Randomized controlled trial of multi-modular motion-assisted memory desensitization and reconsolidation (3MDR) for male military veterans with treatment-resistant post-traumatic stress disorder

Bisson, J.I.; Deursen, R. van; Hannigan, B.; Kitchiner, N.; Barawi, K.; Jones, K.; ... ; Vermetten, E.

Acta Psychiatrica Scandinavica

Acta Psychiatr Scand 2020: 142: 141–151

DOI: 10.1111/acps.13200

Randomized controlled trial of multi-modular motion-assisted memory desensitization and reconsolidation (3MDR) for male military veterans with treatment-resistant post-traumatic stress disorder

Bisson JI, van Deursen R, Hannigan B, Kitchiner N, Barawi K, Jones K, Pickles T, Skipper J, Young C, Abbott LR, van Gelderen M, Nijdam MJ, Vermetten E. Randomized controlled trial of multi-modular motion-assisted memory desensitization and reconsolidation (3MDR) for male military veterans with treatment-resistant post-traumatic stress disorder.

Objective: To explore the potential efficacy of multi-modular motion-assisted memory desensitization and reprocessing (3MDR) in British military veterans with treatment-resistant service-related PTSD.
Methods: Exploratory single-blind, randomized, parallel arm, cross-over controlled trial with nested process evaluation to assess fidelity, adherence and factors that influence outcome.
Results: A total of 42 participants (all male) were randomized with 83% retention at 12 weeks and 86% at 26 weeks. The difference in mean Clinician-Administered PTSD Scale for DSM-5 scores between the immediate and delayed 3MDR arms was −9.38 (95% CI −17.33 to −1.44, $P = 0.021$) at 12 weeks and −3.59 (−14.39 to 7.20, $P = 0.513$) at 26 weeks when both groups had received 3MDR. The likely effect size of 3MDR was found to be 0.65. Improvements were maintained at 26-week follow-up. 3MDR was found to be acceptable to most, but not all, participants. Several factors that may impact efficacy and acceptability of 3MDR were identified.
Conclusion: 3MDR is a promising new intervention for treatment-resistant PTSD with emerging evidence of effect.

J. I. Bisson[1], R. van Deursen[2], B. Hannigan[2], N. Kitchiner[3], K. Barawi[1], K. Jones[2], T. Pickles[4], J. Skipper[1], C. Young[5], L. R. Abbott[2], M. van Gelderen[6], M. J. Nijdam[7,8], E. Vermetten[6]

[1]School of Medicine, Cardiff University, Cardiff, UK, [2]School of Healthcare Sciences, Cardiff University, Cardiff, UK, [3]Veterans' NHS Wales, Cardiff and Vale University Health Board, Cardiff, UK, [4]Centre for Trials Research, Cardiff University, Cardiff, UK, [5]Cardiff and Vale University Health Board, Cardiff, UK, [6]Department of Psychiatry, Leiden University Medical Center, Leiden, The Netherlands, [7]ARQ Centrum'45, ARQ National Psychotrauma Centre, Diemen, The Netherlands and [8]Department of Psychiatry, Amsterdam University Medical Centres, Amsterdam, The Netherlands

Key words: PTSD; treatment; RCT; 3MDR; military veterans

Jonathan Bisson, School of Medicine, Cardiff University, Cardiff, UK. E-mail: bissonji@cf.ac.uk

Trial Registration Number – ISRCTN80028105

Accepted for publication May 28, 2020

Significant outcomes

- 3MDR reduced symptoms in male military veterans with treatment-resistant PTSD.
- 3MDR was well tolerated by most but not all participants.
- Improvements following 3MDR were maintained at three-month follow-up.

Limitations

- The sample size of 42 is relatively small.
- The results may not be generalizable to non-military veteran populations.
- The follow-up period was restricted to three months.

Introduction

The majority of those who serve in the armed forces do well after they leave, but over 7% have post-traumatic stress disorder (PTSD) (1). Unfortunately, many veterans remain symptomatic despite evidence-based treatment and research suggest that psychological treatments for PTSD may not be as effective for veterans as for other populations (2, 3). There is a clear need for more effective interventions. Multi-modular motion-assisted memory desensitization and reconsolidation (3MDR) (4) is a new treatment that aims to reduce cognitive avoidance and augment engagement with therapy. It is based on known therapeutic principles of virtual reality exposure therapy (5) and eye movement desensitization and reprocessing (EMDR) (6), embedded in a novel context in which the patient walks on a treadmill whilst immersing in and interacting with a series of self-selected images that are displayed on a large screen. Preliminary research conducted by the originators of 3MDR has been promising (4), and there is a need for further research to determine its true potential for treatment-resistant PTSD.

Aims of the study

To explore the potential efficacy of multi-modular motion-assisted memory desensitization and reconsolidation further by determining whether it is able to reduce traumatic stress symptoms in British military veterans with treatment-resistant service-related PTSD, to a significantly greater degree than a waiting list and to explore factors associated with its feasibility.

Material and methods

Design

This was an exploratory single-blind, randomized, parallel arm, cross-over, controlled trial with a one-to-one allocation ratio and nested process evaluation to assess fidelity, adherence and factors that influence outcome. The trial followed CONSORT guidelines (7) and was granted approval by the South East Wales Research Ethics Committee. The trial was conducted between July 2017 and July 2019.

