo), and tiredness or fatigue in two participants (one had received placebo; the other 800 mg CBD).

5. Synthetic Cannabidiol (CBD) for Tobacco Use Disorder (TUD): Standalone intervention

Citation	Hindocha et al. (2018)
Study Design	• Double-blind, randomised, placebo-controlled, trial. • Crossover design.
Sample Size	• 30 participants (per-protocol sample). • 44 participants were enrolled; 14 participants (> 30%) were excluded from analyses following baseline (satiation) assessments: 5 participants were excluded due to low carbon monoxide readings; 2 participants were excluded due to positive drug urine screens; and 7 participants voluntarily dropped out of the study.
Population	• United Kingdom. • Nicotine dependent, cigarette smokers. • Not treatment seeking. • Total sample: M = 28.07 years (SD = 8.66); 54% male.
Intervention/s (I) and Comparator/s (C)	• After overnight smoking abstinence, all participants received two interventions (oral capsules) in a crossover design (with intervention order randomised, and counterbalanced across gender, and a washout period of at least one week between conditions). • I (n = 30): 800 mg CBD (pure synthetic CBD product). • C (n = 30): matched placebo (lactose powder).

Outcome Measure/s	• Primary:
	   o Withdrawal: Mood and Physical Symptoms Scale (MPSS).
	   o Craving: Questionnaire of Smoking Urges – Brief (QSU-B).
	• Secondary:
	   o Attentional bias to pictorial tobacco cues recorded using a visual probe task and a pleasantness rating task (PRT).
	   o Side effects: 6-item, 10-point, Visual Analogue Scale (VAS).

General	• The participant sample had an average Fagerström Test for Nicotine Dependence (FTND) score indicating moderate dependence (M = 5.56; SD = 1.13).

Citation	Hindocha et al. (2018)
	• On average, the study participants smoked slightly more cigarettes per day (M = 13.5; SD = 2.39), than the national average for UK adults (i.e., 11.5 cigarettes per day). • Period study was conducted: not reported.
Inclusion Criteria	• 18 to 50 years old. • Smoking at least (≥) 10 cigarettes per day for a minimum of one year. • Score of at least (≥) 4 (moderate dependence) on the Fagerström Test for Nicotine Dependence (FTND). • Smoking first cigarette within an hour of waking. • Negative drug urine screen for all major drugs of abuse at baseline.
Exclusion Criteria	• Nicotine replacement or cessation pharmacotherapy. • Self-reported recent use of cannabis or other illicit drugs. • Recent (past 4 weeks) or ongoing use of e-cigarettes. • Current mental or physical health issues or learning impairments. • Pregnant or breastfeeding. • Allergic to CBD, gelatine, lactose, microcrystalline cellulose, or chocolate.

Assessment Time-Point/s	• Baseline "satiated' session (smoking "as normal" prior to the session).
	  o 0 minutes: arrival.
	  o 12 minutes (T1): QSU-B, MPSS.
	  o 30 minutes: cigarette administration.
	  o 35 minutes (T2): QSU-B, MPSS.
	  o 60 minutes: visual probe task.
	  o 68 minutes: pleasantness rating task (PRT).
	  o 75 minutes (T3): QSU-B, MPSS.
	• Abstinent sessions (overnight smoking abstinence prior to each session):
	  o 0 minutes: arrival.
	  o 5 minutes (T1): QSU-B, MPSS, HR, BP.
	  o 10 minutes: drug administration.
	  o 70 minutes (T2): QSU-B, MPSS, HR, BP.
	  o 130 minutes (T3): QSU-B, MPSS, HR, BP.
	  o 190 minutes: visual probe task.
	  o 198 minutes: pleasantness rating task (PRT).
	  o 200 minutes (T4): QSU-B, MPSS.

Main Findings	• Craving:
	  o Prior to drug administration, craving (as measured by the QSU-B) was greater under the abstinent (intervention) conditions than under the satiation (baseline) condition (p < 0.001), suggesting that abstinence increased craving.
	  o Prior to drug administration, there was no difference in craving symptoms between the CBD and placebo (intervention) conditions (p = 0.99; confirmed by a Bayesian analysis: JZS BF = 7.08).
	  o Following drug administration in the abstinence sessions, there was a main effect of time (p < 0.001); however, there was no main effect of drug (p = 0.81; confirmed by a Bayesian analysis: JZS BF = 6.87), or drug by time interaction (p-value not reported), suggesting no difference between the CBD and placebo (intervention) conditions on craving symptoms.
	• Withdrawal:
	  o Prior to drug administration, withdrawal (as measured by the MPSS scores) was greater under the abstinent (intervention) conditions than under the satiation (baseline) condition (p < 0.001), suggesting that abstinence increased withdrawal.

Citation	Hindocha et al. (2018)
	o Prior to drug administration, there was no difference in withdrawal symptoms between the CBD and placebo (intervention) conditions (p = 0.85; confirmed by a Bayesian analysis: JZS BF = 6.95). o Following drug administration in the abstinence sessions, there was a main effect of time (p < 0.001); however, there was no main effect of drug (p = 0.64; confirmed by a Bayesian analysis: JZS BF = 6.35), or drug by time interaction (p-value not reported), suggesting no difference between the CBD and placebo groups on withdrawal symptoms.
Safety and Adverse Events	• Heart rate (HR): o There was a main effect of time (p < 0.001), which showed that HR decreased over time. o There was no main effect of drug (p = 0.30; confirmed by a Bayesian analysis (JZS BF = 4.17). o There was no interaction between drug and time (p-value not reported). • Blood pressure (BP): o Systolic BP: There was a main effect of time (p < 0.001), which indicated that systolic BP decreased over time. There was a main effect of drug (p = 0.015), which indicated that systolic BP was higher after placebo than after CBD. o Diastolic BP: There were no main effects or interactions. • Side effects (self-reported): o There was a significant interaction between drug and time for 'headache' but no significant pairwise comparisons emerged (p-values not reported). o No other main effects of drug or interactions were observed between drug and time (p-values not reported).

6. Synthetic Cannabidiol (CBD) for Cannabis Use Disorder (CUD): Combined intervention

Citation	Freeman et al. (2020)
Study Design	• Double-blind, randomised, placebo-controlled, trial.
Sample Size	• 82 participants (intention-to-treat, Bayesian analysis). • 48 participants enrolled in first phase of study recruitment and randomised to four study conditions (CBD: 200 mg vs. 400 mg vs. 800 mg vs. placebo). • 200 mg CBD condition dropped following interim Bayesian analysis. • 34 participants enrolled in second phase of study recruitment and randomised to three study conditions (CBD: 400 mg vs. 800 mg vs. placebo).
Population	• United Kingdom. • Cannabis use disorder (DSM-5 criteria). • Treatment seeking. • I [800 mg]: M = 27.4 years (SD = 21.9); 70% male. • I [400 mg]: M = 26.6 years (SD = 27.6); 71% male. • I [200 mg]: M = 27.3 years (SD = 17.5); 75% male. • C [placebo]: M = 24.9 years (SD = 30.3); 74% male.
Intervention/s (I) and Comparator/s (C)	• All participants received six (30-minute) sessions of motivational interviewing. • Two phases of study recruitment. At the interim Bayesian analysis, the 200 mg CBD condition was found to be ineffective, and no additional participants were randomised to this study condition in the second phase of recruitment. • All participants received two oral capsules (twice per day for four weeks) to achieve daily doses of (n = first phase, second phase):

Citation	Freeman et al. (2020)

	o I (n = 12, 0): 200 mg CBD.
	  o I (n = 12, 24): 400 mg CBD.
	  o I (n = 12, 23): 800 mg CBD.
	  o C (n = 12, 23): placebo (cellulose).

