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Non-trauma-focused meditation versus exposure therapy in veterans with post-traumatic stress disorder: a randomised controlled trial

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Summary

Background Post-traumatic stress disorder (PTSD) is a complex and difficult-to-treat disorder, affecting 10–20% of military veterans. Previous research has raised the question of whether a non-trauma-focused treatment can be as effective as trauma exposure therapy in reducing PTSD symptoms. This study aimed to compare the non-trauma-focused practice of Transcendental Meditation (TM) with prolonged exposure therapy (PE) in a non-inferiority clinical trial, and to compare both therapies with a control of PTSD health education (HE).

Methods We did a randomised controlled trial at the Department of Veterans Affairs San Diego Healthcare System in CA, USA. We included 203 veterans with a current diagnosis of PTSD resulting from active military service randomly assigned to a TM or PE group, or an active control group of HE, using stratified block randomisation. Each treatment provided 12 sessions over 12 weeks, with daily home practice. TM and HE were mainly given in a group setting and PE was given individually. The primary outcome was change in PTSD symptom severity over 3 months, assessed by the Clinician-Administered PTSD Scale (CAPS). Analysis was by intention to treat. We hypothesised that TM would show non-inferiority to PE in improvement of CAPS score ($\Delta=10$), with TM and PE superior to PTSD HE. This study is registered with ClinicalTrials.gov, number NCT01865123.

Findings Between June 10, 2013, and Oct 7, 2016, 203 veterans were randomly assigned to an intervention group (68 to the TM group, 68 to the PE group, and 67 to the PTSD HE group). TM was significantly non-inferior to PE on change in CAPS score from baseline to 3-month post-test (difference between groups in mean change -5.9 , 95% CI -14.3 to 2.4 , $p=0.0002$). In standard superiority comparisons, significant reductions in CAPS scores were found for TM versus PTSD HE (-14.6 95% CI, -23.3 to -5.9 , $p=0.0009$), and PE versus PTSD HE (-8.7 95% CI, -17.0 to -0.32 , $p=0.041$). 61% of those receiving TM, 42% of those receiving PE, and 32% of those receiving HE showed clinically significant improvements on the CAPS score.

Interpretation A non-trauma-focused-therapy, TM, might be a viable option for decreasing the severity of PTSD symptoms in veterans and represents an efficacious alternative for veterans who prefer not to receive or who do not respond to traditional exposure-based treatments of PTSD.

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Introduction

Post-traumatic stress disorder (PTSD) is a serious and disabling condition, estimated to affect 14% of those deployed in or returning from combat in Afghanistan and Iraq.¹ PTSD takes a severe toll on the mental, physical, and financial wellbeing of veterans, which is shared by their families.^{2,3} The adverse physiological consequences of traumatic stress leading to PTSD are widely known.⁴⁻⁶

Prolonged exposure (PE) is of one the most widely accepted and well validated psychotherapies for the treatment of PTSD. PE is a type of trauma-focused treatment, helping patients reduce PTSD symptoms through repeated exposure to trauma-related reminders (in-vivo exercises) and memories (imaginal retelling of trauma experiences). Although PE has shown consistent and clinically significant benefits across

many types of PTSD trauma, it also shows low efficacy for some patients; 30–50% of veterans participating in PE treatments do not show clinically significant improvements.^{7,8} Additionally, dropout in patients receiving PE treatment shown in randomised trials and clinic-based visits can be high, ranging from 30% to 44%.^{9,10} This high proportion of dropouts in PE might be due to the discomfort and anxiety often reported by patients completing the therapy.⁹ Given the growing evidence that PTSD affects—other than psychiatric status—cardiovascular health, occupational functioning, metabolic function, and possibly even dementia risk, it is important to consider treatments that could complement evidence-based psychotherapies such as PE to assist patients who do not respond to or cannot tolerate these treatments.^{2,3}

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Research in context

Evidence before this study

We searched PubMed for articles published between Jan 1, 2000, and August 31, 2018, using the search terms “posttraumatic stress disorder”, “PTSD”, “meditation”, “Transcendental Meditation”, “stress reduction”, “stress management for veterans”, “prolonged exposure”, “cognitive processing therapy”, “exposure therapy”, and “cognitive behavioural therapy”. We were unable to find any comparative effectiveness studies, non-random or randomised assignment, that included Transcendental Meditation (TM) or any other meditation programme in comparison to a first-line, US Veterans Administration (VA)-approved psychotherapy treatment. Additionally, none of the systematic reviews on post-traumatic stress disorder (PTSD) during this timeframe included studies that compared meditation directly with a first-line psychotherapy treatment. Previous uncontrolled and non-randomised studies on TM have suggested its efficacy in addressing PTSD symptoms. A randomised controlled

comparative effectiveness trial was therefore done to assess the efficacy of TM relative to prolonged exposure (PE), a first-line VA-approved treatment, and an active PTSD health education (HE) control group, in veterans with documented PTSD.

Added value of this study

The findings of this comparative effectiveness clinical trial expand the current evidence base by showing the feasibility and efficacy of TM as an alternative therapy to PE for the treatment of military veterans diagnosed with PTSD.

Implications of all the available evidence

Over the past 50 years, PTSD has expanded to become an important public health problem. Due to the increasing need to address the public health-care problem of PTSD in the USA, UK, and worldwide, there is a compelling need to implement governmental policy to include alternative therapies such as TM as an option for treating veterans and other groups with PTSD.

