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Research Paper

Psilocybin-assisted psychotherapy for the treatment of PTSD in UK armed forces veterans: A feasibility study protocol

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ABSTRACT

Veterans with posttraumatic stress disorder (PTSD) have poorer treatment responses than the general public, which suggests that alternative treatment approaches may be required to support veterans who do not benefit from standard evidence-based approaches. Psilocybin-assisted psychotherapy (PAP) involves administration of psilocybin in a supportive therapeutic setting. PAP has been evidenced to be safe and feasible in a range of recent studies supporting individuals with mental health difficulties including depression, obsessive compulsive disorder, and anxiety. This protocol paper outlines a study aiming to explore the safety and feasibility of PAP for veterans ($n = 8$) with PTSD. Participants will be offered two dosing sessions of 25 mg of psilocybin, followed by Cognitive Processing Therapy. Eligible participants are UK military veterans who meet criteria for current PTSD and who have completed thorough physical and psychological assessment. The study is subject to ethical approval by the Health Research Authority and Medicines and Healthcare products Regulatory Agency combined review.

Introduction

UK Armed Forces veterans experience higher rates of posttraumatic stress disorder (PTSD) than the general population (8 % v. 5 %; Rhead et al., 2022), particularly those deployed in combat roles, where prevalence rates of 17 % have been observed (Stevelink et al., 2018). Veterans with PTSD also experience high rates of mental and physical health comorbidities, as well as functional impairment (Williamson et al., 2022). There is therefore a need to understand how best to support this population clinically. In the UK, the National Institute for Health and Care Excellence guidelines (NICE, 2018) recommend trauma-focused psychotherapies as a first line treatment for PTSD, including Cognitive Processing Therapy (CPT), Trauma-focused Cognitive Behavioural Therapy (CBT), Eye Movement Desensitisation and Reprocessing (EMDR) and Narrative Exposure Therapy (NET). Broadly, these psychotherapies aim to alleviate PTSD symptoms of hyperarousal, avoidance, and re-experiencing through exposure to and reprocessing of traumatic memories (Brewin et al., 1996; Kline et al., 2018).

PTSD treatments

Trauma-focused therapies have high dropout rates (c.30 %; Cloitre, 2009; Gutner et al., 2016; Steenkamp et al., 2015) potentially due to the distress arising from exposure. Research suggests UK veterans with PTSD have a poorer response to gold-standard treatments (Murphy & Smith, 2018), and overall lower response rates than the general public (Kitchiner et al., 2012; Straud et al., 2019). This pattern is also observed in US and Australian military samples (Phelps et al., 2018). Pharmacological interventions for PTSD are also available, including antidepressants sertraline and paroxetine (NICE, 2018), to which around 60 % of PTSD patients respond, although only half of this group achieve remission (Alexander, 2012). PTSD not only negatively impacts the lives of individual patients, but also contributes a significant economic burden in terms of direct healthcare costs and overall loss of productivity (Davis et al., 2022; Ferry et al., 2015; Holmes, 1994). Due to the economic and personal burden of the illness, it is necessary to develop robust and effective psychopharmacological treatments for PTSD, which are also tailored to the complexity of presentations in different populations, such

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as in military veterans.

Psychedelic renaissance

Psychedelics (such as ayahuasca) have been used for millennia in cultures around the world (El-Seedi et al., 2005; Nichols & Walter, 2021; Tupper, 2009; Wasson, 1957). Associated with mystical type experiences and changes in consciousness, perceptions of reality and mood, psychedelics were first reported as having potential use in psychotherapeutic contexts in Western medicine in the 1950s (Hoffman, 2014). Such studies observed that an emphasis on preparation for dosing and interpersonal support resulted in more positively-rated experiences with fewer adverse reactions (e.g., (Hofmann et al., 1958; Carbonaro et al., 2016). However, further investigation of the therapeutic potential for psychedelics; such as psilocybin, was halted 20 years later due to social and political pressures.

