Contemporary Clinical Trials 44 (2015) 70–76

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Yoga for generalized anxiety disorder: design of a randomized controlled clinical trial

Stefan G. Hofmann [a,*], Joshua Curtiss [a], Sat Bir S. Khalsa [b], Elizabeth Hoge [c], David Rosenfield [d], Eric Bui [c], Aparna Keshaviah [c], Naomi Simon [c]

[a] Boston University, United States
[b] Brigham and Women's Hospital, Harvard Medical School, United States
[c] Massachusetts General Hospital, United States
[d] Southern Methodist University, United States

ARTICLE INFO

Article history:
Received 20 May 2015
Received in revised form 31 July 2015
Accepted 3 August 2015
Available online 6 August 2015

Keywords:
Clinical trial
Generalized anxiety disorder
Kundalini yoga
Alternative medicine
Cognitive behavioral therapy
Mindfulness

ABSTRACT

Generalized anxiety disorder (GAD) is a common disorder associated with significant distress and interference. Although cognitive behavioral therapy (CBT) has been shown to be the most effective form of psychotherapy, few patients receive or have access to this intervention. Yoga therapy offers another promising, yet underresearched, intervention that is gaining increasing popularity in the general public, as an anxiety reduction intervention. The purpose of this innovative clinical trial protocol is to investigate the efficacy of a Kundalini Yoga intervention, relative to CBT and a control condition. Kundalini yoga and CBT are compared with each other in a noninferiority test and both treatments are compared to stress education training, an attention control intervention, in superiority tests. The sample will consist of 230 individuals with a primary DSM-5 diagnosis of GAD. This randomized controlled trial will compare yoga (N = 95) to both CBT for GAD (N = 95) and stress education (N = 40), a commonly used control condition. All three treatments will be administered by two instructors in a group format over 12 weekly sessions with four to six patients per group. Groups will be randomized using permuted block randomization, which will be stratified by site. Treatment outcome will be evaluated bi-weekly and at 6 month follow-up. Furthermore, potential mediators of treatment outcome will be investigated. Given the individual and economic burden associated with GAD, identifying accessible alternative behavioral treatments will have substantive public health implications.

1. Introduction

Generalized anxiety disorder (GAD) has been determined to be one of the most ubiquitous anxiety disorders, with one-year prevalence rates ranging from 3% to 8% [1,2]. In light of its prevalence, significantly deleterious impact on life functioning [3,4], and high comorbidity [5–7], the identification and dissemination of efficacious treatments for GAD is imperative. Traditional cognitive behavior therapy (CBT) has received the most empirical support as an efficacious intervention for GAD [8]. Although CBT is a gold-standard treatment for anxiety disorders, it remains inaccessible to many patients. Several barriers deter individuals from undergoing empirically supported psychotherapy, including prohibitively exorbitant costs, the predominance of a face-to-face model of delivery, the paucity of available resources to address increasing mental health needs, etc. [9]. Current circumstances warrant the investigation of alternative treatment strategies to reduce this burden. A promising intervention that has become more widely adopted and accessible is yoga [10,11]. Yoga, practiced in its traditional contemplative practice format, is a multicomponent behavioral practice incorporating physical postures and exercises, breath regulation practices, deep relaxation techniques, and meditation/mindfulness. In fact, a recent survey revealed that 8.9% of the population had used yoga as a therapeutic intervention and that yoga and its component practices of deep breathing and meditation were among the ten most prevalent alternative practices, as evidenced by its rapid adoption in the previous five years [11,12].

Converging evidence underscores the presence of mindfulness deficits among individuals with GAD and other emotional disorders [13,14]. Though several mindfulness based interventions currently exist (e.g., mindfulness based stress reduction (MBSR), mindfulness based cognitive behavioral therapy (MBCT), etc.) [15], difficulties in the dissemination of such treatments undermine their potential to reduce the overall burden of GAD. As yoga comprises several empirically supported components (e.g., meditation, breath regulation, physical exercise, and relaxation techniques) [16–18], it would be profitable to determine the efficacy of yoga in its full form. A thorough investigation of MBSR revealed that yoga exercises accounted for the largest

* Corresponding author.

http://dx.doi.org/10.1016/j.cct.2015.08.003
1551-7144/

contribution to treatment efficacy, despite being applied less than other MBSR components [19].

The therapeutic benefit of CBT and yoga is likely a consequence of differential treatment mechanisms. Extant literature attests to maladaptive cognitions as mediators of treatment change in CBT for anxiety disorders [20]. In virtue of the similarity between yoga and mindfulness based interventions, yoga likely conveys its effect by way of changes in mindfulness [21]. Basic research on yoga and its component techniques suggests it might facilitate reductions in arousal, targeting different mechanisms than does CBT [22–25]. Although there is evidence supporting the efficacy of yoga in reducing anxiety in general [26,27], there are few trials of yoga for GAD, none of which are randomized controlled trials. Of the currently published uncontrolled trials reporting efficacy of yoga for GAD, two employed a yoga breathing intervention [28,29], one employed a yoga mantra practice [30], and one applied an intervention combining CBT and Kundalini yoga practices [31]. The Kundalini yoga study showed statistically significant improvements in state and trait anxiety, depression, panic, sleep and quality of life with strong effect sizes for state and trait anxiety [31,32]. In light of the paucity of high quality clinical trials of yoga for anxiety disorders, methodologically rigorous research undertakings are warranted to extend our current knowledge about the empirical status of yoga for GAD.

This paper describes the procedures and methodology of a five-year, multi-site randomized controlled trial investigating the comparative efficacy of yoga, CBT, and a stress education (SE) intervention, a frequently employed control condition for patients with GAD. The interventions will be administered over the course of twelve weeks. By employing a non-inferiority test of yoga for GAD, the results of this study will inform current literature regarding its utility and efficacy.