Limitations of current PTSD therapies have led researchers to explore treatments that are non-trauma-focused, such as mindfulness meditation¹¹ and interpersonal psychotherapy (IPT).¹² Markowitz and colleagues¹² directly compared IPT to the gold-standard trauma exposure therapy, PE. Their trial of 110 civilian participants found interpersonal psychotherapy to be non-inferior to PE in the reduction of trauma symptom severity. IPT emphasises expressing one’s feelings in non-trauma-related interpersonal situations and addressing problem areas such as life transitions.¹²

Our study is a randomised controlled trial of another non-trauma-focused intervention, Transcendental Meditation (TM), compared with PE and an active control condition of PTSD health education (HE). Although TM and mindfulness are common forms of meditation, TM fundamentally differs from mindfulness practice; mindfulness involves focusing on the present moment in a specifically recommended way whereas TM involves the effortless thinking of a mantra (sound), without concentration or contemplation, to produce a settled, and progressively lesser excited psychophysiological state of so-called restful alertness.^{13,14}

Previous research on anxiety and PTSD symptoms has yielded encouraging results with TM in military veterans and active military personnel^{15–18} as well as in other at-risk groups;^{19,20} however, previous TM research in this area is constrained by small sample sizes and other methodological limitations. There are also physiological reasons to hypothesise that TM might be helpful in patients with PTSD, who exhibit sympathetic hyperarousal, for example, hypervigilance and an exaggerated startle response. TM seems to attenuate sympathetic responses to loud noises²¹ and violent images in patients with PTSD,²² and might thus be expected to attenuate the

hyperarousal caused by the memories of traumatic events. Additionally, TM has been shown to decrease anxiety,²³ reduce blood pressure,^{24,25} and be therapeutic in various stressful situations.^{20,26,27} How these TM benefits might compare with an established psychotherapy such as PE, however, is unknown.

We directly compared a non-trauma-focused meditation programme with a gold-standard trauma-focused psychotherapy. We hypothesised that TM would show non-inferiority to PE on the change in the Clinician-Administered PTSD Scale (CAPS) score,^{12,28} with TM and PE superior to HE. We secondarily hypothesised that a clinically meaningful reduction in PTSD symptoms (through self-report) using the PTSD Checklist–Military version (PCL–M) would be greater with TM and PE than with PTSD HE. We also investigated treatment effects comorbid depression using the Patient Health Questionnaire–(PHQ)–9.

Methods

Study design and participants

This single-blind, three-arm randomised controlled trial was a multidisciplinary, collaborative research project comprising investigators from the VA San Diego Healthcare System, the University of California at San Diego, CA, USA, and the Maharishi University of Management Research Institute in Fairfield, IA, USA. This study was approved by the VA San Diego Healthcare System and Maharishi University of Management Research Institute review boards and monitored by an external data safety and monitoring board.

We recruited participants between June 10, 2013, and Oct 7, 2016, using within-hospital paper and electronic advertising, with regular, direct contact between study staff and PTSD treatment providers at the VA San Diego

Healthcare System for referrals. The study was neutrally advertised within the VA hospital using brochures, in-person announcements at clinic meetings, and the hospital's electronic message board. The study was presented as being for veterans with PTSD, offering 12 weeks of free treatment and compensation for participation. Inclusion criteria were: current medical diagnosis of PTSD by chart review, additionally with a CAPS score of 45 or more; PTSD symptoms resulting from an event experienced during active military service; 3 or more months since the service-related traumatic event; agreement to not receive other psychotherapy or other meditation therapy for PTSD during study treatment, although psychotherapy for other problems was allowed; and if treated with psychoactive medications, the maintenance of a stable regimen for at least 2 months before enrolment. Exclusion criteria were current unstable psychotic symptoms, mania, or bipolar disorder as shown by self-report, medical chart, or psychiatric hospitalisations in the past 6 months; current suicidal or homicidal ideation with intent or plan; moderate or greater cognitive impairment indicated by chart diagnosis or observable cognitive difficulties; and any previous participation in either TM or PE. All participants completed written informed consent before baseline testing.

Randomisation and masking

Men and women with military-related PTSD were recruited by study staff from all service eras. After baseline testing, eligible participants (confirmed by the study staff with the on-site principal investigator [TR]) were randomly allocated to receive TM, PE, or HE. Stratified block randomisation, stratified on gender and years since military service release, was used to assign participants to their study treatment. Treatment groups were matched on number of treatment visits (12 sessions), length of each session (90 minutes), and duration of treatment (12 weeks). All participants continued to receive their standard medical care. Because the treatments have different training requirements for the providers (eg, psychotherapies such as PE generally require that therapists have advanced degrees, whereas TM does not), the education backgrounds of the treatment providers were not the same. Because we attempted to implement the treatments according to their standard practices, the 12 sessions were organised as multiple sessions in the first week followed by gradually spaced subsequent sessions over 12 weeks for TM versus weekly treatments for 12 weeks for PE and HE groups. Treatment adherence and fidelity were maintained by providing professional-level training for the therapists before delivering treatment, weekly supervision with a dedicated treatment supervisor to maintain treatment fidelity, and reviews of audio recordings of the sessions by the individual supervisors for the PE and HE conditions.

Allocation concealment was achieved by an off-site co-investigator (JS), who randomly assigned each participant

to a treatment group and informed the study coordinator (EM) of the treatment assignments (who then notified the participant). All baseline and post-test data were collected by two research assistants (MG and AR in the acknowledgments), masked to treatment assignment and uninvolved in any aspect of treatment delivery. Additionally, all participants were asked not to divulge their treatment assignment. Administration of the CAPS interview was supervised by two psychologists (TR and PH, study psychologists). TR, the on-site partnering principal investigator, was responsible for the day-to-day conduct of the trial and reviewed cases as needed.

Procedures

Transcendental Meditation

TM is a simple, effortless technique, practiced for 20 min twice a day, sitting with eyes closed. TM allows ordinary thinking processes to become more quiescent, resulting in a unique state of restful alertness.¹⁴ TM was delivered by certified instructors in the same standardised format offered in a community setting¹³ and in previous TM clinical trials sponsored by the US National Institutes of Health.^{29–32} No modifications were made to specifically address PTSD symptoms, and sessions did not involve PTSD psychoeducation. The TM treatment was delivered by one female instructor educated to master's level (for female veterans) and two male instructors, one educated to BA and one to master's level (each having been instructing for approximately 2 years) across the study enrolment period. One male TM instructor left for reasons not related to the study.

The core instruction for learning the TM technique was taught over 5 days in a group format with individual personal instruction (session 2). Session 1 consisted of, first, an introductory lecture, involving an overview of previous scientific research on the TM programme and a preview of possible benefits; second, a preparatory lecture, consisting of discussion of the mechanics and origin of TM; and third, a brief personal interview with the instructor. Session 2 was one-to-one instruction in the practice of TM. Sessions 3, 4, and 5 involved continuing TM instruction and verifying the correctness of practice. Sessions 2–5 were delivered on consecutive days, as is standard practice.