Outcome Measure/s	Primary: • Cannabis use as measured by urine screen (THC-COOH:creatinine concentration). • Cannabis abstinence (number of days per week; self-report). Secondary: • Cannabis Withdrawal Scale (total score). • Tobacco use as measured by urine screen (cotinine:creatinine concentration) and self-report (number of cigarettes smoked using the Timeline Followback, TLFB, method). • Alcohol consumption (self-report using the TLFB method). • Pittsburgh Sleep Quality Index (PSQI). • Beck Depression Inventory (BDI). • Beck Anxiety Inventory (BAI).
General	• DSM-5 diagnosis of cannabis use disorder, with the majority (96%) of participants in the severe range. • The primary objective was to identify the Most Effective Dose (MED) of CBD for reducing cannabis use. • 94% of participants completed treatment as evidenced by medication compliance of at least 70% at each treatment week (for both self-report and returned medication) and attending all treatment week visits within two days of the scheduled appointment. • Period study was conducted: May 2014 to May 2018.
Inclusion Criteria	• 16 to 60 years of age. • Cannabis use disorder with at least moderate severity (DSM-5 criteria). • Desire to stop using cannabis, and intending to do so in the next month, based on an adapted Motivation To Stop Scale (MTSS). • At least one failed attempt to quit cannabis use. • Must co-administer cannabis with tobacco (i.e., most common method of cannabis use in Europe). • Urine sample positive for THC-COOH. • Capacity to give informed consent as defined by Good Clinical Practice (GCP) guidelines. • Females of childbearing potential: negative pregnancy test within seven days of starting treatment. • Male participants and females of childbearing potential: medically acceptable contraceptive method from the time consent was signed until six weeks after the discontinuation of treatment.
Exclusion Criteria	• Allergies to CBD, microcrystalline cellulose, or gelatin. • Currently using prescribed psychotropic drugs. • Use of illicit drugs (other than cannabis) more than twice per month at screening. • Evidence of inaccurate self-reported drug use (i.e., a positive urine test for a drug that was not reported during screening). • Current or prior diagnosis of a psychotic disorder (self-report). • Pregnant or breastfeeding. • Any physical health problem deemed clinically significant by the investigator team.

Citation	Freeman et al. (2020)
	• Not English speaking (cf. verbal assessments).
Assessment Time-Point/s	• Baseline: week 0. • During treatment: week 1 to 4 (site visit). • Follow-up: week 6, 12, 16 (site visit); week 8, 20, 24 (telephone).

Main Findings	• The interim Bayesian analysis indicated that the 200 mg CBD treatment was ineffective for reducing cannabis use, and this condition was eliminated from the study.
	• The final Bayesian analysis indicated that the 400 mg CBD and the 800 mg CBD conditions exceeded the prior probabilities for Most Effective Dose (MED) given the data [Pr (MED|Data > 0.9] on both primary outcomes:
	  o Cannabis use (urinary THC-COOH:creatinine):
	    ▪ 400 mg CBD group: Pr (MED|Data) = 0.9995.
	    ▪ 800 mg CBD group: Pr (MED|Data) = 0.9965.
	  o Cannabis abstinence (days per week; self-report):
	    ▪ 400 mg CBD group: Pr (MED|Data) = 0.9966.
	    ▪ 800 mg CBD group: Pr (MED|Data) = 0.9247.
	• Compared to placebo, 400 mg CBD decreased urinary THC-COOH:creatinine concentrations by -94.21 ng/ml (95% CI = -161.83 to -35.56) and increased cannabis abstinence by 0.48 days per week (95% CI = 0.15 to 0.82).
	• Compared to placebo, 800 mg CBD decreased urinary THC-COOH:creatinine concentrations by -72.02 ng/ml (95% CI = -135.47 to -19.52) and increased cannabis abstinence by 0.27 days per week (95% CI = -0.09 to 0.64).

Safety and Adverse Events	o CBD was well tolerated with no severe adverse events.
	o Mild adverse events (does not interfere with the participant's daily routine and does not require intervention; causes slight discomfort): 65 in placebo group; 42 in 200 mg group; 96 in the 400 mg group; 78 in 800 mg group. The number of mild adverse events did not differ between placebo and:
	  o 200 mg CBD (RR = 1.24; 95% CI = 0.73 to 2.09).
	  o 400 mg CBD (RR = 1.39; 95% CI = 0.91 to 2.14).
	  o 800 mg CBD (RR = 1.19; 95% CI = 0.77 to 1.86).
	o Moderate adverse events (interferes with some aspects of daily routine, or requires intervention, but is not damaging to health; causes moderate discomfort): 9 in placebo group; 4 in 200 mg group; 8 in 400 mg group; 8 in 800 mg group. The number of moderate adverse events did not differ between placebo and:
	  o 200 mg CBD (RR = 0.85; 95% CI = 0.26 to 2.58).
	  o 400 mg CBD (RR = 0.84; 95% CI = 0.35 to 2.24).
	  o 800 mg CBD (RR = 0.89; 95% CI = 0.40 to 2.45).
	o Severe adverse events (results in alteration, discomfort or disability which is clearly damaging to health): None recorded across all groups.

7. Natural Cannabis Extract (THC&CBD) for Cannabis Use Disorder (CUD): Combined intervention

Citation	Lintzeris et al. (2019)
Study Design	• Double-blind, randomised, placebo-controlled, trial.
Sample Size	• 60 participants (per-protocol sample). • 137 participants enrolled. • Nabiximols group: 64 participants randomised and 34 participants excluded for various reasons prior to the end of the 12-week trial protocol.

Citation	Lintzeris et al. (2019)
	• Placebo group: 73 participants randomised and 43 participants excluded for various reasons prior to the end of the 12-week trial protocol.
Population	• Australia. • Cannabis use disorder (ICD-10 criteria). • Treatment seeking. • I (nabiximols): M = 36.2 years (SD = 11.5); 74% male. • C (placebo): M = 33.8 years (SD = 10.3): 79% male.
Intervention/s (I) and Comparator/s (C)	• All participants were offered six sessions of individual (CBT-based) counselling, and weekly clinical reviews to titrate the dose (and optimise the effect) of their assigned medication. • All participants received an oromucosal spray. • I (n = 64) nabiximols (natural cannabis extract: THC&CBD); maximum of 32 sprays (86.4mg of THC and 80mg of CBD) per day in 4 divided doses. • C (n = 73) placebo (matched carrier and flavouring).

Outcome Measure/s	• Primary:
	  o Total days of self-reported illicit cannabis use (week 1 to 12; maximum 84 days): number of days of cannabis use in the preceding 28 days using Timeline Followback (TLFB) method (week 0, 4, 8, 12).
	• Secondary:
	  o Treatment retention (participants who completed the 12-week treatment protocol).
	  o Cannabis Problems Questionnaire (CPQ).
	  o Cannabis Withdrawal Scale (CWS).
	  o Marijuana Craving Questionnaire (MCQ).
	  o Fagerström Test for Nicotine Dependence (FTND).
	  o Alcohol Use Disorders Identification Test (AUDIT).
	  o Short Form Survey, 36-item (SF-36).
	  o Opioid Treatment Index (OTI); crime subscale.
	  o Adverse events (evaluated by a study medical officer).
	  o Opioid-Related Behaviours In Treatment (ORBIT) scale.

General	• All participants met ICD-10 criteria for a cannabis use disorder, with similar a baseline severity across the study conditions. • Period study was conducted: February 2016 to June 2017.
Inclusion Criteria	• Age range 18 to 65 years. • ICD-10 criteria for cannabis dependence. • Unable to cease cannabis use in previous quit attempts. • Able to provide informed consent and agree to study procedures (including not driving and using reliable contraception).
Exclusion Criteria	• Court-mandated addiction treatment. • Another substance use disorder (other than nicotine or caffeine). • Severe medical or psychiatric disorder (including a history of epilepsy or psychosis). • Treatment for cannabis dependence in the past month. • Pregnant or lactating women, or those planning pregnancy. • Unable to safely store medication. • Not available for follow-up.
Assessment Time-Point/s	• Baseline (week 0). • During intervention (week 4 and 8). • Post-intervention (week 12).