This study is funded as a multi-site linked R01 grant R01AT007257 (Hofmann) and R01AT007258 (Simon) by the National Institute of Health/National Center for Complementary and Integrative Health (NCCIH). ClinicalTrials.gov identifier: NCT01912287

2. Materials and methods

2.1. Participants

To satisfy eligibility requirements for the current study, participants must be English fluent outpatients that are 18 years of age or older with a primary psychiatric diagnosis of GAD according to the criteria of the DSM-5. Comorbidity is permitted with other anxiety and depressive disorders, with the exception of concurrent post-traumatic stress disorder, substance use disorders, eating disorders, significant suicidal ideation, or an organic mental disorder. These exclusion criteria extend to individuals with a lifetime history of psychosis, bipolar disorder, or a developmental disorder.

To minimize confounds, participants are required to have limited prior experience with CBT and yoga (i.e., no more than five yoga classes or CBT sessions within the last five years). Though concomitant and prior pharmacotherapy is permitted, participants must undergo appropriate stabilization periods prior to treatment. Please refer to Table 1 for the complete catalogue of inclusion and exclusion criteria.

2.2. Recruitment and screening procedures

Participant recruitment will occur at the Center for Anxiety and Related Disorders at Boston University (CARD) and the Center for Anxiety and Traumatic Stress Disorders (CATSD) at Massachusetts General Hospital (MGH). Recruitment strategies will include advertisements in the media, postings online, particular email services, and clinical referrals from patients presenting at the abovementioned clinics. At CARD and MGH, we will post information on our respective clinic websites and distribute study information through the MGH All-User Broadcast and the RSVP for Health program.

Individuals who contact study personnel in either site will undergo an initial phone screen to determine potential eligibility and interest in research participation. Data for participants who undergo the phone screening process will be de-identified and recorded in the study database phone screening log. Furthermore, we will record reasons for ineligibility and for non-participation of eligible subjects. Interested patients who satisfy eligibility criteria will be scheduled for an evaluation meeting where informed consent will be obtained.

2.3. Study design

The purpose of the proposed randomized controlled trial is to examine the efficacy of yoga for GAD relative to standard psychosocial interventions. Using superiority tests, yoga (N = 95) will be compared to SE (N = 40). Using non-inferiority tests, yoga will compared to standard CBT for GAD (N = 95). All three treatments will be administered by two therapists/yoga instructors/SE instructors in a group format over 12 weekly sessions with 4–6 patients per group. For all interventions, a credible rationale for the efficacy of their assigned treatments,

Table 1
Inclusion and exclusion criteria and rationale.

	Rationale
Inclusion criteria	
Male or female outpatients 18 years of age or older with a primary psychiatric diagnosis of generalized anxiety disorder	Population under study
CGI-severity score of 4 or higher	Adequate pre-treatment severity
Off concurrent psychotropic medication for at least 2 weeks prior to initiation of randomized treatment, OR stable on current medication for a minimum of 6 weeks and willing to maintain a stable dose	Treatment confound
Willingness and ability to perform the yoga intervention and to comply with the requirements of the study protocol.	Human subjects concerns
For women of childbearing potential, willingness to use a reliable form of birth control	Human subjects safety
Exclusion criteria	
Patients unable to understand study procedures and participate in the informed consent process.	Human subjects concern
Pregnancy as assessed by a urine pregnancy test at screen for women of childbearing age	Human Subjects Safety
Women who are planning to become pregnant.	Human Subjects Safety
Serious medical illness or instability for which hospitalization may be likely within the next year	Feasibility, subject safety
Significant current suicidal ideation or suicidal behaviors within the past 6 months (assessed with the BDI-II)	Subject safety
History of head trauma causing loss of consciousness, or seizure disorder resulting in ongoing cognitive impairment	Treatment confound, subject safety
Posttraumatic stress disorder, substance use disorder, eating disorder, or organic mental disorder within the past 6 months	Treatment confound
Lifetime history of psychotic disorder, bipolar disorder, or developmental disorder	Treatment confound
Significant personality dysfunction likely to interfere with study participation (assessed during the clinical interview)	Treatment confound
Prior experience with (more than 5 Yoga classes or CBT sessions within the last 3 years) and/or current practice of mind–body techniques (e.g., yoga, meditation, Tai-Chi, etc) or CBT	Treatment confound
Concomitant psychotherapy for GAD (any psychotherapy)	Treatment confound
Physical conditions that might cause injury from yoga (pregnancy, physical injuries and musculoskeletal problems)	Human subjects concern and subject safety
Cognitive impairment (MOCA ≤ 21)	Human subjects concern and safety

including SE, is provided, with all studies presented equally throughout the study. Various psychological measures will be completed by the participants at each study visit. The four independent evaluator blinded assessments occur pre-treatment (screening visit), mid-treatment (Week 6), post-treatment (Week 12), and at a six-month follow-up. Follow-up visits are scheduled at the termination of treatment to prevent attrition, and further contact is maintained to ensure patients' availability for the follow-up visit.

2.4. Assessment instruments and procedures

All clinician-rated assessments will be undertaken by independent evaluators (IEs) blind to treatment assignment. The IEs will be M.D., Ph.D., or experienced Masters level diagnosticians experienced in the administration of structured clinical interviews who will receive further training and certification for this study under the direction of an IE trainer. Monthly inter-rater reliability checks for the assessments will be undertaken by IEs who did not conduct the initial interview. The ratings will be used to calculate kappa coefficients and to facilitate supervision, during which supervisors will discuss potential disagreement and provide instruction to enhance inter-rater reliability. Please refer to Table 2 for a schedule of assessment instruments.

