Written exposure therapy and app-delivered mindfulness-based meditation for PTSD and subthreshold PTSD in China: Design of a randomized controlled trial

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A B S T R A C T

Background: Posttraumatic stress disorder (PTSD) and subthreshold PTSD are still major global concerns, especially in developing areas short of mental health resources. Written exposure therapy (WET), a brief 5-session treatment, has been found to be effective in reducing PTSD symptoms, but no studies have examined it in an Eastern context. Mindfulness-based meditation mobile application may be a promising approach to reduce insomnia comorbid with PTSD. The current study aims to: 1) examine the effectiveness of WET for Chinese PTSD and subthreshold PTSD patients, and 2) examine the effectiveness of adding a mindfulness-based application (MBA) to WET for reducing comorbid insomnia.
Methods: The randomized controlled trial will enroll 150 adults with subthreshold/full PTSD and comorbid insomnia. Participants will be randomly assigned to written exposure therapy plus mindfulness-based application condition (WET + MBA, n = 50), written exposure therapy alone (WET, n = 50), or minimal contact control (MMC, n = 50). Clinical interview of the primary outcome (PTSD symptoms) will be administrated at baseline, posttreatment, 3- and 6- month follow-up, while self-reported PTSD symptoms and secondary outcomes (insomnia severity) will be administrated at baseline, every week and all follow-ups.
Discussion: This is the first study applying WET in Chinese PTSD patients, as well as examining a mindfulness-based mobile application as a treatment add-on for comorbid insomnia. Study findings will contribute to the knowledge of the effectiveness of WET and a mindfulness-based mobile application, and the development of a culture-adapted treatment protocol.
Trial registration: ChiCTR, ChiCTR2000034119. Registered 24 June 2020, http://www.chictr.org.cn/showproj. aspx?proj=55,467.

1. Introduction

Posttraumatic stress disorder (PTSD) is a serious mental disorder with lifetime prevalence of 6.4% [1], and continues to be a major global concern. Subthreshold PTSD is almost as common as PTSD [2], associated with impairment comparable to full PTSD [2,3]. A meta-analysis

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with mixed trauma samples indicated that 26.2% of subthreshold PTSD eventually develop into full PTSD [4]. The prevalence of PTSD including subthreshold PTSD in China is similar to that in other regions, ranging from 13.0% to 37.8% depending on different trauma types [5,6]. Considering the large population and limited resources for mental health, an easy and cost-efficient PTSD treatment is of urgent need.

Written exposure therapy (WET), compared to cognitive processing therapy (CPT), is a non-inferior treatment with less training for therapists [7]. It is a 5-session weekly individual writing intervention, requiring less direct face-to-face patient-therapist contact than traditional psychotherapies. Similar to other exposure therapies, the rationale of WET is extinction learning and emotional habituation [8–10]. Considering written narrative is cross-culturally acceptable, WET may be a promising intervention for Chinese PTSD patients, but no studies have yet examined its effectiveness in non-western populations.

Insomnia, a common comorbid condition among patients with full [11] and subthreshold PTSD [12], is significantly associated with more severe PTSD and depressive symptoms and functioning impairment [13]. However, current first-line PTSD treatments cannot fully address comorbid insomnia [14,15]. It has been suggested that insomnia treatment could be used as an adjunct PTSD treatment [16]. Many individuals with insomnia exhibited preferences for non-pharmaceutic and self-help interventions [17]. Now the recommended non-pharmaceutic treatment for insomnia, cognitive behavioral therapy-insomnia (CBT-i), usually takes 2–14 weeks [18], which would significantly increase treatment burden, regardless of the scarce resource of CBT-i in China [19]. However, previous studies indicated mindfulness-based therapy reduced insomnia in clinical samples [20, 21], probably by improving insomniacs' struggling to control the dysfunctional thoughts about sleep [22,23]. Since mental health applications (MHApps) are convenient and have thrived in recent years, operating a mindfulness-based intervention through a MHApp may ease the treatment for comorbid insomnia. Nevertheless, very few studies have examined effectiveness and generalizability of MHApps [24]. A pilot RCT indicated that an English mindfulness app improved insomnia in a community sample [25], but it does not have a Chinese version, and no Chinese apps have been tested. Thus, we will examine a Chinese mindfulness-based app which covers the key elements of mindfulness [26] for improving insomnia.

