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Randomized Controlled Trial of Mindfulness Meditation for Generalized Anxiety Disorder: Effects on Anxiety and Stress Reactivity

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Abstract

Objective—Mindfulness meditation has met increasing interest as a therapeutic strategy for anxiety disorders, but prior studies have been limited by methodological concerns, including a lack of an active comparison group. This is the first randomized, controlled trial comparing the manualized Mindfulness-Based Stress Reduction (MBSR) program with an active control for Generalized Anxiety Disorder, a disorder characterized by chronic worry and physiological hyperarousal symptoms.

Method—Ninety-three individuals with DSM-IV-diagnosed GAD were randomized to an 8-week group intervention with MBSR or to an attention control, Stress Management Education (SME) between 2009 and 2011. Anxiety symptoms were measured with the Hamilton Anxiety Scale (HAM-A, primary outcome measure), the Clinical Global Impression of Severity and Improvement (CGI-S and CGI-I), and the Beck Anxiety Inventory (BAI). Stress reactivity was assessed by comparing anxiety and distress during pre- and post-treatment Trier Social Stress Tests (TSST).

Results—A modified intent-to-treat analysis including participants who completed at least one session of MBSR (N=48) or SME (N=41) showed that both interventions led to significant reductions in HAM-A scores at endpoint, but did not significantly differ. MBSR, however, was associated with a significantly greater reduction in anxiety as measured by the CGI-S, the CGI-I, and the BAI (all *P*s<0.05). MBSR was also associated with greater reductions than SME in anxiety and distress ratings in response to the TSST stress challenge (*P*<0.05), and a greater increase in positive self-statements (*P*=0.004).

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Conclusions—These results suggest that MBSR may have a beneficial effect on anxiety symptoms in GAD, and may also improve stress reactivity and coping as measured in a laboratory stress challenge.

Keywords

Mindfulness Based Stress Reduction; Mindfulness Meditation; Generalized Anxiety Disorder; Meditation; Anxiety; Stress Reactivity

I. Introduction

Generalized Anxiety Disorder (GAD), characterized by worry that is difficult to control, and symptoms such as poor sleep, muscle tension, and irritability, is relatively common, with a lifetime prevalence rate of 5.7%.[1]While pharmacotherapy and psychotherapy are common treatment strategies, 30 to 60% of patients do not achieve remission after treatment.[2-6]In one early naturalistic study of 164 patients with GAD predominantlytreated with pharmacotherapy,remission was as low as 15%.[7]Further, individuals with GAD may not seek care in psychiatric settings due to perceived stigma.

Recently, mindfulness-based interventions have been of increasing interest as a cost-effective, low-stigma, accessible treatment option for a variety of psychological and medical symptoms, including anxiety.[8]Mindfulness training teaches participants meditation techniques that increase awareness of present-moment experiences, including thoughts, emotions, and bodily sensations, with a gentle and accepting attitude towards oneself.[9] Roemer et al[10]found that patients with GAD have lower levels of trait mindfulness and more difficulties with emotion regulation than healthy controls and suggested that mindfulness training may be helpful.

Although several studies have examined the effect of mindfulness meditation on GAD, most are small or lack an attention control group to control for non-specific effects of treatment, such as group support effects, expectancy bias, and attention from an instructor or experimenter. Early research by Kabat-Zinn et al[11] found a decrease in anxiety symptoms after Mindfulness-Based Stress Reduction (MBSR) in patients with GAD, although there was no comparison group. Vollestad et al[12] used MBSR with Panic Disorder, GAD, and Social Anxiety Disorder, but utilized a wait-list comparison group that could not control for expectancy and attention effects. Mindfulness has also been combined with cognitive therapy in Mindfulness-Based Cognitive Therapy (MBCT) treatment,[13, 14]however, since cognitive therapy alone has been shown to decrease anxiety in some studies, the combination of mindfulness meditation training and cognitive therapy makes it difficult to ascertain the proportion of effect due to each strategy.

Although a recent meta-analysis found a moderate effect size for mindfulness-based interventions for anxiety,[8]other reviews and meta-analyses have noted significant deficits in methodology in meditation studies including a Cochrane review cautioning implementation prior to more randomized, controlled data confirming efficacy.[15-18]To our knowledge, this is the first randomized, controlled trial (RCT) of mindfulness meditation without added cognitive therapy, compared to an active control condition (incorporating elements of group treatment including attention from instructor, group support, education, but not meditation training) for GAD.

