Pioneer Programme

MDMA-assisted therapy research for treatment-resistant PTSD in veterans

End of trial report – August 2024

MAPS MULTIDISCIPLINARY ASSOCIATION FOR PSYCHEDELIC STUDIES

SUPPORTING WOUNDED VETERANS REHABILITATION TO EMPLOYMENT

KING'S College LONDON

NHS

FiMT forces in mind trust

COMMUNITY FUND

Institutions

The Multi-disciplinary Association for Psychedelic Studies

Founded in the USA in 1986, the Multidisciplinary Association for Psychedelic Studies (MAPS) is a non-profit research and educational organisation that develops medical and legal contexts for people for the beneficial use of psychedelics.

Supporting Wounded Veterans

Supporting Wounded Veterans (SWV), founded in 2012, supports severely wounded veterans to transition from military to civilian life through a number of programmes, including establishing pain clinics at King Edward's VII's Hospital, mentoring, occupation, training & employment (OTE) and initiating trials for MDMA-assisted therapy for PTSD in the UK.

King's College London, the Institute of Psychiatry, Psychology & Neuroscience

The Institute of Psychiatry, Psychology & Neuroscience (IoPPN) is a leading centre for mental health and neuroscience research in Europe. It is rated in the global top five of medical establishments for highly cited neuroscience outputs.

Acknowledgements

SWV is very grateful to the Forces in Mind Trust (FiMT) for enabling SWV and its partners to initiate and complete this important Phase II Trial. This can only provide a very strong base for the next phases of research into the use of MDMA-assisted therapy for veterans suffering with moderate to severe treatment-resistant Post Traumatic Stress Disorder (PTSD). We are particularly grateful for the support and guidance of Kirsteen Waller (Health Programme Manager) during this period.

> The MDMA-assisted therapy trial for PTSD in the UK demonstrated that recruitment, intervention delivery and therapist training are all feasible. We established the essential clinical and operational capacities for future research in this area, as well as the principle of delivery of the intervention if it is licensed and funded.
>
> The success of this trial underscores the need for larger, randomized studies to further validate and expand our understanding of this novel treatment. This is even more pressing in light of the FDA's recent decision to ask for more clinical trial evidence to be gathered in this area.
>
> Your continued support will be instrumental in advancing this critical work, which signifies an important step forward for UK veterans in urgent need of innovative and effective treatments.

Dr James Rucker

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Executive summary

Supporting Wounded Veterans (SWV) has worked in conjunction with the Institute of Psychiatry, Psychology & Neuroscience (IoPPN) at King's College London, the Multidisciplinary Association for Psychedelic Studies (MAPS) and NHS England to bring the first Methylenedioxymethamphetamine (MDMA)-assisted therapy in the treatment of moderate to severe treatment-resistant Post-Traumatic Stress Disorder (PTSD) clinical trial to the UK.

This research was approved by the Medicines and Healthcare products Regulatory Agency (MHRA) and approved by the Health Research Authority (HRA).

The MDMA-assisted therapy research consisted of two trials executed in the USA and five sites in Europe, including this trial in UK:

- Phase II Trial (MP18): an Open-Label, Phase II, Multicentre Feasibility Study of Manualised MDMA-Assisted Psychotherapy in subjects with PTSD.
- Phase III Trial (MAPP3): A Multicentre, randomised, double-blind, inactive placebo-controlled study of the efficacy and safety of MDMA-assisted therapy in veterans with severe PTSD.

The research was subsequently reduced to Phase II only, the Safety part of the Trial. MAPS made the unexpected decision to focus on the US market only and further research in UK and Europe was halted.

On 9 January 2024, the MAPS Public Benefit Corporation rebranded to Lykos Therapeutics but will be referred to as MAPS throughout given the study completed in December 2023 while still branded as MAPS.

For Phase II (Safety) the MHRA recommended having five veterans only due to MAPS having completed their own Phase II Trials successfully. Five UK veterans with experience of moderate to severe PTSD were recruited to take part in the trial, with each participant receiving a combination of MDMA and established talking therapies.

The initial trial was successful. The treatment was well tolerated by the veterans, refined operational processes and provided the trials team with the confidence to proceed to the next stage including the potential for larger trials. The latter ability would enable more veterans suffering with PTSD to be potentially treated in a shorter timeframe.