Citation	Lintzeris et al. (2019)
Main Findings	• In a modified intention-to-treat (ITT) analysis (defined as participants who attended all four assessment time-points across the 84-day trial; placebo: *n* = 36; nabiximols: *n* = 31), the placebo group reported significantly more days using cannabis (mean = 53.1 days; SD = 33.0 days) than the nabiximols group (mean = 35.0 days; SD = 32.4 days); the estimated difference, adjusted for baseline cannabis use, was 18.6 days (95% CI = 3.5 to 33.7 days; p = 0.02). With multilevel multiple-imputation, the estimated difference was 10.6 days (95% CI = 1.0 to 20.2 days; p = 0.04). In the per-protocol analysis, the estimated difference was 20.3 days (95% CI = 3.2 to 37.4 days; p = 0.02). • No significant between-group difference in treatment retention was observed (nabiximols group: 49.2%; placebo group: 44.8%; p-value not reported). • No significant between-group difference in abstinence rates (i.e., one or more 4-week periods of abstinence over the 12-week trial) was observed in the nabiximols group (26.5%) compared to the placebo group (18.2%; p = 0.31). • No significant between-group difference in cannabis-related problems (p = 0.91), cannabis withdrawal (p = 0.60), or cannabis craving (p = 0.56), was observed. • No significant between-group difference in nicotine use (p = 0.85), or alcohol use (p = 0.28), was observed. • Significant improvements in various dimensions of health-related quality of life (as measured by the SF-36) were observed for both groups over time (e.g., energy; emotional wellbeing; social; pain). However, there were no significant between-group differences observed. • The proportion of participants who correctly guessed their allocation to study condition was significantly lower in the placebo (n = 27/55; 49.1%) group than in the nabiximols (n = 42/51; 82.4%) group (odds ratio = 0.21; 95% CI = 0.08 to 0.50; p = 0.001).
Safety and Adverse Events	• Study medications were generally well tolerated with no significant between-group differences in adverse events. • 32 participants reported an adverse event: 17 of 67 (25.4%) participants in the placebo group, and 15 of 61 (24.6%) participants in the nabiximols group. • 14 participants reported two or more adverse events. • Headache was the only adverse event reported by more than 5% of participants (n = 7/128; 5.5%): 2 of 67 (3.0%) participants in the placebo group, and 5 of 61 (8.2%) participants in the nabiximols group. • One serious adverse event was reported by a participant in the placebo group who was hospitalised for suicidal ideation in the first week of the study and subsequently discontinued treatment.

8. Natural Cannabis Extract (THC&CBD) for Cannabis Use Disorder (CUD): Combined intervention

Citation	Trigo et al. (2018)
Study Design	• Double-blind, randomised, placebo-controlled, trial.
Sample Size	• 27 participants (per-protocol sample). • 50 participants enrolled; 10 participants withdrew prior to the first dosing session; randomised in blocks of 10. • Nabiximols group: 7 of the 20 participants did not complete the 12-week trial protocol. • Placebo group: 6 of the 20 participants did not complete the 12-week trial protocol.

Citation	Trigo et al. (2018)
Population	• Canada. • Cannabis use disorder (DSM-IV criteria). • Treatment seeking.
Intervention/s (I) and Comparator/s (C)	• All participants received 12 (1-hour) sessions (one session per week) of Motivational Enhancement Therapy and Cognitive Behavioural Therapy (MET/CBT). • All participants received an oromucosal spray (weekly) and were instructed to self-titrate the study medication. • I (n = 20): nabiximols (natural cannabis extract: THC&CBD); maximum of 42 sprays (113.4mg of THC and 105mg of CBD) per day. • C (n = 20): placebo (matched carrier and flavouring).

Outcome Measure/s	Primary:
	• Tolerability of the self-titrated dose of oromucosal spray (sprays per day); self-report using the smoking diary.
	• Cannabis use and abstinence:
	   ○ total average cannabis intake (grams per week); self-report using the Timeline Followback (TLFB) method (week 0) and smoking diary (week 1 to 12).
	   ○ regular ten-panel urine drug tests were performed and blood samples were collected for cannabinoid analyses (NB: THC is present in nabiximols so abstinence relied on self-report).
	• Marijuana Craving Questionnaire – Short Form (MCQ-SF).
	• Marijuana Withdrawal Checklist (MWC).
	Secondary:
	• Brief Psychiatric Rating Scale (BPRS).
	• Systematic Assessment for Treatment Emergent Events (SAFTEE).
	• Hamilton Anxiety Scale (HAM-A).
	• Hamilton Depression Rating Scale (HDRS).
	• Timeline Followback (TLFB) method for tobacco, caffeine, and alcohol.
	• Fagerstrom Test for Nicotine Dependence (FTND).
	• Addiction Severity Index (ASI).
	• Beck Depression Inventory (BDI).
	• Drug Effects Questionnaire (DEQ).
	• Profile of Mood States.
	• St Mary's Hospital Sleep Questionnaire (SMHSQ).

General	• All participants met DSM-IV criteria for current cannabis dependence. • Participants were compensated up to CDN $855.00 for their time. • Twice-weekly visits (week 1 to 12): One weekly visit was for the MET/CBT group therapy session. The other weekly visit was for clinical review and completion of assessments. • Maximum doses of nabiximols were reached at day 10 of the treatment course. • The target quit date for cannabis was set at day 21. • Participants were provided with a "smoking diary" during the first study visit and instructed to enter information regarding the frequency of cannabis and medication use each study day. • Period study was conducted: March 2013 to November 2015.
Inclusion Criteria	• 18 to 65 years. • Cannabis is primary drug of abuse. • Cannabis use at least 5 days a week for at least one month. • Positive urine drug screen for cannabinoids.

Citation	Trigo et al. (2018)
	• Smoke equivalent of four or less joints per day (or four grams per day if cannabis is smoked in other forms). • Physically healthy based on medical history, physical exam, vitals, ECG and chemistry and haematological laboratory results. • Willing to use appropriate contraceptive method throughout the study. • Able to understand, and willing to comply with, study requirements and restrictions.
Exclusion Criteria	• Current Axis I Disorder (DSM-IV criteria) including a substance use disorder other than cannabis, nicotine, or caffeine dependence. • Currently taking psychotropic medication for any indication other than treatment of insomnia. • First-degree relative with schizophrenia. • History of seizures, cardiovascular disease, or pulmonary disease (e.g., asthma or COPD). • Clinically significant pathology in oral cavity and poor oral hygiene. • Known sensitivity to dronabinol, cannabidiol, propylene glycol, ethanol, or peppermint oil (used in Sativex buccal spray). • Unstable medical conditions. • Pregnant or breastfeeding. • Occupational role that involves driving or operating heavy machinery.
Assessment Time-Point/s	• Baseline (week 0). • During treatment (week 1 to 12).

Main Findings	• Tolerability (self-titrated dose of oromucosal spray): weekly average of sprays per day.
	  o Nabiximols group: 4.1 to 12.8 sprays per day (i.e., 11.0 mg THC & 10.2 mg CBD to 34.5 mg THC & 31.9 mg CBD).
	  o Placebo group: 2.5 to 9.7 sprays per day.
	• Cannabis abstinence:
	  o The rate of cannabis abstinence (seven-day point prevalence) measured one week after the medication phase was 30.8% (n = 4) for the nabiximols group and 42.9% (n = 6) for the placebo group.
	  o There was no significant difference in abstinence rates between the two groups ($p < 0.05$).
	• Quantity and frequency of cannabis use (baseline to end-of-treatment):
	  o Baseline: Participants were using cannabis an average of 6.4 days/week (SD = 1.3) and consuming an average of 6.0 grams/week (SD = 5.0).
	    ▪ Nabiximols group (n = 20): using an average of 6.7 days/week (SD = 0.8), consuming 6.2 grams/week (SD = 5.0).
	    ▪ Placebo group (n = 20): using an average of 6 days/week (SD = 1.8), consuming an average of 5.9 grams/week (SD = 5.0).
	  o Quantity of cannabis use (grams):
	    ▪ Nabiximols group: 70.5% reduction in cannabis use (from 6.1 to 1.8 grams).
	    ▪ Placebo group: 42.6% reduction in cannabis use (from 5.4 to 3.1 grams).
	    ▪ Quantity of cannabis use (grams) decreased over time ($p < 0.001$). However, no significant between-group differences in cannabis use (grams) were observed ($p = 0.179$), and cannabis use (grams) did not significantly differ between the nabiximols and placebo groups over time ($p = 0.664$).
	  o Quantity of cannabis use (grams) sub-group analysis (high vs. low medication use):

