Technical Report

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

A Rapid Evidence Assessment

D-Cycloserine Interventions

2023

GALLIPOLI
MEDICAL RESEARCH FOUNDATION

Technical Report (2023)

Emerging and Adjunct Treatments for Common Mental Health Conditions Affecting Veterans: A Rapid Evidence Assessment – D-Cycloserine Interventions.

Disclaimer

The materials contained in this report (including the articles selected and analyses conducted) are the responsibility of the Gallipoli Medical Research Foundation, and do not necessarily reflect the views of the Australian Government. The Gallipoli Medical Research Foundation does not endorse any approach presented in the report. The evidence in the report is based on peer-reviewed literature that was indexed in electronic databases, and published in scientific journals, during the period 1 January 2017 to 8 February 2022. It is recommended that the reader consider evidence published before and after these dates. Sources of evidence that were excluded from the report include non-English language literature, non-peer-reviewed literature (e.g., reports), and other information in the public domain (e.g., newspapers, websites, and blogs).

ISBN 978-0-6451779-8-5

Suggested reference:

Maguire, A. M., Soole, R., Beilby, H., Tabinga, A., Barker, N., Fear, N. T., Kenardy, J., Tuffaha, H., & Khoo, A. (2023). *Emerging and adjunct treatments for common mental health conditions affecting veterans: A rapid evidence assessment – D-cycloserine interventions*. Technical report prepared by Gallipoli Medical Research Foundation for the Department of Veterans' Affairs, Australian Government. Canberra: Commonwealth of Australia.

This report is available from:

The Department of Veterans' Affairs, Australian Government. Research and Studies | Department of Veterans' Affairs (dva.gov.au)

Authors

Dr Angela M Maguire[1,2] - https://orcid.org/0000-0002-1564-9457

Dr Rebecca Soole[1] - https://orcid.org/0000-0002-4262-3850

Ms Hannah Beilby[3] - https://orcid.org/0000-0001-7361-6023

Ms Angeli Tabinga[1,2] - https://orcid.org/0000-0001-7552-1044

Ms Natalie Barker[4] - https://orcid.org/0000-0002-2418-8007

Professor Nicola T Fear[1,5] - https://orcid.org/0000-0002-5792-2925

Emeritus Professor Justin Kenardy[1,6,7] - https://orcid.org/0000-0001-9475-8450

Associate Professor Haitham Tuffaha[3] - https://orcid.org/0000-0003-2993-3480

Dr Andrew Khoo[1,2,8] - https://orcid.org/0000-0002-4851-6431

Authors' details

1. Gallipoli Medical Research Foundation, Greenslopes Private Hospital, Greenslopes Qld 4120, Australia.
2. The University of Queensland, Faculty of Medicine, St Lucia Qld 4072, Australia.
3. The University of Queensland, Centre for the Business and Economics of Health, St Lucia Qld 4072, Australia.
4. The University of Queensland, UQ Library, Herston Qld 4006, Australia.
5. King's College London, Weston Education Centre, London SE5 9RJ, United Kingdom.
6. The University of Queensland, Faculty of Health and Behavioural Sciences, St Lucia Qld 4072, Australia.
7. Jamieson Trauma Institute, Royal Brisbane and Women's Hospital, Herston Qld 4029, Australia.
8. Toowong Private Hospital, Toowong Qld 4066, Australia.

Acknowledgements

This project was funded by the Department of Veterans' Affairs (DVA). We would like to thank Dr Rebecca Mellor for her contributions to the project concept and funding submission, Mr Lars Eriksson for peer-reviewing the search strategies, and Dr Jie Hu for reviewing the risk-of-bias and GRADE assessments. We would like to acknowledge the DVA Emerging Treatments Project Team for their contributions to the development of the search strategies, and for their feedback on the PROSPERO protocol and the final version of the report.

Keywords

rapid review, emerging treatment, adjunct treatment, posttraumatic stress disorder, anxiety disorders, mood disorders, depressive disorders, substance-related disorders, addictive disorders, trauma- and stressor-related disorders, veterans.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

AE – Adverse Event

BMI – Body Mass Index

BDNF – Brain-Derived Neurotrophic Factor

CBD – Cannabidiol

CBN – Cannabinol

CBT – Cognitive Behavioural Therapy

DCS – D-cycloserine

DDVA – Departments of Defence and Veterans' Affairs (Australian Government)

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

MAOI – Monoamine Oxidase Inhibitor

MDMA – Methylenedioxymethamphetamine

NHMRC – National Health and Medical Research Council

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

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
Agoraphobic Cognitions Questionnaire	ACQ
Anxiety Sensitivity Index	ASI
Anxiety Sensitivity Index – Version 3	ASI-3
Approach Avoidance Task	AAT
Beck Anxiety Inventory	BAI
Beck Depression Inventory	BDI
Beck Depression Inventory II	BDI-II
Behavioural Approach Test	BAT
Body Sensations Questionnaire	BSQ
Brief Symptom Inventory	BSI
Clinician-Administered PTSD Scale for DSM-IV	CAPS
Clinical Global Impressions scale	CGI
Cocaine Craving Questionnaire – Now	CCQ-Now
Dimensional Obsessive-Compulsive Scale – Short Form	DOCS-SF
Extrinsic Affective Simon Task	EAST
Faces Dot Probe Task	FDOT
Fear of Spiders Questionnaire	FSQ
Generalized Anxiety Disorder, 7-item	GAD-7
Hamilton Depression Rating Scale	HAM-D[1]
Liebowitz Social Anxiety Scale	LSAS
Mobility Inventory	MI
Obsessive-Compulsive Inventory – Revised	OCI-R
Panic and Agoraphobia Scale	PAS
Panic Attack Scale	PAS
Panic Disorder Severity Scale	PDSS
Panic Disorder Severity Scale – Self Report	PDSS-SR
Patient Health Questionnaire, 9-item	PHQ-9
Profile of Mood States	POMS
Situational Confidence Questionnaire-Cocaine	SCQ
Social Phobic Disorders – Severity form	SPD-S
Spider Anxiety Screening	SAS
State Trait Anxiety Inventory – State scale	STAI-S
State Trait Anxiety Inventory – Trait scale	STAI-T
Structural Clinical Interview for DSM-IV Axis I Disorders	SCID-I
Subjective Units of Distress	SUDs
Timeline Followback	TLFB
Visual Analogue Scale	VAS
Warwick-Edinburgh Mental Well-Being Scale	WEMWBS
Yale-Brown Obsessive Compulsive Scale	Y-BOCS

Notes. 1. The acronyms Ham-D or HDRS are also used in the literature to refer to the Hamilton Depression Rating Scale.

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:

1. Psychedelic compounds; specifically:
    a. Ketamine;
    b. Methylenedioxymethamphetamine (MDMA);
    c. Lysergic acid diethylamide (LSD);
    d. Psilocybin;
    e. Dimethyltryptamine (DMT) including ayahuasca.
2. Medicinal cannabis; specifically:
    a. Cannabidiol (CBD);
    b. Cannabinol (CBN);
    c. Tetrahydrocannabinol (THC).
3. D-cycloserine (DCS).
4. Stellate ganglion block (SGB).
5. 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: D-cycloserine interventions

From the four databases that were searched, 25 studies met the inclusion criteria, including 12 secondary sources: four (4) systematic reviews (SRs) and eight (8) 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 (281 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 13 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: D-cycloserine 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 13 RCTs of D-cycloserine (DCS) interventions included in the REA, one (1) study was judged to have a low risk of bias, seven (7) studies were judged to have some concerns, and five (5) studies were judged to have a high risk of bias (see Appendix 8).

GRADE certainty of evidence summary: D-cycloserine 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 summary for the DCS interventions is 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]
DCS (13)	Parallel arm RCT (13)	Serious (5 high risk; 7 some concerns; 1 low risk)	Serious	Not serious	Suspected, pending further analysis	Low ⨁⨁

Notes. DCS = D-cycloserine. RCT = Randomised controlled trial. RoB = Risk of bias. 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 studies included in the REA employed various participant samples, a variety of treatment regimens, and a variety of outcome measures. The findings from these studies were mixed, and many studies were judged to have risk-of-bias concerns. Specifically, only one study (Smits et al., 2020a) had a low risk of bias. Seven (7) studies were judged to have some risk-of-bias concerns. These risk-of-bias concerns were primarily due to the unavailability of the researchers' pre-specified analysis intentions (i.e., the planned outcome measurements and statistical analyses could not be compared with those presented in the published articles). One study (Chen et al., 2019) was judged to have some concerns across multiple risk-of-bias domains, which substantially lowered confidence in the study findings and resulted in an overall high risk-of-bias judgment. The remaining four studies (Inslicht et al., 2021; Johnson et al., 2020; Rauch et al., 2018; Smits et al., 2020b) were judged to have a high risk of bias in at least one domain. Further methodologically robust research on DCS interventions is warranted.

Conclusions and recommendations for future research

It is difficult to draw conclusions and recommendations regarding DCS interventions from the body of evidence considered by the REA. DCS is proposed to enhance fear extinction or extinction learning via partial agonism of the NMDA receptor (neurobiological mechanism of action). Thus, most of the included studies examined the effects of DCS administration in combination with exposure-based psychotherapy for anxiety disorders. Some studies appear to indicate that DCS improves outcomes from evidence-based psychotherapy. However, due to the mixed findings across studies, it is difficult to recommend the use of DCS interventions in specific clinical situations. Further high-quality research is required.

A productive direction for future research efforts would be to focus on interventions that combine DCS administration with evidence-based psychotherapy. The REA identified two (2) clinical trial records for ongoing RCTs focusing on mood/depressive disorders (see Appendix 4 for details). The findings from these studies may be relevant to future reports.

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 ⊕⊕⊕⊕	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).

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: D-cycloserine

Figure 1 presents the number of articles 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, 25 studies met the inclusion criteria, including 12 secondary sources: four (4) systematic reviews (SRs) and eight (8) 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 (281 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 13 RCTs (see Appendix 5). The findings from these studies were narratively synthesised, and risk of bias assessments were conducted for each RCT.

D-cycloserine: Standalone and combined interventions

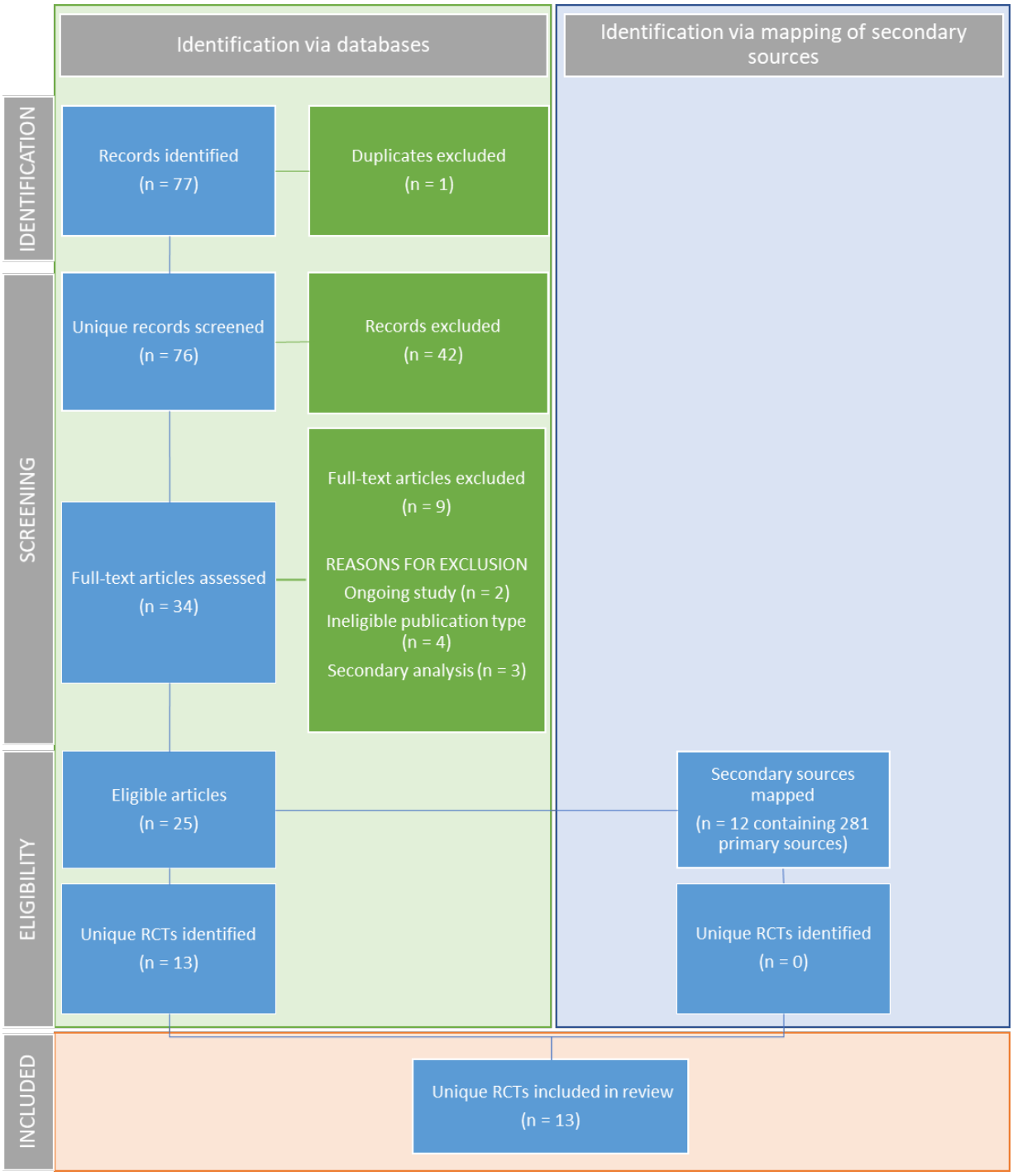

Figure 1. PRISMA diagram detailing the number of records under consideration at each stage of the REA for the D-cycloserine interventions.

Summary of the Evidence: D-cycloserine Interventions

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

Thirteen (13) studies of DCS interventions met the inclusion criteria for the REA. All 13 studies examined combined interventions: in 12 studies, a DCS intervention was used in conjunction with a psychotherapeutic intervention (e.g., exposure-based cognitive behavioural therapy, CBT); and one study examined a combined DCS and ketamine intervention. It is important to note that some studies did not exclude participants who were stabilised on other pharmacological intervention/s (e.g., antidepressants; anti-psychotics; mood stabilisers) or engaged in other psychotherapeutic intervention/s (e.g., cognitive behavioural therapy, CBT).

Appendix 6 provides a matrix of the combined DCS interventions for the 13 studies, broken down by the disorder categories of interest. Appendix 7 provides a detailed summary of the evidence from each of the 13 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

No studies included in the REA examined a standalone DCS intervention for anxiety disorders.

Anxiety Disorders: Combined interventions

Eight studies examined a combined DCS and psychotherapy intervention (predominantly exposure-based CBT with response prevention for OCD) in participants with anxiety disorders:

- Two studies recruited participants with a social anxiety disorder (Smits et al., 2020; Roque et al., 2018).
- Two studies recruited participants with an obsessive compulsive disorder (Kvale et al., 2020; de Leeuw et al., 2017);
- Three studies recruited participants with a panic disorder and/or agoraphobia (Reinecke et al., 2020; Hofmeijer-Sevink et al., 2019; Pyrkoscha et al., 2018); and
- One study recruited participants with a specific phobia of spiders (Kappelmann et al., 2020).

Social Anxiety Disorder

Two studies examined a combined DCS and psychotherapy intervention in participants with a social anxiety disorder (SAD; Smits et al., 2020a; Roque et al., 2018). Both studies compared DCS (adjunct treatment) with placebo in participants receiving group, exposure-based, cognitive behavioural therapy (CBT).

Smits and colleagues (2020a; n = 152) recruited participants with a diagnosis of social anxiety disorder (DSM-5 criteria) from three (3) university sites. All participants received five (5) sessions of group, exposure-based CBT (one session per week over a five-week period). Participants were randomised to four groups: (i) placebo (n = 38); (ii) pre-session DCS (50 mg; n = 38), (iii) post-session DCS (50 mg; n = 36), or (iv) tailored post-session DCS (50 mg; n = 40). Individuals were not included in the study if they were currently undergoing pharmacotherapy or psychotherapy. The outcome measures (assessors blind to study condition) were the Liebowitz Social Anxiety Scale (LSAS) and the Social Phobic Disorders – Severity Form (SPD-S). Assessments were conducted at multiple time-points: baseline, during treatment (session 2 to 5), and follow-up (post-treatment: 1 week, 1 month, and 3 months). Clinical treatment response was not defined in the study. At the 3-month follow-up, a significant improvement in social anxiety symptoms was observed for the pre-session DCS group (LSAS: $p < 0.001$; SPD-S: $p < 0.001$), and post-session DCS group (LSAS: $p = 0.002$; SPD-S: $p = 0.002$), compared with the placebo group. Similarly, at the 3-month follow-up, a significant improvement in social anxiety symptoms was observed for the pre-session DCS group (LSAS: $p < 0.001$; and SPD-S: $p = 0.004$), and post-session DCS group (LSAS: $p = 0.008$; SPD-S: $p = 0.008$), compared with the tailored post-session DCS group. For the pre- and post-session DCS groups, no significant differences were observed in symptom improvement ($p = 0.43$), or symptom severity ($p = 0.88$). For the tailored post-session DCS group and the placebo group, no significant differences were observed in symptom improvement ($p = 0.62$), or symptom severity ($p = 0.64$). That is, pre- and post-session DCS dosing significantly improved treatment outcomes, but there was no evidence that tailoring DCS dosing to "successful" sessions of exposure-based CBT differed from placebo. This study was judged to have a low risk of bias.