As depicted in Table 2, the two Clinician Global Impressions Scales measuring symptom severity and symptom improvement (i.e., CGI–S and CGI–I, respectively) will be used for the primary analyses. More specifically, the primary outcome measure is the binary responder status value determined from the CGI–I, with a score of 1 (very much improved) or 2 (much improved) indicating responder status. The self-report measures of state anxiety, depression, worry, and quality of life constitute the secondary outcome measures. For the mediator analyses, we will be investigating whether self-report measures of mindfulness and metacognition andrespiratory sinus arrhythmia, mediate treatment outcome.

2.4.1. Primary outcome measures

Clinical Global Impression of Severity and Improvement (CGI–S, CGI–I; [33]): This two part clinician administered instrument assesses overall level of illness severity and level of symptom change across the course of treatment. The CGI–I ranges from 1 to 7, with scores less than 4 reflecting symptom improvement and scores greater than 4 indicating symptom worsening. A score of 1 (very much improved) or 2 (much improved) defines treatment response.

2.4.2. Secondary outcome measures

State Trait Anxiety Inventory (STAI; [34]): The STAI is a 40-item, multiple-choice questionnaire that differentiates between the temporary condition of "state anxiety" and the more general and long-standing quality of "trait anxiety."

Beck Anxiety Inventory (BAI; [35]): This 21-item self-report inventory designed to measure severity of anxiety symptoms in psychiatric populations has high internal consistency and test–retest reliability.

Beck Depression Inventory—Version II (BDI-II; [36]): The BDI-II contains 21 items that assess severity of depression symptoms in psychiatric populations has high internal consistency and test–retest reliability.

Perceived Stress Scale (PSS; [37]): This 10-item scale is the most widely used psychological instrument for measuring the perception of stress. It is a measure of the degree to which situations in one's life are appraised as stressful.

Quality of Life Scale (WHOQOL-BREF; [38]): This instrument assesses quality of life and overall satisfaction.

Symptom Checklist Version 90 (SCL-90; [39]): The SCL-90 contains 90 items that assess to what degree certain problems and complaints bothered or distressed an individual during the past week.

Penn State Worry Questionnaire (PSWQ; [40]): This instrument contains 15 items that measure trait levels of worry. The PSWQ has excellent psychometric properties in student, community, and clinical samples.

Table 2
Schedule of evaluations.

Form type	Measure	Admin by	Mo. −1 (screen*)	Wk 0 (baseline)	Wks 1–5	Wk 6 (mid Tx)	Wks 7–11	Wk 12–13 (post Tx)	Wk 36–37 (6 mo. FU)	Reference
Diagnosis & screening	Informed consent	IE	X							
	Urine pregnancy test	RA	X							
	SCID/ADIS-5	IE	X							[63,64]
	SIGH-A	IE	X	X		X		X	X	[65]
	Demographics	Self	X							
	Medical review (history and exam)	MD/NP	X							
	MoCA	MD/NP	X							[66]
Primary outcome	CGI–S/CGI–I	IE	X	X	X	X	X	X	X	[33]
Secondary outcomes	STAI	Self		X		X		X	X	[34]
	BAI	Self		X		X		X	X	[35]
	BDI-II	Self		X		X		X	X	[36]
	PSS	Self		X		X		X	X	[37]
	QOL	Self		X		X		X	X	[38]
	SCL-90	Self		X		X		X	X	[39]
	PSWQ	Self		X		X		X	X	[40]
	ISI	Self		X				X		[42]
	PSQI	Self		X				X		[41]
	ASQ	Self		X		X		X	X	[43]
Mediators	MCQ	Self		X		X		X	X	[44]
	FFMQ	Self		X		X		X	X	[13,45]
Psycho-physiological & Biological stress	ECG (RSA)	RA		X		X		X	X	
	Cortisol samples			X		X		X	X	
Tx details	Credibility/expectancy			X		X		X	X	
	Homework compliance				X (weekly)	X	X (weekly)	X	X	
Safety	Adverse events	IE			X (weekly)	X	X (weekly)	X	X	
	Concomitant medications	IE			X (weekly)	X	X (weekly)	X	X	
	Working alliance				X (weekly)	X	X (weekly)	X	X	

Note: IE = independent evaluator; self = self-report; MD/NP = doctor of medicine/nurse practitioner; RA = research assistant; SCID = Structured Clinical Interview for DSM-IV TR Axis I Disorders; ADIS-5 = Anxiety Disorders Interview Schedule-5; CGI–S/CGI–I = Clinical Global Impressions Scale-Severity/Improvement; SIGH-A = Structured Interview Guide for the Hamilton Anxiety Rating Scale; MoCA = Montreal Cognitive Assessment; STAI = State Trait Anxiety Inventory; BAI = Beck Anxiety Inventory; BDI-II = Beck Depression Inventory; PSS = perceived stress scale; QOL = The World Health Organization's quality of life assessment; SCL-90 = Symptom Checklist Version 90 Revised; PSWQ = Penn State Worry Questionnaire; MCQ = Meta-Cognitive Questionnaire; FFMQ = Five Facet Mindfulness Questionnaire; ECG = electrocardiogram.

Pittsburg Sleep Quality Index (PSQI; [41]): This is a 19-item measure of sleep quality over a one month duration. The items make up seven different component scores consisting of sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication and daytime dysfunction. This measure also generates a global sleep quality score.

Insomnia Severity Index (ISI; [42]): This 7-item instrument assesses symptoms of insomnia.

Affective Style Questionnaire (ASQ; [43]): The ASQ contains 20 items that measures individual differences in emotion regulation. This instrument demonstrates good psychometric properties and comprises three subscales: concealing (i.e., habitual attempts to conceal affect), adjusting (i.e., adjusting emotions to be congruent with external goals), and tolerating (i.e., acceptance of emotions).

2.4.3. Mediators

Meta-Cognition Questionnaire (MCQ; [44]): This is a 65-item instrument used to assess meta-cognitive beliefs people have about their thinking styles.