Sample size

To detect a mean 15-point difference on the Clinician-Administered PTSD Scale between 3MDR and delayed 3MDR at a 0.05 confidence level and 80% power, assuming a standard deviation of 15.18, based on a previous study of PTSD treatment, 17 subjects would be needed in each arm. Allowing for a 20–25% drop-out, a total proposed sample size of 42 was determined. For the qualitative aspects, based on previous research (8), we anticipated that interviews would be conducted with around 10 purposively sampled participants, selected to ensure the inclusion of those with a wide range of therapy experiences, and all six therapists.

Inclusion/exclusion criteria

Wide eligibility criteria were used to ensure good external validity. Participants were aged 18 or over, provided informed consent, met DSM5 (9) criteria for PTSD and had previously received trauma-focused psychological treatment without loss of PTSD diagnosis. Exclusion criteria were psychosis, DSM5 severe depressive episode, substance dependence, change in psychotropic medication within one month, suicidal intent and inability to walk for 30–45 min on a treadmill. Individuals with comorbidity were included if PTSD was considered the primary diagnosis.

Recruitment and consent

Potentially eligible British military veterans who attended NHS clinics in South Wales were

approached by clinicians involved in their care, screened and then fully assessed by one of two researchers after providing informed consent. If individuals met the eligibility criteria, they were randomized to receive 3MDR immediately or after a delay of 12 weeks. A statistician used a computer programme to generate randomization codes on a 1:1 basis with a block size of 6 and no stratification. The codes were sealed in opaque brown envelopes numbered from 1 to 42. The 3MDR laboratory researcher (who was blind to their content) opened the envelopes consecutively, advised the participant of the arm they had been allocated to and the date of their first 3MDR session.

Outcome measures

All outcome measures were administered by one of two postgraduate researchers blind to randomization allocation at baseline, 12 and 26 weeks after randomization. The primary outcome was symptoms of PTSD measured by the Clinician-Administered PTSD Scale for DSM5 (CAPS5) (10), a 29-item structured interview for assessing PTSD diagnostic status and symptom severity and widely considered the gold standard in PTSD assessment. The researchers were trained in administration of the CAPS5 and demonstrated good inter-rater reliability with each other and with their trainers. Regular discussions of the scoring of individual items between the researchers and the lead author (who was one of the trainers), along with independent rating of training videos during the trial, were used to maintain good inter-rater reliability (Kappa = 0.74). Secondary outcome measures were brief, well-validated self-report measures (PTSD Checklist) (11) for traumatic stress; Work and Social Adjustment Scale (WSAS) (12) for quality of life/functional impairment; Patient Health Questionnaire-9 (PHQ-9) (13) for depression; General Anxiety Disorder-7 (GAD-7) (14) for anxiety; AUDIT-O (15) for alcohol use; and the Insomnia Severity Index (ISI) (16) for sleep difficulties. In addition, the Multidimensional Scale for Perceived Social Support (17) was used to assess perceived social support and changes in health-related quality of life were measured by the EQ-5D-5L (18).

3MDR intervention

3MDR therapy was delivered weekly over nine weeks (two weeks preparation, six weeks 3MDR and one concluding session) by experienced psychological therapists working with Veterans' NHS Wales. Therapists were extensively trained in 3MDR and supervised by its originators throughout the trial. 3MDR sessions used the Motek Gait Real-time Analysis Interactive Lab (GRAIL) system at Cardiff University which uses an instrumented dual-belt treadmill, a motion-capture system and synchronized virtual reality (VR) environment, which comprises a 180° projection screen with 4 projectors and a surround sound system (see Figure S1). The 3MDR protocol involved projection of purpose-built tunnels to walk in and projection of self-selected digital pictures integrated into the software used for treatment.

Prior to the 3MDR sessions, participants were asked to select 12 pictures that evoked memories of the traumatic event. The therapists guided the participant to limit avoidance during picture selection. Supported by the therapist, the pictures were arranged according to 0–10 subjective units of distress (SUD) score and theme. For each session, a maximum of seven digital pictures were used for projection on the screen. Participants also chose two pieces of music. The first for the warm-up walk aimed to take the participant back to the time of the trauma, for example music played a lot during this period. The second, for the cool-down, aimed to bring the participant back to the here and now.

During sessions, participants walked at their preferred walking speed. The sessions started with an introduction phase, in which participants saw an outdoor pathway ahead and their music began to play whilst verbal guidance prepared them for the intervention phase. Participants entered a tunnel to approach their first picture whilst being guided by instructions on what to do. As soon as they saw their chosen picture, a literal description of this was requested with a brief account of the related memories, feelings and bodily sensations. These were entered as key phrases so they became visible on the screen. When participants confirmed there were no more new feelings, the dual task was started: a red ball moved across the screen from left to right and back to create bilateral stimulation. Whilst focusing on the phrases on the screen, participants were asked to track the ball and call out random numbers displayed on it. After 30–45 s, the ball was removed, the image faded away, and a SUD score was requested and recorded. The tunnel then re-appeared, and the process was repeated for the other pictures. After the last picture, the final phase began with their second selected piece of music, assisting return to the here and now, and positive feedback was given about what had been achieved, to conclude the session.

After the platform phase, a therapist-led discussion occurred to elicit how the session was and to discuss the meaning of the re-experiencing to the participant in this setting. The therapist ensured

that the participant was completely returned to the here and now and aimed to enable the participant to attach a positive meaning to the 3MDR session. Every 3MDR session was video-recorded, and a report summarizing the behavioural response to the intervention was produced. One session for each participant was randomly selected and checked for fidelity by either EV, MN or MvG (three of the originators of 3MDR) using a scale specifically developed by them and JIB for this study. The raters independently rated the videos assigned to them and discussed their ratings to support inter-rater reliability. Further discussion occurred if there were concerns about specific ratings. The scale included items on the following: supporting selection of pictures and music; education about 3MDR; preparation for the session; encouraging approach behaviour to selected images; addressing hotspots; supporting narrative unfolding; eliciting key physical, cognitive and emotional associations; empowering participant and encouraging togetherness; stimulating integration and postsession processing; and reflecting on newly acquired memories, experiences and skills.