Roque and colleagues (2018; *n* = 169) recruited participants with a diagnosis of social anxiety disorder (DSM-IV criteria) from the community (via referrals from clinical facilities and programs). All participants received 12 (2.5-hour) sessions of group, exposure-based CBT (one session per week over a 12-week period). Participants were randomised to receive an oral tablet of either DCS (50mg; *n* = 87) or placebo (polyethylene glycol 3350; *n* = 82) one hour before each of the five (5) exposure therapy sessions (session 3 to 7). There were no significant between-group differences for demographic variables except gender: there were significantly more males in the DCS group (64%) compared with the placebo group (49%). Individuals were not included in the study if they had been taking psychotropic medications (e.g., antidepressants, anxiolytics, beta-blockers) for two (2) weeks prior to study entry, or had been engaged in psychotherapy (targeting symptoms of social anxiety disorder) in the last three (3) months (except for general supportive therapy). The outcome measures were the Liebowitz Social Anxiety Scale (LSAS; assessed by independent rater), and homework compliance (three components measured on a Likert scale: (i) completion, (ii) effort, and (iii) relevance; assessed by the therapist). Assessments were conducted at multiple time-points: weekly at each therapy session (week 1 to 12) and post-treatment (week 13). Clinical treatment response was not defined in the study. Homework compliance (in the week leading up to a therapy session) was associated with lower social anxiety symptoms (as measured by the LSAS; $p < 0.001$). However, social anxiety symptoms did not significantly differ for the DCS group compared with the placebo group, irrespective of whether the previous week's LSAS was controlled ($p = 0.980$) or not ($p = 0.531$). The authors attributed the lack of treatment effect to the "small number of DCS-enhanced sessions" (i.e., session 3 to 7). It is important to note that this study included five (5), 2.5-hour, DCS-assisted exposure therapy sessions – the Smits et al. (2020a) study included four (4), 1.5-hour, DCS-assisted exposure therapy sessions – and there were a similar number of participants in each study. This study was judged to have some risk-of-bias concerns, as the researchers' pre-specified analysis plan was not included in the clinical trial protocol; therefore, the planned outcome measurements and statistical analyses could not be compared with those presented in the published article.

Obsessive Compulsive Disorder

Two studies examined a combined DCS and psychotherapy intervention in participants with obsessive compulsive disorder (OCD; Kvale et al., 2020; de Leeuw et al., 2017). Both studies compared adjunct DCS treatment with placebo in participants receiving group, exposure and response prevention (ERP); that is, evidence-based CBT for OCD.

Kvale and colleagues (2020; *n* = 163) recruited participants (outpatients) with a diagnosis of OCD (DSM-5 criteria) via specialist OCD teams operating within a national public health authority. All participants received the Bergen 4-day treatment protocol (i.e., individual, concentrated ERP delivered over four consecutive days in a group setting). Participants were randomised to three study conditions: (i) 100 mg DCS (*n* = 65), (ii) 250 mg DCS (*n* = 67), or (iii) placebo (*n* = 31). Participants were included in the study if they had received a stable dose of antidepressants for at least 12 weeks, or were willing to receive a stable dose during the four (4) intervention days. The outcome measures were the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), the Dimensional Obsessive-Compulsive Scale Short Form, the Obsessive-Compulsive Inventory–Revised (OCI-R), the Generalized Anxiety Scale (GAD-7), the Patient Health Questionnaire (PHQ-9), and the Warwick-Edinburgh Mental Well-Being Scale (WEMWBS). Assessments were conducted at four (4) time-points: baseline, post-treatment, and follow-up (post-treatment: 3 and 12 months). Clinical treatment response was defined as a reduction of at least (≥) 35% in the baseline Y-BOCS score. Remission was defined as the response criterion plus a post-treatment Y-BOCS score of no more than (≤) 12. Overall, 56.5% (*n* = 91) of participants achieved remission of OCD at post-treatment; and 47.9% (*n* = 70) of participants achieved remission at the 12-month follow-up. No significant difference in rates of remission were observed for the DCS groups (100 mg; 250 mg) compared with the placebo group ($p > 0.05$). There was a significant reduction in OCD symptoms (as measured by the Y-BOCS) for all groups at the 12-month follow-up (all p's < 0.001). However, at the 12-month follow-up, no significant effect of DCS group (100 mg; 250 mg) compared with placebo group was observed for OCD symptoms ($p > 0.05$). That is, DCS did not enhance the effect of ERP treatment, but concentrated ERP treatment was associated with improved mental health outcomes for all groups. This study was judged to have some risk-of-bias concerns as the researchers' pre-specified analysis plan was not available; therefore, the planned outcome measurements and statistical analyses could not be compared with those presented in the published article.

De Leeuw and colleagues (2017; *n* = 39) recruited participants with a diagnosis of OCD (DSM-IV criteria) from two anxiety disorder clinics. All participants received six (6) sessions of guided exposure and response prevention (ERP) therapy (1 session per week for 6 weeks). Participants were randomised to receive either DCS (125mg; *n* = 19) or placebo (*n* = 20) one hour before each therapy session. Individuals who were taking pharmaceutical medications (except benzodiazepines) were included in the study, but only if the medication regimen was stable for at least two (2) months prior to study commencement (and remained stable throughout the study). The outcome measures were the participants' score on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS; primary outcome) and the Clinical Global Impression Scale (CGI). Assessments were conducted at three (3) time-points: baseline, mid-treatment (before the fifth session), and post-treatment. Clinical treatment response was defined as a reduction of at least (≥) 30% on the Y-BOCS score at post-treatment. Treatment response did not significantly differ for the DCS and placebo groups (37% and 15%, respectively; $p = 0.155$). However, in the 'cleaning/contamination' subgroup (formed according to symptom dimensions), a significant difference in treatment response was observed for the DCS group compared with the placebo group ($p = 0.033$). No significant difference in OCD symptoms (as measured by the Y-BOCS) was observed for the DCS group compared with the placebo group ($p = 0.076$). This study was judged to have some risk-of-bias concerns. A protocol or pre-specified statistical analysis plan was not available; therefore, the planned outcome measures and analyses could not be compared with those reported in the published article.

Panic Disorder and/or Agoraphobia

Three studies examined a combined DCS and psychotherapy intervention in participants with a panic disorder and/or agoraphobia (Reinecke et al., 2020; Hofmeijer-Sevink et al., 2019; Pyrkoscha et al., 2018).

Reinecke and colleagues (2020; *n* = 33) recruited participants with a primary diagnosis of panic disorder with or without agoraphobia (DSM-IV criteria) from the community. All participants received one session of exposure therapy. Participants were randomised to receive either a single dose of DCS (250 mg; *n* = 17) or placebo (microcrystalline cellulose; *n* = 16) two hours before the exposure therapy session. Participants were required to refrain from benzodiazepine or beta-blocker medication at least 48 hours prior to study treatment. The outcome measures were the State Trait Anxiety Inventory (STAIS/STAIT), Beck Depression Inventory (BDI), Body Sensations Questionnaire (BSQ), Agoraphobic Cognitions Questionnaire (ACQ), Mobility Inventory (MI), Panic Attack Scale (PAS), and Panic Disorder Severity Scale (PDSS). Assessments were conducted at four (4) time-points: baseline, post-treatment, and follow-up (1 month and 6 months). Clinical treatment response was defined as agoraphobic avoidance scores (as measured by the MI) that were within the range reported for healthy persons. A significantly higher percentage of treatment responders were reported for the DCS group compared to the placebo group at 1-month follow-up (70.6% and 25.0%, respectively; $p = 0.015$). At the 6-month follow-up, there was no significant difference in the percentage of treatment responders for the DCS group compared with the placebo group ($p = 0.17$). There were no significant between-group differences in BSQ, MI, ACQ, PAS, or PDSS scores across all time-points (all p's > 0.095). This study was judged to have some risk-of-bias concerns. A pre-specified statistical analysis plan was not available; therefore, the planned outcome measures and analyses could not be compared with those reported in the published article.

Hofmeijer-Sevink and colleagues (2019; *n* = 57) recruited participants with a diagnosis of panic disorder and comorbid agoraphobia (DSM-IV criteria) from outpatient clinics. All participants received 12 sessions of exposure and response prevention (ERP) therapy. All participants received an oral tablet half an hour before each of the first six exposure therapy sessions, and directly after each of the first six exposure therapy sessions, within the 12-session ERP protocol. Participants were randomised to one of three conditions: (1) pre-exposure DCS (125 mg; *n* = 19; post-exposure: placebo); (2) post-exposure DCS (125 mg; *n* = 19; pre-exposure: placebo); or (3) placebo (*n* = 19; pre- and post-exposure placebo). Participants who were undergoing treatment with selective serotonin reuptake inhibitors (SSRIs) were included in the study, but only if the medication regimen was stable for at least three (3) months prior to study commencement (and remained stable throughout the study). The outcome measures were the "alone" subscale of the Mobility Inventory (MI-alone; i.e., agoraphobic avoidance; primary outcome), the "accompanied" subscale of the MI (MI-accompanied), Beck Anxiety Inventory (BAI), Beck Depression Inventory II (BDI-II), and Panic Disorder Severity Scale (PDSS). Assessments were conducted at six (6) time-points: baseline, mid-treatment (before session 4 and 8), post-treatment (after session 12), and follow-up

(3 months and 6 months). Clinical treatment response was defined as at least (≥) 25% symptom reduction on the MI-alone subscale (baseline to post-treatment). Subgroup analyses (treatment responders vs. non-responders, early vs. late responders, severely vs. mildly affected participants) did not reveal any significant differences between the DCS and placebo groups. No significant between-group differences (DCS vs. placebo) were observed for the primary outcome measure (MI-alone subscale) at any time-point (all *p*'s > 0.121). At the 3-month follow-up, greater symptom reduction (on the MI-alone subscale) was observed for the DCS post-exposure group compared with DCS pre-exposure group ($p = 0.009$). The findings for the DCS and placebo groups did not differ for successful exposure sessions relative to non-successful sessions (i.e., tailored DCS). That is, no preferential DCS effects were observed for specific subgroups, or for successful exposure therapy sessions. The authors noted that a small effect of post-exposure DCS treatment could not be ruled out due to the small sample size of the study. This study was judged to have some risk-of-bias concerns as a pre-specified analysis plan was not available; therefore, the planned outcome measures and analyses could not be compared with those reported in the published article.

Pyrkosch and colleagues (2018; $n = 73$) recruited participants with a diagnosis of agoraphobia with or without panic disorder (ICD-10 criteria). All participants received 12 sessions of cognitive behavioural therapy (CBT) including three (3) sessions of in-vivo exposure (session 7 to 9). Participants were randomised to receive either post-exposure DCS (50 mg; $n = 36$) or placebo ($n = 37$) following successful exposure sessions. Participants who were undergoing treatment with medications (not specified) were included in the study, but only if the medication regimen was stable for at least four (4) weeks prior to study enrolment (and remained stable throughout the study). The outcome measures were the Panic and Agoraphobia Scale (PAS: observer rated and self-rated; primary outcomes), Agoraphobic Cognitions Questionnaire (ACQ), Body Sensations Questionnaire (BSQ), Mobility Inventory (MI), Anxiety Sensitivity Index (ASI), Beck Anxiety Inventory (BAI), Beck Depression Inventory II (BDI-II), Brief Symptom Inventory (BSI), and Clinical Global Impression (CGI) scale. Assessments were conducted at four (4) time-points: session 1 (baseline), session 4 (2 months), session 10 (3 months), and session 11 (4 months). Clinical treatment response was not defined in the study. Significant decreases in panic and agoraphobic symptoms were observed over time (observer-rated PAS: $p < 0.001$; self-rated PAS: $p < 0.001$). However, no significant between-group differences (DCS vs. placebo) were observed on either the observer-rated PAS ($p = 0.22$) or self-rated PAS ($p = 0.50$), and the groups did not significantly differ over time (observer-rated PAS: $p = 0.72$; self-rated PAS: $p = 0.61$). In subgroup analyses (severely ill participants; those with high anxiety and strong habituation during exposure), DCS administration was associated with increased symptom improvement during the 1-month follow-up period (session 10 to 11). The authors concluded that the findings were consistent with recent research Indicating a beneficial effect of adjunct DCS treatment for subgroups of anxiety patients. They suggested that the failure to find a significant effect of DCS treatment for the entire sample may be explained by a dual mechanism in fear conditioning and extinction (i.e., different cognitive processes depending on the degree of anxiety experienced by the participant during exposure). This study was judged to have some risk-of-bias concerns. Despite randomisation, a significant age difference was observed between the two treatment groups, with the placebo group being significantly older. Accordingly, the placebo group also had a significantly longer duration of illness. The authors acknowledged that baseline severity may have moderated symptom improvement (i.e., participants with higher baseline severity would be expected to improve more than those with low baseline severity). Finally, a pre-specified statistical analysis plan was not available; therefore, the planned outcome measures and analyses could not be compared with those reported in the published article.

Specific Phobia

One study examined a combined DCS and psychotherapy intervention in participants with a specific phobia of spiders (Kappelmann et al., 2020).

Kappelmann and colleagues (2020; $n = 38$) recruited participants with a diagnosis of spider phobia (DSM-IV criteria) from the community (via flyers and community websites). Participants were randomised to receive either DCS (250 mg) or placebo, three (3) hours prior to a single session of computerised CBT (psychoeducation and exposure therapy). Individuals who were undergoing treatment with psychoactive medication in the six (6) weeks prior to enrolment were not included in the study. The outcome measures were the Fear of Spiders

Questionnaire (FSQ), Spider Anxiety Screening (SAS), a Behavioural Approach Test (BAT), Extrinsic Affective Simon Task (EAST), Approach Avoidance Task (AAT), and Visual Analog Scale (VAS). Assessments were conducted at four (4) time-points: baseline, post-treatment, and follow-up (1 day and 1 month). Clinical treatment response was not defined in the study. Significant improvements were observed over time on the self-report and behavioural measures of spider fear (SAS: $p < 0.001$; FSQ: $p < 0.001$; BAT: $p < 0.001$), but not on the cognitive bias measures (EAST: $p = 0.19$; AAT: $p = 0.65$). There was no evidence of an effect of DCS dosing on any outcome (SAS: $p = 0.67$; FSQ: $p = 0.88$; BAT: $p = 0.21$; EAST: $p = 0.92$; AAT: $p = 0.82$). The authors noted the study findings might be biased due to the "limited representativeness of the sample (high education and intelligence, largely Caucasian ethnicity, young age)" (p. 1). Additionally, the study was only powered to detect a medium effect of the DCS intervention (i.e., was not adequately powered to detect a small effect). This study was judged to have some risk-of-bias concerns. A pre-specified statistical analysis plan was not available; therefore, the planned outcome measures and analyses could not be compared with those reported in the published article.

Mood/Depressive Disorders: Standalone interventions

No studies included in the REA examined a standalone DCS intervention for mood/depressive disorders.

Mood/Depressive Disorders: Combined interventions

One study examined a combined DCS and ketamine intervention in participants with mood/depressive disorders (Chen et al., 2019).

Chen and colleagues (2019; $n = 32$) recruited participants with a diagnosis of treatment-resistant depression (TRD) in the context of a diagnosis (DSM-IV criteria) of either major depressive disorder (MDD; $n = 17$) or bipolar disorder (BP; $n = 15$). TRD in participants with MDD was defined as non-response (with adequate dose and duration) to at least two different antidepressants. TRD in participants with BP was defined as non-response response (with adequate dose and duration) to at least two antidepressants or mood stabilisers with a documented efficacy in bipolar depression (i.e., lithium, lamotrigine, quetiapine, or olanzapine). Participants who responded to an open-label ketamine infusion (phase 1 trial) were randomised to receive a 6-week treatment protocol of either ascending-dose DCS (250 mg for 2 days, 500 mg for 2 days, 750 mg for 3 days, and 1000 mg for 5 weeks; $n = 16$) or placebo ($n = 16$). In the DCS group, the final dose was adjusted in the range of 500 mg to 1000 mg per day based on the participant's tolerability. Medications for TRD were not discontinued during the study. The outcome measure was the Hamilton Depression Rating Scale (HAM-D). Assessments were conducted at multiple time-points: at every dose titration and weekly for six (6) weeks. Clinical treatment response was not defined in the study. During the 6-week treatment, no significant differences in depressive symptoms (as measured by the HAM-D) were observed for the DCS group compared with the placebo ($p = 0.30$). Separate analyses for individuals with major depression ($p = 0.77$) and with bipolar depression ($p = 0.14$) demonstrated that the maintenance of the antidepressant effect of the ketamine infusion was similar for the DCS and placebo groups. Superior maintenance of the anti-suicidal effect of ketamine was observed in the DCS group compared with the placebo group ($p = 0.01$). The authors concluded that DCS treatment may be beneficial for patients with treatment-resistant depression, who respond to ketamine infusion, but have a residual suicidal risk. This study was judged to have some concerns across multiple risk-of-bias domains. Specifically, detailed information on the method of randomisation was not available (i.e., beyond stating that the participants were "randomised" to study conditions). Similarly, no information was provided on blinding (i.e., whether the participants or researchers were aware of the assigned interventions during the study). Finally, a pre-specified statistical analysis plan was not available; therefore, the planned outcome measures and analyses could not be compared with those reported in the published article.