In addition, we assessed the effect of meditation training on stress reactivity by employing a laboratory stress task, the Trier Social Stress Test (TSST). We hypothesized that MBSR

training would result in greater reduction in anxiety symptoms and greater reduction in stress reactivity to the TSST than SME.

II. Method

A. Participants

Participants were recruited by referral and media advertisement between December 2008 and February 2011 for a study on "Stress Reduction." After telephone screening, outpatients who completed the informed consent process received the Structured Clinical Interview for the DSM-IV (SCID)[19]administered by a trained graduate or higher level psychologist or psychiatrist independent evaluator (IE) at the Center for Anxiety and Traumatic Stress Disorders at Massachusetts General Hospital (MGH). Training in the use the SCID was done using co-rated recorded and live interviews until a diagnostic concordance of 100% was reached. Individuals age 18 or older were eligible if they: (a) met DSM-IV criteria for current primary GAD and designated GAD as the primary problem, and (b) scored 20 or above on the Hamilton Anxiety scale (HAM-A).[20]

Exclusion criteria included: (1) a lifetime history of schizophrenia or any other psychosis, mental retardation, organic medical disorders, bipolar disorder, post-traumatic stress disorderor obsessive compulsive disorder, (2) alcohol or substance abuse or dependence within the past 6 months, (3) significant suicidal ideation or behaviors within past 6 months, (4)if on medication, on a stable dose for less than 4 weeks, orunwilling to remain on thatdose throughout the study, (5) serious medical illness or instability, (6) concurrent psychotherapy directed toward GAD, (7) more than 4 classesof meditation training and practice (including yoga and tai-chi) in the past 2 years; (8) pregnancy or lactation, and (9) significant personality disorder likely to interfere with study participation. A CONSORT flowchart provides information about participants (see Figure 1), and Table 1 provides descriptive information on the study sample.

B. Measures

1. Anxiety Symptoms—Symptoms of anxiety were assessed at baseline and week 8 (endpoint) with the Structured Interview Guide for the HAM-A (SIGH-A), an adaptation of the 14-item HAM-A designed to standardize clinician assessment;[20]the Clinical Global Impression of Severity (CGI-S) and of Improvement(CGI-I).[21]Self-reported anxiety was measured with the 21-item Beck Anxiety Inventory.[22]Sleep was assessed at baseline and endpoint with the 24-item self-report Pittsburgh Sleep Quality Index (PSQI).[23]IEs, blinded to treatment assignment, completed the assessments.

2. Ratings used during TSST—Anxiety during the stress task was assessed with the "state anxiety" section of the State-Trait Anxiety Inventory (STAI), a widely used 40-item, multiple-choice questionnaire.[24]The Subjective Units of Distress Scale (SUDS) assessed overall distress during the task; this widely used, highly reliable single-item question measures the intensity of current distress on a scale from 0 to 100.[25,26-28]

To assess the participants'evaluation of their speech, we used the 10-item self-report Self-Statements during Public Speaking scale (SSPS), which consists of two 5-item subscales, the "Positive Self-Statements" (SSPS-P, e.g. "I can handle everything") and the "Negative Self-Statements" subscale (SSPS-N, e.g. "I'll probably 'bomb out' anyway"). Subjects rated their agreement with several statements about their performance to measure negative and positive self-perceptions and perceived negative or positive evaluation by others.[29]

C. Procedure

Study procedures were approved by the MGH institutional review board. All diagnostic screens and baseline clinician ratings, self-report questionnaires, and TSST's were completed before treatment initiation. Patients underwent group randomization to either MBSR or the Stress Management Education. To prevent loss of IE blinding, participants were instructed not to discuss any details about their class with the evaluators.

Trier Social Stress Test—Participants arrived between 1 and 3pm for the TSST. The TSST has been well described elsewhere;[30]in summary, it consists of an 8-minute public speaking task and a subsequent 5-minute mental arithmetic task (serial subtraction) performed in front of a panel of two strangers dressed in white lab coats and holding clipboards, introduced as "the evaluators," and a large conspicuous video camera. The TSST procedure followed a detailed script to ensure its systematic and controlled delivery.