Analyses

Quantitative outcome data – all continuous outcomes were analysed, by comparing means between arms using ANCOVA, with the individual's baseline scores as covariate, as well as age, baseline PHQ-9 and time since trauma. All randomized participants were considered for analyses under the intention to treat principle. Sensitivity analyses of CAPS-5 at 12 and 26 weeks were undertaken via multiple imputation using randomized arm, baseline CAPS-5, age, baseline PHQ-9 and time since trauma as model covariates. The number of imputations required was determined from the proportion of missing CAPS-5 data at 12 and 26 weeks. All analyses were performed at the end of the data collection period using SPSS version 25 (19) and Stata/IC 15.1 (20).

Qualitative data – semistructured interviews were audio-recorded and transcribed verbatim. Transcripts were imported into QSR NVivo 10 (21) software for computer-aided qualitative data analysis (CAQDA). Following a process of inductive thematic analysis (22), interview data were examined for recurring patterns found across different transcripts as well as for deviant cases, or views and experiences found in single transcripts only (23). The aim was to reveal the fullest range of views and experiences. To ensure comprehensiveness and validity, a preliminary analysis was shared and discussed with the research team.

Results

Quantitative

Fifty-two military veterans were referred to the trial, and 42 participants (all male) were recruited and randomized. The retention rate was 83% at 12 weeks and 86% at 26 weeks (see Fig. 1). The primary traumatic events suffered were the following: severe human suffering (11, 26.2%); serious injury, harm or death you caused to someone (10, 23.8%); fire or explosion (9, 21.4%), combat or exposure to a war zone, sudden violent death, sudden unexpected death of someone close to you and missing data (all 2, 4.8%); and physical assault, assault with a weapon, sexual assault and captivity (e.g. kidnapping) (all 1, 2.4%). All participants had tried at least one trauma-focused psychological treatment, many had received both EMDR and TFCBT, and the majority had also received other psychological treatments, including CBT without a trauma focus, supportive counselling and group therapy. All participants had been treated with medication in an attempt to reduce their PTSD symptoms and had been under service military mental health services and/or veterans mental health services. The majority had been under mental health services for many years.

Table 1 summarizes participants' demographic characteristics and allows comparison of those randomized to immediate 3MDR and delayed 3MDR. The average age of participants was 42, and time since their worst traumatic event was over 19 years. The vast majority of participants were White British (95%), around a third were employed and a third unable to work. Almost half the participants had a comorbid depressive disorder. The 3MDR sessions lasted on average 63.3 (SD 14.5) minutes. Participants walked an average distance of 3.7 (SD 1.2) km on the treadmill per session with an average speed of 0.99 (SD 0.21) m/s; a relatively slow walking speed.

Table 2 provides data on the outcome measures at baseline, 12 weeks and 26 weeks postrandomization. Table 3 demonstrates statistically significant greater improvement for participants in the 3MDR versus delayed 3MDR arm at the primary outcome points of 12 weeks on the CAPS-5, PCL-5, GAD-7 and ISI. There was no significant difference between the arms on WSAS, PHQ-9, EQ-5D-5L, Audit-O and MSPSS.

There were no statistically significant differences between the immediate and delayed 3MDR arms at 26 weeks (after both had received 3MDR) with the exception of the ISI (in favour of the immediate 3MDR arm) and the EQ-5D-5L (in favour of the delayed 3MDR arm) (see Table S1). From the