Substance-Related and Addictive Disorders: Standalone interventions

No studies included in the REA examined a standalone DCS intervention for substance-related and addictive disorders.

Substance-Related and Addictive Disorders: Combined interventions

Two studies examined a combined DCS and psychotherapy intervention in participants with a substance-related disorder (Johnson et al., 2020; Smits et al., 2020b).

Johnson and colleagues (2020; *n* = 52) recruited participants with a diagnosis of cocaine use disorder (DSM-IV criteria). All participants received 9 sessions (three sessions per week) of urinalysis-based contingency management (CM; i.e., a financial incentive for providing cocaine-negative urine samples) and exposure therapy in a naturalistic environment. Participants were randomised to receive an oral capsule of either DCS (50 mg; *n* = 30) or placebo (*n* = 22) one hour prior to each exposure therapy session (i.e., following the delivery of urinalysis feedback with potential monetary reward). The outcome measures were the urinalysis tests (primary outcome), Cocaine Craving Questionnaire – Now (CCQ-Now), Situational Confidence Questionnaire – Cocaine (SCQ), Profile of Mood States (POMS), and drug use assessed using the Timeline Followback (TLFB; self-report) method. Assessments were conducted at multiple time-points (i.e., each session; total 21 sessions): induction (week 1 to 2: 6 sessions), treatment (week 3 to 5: 9 sessions), and post-treatment (week 6 to 7: 6 sessions). Additionally, a battery of cognitive tasks was completed following administration of an oral capsule (DCS vs. placebo) at induction session 6. Clinical treatment response was not defined in the study. There were no significant differences on quantitative, qualitative, or new use measures of cocaine use for the DCS group compared with the placebo group. However, significant reductions in qualitative cocaine use (percent positive samples) were observed for both groups ($p < 0.001$); the reductions in use were specific to the treatment phase ($p \leq 0.001$ for all pairwise comparisons involving this phase). A similar pattern for quantitative cocaine use emerged (i.e., lower quantitative cocaine use during the treatment phase); however, was not statistically significant ($p > 0.14$). During the post-treatment phase, the withdrawal of CM contingencies and return to baseline conditions was associated with a general increase in cocaine use, which was near the level of use observed during the induction phase. Self-reported cocaine craving (as measured by the CCQ-Now) fluctuated throughout the trial ($p < 0.001$): craving decreased for both groups following the introduction of CM and then, for the DCS group, increased significantly during the post-treatment phase (post hoc pairwise comparison: $p = 0.01$). Self-reported drug use (as measured by the TLFB) did not significantly differ between the groups. A decrease in alcohol and cocaine use coincided with the introduction of the treatment phase: the number of days using alcohol and cocaine decreased significantly throughout the trial (alcohol use: $p < 0.001$; cocaine use: $p < 0.001$). Although the cognitive tasks showed that DCS was associated with improved learning, enhancement of learning-based therapy was not observed. This study was judged to have a high risk of bias. The study employed per-protocol analysis (rather than intention-to-treat analysis), excluding 13 participants following randomisation: 4 withdrew from the DCS group; and 9 participants were excluded due to protocol deviations (DCS: 6; placebo: 3). Additionally, a pre-specified statistical analysis plan was not available; therefore, the planned outcome measures and analyses could not be compared with those reported in the published article.

Smits and colleagues (2020b; *n* = 53) recruited participants with a primary diagnosis of tobacco use disorder and a history of comorbid panic attacks (DSM-IV criteria) from the community. All participants received seven (90-minute) sessions (one per week for seven weeks) of Panic and Smoking Reduction Treatment (PSRT). Nicotine replacement therapy was initiated at session 5 (quit date). Participants were randomised to receive either DCS (250 mg; *n* = 27) or placebo (*n* = 26) prior to the sessions that emphasised interoceptive exposure practice (session 3 to 5). Individuals who were undergoing pharmacotherapy or psychotherapy for smoking cessation, or anxiety and mood disorders, were not included in the study. The outcome measures were the Anxiety Sensitivity Index (ASI-3), Panic Disorder Severity Scale Self Report (PDSS-SR), and smoking abstinence assessed using the Timeline Followback (TLFB; self-report) method. Assessments were conducted at multiple time-points: baseline, all treatment sessions, and follow-up (1 month, 4 month, and 6 month). Clinical treatment response was not defined in the study. A significantly greater reduction in anxiety sensitivity was observed for the DCS group compared with the placebo group at post-treatment *(p* = 0.038). Faster improvements in anxiety sensitivity scores were reported in the DCS group compared to the placebo group ($p = 0.026$), but were not maintained at the 6-month follow-up ($p = 0.802$). A significant between-group difference in panic-related symptoms (as measured by the PDSS-SR) was found at the 6-month follow-up ($p = 0.003$), but not at any other assessment time-point. No differences in successful smoking cessation were observed between groups at the treatment endpoint or at the follow-up evaluations. This study was judged to have a high risk of bias as the published analysis differed from the pre-specified analysis plan.

Trauma- and Stressor-Related Disorders: Standalone interventions

No studies included in the REA examined a standalone DCS intervention for trauma- and stressor-related disorders.

Trauma- and Stressor-Related Disorders: Combined interventions

Two studies examined a combined DCS and psychotherapy intervention in participants with a trauma- and stressor-related disorder (Inslicht et al., 2021; Rauch et al., 2018).

Inslicht and colleagues (2021; *n* = 90) recruited participants with a diagnosis of PTSD (or sub-syndromal PTSD; DSM-IV criteria) from military-connected outpatient and community clinics. All participants received fear conditioning with stimuli that were paired (CS+) or unpaired (CS-) with shock. Extinction learning occurred 72 hours later, and extinction retention was tested one (1) week after extinction. All participants received one oral encapsulated pill one hour prior to fear extinction learning. Participants were randomised to three groups: (i) DCS (50 mg; *n* = 29); (ii) hydrocortisone (HC; 25 mg; *n* = 31); or (iii) placebo (*n* = 30). Individuals were not included in the study if they were undergoing treatment with alpha- and beta-adrenergics, antipsychotics, benzodiazepines, mood stabilisers, anticonvulsants, antihypertensives, sympathomimetics, anticholinergics, or steroids. The outcome measure was the skin conductance level (SCL) as measured by a Coulbourn Isolated Skin Conductance coupler. Assessments were conducted at three (3) time-points: baseline (fear conditioning phase), during treatment (fear extinction phase), and post-treatment (one week after extinction learning). Clinical treatment response was not defined in the study. During habituation, there were no significant group or CS type effects, or any significant interactions involving these factors (all p's > 0.44). The skin conductance response (SCR) to both CS+ and CS- significantly decreased over trials indicating successful habituation to the CS stimuli ($p < 0.001$). During fear conditioning, there were no significant group differences for the differential SCR to CS+ vs. CS- trials ($p = 0.53$). There was a significant effect of CS+ vs. CS- ($p < 0.001$), indicating successful acquisition of fear responding. During extinction learning, the DCS and HC groups showed a reduced differential CS+/CS- SCR compared to placebo ($p = 0.042$ and $p = 0.005$, respectively). At retention testing (one-week post-treatment), extinction learning was not retained for the DCS group ($p = 0.089$), or the HC group ($p = 0.883$). This study was judged to have a high risk of bias. The study excluded 16 of the 106 participants following randomisation due to missing outcome data. The supplementary file describing the flow of participants through the study was not available; thus, the differences in missing outcome data for the DCS and placebo groups could not be assessed. Additionally, the clinical trial identifier and a pre-specified statistical analysis plan was not available; therefore, the planned outcome measures and analyses could not be compared with those reported in the published article.

Rauch and colleagues (2018; *n* = 156) recruited military veterans with a diagnosis of PTSD (DSM-IV criteria). All participants received six sessions of therapy: an initial 90-minute treatment session (information gathering, treatment planning, and explanation of the treatment rationale) followed by five sessions (one per week for five weeks) of Virtual Reality Exposure (VRE) therapy. All participants received an oral pill 30 minutes prior to the VRE sessions (session 2 to 6). Participants were randomised to receive either: (i) DCS (50 mg; *n* = 53), (ii) alprazolam (0.25 mg; *n* = 50), or (iii) placebo (*n* = 53). Individuals who were undergoing treatment with glucocorticoids, benzodiazepines, or chronically used opioids, were not included in the study. The outcome measures were the Clinician-Administered PTSD Scale for DSM-IV (CAPS), and Subjective Units of Distress (SUDs). Assessments were conducted at multiple time-points: baseline, each treatment session, and follow-up (month 3, 6, and 12). SUDs were collected every 5 minutes during the VRE (session 2 to 6). Clinical treatment response was not defined in the study. There was no significant difference in PTSD symptoms (as measured by the CAPS) between any pair of treatment groups at post-treatment (DCS vs. alprazolam: $p = 0.88$; DCS vs. placebo: $p = 0.46$; alprazolam vs. placebo: $p = 0.57$). The number of treatment sessions significantly predicted SUDs ratings ($p < 0.001$). Time-in-session served as a significant predictor of SUDs ($p < 0.001$). Specifically, engagement increased within session, and then reduction (extinction/habituation) was apparent across sessions. Treatment group was a predictor of SUDs rating within treatment sessions ($p < 0.05$) but not across sessions: greater increases in within-session SUDs were observed for the DCS and alprazolam groups compared with the placebo group. Status as a treatment responder was a predictor of SUDs reduction across treatment sessions ($p < 0.001$), but did not produce an overall, or within-session, effect on SUDs. This study was judged to have a high risk of bias. The study

employed per-protocol analysis (rather than intention-to-treat analysis), excluding participants following randomisation (33 to 59 depending on the analysis) due to missing data and study dropout: of the 156 participants randomised, 123 participants had pre-treatment CAPS scores and SUDs data for at least one treatment session; and 97 participants had post-treatment CAPS scores, which were necessary to calculate CAPS reduction across sessions. The flow of participants through the trial was not reported; thus, the differences in missing outcome data for the DCS and placebo groups could not be assessed. Additionally, a pre-specified statistical analysis plan was not available; therefore, the planned outcome measures and analyses could not be compared with those reported in the published article.

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 studies included in the REA employed various participant samples, a variety of treatment regimens, and a variety of outcome measures. The findings from these studies were mixed, and many studies were judged to have risk-of-bias concerns. Specifically, only one study (Smits et al., 2020a) had a low risk of bias. Seven (7) studies were judged to have some risk-of-bias concerns. These risk-of-bias concerns were primarily due to the unavailability of the researchers' pre-specified analysis intentions (i.e., the planned outcome measurements and statistical analyses could not be compared with those presented in the published articles). One study (Chen et al., 2019) was judged to have some concerns across multiple risk-of-bias domains, which substantially lowered confidence in the study findings and resulted in an overall high risk-of-bias judgment. The remaining four studies (Inslicht et al., 2021; Johnson et al., 2020; Rauch et al., 2018; Smits et al., 2020b) were judged to have a high risk of bias in at least one domain. Further methodologically robust research on DCS interventions is warranted.

Conclusions and Recommendations for Future Research

It is difficult to draw conclusions and recommendations regarding DCS interventions from the body of evidence considered by the REA. DCS is proposed to enhance fear extinction or extinction learning via partial agonism of the NMDA receptor (neurobiological mechanism of action). Thus, most of the included studies examined the effects of DCS administration in combination with exposure-based psychotherapy for anxiety disorders. Some studies appear to indicate that DCS improves outcomes from evidence-based psychotherapy. However, due to the mixed findings across studies, it is difficult to recommend the use of DCS interventions in specific clinical situations. Further high-quality research is required.

A productive direction for future research efforts would be to focus on interventions that combine DCS administration with evidence-based psychotherapy. The REA identified two (2) clinical trial records for ongoing RCTs focusing on mood/depressive disorders (see Appendix 4 for details). The findings from these studies may be relevant to future reports.

Reference List

American Psychiatric Association. (2022). *DSM history*. https://www.psychiatry.org/psychiatrists/practice/dsm/history-of-the-dsm

Araújo, A. M., Carvalho, F., de Lourdes Bastos, M., de Pinho, P. G., & Carvalho, M. (2015). The hallucinogenic world of tryptamines: An updated review. *Archives of Toxicology, 89*(8), 1151-1173. https://doi.org/10.1007/s00204-015-1513-x

Arnold, J. C. (2021). A primer on medicinal cannabis safety and potential adverse effects. *Australian Journal of General Practice*, *50*(6), 345-350. https://doi.org/10.31128/ajgp-02-21-5845

Arnold J. C., Nation T., & McGregor I. S. (2020). Prescribing medicinal cannabis. *Australian Prescriber, 43*, 152-159. https://doi.org/10.18773/austprescr.2020.052

Bonn-Miller, M. O., Sisley, S., Riggs, P., Yazar-Klosinski, B., Wang, J. B., Loflin, M. J. E., Shechet, B., Hennigan, C., Matthews, R., Emerson, A., & Doblin, R. (2021). The short-term impact of 3 smoked cannabis preparations versus placebo on PTSD symptoms: A randomized cross-over clinical trial. *PLOS ONE*, *16*(3), Article e0246990. https://doi.org/10.1371/journal.pone.0246990

Bridgeman, M. B., & Abazia, D. T. (2017). Medicinal cannabis: History, pharmacology, and implications for the acute care setting. *Pharmacy and Therapeutics*, *42*(3), 180-188. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5312634/

Carmi, L., Tendler, A., Bystritsky, A., Hollander, E., Blumberger, D. M., Daskalakis, J., Ward, H., Lapidus, K., Goodman, W., Casuto, L., Feifel, D., Barnea-Ygael, N., Roth, Y., Zangen, A., & Zohar, J. (2019). Efficacy and safety of deep transcranial magnetic stimulation for obsessive-compulsive disorder: A prospective multicenter randomized double-blind placebo-controlled trial. *The American Journal of Psychiatry*, *176*(11), 931-938. https://doi.org/10.1176/appi.ajp.2019.18101180

Centers for Disease Control and Prevention. (2020). *Outbreak of lung injury associated with the use of e-cigarette, or vaping, products.* https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html#key-facts

Clarivate. (2022). *EndNote* [Computer software]. https://endnote.com/product-details

Cohen, S. L., Bikson, M., Badran, B. W., & George, M. S. (2022). A visual and narrative timeline of US FDA milestones for Transcranial Magnetic Stimulation (TMS) devices. *Brain Stimulation*, *15*(1), 73-75. https://doi.org/10.1016/j.brs.2021.11.010

Chen, M. H., Cheng, C. M., Gueorguieva, R., Lin, W. C., Li, C. T., Hong, C. J., Tu, P. C., Bai, Y. M., Tsai, S. J., Krystal, J. H., & Su, T. P. (2019). Maintenance of antidepressant and antisuicidal effects by D-cycloserine among patients with treatment-resistant depression who responded to low-dose ketamine infusion: A double-blind randomized placebo-control study. *Neuropsychopharmacology, 44*(12), 2112-2118. https://doi.org/10.1038/s41386-019-0480-y

de Leeuw, A. S., van Megen, H. J., Kahn, R. S., & Westenberg, H. G. (2017). D-cycloserine addition to exposure sessions in the treatment of patients with obsessive-compulsive disorder. *European Psychiatry, 40*, 38-44. https://doi.org/10.1016/j.eurpsy.2016.06.011

Department of Veteran'' Affairs. (2020). *Transition and wellbeing research programme*. Australian Government. https://www.dva.gov.au/about-us/overview/research/transition-and-wellbeing-research-programme

Di Lazzaro, V., Pilato, F., Saturno, E., Oliviero, A., Dileone, M., Mazzone P., Tonali, F., Ranieri, Y., Huang, Z., & Rothwell, J. C. (2005). Theta-burst repetitive transcranial magnetic stimulation suppresses specific excitatory circuits in the human motor cortex. *The Journal of Physiology, 565*(3)*,* 945-950. https://doi.org/10.1113/jphysiol.2005.087288

Dutcher, C. D., Dowd, S. M., Zalta, A. K., Taylor, D. J., Rosenfield, D., Perrone, A., Otto, M. W., Pollack, M. H., Hofmann, S. G., & Smits, J. A. J. (2021). Sleep quality and outcome of exposure therapy in adults with social anxiety disorder. *Depression and Anxiety*, *38*(11), 1182-1190. https://doi.org/10.1002/da.23167

Farace, D. J., & Schopfel, J. (Eds.). (2010). *Grey literature in library and information studies*. De Gruyter Saur. https://directory.doabooks.org/handle/20.500.12854/31873