Case for psilocybin

More recently, psilocybin has been designated "breakthrough status" from the U.S. Food and Drug Administration for the treatment of depression. Psilocybin, of the psilocybe mushroom species is a naturally occurring hallucinogen which metabolises to psilocin and acts as an antagonist on a range of serotonin receptors, primarily 5-HT2A (López-Giménez & González-Maeso, 2017; Nichols, 2004). In recent clinical trials, psilocybin use, offered in a structured therapeutic setting, is reported to improve symptoms associated with depression (Bird et al., 2021; Carhart-Harris et al., 2018; Gukasyan et al., 2022), Obsessive Compulsive Disorder (Moreno et al., 2006), addiction disorders (e.g., Bogenschutz et al., 2015, 2022; Johnson et al., 2017), eating disorders (Spriggs et al., 2021), and anxiety associated with long term and terminal illnesses (Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016).

Psilocybin and PTSD

There is significant overlap in symptoms of depression, anxiety and PTSD, which are often comorbid in veterans (Williamson et al., 2022). Further, veterans with PTSD and co-morbid depression have consistently been shown to respond less favourably to existing gold-standard trauma-focused therapies than those with PTSD alone (Murphy & Smith, 2018). As such, the demonstrated efficacy of psilocybin in alleviating symptoms of depression and anxiety could be paralled in PTSD. Several individual and possibly convergent mechanisms for the potential effectiveness of psilocybin for PTSD are possible. Psilocybin may enhance cognitive flexibility (Doss et al., 2021), which has been proposed to alleviate the negative rumination and rigid thought patterns associated with depression (Carhart-Harris et al., 2016) and PTSD. In a functional magnetic resonance imaging (fMRI) study, activity in brain areas associated with the default mode network (DMN) reduced following psilocybin administration (Carhart-Harris et al., 2012). The DMN encompasses the medial prefrontal cortex, anterior and cingulate cortices and is functionally associated with activities which are self-referential, viz. considering one's place in the world (e.g., Gusnard et al., 2001). Activity in the DMN is high when attention is focused inwardly on the self, and when dreaming (Pace-Schott & Picchioni, 2017). One proposed hypothesis is that psilocybin alters functional connectivity within the DMN (Roseman et al., 2017), which suggests possible re-structuring of pathways associated with internalising disorders such as depression. Commonly reported effects following psilocybin-assisted psychotherapy (PAP) include enhanced introspection, self-acceptance, and compassion (Watts et al., 2017), which are also key mechanisms in the cognitive reappraisals of trauma memories (e.g., Creaser et al., 2022).

A second possible way psilocybin may alleviate PTSD symptoms is through enhanced fear extinction via suppressed amygdala activity and the promotion of hippocampal neural connectivity associated with use of the psychedelic (Catlow et al., 2013; Du et al., 2023; Kraehenmann et al., 2015). Severe PTSD is also associated with emotional avoidance and dissociation (Chawla & Ostafin, 2007). Some evidence indicates psilocybin may decrease avoidance behaviour and improve mindfulness-related capacities (Nichols, 2016). Psilocybin may also support the development of a strong therapeutic alliance during dosing sessions and in any subsequent psychotherapy via the promotion of empathy (Dos Santos & Hallak, 2020), which may help reduce treatment drop-out rates and improve psychotherapeutic efficacy. Furthermore, anecdotal reports from the previous century suggest promising effects for psilocybin use in traumatised patients. For example, concentration camp victims were offered the intervention aimed at allowing the re-experiencing of traumatic material within a supportive environment, possibly helping to reduce the risk of dissociation (Bastiaans, 1993). More recently, a study found psilocybin reduced symptoms associated with PTSD such as demoralisation and emotional avoidance in AIDS survivors, measured using self-report scales (Anderson et al., 2020). Taken together, this evidence suggests the potential for psilocybin in treating PTSD.

