

Design and rationale of a comparative effectiveness trial evaluating transcendental meditation against established therapies for PTSD[☆]

Thomas Rutledge^{a,b,*}, Sanford Nidich^c, Robert H. Schneider^c, Paul J. Mills^b, John Salerno^c, Pia Heppner^{a,b}, Mayra A. Gomez^d, Carolyn Gaylord-King^c, Maxwell Rainforth^c

^a VA San Diego Healthcare System, 3350 La Jolla Village Drive, San Diego, CA 92161, United States

^b University of California, 9500 Gilman Dr, La Jolla, CA 92093, United States

^c Maharishi University of Management Research Institute, 1000 North Fourth Street Fairfield, IA 52557, United States

^d Veterans Medical Research Foundation, 3350 La Jolla Village Drive, Building 13, San Diego, CA 92161, United States

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ABSTRACT

Background: Although meditation therapies such as the Transcendental Meditation (TM) technique are commonly used to assist with stress and stress-related diseases, there remains a lack of rigorous clinical trial research establishing the relative efficacy of these treatments overall and for populations with psychiatric illness. This study uses a comparative effectiveness design to assess the relative benefits of TM to those obtained from a gold-standard cognitive behavioral therapy for posttraumatic stress disorder (PTSD) in a Veteran population.

Methods and design: This paper describes the rationale and design of an in progress randomized controlled trial comparing TM to an established cognitive behavioral treatment – Prolonged Exposure (PE) – and an active control condition (health education [HE]) for PTSD. This trial will recruit 210 Veterans meeting DSM-IV criteria for PTSD, with testing conducted at 0 and 3 months for PTSD symptoms, depression, mood disturbance, quality of life, behavioral factors, and physiological/biochemical and gene expression mechanisms using validated measures. The study hypothesis is that TM will be noninferior to PE and superior to HE on changes in PTSD symptoms, using the Clinician Administered PTSD Scale (CAPS).

Discussion: The described study represents a methodologically rigorous protocol evaluating the benefits of TM for PTSD. The projected results will help to establish the overall efficacy of TM for PTSD among Veterans, identify bio-behavioral mechanisms through which TM and PE may improve PTSD symptoms, and will permit conclusions regarding the relative value of TM against currently established therapies for PTSD.

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Abbreviations: TM, The Transcendental Meditation technique; PE, Prolonged exposure therapy; HE, Health education; CVD, Cardiovascular disease; PTSD, Posttraumatic stress disorder; CAPS, Clinician Administered PTSD Scale; PCL-M, PTSD checklist-military version; PHQ-9, Patient Health Questionnaire-9.

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* Corresponding author at: Psychology Service 116B, VA San Diego Healthcare System, 3350 La Jolla Village Drive, San Diego, CA 92161, United States. Tel.: +1 858 552 8585x7273.

E-mail addresses: Thomas.Rutledge@va.gov (T. Rutledge), snidich@mum.edu (S. Nidich), rschneider@mum.edu (R.H. Schneider), pmills@ucsd.edu (P.J. Mills), jsalerno@mum.edu (J. Salerno), psantiago@ucsd.edu (P. Heppner), Mayra.Gomez@va.gov (M.A. Gomez), cking@mum.edu (C. Gaylord-King), rainforth@mum.edu (M. Rainforth).

1. Introduction

Integrative medicine treatments for medical and psychiatric conditions are a rapidly growing area of research [1,2]. For example, recent reviews of meditation therapies report evidence of efficacy for improving conditions ranging from cardiovascular disease (CVD) to posttraumatic stress disorder (PTSD), along with a surge in interventional meditation research [3–5]. There remains, however, a shortage of high quality clinical trial data to guide clinical decision making, particularly in psychiatric populations. One of the deficits in the current literature is the lack of comparative effectiveness trials permitting comparisons of meditation therapies to established treatments. Using methods such as noninferiority designs [6], data from comparative effectiveness trials can clarify the extent to which meditation therapies represent empirically supported alternatives to validated treatments for problems such as PTSD. Noninferiority trials are an applicable approach to testing meditation as a PTSD treatment because: 1) there are established comparison treatments for PTSD (cognitive behavior therapy [CBT]); 2) meditation therapies have potential advantages for treating PTSD (e.g., meditation is low cost, widely available, few side effects); and 3) because the goal is to establish the relative equivalence of meditation to CBT for PTSD rather than superiority [6,7].