Citation	Trigo et al. (2018)
	- There was high variability in the number of sprays used by participants. Thus, an additional analysis of the study outcomes was performed by sub-dividing each treatment group into a high medication user sub-group (at least 20 sprays on any treatment day; nabiximols: n = 5; placebo: n = 3) and a low medication user sub-group (less than 20 sprays on all treatment days; nabiximols: n = 8; placebo: n = 11). - There was a trend for a reduction in cannabis use (grams) for the high medication use sub-groups (nabiximols vs. placebo), whereas cannabis use (grams) was similar in the nabiximols and placebo groups in the low medication use sub-groups. - In the high medication subgroups, cannabis use (grams) significantly decreased over time (p < 0.001); no significant between-group difference in cannabis use (grams) was observed (p = 0.098); and cannabis use (grams) significantly differed between the nabiximols and placebo group over time (p < 0.01). Nonetheless, a follow-up analysis indicated no significant differences between groups at any timepoint during treatment. - Frequency of cannabis use (% days per week): - Frequency of cannabis use (% days per week) decreased over time (p < 0.001). However, no significant between-group differences in cannabis use (% days per week) were observed (p = 0.298), and cannabis use (% days per week) did not significantly differ between the nabiximols and placebo groups over time (p = 0.221). - Cannabis craving (as measured by the MCQ-SF): - Cannabis craving decreased over time (p < 0.001). No significant between-group difference in craving was observed (p = 0.438). However, there was a significant difference in craving between the nabiximols and placebo groups over time (p < 0.05). A follow-up analysis indicated this difference appeared to be primarily driven by higher craving scores in the placebo condition (relative to the nabiximols condition) at the week-7 timepoint. - Cannabis withdrawal (as measured by the MWC): - Cannabis withdrawal decreased over time ($p < 0.001$). However, no significant between-group difference in cannabis withdrawal was observed (p = 0.593), and cannabis withdrawal did not significantly differ for the nabiximols and placebo groups over time (p = 0.601).
Safety and Adverse Events	- Medication was well tolerated, and no serious adverse events were observed in either study condition. - The rate of adverse events did not significantly differ between the study conditions (p = 0.654). - The observed adverse events included some expected side effects of the study medication (e.g., sleep problems, headaches, or diarrhoea), and some events that were deemed unrelated to the study medication (e.g., mild cold, tension headache, or hot flashes).

9. Synthetic Cannabinoid (THC) for Cannabis Use Disorder (CUD): Combined intervention

Citation	Hill et al. (2017)
Study Design	Double-blind, randomised, placebo-controlled, trial.
Sample Size	18 participants (intention-to-treat analysis).

Citation	Hill et al. (2017)
	• Nabilone group: 10 participants randomised; 4 participants did not complete the 10-week trial protocol. • Placebo group: 8 participants randomised; 2 participants did not complete the 10-week trial protocol.
Population	• United States. • Cannabis use disorder (DSM-IV criteria). • Treatment seeking. • I [nabilone]: M = 24.4 years (SD = 5.2); 70% male. • C [placebo]: M = 28.9 years (SD = 7.5): 63% male.
Intervention/s (I) and Comparator/s I	• All participants received 10 sessions (one session per week) of physician-guided Medical Management (MM; 45-minute initial session; 15- to 25-minute follow-up sessions). • All participants received oral capsules (one per day) containing riboflavin (25 mg) to confirm medication adherence. 1. I (n = 10): 2 mg nabilone (synthetic THC). 2. C (n = 8): placebo (agent not specified).
Outcome Measure/s	Primary: Cannabis use (baseline to end of treatment): • Urinalysis (THC-COOH:creatinine). • Timeline Followback (TLFB) method (self-report): days of use, use sessions per day, and inhalations per day. Secondary: • Marijuana Craving Questionnaire (MCQ). • Beck Anxiety Inventory (BAI). • Quick Inventory for Depressive Symptoms (QIDS).
General	• Medical management (MM) sessions aimed to approximate a primary care approach and included monitoring of medication side effects, providing strategies to increase medication adherence, and supporting abstinence. The treatment was delivered by a medical professional. • The nabilone (synthetic THC) dose was titrated up to 2 mg per day (initially 0.5 mg daily for 7 days; increased to 1 mg daily for 7 days; increased to 1.5 mg daily for 7 days; increased to 2 mg daily for 4 weeks) before tapering the medication over the final 3 weeks of the study (by reversing the titration schedule). • Participants were compensated up to US $955 for study participation. • Period study was conducted: September 2010 to June 2017.
Inclusion Criteria	• 18 to 45 years old. • DSM-IV diagnosis of cannabis dependence as determined by the Structured Clinical Interview for DSM-IV (SCID). • Desire to quit cannabis use within the next 30 days. • Cannabis use on more than 4 days within the past 30 days. • For women of childbearing age, a negative pregnancy test at screening with agreement to use adequate contraception to prevent pregnancy, and monthly pregnancy tests. • Willing and able to sign informed consent.
Exclusion Criteria	• Current diagnosis of other drug or alcohol dependence (excluding caffeine and nicotine). • Recent (last 3 months) significant cardiac disease. • Current serious psychiatric illness or history of psychosis, schizophrenia, or bipolar I disorder. • Mental retardation or organic mental disorder. • Acutely dangerous or suicidal behaviour

Citation	Hill et al. (2017)
	• Currently in a residential treatment setting. • History of seizures, head trauma, or other history of central nervous system injury. • Current treatment with opioid analgesics, sedative hypnotics, or other known central nervous system depressants. • Disease of the gastrointestinal system, liver, or kidneys that may impede metabolism or excretion of nabilone. • Pregnant or breastfeeding, or using inadequate contraception. • Known hypersensitivity to cannabinoids or sesame oil. • Inability to read or write in English. • Unwilling or unable to participate in MRI scanning (e.g., those having pacemakers, bone plates, screws, etc.; claustrophobia).
Assessment Time-Point/s	• Baseline: cannabis use (urinalysis and self-report using the TLFB method); symptoms of anxiety and depression (as measured by BAI and QIDS). • During treatment (week 1 to 10): cannabis use (urinalysis twice per week; TLFB once per week); cannabis craving (MCQ once per week); and anxiety and depression symptoms (as measured by the BAI and QIDS: week 4, 10, and 14). • Follow-up (week 14; 4 weeks post-treatment).
Main Findings	• During the 10-week treatment period, the nabilone group reported an average of 2.55 (± 0.86) cannabis use sessions per day, and the placebo group reported an average of 3.14 (± 1.91) cannabis use sessions per day. • There was no significant effect of the treatment on changes in cannabis use sessions for the nabilone group compared with the placebo group at the end of treatment ($z = -1.05$, $p = 0.29$) or at the 4-week follow-up ($z = 0.63$, $p = 0.53$). • There was no significant effect of the treatment on changes in urine cannabinoid levels for the nabilone group compared with the placebo group at the end of treatment ($z = 1.39$, $p = 0.17$) or at the 4-week follow-up ($z = 0.96$, $p = 0.34$). • A reduction in cannabis craving (as measured by the MCQ) was observed in both the nabilone and placebo group; however, there were no significant between-group differences at the end of treatment ($z = -0.34$, $p = 0.74$) or at the 4-week follow-up ($z = -0.40$, $p = 0.69$). • There were no significant changes in anxiety symptoms (as measured by the BAI) between the two groups at the end of treatment ($z = 0.68$, $p = 0.50$) or at the 4-week follow-up ($z = -0.10$, $p = 0.92$). • There was no significant difference in depressive symptoms (as measured by the QIDS) between groups at the end of treatment ($z = 0.76$, $p = 0.46$) or at the 4-week follow-up ($z = 0.91$, $p = 0.36$).

Safety and Adverse Events	• No serious adverse events were reported.
	• All reported adverse events were rated mild-to-moderate.
	• Eight adverse events were reported by two participants in the nabilone group.
	• Six adverse events were reported by four participants in the placebo group.
	• Nausea, vomiting, and sedation were the most reported adverse events:
	  o nausea was reported by one participant in both the nabilone and the placebo groups.
	  o vomiting was reported by two participants in the placebo group.
	  o sedation was reported by one participant in both groups.