Introduction

PTSD is a psychiatric disorder caused by traumatic experiences such as those experienced in war, accidents and abuse. People who suffer from PTSD repeatedly relive their traumatic experiences, leading to anxiety, insomnia, broken relationships, loss of employment, substance abuse, depression and suicide.

Data from MAPS demonstrates MDMA-assisted psychotherapy has been shown to significantly reduce the symptoms of PTSD in randomised controlled clinical trials.

An estimated 40-60% of patients suffering with PTSD do not respond to sertraline and paroxetine which are approved first-line therapeutics for the treatment of PTSD.[1. 2.]

Evidenced-based trauma-focused psychotherapies such as prolonged exposure and Cognitive Behavioural Therapy (CBT) are considered the optimum treatments for PTSD. However, the FiMT report dated May 2020 entitled "The Mental Health needs of serving and ex-service personnel – A Systemic Review" found that evidence-based, cognitive behavioural treatments remained at less than 30% effectiveness whilst Eye movement desensitization and reprocessing (EMDR) had negligible results.[3.]

Clinical trials for MDMA-assisted therapy have shown promising results in the USA, as demonstrated by the MAPS Trial details below:

- 345 potential participants were assessed for eligibility.
- 131 were enrolled and 91 were put forward for the study.
- Of the 91, 46 were confirmed for MDMA treatment and 44 to placebo.

In the trial run by MAPS, 67% of the subjects on MDMA treatment therapy, who on average had suffered from PTSD for nineteen years, including veterans, first responders or those who had suffered abuse, no longer qualified for a diagnosis of PTSD after three months. Of those treated with the placebo, 32% of the subjects no longer qualified for a PTSD diagnosis.

At the one year follow on, 68% of all subjects treated with full dose MDMA no longer met the diagnostic criteria for PTSD, demonstrating the durability of positive treatment outcomes and continued improvement over time.

SWV, a veterans' charity, co-funded MAPS and KCL to complete a Phase II Trial which involved five veterans undergoing MDMA-assisted Psychotherapy. Through this Trial the team firstly, aimed to establish the safety and feasibility of this innovative approach, and secondly, to focus on UK veterans suffering with a severe and chronic condition, the numbers of which had risen with conflicts in Iraq and Afghanistan.

The Trial specifically focused on practising and finalising safety procedures. To this end it involved a low number of participants and sourced and trained therapists with the trial protocol (the step-by-step guide through the drug administering and therapy process).

Phase II was completed by December 2023. Phase III was scheduled to have included 20 further UK veterans but did not take place because MAPS fundamentally changed course from its original pan-European Trial to focus on US FDA approval, potentially in the second half of 2024.

Subsequent to the Phase II Trial starting in May 2022 there were also a number of changes to the UK medicines regulatory framework. Firstly, the UK was no longer regulated by European regulation (effective January 2021) and was subject to regulatory requirements by the MHRA and secondly that the UK government (effective January 2024) introduced the International Recognition Process (IRP) whereby innovative treatments could potentially receive sign off if already authorised by a trusted foreign regulatory body.

SWV aims to facilitate further studies into MDMA-assisted therapy to enable veterans to receive the treatment as soon as possible. There are a number of avenues being actively explored: firstly, by SWV funding continued work with KCL with a new protocol and independently sourced MDMA or secondly, to wait for MAPS to gain approval from the FDA. These remain options and work on a new protocol is well underway as is identifying new sources of MDMA. This work is being completed in close association with similar work being progressed in Israel, the Netherlands, the Veterans Association (VA) in the USA and Australia.

Trial methodology

Initially the Trial included two distinct Phases. The first Phase II Trial was an Open-Label, multicentre feasibility study of manualised MDMA-assisted psychotherapy focused on five UK veterans. The subsequent Phase III Trial was to be a multicentre, randomised, double-blind, inactive placebo-controlled study of the efficacy and safety of MDMA-assisted therapy on 20 UK veterans with moderate to severe treatment-resistant PTSD.

The timeframe for all phases was initially estimated at 28 months. As previously described, in Q3, 2023, MAPS unexpectedly decided to reduce its responsibilities outside the USA in order to progress its FDA approval process. This subsequently prevented Phase III going ahead as planned as MDMA sourcing and the Trial Protocol were MAPS' proprietary property and no longer available to UK or European Trials.