Because the TSST was administered before and at the end of the trial, several measures were taken to lower the potential for stress habituation and to improve methodological rigor for the second TSST: 1) the evaluators were switched so that they would be strangers, 2) the TSST was moved to a different room, 3) a different arithmetic task was employed to avoid practice effects and 4) participants were told that their performance on the first speech was in the low range, and that this was their chance to improve their score (method used by T.D. Pace, PhD, personal communication, oral, 4-27-2012).

D. Interventions

1. Mindfulness-Based Stress Reduction (MBSR)—The MBSR program has been described previously.[11]Briefly, this intervention is comprised of 8 weekly group classes with a single weekend "retreat" day, and daily home practice guided by audio recordings. In-class practices (breath-awareness, a body-scan, and gentle Hatha yoga) are used to cultivate awareness of internal present-moment experiences with an accepting, non-judgmental stance. For example, breath-awareness practice starts with the awareness of the sensations of breathing, then expands to other body sensations, thoughts and emotions, all of which are treated with acceptance and non-judgment, and are allowed to "pass by" in order to return mental focus to the breath. The Body-Scan exercise guides the attention sequentially through the body, focusing on sensations of each area, and the yoga practices contain gentle stretching and slow movements, focusing on present experience and treating the body kindly. Participants were also instructed in "informal" home mindfulness practice (e.g. present-focused awareness during eating, bathing, or cleaning).

For this protocol, some small adjustments were made to improve adherence and practicality: classes were shortened from 2.5 to 2 hours, the day-long retreat to 4 hours, and the homework from 45 to 20 minutes. In addition, *metta* (loving-kindness) was introduced in the first class, and a *metta* CD for home practice was included. The class was taught by an MBSR instructor with over 8 years of experience.

2. Stress Management Education—The SME course was designed as an active control, for comparison with MBSR, and did not contain any mindfulness components. It alsoconsisted of an 8-week two-hour class, with 20 minute homework exercises, and a 4-hour weekend "Special Class", such that the total number of minutes of both class and home activities were exactly matched with MBSR. The SME course was taught in a didactic format, covering topics relevant to stress, stress physiology, effect of stress on body systems, time management techniques, sleep physiology, insomnia, optimal nutrition, effects of stress on diet, caffeine, exercise, stress hardiness, and factors that can buffer the impact of stress, such as humor, altruism, and volunteering. The course content was based on the control

condition used by Dusek et al[31] but delivered in a group lecture format. To more closely match the yoga portion of MBSR, SME included gentle strength and posture exercises with a physical therapist for the same number of total minutes. Extra resistance bands were provided forassigned home exercises. There was no aerobic exercise in the course.

The weekend Special Class included stability ball exercise instruction, a lecture on functional movement and individual postural assessments with a fitness instructor, a short massage, and a lecture from a licensed dietician. Similar to the MBSR class, participants in SME were provided 20 minute audio book recordings to listen to at home (same total number of minutes). The SME class was taught by an instructor with 9 years of experience in providing health and wellness courses in a hospital-based clinic to groups of patients with physical health conditions, and a physical therapist with 22 years of experience.

All the MBSR and SME classes were audiotaped, and 20% of the classes randomly reviewed by one of the authors not involved in assessments (EAH) for content, using a classes' weekly content checklist to assess fidelity.

E. Statistical Analysis

Data analysis was performed using STATA version 11.1 (College Station, Texas).Analyses were conducted for a modified intent-to-treat (ITT) sampledefined as all participants who had at least one treatment session (n=48, MBSR vs. n=41, SME), with last observation carried forward (LOCF). The HAM-A was defined a priori as the primary and the CGI-Sas the secondary outcome variable. A mean imputation method for measures with 15% or less missing items was employed.

Demographic data were examined using independent samples t-tests, and Fisher's exact tests for dichotomous variables. Independent samples t-tests and repeated measure ANOVAs were employed to compare changes in clinical symptoms and other psychometric ratings. Primary univariate analyses consisted of t-tests for continuous outcome variables (i.e. HAM-A, BAI and PSQI scores) and Fisher's exact test for binary variables (responder status). The level of statistical significance was set to 0.05 (two-tailed).