10. Synthetic Cannabidiol (CBD) for Cocaine Use disorder (CocUD): Combined intervention

Citation	Meneses-Gaya et al. (2021)
Study Design	• Double-blind, randomised, placebo-controlled, trial.
Sample Size	• 31 participants (intention-to-treat sample). • 6 participants dropped out of the study and left the specialised therapeutic community unit. • CBD group: 14 participants randomised; 3 participants did not complete the 10-day trial protocol. • Placebo group: 17 participants randomised; 3 participants did not complete the 10-day trial protocol.
Population	• Brazil. • Crack-cocaine dependence (DSM-IV criteria). • Treatment seeking. • 100% male. • I [CBD]: M = 32.5 years (SD = 6.9). • C [placebo]: M = 33.2 years (SD = 6.9).
Intervention/s (I) and Comparator/s (C)	• All participants received two (150 mg) oral capsules per day and were offered weekly group psychotherapy. • I (n = 14): 300 mg CBD (99.9% pure CBD powder). • C (n = 17): placebo (corn oil).
Outcome Measure/s	Primary: Crack cocaine craving 1. Cocaine Craving Questionnaire – Brief (CCQ-Brief). 2. Minnesota Cocaine Craving Scale (MCCS). Secondary: 3. Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST). 4. Beck Depression Inventory (BDI). 5. Beck Anxiety Inventory (BAI). • Visual Analog Sleep Scales: sleep disturbance; sleep effectiveness; and sleep supplementation. • UKU Side Effects Rating Scale (UKU-SERS).
General	• The trial site was a therapeutic community unit specialising in the treatment of substance-related disorders, which receives patient referrals from the Brazilian public health system. • During the study, participants were offered weekly group psychotherapy as the standard psychosocial intervention provided by the institution. • For the craving induction procedure, participants were shown a (3-minute) video with "places (areas of drug use known by users), scenes of real crack use, and objects related to crack use (crack rocks, handling of the drug, preparation of the pipe, other instruments involved in the use of crack-cocaine)" (p. 469). • The study employed a modified intention-to-treat analysis (defined as all participants with at least one post-baseline craving assessment). • The efficacy of the treatment (CBD vs. placebo) was tested using a mixed model repeated-measures analysis of variance (RMANOVA), which allows patients with incomplete data to be included, and utilises the data that is available for all participants. • Period study was conducted: not reported.
Inclusion Criteria	• 18 years of age and older. • DSM-IV diagnosis of crack-cocaine dependence as determined by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). • Abstinence for a maximum of 30 days (ranging from 8 to 30 days).

Citation	Meneses-Gaya et al. (2021)
	• Agreed to participate by signing an informed consent form.
Exclusion Criteria	• Current major psychiatric comorbidity (DSM-IV criteria). • Currently taking antidepressants or antipsychotics. • Severe or unstable medical conditions including chronic infectious disease. • History of brain injury with loss of consciousness. • History of allergies or idiosyncratic reactions to Cannabis sativa. • Illiterate or functionally illiterate.
Assessment Time-Point/s	• Baseline: ASSIST, CCQ-Brief, MCCS, BDI, BAI, VAS. • Day 1 to 10: Daily assessment of crack-cocaine craving (before and after the craving-induction procedure): CCQ-Brief, MCCS. • Day 10: CCQ-Brief, MCCS, BDI, BAI, VAS, and UKU-SERS.

Main Findings	• Primary: Cocaine craving (as measured by the CCQ-Brief and MCCS):
	   o Cocaine craving significantly decreased over the 10-day trial (CCQ-Brief: p < 0.001; MCCS: p < 0.001). However, no between-group difference in craving was observed (CCQ-Brief: p = 0.116; MCCS: p = 0.130), and craving did not significantly differ for the CBD and placebo groups over time (CCQ-Brief: p = 0.897; MCCS: p = 0.113).
	 • Secondary:
	   o Significant reductions in anxiety symptoms (as measured by the BAI) were observed in both groups (CBD group: p = 0.02; placebo group: p < 0.01), but no significant differences were observed between groups (p = 0.80).
	   o Significant reductions in depression symptoms (as measured by the BDI) were observed in both groups (CBD group: p = 0.06; placebo group: p < 0.01), but no significant differences were observed between groups (p = 0.46).
	   o No significant differences were observed in sleep disturbance, sleep effectiveness, or sleep supplementation (as measured by the Visual Analogue Sleep Scales) in both groups (all p's > 0.05), and no significant differences were observed between groups (all p's > 0.05).

Safety and Adverse Events	• No serious adverse event occurred during the trial.
	 • All adverse events were of mild or moderate severity.
	 • The adverse events (as measured by the UKU-SERS) were:
	   o sleepiness and increased sleep duration (five participants in the CBD group and three participants in the placebo group; p = 0.45);
	   o nausea (two participants in the CBD group and one participant in the placebo group; p = 0.59); and
	   o headache (two participants in the CBD group and one participant in the placebo group; p = 0.59).
	 • The frequency of adverse events did not differ between groups (p = 0.34).

11. Synthetic Cannabidiol (CBD) for Cocaine Use Disorder (CocUD): Combined intervention

Citation	Mongeau-Pérusse et al. (2021)
Study Design	• Double-blind, randomised, placebo-controlled, trial.
Sample Size	• 50 participants (per-protocol sample). • 78 participants randomised and 28 participants did not complete the trial for various reasons (i.e., treatment refusal; investigator decision; lost to follow-up; study withdrawal).

Citation	Mongeau-Pérusse et al. (2021)
	• CBD group: 40 participants randomised and 13 participants excluded for various reasons (5 participants did not complete Phase I; and 8 participants did not complete Phase II). • Placebo group: 38 participants randomised and 15 participants excluded for various reasons (11 participants did not complete Phase I; and 4 participants did not complete Phase II).
Population	• Canada. • Cocaine use disorder (DSM-5 criteria). • Treatment seeking. • I [CBD]: M = 46.0 years (SD = 10.7); 82.5% male. • C [placebo]: M = 45.8 years (SD = 11.8); 81.6% male.
Intervention/s (I) and Comparator/s (C)	• All participants received an oral solution and were offered group psychotherapy. • Phase I (10-day inpatient detoxification): nurse-administered medication provided every day with group psychoeducation session and standard medical care. • Phase II (12-week outpatient follow-up): self-administered medication provided every week with group relapse prevention session and standard medical follow-up. • I (n = 40): 800 mg CBD. • C (n = 38): matched placebo.

Outcome Measure/s	• Phase I (10-day inpatient detoxification):
	  ○ Primary: drug-cue-induced craving as measured by the Visual Analog Scale for Craving (VAS-C; self-report) during a guided-imagery session (drug, stress, and neutral cues) on day 8.
	  ○ Secondary: stress-cue-induced craving as measured by the Visual Analog Scale for Craving (VAS-C; self-report) during a guided-imagery session (drug, stress, and neutral cues) on day 8.
	• Phase II (12-week outpatient):
	  ○ Primary: Time-to-relapse cocaine use (number of days from inpatient discharge to first cocaine use) using the Timeline Followback (TLFB) method (self-report) and weekly urinalysis.
	  ○ Secondary: Cocaine use (% positive urine tests out of the 12 urine samples collected during follow-up).
	• Blood pressure (BP) and heart rate (HR).

General	• The trial was divided into two phases: a 10-day inpatient detoxification (Phase I) followed by a 12-week outpatient follow-up (Phase II). • Only participants who remained inpatient for all 10 days (Phase I) were eligible for Phase II. • Participants who were lost to follow-up (Phase II) were considered to have relapsed. • All missing urine tests were considered positive. • Participants were compensated up to $400.00 for study participation. • Period study was conducted: July 2016 to June 2019.
Inclusion Criteria	• 18 to 65 years of age. • Cocaine use disorder as determined by the Structured Clinical Interview for DSM-5 (SCID-5). • Cocaine use in the two-week period prior to the inpatient (detoxification) admission using the Timeline Followback (TLFB) method. • English or French speaking. • Able to provide informed consent.