Five Facet Mindfulness Questionnaire (FFMQ; [13,45]): The FFMQ contains 39 items that assess five components of mindfulness, including observing, describing, acting with awareness, non-judging, and non-reacting. This scale has evidenced good psychometric properties and has been validated in clinical and non-clinical samples.

2.5. Treatment interventions

All treatments were matched for time and attention; each treatment entails 120 min of training and practice in group sessions let by two instructors. Participants will receive a credible rationale for the efficacy of their assigned treatment. Participants in the CBT arm will be informed of the role of CBT in the efficacy of changing dysfunctional thought patterns and beliefs, those in the yoga arm will be informed of the role of yoga in changing cognitive and physical emotional and stress reactivity through the postures, breath regulation and meditation components of yoga practice, and those in the SE control will be informed of the role of stress education in understanding the psychophysiological basis of stress and anxiety as a basis for overcoming stress and anxiety. All three interventions are standardized protocols with formalized treatment manuals for consistency.

2.5.1. Cognitive behavioral therapy

The 12 session CBT treatment will occur over the course of 12 sessions and will be derived from the standardized protocol developed at one of our centers (CARD) [46]. This intervention has received empirical support in both individual and group settings [47]. This protocol comprises four primary treatment modules including cognitive restructuring, progressive muscle relaxation, worry exposures, and in vivo exposure exercises. The initial sessions provide psychoeducation, elucidating the cognitive behavioral model of worry and GAD. Each session consists of a different "lesson", which initially teaches basic information about the nature and possible function of the anxiety and worry, the negative consequences of sustained worrying, the maladaptive effects of attempting to suppress one's thoughts, the basic cognitive errors of probability overestimation and catastrophic thinking, and adaptive strategies to successfully deal with worries. In addition, our treatment protocol will target meta-cognitions (i.e., worrying about worrying) [48]. Subjects will also be requested to complete approximately 20 min of homework daily, which will be recorded in a homework log.

2.5.2. Yoga

The yoga intervention will employ Kundalini Yoga as taught by Yogi Bhajan. Dr. Sat Bir Khalsa, one of the co-investigators who will train and supervise the instructors providing the yoga intervention, is a certified Kundalini Yoga instructor and has conducted clinical trials of yoga interventions. Kundalini yoga is a well-known, accessible yoga practice that includes physical postures and exercises, breathing techniques, relaxation exercises, and meditation practices. At study entry, subjects' current physical health, flexibility and endurance will be assessed in the event that adjustments and modifications of the yoga practices need to be made to accommodate subject limitations. This yoga intervention will involve 12 weekly classes administered in group format led by qualified and certified Kundalini Yoga instructors. The weekly intervention itself entails yoga theory, philosophy and psychology, physical postures/exercises, breathing techniques, meditation, and deep relaxation practice, with the weekly group practices varying in content but increasing in intensity throughout the 12-week standardized protocol. Practices will include individual breathing practices (Sitali Breath, Alternate Nostril Breathing, Pauri Kriya), full hour-long Kundalini yoga sets/series (Basic Spinal Energy Series, Calmness and Anti-anxiety Series, Stress Set for Adrenals and Kidneys) and individual yoga meditations with coordinated breathing (Segmented Breath for Anxiety, Tattva Balance Beyond Stress and Duality, Shabd Kriya) (accessible at the website: The Yogi Bhajan Library of Teachings, http://www.libraryofteachings.com/) Daily home practice assigned and instructed during the first treatment session will be facilitated with audio CDs to guide subjects throughout the 12-week intervention. The same home practices will be used throughout in order for subjects to achieve mastery and self-efficacy. The 20-minute home practice session will begin with physical exercises for spinal flexibility and release of tension with coordinated breathing and maintenance of mind-body awareness, as follows: 1) seated spine flexes forward and back (1 min), 2) seated spinal twists (2 min), 3) shoulder shrugs (2 min), 4) neck rolls in both directions (2 min total), and 5) cat–cow spinal flexes on the hands and knees (2 min). These exercises are followed by the "Segmented Breath for Anxiety" involving slow, rhythmic, segmented inhales in 4 parts followed by segmented exhales in 8 parts maintaining a 1:2 ratio between the duration of the inhales and the duration of the exhales for 11 min.

2.5.3. Stress education training

This intervention also entails 12 weeks of group and home practice sessions and will function as a control for attention from instructors, expectancy effects, and group support effects. In this condition, participants will receive extensive information about stress and health, but will not receive any of the active therapeutic ingredients used in CBT, yoga, or other mind–body training techniques. Instead, psychoeducational information will be provided, such as definitions of stress and the stress response, the fight or flight response, physiological and psychological effects of stress, stress and performance, the negative stress cycle, stress and health/illness, stress and immunity, stress buffers, stress hardiness, stress and heart disease, the role of genes and environment in health, the contribution of lifestyle behaviors such as caffeine and alcohol intake and cigarette smoking, and the importance of regular exercise and proper diet (without specific instructions for exercise or dietary changes). For the daily 20 min home practice, subjects will listen to CDs that provide information about nutrition and positive perspectives on lifestyle and emotions.

2.6. Safety protocol

In the service of optimizing safety for participants in the yoga and CBT interventions, we exclude all potential subjects with physical disabilities or cognitive disabilities severe enough to compromise safety or ability to participate in either of the interventions. For reasons of safety, all women of childbearing potential will be required to use a reliable form of birth control throughout the study, as there is insufficient information regarding the safety of yoga during pregnancy. Adverse events will be assessed at each visit by inquiring whether any major change in mental or physical health occurred since the participant's previous visit. Furthermore, the clinical global impression of severity scale

(CGI–S), clinical global impression of improvement (CGI–I), Beck Depression Inventory (BDI-II), and a suicide risk assessment will be administered to evaluate any potential worsening symptoms biweekly from baseline to termination of treatment.