Among meditation therapies, mindfulness meditations and Transcendental Meditation (TM) boast the largest bodies of clinical trial support for treating mental health [3,5]. Mindfulness training fosters a judgment free awareness of thoughts that may help mitigate anxious and depressed thinking patterns [3]. The TM technique, in contrast, trains users to transcend to a quieter, less active state of consciousness that may also reduce anxiety and mood symptoms [5]. A distinction between these forms of meditation is suggested by studies using electroencephalography, demonstrating, for example, patterns of relatively increased theta wave activity in mindfulness meditations versus increased alpha wave activity in TM [8]. In comparison to CBT treatments for PTSD such as exposure therapy that involve repeated, deliberate contact with anxiety-provoking stimuli and have high rates of drop-outs [9], meditation offers a less aversive and potentially more engaging approach to treatment. Populations such as Veterans – among whom anxiety-related conditions such as PTSD affect nearly 1 in 5 [10] – are perhaps an especially fruitful group in which to evaluate the comparative benefits of meditation therapies as a viable treatment option in the VA healthcare system.

This paper describes the methodology of a comparative effectiveness trial evaluating TM in a Veteran population with PTSD using an intent to treat, noninferiority design. Improving the treatment of PTSD for Veterans returning from military conflicts remains a priority healthcare objective for the Department of Veterans Affairs [11]. Currently defined as a trauma or stress-related disorder in the Diagnostic and Statistical Manual of Mental Disorders-5 [12] (DSM-5), PTSD is associated with adverse psychological and medical consequences [10]. Because TM has shown benefits in previous TM studies addressing PTSD [13,14], depression [15], and CVD [16], our outcomes will include measures of PTSD symptoms along with mood, blood pressure, and stress-related biomarkers (cortisol, telomerase). The current trial will compare TM for PTSD relative to the evidence-based standard of care treatment – prolonged exposure

therapy [12] (PE) – and a time and treatment intensity matched control treatment (health education [HE]).

2. Materials & methods

2.1. Participants

This study consists of a multi-institutional research project comprising investigators from the VA San Diego Healthcare System (VASDHS), the University of California at San Diego, and Maharishi University of Management Research Institute in Maharishi Vedic City, Iowa.

Veterans from the San Diego community and those obtaining care at the VASDHS are eligible for study participation. We will recruit a total of 210 men and women with interview-diagnosed, military related PTSD from all service eras. Based on the demographic composition of Veterans receiving care in the PTSD clinics at VASDHS, we estimated an approximately 20% enrollment of female Veterans and 40% enrollment of ethnic minorities. Following informed consent and baseline testing, eligible participants receive random assignments to the TM, PE, or HE treatment conditions.

Eligible Veterans include those meeting both DSM-IV criteria for PTSD on the Clinician Administered PTSD Scale (CAPS) interview [17] for and a minimum PTSD symptom severity score ≥ 45 on the CAPS in order to ensure that participants were experiencing clinically significant PTSD at the time of participation. This standard is consistent with enrollment criteria in other recent high quality PTSD trials [9]. As part of the enrollment process, we evaluated patients for suicidality and cognitive impairment using standardized measures (see below) and reviewed participant's medical records with their consent to identify evidence of unstable psychiatric function. Veterans demonstrating suicidality (ideation with intent or recent psychiatric hospitalization), moderate or greater cognitive impairment, or unstable psychiatric function (e.g., unmanaged bipolar or schizophrenia conditions) were excluded.

A critical decision juncture in the design of the study was how to address Veterans receiving concurrent mental health treatments. The VA system in San Diego boasts a large, multi-site, evidence-based treatment program for PTSD and other mental health conditions and further employs provider-completed screenings for PTSD at the time of a Veteran's enrollment into the system and at least annually thereafter. Positive screens prompt the provider to consider treatment referrals. The result is that many Veterans with PTSD receive psychiatric or psychotherapy treatments at VASHDS.

Because of this active treatment environment, it was unrealistic for us to recruit only Veterans with PTSD not receiving mental health care. Instead, we established parameters for including Veterans with concurrent treatments. Firstly, participants receiving psychotropic medications were encouraged to remain stable regimens and consented to staff conducting weekly medical records reviews to evaluate for medication changes. The study data set included codes for any participants experiencing changes in their psychotropic regimen for statistical adjustment. We further provided written alerts to VASDHS mental health providers via the electronic medical chart to the Veteran's participation and discharge dates from the study. Secondly, we excluded Veterans with prior PE treatment or TM training. Thirdly, we permitted concurrent individual or group

psychotherapy treatments only for non-anxiety conditions and only treatments that did not include an exposure element (based on medical records review and contacting treatment providers where unclear). This approach allowed us to enroll a broadly representative population of Veterans with PTSD.