Citation	Mongeau-Pérusse et al. (2021)
Exclusion Criteria	• Severe and/or unstable medical or psychiatric condition. • Immunodeficiency. • Hypersensitivity to cannabinoids, or undergoing treatment with medications that interact with CBD. • Diagnosed with another substance use disorder (except nicotine) requiring treatment. • Individuals planning to conceive within the year. • Men with a history of fertility problems. • Women who were pregnant or breastfeeding, or women of childbearing age who were not prepared to use a medically acceptable form of contraception.

Assessment Time-Point/s	• Phase I (inpatient: day 1 to 10):
	  ○ Day 1 to 10: blood pressure (BP) and heart rate (HR) three times per day.
	  ○ Day 6: drafting of (5-minute) personalised, script-driven, guided imagery scenarios.
	  ○ Day 8: guided-imagery session to measure cue-induced craving to drug-related, stress-related, and neutral cues.
	• Phase II (outpatient: week 1 to 12):
	  ○ Week 1 to 12: Biological sampling (urine and blood) and self-report measures collected.
	  ○ Week 4, 8, and 12: Standard medical follow-up to ensure participants' safety.

Main Findings	• Cannabis craving (Phase I end-point):
	  ○ At day 8, no significant change from baseline craving scores (as measured by the VAS-C; adjusted for gender and baseline SDS score) were observed for the CBD group (n = 36) compared with the placebo group (n = 28) following exposure to the drug-related cues (p = 0.069), stress-related cues (p = 0.887), or neutral cues (p = 0.222).
	• Time-to-relapse cocaine use (Phase II end-point):
	  ○ The median time to relapse cocaine use was four (4) days for the CBD group and seven (7) days for the placebo group.
	  ○ By week 12, all but three participants had relapsed to cocaine use (CBD group: *n* = 33/34; placebo group: *n* = 25/27).
	  ○ The risk of relapse to cocaine use was similar in the CBD group and placebo group (hazard ratio = 1.20, 95% CI = 0.65 to 2.20, p = 0.512; Bayes factor = 0.152).
	• Attendance of psychotherapy sessions:
	  ○ Phase I (10-day inpatient): At least one group therapy session was attended by 62.5% (n = 25/40) of participants in the CBD group and 60.5% (n = 23/38) of participants in the placebo group.
	  ○ Phase II (12-week outpatient): At least one group therapy session was attended by 35.3% (n = 12/34) of participants in the CBD group and 51.9% (n = 14/27) of participants in the placebo group.

Safety and Adverse Events	• The CBD treatment was reportedly well tolerated. • In the CBD group, 42.5% (n = 17/40) participants reported at least one adverse event that was deemed to be medication-related by a blinded study physician. • The most frequent adverse events included diarrhoea (n = 14/40; 35.0%) and nausea (n = 3/40; 7.5%).

12. Natural Dried Cannabis (THC±CBD) for Post-Traumatic Stress Disorder (PTSD): Standalone intervention

Citation	Bonn-Miller et al. (2021)
Study Design	• Double-blind, randomised, placebo-controlled trial. • Crossover design.
Sample Size	• 76 participants (Stage I per-protocol sample). • 80 participants were randomised to conditions. • 4 participants withdrew due to adverse effects prior to completing Stage I and were excluded from the analysis of the primary outcome measure (High THC: 1 participant; High CBD: 1 participant; THC+CBD: 2 participants). • By the end of Stage II, a significant proportion of participants (16.3%; n = 13/80) had dropped out of the study due to adverse events (8) and voluntary withdrawal (5).
Population	• United States. • Post-Traumatic Stress Disorder (DSM-5 criteria). • I [High THC]: M = 45.0 years (SD = 16.6); 95.0% male. • I [High CBD]: M = 40.4 years (SD = 11.2); 90.0% male. • I [THC+CBD]: M = 50.6 years (SD = 13.3); 85.0% male. • C [placebo]: M = 43.7 years (SD = 12.5); 90.0% male.
Intervention/s (I) and Comparator/s (C)	• Two stage trial (n = Stage I, n = Stage II). • I (n = 19, 29) High THC (12% THC/<0.05% CBD; 1.8 g/day smoked). • I (n = 19, 27) High CBD (0.5% THC/11% CBD; 1.8 g/day smoked). • I (n = 18, 18) THC+CBD (7.9% THC/8.1% CBD; 1.8 g/day smoked). • C (n = 20, 0) placebo (< 0.03% THC/< 0.01% CBD; 1.8 g/day smoked).
Outcome Measure/s	Primary: • Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). Secondary: • PTSD Checklist for DSM-5 (PCL-5). • Inventory of Depression and Anxiety Symptoms (IDAS). • Inventory of Psychosocial Functioning (IPF). • Insomnia Severity Index (ISI).
General	• After completion of Stage I, participants were re-randomised to three groups: high THC, high CBD, or combined THC+CBD groups for Stage II. • To measure the validity of study blinding, participants and clinicians were asked to guess whether the participant was randomised to an active treatment (high THC, high CBD, THC+CBD) or placebo treatment at the end of Stage I. • The study blind was maintained when participants were assigned to high CBD and placebo, but not when participants were assigned to high THC or THC+CBD (100% of participants and clinicians accurately guessed that participants assigned to high THC or THC+CBD were randomised to an active treatment). • Period study was conducted: January 2017 to January 2019.
Inclusion Criteria	• 18 years old and older. • US military veteran. • PTSD symptoms of at least six months duration according to DSM-5 criteria. • Moderate to severe PTSD (CAPS-5 score of ≥ 25) at baseline. • Abstain from cannabis use two-weeks prior to baseline, verified by urine toxicology screening. • Abstain from using non-study cannabis throughout the study period. • Stable on any pre-study medications and/or psychotherapy prior to study entry.

Citation	Bonn-Miller et al. (2021)
	• Agree to comply with study procedures.
Exclusion Criteria	• Allergies to cannabis or other contraindication for smoking cannabis. • Moderate-severe cannabis use disorder (DSM-5 criteria; CUDIT-R score ≥ 11). • Current or past serious mental illness as determined by the Structured Clinical Interview for DSM-5 – Research Version (SCID-5-RV). • Family history of psychotic or bipolar disorder. • High risk of suicide as determined by the C-SSRS. • Current diagnosis or evidence of significant or uncontrolled haematological, endocrine, cerebrovascular, cardiovascular, coronary, pulmonary, gastrointestinal, immunocompromising, or neurological disease. • Positive screen for any illicit substance other than cannabis between stages. • Pregnant, nursing, or of childbearing potential and not practicing an effective means of birth control. • Unable to provide informed consent.
Assessment Time-Point/s	Two stage trial with a two-week washout period between stages. • Baseline: primary and secondary outcome measures. • Stage I (visit 1 to 5): two consecutive self-administration sessions followed by three weeks of ad-libitum use; outcome measures assessed. • Cessation period I (visit 6 to 7): secondary outcome measures collected; Stage II baseline measures collected. • Stage II (visit 8 to 12): two consecutive self-administration sessions followed by three weeks of ad-libitum use; outcome measures assessed. • Cessation period II (visit 13 to 14): all outcome measures assessed.