The safety profile of psilocybin use is well-established in clinical trials (Castro Santos & Gama Marques, 2021) as well as in a review of pre-1970s studies (Rucker et al., 2018). Adverse events may include mild nausea, transient increases in blood pressure and headaches, which in previous studies typically resolved by the conclusion of the dosing session or shortly thereafter (Anderson et al., 2020; Bird et al., 2021; Carhart-Harris et al., 2018; Griffiths et al., 2016; Gukasyan et al., 2022; Moreno et al., 2006). In one study using a sample of patients with severe depression, suicide ideation was recorded following dosing and recorded as a serious adverse event following administration of the Columbia Suicide Severity Rating Scale (Posner et al., 2011). However, it is unclear whether suicide ideation was directly related to psilocybin administration in these patients. To the authors' knowledge, no other serious adverse events have been recorded in PAP studies. The psilocybin-assisted psychotherapy (PAP) model includes modifications to standard therapy as detailed in the 'procedures' section below, such as the inclusion of psilocybin dosing sessions and dosing preparation sessions which are offered in addition to standard therapy. In the current protocol, patients will receive Cognitive Processing Therapy following psilocybin dosing sessions. There is also scope for varying subjective experiences following psilocybin administration given the perceptual effects of psychedelics depend on the individual, and the environmental and social setting in which therapy takes place (Winkelman, 2021). As such there is a need for clinical trials of PAP to explore feasibility in relevant populations, and across various settings to understand how the intervention could be integrated into different health systems (Averill & Abdallah, 2022).

In this paper we described a study protocol that aims to investigate the feasibility, acceptability, safety, and efficacy of PAP for veterans with PTSD in a clinical setting. The current protocol has been informed by the MyDecine Investigator's Brochure for PAP for PTSD. The protocol is also informed by the Multidisciplinary Association for Psychedelic Studies (MAPS), who provide a manual for the non-directive psychotherapy delivered in dosing sessions. The authors acknowledge the publication of a protocol for a study of PAP in US veterans with PTSD (Davis et al., 2023), which has not informed the current protocol. The current study is a single-centre, single group design evaluating the feasibility of PAP (two dosing sessions of 25 mg psilocybin followed by Cognitive Processing Therapy) in veterans with PTSD. The psilocybin dose is informed by a range of previous studies, which estimate a psilocybin half-life of 3 $\pm$ 1.1 h (Brown et al., 2017; Hasler et al., 1997).

Methods

Trial objectives and design

The aim of this trial is to investigate the feasibility, efficacy, safety and acceptability of psilocybin assisted psychotherapy ($n = 8$). The study is a single arm, within-participants exploratory design with eight participants, taking place between June 2023 and June 2025. All study visits will take place at study sponsor Combat Stress in Surrey, UK. The study protocol has been peer reviewed at grant application, by an independent third party and internally by the trustee board of the study sponsor.

Sample size

The current study is primarily an acceptability, feasibility, and safety trial. As such, we are targeting a modest sample size of eight. This sample size will allow us to explore feasibility outcomes including whether the target sample size can be recruited, and participant retention, which could inform a larger future trial. As the study is primarily investigating feasibility, which includes whether it is feasible to recruit for the trial, a power calculation was not justified.

Trial activities

See Fig. 1 for a schematic of trial activities.

Recruitment

Participants will be recruited from a national UK charity that offers clinical services to veterans with mental health difficulties. All potential participants will have undertaken a Full Clinical Assessment at the charity, will be seeking treatment for mental health difficulties related to military service, and will have met all service criteria, including being assessed as having a low risk of harm to self and others. A team of professionals in interdisciplinary team meetings will then discuss and either uphold or decline any recommendation to contact a potential participant and offer them the study as part of their treatment with the charity. The research therapist who contacts participants and the research assistant have lawful access to patient information.

Screening and assessment

As part of the consent procedure, participants will be contacted, given information about the study, and be invited to an assessment appointment with a research therapist and psychiatrist. Consented participants will be thoroughly screened for eligibility and undergo a series of physical health assessments as part of an assessment visit to the study site, including electrocardiogram, blood pressure check, and full medical and psychiatric history. For a full description of tests, see inclusion and exclusion criteria.