2.2. Study design

Following a brief phone screen to evaluate basic eligibility criteria, participants complete two baseline visits including a CAPS interview, questionnaire completion, written consent, and blood testing. Fig. 1 provides an illustration of the recruitment, randomization, and study design steps. All participants continue to receive their usual medical care during the study. We stratified participants by time since military service and gender. TM, PE, and HE group conditions are matched on the number of treatment visits (12 sessions), visit length (~90 min/session) and total treatment time (12 weeks). In addition to the treatment therapists, the study team included two staff members blinded to participant assignment that completed all baseline and post-test assessments. We assess expectations for treatment following randomization at baseline prior to beginning treatment. Following treatment, participants return for a pair of post-test visits to re-complete the CAPS, questionnaires, and blood testing, with study hypotheses exploring pre-post changes in PTSD, depression, quality of life, and stress-related biomarkers.

2.3. Study outcome measures

Pre to post-treatment change on the CAPS is the primary study outcome. The CAPS is the “gold standard” for PTSD assessment and diagnosis [17]. A decrease of ≥ 10 points on the CAPS will function as a minimal standard for clinically significant

improvement in PTSD symptoms. PTSD remission using the CAPS will be defined as a score < 20 [18]. Table 1 lists the primary and secondary study measures included in the protocol categorized into biomedical, psychosocial, and behavioral dimensions.

Secondary outcomes include validated self-report measures of psychological distress, depression, adherence to treatment (completing PE & HE homework, daily TM practice), quality of life, and behavioral factors and physiological/biochemical assessments of inflammatory biomarkers, stress hormones, and gene expression mechanisms (Table 2). Community equivalent treatment costs were also computed for comparison (based on the standard TM training fee [1450.00] and estimate hourly rate [~\$150.00] for psychotherapy in Southern California by a licensed psychologist for PE and HE).

2.4. Safety protocols

Participants complete the PCL-M and the PHQ-9 during their baseline assessment, following the first week of treatments, and subsequently at alternating treatment visits leading up to the 3-month treatment completion point. The PHQ-9 contains a specific item assessing the presence and frequency of suicidal ideation. This measurement approach allows us to ascertain patterns of temporal change in PTSD and depression symptoms in response to treatment, as well as provides a means of frequently monitoring participants for possible increases in symptoms such as suicidality that warrant further intervention.

2.5. Study treatments

2.5.1. Overview

Randomized participants receive the TM, PE, or HE treatment, with each treatment consisting of 12, 90-minute sessions

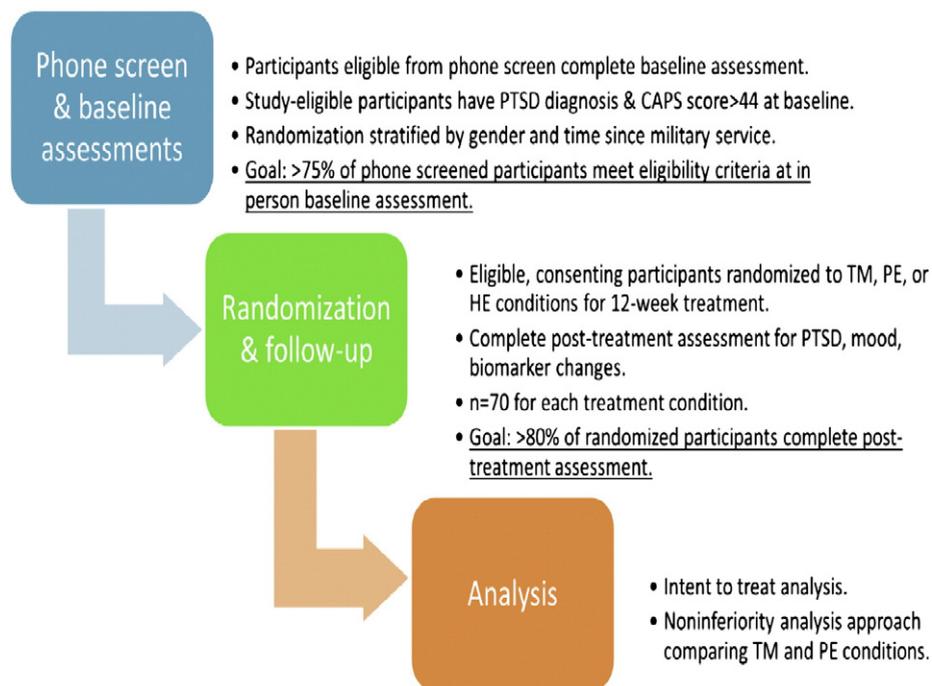


Fig. 1. Enrollment flowchart for the study (PTSD = posttraumatic stress disorder; CAPS = Clinician Administered PTSD Scale; TM = Transcendental Meditation; PE = Prolonged Exposure; HE = Health Education). Color for Web only.