After the core instruction, there were seven maintenance sessions (in a group format) over the rest of the 3-month period. These sessions included verification of correct practice of the TM technique and a discussion of experiences. These follow-up sessions were similar to those of other clinical trials with TM.^{26,28,29} Participants were encouraged to continue to practice two 20-min TM sessions at home each day. CG-K (PhD educator) supervised the delivery of the TM programme, monitoring the content and delivery of the sessions for quality control. CG-K spoke with TM instructors weekly during the first several months and approximately twice a month over the duration of the trial, predominantly by phone.

Prolonged exposure

PE is a trauma-focused behavioural treatment for PTSD involving graduated exposure to imaginal and in-vivo aspects of trauma-related experiences. The treatment is based on exposure principles and emotional processing therapy.³³ Two mental health clinicians licensed in CA, USA, with previous backgrounds in evidence-based psychotherapies, (a master's level family therapist and doctoral level counselling psychologist) delivered the PE treatment across the study. Neither PE therapist had substantial experience with PE before the study. Both therapists completed PE training commensurate with the VA roll-outs offered for VA clinicians delivering PE treatments, consisting of multiday training taught by established PE trainers using the standard PE training manual,³¹ followed by regular supervision of their PE sessions. Supervision consisted of a combination of group consultation (with Dr Steven Thorp, a PE expert at VA San Diego) and weekly 60-min face-to-face and telephone supervision throughout the course of the study by PH, a PE therapist trained by VA and Associate Clinical Professor of Psychiatry and Health Behaviour Coordinator at VA San Diego Healthcare System. The background of our study therapists and how they were trained and supervised throughout the course of the trial was consistent with the training and supervision of novice therapists employed in a national PE demonstration study of nearly 2000 veterans.³⁴

PE treatment was delivered to participants individually, consistent with most PE research.³¹ The 12-week PE treatment followed the session modules in the PE therapy for PTSD workbook.³⁵ PE therapy sessions were recorded (audio only) for consenting participants and reviewed by the supervising PE clinician (PH) during supervision. Session recordings were reviewed to ensure adherence to content presented in each module (eg, common reactions to trauma, constructing the fear hierarchy), use of imaginal exposure exercises, and to review participants' homework (listening to imaginal and engaging in in-vivo exposures). Study therapists were given specific feedback about reinforcing and promoting participants' adherence to in-session and between-session exposure assignments. One PE therapist delivered the treatment for the first 3 study years—approximately 80% of the PE participants—and left for reasons not related to the study. The second therapist provided the treatment during the final year.

PTSD health education

The PTSD HE treatment (control condition) consisted of 12 sessions of PTSD education, delivered weekly by a licensed psychologist, following manualised instructions in small groups (2–4 participants). The group meetings provided basic health education specific to PTSD veterans, 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). We used PTSD HE in this study to provide a credible psychoeducational alternative to control for time and attention and other non-specific factors.

Each 90-min session included a class discussion of lesson content, activities that fostered social support, and participants' expression of their own personal experiences. The first session focused on emotional, physical, and behavioural signs of traumatic stress, and PTSD comorbidities such as depression and substance misuse. Further sessions focused on diet and exercise and other positive lifestyle changes, immediate and long-term effects of negative coping behaviour and addictions, interpersonal relationships, and the importance of using time management skills.

TR trained and supervised the clinician who served as the HE instructor (educated to PsyD level—one HE provider delivered all the treatments in the study) and monitored the content and delivery of the sessions for quality control. TR met with the HE instructor once per week during the first several months and approximately twice per month over the duration of the trial. For home practice, HE participants received a list of general health behaviour activities (including social support, listening to music, reading a book, healthy cooking, physical exercise, etc) to do twice a day for 20 min each. After completing the study (with eight or more sessions attended and post-testing completed), participants in each group were given the option for a referral to practice another study condition, not originally assigned to them, without cost. No additional data were collected for participation.

Outcomes

The primary outcome was change in PTSD symptom severity over 3 months as assessed by the CAPS-IV.^{36,37} A decrease of 10 points or more on the CAPS was considered as a minimal standard for clinically significant improvement in PTSD symptoms.^{7,37} The CAPS questionnaire was administered at baseline and at 3-months post-test. The research assistants administering the CAPS received training with an expert in CAPS administration (PH). The CAPS interview Cronbach's α ranges from 0.87 to 0.94, which indicates adequate internal consistency.³⁷ Secondary outcomes were self-reported PTSD symptoms, using the PCL-M,^{11,28,38} and depression, using the PHQ-9.^{11,39,40} Both measures have good internal consistency^{38,40} (PCL-M Cronbach's α >0.94 and PHQ-9 Cronbach's α =0.83–0.92). Both the PCL-M and PHQ-9 were administered at baseline and at 4, 6, 8, and 10 weeks, and 3 months post-test. A decrease of 10 points or more on the PCL-M¹¹ and 5 points or more on the PHQ-9¹¹ were considered as a minimal standard for clinically significant improvement.

Additional psychological outcomes were the Profile of Mood States Total Mood Disturbance (POMS TMD) scale (Cronbach's α =0.90–0.95)⁴¹ and the Quality

of Life Enjoyment and Satisfaction Questionnaire (Q-LES [Cronbach's $\alpha=0.91-0.96$]).⁴² Demographic and background variables included age, gender, socioeconomic status, education, body-mass index, medication usage, years since end of military service, and baseline social support, using the Social Support Questionnaire (Cronbach's $\alpha=0.94$).⁴³ Compliance with treatment was assessed by number of treatment sessions attended and frequency of self-reported home practice over the past month.³⁰ Other behavioural (smoking, use of alcohol and non-prescribed drugs), physiological, and biochemical (catecholamines, blood pressure, inflammatory markers [C-reactive protein, tumour necrosis factor α , and interleukin-6], and body-mass index) outcomes will be reported elsewhere.