Moreover, we will also examine predictors, moderators, and mediators of symptom changes in treatments. Reduction of negative posttraumatic cognitions has been found to predict the decrease in PTSD symptoms [27,28]. Posttraumatic growth (PTG) and gratitude were found to relate with the outcome of exposure therapy [29,30]. Forgiveness was found to be a crucial pathway to improve quality of life in PTSD veterans [31]. Meaning in life and happiness were found to be protective factors for PTSD [32]. In addition, we also concern physiological markers. Stress induced cortisol level is an indicator of the hypothalamic–pituitary–adrenal axis (HPA axis) functioning, which is dysregulated and generally presents a hypo-response pattern in PTSD patients [33,34]. Secretory Immunoglobulin A (sIgA) level is lower among PTSD patients [35]. Gene polymorphisms is associated with the probability of lifetime PTSD [36]. Thus, these physiological markers will also be examined.

In sum, the proposed trial will examine the effectiveness of WET in Chinese PTSD patients and test MBA as a treatment add-on for comorbid insomnia.

2. Methods

This study will be a three-armed randomized controlled trial (RCT) for Chinese adults with full/subthreshold PTSD and comorbid insomnia. The study protocol has been approved and monitored by the Ethics Committee of School of Psychological and Cognitive Sciences, Peking University.

2.1. Research hypotheses

This study will compare 3 treatment conditions: minimal contact control (MCC), 5-weekly sessions of WET alone (WET), and WET plus MBA (WET + MBA). We hypothesize that:

(1) Compared to the MCC, WET will result in more PTSD symptom reduction.
(2) Compared to the WET, WET + MBA will result in more insomnia reduction.

In addition, the exploratory aim is to examine predictors, moderators, and mediators of treatment outcomes. The other exploratory aim is to examine treatment effects on levels of cortisol and sIgA.

2.2. Participants

Participants will be 150 Chinese adults with full/subthreshold PTSD and comorbid insomnia disorder. The inclusion and exclusion criteria are listed in Table 1. Currently there is no consensus on the clinical definition of subthreshold PTSD. Meeting full criteria for intrusion and at least 2 of 3 other symptom clusters is one of the most utilized criteria [37], and resulted in more diagnoses compared to other 2 commonly used methods (i.e. having at least one symptom in each symptom cluster and meeting all the symptom clusters except avoidance) [37]. Since network analyses have revealed intrusion is the central symptom in PTSD [38], we will use the criterion for subthreshold PTSD as mentioned above.

2.3. Procedure

Potential participants will be recruited through referrals from health care providers in Beijing and public advertisements. Health care providers may forward the contact information of the interested individuals directly to the research team. Potential participants may also self-refer in response to recruitment advertisements by calling or emailing. A research assistant will field incoming phone calls and e-mails, discuss the study treatment and eligibility requirements with the interested person. If the person is likely qualified for the study, an appointment will be made for screening and informed consent (i.e., the intake screening evaluation). Potential risks or discomforts that may arise due to participation in this study include becoming emotionally upset, experiencing a transient increase of PTSD symptoms, and feeling distressed

Table 1
Inclusion and exclusion criteria.

Inclusion Criteria
a) Adult male and female (aged between 18 and 65 years old)
b) A diagnosis of PTSD (diagnosed with PTSD Symptom Scale, Interview Version for DSM-5, PSSI-5), or subthreshold PTSD (meeting full criteria for intrusion and at least 2 of 3 other symptom clusters, i.e., avoidance, negative cognitions, or hyperarousal)
c) If currently taking psychotropic medication, taking a stable one for at least 4 weeks
d) A smartphone owner and no obstacle to the *Now Meditation* app
e) Scoring 15 or more on Insomnia Severity Index (ISI) and symptoms appeared or aggravated after trauma

