Technical Report

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

A Rapid Evidence Assessment

Stellate Ganglion Block Interventions

2023

GALLIPOLI
MEDICAL RESEARCH FOUNDATION

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Emerging and Adjunct Treatments for Common Mental Health Conditions Affecting Veterans: A Rapid Evidence Assessment – Stellate Ganglion Block Interventions.

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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.

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List of Abbreviations

AE – Adverse Event

CBD – Cannabidiol

CBN – Cannabinol

CBT – Cognitive Behavioural Therapy

DCS – D-cycloserine

DVA – Department of Veterans' Affairs (Australian Government)

FDA – Food and Drug Administration (US Government)

GMRF – Gallipoli Medical Research Foundation

GRADE – Grading of Recommendations, Assessment, Development and Evaluation

LSD – Lysergic Acid Diethylamide

MA – Meta-analysis

MDMA – Methylenedioxymethamphetamine

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

PICO – Population, Intervention, Comparison, Outcome

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

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

PROSPERO – International Prospective Register of Systematic Reviews

PTSD – Posttraumatic Stress Disorder

RCT – Randomised Controlled Trial

REA – Rapid Evidence Assessment

RRMG – Rapid Reviews Methods Group

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

SGB – Stellate Ganglion Block

SNRIs – Selective Norepinephrine Reuptake Inhibitors

SR – Systematic Review

SSRIs – Selective Serotonin Reuptake Inhibitors

TBS – Theta-Burst Stimulation

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

THC – Tetrahydrocannabinol

TMS – Transcranial Magnetic Stimulation

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

Scale Name	Abbreviation
Clinician-Administered PTSD Scale for DSM-5	CAPS-5
Generalized Anxiety Scale, 7-item	GAD-7
Kessler Psychological Distress Scale, 6-item	K-6
Patient Health Questionnaire, 9-item	PHQ-9
PTSD Checklist for DSM-5	PCL-5
PTSD Checklist – Civilian Version	PCL-C
Short Form Survey, 12-item	SF-12

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: SGB interventions

From the four databases that were searched, two (2) studies met the inclusion criteria: one randomised controlled trial (RCT) and one systematic review (SR). The studies within this SR were extracted to a database and compared with the primary source (i.e., the RCT). From this set of articles (22 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., the one study in the SR that met the REA inclusion criteria was also directly retrieved by the search strategy). The final set of articles included one (1) RCT (see Appendix 5). The findings from this study were narratively synthesised, and a risk of bias assessment was conducted for the study. The summary of findings table for this RCT is presented in Appendix 7.

Risk of bias assessments: SGB interventions

The revised Cochrane risk-of-bias tool for randomised trials (RoB 2; Sterne et al., 2019) was used to conduct the risk-of-bias assessments for the REA. 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). The one (1) RCT of an SGB intervention was judged to have a high risk of bias (see Appendix 8).

GRADE certainty of evidence summaries: SGB 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 SGB intervention 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]
PTSD (1)	Parallel arm RCT (1)	Very serious (1 high risk; 0 some concerns; 0 low risk)	Serious	Not serious	Not suspected, pending further analysis	Very Low ⊕

Notes. PTSD = Posttraumatic stress disorder; 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 REA identified one study that met the inclusion criteria. This study examined an SGB intervention for PTSD and was judged to have a high risk of bias. Further methodologically robust research on SGB interventions is warranted.

Conclusions and recommendations for future research

The SGB procedure has been performed for neurological indications since the 1940's. An examination of the recently published literature on SGB interventions for common mental health conditions affecting veterans identified one study that met the REA inclusion criteria. This study was judged to have a high risk of bias.

The REA identified three (3) ongoing studies examining an SGB intervention for PTSD (see Appendix 4 for details). The findings from these studies may be relevant to future reports.

SGB remains an emerging intervention for PTSD and common mental health conditions affecting veterans. Given the invasive nature of the procedure, and the potential for adverse events (particularly without radiological guidance), we are not, at this time, in a position to recommend its use for the aforementioned clinical indications.