Statistical analysis

Groups were compared on baseline and demographic variables, with ANOVA for continuous variables and χ^2 tests for categorical variables. We analysed changes in continuous outcomes using ANCOVA on change scores from baseline to 3-months post-test. For between-group comparisons, we adjusted the mean change in each group by using the baseline score of the outcome variable and medications at baseline as covariates (total number of PTSD medications and whether participants took antipsychotics or antidepressants). For consistency between the research design and statistical analysis, randomisation stratification variables—sex and number of years since military service—were also included as covariates. All participants who were

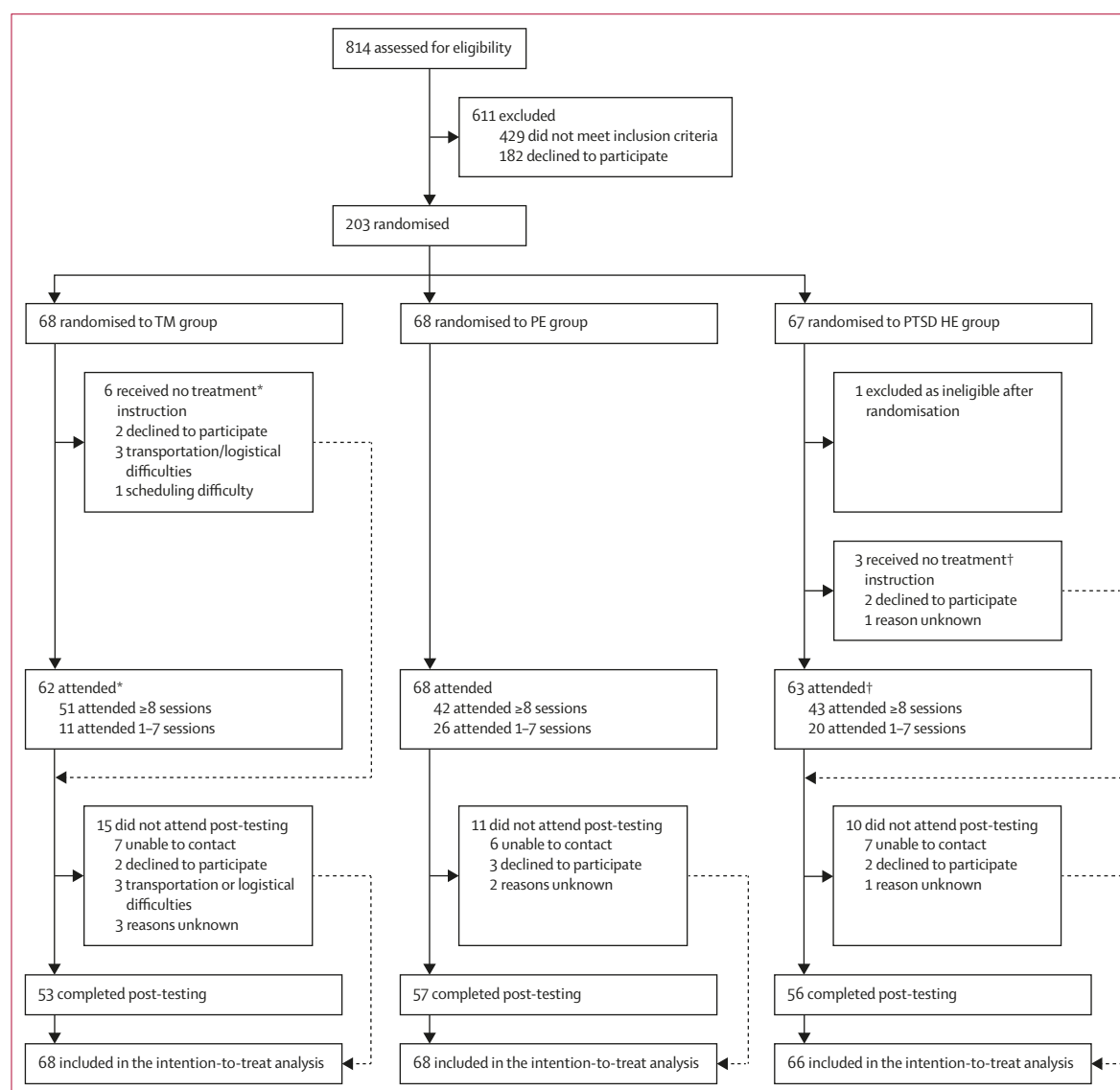


Figure 1: Trial profile

*All participants were considered for post-testing whether or not they participated in treatment. †All participants were considered for post-testing whether or not they participated in treatment. TM=Transcendental Meditation. PE=prolonged exposure. PTSD=post-traumatic stress order. HE=health education.

	TM (n=68)	PE (n=68)	HE (n=66)
Sex			
Male	56 (82%)	56 (82%)	56 (85%)
Female	12 (18%)	12 (18%)	10 (15%)
Age (years)			
	46.4 (14.3)	48.5 (15.6)	46.2 (16.4)
Married or partnership			
	36 (53%)	35 (52%)	36 (55%)
Race			
Black	20 (30%)	14 (21%)	18 (27%)
Asian	5 (7%)	3 (4%)	6 (9%)
White	38 (56%)	43 (63%)	32 (49%)
Native American	0 (0%)	2 (3%)	3 (5%)
Other	5 (7%)	6 (9%)	7 (11%)
Hispanic ethnicity			
	8 (12%)	21 (31%)	16 (24%)
Combat duty			
	33 (49%)	35 (52%)	35 (53%)
Years of active duty			
	8.8 (6.8)	10.5 (8.2)	9.1 (7.7)
Combat exposure			
	56 (82%)	58 (85%)	57 (86%)
Number of years since military discharge			
	17.9 (15.7)	18.3 (17.3)	17.9 (16.3)
Psychiatric comorbidities			
Schizophrenia	1 (2%)	3 (5%)	3 (5%)
Bipolar disorder	8 (12%)	8 (12%)	5 (8%)
Substance use disorder	28 (41%)	23 (34%)	20 (31%)
Major depressive disorder	35 (52%)	34 (50%)	28 (43%)
Anxiety disorder	28 (42%)	24 (36%)	18 (28%)
Suicidal ideation	8 (12%)	9 (13%)	9 (13%)
Cognitive impairment	13 (19%)	13 (19%)	14 (21%)
Traumatic brain injury	13 (19%)	17 (25%)	17 (26%)
Trauma events			
Combat-related trauma	51 (75%)	52 (77%)	46 (70%)
Sexual trauma	16 (24%)	25 (37%)	16 (25%)
Disaster exposure*	60 (88%)	60 (88%)	60 (91%)
Life-threatening illness or injury	23 (34%)	30 (45%)	26 (40%)
Serious injury event	55 (81%)	57 (84%)	51 (77%)
Other trauma	65 (96%)	65 (96%)	61 (93%)
Pre-study PTSD medications			
Antidepressants	47 (69%)	37 (54%)	30 (46%)
Anticonvulsants	14 (21%)	17 (25%)	18 (27%)
Anxiolytics	34 (50%)	31 (46%)	28 (42%)
Mood stabilizers	16 (24%)	8 (12%)	10 (15%)
Antipsychotics	13 (20%)	6 (9%)	4 (6%)
Sleep medications	19 (28%)	16 (24%)	14 (21%)
Any listed PTSD medication	53 (78%)	45 (66%)	40 (61%)