Fitzgerald, P. B., Hoy, K. E., & Daskalakis, S. J. (2021). Left handedness and response to repetitive transcranial magnetic stimulation in major depressive disorder. *The World Journal of Biological Psychiatry, 22*(4), 310-314. https://doi.org/10.1080/15622975.2020.1795255

Frecska, E., Bokor, P., & Winkelman, M. (2016). The therapeutic potentials of ayahuasca: Possible effects against various diseases of civilization. *Frontiers in Pharmacology, 7*, Article 35. https://doi.org/10.3389/fphar.2016.00035

Fuentes, J. J., Fonseca, F., Elices, M., Farré, M., & Torrens, M. (2020). Therapeutic use of LSD in psychiatry: A systematic review of randomized-controlled clinical trials. *Frontiers in Psychiatry*, *10*, Article 943. https://doi.org/10.3389/fpsyt.2019.00943

Garritty, C., Gartlehner, G., Nussbaumer-Streit, B., King, V. J., Hamel, C., Kamel, C., Affengruber, L., & Stevens, A. (2021). Cochrane Rapid Reviews Methods Group offers evidence-informed guidance to conduct rapid reviews. *Journal of Clinical Epidemiology*, *130*, 13-22. https://doi.org/10.1016/j.jclinepi.2020.10.007

Government of Canada. (2019). *Mandate, mission, vision, values and ethics: Definition of a veteran*. https://www.veterans.gc.ca/eng/about-vac/what-we-do/mandate#definition

Grinspoon, P. (2021, August 11). *The endocannabinoid system: Essential and mysterious*. Harvard Health Publishing. https://www.health.harvard.edu/blog/the-endocannabinoid-system-essential-and-mysterious-202108112569

Guyatt, G., Oxman, A. D., Akl, E. A., Kunz, R., Vist, G., Brozek, J., Norris, S., Falck-Ytter, Y., Glasziou, P.,36eBeerr, H., Jaeschke, R., Rind, D., Meerpohl, J., Dahm, P., & Schünemann, H. J. (2011). GRADE guidelines: 1. Introduction – GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology*, *64*(4), 383-394. https://doi.org/https://doi.org/10.1016/j.jclinepi.2010.04.026

Hallit, S., Haddad, C., Hallit, R., Akel, M., Obeid, S., Haddad, G., Soufia, M., Khansa, W., Khoury, R., Kheir, N., Elias Hallit, C. A., & Salameh, P. (2020). Validation of the Hamilton Anxiety Rating Scale and State Trait Anxiety Inventory A and B in Arabic among the Lebanese population. *Clinical Epidemiology and Global Health*, *8*(4), 1104-1109. https://doi.org/https://doi.org/10.1016/j.cegh.2020.03.028

Hamel, C., Michaud, A., Thuku, M., Skidmore, B., Stevens, A., Nussbaumer-Streit, B., & Garritty, C. (2021). Defining rapid reviews: A systematic scoping review and thematic analysis of definitions and defining characteristics of rapid reviews. *Journal of Clinical Epidemiology*, *129*, 74-85. https://doi.org/10.1016/j.jclinepi.2020.09.041

Hofmeijer-Sevink, M. K., Duits, P., Rijkeboer, M. M., Hoogendoorn, A. W., van Megen, H. J., Vulink, N. C., Denys, D. A., van den Hout, M. A., van Balkom, A. J., & Cath, D. C. (2017). No effects of D-cycloserine enhancement in exposure with response prevention therapy in panic disorder with aAgoraphobia: A double-blind, randomized controlled trial. *Journal of Clinical Psychopharmacology*, *37*(5), 531-539. https://doi.org/10.1097/jcp.0000000000000757

Horvath, J. C., Mathews, J., Demitrack, M. A., & Pascual-Leone, A. (2010). The NeuroStar TMS device: Conducting the FDA approved protocol for treatment of depression. *Journal of Visualized Experiments, 45*, Article e2345. https://doi.org/10.3791/2345-v

Huang, Y-Z., Edwards, M. J., Rounis, E., Bhatia, K. P., & Rothwell, J. C. (2005). Theta burst stimulation of the human motor cortex. *Neuron, 45*(2), 201-206. https://doi.org/10.1016/j.neuron.2004.12.033

Huang, Y-Z., Sommer, M., Thickbroom, G., Hamada, M., Pascual-Leonne, A., Paulus, W., Classen, J., Peterchev, A. V., Zangen, A., Ugawa, Y. (2009). Consensus: New methodologies for brain stimulation. *Brain Stimulation, 2*(1), 2-13. https://doi.org/10.1016/j.brs.2008.09.007

Illingworth, B. J., Lewis, D. J. Lambarth, A. T., Stocking, K., Duffy, J. M., Jelen, L. A., & Rucker, J. J. (2021). A comparison of MDMA-assisted psychotherapy to non-assisted psychotherapy in treatment-resistant PTSD: A systematic review and meta-analysis. *Journal of Psychopharmacology, 35*(5), 501-511. https://doi.org/10.1177/0269881120965915.

Inslicht, S. S., Niles, A. N., Metzler, T. J., Lipshitz, S. L., Otte, C., Milad, M. R., Orr, S. P., Marmar, C. R., & Neylan, T. C. (2021). Randomized controlled experimental study of hydrocortisone and D-cycloserine effects on fear extinction in PTSD. *Neuropsychopharmacology, 47,* 1945-1952. https://doi.org/10.1038/s41386-021-01222-z

Johnson, M. W., Bruner, N. R., Johnson, P. S., Silverman, K., & Berry, M. S. (2020). Randomized controlled trial of d-cycloserine in cocaine dependence: Effects on contingency management and cue-induced cocaine

craving in a naturalistic setting. *Experimental and Clinical Psychopharmacology*, *28*(2), 157-168. https://doi.org/10.1037/pha0000306

Jones, K., O'Donnell, M., Stone, C., & Varker, T. (2020). *Understanding evidence: A framework for guiding the use of evidence in decision making for mental health interventions including adjunct therapies.* Report prepared for Department of Veterans' Affairs. Phoenix Australia – Centre for Posttraumatic Mental Health. https://www.dva.gov.au/sites/default/files/2021-10/understanding-evidence-framework.pdf

Kappelmann, N., Suesse, M., Steudte-Schmiedgen, S., Kaldewaij, R., Browning, M., Michael, T., Rinck, M., & Reinecke, A. (2020). D-cycloserine as adjunct to brief computerised CBT for spider fear: Effects on fear, behaviour, and cognitive biases. *Journal of Behavior Therapy and Experimental Psychiatry, 68*, Article 101546. https://doi.org/10.1016/j.jbtep.2019.101546

Kayser, R. R., Haney, M., Raskin, M., Arout, C., & Simpson, H. B. (2020). Acute effects of cannabinoids on symptoms of obsessive-compulsive disorder: A human laboratory study. *Depression and Anxiety, 37*, 801-811. https://doi.org/10.1002/da.23032

Kessler, R. C., & Ustün, T. B. (2004). The World Mental Health (WMH) Survey Initiative Version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). *International Journal of Methods in Psychiatric Research*, *13*(2), 93-121. https://doi.org/10.1002/mpr.168

Khan, Z., & Bollu, P. C. (2022). Horner syndrome. In *StatPearls*. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK500000/

Kisely, S., Connor, M., & Somogyi, A. (2021). *An evaluation of the therapeutic value, benefits and risks of methylenedioxymethamphetamine (MDMA) and psilocybin for the treatment of mental, behavioural or developmental disorders: A report to the Therapeutic Goods Administration.* https://www.tga.gov.au/node/940601

Klomjai, W., Katz, R., & Lackmy-Vallée, A. (2015). Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). *Annals of Physical and Rehabilitation Medicine, 58*(4), 208-213. https://doi.org/https://doi.org/10.1016/j.rehab.2015.05.005

Kvale, G., Hansen, B., Hagen, K., Abramowitz, J. S., Børtveit, T., Craske, M. G., Franklin, M. E., Haseth, S., Himle, J. A., Hystad, S., Kristensen, U. B., Launes, G., Lund, A., Solem, S., & Öst, L. G. (2020). Effect of D-cycloserine on the effect of concentrated exposure and response prevention in difficult-to-treat obsessive-compulsive disorder: A randomized clinical trial. *JAMA Network Open*, *3*(8), Article e2013249. https://doi.org/10.1001/jamanetworkopen.2020.13249

Lipov, E. G., Joshi, J. R., Sanders, S. & Slavin, K. V. (2009). A unifying theory linking the prolonged efficacy of the stellate ganglion block for the treatment of chronic regional pain syndrome (CRPS), hot flashes, and posttraumatic stress disorder (PTSD). *Medical Hypotheses, 72*, 657-661. https://doi.org/10.1016/j.mehy.2009.01.009

Liu, X., Zhao, X., Liu, T., Liu, Q., Tang, L., Zhang, H., Luo, W., Daskalakis, Z. J., & Yuan, T. F. (2020). The effects of repetitive transcranial magnetic stimulation on cue-induced craving in male patients with heroin use disorder. *eBioMedicine*, *56*, Article 102809. https://doi.org/10.1016/j.ebiom.2020.102809

Loflin, M., & Earleywine, M. (2015). No smoke, no fire: What the initial literature suggests regarding vapourized cannabis and respiratory risk. *Canadian Journal of Respiratory Therapy, 51*(1), 7-9. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4456813/

Maguire, A. M. (2020, July). *The Australian Defence Community needs assessment report: Priority areas for service planning*. Gallipoli Medical Research Foundation & RSL Queensland.

Microsoft Corporation. (2022). *Microsoft Excel* [Computer software]. https://office.microsoft.com/excel

Murad, M. H., Mustafa, R. A., Schünemann, H. J., Sultan, S., & Santesso, N. (2017). Rating the certainty in evidence in the absence of a single estimate of effect. *Evidence Based Medicine*, *22*(3), 85-87. https://doi.org/10.1136/ebmed-2017-110668

National Institute for Health Research. (n.d.). *PROSPERO: International prospective register of systematic reviews*. https://www.crd.york.ac.uk/prospero/

New Zealand Defence Force. (2018). *The veteran rehabilitation strategy*. Wellington, NZ: Veterans' Affairs, New Zealand Government. https://www.veteransaffairs.mil.nz/assets/Corporate/ce8a5db85a/The-Veteran-Rehabilitation-Strategy-2018-2021.pdf

NHMRC. (2019). *Guidelines for guidelines: Assessing certainty of evidence*. https://www.nhmrc.gov.au/guidelinesforguidelines/develop/assessing-certainty-evidence

Norberg, M. M., Krystal, J. H., & Tolin, D. F. (2008). A meta-analysis of D-cycloserine and the facilitation of fear extinction and exposure therapy. *Biological Psychiatry*, *63*(12), 1118-1126. https://doi.org/10.1016/j.biopsych.2008.01.012

Oberman, L., Edwards, D., Eldaief, M., & Pascual-Leone, A. (2011). Safety of theta burst transcranial magnetic stimulation: A systematic review of the literature. *Journal of Clinical Neurophysiology, 28*(1), 67-74. https://doi.org/10.1097/WNP.0b013e318205135f

Pilecki, B., Luoma, J. B., Bathje, G. J., Rhea, J., & Narloch, V. F. (2021). Ethical and legal issues in psychedelic harm reduction and integration therapy. *Harm Reduction Journal, 18*, Article 40. https://doi.org/10.1186/s12954-021-00489-1

Popay, J., Roberts, H., Sowden, A., Petticrew, M., Arai, L., Rodgers, M. Britten, N., Roen, K., & Duffy, S. (2006). *Guidance on the conduct of narrative synthesis in systematic reviews: A product from the ESRC methods programme*. https://www.lancaster.ac.uk/media/lancaster-university/content-assets/documents/fhm/dhr/chir/NSsynthesisguidanceVersion1-April2006.pdf

Pyrkosch, L., Mumm, J., Alt, I., Fehm, L., Fydrich, T., Plag, J., & Strohle, A. (2018). Learn to forget: Does post-exposure administration of d-cycloserine enhance fear extinction in agoraphobia? *Journal of Psychiatric Research*, *105*, 153-163. https://doi.org/10.1016/j.jpsychires.2018.08.016

Rae Olmsted, K. L., Bartoszek, M., Mulvaney, S., McLean, B., Turabi, A., Young, R., Kim, E., Vandermaas-Peeler, R., Morgan, J. K., Constantinescu, O., Kane, S., Nguyen, C., Hirsch, S., Munoz, B., Wallace, D., Croxford, J., Lynch, J. H., White, R., & Walters, B. B. (2019). Effect of stellate ganglion block treatment on posttraumatic stress disorder symptoms: A randomized clinical trial. *JAMA Psychiatry, 77*(2), 130-138. https://doi.org/10.1001/jamapsychiatry.2019.3474

Rauch, S. A. M., Koola, C., Post, L., Yasinski, C., Norrholm, S. D., Black, K., & Rothbaum, B. O. (2018). In session extinction and outcome in virtual reality exposure therapy for PTSD. *Behaviour Research and Therapy*, *109*, 1-9. https://doi.org/10.1016/j.brat.2018.07.003

Reinecke, A., Nickless, A., Browning, M., & Harmer, C. J. (2020). Neurocognitive processes in d-cycloserine augmented single-session exposure therapy for anxiety: A randomized placebo-controlled trial. *Behaviour Research and Therapy*, *129*, Article 103607. https://doi.org/10.1016/j.brat.2020.103607

Rethlefsen, M. L., Kirtley, S., Waffenschmidt, S., Ayala, A. P., Moher, D., Page, M. J., Koffel, J. B., & PRISMA-S Group. (2021). PRISMA-S: An extension to the PRISMA Statement for reporting literature searches in systematic reviews. *Systematic Reviews*, *10*(1), Article 39. https://doi.org/10.1186/s13643-020-01542-z

Roque, A. D., Rosenfield, D., Smits, J. A. J., Simon, N., Otto, M. W., Marques, L., Pollack, M. H., Hofmann, S. G., & Meuret, A. E. (2018). Does d-cycloserine facilitate the effects of homework compliance on social anxiety symptom reduction? *Journal of Anxiety Disorders*, *53,* 85-90. https://doi.org/10.1016/j.janxdis.2017.11.004

Rosenbaum, S. B., Gupta, V., & Palacios, J. L. (2022). Ketamine. In *StatPearls*. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK470357/

Rossi S., Antal A., Bestmann S., Bikson M., Brewer C., Brockmöller J., Carpenter L. L., Cincotta M., Chen R., Daskalakis J. D., Di Lazzaro V., Fox M. D., George M. S., Gilbert D., Kimiskidis V. K., Koch G., Ilmoniemi R. J., Lefaucheur J. P., Leocani L., … Hallett, M. (2021). Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert guidelines. *Clinical Neurophysiology*, *132*(1), 269-306. https://doi.org/10.1016/j.clinph.2020.10.003

Rossi, S., Hallett, M., Rossini, P. M., Pascual-Leone, A., & Safety of TMS Consensus Group (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology, 120*(12), 2008-2039. https://doi.org/10.1016/j.clinph.2009.08.016

Rucker, J. J., & Young, A. H. (2021). Psilocybin: From serendipity to credibility? *Frontiers in Psychiatry, 12*, Article 659044. https://doi.org/10.3389/fpsyt.2021.659044

Russo, E. B., & Marcu, J. (2017). Cannabis pharmacology: The usual suspects and a few promising leads. *Advances in Pharmacology*, *80*, 67-134. https://doi.org/10.1016/bs.apha.2017.03.004

Schade, S., & Paulus, W. (2015). D-cycloserine in neuropsychiatric diseases: A systematic review. *International Journal of Neuropsychopharmacology*, *19*(4), Article pyv102. https://doi.org/10.1093/ijnp/pyv102

Schenberg, E. E. (2018). Psychedelic-assisted psychotherapy: A paradigm shift in psychiatric research and development. *Frontiers in pharmacology*, *9*, Article 733. https://doi.org/10.3389/fphar.2018.00733

Sessa, B., Higbed, L., & Nutt, D. (2019). A review of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy. *Frontiers in Psychiatry, 10*, Article 138. https://doi.org/10.3389/fpsyt.2019.00138

Sihota, A., Smith, B. K., Ahmed, S. A., Bell, A., Blain, A., Clarke, H., Cooper, Z. D., Cyr, C., Daeninck, P., Deshpande, A., Ethans, K., Flusk, D., Le Foll, B., Milloy, M. J., Moulin, D. E., Naidoo, V., Ong, M., Perez, J., Rod, K., Sealey, R., … ''Connell, C. (2021). Consensus-based recommendations for titrating cannabinoids and tapering opioids for chronic pain control. *International Journal of Clinical Practice, 75*(8), Article e13871. https://doi.org/10.1111/ijcp.13871

Smits, J. A. J., Pollack, M. H., Rosenfield, D., Otto, M. W., Dowd, S., Carpenter, J., Dutcher, C. D., Lewis, E. M., Witcraft, S. M., Papini, S., Curtiss, J., Andrews, L., Kind, S., Conroy, K., & Hofmann, S. G. (2020a). Dose timing of D-cycloserine to augment exposure therapy for social anxiety disorder: A randomized clinical trial. *JAMA Network Open*, *3*(6)*,* Article e206777. https://doi.org/10.1001/jamanetworkopen.2020.6777