Inclusion and exclusion criteria

For study inclusion, veterans will need to meet probable criteria for PTSD on the PTSD Checklist for DSM-5 (PCL-5; Weathers et al., 2013), which requires a score of 33 or higher and live within a two hour driving radius of the charity and study site. Study exclusion criteria includes any personal or family history of psychiatric or cardiac disorders, pregnancy, and some medications. For full inclusion and exclusion criteria please see supplementary materials. The main exclusion and inclusion criteria are described in Table 1.

Preparatory phase

Participants will receive two remote 90-minute preparatory sessions with the research therapist prior to their first dosing session. The aim of these sessions is to establish expectations about, and goals for, dosing sessions, minimise any participant worries about the experience, and build familiarity and a trusting therapeutic relationship prior to psilocybin administration. Preparatory sessions will also comprise discussion of any changes in health status.

Dosing sessions

One day prior to dosing sessions, participants will be contacted to arrange transportation and confirm participation. On the dosing days the medication will be delivered to, and stored by, the prescribing doctor (research psychiatrist), who will have confirmed that the patient is in taxi en route before taking receipt of the medication. Dosing will take place in a quiet treatment room at the study site. Before administering psilocybin, the research psychiatrist will conduct an assessment to confirm the participant still meets the study criteria and the research therapist will again discuss the participant's expectations and any worries about the experience. During the dosing session both a research therapist and research assistant will remain in the room with the participant and two research psychiatrists will remain on site.

Following administration of 25 mg psilocybin via oral capsule with

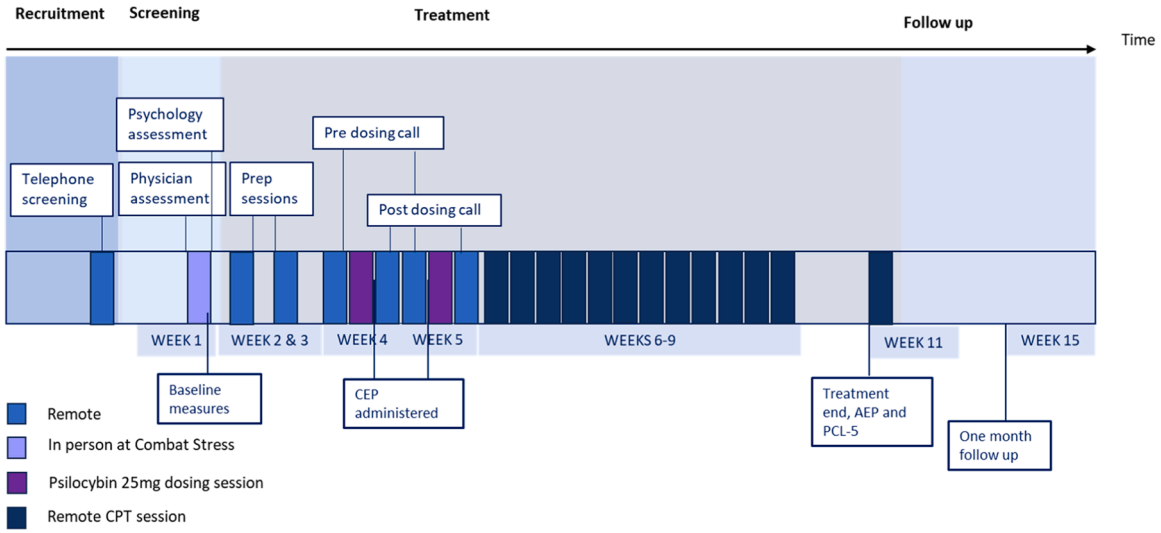

Fig. 1. Schematic of trial activities. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 1
Main inclusion and exclusion criteria.