Exclusion Criteria
a) A diagnosis of bipolar disorder or psychotic disorder
b) Current substance dependence
c) Evidence of a moderate or severe traumatic brain injury (as determined by the obstacle to comprehending the baseline screening questionnaires)
d) Serious suicidal ideation (as determined by the Scale for Suicidal Ideation)
e) Other psychiatric disorders severe enough to warrant designation as the primary disorder
f) Receiving psychotherapy for PTSD currently

Note. PTSD = posttraumatic stress disorder, DSM-5 = Diagnostic and Statistical Manual of Mental Disorders-5 [39].

due to the exposure of traumatic experiences. There is no foreseeable risk for MCC.

Participants who consent to the study will then take a baseline evaluation (Week 0) and be randomly assigned to one of the three study conditions evenly: MCC, WET, or WET + MBA (see Fig. 1). The participants will not be blinded due to the nature of psychological treatments. The randomization will be implemented by a computer-generated schedule with block sets of 3 by an independent researcher (see Appendix A for more details). Following randomization, participants in WET and WET + MBA groups will be assessed weekly during the treatment, immediately after the treatment, 3 and 6 months after intervention completion. The follow-up assessments will provide evidence on the maintenance of treatment gains. The MCC group will complete assessments at the end of week 3 and week 5, and then they will be randomly assigned to WET + MBA or WET. They will also be assessed along with the treatment sessions, immediately upon completion of 5 sessions, 3 and 6 months after completing treatments. Saliva samples will be collected from a certain number of the participants in WET and WET + MBA for assessing sIgA, cortisol levels, and gene polymorphism. Collections will occur at each session. Within-participants saliva collection times will be recorded to control for the circadian rhythm of cortisol and sIgA levels [40–42]. A total of 120 yuan compensation will be offered for completion of the posttreatment, 3- and 6-month follow-up assessments.

All clinical interviews will be conducted by trained independent evaluators who are senior grade clinical psychology majored master or doctoral students blind to the treatment condition. Since the study therapists will deliver WET only, they will be blinded to the group allocation. Subjective Units of Distress Scale (SUDs) [43] will be administered by therapists to monitor the writing process. In the first one or two sessions, score increases on SUDs will be considered as a sign of engagement, and score decreases in the following sessions will be viewed as a prediction of good treatment outcomes [44]. Participants will also complete a series of self-report measures.

2.4. Interventions

2.4.1. Written exposure therapy (WET)

WET is a manualized exposure-based therapy consisting of 5 sequential weekly individual sessions. Sessions are scheduled to last for 1 h in the first session and 40 min in other sessions. In Session 1, the therapist will present the overall rationale for the treatment program, read the instruction verbatim to the participant, and then leave the participant to write without interruption for 30 min and check-in with the participant at the end of the session. In Session 2 to 5, feedbacks about the prior session will be discussed first, and then the participant will write for 30 min without interruption, followed by the check-in. The check-in takes less than 10 min, and the discussion prior to writing requires approximately 5 min. There are no assignments between sessions [44].

As for the rationale of WET, extinction learning indicates participants would repeatedly recount the traumatic event to learn that the once-feared objects or scenarios are not as dangerous as they thought, a new association with the traumatic clues is learned that inhibits the expression of the original fear memory [45]. Another mechanism, emotional habituation, refers to the weakened neural or behavioral response when the same stimulus is repeated [46,47].

The writing work of participants will be collected, and the feedback given by therapists will be videotaped for supervision and treatment fidelity monitoring. Any significant deviation from the study protocol will be brought to the attention of corrective actions.