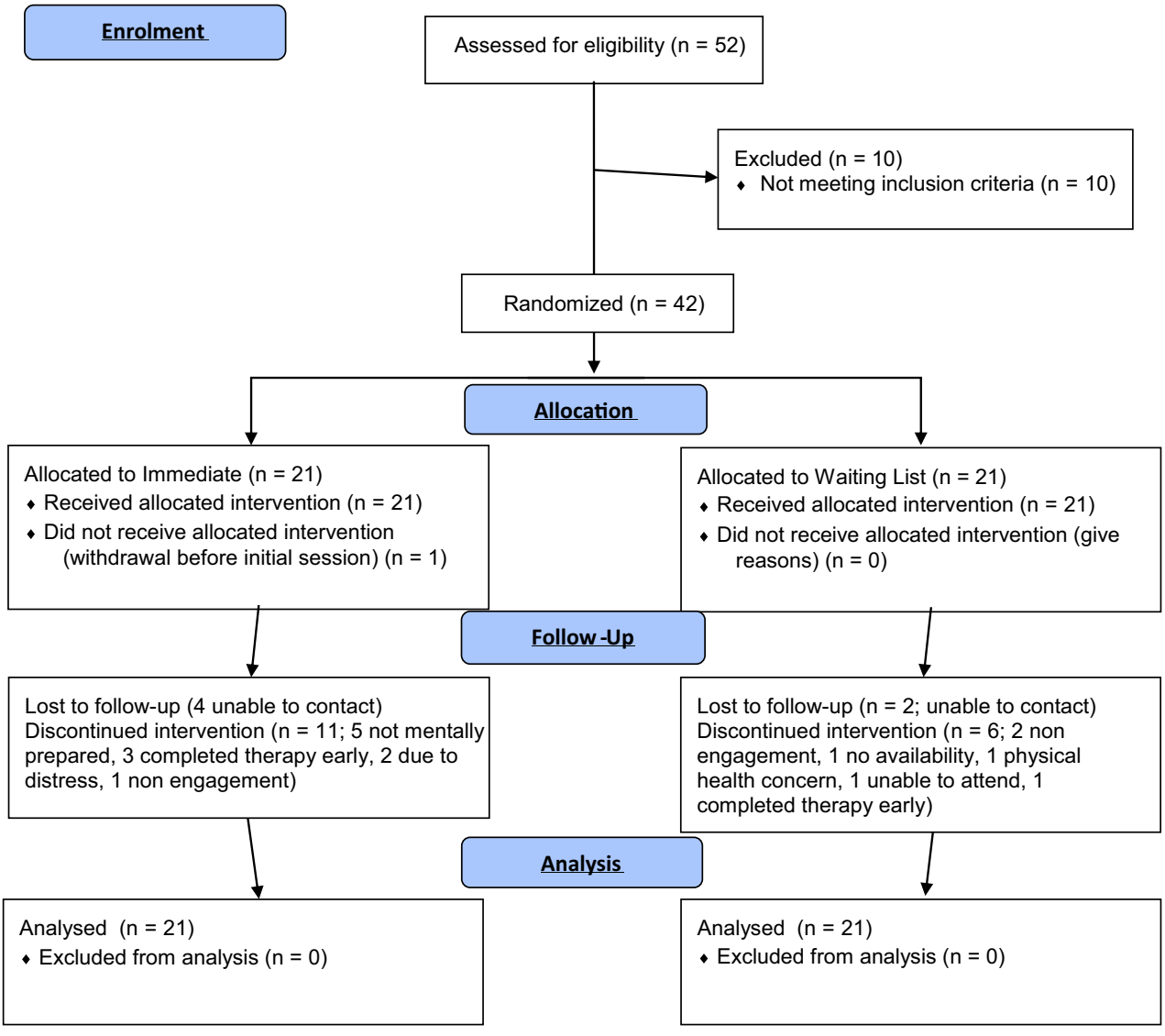

Fig. 1. CONSORT flow diagram. [Colour figure can be viewed at wileyonlinelibrary.com]

multiple imputation sensitivity analyses, the difference in mean CAPS-5 scores between the immediate and delayed 3MDR arms was −9.38 (95% CI −17.33 to −1.44, $P = 0.021$) at 12 weeks and −3.59 (−14.39 to 7.20, $P = 0.513$) at 26 weeks. In proportion with the number of cases missing the outcome, 17 imputations were used for Week 12 and 15 for Week 26. Figure 2 illustrates the relative reductions in CAPS-5 scores over time between the two arms. The likely effect size of 3MDR was found to be 0.65, representing a moderate treatment effect (24).

Fidelity

Fidelity ratings of the therapy sessions were high. All but one session viewed was felt to adhere to the 3MDR treatment protocol well. This session involved a participant who was initially assessed as able to walk on the treadmill but felt unable to do so because of musculoskeletal issues and, therefore, sat behind the treadmill for the 3MDR session.

Qualitative

Eleven purposively selected participants, all six therapists and the researcher responsible for the technical operation of 3MDR completed semistructured interviews. Participants were selected on an ongoing basis as the trial progressed. To learn from as wide a range of veterans as possible, individuals with a range of characteristics and experiences were recruited, including participants judged to have accommodated both well to 3MDR (e.g. participating in all sessions, voicing

Table 1. Demographics and clinical characteristics

		Arm							
		Immediate			Delayed			Total	
		N	%/Mean|SD		*n*	%/Mean|SD		*n*	%/Mean|SD
Age		21	40.2	10.13	21	44.0	11.97	42	42.1 |11.12
Time since trauma (months)		21	191.2	145.42	21	271.4	186.42	42	231.3|170.05
Ethnic origin	White British	21	100		19	90.5		40	95.2
	Any other Mixed/multiple ethnic background	0	0		1	4.8		1	2.4
	African	0	0		1	4.8		1	2.4
Highest level of qualification	No qualifications	0	0.0		1	5.0		1	2.6
	1-4 GCSEs or equivalent	7	36.8		6	30.0		13	33.3
	5 + GCSEs or equivalent	7	36.8		3	15.0		10	25.6
	Apprenticeship	0	0.0		1	5.0		1	2.6
	2 + A Levels or equivalent	1	5.3		4	20.0		5	12.8
	Degree level or above	4	21.1		5	25.0		9	23.1
	Other qualifications	0	0.0		0	0.0		0	0.0
Current employment status	Employed	4	19.0		10	50.0		14	34.1
	Self-employed or freelance	1	4.8		2	10.0		3	7.3
	Been made redundant	1	4.8		0	0.0		1	2.4
	Homemaker	1	4.8		0	0.0		1	2.4
	Retired	3	14.3		1	5.0		4	9.8
	Volunteering	3	14.3		0	0.0		3	7.3
	Unable to work	8	38.1		7	35.0		15	36.6
Diagnosis of depressive disorder	No	11	52.4		12	57.1		23	54.8
	Yes	10	47.6		9	42.9		19	45.2