Table 1

Biomedical, psychosocial, and behavior study outcome measures.

Outcome measures	Baseline	Every 2 weeks during treatment	3 months
Primary outcome: clinician administered CAPS	X		X
Secondary outcomes: self-report PCL-M and PHQ-9, treatment adherence	X	X	X
Other psychosocial factors and QOL: POMS, SSQ, Q-LES-Q	X		X
Behavioral factors: smoking, alcohol, non-prescribed drugs	X		X
Stress hormones and physiological/immune factors: cortisol, catecholamines, blood pressure, CRP, TNF-a, and IL-6, body mass index, telomerase, gene expression	X		X

CAPS = Clinician Administered PTSD scale (DSM-IV); PCL-M = PTSD checklist-military version; PHQ-9 = Patient Health Questionnaire-9; QOL = Quality of life; POMS = Profile of Mood States; SSQ = Social Support Questionnaire; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire.

over a three month interval. Treatment sessions are conducted in individual (PE) or individual/small group (TM & HE) format. Each treatment is delivered by a single therapist to eliminate between-therapist differences and help maintain a consistent quality of treatment across the study. Each of the treatment therapists receives weekly supervision by the investigator team (Dr. Nidich-TM; Dr.'s Heppner-PE; Rutledge-HE). Participants further consented to audio/video recordings of treatment sessions for quality control and review by the treatment supervisors.

2.5.1.1. The Transcendental Meditation (TM) technique. The TM technique is described as a simple, natural, effortless technique to experience lesser excited levels of the mind and correspondingly greater degrees of physical relaxation. TM is traditional meditation modality that has its origin in the ancient Vedic

(*Veda* means knowledge) tradition [19]. Maharishi Mahesh Yogi is credited with reviving and restoring this meditation practice in accordance with classical Vedic texts [20]. Meta-analyses comparing different relaxation and meditation techniques across approximately 300 independent experimental samples have reported that Transcendental Meditation practice, compared to other approaches of stress reduction, is associated with greater reductions in physiological arousal, trait anxiety, smoking and drug abuse, and blood pressure and with greater improvement of psychological health e.g., [21–23].

The core instruction in the TM technique involves a seven-step course, taught over five days during the first week of treatment by a certified TM instructor. The five core instruction sessions (approximately 90 min each) include: a) Introductory Lecture—review of previous scientific research on the TM program and a vision of possible benefits; b) Preparatory Lecture—discussion of the mechanics and origin of the TM technique; c) Personal Interview—with a teacher of the TM program; d) Personal Instruction—individual-learning of the TM technique; e) First Day of Checking—verifying the correctness of practice and further instruction; f) Second Day of Checking—understanding the mechanics of the TM technique; and g) Third Day of Checking—understanding the mechanics of the development of higher states of wellness.

Following this initial phase of TM, there are seven additional group sessions for the duration of the three-month intervention period. These sessions include: a) checking of correct practice of the TM technique and b) advanced lectures and seminars to ensure complete understanding of benefits of the practice for physiological, psychological, and behavioral health (90 min each). Home practice consists of two 20-minute TM sessions encouraged daily.

2.5.1.2. Prolonged exposure (PE). PE is a manualized, trauma-focused behavioral treatment for PTSD based on exposure principles and emotional processing theory [24,25]. Empirical support for PE spans two decades of research using controlled trials and multiple trauma populations. PE is one of the two cognitive-behavior therapies currently disseminated within the VA healthcare system as an evidence-based treatment for PTSD [26]. A 2010 meta-analysis [9] of PE in military and non-military populations included 13 randomized controlled trials comparing PE to control conditions (wait-list or psychological placebo). This paper reported large pre- to post-treatment effect sizes on PTSD symptoms (Hedge's $g = 1.08$) and other measures of emotional distress (Hedge's $g = 0.77$). These improvements were maintained over time, with moderate to

Table 2

Strategies employed to increase participant attendance and retention.