2.4.2. Written exposure therapy plus mindfulness-based app (WET + MBA)

Participants randomized to WET + MBA will receive WET as described above and practice MBA using "Now Meditation", which is
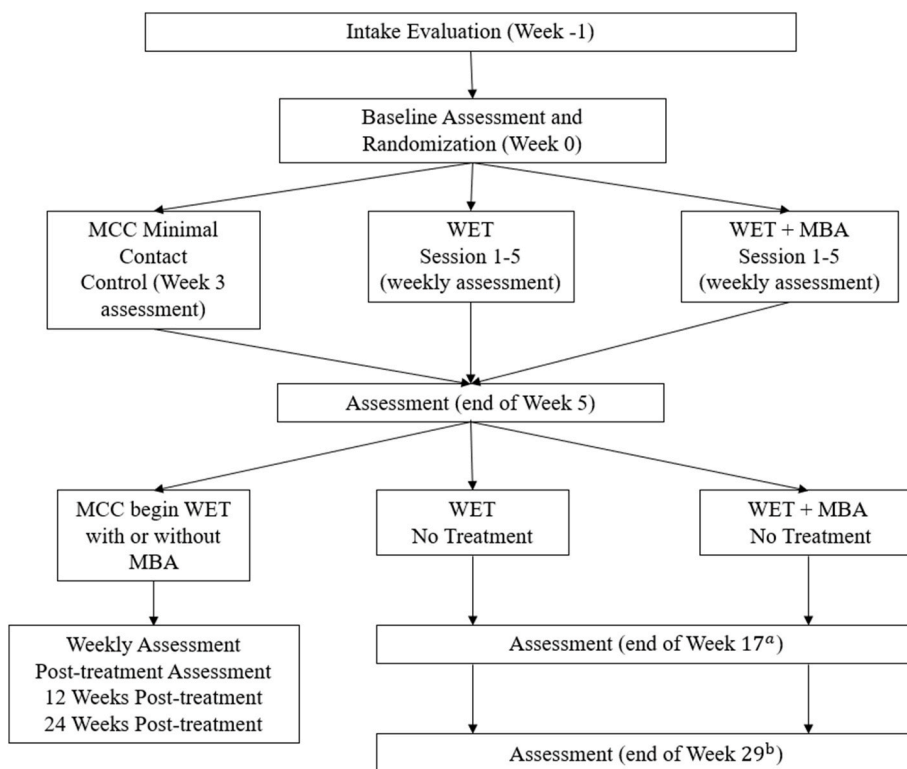

Fig. 1. The Overall Design of the Protocol (Color should not be used). *Note.* MCC = minimal contact control condition, WET = written exposure therapy condition, WET + MBA = written exposure therapy plus mindfulness-based app condition. [a] End of week 17 = 17 weeks post-baseline = 12 weeks post-treatment; [b] End of week 29 = 29 weeks post-baseline = 24 weeks post-treatment.

one of the most popular mindfulness apps in China with over 6 million downloads, as their homework. Participants will be asked to download "Now Meditation" on their smartphones under the guidance of a research assistant before the first session. The research assistant will then introduce the inbuilt series of mindfulness-based meditation (MM) instructions in the app called "7-Day Basic Meditation", which includes 7 separate instructions with progressive themes as listed in Table 2. Considering that participants may vary in their mastery of mindfulness and preference for the practice focus (e.g., breath awareness or body scan), and to simulate natural using condition, they will be asked to conduct 3 meditation exercises following any of the 7 instructions in a week. However, they are highly recommended to follow the original order of the instructions. In the following session, the research assistant will check and record the participant's "Practice History" in the "Personal Center" of the app. The research assistant will send reminding text messages to participants once a week in the middle of a week.

2.4.3. Minimal contact control (MCC)

Participants assigned to MCC will be asked to not work with other therapists or seek additional treatment for trauma-related difficulties during the 5-week MCC period. They will be called once per week by a study therapist to monitor their status and to provide support as needed. The call will be limited to 10–15 min. Participants in the MCC will also be given contact information in case of experiencing worsened symptoms or increased distress.

2.5. Adverse events

An adverse event will be defined as any untoward significant worsening of medical occurrence in a participant which does not necessarily have a causal relationship with this treatment. Adverse events will be collected from post enrollment to the second follow-up assessment and will be reported by therapists or evaluators during the assessments. If an adverse event is reported after the enrollment and before the intervention, it will be recorded as not related to the study intervention. If the participant is discontinued because of an adverse event, circumstances and data leading to discontinuation of treatment will be documented. In case of adverse events, participants will be referred to hospitals in Beijing immediately.