Table 2. Primary and secondary outcome mean (SD) scores at all time points

		Time point								
		Baseline			Week 12			Week 26		
		n	Mean	SD	*n*	Mean	SD	*N*	Mean	SD
CAPS-5	Immediate	21	48.5	8.39	16	30.8	17.09	17	30.8	18.30
	Delayed	21	47.6	7.05	19	40.8	10.80	19	29.5	17.67
	Total	42	48.0	7.67	35	36.3	14.71	36	30.1	17.72
PCL-5	Immediate	21	58.0	7.22	14	46.1	16.57	12	39.4	22.80
	Delayed	21	60.0	9.83	15	59.0	5.98	17	48.2	17.90
	Total	42	59.0	8.58	29	52.8	13.73	29	44.6	20.17
WSAS	Immediate	21	26.6	5.86	14	24.6	9.25	12	18.8	13.17
	Delayed	21	24.7	8.00	15	25.1	7.91	17	17.7	11.56
	Total	42	25.6	6.99	29	24.8	8.43	29	18.2	12.03
PHQ-9	Immediate	21	17.1	5.14	13	14.8	6.14	13	14.1	8.26
	Delayed	21	17.2	5.70	15	17.5	5.67	17	14.3	6.01
	Total	42	17.2	5.36	28	16.3	5.95	30	14.2	6.94
GAD-7	Immediate	21	14.6	3.94	14	10.6	5.40	12	12.3	6.83
	Delayed	21	16.6	4.42	15	15.1	5.13	17	13.3	5.64
	Total	42	15.6	4.25	29	12.9	5.66	29	12.9	6.06
ISI	Immediate	21	19.8	6.43	14	13.4	5.99	12	14.7	9.00
	Delayed	21	20.0	5.19	15	21.7	4.94	17	19.6	6.00
	Total	42	19.9	5.77	29	17.7	6.84	29	17.6	7.65
EQ-5D-5L*	Immediate	21	0.54	0.25	14	0.52	0.33	12	0.47	0.41
	Delayed	20	0.44	0.28	15	0.46	0.26	17	0.51	0.27
	Total	41	0.49	0.27	29	0.49	0.29	29	0.49	0.33
AUDIT-O	Immediate	21	7.3	9.29	14	6.8	9.41	12	5.8	9.50
	Delayed	21	7.9	5.64	15	5.7	5.21	17	8.2	8.56
	Total	42	7.6	7.59	29	6.2	7.41	29	7.2	8.88
MSPSS	Immediate	21	47.0	12.50	14	52.9	14.82	12	54.3	20.89
	Delayed	21	55.3	19.59	15	58.9	19.85	17	55.8	19.20
	Total	42	51.1	16.77	29	56.0	17.56	29	55.2	19.56

*Crosswalk to EQ-5D-3L UK Value Index.

Table 3. Primary and secondary outcome analyses for differences at week 12

		Time point								
		Immediate			Delayed					
		n	Mean	SD	*n*	Mean	SD	Diff in means	95% confidence interval	*P*-value
CAPS-5	Baseline	16	47.0	8.63	19	47.6	7.34	**−9.561**	**−17.147 to −1.974**	**0.014**
	Week 12	16	30.8	17.09	19	40.8	10.80			
PCL-5	Baseline	14	57.3	7.06	15	59.4	9.42	**−11.667**	**−20.063 to −3.271**	**0.006**
	Week 12	14	46.1	16.57	15	59.0	5.98			
WSAS	Baseline	14	26.4	5.65	15	24.5	8.58	−1.196	−6.565 to 4.173	0.662
	Week 12	14	24.6	9.25	15	25.1	7.91			
PHQ-9	Baseline	13	16.8	5.26	15	16.2	5.47	−3.045	−6.610 to 0.520	0.094
	Week 12	13	14.8	6.14	15	17.5	5.67			
GAD-7	Baseline	14	13.9	3.94	15	15.6	4.69	**−5.143**	**−9.421 to −0.864**	**0.018**
	Week 12	14	10.6	5.40	15	15.1	5.13			
ISI	Baseline	14	19.6	6.95	15	19.3	5.33	**−7.344**	**−10.643 to −4.045**	**<0.001**
	Week 12	14	13.4	5.99	15	21.7	4.94			
EQ-5D-5L*	Baseline	14	0.57	0.26	15	0.46	0.26	−0.055	−0.211 to 0.101	0.490
	Week 12	14	0.52	0.33	15	0.46	0.25			
AUDIT-O	Baseline	14	6.1	9.57	15	5.4	3.89	0.139	−1.738 to 2.016	0.843
	Week 12	14	6.8	9.41	15	5.7	5.21			
MSPSS	Baseline	14	48.1	13.14	15	56.7	21.71	0.086	−10.045 to 10.218	0.987
	Week 12	14	52.9	14.82	15	58.9	19.85			

Bold has been used to highlight results that were statistically significant at the $\alpha = 0.05$ level.

Model covariates: baseline version of outcome, age, baseline PHQ-9 (for comorbidity of depression)[removed for analysis of PHQ-9 as an outcome else duplicated from before] and time since trauma (in months).

Difference in means between randomization arms: delay is the reference.

*Crosswalk to EQ-5D-3L UK Value Index.

hope about being helped) and poorly to 3MDR (e.g. missing sessions, voicing anxieties). Table S2 summarizes findings across all interviewees. Interview data generated with both veterans and therapists revealed 3MDR to be a complex, powerful, intervention. For those engaging in 3MDR it involved much more than just the time spent on the treadmill, encompassing the initial time spent learning about what 3MDR involves, followed by locating images and music alone or in the company of others. It often included significant travel before the therapy sessions and being supported by others, where necessary, outside of the clinic.