Smits, J. A. J., Zvolensky, M. J., Otto, M. W., Piper, M. E., Baird, S. O., Kauffman, B. Y., Lee-Furman, E., Alavi, N., Dutcher, C. D., Papini, S., Rosenfield, B., & Rosenfield, D. (2020b). Enhancing panic and smoking reduction treatment with D-cycloserine: A pilot randomized clinical trial. *Drug Alcohol Dependence, 208*, Article 107877. https://doi.org/10.1016/j.drugalcdep.2020.107877

Sounderajah, V., Patel, V., Varatharajan, L., Harling, L., Normahani, P., Symons, J., Barlow, J., Darzi, A., & Ashrafian, H. (2021). Are disruptive innovations recognised in the healthcare literature? A systematic review. *BMJ Innovations, 7*(1), 208-216. https://doi.org/10.1136/bmjinnov-2020-000424

Sterne, J. A. C., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., Cates, C. J., Cheng, H. Y., Corbett, M. S., Eldridge, S. M., Emberson, J. R., Hernán, M. A., Hopewell, S., Hróbjartsson, A., Junqueira, D. R., Jüni, P., Kirkham, J. J., Lasserson, T., Li, T., McAleenan, A., … Higgins, J. P. T. (2019). RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ, 366*, Article l4898. https://doi.org/10.1136/bmj.l4898

Stultz, D. J., Osburn, S., Burns, T., Pawlowska-Wajswol, S., & Walton, R. (2020). Transcranial magnetic stimulation (TMS) safety with respect to seizures: A literature review. *Neuropsychiatric Disease and Treatment, 16,* 2989-3000. https://doi.org/10.2147/NDT.S276635

Summers, M. R., & Nevin, R. L. (2017). Stellate ganglion block in the treatment of post-traumatic stress disorder: A review of historical and recent literature. *Pain Practice, 17*(4), 546-553. https://doi.org/10.1111/papr.12503

Temesi, J., Gruet, M., Rupp, T., Verges, S., Millet, G. Y. (2014). Resting and active motor thresholds versus stimulus-response curves to determine transcranial magnetic stimulation intensity in quadriceps femoris. *Journal of NeuroEngineering and Rehabiliation, 11*, Article 40. https://doi.org/10.1186/1743-0003-11-40

Therapeutic Goods Administration. (2022). *Medicinal cannabis products by active ingredients.* Department of Health and Aged Care, Australian Government. https://www.tga.gov.au/medicinal-cannabis-products-active-ingredients

Therapeutic Goods Administration. (2021). *Notice of final decision to not amend the current Poisons Standard – Psilocybin and MDMA: 15 December 2021*. Department of Health, Australian Government. https://www.tga.gov.au/sites/default/files/notice-final-decisions-amend-or-not-amend-current-poisons-standard-relation-psilocybin-and-mdma.pdf

Therapeutic Goods Administration. (2017). *Guidance for the use of medicinal cannabis in Australia: Patient information.* Department of Health and Aged Care, Australian Government. https://www.tga.gov.au/resources/publication/publications/guidance-use-medicinal-cannabis-australia-patient-information

The GRADE Working Group. (2022). *GRADE*. https://www.gradeworkinggroup.org/

Thompson, E. (2015). Hamilton Rating Scale for Anxiety (HAM-A). *Occupational Medicine*, *65*(7), 601. https://doi.org/10.1093/occmed/kqv054

UK Office for Veterans' Affairs. (2020). *Veterans factsheet 2020*. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/874821/6.6409_CO_Armed-Forces_Veterans-Factsheet_v9_web.pdf

US Department of Veterans Affairs. (2019). *Verification assistance brief: Determining veteran status.* https://www.va.gov/OSDBU/docs/Determining-Veteran-Status.pdf

Van Hooff, M., Lawrence-Wood, E., Hodson, S., Sadler, N., Benassi, H., Hansen, C., Grace, B., Avery, J., Searle, A., Iannos, M., Abraham, M., Baur, J., & McFarlane, A. (2018). *Mental health prevalence report*. Department of Veterans' Affairs. https://www.dva.gov.au/documents-and-publications/mental-health-prevalence-report

Varker, T., Forbes, D., Dell, L., Weston, A., Merlin, T., Hodson, S., & O'Donnell, M. A. (2014). *A developer's guide to undertaking Rapid Evidence Assessments (REAs).* Guide prepared for the Department of Veterans' Affairs. Australian Centre for Posttraumatic Mental Health.

Veritas Health Innovation. (n.d.). *Covidence* [Computer software]. https://www.covidence.org/

Vollenweider, F. X. (2001). Brain mechanisms of hallucinogens and entactogens. *Dialogues in Clinical Neuroscience*, *3*(4), 265-279. https://doi.org/10.31887/dcns.2001.3.4/fxvollenweider

Williams E. (2017). Towards breakthrough healing: A history and overview of clinical MDMA research. *MAPS Bulletin Spring*. https://maps.org/news/bulletin/towards-breakthrough-healing-a-history-and-overview-of-clinical-mdma-research-3/

World Health Organization. (2022). *International statistical classification of diseases and related health problems (ICD)*. https://www.who.int/classifications/classification-of-diseases

Zıblak, A., Tumkaya, S., & Kashyap, H. (2021). Transcranial magnetic stimulation over orbitofrontal cortex in obsessive compulsive disorder: A double-blind placebo-controlled trial*. Journal of Obsessive-Compulsive and Related Disorders, 31*, Article 100687. https://doi.org/10.1016/J.JOCRD.2021.100687

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. o Limit the number of interventions (R2) and comparators (R3). o 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 o 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. o Use two reviewers for dual screen of at least 20% (ideally more) of abstracts, with conflict resolution. o 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 o 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. o 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)

• 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: D-cycloserine interventions

("d cycloserine"[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* = 9) by reason for exclusion in Figure 1 PRISMA diagram (D-cycloserine: Standalone and combined interventions).

Ongoing study (n = 2)

#	Registry ID	Mental Health Condition	Principal Investigator(s)	Location	Date of Registration	Expected Completion Date
1	NCT03937596	Major Depressive Disorder	McGirr, A.	Canada	2019 (May 6)	2020 (Dec 24)
2	NCT03511599	Major Depressive Disorder	Not reported	Canada	2018 (Apr 30)	2021 (Apr 21)

Ineligible publication type (n = 4)

#	YEAR	Reference	Exclusion reason
1	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
2	2019	Difede, J., Rothbaum, B. O., Rizzo, A. A., Wyka, K., Spielman, L., Jovanovic, T., Reist, C., Roy, M. J., Norrholm, S. D., Glatt, C., & Lee, F. (2019). Enhanced exposure therapy for combat-related Posttraumatic Stress Disorder (PTSD): Study protocol for a randomized controlled trial. *Contemporary Clinical Trials, 87*, Article 105857. https://doi.org/10.1016/j.cct.2019.105857	Study protocol
3	2018	Inslicht, S., Niles, A., Metzler, T., Milad, M., Orr, S. P., Marmar, C., & Neylan, T. (2018). Randomized controlled trial of hydrocortisone and D-cycloserine on fear extinction in PTSD. *Biological Psychiatry, 83*(9), S352. https://doi.org/10.1016/j.biopsych.2018.02.905	Poster abstract
4	2017	Inslicht, S., Milad, M., Orr, S. P., Marmar, C., & Neylan, T. (2017). Randomized controlled trial of hydrocortisone and D-cycloserine on fear extinction in PTSD. *Neuropsychopharmacology, 43*, S481-S482. https://doi.org/10.1038/npp.2017.266	Poster abstract

Secondary analysis (n = 3)

#	YEAR	Reference	Exclusion reason
1	2021	Dutcher, C. D., Dowd, S. M., Zalta, A. K., Taylor, D. J., Rosenfield, D., Perrone, A., Otto, M. W., Pollack, M. H., Hofmann, S. G., & Smits, J. A. J. (2021). Sleep quality and outcome of exposure therapy in adults with social anxiety disorder. *Depression and Anxiety, 38*(11), 1182-1190. https://doi.org/10.1002/da.23167	Secondary analysis
2	2019	Hamdeh, A. A., Bjureberg, J., Lenhard, F., Hedman-Lagerlöf, E., Flygare, O., Lundström, L., Ljótsson, B., Mataix-Cols, D., Rück, C., & Andersson, E. (2019). Sudden gains in internet-based cognitive behavior therapy for obsessive-compulsive disorder. *Journal of Obsessive-Compulsive and Related Disorders, 21*, 75-81. https://doi.org/10.1016/j.jocrd.2018.12.005	Secondary analysis

#	YEAR	Reference	Exclusion reason
3	2019	Peskin, M., Wyka, K., Cukor, J., Olden, M., Altemus, M., Lee, F. S., & Difede, J. (2019). The relationship between posttraumatic and depressive symptoms during virtual reality exposure therapy with a cognitive enhancer. *Journal of Anxiety Disorders, 61*, 82-88. https://doi.org/10.1016/j.janxdis.2018.03.001	Secondary analysis

Appendix 5: List of Included Studies

D-cycloserine: Standalone and combined interventions (n = 13)

#	Citation	Experimental intervention	Target condition	Combined intervention details (if applicable)
1	Smits et al. (2020a)	D-cycloserine	SAD	Exposure-Based CBT – Group
2	Roque et al. (2018)	D-cycloserine	SAD	Exposure-Based CBT – Group
3	Kvale et al. (2020)	D-cycloserine	OCD	Exposure and Response Prevention (ERP) – Group
4	de Leeuw et al. (2017)	D-cycloserine	OCD	Exposure and Response Prevention (ERP)
5	Reinecke et al. (2020)	D-cycloserine	PD	Exposure Therapy (one session)
6	Hofmeijer-Sevink et al. (2019)	D-cycloserine	PD (with comorbid AG)	Exposure and Response Prevention (ERP)
7	Pyrkosch et al. (2018)	D-cycloserine	AG	CBT with in-vivo exposure
8	Kappelmann et al. (2020)	D-cycloserine	SP (spider)	CBT (one session)
9	Chen et al. (2019)	D-cycloserine	MDD and BP	Ketamine
10	Johnson et al. (2020)	D-cycloserine	CocUD	Naturalistic Exposure Therapy
11	Smits et al. (2020b)	D-cycloserine	TUD (with comorbid panic attacks)	Panic and Smoking Reduction Treatment (PSRT)
12	Inslicht et al. (2021)	D-cycloserine	PTSD	Fear Extinction Learning
13	Rauch et al. (2018)	D-cycloserine	PTSD	Virtual Reality Exposure (VRE) Therapy

Notes. AG = Agoraphobia. BP = Bipolar Disorder. CBT = Cognitive Behavioural Therapy. CocUD = Cocaine Use Disorder. MDD = Major Depressive Disorder. OCD = Obsessive Compulsive Disorder. PD = Panic Disorder. PTSD = Posttraumatic Stress Disorder. SAD = Social Anxiety Disorder. SP = Specific Phobia. TUD = Tobacco Use Disorder. VRE = Virtual Reality Exposure Therapy.

Appendix 6: Matrix of Included Studies

D-cycloserine: Standalone and combined interventions (n = 13)

	Anxiety Disorders	Mood/Depressive Disorders	Substance Use Disorders	Trauma and Stressor-Related Disorders
D-cycloserine	2 x combined Tx (SAD) 2 x combined Tx (OCD) 1 x combined Tx (PD) 1 x combined Tx (PD with comorbid AG) 1 x combined Tx (AG) 1 x combined Tx (SP of spiders)	1 x combined Tx (MDD and BP)	1 x combined Tx (CocUD) 1 x combined Tx (TUD with comorbid panic attacks)	2 x combined Tx (PTSD)

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. AG = Agoraphobia. BP = Bipolar Disorder. CocUD = Cocaine Use Disorder. MDD = Major Depressive Disorder. OCD = Obsessive Compulsive Disorder. PD = Panic Disorder. PTSD = Posttraumatic Stress Disorder. SAD = Social Anxiety Disorder. SP = Specific Phobia. TUD = Tobacco Use Disorder.

Appendix 7: Summary of Findings

1. D-Cycloserine for Social Anxiety Disorder: Combined intervention (Exposure-Based Group CBT)

Citation	Smits et al. (2020a)
Study Design	• Double-blind, randomised, placebo-controlled, trial. • Multi-site.
Sample Size	• 152 participants.
Population	• USA. • Social Anxiety Disorder (SAD; DSM-5 criteria). • Total sample: M = 29.24 years (SD = 10.16); 55.26% male. • DCS (pre-session): M = 29.73 years (SD = 10.42); 42.11% male. • DCS (post-session): M = 27.54 years (SD = 8.29); 41.67% male. • DCS (tailored): M = 30.73 years (SD = 9.88); 50% male. • Placebo: M = 28.76 years (SD = 11.81); 42.11% male.
Intervention/s (I) and Comparator/s (C)	• All participants received group, exposure-based, CBT (5 sessions delivered over 5 weeks): one (60-minute) psychoeducation session and four (90-minute) exposure therapy sessions. • All participants received an oral capsule before and after each exposure therapy session; participants were randomised to one of four medication groups at session 2 (i.e., first exposure therapy session). • I (n = 114): DCS (50 mg) and polyethylene glycol 3350 powder; three groups: o Pre-session (n = 38): DCS before, and placebo after, exposure therapy session. o Post-session (n = 36): Placebo before, and DCS after, exposure therapy session. o Tailored (n = 40): Placebo before exposure therapy session. DCS after successful therapy session and placebo after unsuccessful therapy session (where successful therapy session was defined as low fear at the end of exposure practice). • C (n = 38): Placebo (polyethylene glycol 3350 powder).
Outcome Measure/s	• Liebowitz Social Anxiety Scale (LSAS). • Social Phobic Disorders – Severity (SPD-S) Form.
General	• Period study was conducted: February 2015 to January 2018 (recruitment); September 2019 to March 2020 (data analysis).
Inclusion Criteria	• Adults. • Social Anxiety Disorder (SAD) diagnosis (DSM-5 criteria). • Score of at least (≥) 60 on the Liebowitz Social Anxiety Scale (LSAS).
Exclusion Criteria	• Lifetime history of bipolar, psychotic, or obsessive compulsive disorder. • Eating disorder, PTSD, or substance use disorder in the past 6 months. • Any potentially interfering cognitive dysfunction. • Significant suicidal ideation or suicidal behaviours in the past 6 months. • Serious medical illness or history of seizures. • Pregnancy, lactation, or of childbearing potential and not using contraception. • Concurrent psychotherapy or pharmacotherapy or prior nonresponse to exposure therapy.
Assessment Time-Point/s	• Baseline: pre-treatment (one week prior to first session). • During: weekly for 5 weeks.

Citation	Smits et al. (2020a)
	• Follow-up: 1 week, 1 month, and 3 months post-treatment (end of session 5).
Main Findings	• At 3-month follow-up: o The pre- and post-session DCS groups did not significantly differ on symptom improvement ($p = 0.43$) or symptom severity ($p = 0.88$). o Compared with the tailored DCS group, greater symptom improvement was observed for the pre- and post-session DCS groups ($p < 0.001$ and $p = 0.008$, respectively) and lower symptom severity was observed for the pre- and post-session DCS groups ($p = 0.004$ and $p = 0.008$, respectively). o Compared with the placebo group, greater symptom improvement was observed for the pre-session DCS and post-session DCS groups ($p < 0.001$ and $p = 0.002$, respectively) o Compared with the placebo group, the tailored DCS group did not significantly differ on symptom improvement ($p = 0.62$) or symptom severity ($p = 0.64$).
Safety and Adverse Events	• The authors stated that "adverse effects potentially attributable to the drug were mild" (no further detail reported).

2. D-Cycloserine for Social Anxiety Disorder: Combined intervention (Exposure-Based Group CBT)

Citation	Roque et al. (2018)
Study Design	• Double blind, randomised, placebo-controlled, trial. • Multi-site.
Sample Size	• 169 participants.
Population	• USA. • Social Anxiety Disorder (SAD; DSM-IV criteria). • Total sample: M = 32.6 years (SD = 10.36); 56.8% male. • DCS: age not reported by group; 64% male. • Placebo: age not reported by group; 49% male.
Intervention/s (I) and Comparator/s (C)	• All participants received 12 (2.5-hour) sessions of exposure-based, group CBT (4 to 6 participants in each group led by 2 therapists). • All participants received an oral tablet one hour before each of the five (5) exposure therapy sessions (i.e., session 3 to 7) of the 12-session protocol. • I (n = 87): DCS (50 mg). • C (n = 82): Placebo (polyethylene glycol 3350).
Outcome Measure/s	• Liebowitz Social Anxiety Scale (LSAS). • Homework compliance was assessed across three dimensions on a Likert scale: (i) completion; (ii) effort; and (iii) relevance.
General	• No significant differences on any demographic information except gender: there were significantly more males in the DCS group compared with the placebo group (64% vs. 49%). • Period study was conducted: not reported.
Inclusion Criteria	• 18 to 65 years old. • Primary diagnosis of Social Anxiety Disorder (DSM-IV criteria). • Score of at least (≥) 60 on the Liebowitz Social Anxiety Scale (LSAS). • Willingness to participate in CBT treatment and take pharmacological treatment.