Main inclusion criteria
1 Aged 18–65
2 Lives within 2 h driving radius of clinical service
3 Meeting all usual clinical service inclusion criteria: access to internet via laptop or tablet, "ready" for trauma-focussed therapy, risk is managed
4 PCL-5 score ≥ 33
5 At least one previous unsuccessful evidence-based psychotherapy/pharmaco-therapy for PTSD
Main exclusion criteria
1 Engaged in compensation litigation whereby financial gain would be achieved from prolonged symptoms of PTSD or any other psychiatric disorders
2 Has a hearing impairment that could interfere with ability to participate in the study
3 Pregnant or breastfeeding
4 BMI <18 or >35
5 Has been diagnosed with, or has first degree relative with schizophrenia, psychotic disorder (unless substance induced or due to medical condition), or bipolar I disorder
6 Current alcohol or substance use disorder; exception for milder disorder if realistic plan agreed to mitigate risk to participation, safety, and/or efficacy of the treatment
7 History of heart conditions or problems (see protocol for full list)
8 Previous indication of liver or kidney damage
9 Current Hepatitis C virus (HCV) infection - Asymptomatic HCV permitted if previously undergone evaluation and treatment as needed
10 Current uncontrolled Type 2 diabetes mellitus
11 Current uncontrolled hypothyroidism
12 Current or historic glaucoma unless participation approved by an ophthalmologist
13 History of TBI/cognitive impairment limiting ability to engage in treatment (e.g., memory or concentration problems, impulsivity related to brain injury)
14 Current neurological illness
15 Previous use of psilocybin or other psychedelic substance (except cannabis) on more than 5 occasions and/or use of the same within the past 5 years
16 Previous use of psilocybin, MDMA, ketamine (or substances reportedly containing psilocybin, MDMA, or ketamine) with therapeutic aim for current PTSD diagnosis
Medication exclusion criteria:
1 Efavirenz
2 Lithium
3 "Rest-Category" Antidepressants (e.g., mirtazapine, trazodone, bupropion); Exception if ≤7.5 mg mirtazapine, or ≤50 mg trazodone as sleeping medication
4 Antipsychotics/Neuroleptics; Exception if ≤50 mg quetiapine as sleeping medication
5 The following medications are permitted if the dose is hypnotic: SSRIs; TCAs; MAOIs
6 The following medications are permitted if their use is unaltered during the study: Benzodiazepines "Z-drugs" (e.g., zolpidem); Anticonvulsants; Antihistamines
7 Medications which are permitted as determined case-by-case by research psychiatrist: non-psychiatric, but mind-altering medication (e.g., morphine, dexamethasone, etc.).

water, participants will begin the session listening to music and wearing an eye mask. For a full summary of pharmacokinetics of psilocybin, see the Investigator's Brochure. Several playlists have been curated by MAPS based on their own research into suitable music for PAP. These playlists are publicly available on a popular music streaming platform. The research therapy team will encourage participants to stay present with their own experience and will use non-directive psychotherapy throughout the 8-hour dosing session to create a safe environment that fosters willingness to explore new and unexpected perceptions that may arise. A manual detailing the application of non-directive psychotherapy is provided separately. Participants will be offered plain food of their choice four hours post-dose by the research assistant and research therapist. Vital signs will be assessed four hours and eight hours post dose by the research psychiatrist, including blood pressure and heart rate.

The dosing session will end when all medical and psychiatric parameters are acceptable, that is: elevations in vital signs (heart rate and blood pressure) have resolved to pre-dosage levels, and the subject is alert, ambulatory, and emotionally stable – orientated to time and place, not in distress and grounded in the present moment. Subjects will be released into the custody of a close companion who has accompanied them to their visit and will return home via pre-booked taxi. All participant and close companion travel expenses are funded. Study staff will contact the participant 24 h after their dosing session to assist with any post-session adverse reactions or if the subject requires additional support. If the participant requires any assistance prior to this, they will be directed to contact their GP, or an out of hours GP service such as NHS 111 should they be experiencing mild side effects. If they feel very unwell, they will be encouraged to contact emergency services.