Any participant with a CGI–I of 5 or greater at any time will undergo weekly assessment by a study clinician including clinical and safety assessments, CGI–S and CGI–I ratings, and suicidality assessment. To ensure participants are able to benefit from some form of treatment, we will discontinue participants who endorse 'much worse' (i.e., >5) on the CGI–I for 2 consecutive weeks or who develop significant suicidality at any point. Appropriate referrals will be made to ensure they receive care from certified mental health providers. In addition, if the BDI-II suicidality item (i.e., item number 9) exceeds 1 or the CSS suicide checklist exceeds 2, the patient will be assessed weekly to monitor suicidality and receive any indicated clinical intervention.

2.7. Fidelity monitoring

All of the group intervention sessions will be audio recorded. We will rate 20% of the recordings for adherence and fidelity to ensure that individuals receive the form of treatment appropriate to their assigned group. Failure to satisfy minimum standards (i.e., receives an adherence or competence rating below the certification standard for 2 consecutive sessions (≤5 for adherence, ≤3 for competence)), will be redressed with supplemental training provided by the supervising clinician. Furthermore, the next two sessions will be reviewed to appraise whether they meet certification standards. In the unlikely event therapists do not meet these standards, they will be replaced.

2.8. Data analytic strategy

Randomization will be stratified by site. Treatment groups will be assigned using a permuted block randomization for each site [49]. One block will be generated for each site. Conservatively assuming an average of 4 participants per treatment group, the block will consist of 12 Yoga groups, 12 CBT groups, and 5 SE groups to achieve the appropriate allocation ratio of participants to treatment conditions. We will use the Sealed Envelope program to generate the randomization. After all participants in a potential treatment group have completed their baseline assessment, the study coordinator will inform the study statistician that the next group is ready for randomization, and the statistician will then inform the treatment coordinator of the randomization for that group.

Our primary analyses will use mixed-effects regression models (MRMs) with a logistic linking function, a general linear mixed model (GLMM) analysis, as our primary outcome measure (response to treatment, defined as CGI–I ≤ 2) is dichotomous. Analyses of secondary outcomes will be performed using MRM. MRM and GLMM easily accommodate nesting of repeated observations within subjects, include all subjects with at least one assessment, and are the preferred method to analyze longitudinal data [50]. Since these analyses will include all subjects who are randomized and complete at least one assessment, it is an intent-to-treat analysis. Also, since subjects will undergo treatment in groups, our MRM and GLMM models will include 3 levels: repeated measurements (level 1) nested within subjects (level 2) who will be nested within their treatment cohort (level 3).

The three treatment conditions (yoga, CBT, and SE) will be coded using 2 dummy variable contrasts, with SE as the "reference" treatment. The first dummy variable will contrast yoga vs. SE, and the second will contrast CBT to SE. Time will be centered at week 12 and coded as weeks since baseline. In MRM or GLMM analyses in which this Time centered variable is used, the significance of the dummy variable contrasts (yoga vs. SE and CBT vs. SE) provides the test of the differences between these treatment conditions at post-treatment. A similar approach can be used to test differences between treatment conditions at follow-up.

The mediation analysis includes 2 independent variables (i.e., the contrast of yoga vs. SE and the contrast of CBT vs. SE) and 3 mediators: mindfulness, vagal tone, and maladaptive cognitions. The 3 mediators will be included in the growth curve model as additional simultaneous predictors of response. Significance of mediated pathways will be determined using bias-corrected bootstrap mediation analysis [51]. We predict that changes in mindfulness will mediate changes in outcome over time for patients in the yoga condition, and changes in cognitions will mediate changes in CBT. Plus, changes in RSA and cortisol may also mediate changes in outcome across conditions.

To address missing data, we will use pattern mixture modeling [52,53] and re-conduct the analyses to identify potential missing data patterns (e.g., no missing data, early dropouts, late dropouts, FU dropouts, etc.) and determine whether missingness influences our findings.

2.9. Sample size

The sample will consist of 230 patients with a primary DSM-5 diagnosis of GAD. We will compare yoga (N = 95) to both CBT for GAD (N = 95) and stress education (SE) (N = 40), a commonly used attention control condition [54]. To directly appraise our hypothesis that yoga will have comparable short-term and long-term efficacy with that of CBT, we will adopt a non-inferiority test framework for the primary outcome, which is the binary responder status value determined from the CGI–I, with a score equal to or less than 2 indicating responder status. To address potential attrition, we will conduct an intent-to-treat analysis. The non-inferiority margin will be half the difference in response rates between the active comparison (CBT) and control condition. In accord with prior literature, we estimated response rates for our particular interventions (i.e. 57.9% in CBT and 22.2% in control). Thus, our non-inferiority margin will be set at half the difference between 57.9 and 22.2, or 17.85%. Using the power analysis program PASS 12 [55], we determined that the number of subjects required to obtain .80 power for the non-inferiority test comparing CBT and yoga is 95 participants in each of the 2 conditions.

For the superiority tests on responder status (a greater proportion of participants will respond to treatment in CBT and in Yoga than in SE), we will use GLMM with a logistic linking function. We performed various Monte Carlo simulations to determine the smallest percentage difference between the treatments and the control group that we could detect with .80 power. Assuming a sample size of 230 and 25% missing data, we found that we could detect a difference in response rate as little as 22% between the treatments and the control (e.g., if the control response rate was 22.2%, we have .80 power to detect a significant difference between either treatment condition and the control condition if the treatment condition response rate is 44.2% or higher). This difference is equivalent to an effect size of $\omega = .24$, smaller than a medium effect size (a medium effect size for proportions is $\omega = .30$, and a small effect size is $\omega = .10$).