Strategy	Rationale
1. Obtaining detailed contact information from participants at baseline with permission to contact family members.	Intended to maximize the number of ways to reach participants following no-shows to treatment or test visits.
2. Participants complete a “reasons for participation checklist” at baseline.	Highlights reasons, motivations, and benefits participants expect to obtain.
3. Participants complete a separate willingness to complete post-testing form.	Creates opportunity for separate discussion of the importance of attending the post-test visits.
4. Participants receive a thank you letter from study principal investigators.	Intended to offer positive feedback to participant for enrolling and reminding them of benefits of their participation for themselves and other Veterans.
5. Rapid and multiple efforts to contact participants following no-show visits. Reminder calls for all visits	Intended to facilitate regular contact between participants and study staff, maintain continuity, and provide opportunity to assist with participation challenges.
6. Relative compensation increase for attending post-testing visits.	Intended to create extra incentive for attending the post-testing visits even in the case of partial participation in treatment.
7. “Bonus program” for transcendental meditation (TM)	For participants not randomized to TM but that are interested in learning the technique, their training fee for learning TM is waived at a community TM site if they complete their assigned study treatment (at least 8/12 sessions attended and post-testing).

large effect sizes (Hedge's $g = 0.68 \pm 0.21$) observed from one to 12 months following completion of treatment.

Prolonged exposure consists of 12 weekly individual 90-minute treatment sessions [24] delivered by a therapist with specific PE training. PE sessions consist of psychoeducation about common reactions to trauma and breathing retraining (sessions 1–2), identification of a hierarchy of feared situations (session 3), and prolonged recounting (imaginal exposure) of trauma events during treatment sessions (introduced at session 3 and implemented from sessions 4–12).

At-home practice includes reviewing information on common reactions to trauma, listening to imaginal exposure and completing in-vivo exposure assignments corresponding to the fear hierarchy. PE particularly focuses on the reduction of avoidance behaviors and promotion of habituation to stimuli that would previously cause hyperarousal symptoms.

2.5.1.3. PTSD health education (HE). The HE treatment consists of 12 weekly 90-minute group health education interactive lectures delivered by a doctoral level psychologist. The group meetings provide basic health education specific to the PTSD Veterans population, including discussion of the symptoms, prevalence and biological aspects of PTSD, research on the benefits of a healthy lifestyle for coping with PTSD, and rationale and mechanics for incorporating healthy lifestyle factors into one's daily routine (diet, physical activity, sleep hygiene). Additional modules of the PTSD health education program include lectures on coping with PTSD symptoms, improving diet and exercise, and will also serve to provide social support to participants attending the group meetings. For home practice, HE participants receive a list of general health behavior activities (including social support, listening to music, reading a book, healthy cooking, exercise, etc.).

2.6. Therapist training & fidelity monitoring

A critical objective of the study was to ensure that each of the three study treatments was delivered by therapists receiving training specific to their intervention and ongoing supervision across the study. To mitigate therapist effects, a single provider delivers each treatment. The TM treatment is delivered by an experienced TM instructor receiving their TM training and study supervision through the MUMRI. This standard for TM delivery is consistent with previous high quality clinical trials using TM [5]. A licensed mental health therapist delivers the PE treatment. This therapist completed a multi-day training in manualized PE treatment for PTSD at the VASDHS prior to study onset and receives weekly clinical supervision from a licensed clinical psychologist on the research team with PE and PTSD treatment expertise in research. A PsyD-level therapist provides the HE treatment, developing the HE treatment protocol and receiving weekly supervision with a board certified clinical health psychologist on the research team.

2.7. Participant enrollment and retention strategies

Table 2 contains a more detailed description of the multiple strategies we are using to help achieve the enrollment and retention goals listed above in Fig. 1 (e.g., having 80+% of

randomized participants complete post-testing). Many of these strategies were drawn from previous reviews on retention techniques for clinical trials [27] and modified to fit the design of the current study. The “TM bonus program” (strategy 7 from Table 2) resulted from a supplementary grant to the investigators that gave PE and HE ‘completers’ (defined as those completing at least 75% of treatment sessions and post-testing over their 3 months of participation) the option to receive TM training at a local TM center in San Diego free of the standard TM training fee. We pursued the bonus program feature in part as an additional incentive to Veterans desiring TM but not receiving this treatment by randomization to complete their assigned treatment. We do not collect data from participants after they complete their originally assigned treatment.