2.6. Measures

2.6.1. Primary outcomes

PTSD Symptom Severity. The PTSD Symptom Scale, Interview Version for DSM-5 (PSSI-5) [48], a 24-item clinician-administered interview, will be used for PTSD diagnosis and measure PTSD symptom severity. The PSSI-5 rates the frequency and severity of PTSD symptoms in the past 4 weeks on a 5-point Likert scale from 0 (*not at all*) to 4 (*very much*). The PSSI-5 has demonstrated excellent reliability and validity but takes less time than the gold standard mostly used [58], the Clinician-Administered PTSD Scale for DSM-5 (CAPS5).

The PTSD CheckList-DSM5 (PCL-5) [49], a 20-item self-report measurement, will be used for self-report PTSD symptoms. The Chinese versions of PSSI-5 and PCL-5 have both been validated [50,51].

Table 2
Contents *of the "7-Day Basic Meditation".*

Date	Theme	Duration (mins)
Day 1	Meditation for the First Time	11:50
Day 2	Breath Awareness	10:26
Day 3	Body Scan	8:41
Day 4	Mindfulness Awareness	10:44
Day 5	Persistence in Practicing	10:07
Day 6	Acceptance Meditation	8:57
Day 7	Integration into Life	10:45

2.6.2. Secondary outcomes

Insomnia. The Insomnia Severity Index (ISI) [52], a 7-item self-report measurement, will be used to assess participants' insomnia severity. It assesses the severity of insomnia symptoms, degree of satisfaction with sleep, daytime fatigue, and concerns caused by sleep difficulties. Each item is rated on a 5-point scale. The Chinese version of ISI has good psychometric properties [53].

2.6.3. Other measures

Participants Demographic. A demographics information questionnaire measuring standard demographics (gender, age, education, etc.) will be administered at intake evaluation.

Distress. Subjective Units of Distress (SUDs) [43] will be used to measure what levels of anxiety or distress is experienced during the treatment. The participant will rate their anxiety and distress on a 0 to 100 scale (0 = *no discomfort at all, or complete relaxation* to 100 = *extremely upset, the most you have been in your life*). The Chinese version of the SUDs has good psychometric properties [54].

Posttraumatic cognition. The brief version of Posttraumatic Cognition Inventory (PTCI-9) [55] will be used to measure negative posttraumatic cognition changes. It has three subscales: negative cognitions about self, negative cognitions about the world, and self-blame. The 9 questions are rated on a 7-point Likert scale (1 = *totally disagree* to 7 = *totally agree*). The Chinese version has good psychometric properties [56].

Posttraumatic growth. The posttraumatic growth will be assessed by 2 measurements, the Post Traumatic Growth Inventory (PTGI) [57] and the Short Form of the Changes in Outlook Questionnaire (CiOQ-S) [58]. PTGI has 21 items and measures positive changes in 5 domains: appreciation of life, new possibilities, relating to others, personal strength and spiritual change, rating on a 6-point scale (0 = *not at all* to 5 = *extremely*). The 10-item CiOQ-S assesses both positive and negative posttraumatic changes. Each item will be scored on a 6-point scale (1 = *strongly disagree* to 6 = *strongly agree*). The Chinese versions of both scales have good psychometric properties [59,60].

Gratitude. The Gratitude Questionnaire-5 (GQ-5) [61], a 5-item self-report scale, with each item rated on a 7-point Likert scale (1 = *strongly disagree* to 7 = *strongly agree*), will be used to assess levels of gratitude. The Chinese version of GQ-5 has good psychometric properties [62].

Forgiveness. The Heartland Forgiveness Scale (HFS) [63] measures forgiveness of self, others, and situations. Participants rate each item on a 7-point Likert scale (1 = *almost always false of me* to 7 = *almost always true of me*). Higher scores correspond to higher levels of forgiveness. The Chinese version shows good psychometric properties [64].

Meaning in Life. The Meaning in Life Questionnaire (MLQ) [65] will be used to assess the current stage of meaning in life and the degree of the pursuit of meaning. Responses to 10 statements ranges from 1 = *Absolutely Untrue* to 7 = *Absolutely True*. The Chinese version shows acceptable psychometric properties [66].