For the superiority tests (CBT vs. SE and Yoga vs. SE) on the secondary outcomes (which are the continuous self-report measures presented in Table 2), we used the mixed-effects regression models (MRM) power analysis program PinT 2.12 [56]. We assumed 25% missing data, and used data from our recent CBT trials [57] to estimate the variances and covariances needed for PinT. PinT indicated greater than .80 power to detect an effect size as small as $d = 0.27$, between a small ($d = 0.20$) and medium ($d = 0.50$) effect size.

3. Discussion

The study will examine the efficacy of Kundalini Yoga for GAD as compared to CBT and a psychological attention control condition. Extant literature suggests that CBT conveys its therapeutic effect, in part, through modification of maladaptive cognitions [20]. Yoga entails the cultivation of physical and psychological health through a variety of techniques including physical posture exercises, breathing exercises,

relaxation strategies, and meditation practice. As mindfulness based interventions comprise several of these components [58], we hypothesize that increases in mindfulness will function as a core treatment mechanism in yoga. Furthermore, we are evaluating the presence of biological mechanisms in yoga, namely vagal tone. The chief pathological process underling GAD is worry. Several studies have established that excessive worry entails reduced autonomic flexibility as a result of low cardiac vagal tone [59,60]. Assessment of this biomarker is accomplished by recording respiratory sinus arrhythmia, which reflects rhythmic variations in heart rate that occur at the frequency of respiration. Because yoga exercises emphasize breathing techniques, we predict that symptom improvement will also be a consequence of changes in vagal tone. By ascertaining the chief mechanisms responsible for treatment efficacy, the results of the current study can facilitate the development of more parsimonious, effective treatments for GAD.

Adopting a randomized controlled trial design provides a stringent experimental framework to examine our hypotheses. Moreover, the data analytic and methodological strategies used in the current study include prospective efforts to address potential limitations related to attrition. To retain sufficient power for group comparisons, our initial sample size was estimated under the assumption of 25% missing data, and our complementary use of mixed-effects regression models and pattern mixture modeling will foster greater confidence in the validity of our results. Certain limitations do warrant mention, however. It would be desirable to assess our proposed mechanisms more frequently, which would provide a more robust test of mediation. As these variables are measured at pre-, mid-, and post-treatment, the current study might be unable to discern whether changes in the mediator variables precede improvement in symptoms [61]. Though our mediational hypotheses represent only a secondary aim, we recommend that future research measure mediator variables at more frequent time points to better establish temporal precedence.

Although there are several empirically supported behavioral and pharmacological interventions that ameliorate symptoms of GAD [62], there may be a distinct opportunity to contribute to the provision of care by exploring alternative treatments. Given the great deal of overlap between yoga and other empirically supported interventions (i.e., mindfulness based interventions), there may be potential for yoga to have a substantive impact on the clinical and economic burden posed by GAD. The current research endeavor represents an innovative effort to address clinically and scientifically relevant questions related to the treatment of GAD. In addition, it will provide a rigorous test of the efficacy of yoga for a prevalent mental health condition.

Conflict of interest

Dr. Hofmann receives compensation for his work as an advisor from the Palo Alto Health Sciences and Otsuka America Pharmaceutical, Inc., and for his work as a Subject Matter Expert from John Wiley & Sons, Inc. and SilverCloud Health, Inc. He also receives royalties and payments for his editorial work from various publishers. Dr. Khalsa is a paid consultant for three nonprofit yoga organizations and is engaged in the practice and promotion of yoga. Dr. Simon receives compensation for her work as a consultant for Pfizer Pharmaceuticals and Massachusetts General Hospital Psychiatry Academy. Dr. Hoge, Dr. Bui, Dr. Rosenfield, Ms. Keshaviah, and Mr. Curtiss do not report any potential conflict of interest.