III. Results

A. Study Population

The 89 subjects who enrolled in the study and attended at least one class were included in the modified ITT analysis. Socio-demographic and clinical characteristics are reported in Table 1. Three participants in the SME group discontinued before any treatment, and one was removed due to later discovery of lack of eligibility. BAI scores were not available for the first 7 participants, and the CGI-S score was missing for one subject.Adverse events were 2% for MBSR (n=1, "muscle soreness") and 2% for SME (n=1, "sleep disruption").

B. Anxiety Symptom Outcomes

A repeated measure analysis of variance (ANOVA), with time (baseline and endpoint) as the repeated measure, treatment arm as between-subjects factor and HAM-A score as the dependent variable was significant ($F(1, 87)=2.86$, $P<0.001$). The analyses revealed a main effect of time, $F(1,87)=66.93$, $P<0.001$ but no significant treatment arm × time interaction, $F(1,87)=1.38$, $P=0.244$. To further examine the main effect of time, we conducted two dependent samples t-test examining changes from baseline to endpoint within the MBSR and SME group (see table 2).HAM-A scores decreased significantly for both groups (see Table 2).

A repeated measure ANOVA, with time (baseline and endpoint) as the repeated measure, treatment arm as between-subjects factor and BAI score as the dependent variable, found a main effect of time, $F(1,79)=28.52$, $P<0.001$ and a significant treatment arm × time interaction, $F(1,79)=4.31$, $P=0.041$. Mean BAI scores decreased for the MBSR group and for the SME group but showed a significantly greater decrease in the MBSR group. Similarly, a repeated measure ANOVA, with time as the repeated measure, treatment arm as between-subjects factor and CGI-S score as the dependent variable, found a main effect of time ($F(1,84)=62.19$, $P<0.001$) and a significant treatment arm × time interaction ($F(1,84)=4.51$, $P=0.0366$). Change scores for symptom measuresappear in Figure 2.

Responder status was defined as a CGI-I of 1 (“Very Much Improved”) or 2 (“Much Improved”) at endpoint. Response rate was greater for MBSR (29/44; 66%) than for SME (14/35; 40%); ($P=0.025$). The risk ratio for response to MBSR was 1.65 (95% CI, 1.04-2.60) and the number needed to treat was 3.9 (95% CI, 2.23-26.19).

Sleep Quality—Because the allowed psychiatric medications (SSRIs and benzodiazepines) affect sleep and can potentially obscure treatment-related effects, the measurement of sleep changes was restricted to participants not taking psychiatric medications (N=61).A repeated measure ANOVA, with time (baseline and endpoint) as the repeated measure, treatment arm as between-subjects factor and PSQI score as the dependent variable found a main effect of time ($F(1,59)=24.55$, $P<0.001$) and a significant treatment arm × time interaction ($F(1,59)=4.69$, $P=0.035$). AlthoughPSQI scoresimproved from baseline to endpointin both treatment groups, the MBSR group had a greater reduction (mean change score(SD) for MBSR=2.6(3.6), SME=1.0(1.9).

C. Stress Reactivity

Ratings of distress, anxiety, and self-judgment were assessed during each of the two TSST’s and the changes compared between groups as a measure of how ‘resilient’ individuals were to subsequent stress. Scores of the participants who completed the protocol were compared. Although study participants were asked to avoid starting new treatments during the study, three individuals initiated antidepressant or benzodiazepine medications, all in MBSR. These three subjects were included in the modified ITT analysis of clinical outcome measures above but were not included in the TSST stress reactivity analyses due to their known effect on the TSST response[32].Removing these three subjects from the clinical outcome measure analyses above did not change the direction, magnitude, or significance of the results.

A repeated measure ANOVA, with time (baseline and endpoint) as the repeated measure, treatment arm as between-subjects factor and state STAI (STAI-S) score as the dependent variable found a main effect of time ($F(1,73)=47.11$, $P<0.001$) and a significant treatment arm × time interaction ($F(1,73)=4.37$, $P=0.040$).STAI-S scores dropped from 53.9 to 40.8 in the MBSR group and 52.2 to 45.2 in the SME group. Similarly, a repeated measure ANOVAwith time as the repeated measure, treatment arm as between-subjects factor and SUDS score as the dependent variable found a main effect of time ($F(1,68)=37.10$, $P<0.001$) and a significant treatment arm × time interaction ($F(1,68)=5.25$, $P=0.025$). SUDS scores dropped from 53.2 to 28.7 in the MBSR group and 50.5 to 39.4 in the SME group.