Citation	Roque et al. (2018)
Exclusion Criteria	• Clinically significant abnormalities, medical illness, or cognitive illness. • Lifetime history of seizures, organic brain syndrome, mental retardation, cognitive dysfunction, head trauma, OCD, bipolar disorder, psychosis, schizophrenia, or delusional disorders. • Eating or substance use disorders (except nicotine), PTSD, or significant suicidal ideation in the last 6 months. • Pregnant, lactating, or not using medically accepted forms of contraception. • Current treatment with isoniazid. • Prior non-response to adequately delivered exposure treatment. • No concurrent psychotropic medication (e.g., antidepressants, anxiolytics, beta-blockers) for at least 2 weeks prior to study entry. • Any concurrent psychotherapy targeting symptoms of social anxiety disorder (except for general supportive therapy) in the last 3 months.
Assessment Time-Point/s	• During treatment: o Social anxiety was assessed by an independent rater at each therapy session (week 1 to 12). o Homework compliance during the previous week was assessed by the therapist at therapy sessions 2 to 8, 10, and 12. • Post-treatment: social anxiety was assessed by an independent rater who was blind to study condition (week 13).
Main Findings	• Greater homework compliance during the week leading up to a therapy session was associated with lower social anxiety symptoms (as measured by the LSAS; $p < 0.001$). • However, social anxiety symptoms did not significantly differ for the DCS group compared with the placebo group, irrespective of whether the previous week's LSAS was controlled ($p = 0.980$) or not ($p = 0.531$). • Compared to placebo, DCS augmentation did not enhance homework compliance in the next week, controlling for homework compliance in the previous week ($p = 0.326$). • There were no significant differences in the levels of homework compliance (low; average; high) in the DCS group compared with the placebo group, either after the tablet administration sessions (week 3 to 7; $p = 0.872$), or over the course of the study (week 1 to 12; $p = 0.622$). • Homework compliance did not increase any faster in the DCS group compared with the placebo group, either during the tablet administration sessions (week 3 to 7; $p = 0.627$) or over the course of the study (week 1 to 12; $p = 0.992$). • Homework compliance at the last session (week 12) was not significantly higher in the DCS group compared with the placebo group ($p = 0.789$).
Safety and Adverse Events	• None reported.

3. D-Cycloserine for Obsessive Compulsive Disorder: Combined intervention (Exposure and Response Prevention)

Citation	Kvale et al. (2020)
Study Design	• Triple-masked, randomised, placebo-controlled, trial. • Multi-site.
Sample Size	• 163 participants.
Population	• Norway.

Citation	Kvale et al. (2020)
	• Obsessive Compulsive Disorder (OCD; DSM-5 criteria). • "Difficult-to-treat". • Total sample: M = 34.5 years (SD = 10.9); 28.2% male. • DCS (100 mg): M = 35.38 years (SD = 11.42); 24.6% male. • DCS (250 mg): M = 34.82 years (SD = 11.75); 32.85% male. • Placebo: M = 32.42 years (SD = 7.06); 25.8% male.
Intervention/s (I) and Comparator/s (C)	• All participants received the Bergen 4-day treatment protocol: individual, concentrated, ERP delivered over four consecutive days in a group setting. • All participants received an oral capsule on each of the two days of exposure and response prevention (ERP) therapy (day 2 and 3 of the 4-day protocol). • I-1 (n = 65): DCS (100 mg). • I-2 (n = 67): DCS (250 mg). • C (n = 31): Placebo (not reported).
Outcome Measure/s	• Primary: o Yale-Brown Obsessive Compulsive Scale (Y-BOCS). • Secondary: o Dimensional Obsessive-Compulsive Scale – Short Form (DOCS-SF). o Generalized Anxiety Disorder, 7-item (GAD-7). o Obsessive-Compulsive Inventory – Revised (OCI-R). o Patient Health Questionnaire, 9-item (PHQ-9). o Warwick-Edinburgh Mental Well-Being Scale (WEMWBS).
General	• Participants had experienced OCD for a mean of 16.2 years (SD = 10.2); most had moderate to severe symptoms. • Most participants had comorbid diagnoses (*n* = 113; 69.3%); the most common comorbidities were generalized anxiety disorder (*n* = 52; 31.9%) and major depressive disorder (*n* = 51; 31.3%). • Clinical treatment response was defined as a reduction of at least (≥) 35% in the baseline Y-BOCS score. • Remission was defined as the response criterion plus a post-treatment Y-BOCS score of no more than (≤) 12. • Period study was conducted: January 2016 to August 2017.
Inclusion Criteria	• 18 years of age and over. • OCD diagnosis (DSM-5 criteria). • Able to be treated as an outpatient. • Fluent in Norwegian. • "Difficult-to-treat" OCD was defined as prior treatment with ERP (at least 6 sessions) and either responded to treatment and relapsed; or did not respond to treatment. • Response to earlier ERP was defined as at least (≥) 35% reduction and a post-treatment Y-BOCS score of no more than (≤) 15. • Relapse was defined as at least (≥) 35% increase in Y-BOCS score from post-treatment, a Y-BOCS score of at least (≥) 16, and a Clinical Global Impression (CGI) improvement score of at least (≥) 6 (i.e., "much worse"). • Non-responders were defined as those with a reduction in Y-BOCS scores from pre-treatment to post-treatment of less than (<) 35% and a Y-BOCS score of at least (≥) 16 after treatment.
Exclusion Criteria	• Ongoing substance abuse and/or dependence; bipolar disorder or psychosis. • Active suicidal ideation or plans. • Not receiving a stable dose of antidepressants for at least 12 weeks, or not willing to receive a stable dose during the four (4) intervention days.

Citation	Kvale et al. (2020)
	• Unwilling to refrain from anxiety-reducing substances during the 2 days of exposure. • Intellectual disability. • Residing more than one (1) hour by car or train from the treatment location. • Pregnant or breastfeeding. • Kidney impairment, hypersensitivity to DCS, porphyria, and epilepsy.
Assessment Time-Point/s	• Pre-treatment. • Post-treatment. • Follow-up: month 3 and 12.
Main Findings	• Overall, 91 participants (56.5%) achieved remission at post-treatment, while 70 participants (47.9%) achieved remission at the 12-month follow-up. • There were no significant differences in remission rates between groups. • The reduction in Y-BOCS score from pre- to post-treatment was significant for all treatment groups (250 mg DCS, 100 mg DCS, and placebo; $p < 0.05$). • There was a significant reduction in OCD symptoms at 12 months, and within-group effect sizes ranged from 3.01 for the group receiving 250 mg DCS to 3.49 for the group receiving 100 mg DCS (all's $p < .001$). • Compared with the placebo group: o No significant effect of DCS group was observed for OCD symptoms (as measured by the Y-BOCS) at the 12-month follow-up (250 mg DCS: d = -0.07, 95% CI = -0.51 to 0.37; 100 mg DCS: d = -0.01, 95% CI = -0.45 to 0.42). o No significant effect of DCS group was observed for depression symptoms (as measured by the PHQ-9) at the 12-month follow-up (250 mg DCS: d = 0.30, 95% CI = -0.17 to 0.76; 100 mg DCS: d = -0.01, 95% CI = -0.47 to 0.45). o No significant effect of DCS group was observed for anxiety symptoms (as measured by the GAD-7) at the 12-month follow-up (250 mg DCS: d = 0.43, 95% CI = -0.03 to 0.90; 100 mg DCS: d = 0.27, 95% CI = -0.19 to 0.73). o No significant effect of DCS group was observed for mental well-being (as measured by the WEMWBS) at the 12-month follow-up (250 mg DCS: d = 0.10, 95% CI = -0.42 to 0.63; 100 mg DCS: d = 0.34, 95% CI = -0.19 to 0.86).
Safety and Adverse Events	• No serious adverse events were reported. • A total of 25 participants reported 28 adverse events: headaches (n = 9/25; 36.0%); diarrhea (n = 5/25; 20.0%); constipation (n = 1/25; 4.0%), tiredness (n = 2/25; 8.0%), dizziness (n = 1/25; 4.0%), vomiting (n = 2/25; 8.0%), and pain (n = 1/25; 4.0%). • Adverse effects were not systematically related to DCS or placebo group: 9 participants (36.0%) from the 250 mg DCS group; 10 participants (40.0%) from the 100 mg DCS group; and 6 participants (24.0%) from the placebo group.

4. D-Cycloserine for Obsessive Compulsive Disorder: Combined intervention (Exposure and Response Therapy)

Citation	de Leeuw et al. (2017)
Study Design	• Double-blind, randomised, placebo-controlled, trial.
Sample Size	• 39 participants.
Population	• The Netherlands. • Obsessive Compulsive Disorder (OCD; DSM-IV criteria).

Citation	de Leeuw et al. (2017)
	• DCS: M = 38.1 years (SD = 14.2). • Placebo: M = 32.2 years (SD = 8.9). • Gender not reported.
Intervention/s (I) and Comparator/s (C)	• All participants received six (6) guided exposure sessions (one per week). • All participants received an oral tablet one hour before each exposure session. • I (n = 19): DCS (125 mg). • C (n = 20): placebo.
Outcome Measure/s	• Primary: o Yale-Brown Obsessive Compulsive Scale (Y-BOCS). • Secondary: o Clinical Global Impressions Scale (CGI).
General	• Full and partial treatment response was defined as 30% and 25% reductions on the Y-BOCS respectively. • The screening procedure consisted of a psychiatric and medical investigation and confirmation of the diagnoses using the Structural Clinical Interview for DSM-IV Axis I Disorders (SCID-I). • Period study was conducted: March 2009 to December 2011.
Inclusion Criteria	• 18 years of age and over. • Primary diagnosis of OCD (DSM-IV criteria). • Concurrent medication was permitted (except for benzodiazepines) but doses had to be stable for the last two months and during the trial period. • Female participants were required to use a reliable contraceptive.
Exclusion Criteria	• Substance addiction or abuse. • primary diagnosis of a personality disorder. • psychotic disorder (current or in the past). • Severe somatic disorders and disorders that may interfere with the behaviour therapy. • Suicidal intentions. • Pregnancy or breastfeeding. • Usage of medication possibly interfering with DCS (e.g., isoniazide, protonionamide) and/or benzodiazepines. • Currently undergoing psychotherapy. • Intellectual disability and/or not understanding the rationale of exposure therapy.
Assessment Time-Point/s	• Baseline. • Mid-treatment: before the fifth session. • Post-treatment: One week after the last session.
Main Findings	• Symptoms of OCD (as measured by the Y-BOCS) did not significantly differ for the DCS and the placebo group (p = 0.076). • Rates of full treatment response (30% reduction on the Y-BOCS) did not significantly differ for the DCS and the placebo group (37% and 15%, respectively; p = 0.155). • Rates of partial treatment response (25% reduction on the Y-BOCS) significantly differed for the DCS and placebo group (53% and 20%, respectively; p = 0.048).
Safety and Adverse Events	• One participant in the DCS group complained of mild headache and dizziness after one dose of DCS. Otherwise, no adverse effects were reported.

5. D-Cycloserine for Panic Disorder: Combined intervention (Single-session Exposure Therapy)

Citation	Reinecke et al. (2020)
Study Design	• Double blind, randomised, placebo-controlled, trial.
Sample Size	• 33 participants.
Population	• UK. • Panic Disorder (DSM-IV criteria). • I (DCS): M = 42.1 years (SD = 16.7); 29% male. • C (placebo): M = 41.9 years (SD = 13.7); 19% male.
Intervention/s (I) and Comparator/s (C)	• All participants received a single session of manualised exposure therapy. • All participants received an oral tablet (250mg) two hours prior to the therapy session. • I (n = 17): DCS (250 mg). • C (n = 16): placebo (250 mg; microcrystalline cellulose).
Outcome Measure/s	• Primary: o Faces dot probe task (FDOT). • Secondary: o State Trait Anxiety Inventory (STAI-S/STAI-T). o Beck Depression Inventory (BDI). o Body Sensations Questionnaire (BSQ). o Agoraphobic Cognitions Questionnaire (ACQ). o Mobility Inventory (MI). o Panic Attack Scale (PAS). o Panic Disorder Severity Scale (PDSS).
General	• Clinical recovery was defined as agoraphobic avoidance scores (as measured by the MI) falling within the range reported for healthy persons. • Period study was conducted: November 2013 to April 2016.
Inclusion Criteria	• Panic disorder diagnosis using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). • At least moderate agoraphobic avoidance as measured by the Structured Panic Assessment Interview (i.e., a “yes” response to more than two situations listed under “(2) Avoidance”). • Occasional benzodiazepine or beta-blocker medication was permitted but participants were required to refrain from using these medications for 48 hours before the treatment and testing sessions. • Participants with MRI contraindications (e.g., metal implant) were included but not enrolled in MRI (DCS: n = 13; placebo: n = 14).
Exclusion Criteria	• Insufficient English skills. • Current or past psychotic disorder or bipolar disorder, substance abuse or dependence, epilepsy, or current primary depressive disorder. • CNS-active medication in the last 6 weeks, current treatment with D-cycloserine, ethionamide, or isoniazid medications (antibiotics used for the treatment of tuberculosis). • Exposure-based CBT for panic disorder in the last 3 months. • Pregnant or lactating. • Severe renal insufficiency (or other serious medical conditions) that may put the participant at risk.
Assessment Time-Point/s	• Neurocognitive markers were assessed one day after treatment. • Clinical symptom severity was measured:

Citation	Reinecke et al. (2020)
	o Pre-treatment: day before. o Post-treatment: day after. o Follow-up: 1 month. o Follow-up: 6 months.
Main Findings	• Next-day threat bias for fearful faces (as measured by FDOT) was significantly lower in the DCS group compared with the placebo group (p = 0.042). • At the one-month follow-up, a significantly higher percentage of clinical recovery (as measured by the MI) was observed for the DCS group (71%) compared with the placebo group (25%; p = 0.015). • At the six-month follow-up, there was no significant difference in clinical recovery (as measured by the MI) for the DCS group (70.6%) compared with the placebo group (43.8%; p = 0.17). • There were no significant differences in panic-specific outcome measures across all time-points (pre-treatment; post-treatment; 1-month follow-up; and 6-month follow-up), including fear of physical symptoms (BSQ), agoraphobia severity (MI), agoraphobic cognitions (ACQ), panic attack frequency (PAS), or panic severity (PDSS; all p's > 0.095).
Safety and Adverse Events	• No serious adverse events were reported.

6. D-Cycloserine for Panic Disorder with Agoraphobia: Combined intervention (Exposure and Response Prevention)

Citation	Hofmeijer-Sevink et al. (2019)
Study Design	• Double-blind, randomised, placebo-controlled, trial.
Sample Size	• 57 participants.
Population	• The Netherlands. • Panic Disorder with Agoraphobia (DSM-IV criteria). • Total sample: M = 35.4 years (SD = 10.6); 40.4% male. • Pre-exposure DCS: M = 29.5 years (SD = 6.2); 42.1% male. • Post-exposure DCS: M = 38.4 years (SD = 11.3); 36.8% male. • Placebo: M = 38.3 years (SD = 11.4); 42.1% male.
Intervention/s (I) and Comparator/s (C)	• All participants received 12 (90-minute) individual sessions of exposure and response prevention (ERP) using a standardised treatment protocol (including 6 within-session exposure treatments). • All participants received an oral tablet half an hour before each of the first six exposure therapy sessions, and directly after each of the first six exposure therapy sessions, within the 12-session ERP protocol. • I (n = 19): Pre-exposure DCS (125 mg; post-exposure: placebo). • I (n = 19): Post-exposure DCS (125 mg; pre-exposure placebo). • C (n = 19): Placebo (pre- and post-exposure placebo).
Outcome Measure/s	• Primary: o Mobility Inventory (MI); mean score on the "alone" subscale. • Secondary: o Mobility Inventory (MI); mean score on the "accompanied" subscale. o Beck Anxiety Inventory (BAI). o Beck Depression Inventory II (BDI-II). o Panic Disorder Severity Scale (PDSS).