References

[1] B.J. Sadock, V.A. Sadock, Kaplan and Sadock's Synopsis of Psychiatry: Behavioral Sciences/clinical Psychiatry, Lippincott Williams & Wilkins, 2011.
[2] R.C. Kessler, P. Berglund, O. Demler, R. Jin, K.R. Merikangas, E.E. Walters, Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication, Arch. Gen. Psychiatry 62 (2005) 593–602.
[3] J. Ormel, M. VonKorff, T.B. Ustun, S. Pini, A. Korten, T. Oldehinkel, Common mental disorders and disability across cultures: results from the WHO Collaborative Study on Psychological Problems in General Health Care, JAMA 272 (1994) 1741–1748.
[4] W.H. Schonfeld, C.J. Verboncoeur, S.K. Fifer, R.C. Lipschutz, D.P. Lubeck, D.P. Buesching, The functioning and well-being of patients with unrecognized anxiety disorders and major depressive disorder, J. Affect. Disord. 43 (1997) 105–119.
[5] O. Brawman-Mintzer, N. Emmanuel, M.P. Jarrell, J.C. Ballenger, Psychiatric comorbidity in patients with generalized anxiety disorder, Am. J. Psychiatry 2 (1993) 4.
[6] T.A. Brown, D.H. Barlow, M.R. Liebowitz, The empirical basis of generalized anxiety disorder, Am. J. Psychiatry 151 (1994) 1272–1280.
[7] T.A. Brown, L.A. Campbell, C.L. Lehman, J.R. Grisham, R.B. Mancill, Current and lifetime comorbidity of the DSM-IV anxiety and mood disorders in a large clinical sample, J. Abnorm. Psychol. 110 (2001) 585.
[8] S.G. Hofmann, J.A. Smits, Cognitive-behavioral therapy for adult anxiety disorders: a meta-analysis of randomized placebo-controlled trials, J. Clin. Psychiatry 69 (2008) 621.
[9] A.E. Kazdin, S.L. Blase, Rebooting psychotherapy research and practice to reduce the burden of mental illness, Perspect. Psychol. Sci. 6 (2011) 21–37.
[10] B. Tsui, Yoga magazine gets boost from spirituality surge, Advert. Age 71 (2000) 20.
[11] T.C. Clarke, L.I. Black, B.J. Stussman, P.M. Barnes, R.L. Nahin, Trends in the use of complementary health approaches among adults: United States, 2002–2012, National health statistics reports 2015, pp. 1–16.
[12] P.M. Barnes, B. Bloom, R.L. Nahin, Statistics NCfH, Complementary and Alternative Medicine Use among Adults and Children: United States, 2007, US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, Hyattsville, MD, 2008.
[13] J. Curtiss, D.H. Klemanski, Factor analysis of the five facet mindfulness questionnaire in a heterogeneous clinical sample, J. Psychopathol. Behav. 36 (2014) 683–694.
[14] J. Curtiss, D.H. Klemanski, Teasing apart low mindfulness: Differentiating deficits in mindfulness and in psychological flexibility in predicting symptoms of generalized anxiety disorder and depression, J. Affect. Disord. 166 (2014) 41–47.
[15] J.D. Herbert, E.M. Forman, Acceptance and Mindfulness in Cognitive Behavior Therapy: Understanding and Applying the New Therapies, John Wiley & Sons, 2011.
[16] G.L. Stonerock, B.M. Hoffman, P.J. Smith, J.A. Blumenthal, Exercise as treatment for anxiety: systematic review and analysis, Ann. Behav. Med. (2015) 1–15.
[17] R.P. Brown, P.L. Gerbarg, F. Muench, Breathing practices for treatment of psychiatric and stress-related medical conditions, Psychiatr. Clin. N. Am. 36 (2013) 121–140.
[18] G.M. Manzoni, F. Pagnini, G. Castelnuovo, E. Molinari, Relaxation training for anxiety: a ten-years systematic review with meta-analysis, BMC Psychiatry 8 (2008) 41.
[19] J. Carmody, R.A. Baer, Relationships between mindfulness practice and levels of mindfulness, medical and psychological symptoms and well-being in a mindfulness-based stress reduction program, J. Behav. Med. 31 (2008) 23–33.
[20] S.G. Hofmann, Cognitive mediation of treatment change in social phobia, J. Consult. Clin. Psychol. 72 (2004) 392.
[21] T. Gard, N. Brach, B.K. Hölzel, J.J. Noggle, L.A. Conboy, S.W. Lazar, Effects of a yoga-based intervention for young adults on quality of life and perceived stress: the potential mediating roles of mindfulness and self-compassion, J. Posit. Psychol. 7 (2012) 165–175.
[22] O. Bhatnagar, A. Ganguly, V. Anantharaman, Influence of Yoga training on thermoregulation, Indian J. Med. Res. 67 (1978) 844.
[23] M. Gharote, A psychophysiological study of the effects of short-term yogic training on adolescent high school boys, Yoga Mimamsa 11 (1971) 92–99.
[24] S. Joseph, K. Sridharan, S. Patil, M. Kumaria, W. Selvamurthy, N. Joseph, et al., Study of some physiological and biochemical parameters in subjects undergoing yogic training, Indian J. Med. Res. 74 (1981) 120.
[25] U. Ray, S. Mukhopadhyaya, S. Purkayastha, V. Asnani, O. Tomer, R. Prashad, et al., Effect of yogic exercises on physical and mental health of young fellowship course trainees, Indian J. Physiol. Pharmacol. 45 (2001) 37.
[26] A.W. Li, C. Goldsmith, The effects of yoga on anxiety and stress, Altern. Med. Rev. 17 (2012) 21–35.
[27] N. Chugh-Gupta, F. Baldassarre, B. Vrkljan, A systematic review of yoga for state anxiety: considerations for occupational therapy, Rev. Can. Ergo. 80 (2013) 150–170.
[28] S. Doria, A. de Vuono, R. Sanlorenzo, F. Irtelli, C. Mencacci, Anti-anxiety efficacy of Sudarshan Kriya yoga in general anxiety disorder: A multicomponent, yoga based, breath intervention program for patients suffering from generalized anxiety disorder with or without comorbidities, J. Affect. Disord. 184 (2015) 310–317.
[29] M.A. Katzman, M. Vermani, P.L. Gerbarg, R.P. Brown, C. Iorio, M. Davis, et al., A multicomponent yoga-based, breath intervention program as an adjunctive treatment in patients suffering from generalized anxiety disorder with or without comorbidities, Int. J. Yoga 5 (2012) 57.
[30] V. Dhansoia, H. Bhargav, K. Metri, Immediate effect of mind sound resonance technique on state anxiety and cognitive functions in patients suffering from generalized anxiety disorder: A self-controlled pilot study, Int. J. Yoga 8 (2015) 70.
[31] M.K. Khalsa, J.M. Greiner-Ferris, S.G. Hofmann, S.B.S. Khalsa, Yoga-enhanced cognitive behavioural therapy (Y-CBT) for anxiety management: a pilot study, Clin. Psychol. Psychother. 22 (2014) 364–371.
[32] S.A. Saeed, D.J. Antonacci, R.M. Bloch, Exercise, yoga, and meditation for depressive and anxiety disorders, Am. Fam. Physician 81 (2010) 981–986.
[33] M. Berk, F. Ng, S. Dodd, T. Callaly, S. Campbell, M. Bernardo, et al., The validity of the CGI severity and improvement scales as measures of clinical effectiveness suitable for routine clinical use, J. Eval. Clin. Pract. 14 (2008) 979–983.
[34] C.D. Spielberger, R.L. Gorsuch, R.E. Lushene, State-trait anxiety inventory, Consulting Psychologists Press, Palo Alto. Cal, 1970.
[35] A.T. Beck, N. Epstein, G. Brown, R.A. Steer, An inventory for measuring clinical anxiety: psychometric properties, J. Consult. Clin. Psychol. 56 (1988) 893.