Safety protocol and use of rescue medication

For full safety protocol in the event of an adverse reaction or event, please refer to the study protocol document. Should a physical adverse event arise, in the first instance the research psychiatrist will take physical observations of patient health status and formulate a plan for treatment. If this is deemed to be a serious adverse event that requires hospitalisation the research psychiatrist will contact emergency services to request an ambulance. Should the participant experience emotional distress, in the first instance, the research therapist will utilise emotional regulation strategies. If an individual is assessed as at risk of endangering themself or others, or is experiencing severe, persisting emotional distress, such as panic attacks or severe generalised anxiety during a dosing session, rescue medication may be prescribed to alleviate such symptoms. Appropriate rescue medications include benzodiazepines, zolpidem, or other anxiolytic or sedative according to the research psychiatrist's clinical judgement.

Cognitive processing therapy

Cognitive Processing Therapy is a short-term Cognitive Behavioural Therapy for PTSD and related difficulties, typically consisting of 8–15 sessions (APA, 2017). Cognitive Processing Therapy targets unhelpful thoughts related to traumatic events, which may be perpetuating an individual's difficulties in processing the traumatic memory. Treatment will be delivered remotely between therapist and patient in 60-minute sessions. These sessions will also incorporate the elements of integration typically offered in psychedelic therapy manuals, such as reflecting on experiences which may have occured during dosing. CPT is the selected modality for these sessions as it is a NICE-recommended treatment for PTSD (NICE, 2018) and is manualised, which allows for strong treatment fidelity.

A total of three sessions will be delivered per week, over a four week period, for a total of 12 sessions commencing one week after the second dosing session. Sessions will focus on exploring the patient's thoughts about the trauma and the impact this may have had on the patient's belief about themselves and the world around them. Patients will be asked to provide a written account of the trauma during treatment, as well as record their thought patterns and thoughts of the trauma since it took place. By understanding these thought patterns, cognitive change can be encouraged through cognitive-restructuring tools and discussion to provide the patient with an opportunity to process the trauma and re-write problematic belief changes. The final CPT session will take place two weeks after the twelfth session.

Follow up

Four weeks after the end of treatment, participants will be administered the following follow-up psychometric evaluations: the PCL-5 (Weathers et al., 2013); the International Trauma Questionnaire (ITQ; Cloitre et al., 2018); the Dimensions of Anger Reactions (DAR-5; Forbes et al., 2014); the Patient Health Questionnaire (PHQ-9; Korenke & Spitzer, 2002); the Generalised Anxiety Disorder (GAD-7; Spitzer et al., 2006); the Oslo Social Support Scale (OSS-3; Kocalevent et al., 2018) and the Short Warwick-Edinburgh Mental Wellbeing Scale (SWEMWBS; Stewart-Brown et al., 2021). These outcome measures are fully

described below.

Results

Outcomes

The primary efficacy outcome of the study is change from baseline to one month follow-up in PTSD symptoms as measured by the Post-traumatic Stress Disorder Checklist For DSM-5 (PCL-5; Weathers et al., 2013), a 20-item measure of the 20 DSM-5 symptoms of PTSD.

Secondary outcomes are as follows:

Feasibility

Feasibility will be assessed through whether the target sample size can be recruited, did not attend (DNA) rate and retention rate across the duration of the study. The recruitment metric will be calculated as a binary outcome: yes if the sample size is recruited, no if it isn't. The DNA rate will be calculated as the number of sessions not attended out of the total number of sessions. The retention rate will be calculated as the proportion of participants who completed the full study out of the total number of participants.

Acceptability

The acceptability of PAP to veterans will be assessed through qualitative semi-structured interviews which will be conducted one-month following treatment completion with consenting participants, as well as via the Adverse Experiences in Psychotherapy questionnaire (AEP; (Hutton et al., 2017). The AEP is a 28-item measure of a variety of possible adverse experiences that may occur in therapy.