Citation	Hofmeijer-Sevink et al. (2019)
	○ Subjective Units of Distress (SUD): subjective self-reported fear and credibility levels (SUD anxiety and SUD credibility).
General	• The following subgroups were examined to explore whether DCS facilitated a treatment effect for specific participants: ○ responders versus non-responders; where treatment response was defined as at least 25% symptom reduction on the MI "alone" subscale after session 12; ○ early responders versus late responders; where early response was defined as at least 25% symptom reduction on the MI "alone" subscale after session 7 (versus later or no response); and ○ severely versus mildly affected; where severely affected was defined as a baseline MI "alone" score above the median. • Participants receiving DCS before an exposure session were significantly younger than the other study groups (p = 0.009). • Eight (14%) participants dropped out of the study during therapy. ○ There were no differences between treatment completers and those who dropped out of the study on the baseline MI "alone" score, or on sociodemographic or treatment condition parameters. ○ Participants who dropped out of the study had significantly higher depression scores at baseline than the treatment completers (p = 0.009). • Period study was conducted: October 2010 to October 2013.
Inclusion Criteria	• Adults. • Panic disorder with agoraphobia.
Exclusion Criteria	• Severe major depressive disorder according to the SCID-I interview and/or scores greater than (>) 29 on the Beck Depression Inventory II (BDI-II). • Current bipolar disorder, current psychotic disorder, and dependence and abuse of alcohol or drugs during the past 3 months as determined by the SCID-I interview. • Intellectual disability: verbal IQ less than (<) 80 as assessed by the Dutch Reading Test for adults. • Inability to adequately read or speak Dutch. • History of neurological disease, renal, or liver abnormalities. • Pregnant or lactating. • History of severe adverse reactions to penicillin. • Unsuccessful evidence-based behavioural therapy for panic disorder in the preceding 12 months. • Current daily, daytime use of benzodiazepines.
Assessment Time-Point/s	• Baseline: one week prior to the start of therapy. • During treatment: before session 4 (mid-study medication period) and before session 8 (post-study medication period). • Post-treatment: after session 12 (post-ERP). • Follow-up: 3 and 6 months.
Main Findings	• No significant between-group differences (DCS vs. placebo) were observed for the primary outcome measure (MI-alone subscale) at any time-point (all p's > 0.121). • No significant differences in treatment outcome were observed for the DCS (pre- or post-exposure) groups and placebo group (all p's > 0.121). • At the 3-month follow-up, a greater symptom reduction on the MI-alone subscale was observed for the post-exposure DCS group compared with the pre-exposure DCS group (p = 0.009).

Citation	Hofmeijer-Sevink et al. (2019)
	• At the 3-month follow-up, a significantly larger reduction in anxiety symptoms (as measured by the BAI) was observed for the post-exposure DCS group compared with the pre-exposure DCS group (p = 0.049). • Ancillary analyses in specific subgroups (responders vs. non-responders, early vs. late responders, severely vs. mildly affected participants) did not reveal any between-group differences for the DCS groups compared with placebo.
Safety and Adverse Events	• Four participants receiving DCS reported mild adverse effects (nausea, fatigue); however, none required action.

7. D-Cycloserine for Agoraphobia: Combined intervention (CBT including in-vivo exposure)

Citation	Pyrkosch et al. (2018)
Study Design	• Double-blind, randomised, placebo-controlled, trial.
Sample Size	• 73 participants.
Population	• Germany. • Agoraphobia with or without panic disorder (ICD-10 criteria). • DCS: M = 34.11 years (SD = 10.37); 38.88% male. • Placebo: M = 40.86 years (SD = 12.94); 29.72% male.
Intervention/s (I) and Comparator/s (C)	• All participants received 12 manualised sessions of cognitive behavioural therapy (CBT) including three exposure sessions (session 7 to 9). • All participants received an oral tablet immediately after the each exposure session. • I (n = 36): DCS (50 mg). • C (n = 37): placebo.
Outcome Measure/s	• Primary: o Panic and Agoraphobia Scale (PAS). • Secondary: o Agoraphobic Cognitions Questionnaire (ACQ). o Body Sensations Questionnaire (BSQ). o Mobility Inventory (MI). o Anxiety Sensitivity Index (ASI). o Beck Anxiety Inventory (BAI). o Beck Depression Inventory II (BDI-II). o Brief Symptom Inventory (BSI). o Clinical Global Impressions (CGI) scale.
General	• Period study was conducted: November 2011 to May 2014.
Inclusion Criteria	• Diagnosis of agoraphobia with or without panic disorder according to ICD-10 criteria (F40.00, F40.01) based on clinical exploration as well as the SCID-I Screening and the coordinated use of IDCL-checklists. • Minimum score of 4 on the Clinical Global Impression (CGI) scale (i.e., 'moderately ill'). • Medications were unchanged during the four (4) weeks before enrolment and were required to remain stable throughout treatment.
Exclusion Criteria	• No specific exclusion criteria were reported.

Citation	Pyrkosch et al. (2018)
	• The authors stated that participants were included in the study "if they fulfilled Good Clinical Practice (GCP) conformal inclusion and exclusion criteria" (p. 155).
Assessment Time-Point/s	• Baseline: session 1. • During treatment: session 4 (2 months). • End of therapy: session 10 (3 months). • Follow-up: session 11 (4 months).
Main Findings	• Significant decreases in panic and agoraphobic symptoms were observed over time (observer-rated PAS: $p < 0.001$; self-rated PAS: $p < 0.001$). However, no significant between-group differences (DCS vs. placebo) were observed on either the observer-rated PAS ($p = 0.22$) or self-rated PAS ($p = 0.50$), and the groups did not significantly differ over time (observer-rated PAS: $p = 0.72$; self-rated PAS: $p = 0.61$). • For the secondary outcome measures (BSQ, MI alone, MI alone mean, MI accompanied mean, ASI, BAI, BDI-II, and BSI sum), there were significant main effects of time (all *p's* < 0.001), but no significant main effects for group, and no significant time by group interactions (all *p's* > 0.05). The exceptions were a main effect of group for the CGI score ($p = 0.002$), and a time by group interaction for the ACQ score (p = 0.03).
Safety and Adverse Events	• No serious adverse events or instances of emergency unblinding were reported.

8. D-Cycloserine for Specific Phobia (Spider): Combined intervention (CBT)

Citation	Kappelmann et al. (2020)
Study Design	• Double-blind, randomised, placebo-controlled, trial.
Sample Size	• 38 participants.
Population	• UK. • Spider-fearful individuals. • Spider phobia diagnosis (DSM-IV criteria): o DCS: 61.90%. o Placebo: 41.18%. • DCS: M = 26.67 years (SD = 5.97); 23.81% male. • Placebo: M = 26.88 years (SD = 7.79); 17.65% male.
Intervention/s (I) and Comparator/s (C)	• All participants received a single session of computerised CBT (psychoeducation and exposure therapy). • All participants received an oral capsule three hours prior to the therapy session. • I (n = 21): DCS (250 mg). • C (n = 17): Placebo (microcrystalline cellulose).
Outcome Measure/s	• Fear of Spiders Questionnaire (FSQ). • Spider Anxiety Screening (SAS). • Behavioural Approach Test (BAT). • Extrinsic Affective Simon Task (EAST). • Approach Avoidance Task (AAT). • Visual Analogue Scale (VAS).
General	• No differences in demographics, clinical characteristics, or subjective and behavioural measures of spider fear between DCS and placebo groups.

Citation	Kappelmann et al. (2020)
	• Period study was conducted: not reported.
Inclusion Criteria	• 18 to 80 years old. • Non-smoker or smoking less than 5 cigarettes per day. • No use of psychoactive medication in the previous six weeks. • Body mass index (BMI) between 18 and 30 kg/m^2. • Score of at least (≥) 14 on the Spider Anxiety Screening (SAS) at pre-screening and baseline.
Exclusion Criteria	• Pregnant or breastfeeding. • Current use of DCS, ethionamide, or isoniazid. • Lifetime history of bipolar disorder, psychosis, alcohol, medication or drug abuse or dependence. • Current primary depressive disorder assessed using the Structured Clinical Interview for DSM-IV (SCID). • First-degree family member with a history of severe psychiatric disease. • Lifetime history of severe physical illness. • Previous exposure-based CBT for spider phobia. • Inadequate English skills.
Assessment Time-Point/s	• Baseline (before drug administration). • Post-treatment (after drug administration). • Follow-up: 1 day; 1 month.
Main Findings	• Significant improvements were observed over time on the self-report and behavioural measures of spider fear (SAS: $p < 0.001$; FSQ: $p < 0.001$; BAT: $p < 0.001$), but not on the cognitive bias measures (EAST: $p = 0.19$; AAT: $p = 0.65$). • There was no evidence of an effect of DCS dosing on any outcome (SAS: $p = 0.67$; FSQ: $p = 0.88$; BAT: $p = 0.21$; EAST: $p = 0.92$; AAT: $p = 0.82$).
Safety and Adverse Events	• There were no significant differences between groups on physiological measures and VAS ratings of alertness, anxiousness, depressiveness, dizziness, flushness, hopelessness, nausea, sadness, sleepiness, tachycardia, or tearfulness (all p's > 0.10). • Participants in the DCS compared to placebo groups, however, became significantly dizzier ($p = 0.011$), more flushed ($p = 0.014$), and reported greater tremor ($p = 0.035$) at peak drug levels.

9. D-Cycloserine for Mood/Depressive Disorder: Combined intervention (Ketamine)

Citation	Chen et al. (2019)
Study Design	• Double-blind, randomised, placebo-controlled, trial. • Phase 2.
Sample Size	• 32 participants.
Population	• Taiwan. • Treatment-resistant depression (TRD) in the context of a diagnosis (DSM-IV criteria) of either major depressive disorder (MDD; n = 17) or bipolar disorder (BP; n = 15). • DCS: M = 43.50 years (SD = 11.00); 31.3% male; major depression (n = 10) and bipolar depression (n = 6). • Placebo: M = 48.81 years (SD = 9.70); 31.3% male; major depression (n = 7) and bipolar depression (n = 9).

Citation	Chen et al. (2019)
Intervention/s (I) and Comparator/s (C)	• Participants who responded to an open-label (phase 1 trial) ketamine infusion (n = 32/49; 65%) were randomised to receive a 6-week protocol of either ascending-dose DCS or placebo (phase 2 trial). • I (n = 16): DCS dose-titration procedure (250 mg for 2 days, 500 mg for 2 days, 750 mg for 3 days, and 1000 mg for 5 weeks). The final dose was adjusted in the range of 500 mg to 1000 mg per day based on the participant's tolerability. • C (n = 16): placebo.
Outcome Measure/s	• Hamilton Depression Rating Scale (HAM-D).
General	• Period study was conducted: August 2015 to May 2018. • Related paper: o Su, Chen, Li et al., (2017): Phase 1, open-label, trial examining ketamine for treatment-resistant depression (TRD).
Inclusion Criteria	• 21 to 65 years old. • Diagnosis (DSM-IV criteria) of major depressive disorder (MDD), bipolar disorder (BP), or major depressive episode (MDE). • Meet criteria for treatment-resistant depression (TRD). o TRD in those with MDD was defined as non-response (with adequate dose and duration) to at least two different antidepressants. o TRD in those with BP was defined as non-response response (with adequate dose and duration) to at least two antidepressants or mood stabilisers with a documented efficacy in bipolar depression (i.e., lithium, lamotrigine, quetiapine, or olanzapine).
Exclusion Criteria	• History of major medical or neurological illness (i.e., stroke or seizure). • Alcohol or substance abuse. • Mild depressive symptoms prior to study entry (i.e., a score less than 16 on the 17-item Hamilton Depression Rating Scale, HAM-D).
Assessment Time-Point/s	• Depression symptoms were rated at multiple time-points: at every dose titration and weekly for 6 weeks.
Main Findings	• Total HAM-D scores did not differ throughout the follow-up period for the DCS and placebo groups (p = 0.30). • The interaction between disorder type and treatment was not significant (p = 0.18). • Separate analyses for individuals with major depression (p = 0.77) and with bipolar depression (p = 0.14) demonstrated that the maintenance of the antidepressant effect of ketamine infusion was similar for the DCS and placebo groups. • The DCS group exhibited lower scores on item 3 of the HAM-D (suicide) compared with the placebo group throughout the follow-up period (p = 0.01).
Safety and Adverse Events	• Adverse effects, including dizziness (18.8% vs. 6.3%; p = 0.600), sedation (18.8% vs. 0%; p = 0.226), hand tremor (12.5% vs. 0%; p = 0.484), and itching (6.3% vs. 0%; p > 0.999) were rare and did not differ between DCS and placebo groups.

10. D-Cycloserine for Cocaine Use Disorder: Combined intervention (Exposure Therapy)

Citation	Johnson et al. (2020)
Study Design	• Double-blind, randomised, placebo-controlled trial.

Citation	Johnson et al. (2020)
Sample Size	• 39 participants (per-protocol sample). o 52 participants randomised. o 13 excluded from analyses: 4 withdrew from the DCS group; 9 excluded due to protocol deviations (DCS: 6; placebo: 3).
Population	• USA. • Cocaine dependent (DSM-IV criteria). • Treatment seeking. • DCS: M = 51.3 years (SD = 5.3); 33% male. • Placebo: M = 52.1 (SD = 4.9); 29% male.
Intervention/s (I) and Comparator/s (C)	• All participants received 9 sessions (three sessions per week) of urinalysis-based contingency management (i.e., a financial incentive for providing cocaine-negative urine samples) and exposure therapy in a naturalistic environment. • An oral capsule was administered prior to each exposure therapy session (i.e., following the delivery of urinalysis feedback with potential monetary reward). • I (n = 30): DCS (50 mg). • C (n = 22): placebo (lactose).
Outcome Measure/s	• Primary: o Urinalysis (quantitative: ng/mL benzoylecgonine; qualitative: positive/negative 7-panel dipsticks). o Instances of new use were calculated from the contingency management phase quantitative cocaine urine results and defined as less than (<) 50% decrease in benzoylecgonine concentration compared to the preceding urine sample. • Secondary: o Cocaine Craving Questionnaire-Now (CCQ-Now). o Situational Confidence Questionnaire-Cocaine (SCQ). o Profile of Mood States (POMS). o Timeline Followback (TLFB) method for reporting drug use. o Battery of cognitive tasks.
General	• Randomisation to the study groups was stratified according to three variables: (i) number of cocaine-positive urine samples during the 6 induction sessions (stratified into one of two categories: 0 to 3 or 4 to 6, based on qualitative results; dichotomous variable); (ii) route of cocaine administration (i.e., intranasal or IV); and (iii) presence or absence of alcohol abuse (DSM-IV criteria). • There were no significant differences in baseline characteristics for the DCS and placebo groups. • A power analysis suggested 45 participants per group would provide sufficient power to detect a significant between-group difference; however, extramural financial support for the trial was exhausted prior to achieving the target sample size. • Period study was conducted: not reported.
Inclusion Criteria	• 18 to 60 years old. • DSM-IV criteria for cocaine dependence using a modified checklist (the checklist alone was used to determine dependence in this study). • Treatment seeking. • Able to complete all study measures.
Exclusion Criteria	• Dependence on a drug other than cocaine or nicotine (DSM-IV criteria; participants could meet abuse criteria for other drugs).

Citation	Johnson et al. (2020)
	• Currently diagnosed with a major psychiatric disorder besides substance abuse or dependence. • History of seizure disorder, severe hepatic impairment, porphyria, serious head trauma, dementia, or significant cognitive impairment. • Reported use of DCS in the past year. • Concurrently prescribed or using ethionamide or isoniazid (i.e., medications for tuberculosis). • Positive urine test for opioids at the in-person screening interview. • Inadequate literacy. • Pregnant, breastfeeding, planning to become pregnant within 3 months, or not willing to use an effective means of birth control during treatment.
Assessment Time-Point/s	• The study included three phases (three sessions per week; total of 21 sessions): o Trial induction (week 1 to 2): 6 sessions. o Treatment (week 3 to 5): 9 sessions. o Post-treatment (week 6 to 7): 6 sessions. • Session 1 to 21: o Breath and urine samples tested for cocaine, amphetamines, benzodiazepines, opioids, and cannabis. o Self-report assessments. • Session 6 (induction) o Cognitive tasks assessing attention, learning, and memory.
Main Findings	• There were no significant differences on quantitative, qualitative, or new use measures of cocaine use for the DCS group compared with the placebo group. • However, significant reductions in qualitative cocaine use (percent positive samples) were observed for both groups [main effect of phase: $F(1, 36) = 28.98$, $p < 0.001$]; the reductions in use were specific to the treatment phase ($p \leq 0.001$ for all pairwise comparisons involving this phase). • A similar pattern for quantitative cocaine use emerged (i.e., lower quantitative cocaine use during the treatment phase); however, was not statistically significant ($p > 0.14$). • During the post-treatment phase, the withdrawal of CM contingencies and return to baseline conditions was associated with a general increase in cocaine use, which was near the level of use observed during the induction phase. • With one exception (THC), other drug use remained stable (i.e., no significant main effect of phase) during the trial. For THC, there was a slight increase in percent positive samples in the placebo group between the treatment and post-treatment phases ($p = 0.03$). • Self-reported cocaine craving (as measured by the CCQ-Now) fluctuated throughout the trial [main effect of phase: $F(2, 74) = 72.8$, $p < 0.001$]: craving decreased for both groups following the introduction of CM and then, for the DCS group, increased significantly during the post-treatment phase (post-hoc pairwise comparison: $p = 0.01$). • Self-reported drug use (as measured by the TLFB) did not differ significantly between the groups. A decrease in alcohol and cocaine use coincided with the introduction of the treatment phase: the number of days using alcohol and cocaine decreased significantly throughout the trial [main effect of phase observed for both drugs; alcohol: $F(2, 74) = 9.86$, $p < 0.001$; cocaine: $F(2, 74) = 24.53$, $p < 0.001$]. • Although the cognitive tasks showed that DCS was associated with improved learning, enhancement of learning-based therapy was not observed.

Citation	Johnson et al. (2020)
Safety and Adverse Events	• Overall, placebo and DCS administration was associated with few minor medication side effects. • Incidence of side effects did not significantly differ between groups.