Main Findings	• In Stage I, no significant between-group differences in change scores (baseline to end of treatment: visit 0 to visit 7) were observed for PTSD severity (as measured by the CAPS-5; $p = 0.15$).
	• However, in Stage I, significant within-participant reductions in PTSD severity were observed for all four treatment groups from baseline to end of treatment (visit 0 to visit 5; all p's < 0.05).
	   ○ Placebo group reported a mean reduction of 13.1 (SD = 12.1) points (p = 0.0002).
	   ○ High THC group reported a mean reduction of 15.2 (SD = 11.3) points (p < 0.0001).
	   ○ High CBD group reported a mean reduction of 8.4 (SD = 10.09) points (p = 0.0181).
	   ○ THC+CBD group reported a mean reduction of 8.5 (SD = 9.88) points (p = 0.0143).
	• Additionally, in Stage I, no significant between-group differences in change scores (visit 0 to visit 6) were observed for self-reported (past week) PTSD symptoms, depression and anxiety symptoms, psychosocial functioning, and insomnia severity (as measured by the PCL-5, IDAS, ISI, and IPF, respectively).
	• In Stage II, significant between-group differences in change scores (baseline to end of treatment: visit 7 to visit 12) were observed for PTSD severity (as measured by CAPS-5; $p = 0.0019$).
	• The authors reported that the follow-up contrasts indicated significant differences in change scores between participants in the high THC and THC+CBD groups (95% CI: 3.82 to 18.88), and between participants in the high CBD and THC+CBD groups (95% CI: 1.19 to 15.86).
	• Notably, in Stage II, a significant within-participant reduction in PTSD symptoms (from baseline to end of treatment: visit 7 to visit 12) was observed for the combined THC+CBD group ($p = .0027$), but not for the high THC ($p = 0.25$) or high CBD ($p = 0.99$) groups.

Citation	Bonn-Miller et al. (2021)
Safety and Adverse Events	37 participants (61.7%) who received an active treatment reported at least one treatment-related adverse effect by the end of Stage I. 45 participants (60.8%) who received an active treatment reported at least one treatment-related adverse effect by the end of Stage II. - The number of participants reporting adverse effects did not significantly differ between treatment groups in either stage (Stage I: $p = 0.38$; Stage II: $p = 0.27$). - The most common adverse effects reported were cough (12.3%), throat irritation (11.7%), and anxiety (10.4%).

Appendix 8: Risk of Bias Assessments (RoB2)

Medicinal Cannabis: Standalone and combined interventions (n = 12)

#	Study	Intervention	Comparator	D1	DS	D2	D3	D4	D5		Overall	n
1	Masataka (2019)	Cannabidiol (CBD) – oral solution	Placebo	--		x	x	--	--		x	40
2	Kayser et al. (2020)	Cannabinoid (THC±CBD) – smoked dried cannabis	Placebo	+	+	x	x	--	+		x	14
3	Schlienz et al. (2018)	Dronabinol (synthetic THC) – oral capsules	Placebo	+	--	x	x	--	x		x	16
4	Hurd et al. (2019)	Cannabidiol (CBD) – oral solution	Placebo	+		x	x	--	+		x	50
5	Hindocha et al. (2018)	Cannabidiol (CBD) – oral capsules	Placebo	+	+	x	x	+	--		x	44
6	Freeman et al. (2020)	Cannabidiol (CBD) – oral capsules	Placebo	+		+	+	+	+		+	82
7	Lintzeris et al. (2019)	Nabiximols (THC+CBD) – oromucosal spray	Placebo	+		x	x	x	+		x	137
8	Trigo et al. (2018)	Nabiximols (THC+CBD) – oromuscosal spray	Placebo	+		--	x	--	+		x	50
9	Hill et al. (2017)	Nabilone (synthetic THC) – oral capsules	Placebo	--		--	x	--	+		x	18
10	Meneses-Gaya et al. (2021)	Cannabidiol (CBD) – oral capsules	Placebo	--		+	x	+	--		x	31
11	Mongeau-Pérusse et al. (2021)	Cannabidiol (CBD) – oral solution	Placebo	+		x	x	+	+		x	78
12	Bonn-Miller et al. (2021)	Cannabinoid (THC±CBD) – smoked dried cannabis	Placebo	--	x	--	x	x	+		x	80

Notes. n = sample size.

Risk of Bias Domains		Risk of Bias Judgments	Symbol
D1. Bias arising from the randomisation process. DS. Bias arising from period and carryover effects.		Low risk	+
D2. Bias due to deviations from the intended interventions. D3. Bias due to missing outcome data.		Some concerns	--
D4. Bias in measurement of the outcome. D5. Bias in selection of the reported result.		High risk	x

Appendix 9: GRADE Certainty of Evidence Summaries

Intervention (no. of studies)	Design (no. of studies)	RoB Assessments (no. of studies)	Precision and Consistency	Directness	Publication Bias	GRADE Summary[1,2]
Natural or synthetic cannabidiol (CBD) (6)	Parallel arm RCT (5) Crossover RCT (1)	Serious (5 high risk; 0 some concerns; 1 low risk)	Serious	Not serious, borderline	Not suspected, pending further analysis	Very Low ⊕
Natural cannabis extract (THC+CBD) (2)	Parallel arm RCT (2)	Very serious (2 high risk; 0 some concerns; 0 low risk)	Serious	Not serious	Not suspected	Very Low ⊕
Dried cannabis (THC±CBD) (2)	Crossover RCT (2)	Serious (2 high risk; 0 some concerns; 0 low risk)	Not serious	Serious	Not suspected	Very Low ⊕
Synthetic cannabinoid (THC) (2)	Parallel arm RCT (1) Crossover RCT (1)	Serious (2 high risk; 0 some concerns; 0 low risk)	Serious	Not serious, borderline	Not suspected	Very Low ⊕

Notes. CBD = Cannabidiol. RCT= Randomised controlled trial. RoB = Risk of bias. THC = Tetrahydrocannabinol. 1. GRADE summary includes the risk of bias assessments, precision of the effect estimates, consistency of the individual study results, how directly the evidence answers the question of interest, and risk of publication or reporting biases (NHMRC, 2019). 2. Commonly used symbols to describe the certainty of evidence in evidence profiles: High ⊕⊕⊕⊕, Moderate ⊕⊕⊕, Low ⊕⊕, and Very Low ⊕.

The interpretation of the four levels of evidence used in the evidence summaries are as follows:

GRADE	Definition
High ⊕⊕⊕⊕	High confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect.
Moderate ⊕⊕⊕	Moderate confidence in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low ⊕⊕	Limited confidence in the effect estimate: the true effect may be substantially different from the estimate of the effect.
Very Low ⊕	Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Source: Adapted from NHMRC (2019).

1. GRADE rating of natural or synthetic cannabidiol (CBD) studies

GRADE domain	Judgement	Concerns about certainty domains
Study limitations (risk of bias)	Of the six studies of (natural or synthetic) CBD, five studies (Hindocha et al., 2018; Hurd et al., 2019; Masataka, 2019; Meneses-Gaya et al., 2021; Mongeau-Pérusse et al., 2021) were judged to have a high risk of bias; primarily due to concerns with missing outcome data. Of the five studies with a high risk of bias, four studies (Hindocha et al., 2018; Hurd et al., 2019; Masataka, 2019; Mongeau-Pérusse et al., 2021) inappropriately used per-protocol analysis (rather than intention-to-treat analysis). Therefore, the studies were judged to have serious methodological limitations.	Serious
Precision and Consistency	The total number of participants enrolled in the six studies was 325; however, 59 participants (18%) did not complete the studies for various reasons (range of non-completion across studies: 7.5% to 35.9%). Of the six studies, three studies (Freeman et al., 2020; Hurd et al., 2019; Masataka, 2019) reported significant effects of the CBD treatment on the primary outcome measure/s, and three studies failed to report a significant CBD treatment effect on the primary outcome measure/s (Hindocha et al., 2018; Meneses-Gaya et al., 2021; Mongeau-Pérusse et al., 2021). The Freeman et al. (2020) study was the largest of the six studies (n = 82) and the only study with a low risk of bias. In the final Bayesian analysis (n = 70) from this study, a statistically significant effect of CBD treatment on self-reported cannabis abstinence was observed in the lower dose (400 mg) CBD group, but not the higher dose (800 mg) CBD group. Therefore, the studies were judged to have serious imprecision and inconsistency.	Serious