2.8. Statistical analyses

This study utilizes an intent to treat, noninferiority research model to compare TM to the evidence-based standard PE treatment on the primary and secondary outcomes of the study. A standard between groups design will be used to compare TM and PE to the HE control.

All data are collected by VASDHS staff blinded to the treatment allocation of participants. The original version of the dataset will remain at the VASDHS study site and a de-identified copy of the dataset is sent to the biostatistics core at the Maharishi University of Management Research Institute for analysis by the study biostatistician. The de-identified database will only include subject study number along with test data. The study biostatistician will conduct all analyses, blinded to group assignments.

Sample size was determined for the noninferiority comparison of TM vs. PE and for the standard efficacy comparison of TM vs. HE. The calculation for TM vs. PE was based upon a two-tailed test of the noninferiority hypothesis with $\alpha = .05$ and a non-inferiority margin $\Delta = 10$ points on the CAPS. For the purpose of the power analysis for TM vs. PE we further assumed: 1) TM and PE will produce equal effects; 2) a conservative standard deviation estimate of 30 for CAPS baseline and posttest scores, based on a study of 253 Veterans in our same San Diego VA setting [28]; 3) correlation of $r = .85$ between CAPS baseline and posttest scores, based upon our pilot data and the test–retest correlation reported in the literature [29,30]; 4) multi-level regression models adjusting for baseline CAPS, an approach consistent with published recommendations for noninferiority models [6]; and 5) attrition rate of approximately 20% from baseline to posttest. With the above data and assumptions, using SAS PROC POWER, an initial sample size of 70 participants in each treatment arm would provide 90% power for the non-inferiority comparison of TM versus PE. We also determined that 70 subjects per group would provide at least 85% power for the two-sided comparison of TM vs. HE, assuming an improvement of at least 10 points on the CAPS for TM relative to HE. Therefore, allowing for attrition, a total sample of 210 participants will provide adequate power for the primary outcome. Statistical analyses will be performed using the SAS statistical package (version 9, SAS Institute, Cary, NC). Missing data will be handled using multiple imputation.

3. Conclusions

This report describes the design of a newly initiated comparative effectiveness trial evaluating the relative efficacy of TM for the treatment of PTSD. Despite the burgeoning interest in TM and other forms of meditation [3–5], the potential application of these practices as evidence-based therapies remains constrained by methodological shortcomings in existing PTSD research. Although no single study design can answer all scientific questions, comparative effectiveness designs permit arguably the most rigorous approach to the evaluation of novel treatments. In this study, we are comparing TM to prolonged exposure, a form of cognitive behavior therapy with the highest current level of empirical support for the treatment of PTSD. By further including an attention control condition in the form of health education, our results will offer important information concerning the efficacy of TM for PTSD relative to both basic and best practices standards of care.

We have taken steps to maximize treatment integrity in this study, employing TM, PE, and HE therapists with credentialed expertise and training in their treatments and receiving supervision from senior practitioners on the investigator team. In addition to the core measures of PTSD, depression, mood disturbance, and quality of life, the research protocol includes a number of behavioral (e.g., rates of substance use) and biological outcomes (e.g., inflammatory markers, telomerase) linked in previous research to stress-related conditions [31,32] for which we anticipate being able to provide some of the first evidence regarding responsiveness to TM in treatment trials in psychiatric populations. With the primary outcome being the CAPS interview recognized as the gold standard measure of PTSD [17], the overall objective of the study is to provide a stringent comparison of the treatments as implemented at a high standard of practice.

Among the many potential targets for integrative medicine approaches such as TM, we believe that there is a distinct opportunity to contribute to the treatment of PTSD. Pharmacotherapies show limited benefits as a standalone treatment for PTSD [33,34]. Even among empirically supported therapies such as PE, treatment dropouts are common and meta-analytic reviews suggest that only about half of patients enrolled in these treatments experience clinically significant reductions in PTSD symptoms [35]. These limitations of PE suggest, at minimum, a need for PTSD treatment alternatives that can assist patients failing to respond to established therapies. Further, in comparison to the exposure and anxiety habituation model utilized in PE that involves direct or imaginal exposure to features of the patient's trauma, the gentle and low effort TM technique may offer a comparatively less stressful approach to PTSD treatment. To the extent that TM is similarly efficacious to PE for improving PTSD symptoms, a less intensive treatment experience could translate into better treatment adherence for some patients. For all of the above reasons, TM and possibly other integrative medicine treatments may have particular value in applications towards PTSD.

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