For the aforementioned reasons, this report only focuses on the completion of the Phase II Trial.

Study design

This was an open-label (i.e. subjects and physicians have knowledge of the assigned treatment) Phase II study intended to gather supportive data on the safety and effectiveness of manualised MDMA-assisted psychotherapy as a treatment for moderate to severe treatment resistant PTSD. It also provided clinical training and supervision to UK therapy teams to build capacity ahead of future studies. **This study was also the first multi-site study of MDMA-assisted psychotherapy for moderate to severe treatment resistant PTSD in Europe and explored reproducibility of findings from US FDA-regulated trials.**

Procedures

Screening: Prospective participants were pre-screened by telephone according to a Research Ethics Committee (REC) approved script to ascertain if they met basic eligibility criteria. If deemed appropriate following the pre-screening, participants were invited to provide consent and begin the screening process. Medical and psychiatric screening took place over multiple visits and then completed in-person and/or via tele-assessment. If deemed eligible by the study team, an independent rater continued the eligibility assessment via tele-assessment.

Enrolment and Preparatory Sessions: Preparatory Sessions during the Preparatory Period focused on psycho-education about PTSD, building safety for the therapeutic relationship, developing the therapeutic alliance, obtaining the background for the trauma, and preparing the participant for the first MDMA-assisted therapy Session.

Treatment Period: During the Treatment Period, which occurred over a duration of 12 weeks, participants completed two open label MDMA-assisted treatments. Each treatment consisted of an MDMA-assisted therapy session. A dose of 80 or 120 mg MDMA was administered alongside specialized psychotherapy. A supplemental half-dose was administered 1.5 to 2 hours after the initial dose unless contraindicated (i.e. the drug should not be used in the case in question). At the end of the treatment session, participants remained overnight in an appropriately furnished room at King's College Hospital. An attendant monitored periodically the participant during the overnight stay. This was followed the morning after by an Integrative Session, phone follow-ups over the next week, a second Integrative Session within two weeks, and a third Integrative Session within three to five weeks. After each MDMA-assisted therapy session, veterans returned home chaperoned by SWV / family.

Follow-up Period and Study Termination: After the last Integrative Session, participants entered follow-up for approximately four weeks (+/- two weeks). No further visits were required by the trial protocol until the final CAPS-5 (the Clinically Administered PTSD Scale) assessment followed by a Study Termination meeting. Participants had access to therapy teams for support if needed, and additional visits.

Trial recruitment

- Phase II of the Trial required five UK veterans, as stipulated by MHRA, to successfully complete the process. Further individuals and groups had also completed Phase II in the joint worldwide multicentre trials as previously described.
- SWV recruited veterans through the SWV network and through the headquarters of services, regiments and corps. Names were forwarded to the KCL team and confidentiality was given due importance.
- There was sensitivity to ONLY allow a slow supply of veteran volunteers in order not to "overpromise" treatment to a larger number of veterans than there were places available.
- Volunteer statistics:
  - 43 veterans volunteered for Phase II.
  - 25 failed screening.
  - 13 did not respond to "follow up" meeting requests.
  - 5 veterans successfully completed Phase II as required.
- Those volunteers who failed screening continue to have or were offered the option of taking part in subsequent Trials.

Data collection

The overall objective of this study was to use standard clinical measures to explore the safety and effects of open-label manualized MDMA-assisted psychotherapy with a flexible dose of MDMA in participants with moderate to severe treatment-resistant PTSD, and to serve as an opportunity for supervision of therapy teams selected to conduct future MDMA-assisted psychotherapy research.

Primary objective and primary end point

- The primary objective of this study was to evaluate the effect of MDMA-assisted psychotherapy on moderate to severe treatment-resistant PTSD, as measured by the estimand of change in CAPS-5 (the Clinically Administered PTSD Scale) Total Severity Score from Baseline (Visit 3) to 13 weeks post Baseline (Visit 14).

- The primary endpoint was the change in CAPS-5 Total Severity Score from Baseline (Visit 3) to 13 weeks post Baseline (Visit 14).