11. D-Cycloserine for Tobacco Use Disorder and Comorbid Panic Attacks: Combined intervention (Panic and Smoking Reduction Treatment)

Citation	Smits et al. (2020b)
Study Design	• Double-blind, randomised, placebo-controlled, trial.
Sample Size	• 53 participants.
Population	• USA. • Tobacco use disorder and comorbid panic attacks (DSM-IV criteria). • DCS: M = 35.19 years (SD = 12.37); 29.63% male. • Placebo: M = 36.64 years (SD = 12.85); 30.77% male.
Intervention/s (I) and Comparator/s (C)	• All participants received seven (90-minute) sessions (one per week for seven weeks) of Panic and Smoking Reduction Treatment (PSRT). • Nicotine replacement therapy was initiated at session 5 (quit date). • All participants received an oral tablet prior to the sessions that emphasised interoceptive exposure practice (i.e., session 3 to 5). • I (n = 27): DCS (250 mg). • C (n = 26): placebo.
Outcome Measure/s	• Anxiety Sensitivity Index (ASI-3). • Panic Disorder Severity Scale – Self Report (PDSS-SR). • Timeline Followback (TLFB; self-report) method for smoking status and abstinence.
General	• Participants reported low to medium nicotine dependence (cigarettes per day: M = 14.22, SD = 6.01), high levels of anxiety sensitivity, and moderate levels of panic and related symptoms. • The groups did not differ on any of the demographic or study variables at baseline (all *p*'s > 0.104). • The overall integrity of treatment sessions was high with protocol adherence averaging 84.70% (SD = 19.04). • Period study was conducted: not reported.
Inclusion Criteria	• Smoked a minimum of 8 cigarettes per day for at least one year. • Motivated to quit smoking (score of at least 5 on a 10-point scale). • History of at least one panic attack within the last year as assessed by the Structured Clinical Interview for DSM-IV (SCID-NP). • Endorsed smoking as an emotion regulation strategy as indicated by a score of at least (≥) 78 on the Smoking Abstinence Expectancy Questionnaire. • Passed a medical screen conducted by the study physician to ensure it was safe for the participant to use DCS and nicotine patches. • Endorsed a willingness to attend all study sessions and adhere to protocol.
Exclusion Criteria	• Current or past diagnosis of a psychotic, bipolar, or developmental disorder. • Current suicidal or homicidal risk with intent or plan. • Active substance abuse or dependence (excluding nicotine) or eating disorder within the past 6 months. • Use of other tobacco products.

Citation	Smits et al. (2020b)
	• Current use of nortriptyline, bupropion, or isoniazid psychotropic ethionamide compounds. • Concurrent use of any pharmacotherapy or psychotherapy for smoking cessation outside of the research study. • Concurrent psychotherapy initiated within three months of baseline, or ongoing psychotherapy specifically targeting treatment of anxiety or mood disorders other than general supportive therapy initiated at least 3 months prior to the study. • Limited mental competency and the inability to give informed, voluntary, written consent to participate. • Planned to move outside of immediate area in the next six months. • Insufficient command of the English language. • Pregnant or breastfeeding, or planning to become pregnant in the next year, or women of childbearing potential not using medically accepted forms of birth control.
Assessment Time-Point/s	• Baseline. • All treatment sessions. • Follow-up: month 1, 4, and 6.
Main Findings	• DCS augmentation led to greater reductions of anxiety sensitivity at post-treatment compared to placebo (p = 0.038). • The DCS group improved faster during the treatment phase than the placebo group (p = 0.026); however, this difference was not maintained at the 6-month follow-up (p = 0.802). • PDSS-SR scores were not significantly different between conditions at post-treatment; however, the DCS group reported significantly lower PDSS-SR scores than the placebo group at the 6-month follow-up (p = 0.003). • There was no evidence of group (DCS vs. placebo) differences in successful smoking cessation at treatment endpoint or follow-up evaluations.
Safety and Adverse Events	• Adverse events were reported by 11.11% of DCS participants and 7.69% of placebo participants, and did not differ significantly across conditions (Fisher Exact Test; p = 1). • One participant in the placebo group reported elevated anxiety symptoms following the first drug administration, which was deemed to be possibly related to the study procedures; further drug administration was discontinued. • All other adverse events (i.e., chipped bone in back, pericarditis, anaemia, migraine) were reported in the follow-up period and deemed to be unrelated to the study procedures by the study physician. • No adverse events related to the use of the nicotine patches were reported.

12. D-Cycloserine for PTSD: Combined intervention (Fear Extinction Learning)

Citation	Inslicht et al. (2021)
Study Design	• Double-blind, randomised, placebo-controlled, trial.
Sample Size	• 90 participants (per-protocol sample). o 106 participants randomised. o 16 excluded due to missing outcome data.
Population	• USA • PTSD or sub-syndromal PTSD (DSM-IV criteria). • DCS: M = 40.1 years (SD = 13.7); 41.4% male. • Hydrocortisone: M = 34.3 years (SD = 11.8); 38.7% male.

Citation	Inslicht et al. (2021)
	• Placebo: M = 39.8 years. (SD = 11.7); 53.3% male.
Intervention/s (I) and Comparator/s (C)	• All participants received fear extinction learning: paired (CS+) or unpaired (CS-) with shock. • All participants received one oral encapsulated pill one hour prior to fear extinction learning. • I (n = 29): DCS (50mg). • I (n = 31): hydrocortisone (25mg). • C (n = 30): placebo (lactose).
Outcome Measure/s	• Psychophysiological measures included skin conductance level (SCL) as measured by a Coulbourn Isolated Skin Conductance coupler.
General	• Period study was conducted: January 2009 to December 2015.
Inclusion Criteria	• PTSD diagnosis (DSM-IV criteria) or sub-syndromal PTSD (i.e., CAPS score > 30 and met criteria on the A1, A2, B, E, and F clusters, and either the C or D clusters) for at least 3 months. • Participants remained alcohol- and drug-free during testing, as determined by self-report, urine drug screen, and breathalyser.
Exclusion Criteria	• Diagnosis of schizophrenia, bipolar disorder, alcohol dependence, drug abuse or dependence, seizure, or neurological disorders. • Previous moderate or severe head injuries, current infectious illness, systemic illness affecting CNS function, or other conditions known to affect psychophysiological responses. • Certain medications including alpha- and beta-adrenergics, antipsychotics, benzodiazepines, mood stabilisers, anticonvulsants, antihypertensives, sympathomimetics, anticholinergics, and steroids.
Assessment Time-Point/s	• Pre-treatment: habituation and fear conditioning. • Treatment (72 hours after pre-treatment): drug administration and fear extinction learning. • Post-treatment (one week after extinction learning): extinction retention was tested.
Main Findings	• During habituation, there were no significant group or CS type effects, or any significant interactions involving these factors (all *p*'s > 0.44). • The SCR to both CS+ and CS- significantly decreased over trials indicating successful habituation to the CS stimuli (main effect of trials: p < 0.001). • During fear conditioning, there were no significant group differences for the differential SCR to CS+ vs. CS- trials (p = 0.53), no significant group by trial interaction (p = 0.36), and no group by trial by CS Type interaction (p = 0.12). There was a significant effect of CS+ vs. CS- (p < 0.001), indicating successful acquisition of fear responding. • During extinction learning, a reduced differential skin conductance response (SCR) was observed for the DCS and HC groups compared with the placebo group (*p* = 0.042 and *p* = 0.005, respectively). • At retention testing (one-week post-treatment), extinction learning was not retained for the DCS group (*p* = 0.089), or the HC group (*p* = 0.883).
Safety and Adverse Events	• None reported.

13. D-Cycloserine for PTSD: Combined intervention (Virtual Reality Exposure Therapy)

Citation	Rauch et al. (2018)
Study Design	• Double-blind, randomised, placebo-controlled, trial.

Citation	Rauch et al. (2018)
Sample Size	• 123 (per-protocol sample). o 156 participants randomised; 27 dropped out of the study; 6 were excluded due to missing SUDs data. o A further 26 participants were excluded from the CAPS analyses due to missing data.
Population	• USA. • PTSD (DSM-IV criteria). • Medically stable Iraq and/or Afghanistan veterans. • Total sample: M = 35 years (SD = 8.4); 95% male. • DCS: M = 34.9 years (SD not reported); 92.5% male. • Alprazolam: M = 36.2 years (SD not reported); 98.0% male. • Placebo: M = 34.3 years (SD not reported); 94.3% male.
Intervention/s (I) and Comparator/s (C)	• All participants received six sessions of therapy: an initial 90-minute treatment session (information gathering, treatment planning, and explanation of the treatment rationale) followed by five sessions (one per week for five weeks) of Virtual Reality Exposure (VRE) Therapy. • All participants received an oral pill 30 minutes prior to the VRE sessions. • I (n = 53): DCS (50 mg). • I (n = 50): Alprazolam (0.25 mg). • C (n = 53): Placebo.
Outcome Measure/s	• Clinician-Administered PTSD Scale (CAPS). • Subjective Units of Distress (SUDs).
General	• This study included observations from 129 participants of the original 156 participants: 27 participants dropped out prior to an exposure session (i.e., prior to any SUDs being collected); and 6 participants were excluded due to missing SUDs data. • A final sample of 123 participants remained that included pre-treatment CAPS scores and SUDs data for at least one treatment session. • Ninety-seven participants had post-treatment CAPS scores, which were necessary to calculate CAPS reduction across sessions. • Within-session extinction was operationalised as the degree in reduction of SUDs ratings over the course of a single session. • Between-session extinction was operationalised as the degree in reduction of SUDs ratings across sessions. • There were no significant differences in dropout rate across conditions at post-treatment (p = 0.19); or at the 3-month (p = 0.16), 6-month (p = 0.25), or 12-month (p = 0.57) follow-up. • Period study was conducted: not reported. • Secondary analyses in other papers: Rothbaum, Price, Jovanovic et al. (2014).
Inclusion Criteria	• PTSD due to military trauma (DSM-IV criteria).
Exclusion Criteria	• Lifetime history of psychosis, bipolar disorder. • Current suicidal risk. • Current alcohol or drug dependence. • Pregnant. • Current use of certain medications that could confound the data (glucocorticoids, benzodiazepines, chronically used opioids).
Assessment Time-Point/s	• Baseline screening assessment. • Six treatment visits: SUDs were collected every 5 minutes during the VR exposure in session 2 to 6. • Follow-up: 3-, 6-, and 12-months post-treatment.

Citation	Rauch et al. (2018)
Main Findings	• There was no significant difference in PTSD symptoms (as measured by the CAPS) between any pair of treatment groups at post-treatment (DCS vs. alprazolam: $p = 0.88$; DCS vs. placebo: $p = 0.46$; alprazolam vs. placebo: $p = 0.57$). • The number of treatment sessions significantly predicted SUDs ratings ($p < 0.001$). • Time-in-session served as a significant predictor of SUDs ($p < 0.001$). Specifically, engagement increased within session, and then reduction (extinction/habituation) was apparent across sessions. • Treatment group was a predictor of SUDs rating within treatment sessions ($p < 0.05$) but not across sessions: greater increases in within-session SUDs were observed for the DCS and alprazolam groups compared with the placebo group. • Status as a treatment responder was a predictor of SUDs reduction across treatment sessions ($p < 0.001$), but did not produce an overall, or within-session, effect on SUDs.
Safety and Adverse Events	• None reported.

Appendix 8: Risk of Bias Assessments (RoB2)

D-cycloserine: Standalone and combined interventions (n = 13)

#	Study	Intervention	Comparator	D1	DS	D2	D3	D4	D5		Overall	n
1	Smits et al. (2020a)	DCS	Placebo	+		+	+	+	+		+	152
2	Roque et al. (2018)	DCS	Placebo	+		+	+	+	--		--	169
3	Kvale et al. (2020)	DCS	Placebo	+		+	+	+	--		--	163
4	de Leeuw et al. (2017)	DCS	Placebo	+		+	+	+	--		--	39
5	Reinecke et al. (2020)	DCS	Placebo	+		+	+	+	--		--	33
6	Hofmeijer-Sevink et al. (2019)	DCS	Placebo	+		+	+	+	--		--	57
7	Pyrkosch et al. (2018)	DCS	Placebo	--		+	+	+	--		--	73
8	Kappelmann et al. (2020)	DCS	Placebo	+		+	+	+	--		--	38
9	Chen et al. (2019)	DCS	Placebo	--		--	+	+	--		x	32
10	Johnson et al. (2020)	DCS	Placebo	+		x	x	+	--		x	39
11	Smits et al. (2020b)	DCS	Placebo	+		+	+	+	x		x	53
12	Inslicht et al. (2021)	DCS	Placebo	+		+	x	+	--		x	106
13	Rauch et al. (2018)	DCS	Placebo	+		x	x	+	--		x	156

Notes. n = sample size. D1 = Bias arising from the randomisation process. DS = Bias arising from period and carryover effects. D2 = Bias due to deviations from the intended interventions. D3 = Bias due to missing outcome data. D4 = Bias in measurement of the outcome. D5 = Bias in selection of the reported result.

Risk of Bias Judgments	Symbol
Low risk	+
Some concerns	--
High risk	x

Appendix 9: GRADE Certainty of Evidence Summary

D-cycloserine: Standalone and combined interventions (n = 13)

Intervention (no. of studies)	Design (no. of studies)	RoB Assessments (no. of studies)	Precision and Consistency	Directness	Publication Bias	GRADE Summary[1,2]
DCS (13)	Parallel arm RCT (13)	Serious (5 high risk; 7 some concerns; 1 low risk)	Serious	Not serious	Suspected, pending further analysis	Low ⨁⨁

Notes. DCS = D-cycloserine. RCT= Randomised controlled trial. RoB = Risk of bias. 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 D-cycloserine studies

GRADE domain	Judgement	Concerns about certainty domains
Study limitations (risk of bias)	Only one study (Smits et al., 2020a) had a low risk of bias. Seven (7) studies had some risk-of-bias concerns. The concerns primarily related to the pre-specified statistical analysis plans being unavailable. Thus, the planned outcome measures and analyses could not be compared with those presented in the published articles. Five studies (Chen et al., 2019; Inslicht et al., 2021; Johnson et al. 2020; Rauch et al., 2018; Smits et al. 2020b) were judged to have a high risk of bias. In the Chen et al. (2019) study, detailed information on the method of randomisation was not available (i.e., beyond stating that the participants were "randomised" to study conditions). Similarly, no information was provided on blinding (i.e., whether the participants or researchers were aware of the assigned interventions during the study). Finally, a pre-specified statistical analysis plan was not available. The Inslicht et al. (2021) study excluded 16 of the 106 participants following randomisation due to missing outcome data. The supplementary file describing the flow of participants through the study was not available. Additionally, the clinical trial identifier and a pre-specified statistical analysis plan was not available. The Johnson et al. (2020) study employed per-protocol analysis (rather than intention-to-treat analysis), excluding 13 participants following randomisation. Additionally, a pre-specified statistical analysis plan was not available. The Rauch et al. (2018) study employed per-protocol analysis (rather than intention-to-treat analysis), excluding participants following randomisation (33 to 59 depending on the analysis) due to missing data and study dropout. The flow of participants through the trial was not reported; thus, the differences in missing outcome data for the DCS and placebo groups could not be assessed. Additionally, a pre-specified statistical analysis plan was not available. In the Smits et al (2020b) study, the published analysis differed from the pre-specified analysis plan. Therefore, the studies were judged to have serious methodological limitations.	Serious
Precision and Consistency	The total number of participants included in the 13 trials was 1,110. The three largest studies with over 150 participants each (Kvale et al., 2020; Rauch et al., 2018; Roque et al., 2018) accounted for 44% of the participants across studies. These three larger studies had conflicting findings; only one study (Smits et al., 2020a) had a significant primary outcome with medium to large treatment effects. Nine of the 13 studies did not have a significant primary outcome. The direction and magnitude of the treatment effects varied across the remaining three trials (Inslicht et al., 2021; Rauch et al., 2018; Reinecke et al., 2020); and the significant primary findings from these studies were limited by risk-of-bias concerns. Therefore, the evidence was judged to have serious imprecision and inconsistency.	Serious

GRADE domain	Judgement	Concerns about certainty domains
Directness	Over half of the trials (8/13) recruited participants with an anxiety disorder; one study recruited participants with treatment-resistant depression (Chen et al., 2019); two studies recruited participants with substance use disorders (cocaine: Johnson et al., 2020; tobacco: Smits et al., 2020b); and two studies (Inslicht et al., 2021; Rauch et al., 2018) recruited participants with PTSD. A wide variety of conditions were assessed across the included studies; thus, the type and severity of symptoms were assessed using different scales and outcome measures as relevant to the condition/s of interest. All studies used a placebo as the comparator and delivered the intervention of interest (i.e., DCS) in combination with psychotherapy (excepting one study: Chen et al., 2019). The adjunct therapy was variable but typically involved some form and duration of exposure therapy. Therefore, the studies were judged to directly address the review question.	Not serious
Publication bias	The REA search strategy identified two clinical trial records for DCS interventions for depressive disorders that are pending publication of findings (clinical trial identifiers: NCT03937596 – completed Dec 2020; and NCT03511599 – completed Apr 2021). The findings from these studies may be relevant to future reports. Further analysis is required.	Suspected, pending further analysis

GALLIPOLI
MEDICAL RESEARCH FOUNDATION