Happiness. The General Happiness Scale (GHS) [67], a 4-item scale, will be used to measure subjective happiness. Each item is completed by choosing one of 7 options that finishes a given sentence fragment. Scores range from 1 to 7, with higher scores reflecting greater happiness. The Chinese version has been validated [68].

We will also assess anxiety, depression, and emotional regulation using the Beck Anxiety Inventory (BAI) [69], the Beck Depression Inventory-II (BDI-II) [70], and the Cognitive Emotion Regulation Questionnaire (CERQ) [71], which all have Chinese versions with acceptable psychometric properties [72–74].

2.6.4. Saliva collection and biomarkers

There will be 5 times of saliva collections, occurring at each session, for a certain number of the participants randomized to WET and WET + MBA. Gene polymorphisms will be examined at the first collection. At each collection, participants will provide 3 saliva samples.

Participants will be instructed to avoid drinking (except for water), eating, smoking, and vigorous exercise within 2 h before the collection. Additionally, all participants will be verbally screened for steroid use before collection, as steroids interfere with cortisol assay [75]. Since female participants' menstrual cycle affects the cortisol level [76], we will record their menstrual cycle and include it as a covariate in subsequent analyses.

To enhance the data quality, independent researchers who in charge of data collection will be trained. When completing self-report measures on a laboratory computer, participants will be allowed to take a break in the middle of the process. See Appendix B for detailed data management plan.

2.7. Data analysis

There are 2 main hypotheses in the current study.

Hypothesis 1. Compared to the MCC, WET will result in more PTSD symptom reduction. Specifically, participants randomized to WET will have less PTSD symptoms at post-treatment than those in MCC, and the treatment effect will be maintained during follow-ups.

Hypothesis 2. Compared to WET, WET + MBA will result in more insomnia reduction. Specifically, participants randomized to WET + MBA will have less insomnia at post-treatment than those in WET, and the treatment effect will be maintained during follow-ups.

The analyses will be intent-to-treat. Multilevel models (MLMs) or mixed effect regression models with repeated measures will be used for analyses for this nested data structure (repeated assessments nested in each participant). MLMs allow the number of observations to vary between participants, and it can deal with missing data effectively without resorting to listwise deletion or imputation of data [77].

Preliminary analyses will be performed to compare the demographic and clinical characteristics of each group at baseline. Baseline variables that are confounded with intervention conditions will be included in the model as covariates as needed.

For Hypothesis 1, MLMs will test group difference on PTSD outcomes (for both PSSI-5 and PCL-5). The model will include time, treatment conditions, and their interaction as the independent variables. For Hypothesis 2, the analysis approach will be similar to that of Hypothesis 1 but using the repeated measures of insomnia as the dependent variable.

Analyses will be conducted to examine whether cortisol levels decrease and sIgA levels increase during and after treatments. Because saliva samples are collected at different time points, the exact collection time will be included in our analyses as a covariate to control for diurnal variability [78]. Exploratory analyses with MLMs will also be carried out to test predictors, moderators, and mediators for treatment effects to further explore the underlying mechanisms.

The sample size in this study was decided by the power analysis and recruitment feasibility. Every participant will be assessed 8 times, including baseline, week 1–5, as well as 3- and 6- month follow-up assessments. Self-reported PTSD severity and insomnia will be measured at every assessment occasion, while PSSI-5 administered PTSD severity will be measured only at baseline, post-treatment, and 2 follow-ups (4 times in total). Hedeker's RMASS2 [79], which estimates power for unadjusted pairwise comparisons of two treatment arms for longitudinal data was used to calculate the sample size. We assumed a rate of treatment noncompliance (i.e., active treatment dropout) of 5% between every two assessments for 4 assessments. For 2-sided tests, n = 50 in each arm yield power > .80 to detect a medium effect size ($d = 0.50$) between WET and MCC in terms of PTSD severity, and small effect size ($d = 0.30$) between WET + MBA and WET regarding insomnia severity.