Secondary objective and secondary end point

- The secondary objective was to evaluate the effect of MDMA-assisted psychotherapy on moderate to severe treatment-resistant PTSD in clinician-rated functional impairment, as measured by the mean change in Sheehan Disability Scale (SDS). The Sheehan Disability Scale is a self-rated, three-item questionnaire that uses a Likert scale from 0 (not at all) to 10 (extremely) to assess impairment in the occupational, social, and family domains.[4]

- The secondary endpoint was the mean change in SDS (see footnote) item scores from baseline (Visit 3) to 13 weeks post Baseline (Visit 14).

Safety objectives

The overall safety objective was to assess severity, incidence and frequency of Adverse Effects (AEs), AEs of Special Interest (AESIs), and Serious Adverse Events (SAEs), concomitant medication use, suicidal ideation and behaviour, and vital signs to support the package insert for MDMA-assisted psychotherapy. The following safety objectives would evaluate the safety of MDMA-assisted psychotherapy:

1. Assess incidence of AEs during Experimental Sessions that may be indicative of a medical complication of the Investigational Product (IP), such as clinical signs and symptoms of chest pain, shortness of breath, or neurological symptoms or any other signs or symptoms that prompt additional vital sign measurements.

2. Assess incidence of AEs by severity.

3. Assess incidence of Treatment Emergent AEs (TEAEs) by severity.

4. Assess incidence of TEAEs by severity taken during an Experimental Session and through two days after IP administration.

5. Assess incidence of AESIs, defined as AEs specified in the protocol related to cardiac function and abuse liability.

6. Assess incidence of AEs by severity categorized as leading to discontinuation of IP, resulting in death or hospitalization, and continuing at Study Termination.

7. Assess incidence of SAEs.

8. Assess incidence of psychiatric concomitant medications taken during an Experimental Session and through two days after IP administration.

9. Assess incidence of any psychiatric concomitant medications taken during the Treatment Period.

10. Assess incidence of serious suicidal ideation and positive suicidal behavior assessed with the Columbia Suicide Severity Rating Scale (C-SSRS). The Columbia-Suicide Severity Rating Scale is a unique suicide risk assessment tool that supports suicide risk assessment through a series of simple, plain-language questions that anyone can ask.[5]

11. Assess mean changes in blood pressure, heart rate, and body temperature from pre-IP administration to end of each Experimental Session.

Exploratory objectives

These objectives may be explored to characterise participants receiving MDMA-assisted psychotherapy to support the primary objective:

1. Explore the effect of presence of secondary traumatic stressors (LEC-5) on the CAPS-5 Total Severity analyses

2. Explore changes within-participants in PTSD symptom clusters of re-experiencing, avoidance, negative alterations in cognition and mood, and hyperarousal, as measured by changes in CAPS-5 subscale scores from Visit 3 (Baseline) to Visit 14 (13 weeks post Baseline)

3. Explore the effect of adverse childhood experiences (ACE) on the CAPS-5 Total Severity analyses

4. Explore changes in:

    - Dissociative symptoms associated with PTSD (DSP-I)
    - Depression (BDI-II)
    - Chronic pain (CPGS)
    - Quality of life (EQ-5D-5L)
    - Self-compassion (SCS)
    - Addictive behaviours including: Alcohol use (AUDIT), Drug use (DUDIT) and Nicotine use (SRNU)
    - Eating habits (EAT-26)
    - Healthcare utilization (UFEC) and economic productivity
    - Subjective effects (SE)

Trial findings

As this Trial was part of an International multicentre trial with MAPS detailed results cannot be shared at this time.

However, the Phase II trial was successful with the treatment well tolerated by the UK veterans and showing encouraging signs of effectiveness that match those seen in larger US trials.

All participants reported that they found this form of intervention acceptable.

Phase II specifically focused on:

- The recruitment of potentially eligible UK veterans was successful but emphasised the importance of having a pool of additional potentially eligible UK veterans available to balance those who failed screening, to ensure the demands of the timeline / budget continued to be met.
- The process, which emphasised and practised the importance of sound logistics and a careful chaperone plan to allow veterans to approach the trial in an appropriate state of mind.
- The recruitment and training of sufficient therapists: the study successfully trained and certified 10 UK therapists.
- The establishment of standard operating procedures (SOPS): the study allowed for the testing and development of intervention-specific SOPS ahead of future trials.