Data are n (%) or mean (SD). *Natural disasters, fires, or explosions.
 TM=Transcendental Meditation. PE=prolonged exposure. PTSD=post-traumatic stress disorder. HE=health education.

Table 1: Baseline characteristics

randomly assigned were included in the analyses, following the intention-to-treat principle. We did multiple imputations to include missing values at each time point, including the interim post-test visits, using the SAS software MI Procedure (Markov Chain Monte Carlo method; [SAS version 9.1.3]). Missing final post-test scores were imputed on the basis of change from

1 baseline to non-missing interim and post-tests, taking into account correlations between non-missing values for primary and all secondary outcome scores at baseline, interim post-tests (PCL-M and PHQ-9 only) and final
 5 post-test. With this approach 100 datasets were created with a missing data point imputed with a value chosen at random from the distribution of the variable of interest. Each of these imputed datasets was analysed separately with standard statistical methods for complete data. The
 10 distribution of results for the imputed datasets was then summarised to estimate treatment effects and p values for the original dataset using SAS PROC MIANALYZE. Multiple imputation is preferable to single imputation methods such as last observation carried forward
 15 (LOCF), which overstate the statistical precision of analysis results because the imputed values are assumed to be precise.⁴⁴ However, we also used the LOCF imputation method to estimate treatment effects in a sensitivity analysis because multiple imputation might
 20 yield less conservative estimates of treatment effects compared with the LOCF method.

A standard between-groups design was used to compare TM and PE groups to HE controls (superiority comparison). The non-inferiority comparisons of TM
 25 versus PE examined whether the mean improvement in scores for TM was at least equal to the mean improvement for PE, minus a prespecified margin representing the smallest clinically meaningful difference (the non-inferiority margin, Δ). Hence, the non-inferiority
 30 comparisons were one-sided. On the basis of our review of the literature, an improvement of 10 points on the CAPS was regarded as the smallest clinically meaningful difference (ie, $\Delta=10$). For changes in other outcome measures, Δ was set to an improvement in scores that
 35 would be equivalent to the CAPS in terms of standard deviations at baseline on each scale (eg, $\Delta=6.86$ for the PCL-M; $\Delta=3.13$ for the PHQ-9).

The primary objective of the study was to compare TM to PE in a non-inferiority analysis. TM and PE were
 40 each compared to HE in a superiority comparison.⁴⁵ Significance levels were set at 0.025. We used two-sided tests of the superiority comparisons and one-sided tests of the non-inferiority comparisons. Effect sizes were calculated with Cohen's d—ie, difference in means
 45 divided by the pooled standard deviation at baseline.

Logistic regression analysis was used to compare the groups on the proportion of participants who achieved clinically significant reductions in PTSD symptoms (ie, reductions in CAPS and PCL-M total scores of
 50 ≥ 10 points, and PHQ-9 scores of ≥ 5 points).^{11,46} In these analyses, we adjusted for the same covariates used in the analysis of the primary outcome.

Power calculations indicated that a target sample size of 210 (70 participants in each treatment group) would provide 90% power for the non-inferiority comparisons of TM versus PE and 85% power for the superiority comparisons of TM and PE versus HE. For the superiority

	Baseline mean (SD)			3-month post-test mean (SD)			Unadjusted mean change within group (95% CI)			Effect size*		
	TM (n=68)	PE (n=68)	PTSD HE (n=66)	TM	PE	PTSD HE	TM	PE	PTSD HE	TM	PE	PTSD HE
CAPS	80.5 (17.7)	80.6 (16.9)	77.6 (18.7)	64.4 (33.0)	69.5 (31.5)	75.1 (26.5)	-16.1 (-22.6 to -9.5), p<0.0001	-11.2 (-17.4 to 5.0), p=0.0006	-2.5 [-8.2, 3.2]	0.90	0.63	0.14
PCL-M	60.5 (12.7)	61.3 (11.6)	58.8 (12.5)	46.9 (18.2)	50.6 (18.5)	55.2 (15.3)	-13.4 (-16.9 to -10.0), p<0.0001	-10.7 (-14.6 to -6.7), p<0.0001	-3.4 (-7.0 to 0.1), p=0.058	1.10	0.87	0.28
PHQ-9	17.0 (6.1)	17.0 (5.0)	15.9 (5.6)	10.2 (7.3)	12.0 (6.6)	14.0 (6.6)	-6.8 (-8.5 to -5.1), p<0.0001	-4.9 (-6.5 to -3.4), p<0.0001	-1.9 (-3.6 to -0.2), p=0.028	1.22	0.89	0.34

Data are mean (SD). Change scores were calculated as baseline minus 3-month post-test. CAPS=Clinician-Administered PTSD Scale. PCL-M=PTSD Checklist–Military Version. PHQ-9= Patient Health Questionnaire. TM=Transcendental Meditation. PE=prolonged exposure. PTSD=post-traumatic stress disorder. HE=health education. *Mean change divided by the standard deviation of the outcome measure at baseline.

Table 2: Within-group changes in primary and secondary outcomes from baseline to 3 months

comparisons we assumed improvements of at least 10 points on the CAPS for TM and PE relative to HE. The target sample size allowed for attrition of up to 20%, with consequent dilution of statistical power in the intention-to-treat analyses. For the actual sample size recruited in the study and variability in change in CAPS scores, post-hoc estimates of statistical power were over 90% for the non-inferiority comparison, 88% for TM versus HE, and 79% for PE versus HE. This study is registered with ClinicalTrials.gov, number NCT01865123.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of this report. The first author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

814 veterans were assessed for eligibility and 203 were randomly assigned to treatment (figure 1). Table 1 shows baseline characteristics of these participants. The mean CAPS total score at baseline was 79.7 (SD 17.8). 128 (68%) participants were taking one or more medications prescribed for PTSD.