Self-Evaluation—Participants completed the Self-Statements during Public Speaking questionnaire (SSPS), indicating their amount of agreement with the provided positive (SSPS-P) and negative self-statements (SSPS-N). A repeated measure ANOVA, with time as the repeated measure, treatment arm as between-subjects factor and SSPS-P score as the dependent variable found a main effect of time ($F(1,72)=4.49$, $P=0.038$) and a significant

treatment arm × time interaction (F(1,72)=8.64, *P*=0.004).There was a greater increase in agreement with the positive statements with MBSR (15.9 to 18.6) compared to SME (16.9 to 16.5).

The mean score for negative statements decreased in both groups, but did not differ between groups. Specifically, a repeated measure ANOVA, with time as the repeated measure, treatment arm as between-subjects factor and SSPS-N score as the dependent variable found a main effect of time (F(1,72)=11.5, *P*=0.001) but a non-significant treatment arm × time interaction (F(1,72)=1.32, *P*=0.26).

IV. Discussion

This is the first RCT employing an active control group to examine the effect of MBSR on GAD. We found significantly larger reductions in most (CGI-S, CGI-I, BAI, PSQI) but not all (HAM-A) of our clinical outcome measures. One possible explanation is that the HAM-A,which heavily weighs somatic symptoms, was not sensitive to the change in psychological symptoms; indeed, the HAM-A scale has been reported to be "dominated by the somatic correlates of anxiety."[33]This was suggested by post-hoc analyses which showed a greater(although non-significant) drop(4.8 versus 3.9), in the psychological symptom HAM-A subscale in the MBSR group compared to the SME group, and a greater drop in the BAI psychological symptom subscale in the MBSR group compared to the SME group (3.12 versus 1.51, t(79)=-1.81, *P*=0.07). Given greater differences in self-report and global improvement ratings than HAM-A scores, it is also possible that the MBSR participants experienced a decrease in overall distress and impairment that was not reflected in GAD symptom change as measured by the HAM-A. This distinction between symptom severity and symptom distress has been made in the pain literature, where mindfulness meditation training was associated with a decrease in "pain unpleasantness."[34, 35]

Using the standard outcome measure of the HAM-A to calculate effect sizes of the active treatment, the MBSR group's effect size (pre- to post-treatment, Cohen's d) was 1.06, which is similar to other psychosocial treatment studies (Cohen's d of 0.73 to 1.37 in studies of CBT; [36,37]also for review see meta-analysis by Stewart and Chambless 2009[38] that reports a Hedges' g overall effect size of 0.92 for CBT).

"Resilience" is defined as "the ability of a substance or object to spring back into shape; the capacity to recover quickly from difficulties" (Oxford English Dictionary); given that this term measures a reaction to something, the use of a paper questionnaire to measures resilience seems wanting. Indeed, the TSST has been used as a measure of resilience in many different populations including healthy controls, as it gives scientists an opportunity to systematically measure how well an individual copes with and recovers from a well-recognized significant stress[39-41].We found a greater reduction in ratings of distress and anxiety after the TSST with MBSR than SME, suggesting meditation training may have improved coping or "resilience" to this performance stress task. Our findings are consistent with Britton and colleagues[42]who found that participants with partially remitted depression had a greater reduction in STAI scores after the TSST with MBCT compared to a wait-list control.

Because mindfulness meditation teaches participants to let thoughts pass by without judgment,[9]it is possible that participants who learned MBSR were less likely to ruminate over negative thoughts about the speech and their performance, and treated themselves with more kindness and less self-judgment, an inherent part of the practice. This hypothesis is supported by the significant increase in positive self-statement agreement in the SSPS, which occurred with MBSR but not SME, and represents a possible growth in positive self-

regard which is distinct from the decrease in anxiety symptoms overall. Indeed, lower positive emotion associated with the TSST has been shown to predict increased depression symptoms over the following year.[43]

The study has several limitations. First, our sample was relatively small, and large-scale replications are needed. Second, although comorbidity rates of depression and anxiety disorders in our sample are consistent with other treatment seeking GAD populations,[44-45] large epidemiological studies have reported higher comorbidity rates among GAD patients, suggesting that our results might not be completely generalizable.“ Third, the study included some participants taking psychiatric medication. While our meditation training had a significant effect (despite the sample comprising a mixed clinical population), the small numbers of participants on medication, balanced between groups, precluded the examination of medications effects on response. Lastly, our study lacked a clinical diagnostic assessment at endpoint.