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). In accordance with the guidelines, the protocol was registered with the international prospective register of systematic reviews (PROSPERO) to provide evidence of the methodological rigour of the project and the independence of the review findings (PROSPERO CRD42022307924: 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 collated and synthesised 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 studies included in the REA (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: Evidence Summaries)
7. Risk of bias assessments (Appendix 8: Risk of Bias Assessments).
8. GRADE certainty of evidence summaries (Appendix 9: GRADE 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, 2022) was used for data extraction, the risk of bias assessments (RoB 2), and for grading the certainty of the evidence (GRADE).

Results: SGB Interventions

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, two (2) studies met the inclusion criteria: one randomised controlled trial (RCT) and one systematic review (SR). The studies within this SR were extracted to a database and compared with the primary source (i.e., the RCT). From this set of articles (22 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., the only study in the SR that met the REA inclusion criteria was also directly retrieved by the search strategy). The final set of articles included one (1) RCT (see Appendix 5). The findings from this study were narratively synthesised, and a risk-of-bias assessment was conducted for the study.

SGB: Standalone and combined interventions

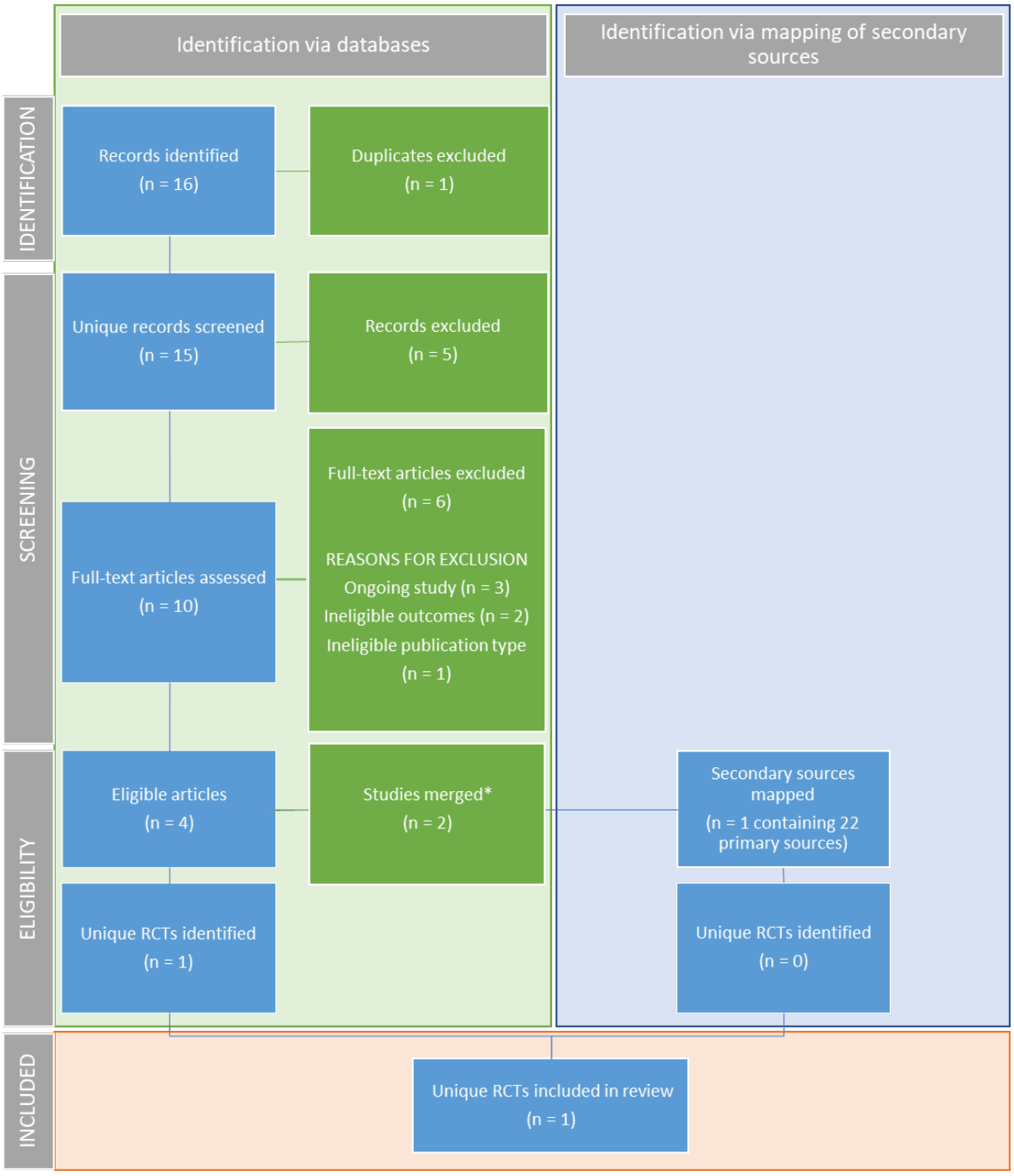

Figure 1. PRISMA diagram detailing the number of records under consideration at each stage of the REA for the SGB interventions. Notes. *Comment (Stein, 2020; *n* = 1) and reply (Rae Olmsted et al., 2020; *n* = 1) merged with primary study (Rae Olmsted et al., 2019).

Summary of the Evidence: SGB Interventions

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

One (1) study met the inclusion criteria for the REA (see Appendix 5). Appendix 6 presents a matrix of SGB interventions, broken down by the disorder categories of interest. Appendix 7 presents a detailed summary of the evidence from the included study. Appendix 8 presents the risk-of-bias assessment for the study. Appendix 9 presents the GRADE (certainty of evidence) summaries.

SGB for PTSD: Standalone intervention