3. Discussion

This study is an RCT of three treatment conditions for Chinese individuals with full/subthreshold PTSD and comorbid insomnia. The dissemination of evidence-based first-line treatments for mental disorders in less-developed areas has long been a challenge [80,81]. Well-studied first-line PTSD treatments such as prolonged exposure (PE) and cognitive processing therapy (CPT) were barely tested in non-western samples, and the long-term training for therapists makes PE and CPT far apart to PTSD patients in developing areas. Therefore, developing an effective, demotic, and culturally adaptable PTSD treatment protocol is of great importance. Although Chinese understanding of PTSD has been developed after the 2008 Wenchuan Earthquake [82], empirical research testing PTSD treatments remains scarce, except two pilot RCTs indicated that the narrative exposure therapy could be effective for Chinese PTSD patients [83,84]. In the present study, we employ a simpler format of exposure therapy. If our findings provide empirical support for WET in Chinese PTSD patients, it will lay the foundation for its further adaptation and implementation as a standardized PTSD treatment in China.

Furthermore, a distinctive feature of this study is to include a MHApp as a treatment add-on for PTSD comorbid insomnia. Now Meditation is one of the most downloaded mindfulness apps in China. The chosen program, "7-Day Basic Meditation", which has been practiced more than 2.1 million times, is a step-by-step guide starting with an introduction of meditation, covers the basics of MM (breath awareness, body scan, awareness, and acceptance), and encourages users to incorporate MM into daily lives. We did a small-scale user survey to ensure it is user friendly and consulted with a senior mindfulness researcher/practitioner to confirm its suitability. To balance the ecological validity and experimental control, participants will be allowed to practice the program at their own paces instead of being strictly stipulated.

This study represents significant advances as it is the first to examine WET in a non-western sample, to test WET in subclinical PTSD patients, to add a MHApp to WET for insomnia, and to explore physiological responses to PTSD treatments in Chinese population. The proposed design has several advantages. Including subthreshold PTSD will extend the study findings to subclinical populations. By replacing a waitlist design with a minimal contact control, it will reduce the bias caused by researcher's attention. Moreover, positive psychology variables (e.g., appreciation, posttraumatic growth) will be measured, as we focus not only on the negative, but also the positive to further understand the comprehensive impact of a mental health intervention.

However, there are also challenges and limitations. First, all study therapists will be trained master students majoring in clinical psychology. Although this responses to the shortage of mental health resources in China as the majority of mental health professionals do not have doctor's degrees [85], deviations from the protocol may arise due to therapists' premature apprenticeship status. In view of this, treatment sessions will be strictly monitored by study supervisors to ensure a good treatment fidelity. Second, findings may show that WET had a smaller treatment effect in subclinical PTSD patients than those found in full PTSD patients as subclinical patients may have less symptoms at baseline to be changed. If this finding is observed, the degree to which WET should be applied for subclinical PTSD will be considered. Third, although the study aims to examine the effect of MBA on insomnia, MM might still interact with writing process. To minimize the interference, we will ask the participants not to practice MM right before or after the sessions, controlling the effect of MM on the writing process and the time a participant spent with the therapist.

In summary, the findings of this trial are expected to advance our understanding of the effectiveness of WET for PTSD in Eastern culture, as well as the usefulness of a MHApp. The trial will be our first study for establishing a standardized and efficient intervention with broad application perspective for Chinese people and may allow us to develop a convenient and effective mindfulness-based intervention via mobile apps for insomnia comorbid with PTSD. We also hope this study will assist us to further understand the underlying mechanism of WET and its physiological impacts.

Ethics approval and consent to participate

The study protocol has been approved and monitored by the Ethics Committee of School of Psychological and Cognitive Sciences, Peking University. Informed consents will be obtained from all participants.

Availability of data and materials

Not applicable.

Funding

Authors' contributions

Study conception and design: ML, BW, and YZ. Analysis and interpretation of data: ML, DG and YZ. Drafting of manuscript: ML and YZ. Critical revision: ML, BW, QC, DG and YZ. YZ supervised the overall project.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A and B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2021.100729.

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