In conclusion, our findings suggest that mindfulness meditation training, in the form of MBSR, can reduce anxiety symptoms in patients with GAD even when compared to an active control condition, and is a treatment option worth pursuing in larger investigational trials. We also observed that patients who learned mindfulness meditation had improved coping during a laboratory stress paradigm, raising the possibility that mindfulness may imbue some resilience to stressful psychological challenges.

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Clinical Points

1. Mindfulness-Based Stress Reduction appears to be an effective tool to reduce anxiety in patients with Generalized Anxiety Disorder.
2. Patients who learned Mindfulness Meditation had less stress reactivity, and were more resilient, to a laboratory stress task.

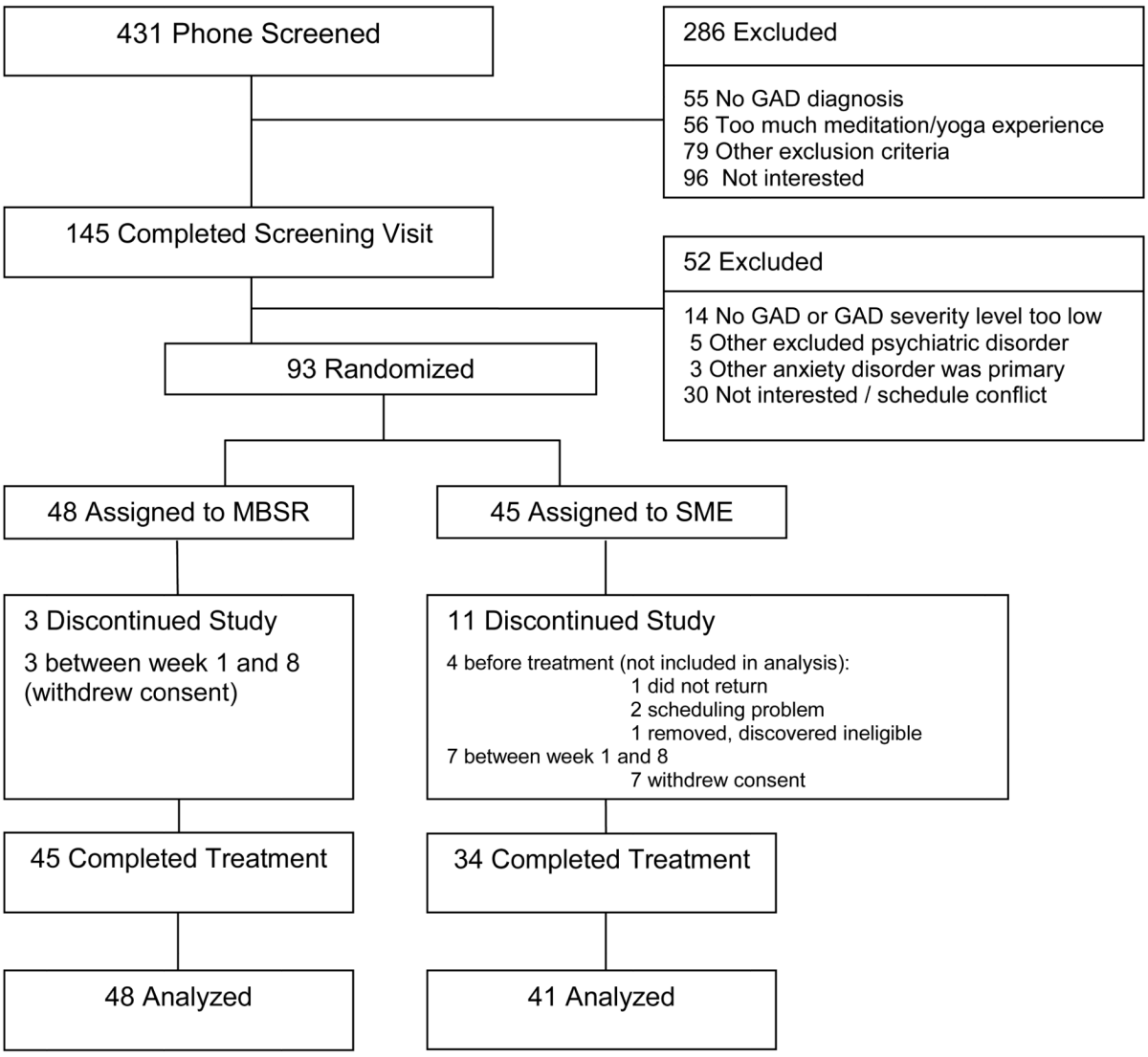

Figure 1.
CONSORT Chart

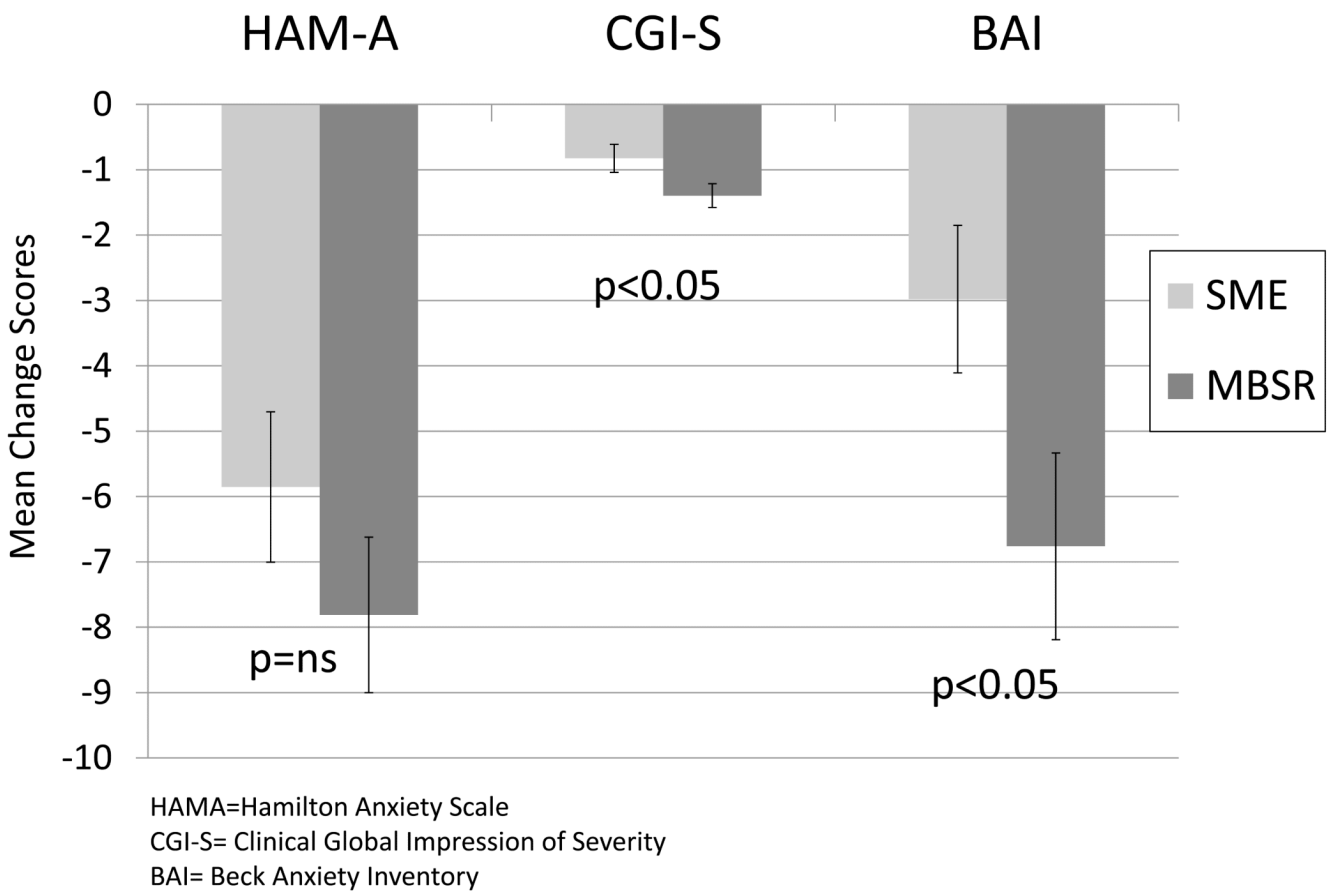

Figure 2.
Anxiety Symptom Change Scores in modified ITT analyses of MBSR compared to SME