[36] A.T. Beck, R.A. Steer, G.K. Brown, Beck Depression Inventory-II, Psychological Corporation, San Antonio. Tx, 1996.
[37] S. Cohen, T. Kamarck, R. Mermelstein, A global measure of perceived stress, J. Health Soc. Behav. 28 (1983) 385–396.
[38] H. Herrman, H. Schofield, B. Murphy, Z. Metelko, S. Szabo, M. Pibernik-Okanovic, et al., Development of the World Health Organization WHOQOL-BREF quality of life assessment, Psychol. Med. 28 (1998) 551–558.
[39] L.R. Derogatis, SCL-90-R: Administration, Scoring and Procedures Manual for the R (evised) Version and Other Instruments of the Psychopathology Rating Scale Series, Clinical Psychometric Research, 1992.
[40] T.J. Meyer, M.L. Miller, R.L. Metzger, T.D. Borkovec, Development and validation of the penn state worry questionnaire, Behav. Res. Ther. 28 (1990) 487–495.
[41] D.J. Buysse, C.F. Reynolds, T.H. Monk, S.R. Berman, D.J. Kupfer, The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research, Psychiatry Res. 28 (1989) 193–213.
[42] C.H. Bastien, A. Vallières, C.M. Morin, Validation of the Insomnia Severity Index as an outcome measure for insomnia research, Sleep Med. 2 (2001) 297–307.
[43] S.G. Hofmann, T.B. Kashdan, The affective style questionnaire: development and psychometric properties, J. Psychopathol. Behav. 32 (2010) 255–263.
[44] M.M. Spada, C. Mohiyeddini, A. Wells, Measuring metacognitions associated with emotional distress: Factor structure and predictive validity of the metacognitions questionnaire 30, Personal. Individ. Differ. 45 (2008) 238–242.
[45] R.A. Baer, G.T. Smith, J. Hopkins, J. Krietemeyer, L. Toney, Using self-report assessment methods to explore facets of mindfulness, Assessment 13 (2006) 27–45.
[46] R.E. Zinbarg, M. Craske, D.H. Barlow, Mastery of Your Anxiety and Worry: Therapist Guide, 2nd ed. Oxford University Press, New York, NY, 2006.
[47] R.J. DeRubeis, P. Crits-Christoph, Empirically supported individual and group psychological treatments for adult mental disorders, J. Consult. Clin. Psychol. 66 (1998) 37–52.
[48] A. Wells, Metacognitive Therapy for Anxiety and Depression, Guilford press, 2011.
[49] J. Efird, Blocked randomization with randomly selected block sizes, Int. J. Environ. Res. Public Health 8 (2010) 15–20.
[50] R.M. Hamer, P.M. Simpson, Last observation carried forward versus mixed models in the analysis of psychiatric clinical trials, Am. J. Psychiatry 166 (2009) 639–641.
[51] M.S. Fritz, D.P. MacKinnon, Required sample size to detect the mediated effect, Psychol. Sci. 18 (2007) 233–239.
[52] D. Hedeker, R.D. Gibbons, Longitudinal Data Analysis, John Wiley & Sons, 2006.
[53] C.K. Enders, Missing not at random models for latent growth curve analyses, Psychol. Methods 16 (2011) 1.
[54] E.A. Hoge, E. Bui, L. Marques, C.A. Metcalf, L.K. Morris, D.J. Robinaugh, et al., Randomized controlled trial of mindfulness meditation for generalized anxiety disorder: effects on anxiety and stress reactivity, J. Clin. Psychiatry 74 (2013) 786.
[55] J. Hintze, PASS 12, NCSS, LLC, Kaysville: Utah, USA, 2013.
[56] T.A. Snijders, Power and sample size in multilevel linear models, Encyclopedia of statistics in behavioral science2005.
[57] J.R. Stern, S.B.S. Khalsa, S.G. Hofmann, A yoga intervention for music performance anxiety in conservatory students, Med. Probl. Perform. Art. 27 (2012) 123.
[58] J. Kabat-Zinn, Full Catastrophe Living: Using the Wisdom of Your Body and Mind to Face Stress. Pain, and Illness, 2008.
[59] S.G. Hofmann, D.A. Moscovitch, B.T. Litz, H.-J. Kim, L.L. Davis, D.A. Pizzagalli, The worried mind: Autonomic and prefrontal activation during worrying, Emotion 5 (2005) 464.
[60] S.G. Hofmann, S.M. Schulz, S. Heering, F. Muench, L.F. Bufka, Psychophysiological correlates of generalized anxiety disorder with or without comorbid depression, Int. J. Psychophysiol. 78 (2010) 35–41.
[61] A.E. Kazdin, Mediators and mechanisms of change in psychotherapy research, Annu. Rev. Clin. Psychol. 3 (2007) 1–27.
[62] K. Mitte, Meta-analysis of cognitive-behavioral treatments for generalized anxiety disorder: a comparison with pharmacotherapy, Psychol. Bull. 131 (2005) 785.
[63] M.B. First, R.L. Spitzer, Miriam Gibbon, Janet B.W. Williams, Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition with Psychotic Screen (SCID-I/PW/PSY SCREEN), Biometrics Research, New York State Psychiatric Institute, New York, 2002.
[64] T.A. Brown, D.H. Barlow, Anxiety and Related Disorders Interview Schedule for DSM-5 (ADIS-5 L): Lifetime Version, Client Interview Schedule, Oxford University Press, 2014.
[65] M.K. Shear, J. Vander Bilt, P. Rucci, J. Endicott, B. Lydiard, M.W. Otto, et al., Reliability and validity of a structured interview guide for the Hamilton Anxiety Rating Scale (SIGH-A), Depress. Anxiety 13 (2001) 166–178.
[66] Z.S. Nasreddine, N.A. Phillips, V. Bédirian, S. Charbonneau, V. Whitehead, I. Collin, et al., The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment, J. Am. Geriatr. Soc. 53 (2005) 695–699.