For TM, the effect sizes for PTSD symptoms measured by CAPS and PCL-M and depression measured by PHQ-9 ranged from 0.90 to 1.2; for PE from 0.63 to 0.89; and for HE from 0.14 to 0.34 (table 2). Figure 2 shows the unadjusted mean changes in the CAPS (point reductions) by treatment group.

TM was significantly non-inferior to PE for CAPS, PCL-M, and PHQ-9 scores when using baseline dependent score, number of PTSD medications, sex, and number of years since discharge from the armed forces as covariates (p=0.0002 table 3). Similar results were obtained when including the following additional covariates: antidepressants and antipsychotic medications at baseline; change in number of PTSD medications; baseline social support; number of treatment sessions attended; or only the outcome measure at baseline as a

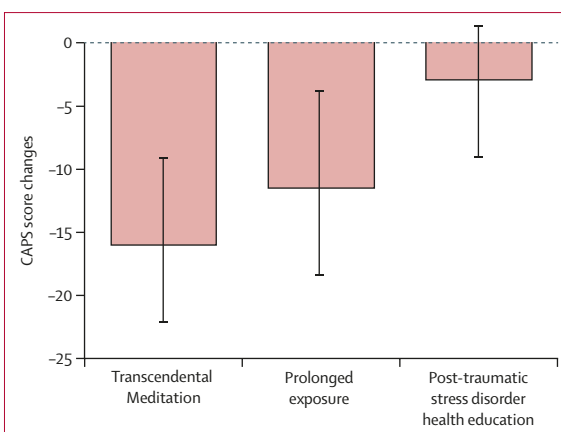


Figure 2: Changes in point scores from baseline to 3-month post-test for all treatment groups on the CAPS score
CAPS=clinician-administered PTSD scale.

covariate (appendix). Treatment expectancy, measured at the first treatment meeting, differed among the groups (p=0.03), with the TM group scoring half a standard deviation higher than the other two groups; findings were significant even after treatment expectancy was also included as an additional covariate (appendix). Mean changes for baseline to 3-month post-test scores, adjusted by ANCOVA, were greater for both the TM and PE groups compared with the PTSD HE group (table 3).

A secondary analysis of change based on the LOCF method of imputing data yielded slightly more conservative results in terms of reductions in PCL-M and PHQ-9 scores compared with the intention-to-treat analysis based on multiple imputation; however, the LOCF method yielded similar results regarding statistical significance of between-group differences (appendix). Percentages of study participants in each group with clinically meaningful reduction on the CAPS, PCL-M, and PHQ-9 depression are shown in table 4. TM showed significantly greater percentages of improvement on the CAPS, PCL-M, and PHQ-9 compared with HE (table 4). In addition to the 3-month

	TM vs PTSD HE		PE vs PTSD HE		TM vs PE	
	Mean change (95% CI)	Effect size	Mean change (95% CI)	Effect size	Mean change (95% CI)	Effect size
CAPS	-14.6 (-23.3 to -5.9), p=0.0009	0.82	-8.7 (-17.0 to -0.3), p=0.041	0.49	-5.9 (-14.3 to 2.4), p=0.0002	0.33
PCL-M	-10.0 (-15.0 to -5.0), p<0.0001	0.82	-6.6 (-11.4 to -1.7), p=0.008	0.54	-3.5 (-8.4 to 1.4), p<0.0001	0.29
PHQ-9	-4.6 (-6.8 to -2.5), p<0.0001	0.83	-2.6 (-4.6 to -0.5), p=0.014	0.46	-2.1 (-4.1 to 0.2), p<0.0001	0.37

CAPS=Clinician-Administered PTSD Scale. PCL-M=PTSD Checklist-Military Version. PHQ=Patient Health Questionnaire. TM=Transcendental Meditation. PE=prolonged exposure. PTSD=post-traumatic stress disorder. HE=health education. Mean change adjusted for baseline measure, number of PTSD medications, sex, and number of years since military discharge. Statistical significance for differences between TM and PE based on a non-inferiority comparison.

Table 3: Between-group changes in primary and secondary outcomes

	TM	PE	HE	TM vs PTSD HE	PE vs PTSD HE
CAPS	61.2%	41.5%	32.3%	p=0.001	p=0.30
PCL-M	57.6%	45.5%	24.7%	p=0.0005	p=0.029
PHQ-9	67.1%	42.2%	27.1%	p<0.0001	p=0.12

Clinically significant reductions on the outcomes from baseline to final post-test were reductions of ≥ 10 points for the CAPS and PCL-M, and reductions of ≥ 5 points on the PHQ-9. CAPS=Clinician-Administered PTSD Scale. PCL-M=PTSD Checklist-Military Version. PHQ=Patient Health Questionnaire. TM=Transcendental Meditation. PE=prolonged exposure. PTSD=post-traumatic stress disorder. HE=health education.

Table 4: Percentages of participants with clinically significant reductions in symptoms of post-traumatic stress disorder

change scores on the PCL-M and PHQ-9 depression measures (tables 2, 3), interim data were obtained with these two measures at 1 month and approximately every 2 weeks thereafter. These data show when reductions took place and the degree of those reductions on PTSD symptoms and depression for all three groups (appendix).

See Online for appendix

A completer analysis was done with CAPS and PCL-M for participants who attended eight or more treatment sessions. Mean CAPS change scores were -17.3 (95% CI -24.4 to -10.3, $d=0.97$) for TM; -13.7 (95% CI -22.2 to -5.2, $d=0.77$) for PE; -2.4 (95% CI -9.1 to 4.4, $d=0.13$) for HE. PCL-M change scores were -14.0 (95% CI -17.5 to -10.6, $d=1.15$) for TM; -14.7 (95% CI -19.8 to -9.7, $d=-1.21$) for PE; and -4.7 (95% CI -9.3 to 0.0, $d=0.38$) for HE. Within the TM and PE groups, effect sizes were larger for veterans who attended eight or more sessions compared with those attending fewer than eight sessions (1.01 vs 0.34 on the CAPS and 1.15 vs 0.51 on the PCL-M for TM, and 0.80 vs 0.41 on the CAPS and 1.21 vs 0.19 on the PCL-M for PE).