Safety

Safety will be measured by reporting the incidences of adverse events (AEs) and serious adverse events (SAEs) across the duration of the study. These will be reported as descriptive statistics, with totals for the number of both SAEs and AEs.

Efficacy

Secondary efficacy measures will be collected as follows:

1 International Trauma Questionnaire (ITQ; Cloitre et al., 2018): 18-item assessment of the core features of PTSD and complex PTSD (CPTSD).
2 Dimensions of Anger Reactions-5 (DAR-5; Forbes et al., 2014): 5-item measure of difficulties with anger.
3 Patient Health Questionnaire (PHQ-9; Kroenke & Spitzer, 2002): 9-item measure of depression symptoms.
4 Generalised Anxiety Disorder-7 (GAD-7; Spitzer et al., 2006): 7-item measure of general anxiety symptoms.
5 Oslo Social Support Scale-3(OSS; Kocalevent et al., 2018): 3-item measure of perceived social support.
6 The Short Warwick-Edinburgh Mental Wellbeing Scale (SWEMWBS; Stewart-Brown et al., 2021): 7-item measure of mental wellbeing.

Experience/Background assessment

1 Alcohol Use Disorder Identification Test (AUDIT; Saunders et al., 1993): 10-item measure of hazardous and harmful alcohol use.
2 Drug Use Disorders Identification Test (DUDIT; Berman et al., 2016): 10-item measure of drug-related problems.
3 Moral Injury Outcome Scale (MIOS; Litz et al., 2022): 14-item measure of difficulties with moral injury in relation to a potentially morally injurious event.
4 Challenging Experiences with Psychedelics questionnaire (Barrett et al., 2016): 26-item assessment of seven factors (grief, fear, death, insanity, isolation, physical distress, and paranoia) that provides a phenomenological profile of challenging aspects of experiences with psilocybin.

Statistical analyses

Multiple imputation will be used for missing observations. To assess the primary efficacy outcome of the study, the PCL-5 total severity score at baseline will be compared with PCL-5 total severity score at 1-month follow-up. To assess the secondary efficacy outcomes, scores at baseline will be compared with scores at 1-month follow-up. If the normality assumption for the Student's *t*-test is not met based on the Shapiro-Wilk test, testing will be conducted with the Wilcoxon signed-rank test. For achieving superiority, the observed p-value must be <0.025 for a one-sided hypothesis. Two-sided 95 % confidence intervals will also be calculated. Feasibility and safety outcomes will be reported descriptive statistics as described in the outcomes section.

All statistical inference tests will be performed at the same significance level (α) of 0.025. For continuous variables, baseline and follow-up will be compared using one-sided parametric or non-parametric tests, as appropriate. For categorical variables, baseline and follow up scores will be compared using chi-square or Fisher's exact tests.

Ethics and dissemination

Participation in the current study is subject to providing written informed consent. The study is subject to approval by combined review of the National Research Ethics Committee (South Central - Hampshire) and Health Research Authority and the Medicines and Healthcare products Regulatory Agency. The trial has been prospectively registered with ClinicalTrials.gov and ISRCTN. A manuscript describing the results of the study will be submitted to a peer-reviewed journal. Study findings will also be disseminated via conferences and other media.

In this paper we have described a study protocol that aims to investigate the feasibility, acceptability, safety, and efficacy of PAP for veterans with PTSD in a clinical setting. Whilst other registered clinical trials are currently exploring PAP, there is a need to investigate the feasibility of PAP across the populations it could be offered to and various settings including clinical settings supporting veterans with PTSD. This is important given outcomes may depend on individual variations in subjective experience and the environmental context in which treatment takes place. The current feasibility trial may therefore inform future studies where PAP could be scaled up, such as a randomised controlled trial of PAP in a clinical setting with a veteran population.

Author contribution statement

All authors contributed to the development of the protocol. DM secured funding. NB drafted the manuscript. All authors edited the manuscript.

Declaration of Competing Interest

There are no declarations of interest or conflicts of interest to declare.

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