Rae OImstead and colleagues (2019; *n* = 113) recruited active-duty military personnel with a diagnosis of PTSD (DSM-5 criteria) from three army interdisciplinary pain centre sites. Participants were randomised (2:1) to receive either right-sided active SGB (7 to 10 mL ropivacaine 0.5%; *n* = 74) or right-sided sham SGB (1 to 2 mL saline; *n* = 39). The intervention comprised two injections administered two weeks apart (week 0 and 2). Participants were included in the study if they were on stable psychotropic medications and had a score of at least (≥) 32 on the PTSD Checklist – Civilian Version (PCL-C) at screening. The outcome measures were the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5; primary outcome measure), the PTSD Checklist for DSM-5 (PCL-5), the PTSD Checklist-Civilian Version (PCL-C), the 9-item Patient Health Questionnaire (PHQ-9), the 7-item Generalised Anxiety Disorder Scale (GAD-7), the 6-item Kessler Psychological Distress Scale (K-6), a "pain scale" (no further detail provided), and the 12-item Short Form Survey (SF-12). Assessments were conducted at two time-points: baseline (week 0) and follow-up (week 8; six weeks after the second injection). The primary outcome measure was the change in the participant's total symptom severity score (TSSS) on the CAPS-5 (baseline to week 8). Clinical treatment response was defined as a 10-point TSSS change on the CAPS-5 (week 8), adjusted for site and baseline TSSS. In the intention-to-treat analysis, the change in the adjusted mean total symptom severity score (TSSS) was -12.6 points (95%CI = -15.5 to -9.7 points) for the active SGB group compared with -6.1 points (95%CI = -9.8 to -2.3 points) for the sham SGB group (p = 0.01). The authors stated that the study findings had limited generalisability due to the (mild to moderate) baseline level of PTSD symptom severity and the short follow-up period.

This study was judged to have a high risk of bias. The study was reportedly powered to detect a between-group difference of at least a 10-point TSSS change on the CAPS-5. The authors stated that they examined the percentage of participants in each group (active vs. sham) with a 10-point TSSS change on the CAPS-5 (baseline to week 8), and the percentage of participants in each group (active vs. sham) who no longer met diagnostic criteria for PTSD on the CAPS-5 (week 8). However, these findings were not reported in the published article.