Discussion

This study marks a significant milestone as it is the first time MDMA-assisted psychotherapy has been used to treat moderate to severe treatment-resistant PTSD in a research setting in the UK. As the military workforce is relatively more susceptible to the impact of PTSD than the general population, this study focuses on five UK veterans. The study provided invaluable data on its safety, feasibility, and efficacy and the outcomes demonstrate that the intervention can be safely administered within the UK's healthcare framework. This establishes a strong foundation for future applications and broader implementation across various settings.

The feasibility of the intervention was clinically assessed by KCL, confirming that it can be integrated into existing therapeutic practices. The recruitment and screening procedures developed during the study proved effective, ensuring that participants who met the inclusion criteria were adequately identified and enrolled. This process not only facilitated the smooth execution of the study but also set a benchmark for future recruitment strategies.

Moreover, the study played a crucial role in training therapists and establishing comprehensive operating procedures. This capacity-building aspect ensures that a well-prepared workforce is ready to deliver the intervention effectively. The operational guidelines developed will serve as a critical resource for future implementations, standardising practices and ensuring consistency in clinical delivery.

In conclusion, this pioneering study provides quality evidence supporting the intervention's safety, feasibility, and efficacy. The insights gained and the infrastructure established will be instrumental in scaling up the intervention and optimising its impact within the UK veteran community.

Conclusions

> I found the trial truly profound & I really see that it shows positive outcomes. I do feel we were really starting to get into the crux of things during my time in the trial. I felt that if it was a licensed therapy I would have stayed in therapy a while longer which I found interesting after the fact due to the US Reports showing that they found three dosing sessions being optimal for therapy.
>
> **Veteran, Phase II volunteer**

- PTSD can severely impact an individual's quality of life, affecting their ability to function in daily activities, maintain relationships and pursue their goals. Only approximately 30% of sufferers respond positively to first-line therapeutics or evidenced-based trauma-focused psychotherapies.[1, 2] Finding evidence based and effective treatments is crucial to support these individuals who have served their communities and countries.
- There remain a large number of veterans suffering from PTSD since The Falkland Islands and Northern Ireland as well those from more recent Balkan, Afghan and Iraq conflicts. Regarding the latter theatres the PTSD rate, in a combined sample of veterans and still serving personnel, was 4% in 2004/6 and 2007/09, but had risen to 6% in 2014/16. This compares to a rate of 4.4% within the civilian population. Evidence can be drawn from:
  - Iraq/Afghan conflicts: The Rise of PTSD. The Conversation 2018
  - New study explores the mental health landscape of veterans resident in Northern Ireland. British Psychological Society 2023
  - Falklands War: "I thought I was the only one like this". BBC 2022
  - Long-term responses to treatment in UK veterans with military-related PTSD: an observational study. BMJ Open Journals
- Rates of PTSD in those who have left service (overall 7.4%), especially those who have deployed in a combat role (17%), do appear to be elevated.
- KCL considers that we can proceed with confidence to future trials regarding MDMA-assisted therapy. Potentially testing this therapy on larger groups to more fully establish its effectiveness and help determine whether and how it can be scaled up.
- SWV and KCL are working together to model next steps based on the successful completion of this Phase II Trial. Whilst the final project model is yet to be finalised SWV and KCL confidence is high that it will commence in the first half of 2025.

> Do I feel "cured", no, however... I do feel I found so much better results from this trial therapy compared to any other type of therapy I've done over the years & really feel it can show positive results for others moving forward.
>
> **Veteran, Phase II volunteer**

If you have any questions please contact Supporting Wounded Veterans:

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1. Nature Medicine, May 2021. MDMA-assisted therapy for severe PTSD: a randomised, double-blind, placebo-controlled phase 3 study
2. Sage Journals, October 2021. A Sobering Look at Treatment Effectiveness of Military-Related Posttraumatic Stress Disorder
3. FiMT report, May 2020. "The Mental Health needs of serving and ex-service personnel – A Systemic Review"
4. Sheehan Disability Scale (SDS). Harmresearch.org
5. Columbia University Severity Rating Scale (C-SSRS). ColumbiaPsychiatry.org