Therapist views on the importance of psychosocial stability and support outside of the clinic were a key theme. Veterans' descriptions of how challenging it was to select images and music suggested a potential for specific support at this earliest stage. Therapeutic continuity may be helped by 3MDR being provided by therapists already known to patients, but views on the absolute importance of this were mixed. The focus 3MDR

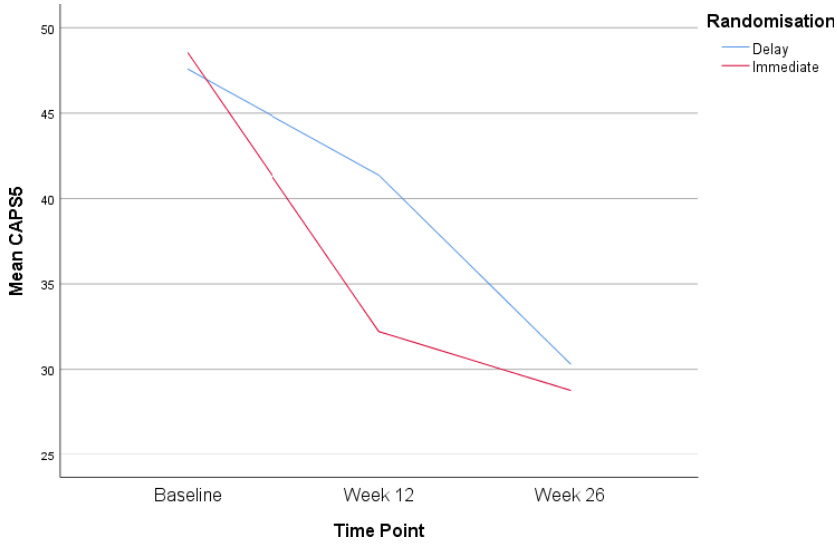

Fig. 2. Mean CAPS-5 over time by randomization arm following imputation at Weeks 12 and 26. [Colour figure can be viewed at wileyonlinelibrary.com]

has on walking, and its use of visual and auditory stimuli, may place less of a premium on the interpersonal than do other therapies, helping explain some therapists' use of the term 'coaching' to describe the work that they did.

Both groups of interviewees spoke of the surrounding context for the provision and receipt of 3MDR, including the location of the clinic and travel. Accurate information on parking arrangements and on how to find the clinic is examples of small actions able to make a difference, along with information on how 3MDR treatment sessions can cause a loss of attention and how being accompanied to and from therapy were important. Out of hours support was important for some veterans, particularly those experiencing increased symptoms, and therapists observed how some people dropping out included those whose personal lives were complex.

For therapists, clarity on the theory underpinning 3MDR was important, along with developing expertise in providing the therapy without having to over-rely on a printed protocol. Related to this was knowing how far 3MDR practices might be augmented through drawing on other bodies of skill and knowledge, such as might be deployed in the post-therapy debriefing component of sessions. Agreement on the parameters of practice may be an important consideration in the future, along with guidance relating to the number of treatments available to each participant and the use of images within individual sessions. With some exceptions, there was broad agreement across all those interviewed that six sessions may not be enough and that therapist 'flex' could usefully include making judgments on treatment duration up to a specified maximum. Therapists also spoke of the benefits of having latitude over the sequencing and, potentially, the number of images used in individual sessions.

Discussion

Main results

This trial confirms that 3MDR can reduce traumatic stress symptoms in military veterans with treatment-resistant service-related PTSD. The mean difference in CAPS5 score of 9.56 points between the two arms at 12 weeks is likely to be clinically significant and represents a 19% reduction in PTSD compared with the baseline mean. It is noteworthy that being on the waitlist resulted in a mean 6.8 point drop on the CAPS5 at 12 weeks, suggesting some form of positive impact at the prospect of treatment in individuals with hitherto treatment refractory symptoms. The total reduction pre- and post-treatment of those receiving 3MDR immediately of 17.7 points on the CAPS5 represents a clear, clinically relevant 37% reduction in PTSD symptoms from presentation that was maintained at 26-week follow-up. The waitlist group improved to a similar degree once they had received 3MDR.

The positive impact of 3MDR on the secondary outcome measures of anxiety and insomnia is encouraging and is consistent with studies of other successful treatments for PTSD, suggesting generalization of positive effects to other groups of symptoms (25). The absence of effect on alcohol use is not surprising as those included did not report significant substance misuse problems at baseline. Improvement for functioning, depression, health-related quality of life and increased perceived social support measures are often reported following effective treatment for PTSD (25) but are not seen here, potentially due to the numbers available. A future, larger Phase III trial may or may not see these improvements.

Acceptability

3MDR was found to be acceptable to most, but not all, participants. Data from the nested process evaluation suggested several factors that may impact efficacy and successful roll-out of 3MDR. These included the appropriate assessment and selection of potential candidates for 3MDR, enhanced preparation in advance of 3MDR, the number of treatment sessions available, ability to tolerate the effect of exposure, support between sessions and greater flexibility with respect to content of later sessions. A number of participants and therapists felt that more sessions either on the platform or to help integrate/facilitate the platform work would have been beneficial. Several therapists felt that some trauma-focused psychological treatment after the platform sessions would have resulted in greater improvement for some participants. Further work is underway with data generated from the trial to help with the refinement of selection criteria for 3MDR.

Mechanism of action

It is difficult to draw mechanistic conclusions from the trial; the potential mechanisms were included in this version of the intervention, but none of them were specifically isolated and tested so all remain speculative. 3MDR is clearly a complex intervention, and it is not known exactly how it works; dismantling studies would be required to

determine this. The results appear to support the combination of elements involved in 3MDR and Van Gelderen et al's (26) model for 3MDR. The model proposes that virtual reality increases presence and attention during treatment to facilitate memory retrieval with the pictures and music personalizing the experience. Walking towards cues of the traumatic memories is felt to decrease avoidance, with bilateral stimulation requiring dual attention postulated to further facilitate new learning and reconsolidation. Novel elements of the intervention, absent from many standard PTSD treatments, including activation and personalization, are also recognized as potentially beneficial.