Stein (2020) raised several concerns about the conduct of the study in a letter to the editor (e.g., the specification of the primary outcome in the article and the clinical trials registry were described as "ambiguous"). Rae Olmsted et al. (2020) responded to Stein's (2020) concerns with corrections and additional data. In their reply, Rae Olmsted et al. (2020) reported 52.9% (*n* = 37/70) participants in the active SGB group, and 34.2% (*n* = 13/38) participants in the sham SGB group, had a TSSS reduction of 10 points or more on the CAPS-5 (p = 0.06). This analysis excluded five participants following randomisation who were lost to follow up (four from the active SGB group and one from the sham SGB group). A comment by Bhakta et al. (2020) raises several additional concerns about the study, including the lack of outcome measurement prior to the second injection.

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 REA identified one study that met the inclusion criteria. This study examined an SGB intervention for PTSD and was judged to have a high risk of bias. Further methodologically robust research on SGB interventions is warranted.

Conclusions and Recommendations for Future Research

The SGB procedure has been performed for neurological indications since the 1940's. An examination of the recently published literature on SGB interventions for common mental health conditions affecting veterans identified one study that met the REA inclusion criteria. This study was judged to have a high risk of bias.

The REA identified three (3) ongoing studies examining an SGB intervention for PTSD (see Appendix 4 for details). The findings from these studies may be relevant to future reports.

SGB remains an emerging intervention for PTSD and common mental health conditions affecting veterans. Given the invasive nature of the procedure, and the potential for adverse events (particularly without radiological guidance), we are not, at this time, in a position to recommend its use for the aforementioned clinical indications.

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Appendix 1: Best-Practice Guidelines for Rapid Reviews

Cochrane Rapid Reviews Methods Group (RRMG) Recommendations (Garritty et al., 2021)
Setting the research question – topic refinement
• Involve key stakeholders (e.g., review users such as consumers, health professionals, policymakers, decision-makers) to set and refine the review question, eligibility criteria, and the outcomes of interest. Consult with stakeholders throughout the process to ensure the research question is fit for purpose, and regarding any ad-hoc changes that may occur as the review progresses. (R1) • Develop a protocol that includes review questions, PICOS, and inclusion and exclusion criteria.
Setting eligibility criteria

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

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

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

Data extraction
• Use a single reviewer to extract data using a piloted form. Use a second reviewer to check for correctness and completeness of extracted data. (R16) • Limit data extraction to a minimal set of required data items. (R17) • Consider using data from existing SRs to reduce time spent on data extraction. (R18)
Risk of bias assessment
• Use a valid risk of bias tool, if available for the included study designs. • Use a single reviewer to rate risk of bias, with full verification of all judgments (and support statements) by a second reviewer. (R19)

• 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: Stellate ganglion block interventions

("stellate ganglion block"[tiab] OR "cervicothoracic sympathetic block"[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 = 6) by reason for exclusion in Figure 1 PRISMA diagram (SGB: Standalone and combined interventions).

Ongoing studies (n = 3)

#	Registry ID	Mental Health Condition	Principal Investigator(s)	Location	Date of Registration	Expected Completion Date
1	NCT05107752	PTSD (veterans)	Bryan, C. J.	United States	2021 (Nov 4)	2023 (Nov 30)
2	DRKS00015817	PTSD (comorbid borderline personality disorder)	Chung, B. Y. & Jörg, C.	Germany	2018 (Oct 31)	Not listed (last update Aug 2022)
3	NCT05169190	PTSD (veterans)	Hollifield, M.	United States	2021 (Dec 23)	2026 (Mar 31)

Ineligible outcomes (n = 2)

#	Year	Reference	Exclusion reason
1	2021	Hughey, S., Schafer, J., Cole, J., Booth, G., Tuttle, R., & Stedje-Larsen, E. (2021). Ultrasound versus fluoroscopy for stellate ganglion block: A cadaveric study. *Pain Medicine, 22*(10), 2307-2310. https://doi.org/10.1093/pm/pnab182	No outcome of interest; cadaveric study.
2	2017	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	Narrative review

Ineligible publication type (n = 1)

#	Year	Reference	Exclusion reason
1	2020	McLean, B., Walters, B., & Olmsted, K. (2020). Stellate ganglion block for treating symptoms of posttraumatic stress disorder. *Neuromodulation*, 23(3), e159. https://doi.org/10.1111/ner.13133	Conference abstract; full-text not available.