GRADE domain	Judgement	Concerns about certainty domains
Directness	Five of the six studies recruited participants with a substance-related disorder; the sixth study (Masataka, 2019) recruited young adults (18 to 19 years old) with a social anxiety disorder and comorbid avoidant personality disorder. Three studies offered psychotherapy to all participants and examined CBD as an adjunct treatment (Freeman et al., 2020; Meneses-Gaya et al., 2021; Mongeau-Pérusse et al., 2021): both the Meneses-Gaya et al. (2021) and Mongeau-Pérusse et al. (2021) studies offered group psychotherapy for cocaine use disorder; while the Freeman et al. (2020) study offered motivational interviewing for cannabis use disorder. The remaining three studies (Hindocha et al., 2018; Hurd et al., 2019; Masataka, 2019) used a standalone CBD intervention. Therefore, the studies were judged to have borderline indirectness in relation to the review question.	Not serious, borderline
Publication bias	Publication bias was not suspected as studies with both positive and negative findings were published, and the search for studies was comprehensive. The REA search strategy identified nine (9) clinical trial records for studies examining a CBD intervention for the mental health conditions of interest (see Appendix 4). The findings from these studies may be relevant to future reports. For three of these studies, the clinical trial records (EUCTR2020-003739-62-NL, NCT04205682, NCT03248167) report an expected date of completion that has expired. Further analysis is required.	Not suspected, pending further analysis

2. GRADE rating of natural cannabis extract (THC&CBD) studies

GRADE domain	Judgement	Concerns about certainty domains
Study limitations (risk of bias)	Both studies examined natural cannabis extract (THC&CBD; nabiximols oromucosal spray) for cannabis use disorder (Lintzeris et al., 2019; Trigo et al., 2018). Both studies were judged to have a high risk of bias; primarily due to missing outcome data: the studies had low retention rates, with approximately 50% of participants failing to complete the 12-week trial protocols. Therefore, the studies were judged to have very serious methodological limitations.	Very serious
Precision and Consistency	The total number of participants enrolled in the two studies was 187; however, 100 participants (53.5%) did not complete the 12-week studies for various reasons (range of non-completion across the studies: 46.0% to 56.2%). In the Lintzeris et al. (2019) study, the number of (self-reported) days of illicit cannabis use was significantly higher in the placebo group compared with the nabiximols group. However, there were no significant between-group differences in treatment retention, 4-week abstinence rate, cannabis-related problems, cannabis craving, cannabis withdrawal, alcohol use, nicotine use, general health	Serious

GRADE domain	Judgement	Concerns about certainty domains
	status and psychosocial functioning, aberrant medication use, or adverse events. In the Trigo et al. (2018) study, there were no significant between-group differences in cannabis abstinence rates, cannabis use (grams; % days per week), or cannabis withdrawal. The findings suggested that the psychotherapy (MET/CBT) intervention, which was offered to all participants, may have improved cannabis outcomes (i.e., abstinence; quantity and frequency of cannabis use; cannabis craving and withdrawal).	
Directness	Both studies recruited participants with a cannabis use disorder. All participants received psychotherapy in combination with the medicinal cannabis intervention. Lintzeris et al. (2019) offered individual (CBT-based) counselling sessions; Trigo et al. (2018) offered Motivational Enhancement Therapy and Cognitive Behavioural Therapy (MET/CBT). Therefore, both studies provided direct evidence on the review question.	Not serious
Publication bias	Publication bias was not suspected as studies with both positive and negative findings were reported, and the search for studies was comprehensive.	Not suspected

3. GRADE rating of dried cannabis (THC±CBD) studies

GRADE domain	Judgement	Concerns about certainty domains
Study limitations (risk of bias)	Two studies examined a (smoked) dried cannabis (THC±CBD) intervention: one study (Kayser et al., 2020) recruited participants with a primary diagnosis of obsessive compulsive disorder (OCD; DSM-5 criteria); the other study (Bonn-Miller et al., 2021) recruited military veterans with a diagnosis of posttraumatic stress disorder (PTSD; DSM-5 criteria). Both studies were judged to have a high risk of bias. The study by Kayser and colleagues (2020) employed per-protocol analysis (rather than intention-to-treat analysis); excluding two participants who dropped out of the study following the first of three study sessions ($n = 2/14$; 14.3%), reporting that the time commitment was "too great". The baseline severity of OCD symptoms was not reported for these participants, which further reduced confidence in the study findings due to the small sample size. Finally, the efficacy of the study blind was not assessed, and the differences in psychoactive effects across the study conditions were potentially discernible (e.g., high THC vs. placebo), which may have influenced participant's responses to the self-reported outcome measures. In the study by Bonn-Miller and colleagues (2021), there were concerns about period and carryover effects in relation to the two-stage crossover design, concerns about failure of the study blind, and concerns about	Serious

GRADE domain	Judgement	Concerns about certainty domains
	missing outcome data. Therefore, the studies were judged to have serious methodological limitations.	
Precision and Consistency	The total number of participants enrolled in the studies was 94, with most participants contributed by the Bonn-Miller et al. (2021) study ($n = 80/94$; 85.1%). In Stage I of the Bonn-Miller et al. (2021) study, no significant between-group differences in change scores (baseline to end of treatment: visit 0 to visit 7) were observed for PTSD severity (as measured by the CAPS-5; $p = 0.15$). In the Kayser et al. (2020) study, self-reported OCD and anxiety symptoms did not vary as a function of the cannabis varietal, and post-hoc analyses indicated state anxiety was significantly lower immediately following placebo treatment, relative to both THC and CBD treatment. Therefore, the evidence was judged to be consistent in terms of demonstrating no benefit of the active treatments over the placebo treatment.	Not serious
Directness	Both studies had serious limitations in terms of their relevance to clinical practice: the smoking of medicinal cannabis is explicitly not recommended by the TGA on medical grounds. Alternative routes of administration (e.g., oral ingestion or oromucosal spray) are applicable to the medical context. Additionally, no psychotherapy intervention was offered to participants in either study. Therefore, the studies were judged to have a serious indirectness in relation to the review question.	Serious
Publication bias	Publication bias was not suspected because both studies reported negative results, and the search for studies was comprehensive.	Not suspected

4. GRADE rating of synthetic cannabinoid (THC) studies

GRADE domain	Judgement	Concerns about certainty domains
Study limitations (risk of bias)	Both studies of synthetic (THC) cannabinoids (Hill et al., 2017; Schlienz et al., 2018) were judged to have a high risk of bias. In the Schlienz et al. (2018) study, carryover effects were not assessed. The analysis did not control for period effects, and baseline values between groups may not have been comparable at different time-points. Additionally, follow-up analyses were not reported for the study conditions in which participants could access placebo cannabis cigarettes (i.e., only the follow-up analyses for self-administration of active cannabis cigarettes were reported). Finally, the study employed per-protocol analysis (rather than intention-to-treat analysis); excluding three participants following study enrolment ($n = 3/16$; 18.8%). In the Hill et al. (2017) study, no information on the method of randomisation was available. Additionally, six participants ($n = 6/18$; 33.3%) did not complete the 10-week	Serious

GRADE domain	Judgement	Concerns about certainty domains
	trial protocol: 40% (*n* = 4/10) of participants in the nabilone group, and 25% (*n* = 2/8) of participants in the placebo group. There was a higher dropout rate in the nabilone group, which could be correlated with baseline severity of cannabis dependence (not reported). The effectiveness of the study blind was not assessed, which may have biased the results if the participants discerned their allocation to study conditions. Therefore, the studies were judged to have serious methodological limitations.	
Precision and Consistency	The total number of participants enrolled in the studies was 34; however, nine participants (26.5%) did not complete the studies for various reasons (range of non-completion across the studies: 18.8% to 33.3%). The Hill et al. (2017) study found no significant difference in self-reported cannabis use for the nabilone and placebo group. The Schlienz et al. (2018) reported self-administration of cannabis was significantly reduced during periods of dronabinol maintenance compared with placebo maintenance; however, the robustness of the treatment effect was uncertain due to the small sample size. Therefore, the evidence was judged to have serious imprecision and inconsistency.	Serious
Directness	Both studies enrolled participants with cannabis use disorder. The Hill et al. (2017) study examined a combined medicinal cannabis intervention designed to approximate a primary care approach: all participants were offered physician-guided medical management (MM) sessions, which included monitoring of medication side effects and strategies to increase medication adherence and support abstinence. The Schlienz et al. (2018) study used a standalone THC intervention. Therefore, the studies were judged to have borderline indirectness in relation to the review question.	Not serious, borderline
Publication bias	Publication bias was not suspected as there was a mix of positive and negative findings across studies, and the search for studies was comprehensive.	Not suspected