Results in the context of other research

There is limited existing research into treatment-resistant PTSD and even more limited significant advances. Emerging work with MDMA-assisted psychotherapy shows promise (27) but is unlikely to be appropriate for all people with treatment-resistant PTSD. Pharmacological augmentation strategies have had modest success (28) but have not achieved the step change required. Results from meta-analyses undertaken for the 2018 International Society for Traumatic Stress Studies (ISTSS) prevention and treatment guidelines (29) found a number of novel treatments to have emerging evidence of effect in individuals who had already tried other treatments (e.g. neurofeedback and transcranial magnetic stimulation (TMS)).

The only other early-phase randomized controlled trial of 3MDR, conducted by the originators of 3MDR in the Netherlands (30), was also positive and taken together with our trial point to the potential effectiveness of 3MDR and its position as a major candidate for further evaluation. The effect sizes found place 3MDR on a level with neurofeedback and TMS, as more complicated treatments with emerging evidence of effect for PTSD in people with more treatment-resistant forms of PTSD. If 3MDR does prove to be effective, this would result in an additional option of treatment for people with PTSD at a point when, currently, effective active treatment possibilities are often exhausted and the prospects of further recovery low.

Strengths and limitations

This was a well-designed RCT that adhered to current methodological recommendations for this type of work. A risk of bias assessment for the trial against the Cochrane Risk of Bias checklist (31) confirmed a low risk of bias that compares very favourably with and is superior to the vast majority of randomized controlled trials of treatments for PTSD (see Table S3). Blinding of participants and personnel (performance bias) was the only risk rated high, as is true for almost all psychological treatment trials; the participants and therapists could not be blinded to the fact the individuals in the immediate 3MDR group were receiving 3MDR. The outcome raters demonstrated good inter-rater reliability based on training videos, but it is a limitation that this was not tested with videos of trial participant assessments.

It is important that the limited scale (42 participants) of this trial is acknowledged when drawing inferences from the results. A major strength of the trial was the careful training and supervision of the therapists, along with fidelity checks demonstrating good adherence to the 3MDR treatment protocol. That said, a number of the therapists reported gaining confidence as they treated more participants and it may be that earlier participants could have done better if treated when the therapists had more confidence and experience with the technique. A limitation is that fidelity ratings were not independently re-rated for reliability.

Another key strength of the trial was the utilization of both quantitative and qualitative approaches and the ability to cross-reference results from different sources to corroborate or challenge outcomes. The quantitative and qualitative results were consistent, which strengthens the belief that the results are likely to provide a true reflection of the efficacy of 3MDR.

The significant improvement in members of the delayed treatment arm before they received 3MDR does make interpretation more difficult than if there had been no response. It is always difficult to identify a perfect control condition, and it may have been that no treatment at all would have provided a better estimate of the absence of treatment at all. This was, however, not felt to be ethically optimal for this trial, and the cross-over design also provided additional information that has been helpful, not least the further improvement post-3MDR in the delayed treatment group. We demonstrated that the intervention effect was substantially larger than and significantly more than the effect of providing hope.

Clinical implications

Because of the preliminary nature of this work, it would be premature to recommend 3MDR for routine clinical practice. If the effects suggested by this trial were to be replicated and then successfully

implemented, thousands more people with PTSD would recover and the availability of 3MDR would herald a new era in the evidence-based care options available to people with PTSD. A more portable version of the system required to deliver 3MDR is now available, which should improve the potential for more affordable, scalable implementation in the future.

Research implications

The main research implication is the desirability of a pragmatic Phase III effectiveness trial of 3MDR. This trial only included military veterans with PTSD secondary to service-related experience. There is no reason to believe that non-military veterans would not benefit from 3MDR, and anecdotal evidence is emerging that 3MDR can help people with PTSD to non-military trauma but this remains an empirical question and one that needs research to determine it. Future evaluation could be enhanced by considering the inclusion of heart rate variability or other biological markers to corroborate symptom severity improvement.

The actual mechanism of 3MDR remains unclear and studies would be required with different designs, including dismantling studies, to shed more light on this. 3MDR is a complex intervention with a number of different elements, and it is not possible to say what is and what is not required at present. The number of 3MDR sessions requires more scrutiny; the results of this trial suggest that more sessions are likely to be needed for some individuals, and some individuals may benefit from booster sessions if their symptoms relapse. It is also unclear as to what the nature of additional sessions should be, and there is a need to further evaluate key issues such as optimal levels of support and the characteristics of people with PTSD most likely to benefit from 3MDR. The ability to walk a reasonable distance was a requirement for this study, and adaptation of 3MDR for other forms of locomotion such as cycle or wheelchair ergometer would be desirable in order to treat people who have difficulty walking.

In addition to considering clinical effectiveness, cost-effectiveness work is required. 3MDR is an expensive intervention; the equipment is costly, and it is resource intensive in terms of therapist time and additional support. Therefore, any effectiveness trial should include a health economic evaluation to allow informed choices to be made in the future with respect to funding and adoption by clinical services.

Acknowledgements

The research team would like to thank Forces in Mind Trust for funding the research costs of the study and the Welsh Government, through Health and Care Research Wales, for funding the NHS costs of the study. We thank the 3MDR therapists, Motek, for their technical support and, most of all, the participants of the study for taking part.