Appendix 5: List of Included Studies

SGB: Standalone and combined interventions (n = 1)

#	Citation	Experimental intervention	Target condition	Combined intervention details (if applicable)
1	Rae Olmsted et al. (2019)	SGB	PTSD	N/A

Notes. N/A = Not applicable. PTSD = Posttraumatic Stress Disorder. SGB = Stellate Ganglion Block.

Appendix 6: Matrix of Included Studies

SGB: Standalone and combined interventions (n = 1)

	Anxiety Disorders	Mood/Depressive Disorders	Substance-Related and Addictive Disorders	Trauma- and Stressor-Related Disorders
SGB	X	X	X	1 x standalone 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. X indicates there were no studies included in the analysis for the intervention of interest and the mental health condition/s of interest. PTSD = Posttraumatic Stress Disorder. SGB = Stellate Ganglion Block.

Appendix 7: Summary of Findings

1. Stellate Ganglion Block for PTSD: Standalone intervention

Citation	Rae Olmsted et al. (2019)
Study Design	• Double blind, randomised, placebo-controlled, trial. • Multi-site.
Sample Size	• 113 participants. ○ 5 participants were lost to follow-up following randomisation (four in the active SGB group and one in the sham SGB group).
Population	• USA. • PTSD (DSM-IV criteria). • I: M = 37.4 years (SD = 6.8); 86.5% male. • C: M = 37.0 years (SD = 6.5); 92.3% male.
Intervention/s (I) and Comparator/s (C)	• All participants received two injections, two weeks apart (week 0; week 2) under ultrasound visualisation. • I (n = 74): Right-sided active SGB (0.5% ropivacaine; 7 to 10 mL). • C (n = 39): Right-sided sham SGB (preservative-free saline; 1 to 2 mL).

Outcome Measure/s	• Primary outcome:
	  ○ Clinician-Administered PTSD Scale (CAPS-5).
	• Secondary outcomes:
	  ○ PTSD Checklist for DSM-5 (PCL-5).
	  ○ PTSD Checklist – Civilian Version (PCL-C).
	  ○ Patient Health Questionnaire, 9 item (PHQ-9).
	  ○ Generalised Anxiety Disorder Scale, 7-item (GAD-7).
	  ○ Kessler Psychological Distress Scale, 6-item (K-6).
	  ○ Pain scale (not specified).
	  ○ Short Form Survey, 12-item (SF-12).

General	• No significant differences in baseline characteristics between SGB and sham treatment groups.
	• Period study was conducted: May 2016 to March 2018.
	• Comment/reply to Rae Olmsted et al. (2019):
	  ○ Comment: Stein (2020).
	  ○ Reply: Rae Olmsted et al. (2020).
	  ○ Comment: Bhakta et al. (2020).

Inclusion Criteria	• Active-duty military status. • Personal access to internet. • Anticipated stable assignment to installation for at least 2 months. • Stable doses of psychotropic medication for at least 3 months. • Score of at least (≥) 32 on the PTSD Checklist – Civilian Version (PCL-C) at screening.
Exclusion Criteria	• Prior SGB treatment. • Allergic to amide local anaesthetics. • History of schizophrenia, another psychotic disorder, bipolar disorder, or personality disorder. • Moderate to severe traumatic brain injury. • Symptoms of moderate to severe substance use disorder in the past 30 days. • Suicidal ideation in the past 2 months. • Ongoing stressor or condition deemed by the clinician to place the participant at risk for injury or a poor outcome.