Within-group changes on the POMS TMD scale showed significant reductions for the TM ($d=0.52$, $p=0.0008$) and PE ($d=0.51$, $p=0.0005$) groups but not for the HE group ($d=0.09$, $p=0.54$). Between-group analyses

on the POMS TMD scale showed a change for TM versus HE ($d=0.43$, $p=0.015$), and for PE versus HE ($d=0.42$, $p=0.038$). TM was non-inferior to PE ($p=0.001$). Within-group changes on the Q-LES total quality-of-life scale showed significant improvements for the TM ($d=0.40$, $p=0.005$) and PE ($d=0.28$, $p=0.03$) groups but not for HE ($d=-0.05$). Between-group analyses on the Q-LES showed overall quality of life changes in the expected direction for TM versus HE ($d=0.45$, $p=0.014$) and PE versus HE [$d=0.27$, $p=0.12$]. TM was non-inferior to PE ($p=0.033$ [appendix]).

193 (96%) of veterans in the study participated in the treatment to which they were assigned. 186 participants attended post-testing (including interim post-test visits) and 166 (82%) completed the final post-test. Compared with 65% (SD 30%) in the HE group, the mean attendance for treatment sessions was 75% (SD 35%) in the TM group and 68% (SD 31%) in the PE group. The mean number of treatment sessions attended was 9.0 (SD 4.3) sessions for the TM group, 8.2 (SD 3.7) sessions for PE, and 7.9 (SD 3.6) sessions for HE. Differences in meeting attendance rates compared with HE for TM and PE were not significant; in the TM group participants attended an average of 1.1 more sessions than did those in the HE group (95% CI, -0.2 to 2.4, $p=0.09$), whereas PE group participants attended an average of 0.3 more sessions than did those in the HE group (95% CI, -1.0 to 1.6, $p=0.62$). Numbers of those reporting a frequency of home practice of at least once per day were 52 (76%) for TM, 51 (75%) for PE, and 46 (70%) for HE. Differences between the three groups in home practice rates were not statistically significant ($p=0.13$). Treatment dropout was defined as fewer than eight treatment sessions attended. Percentages of participants attending less than 8 sessions were 25% for TM, 38% for PE, and 35% for HE ($p=0.23$). 166 (81%) participants completed the final 3-month post-test (53 (78%) of 68 for TM, 57 (84%) of 68 for PE, 56 (85%) of 66 for HE). All 202 eligible patients randomly assigned to treatment were included in the intention-to-treat analyses regardless of treatment dropout or missing post-test data.

There were no treatment-related adverse events for any of the three treatments. The numbers of serious adverse events reported during the trial were not significantly different among treatment groups. There were three serious adverse events in the TM group (two suicide attempts, one death [non-suicidal]), two in the PE group (one drug overdose, one illness), and two in the HE group (two psychiatric hospitalisations).

Discussion

This three-group comparative effectiveness trial examined the efficacy of a non-trauma intervention, TM, in reducing PTSD symptom severity and depression in veterans. TM was significantly non-inferior to PE on both the primary outcome of the study, change in CAPS score from baseline

to 3 months for trauma symptom severity, and on the PCL-M and PHQ-9 depression scores. In comparison with HE, both TM and PE showed significantly greater reductions versus HE from baseline to 3 months on PTSD symptoms and depression. Additionally, participants receiving TM showed improvements in total mood disturbance and overall quality of life, and PE showed significant improvement in total mood disturbance but not quality of life; TM versus PE showed non-inferiority on these measures (appendix).

These results in reducing PTSD symptom severity are consistent with results from previous studies on TM,^{47,48} albeit on a larger and more methodologically rigorous scale. Within-group effect sizes for TM on PTSD symptoms in two previous studies of veterans,^{47,48} one uncontrolled and the other with non-random allocation, ranged from 0.77 to 0.88 on the CAPS and 0.86 to 1.19 on the PCL-specific trauma version (PCL-S). This study and previous studies are similar with the same general range of within-group effects on the CAPS and PCL measures. The PCL-S and PCL-M are self-report measures, with similar test items and response sets; the PCL-S asks for responses to a specific trauma event and is used in military and non-military studies, while the PCL-M asks for responses to military experiences. In the non-randomised study of a total of 79 veterans,⁴⁸ between-group effect sizes for TM versus present-centred therapy were 0.48 on the CAPS score and 0.65 on the PCL-S score. A randomised controlled study of TM compared with treatment as usual in veterans had a large effect size of 1.31 with small numbers of participants (<20 per group).¹⁵

Completer analysis showed a marked improvement in pre-treatment to post-treatment mean change in all groups. This was especially evident on the PCL-M assessment, for both PE and TM groups. Veterans receiving PE who attended at least eight treatment sessions showed a substantially higher dose effect compared with those attending fewer than eight sessions ($d=1.21$ vs $d=0.19$), indicating that the PE treatment was effective, but mainly for those who attended a sufficient number of treatment sessions. For the TM group, effect sizes were twice as large in veterans who attended eight or more sessions compared with those attending fewer than eight sessions, indicating a substantial dose effect.

PE results were not significantly different from those reported by a national PE demonstration study of 1354 US veterans.³⁴ The demonstration study can be generalised to the US veteran population because of its large sample with multisite locations, inclusion of multiple war eras, a predominantly male sample, and few exclusion criteria. The national PE demonstration study and our study used a similar method of training and supervision of novice PE instructors and had similar baseline-level PTSD symptom scores. Unlike our trial, the demonstration study selected participants who were pre-judged to be suitable candidates for PE and included up to 15 PE treatment sessions. For

participants completing eight or more PE sessions, the PCL results of the national PE demonstration study showed a reduction of -18.1 points compared with -14.7 points for our study ($p=0.18$, based on a comparison of the results of our study with the PE demonstration study).