Declaration of interests

Professor Vermetten created 3MDR but would not stand to benefit financially were it to be adopted into routine clinical practice. The other authors have no potential conflicts of interest to declare.

Peer Review

The peer review history for this article is available at https://publons.com/publon/10.1111/acps.13200. [Correction added on 14 October 2020, after first online publication: Peer review history statement has been added.]

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1. Stevelink SAM, Jones M, Hull L et al. Mental health outcomes at the end of the British involvement in the Iraq and Afghanistan conflicts: a cohort study. Br J Psychiatry 2018;**213**:690–697.
2. Kitchiner NJ, Lewis C, Roberts NP, Bisson JI. Active duty and ex-serving military personnel with post-traumatic stress disorder treated with psychological therapies: systematic review and meta-analysis. Eur J Psychotraumatol 2019;**10**:1684226.
3. Steenkamp M, Litz B, Hoge C, Marmar C. Psychotherapy for military-related PTSD. JAMA 2015;**314**:489–500.
4. Vermetten E, Meijer L, van der Wurff P, Mert A. The effect of military motion-assisted memory desensitization and reprocessing treatment on the symptoms of combat-related post-traumatic stress disorder: First preliminary results. Ann Rev Cybertherapy Telemed 2013;**191**:125–127.https://doi.org/10.3233/978-1-61499-282-0-125
5. Rothbaum B, Rizzo A, Difede J. Virtual reality exposure therapy for service-related posttraumatic stress disorder. Ann N Y Acad Sci 2010;**1208**:126–132.
6. Shapiro F. Eye movement desensitization: A new treatment for post-traumatic stress disorder. J Behav Ther Exp Psychiatry 1989;**20**:211–217.
7. Rennie D. CONSORT revised – improving the reporting of randomized trials. JAMA 2001;**285**:2006.
8. Lewis C, Roberts NP, Vick T, Bisson JI. Development of a Guided Self Help (GSH) programme for the treatment of mild to moderate Post Traumatic Stress Disorder (PTSD). Depression and Anxiety 2013;**30**:1121–1128.
9. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
10. Blake D, Weathers F, Nagy L et al. The development of a Clinician-Administered PTSD Scale. J Trauma Stress 1995;**8**:75–90.

11. Ruggiero K, Ben K, Scotti J, Rabalais A. Psychometric properties of the PTSD checklist—civilian version. J Trauma Stress 2003;**16**:495–502.
12. Mundt J, Marks I, Shear M, Greist J. The Work and Social Adjustment Scale: a simple measure of impairment in functioning. Br J Psychiatry 2002;**180**:461–464.
13. Kroenke K, Spitzer R, Williams J. The PHQ-9. J Gen Intern Med 2001;**16**:606–613.
14. Spitzer R, Kroenke K, Williams J, Löwe B. A brief measure for assessing generalized anxiety disorder. Arch Intern Med 2006;**166**:1092.
15. Saunders J, Aasland O, Babor T, De La Fuente J, Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption-II. Addiction 1993;**88**:791–804.
16. Morin C, Belleville G, Bélanger L, Ivers H. The insomnia severity index: psychometric indicators to detect insomnia cases and evaluate treatment response. Sleep 2011;**34**:601–608.
17. Dahlem N, Zimet G, Walker R. The multidimensional scale of perceived social support: a confirmation study. J Clin Psychol 1991;**47**:756–761.
18. Janssen MF, Pickard AS, Golicki D et al. Mesaurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res 2013;**22**:1717–27.
19. IBM Corp. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp, 2017.
20. StataCorp. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC, 2017.
21. NVivo[computer program]. Version 10. Doncaster, Victoria, Australia: QSR International Pty Ltd; 2006.
22. Braun V, Clarke V. Using thematic analysis in psychology. Qualitat Res Psychol 2006;**3**:77–101.
23. Dey I. Qualitative data analysis: a user-friendly guide for social scientists. London: Routledge; 1993.
24. Cohen J. Statistical power analysis for the behavioral sciences. Routledge; 1977.
25. NICE. NICE PTSD guidelines, 2018. https://www.nice.org.uk/guidance/ng116
26. Van Gelederen M, Nijdam MJ, Vermetten E. An innovative framework for delivering psychotherapy to patients with treatment-resistant posttraumatic stress disorder: rationale for interactive motion-assisted therapy. Front Psychiatry 2018;**9**. https://doi.org/10.3389/fpsyt.2018.00176
27. Mithoefer MC, Mithoefer AT, Feduccia AA et al. 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: a randomised, double-blind, dose-response, phase 2 clinical trial. Lancet Psychiatry 2018;**5**:486–497.
28. Raskind MA, Peterson K, Williams T et al. A trial of prazosin for combat trauma PTSD with nightmares in active-duty soldiers returned from Iraq and Afghanistan. Am J Psychiatry 2013;**170**:1003–1010.
29. ISTSS. ISTSS PTSD prevention and treatment guidelines, 2018. https://www.istss.org/treating-trauma/new-istss-prevention-and-treatment-guidelines.aspx
30. Van Gelderen MJ, Nijdam MJ, Haagen JFG, Vermetten E. Interactive motion-assisted exposure therapy for veterans with treatment-resistant posttraumatic stress disorder: a randomized controlled trial. Psychother Psychosom 2020;1–13. https://doi.org/10.1159/000505977.
31. Higgins JP, Green S (Eds.). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration; 2011.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1 3MDR.
Table S1 Primary and secondary outcome analyses for differences at week 26.
Table S2 Summary of qualitative interview findings.
Table S3 Risk of Bias according to the Cochrane criteria.