Citation	Rae Olmsted et al. (2019)
Assessment Time-Point/s	• Baseline. • During treatment: week 0 and 2. • Follow-up: week 4, 6 and 8 (web-based platform); week 8 (in-person).
Main Findings	• In the intention-to-treat analysis, the change in the adjusted mean total symptom severity score (TSSS) was -12.6 points (95%CI = -15.5 to -9.7 points) for the active SGB group compared with -6.1 points (95%CI = -9.8 to -2.3 points) for the sham SGB group (p = 0.01). • Improvement in scores across all secondary outcome measures (baseline to week 8) were observed for the participants in the active SGB group compared with the sham SGB group (small to medium effect sizes): ○ PCL-5 (Cohen's d = 0.53, SD = 0.20). ○ PCL-C (Cohen's d = 0.52, SD = 0.20). ○ PHQ-9 (Cohen's d = 0.60, SD = 0.20). ○ GAD-7 (Cohen's d = 0.58, SD = 0.20). ○ K-6 (Cohen's d = 0.49, SD = 0.20). ○ Pain scale (Cohen's d = 0.34, SD = 0.20). ○ SF-12: mental functioning (Cohen's d = -0.32, SD = 0.20); physical functioning (Cohen's d = -0.38, SD = 0.20). • CAPS-5 score difference adjusted by treatment, site, and treatment by site interaction (from the supplementary file): ○ All sites (n = 113; M = -6.84, SE = 2.52, p = 0.007). ○ Womack site (n = 22; M = -10.16, SE = 5.13, p = 0.048). ○ Tripler site (n = 60; M = -3.13, SE = 3.18, p = 0.326). ○ Landstuhl site (n = 31; M = -7.22, SE = 4.50, p = 0.108).
Safety and Adverse Events	• A total of six (6) adverse (AEs) were recorded during the study. • Three (3) AEs were considered 'possibly' or 'definitely' related to the SGB intervention: ○ Possibly related: (1) coughing caused by temporary irritation of larynx. ○ Definitely related: (2) pain and redness at injection site; and (3) self-resolving episode of bradycardia.

Appendix 8: Risk of Bias Assessments (RoB2)

SGB: Standalone and combined interventions (n = 1)

#	Study	Intervention	Comparator	D1	DS	D2	D3	D4	D5		Overall	n
1	Ray Olmsted et al. (2020)	SGB	Sham SGB (IM)	+		--	+	--	x		x	113

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

SGB: Standalone and combined interventions (n = 1)

Intervention (no. of studies)	Design (no. of studies)	RoB Assessments (no. of studies)	Precision and Consistency	Directness	Publication Bias	GRADE Summary[1,2]
PTSD (1)	Parallel arm RCT (1)	Very serious (1 high risk; 0 some concerns; 0 low risk)	Serious	Not serious	Not suspected, pending further analysis	Very Low ⊕

Notes. PTSD = Posttraumatic stress disorder. 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.**

1. GRADE rating of SGB study

GRADE domain	Judgement	Concerns about certainty domains
Study limitations (risk of bias)	The study by Rae Olmsted et al. (2019) was judged to have a high risk of bias. Specifically, there were concerns about selective reporting of results. The study was reportedly powered to detect a between-group difference of at least a 10-point change in TSSS on the CAPS-5. However, these outcomes were not reported in the published article. Stein (2020) and Bhakta et al. (2020) raised several additional concerns about the published article, particularly in relation to outcome measurement. Therefore, the study was judged to have very serious methodological limitations.	Very serious
Precision and Consistency	The number of participants included in the study was 113. The mean change in the TSSS on the CAPS-5 was reportedly greater in the active SGB group compared with the sham SGB group (p = 0.01). In the correction to the published article, the rate of treatment response was reportedly higher in the intervention group (52.9%) compared with the sham group (34.2%); however, the difference was not statistically significant (p = 0.06). There is insufficient information from a single study with this sample size to assess the quality of the evidence with respect to precision and consistency. Further research is required.	Serious
Directness	The study recruited active-duty military personnel with mild to moderate PTSD. The study compared a right-sided active SGB injection (7 to 10 ml 0.5% ropivacaine) with a right-sided sham SGB injection (1 to 2 ml of saline). Therefore, the study was judged to provide direct evidence on the review question.	Not serious
Publication bias	The search for studies was comprehensive. The REA search strategy identified three clinical trial records for SGB interventions in participants with a PTSD diagnosis (NCT05107752, NCT05169190, DRKS00015817). One trial (DRKS00015817) was registered in Germany in 2018; however, the expected completion date was not reported, and there have been no further updates to the clinical trial record. Further analysis is required.	Not suspected, pending further analysis

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