Because clinical trials for PTSD treatments can vary in terms of study design factors that might influence the degree of treatment efficacy (eg, severity of PTSD symptoms, sex, age, military status, trauma type, medication use, duration of treatment, clinical setting, and internal validity),⁴⁹ between-group analysis might be a better indication of treatment benefit. Between-group changes comparing PE with HE in our study were similar to between-group changes in a study comparing PE to a minimal attention control group, matched for treatment sessions, in a predominantly male veteran sample ($n=52$), with a similar "very severe" level of PTSD symptomology, according to CAPS.⁵⁰ The PE versus minimal attention study showed a between-group difference of -9 points on the CAPS score compared with a difference of -9.8 points in our PE versus HE study, using the same analysis as in Yehuda and colleagues' study ($p=0.94$, based on a comparison of our study with Yehuda and colleagues' study).⁵⁰ Both studies used the same number of treatment sessions over a 3-month intervention period. PTSD HE was originally designed to be more active than a minimal attention control; hence, comparing between-group differences in our study to studies of PE versus minimal attention control could be considered conservative.

An important factor in the interpretation of this comparative effectiveness trial is the quality and performance of the PE treatment used as the comparison treatment in the non-inferiority analyses. We ensured that the PE therapists were licensed psychotherapists with strong backgrounds in evidence-based therapies, who subsequently completed PE-specific training similar to PE training for clinicians provided by the VA health-care system. This training involves multiday in-person workshops based on the gold-standard PE manual by Foa and colleagues (used in VA roll-out trainings for PE nationally),³⁵ followed by weekly supervision of PE cases and reviews of recorded PE sessions by a local PE expert. For this reason, our results probably most accurately reflect treatment effects in a real-world setting, as are likely to be achieved by non-PE specialists obtaining standard VA training in PE.³⁴

Another factor that might have affected the change in PTSD symptoms in all treatment groups is the stricter randomised study design used in our study compared with some other trials. Other research reported being flexible in the number of sessions employed or the timeframe in which the sessions could be completed.^{7,51} In our study, all groups had a clearly defined number of treatment sessions to be completed within a specific timeframe from randomisation to post-test that could

not be altered at the discretion of therapists or study investigators. The background of our participants also might have affected study results compared with other research; our trial had mean average CAPS scores representing very severe PTSD symptoms,¹² high rates of medication usage, a sample who had predominantly experienced combat-related trauma, with a high percentage of participants with comorbid conditions. It is also possible that participants had less time to complete treatment homework or might have had greater incentive to retain their status of being connected to mental health services.

Insofar as PE and TM were superior to the active control treatment, the benefits of these two treatments can reasonably be interpreted as specific to these interventions. The benefit of exposing people with PTSD to traumatic memories has been regarded as an important, if not essential, part of the therapeutic process. However, evidence is increasingly supportive of non-exposure treatments also being beneficial for patients with PTSD.¹² Our findings provide further evidence that PTSD treatments can be effective without an exposure component. Because trauma exposure can be difficult for patients, similarly effective treatments that do not require exposure could be appealing to veterans and other groups with PTSD.

The strengths of the study are that it followed a randomised controlled design, with equal numbers of treatment sessions, length of time of sessions, and intervention periods for all three groups. Treatment allocation concealment was followed and all testing sessions were administered by staff masked to group assignment. Each treatment programme was supervised by a separate study investigator experienced in that particular modality and therapists delivered only one of the study treatment programmes each to guard against potential contamination effects. The daily conduct of the study was overseen by the on-site study principal investigator, and co-investigator, both of whom are experienced practitioners of cognitive behavioural therapy, who did not practice meditation.

There are several important limitations to consider in the interpretation of these findings. First, PE has shown stronger effects on reduction of PTSD symptoms in several other clinical trials compared with what we observed here. Although we took steps to ensure that the training of the PE therapists and delivery of the PE treatment was similar to other studies, the non-inferiority comparisons between TM and PE that we report here best generalise to other studies with novice PE therapists, delivering treatment to a mostly male veteran population with a baseline level of severe PTSD. Further research will be necessary to replicate or extend these findings in other settings. Second, the study lacked a follow-up period that could have offered valuable information regarding further reduction of PTSD symptoms and the durability of the PE and TM benefits observed. Third, treatment

dropout was a potential confound in this study. The meditation group had the lowest treatment dropout rate (25%) and the PE group had the highest (38%), although these differences were non-significant. Other studies with PE had shown dropout rates of 38%,⁵² 32%,⁵⁰, and 29%,^{34,12} which was somewhat similar to our study. Fourth, therapists' previous experience teaching their respective programmes differed among the groups, as well as their level of academic education. Although the TM instructors had more previous experience teaching their programmes to other populations than PE and PTSD HE therapists, TM instructors, similar to the other study therapists, were novices in terms of delivering treatment to PTSD veterans. TM instructors had a lower overall level of academic education than the other group therapists. Finally, we were unable to recruit a substantial sample of women in the study to enable TM and PE comparisons by sex. Given the established benefits of PE for women with military sexual traumas and other forms of PTSD, the absence of data to clarify the effect of TM for PTSD in women remains an issue to be addressed in future research.

Overall, we found that TM was non-inferior compared with PE for treating PTSD symptom severity and comorbid depression in veterans with PTSD. The findings from this first comparative effectiveness trial comparing TM to an established psychotherapy for PTSD suggests the feasibility and efficacy of TM as an alternative therapy for veterans with PTSD and encourages future TM research to explore the durability of the benefits and applications to other populations with PTSD.

Contributors

SN contributed to the overall design and conduct of the study, interpretation of the findings, and writing of the manuscript. TR contributed to the overall design and conduct of the study, training and supervision of the HE treatment, interpretation of the findings, and writing of the manuscript. PJM contributed to the overall design of the study, collection of data, and writing of the manuscript. MR contributed to the overall study design and sample size estimate, statistical analysis, the interpretation of the findings, and writing of the manuscript. PH contributed to the overall study design, training and supervision of the PE treatment, and writing of the manuscript. RHS contributed to the design and conduct of the study, interpretation of the findings, and writing of the manuscript. NER contributed to the design of the study and writing of the manuscript. JS contributed to the conduct of the study and writing and preparation of the manuscript. CG-K oversaw the quality control of the Transcendental Meditation intervention and contributed to the final editing of the manuscript.

Declaration of Interests

TR worked on grants from the US Department of Defense and Department of Veterans Affairs. All other authors declare no competing interests.

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