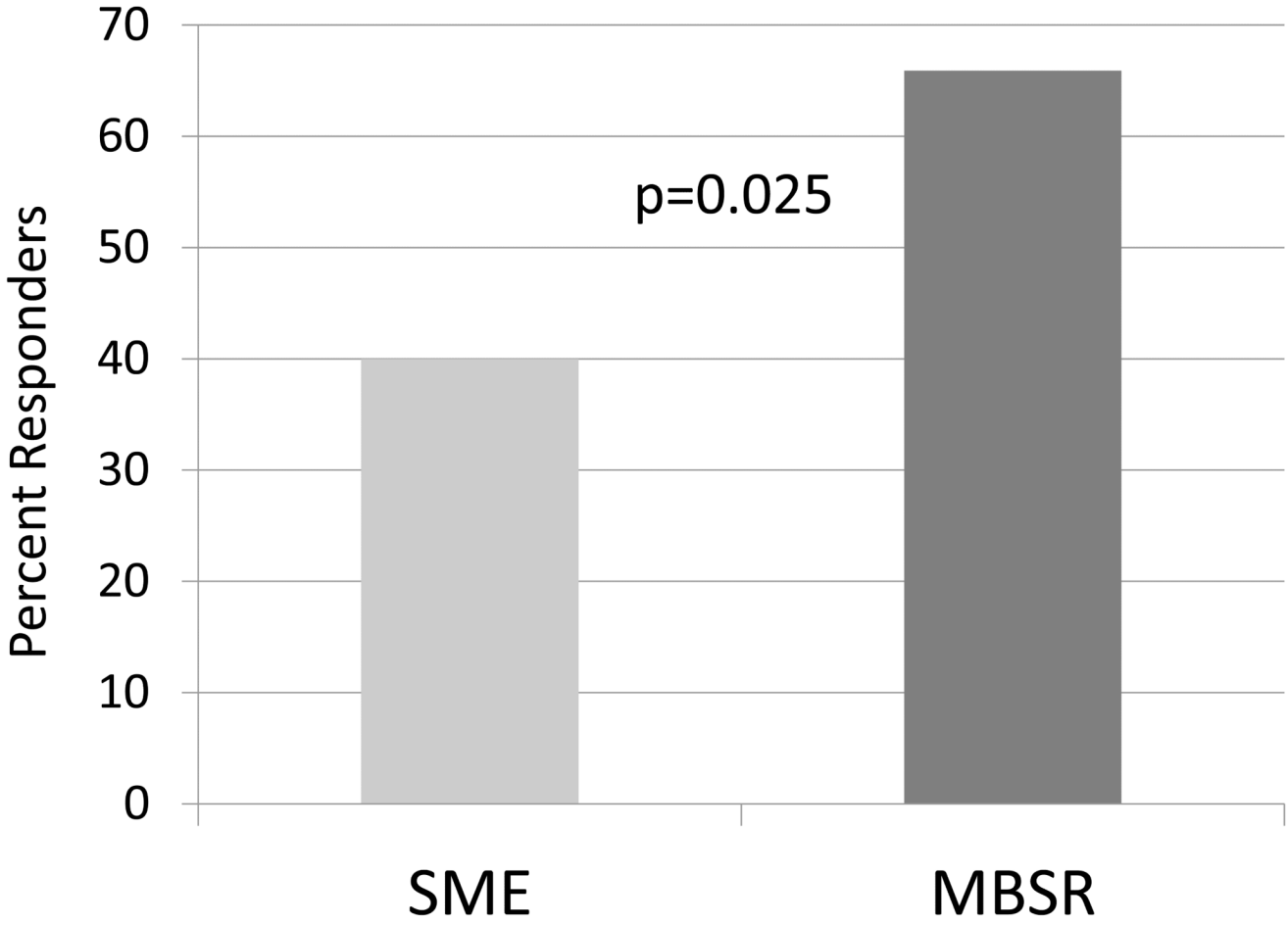

Figure 3.
Treatment Responders (CGI-I of 1 or 2)

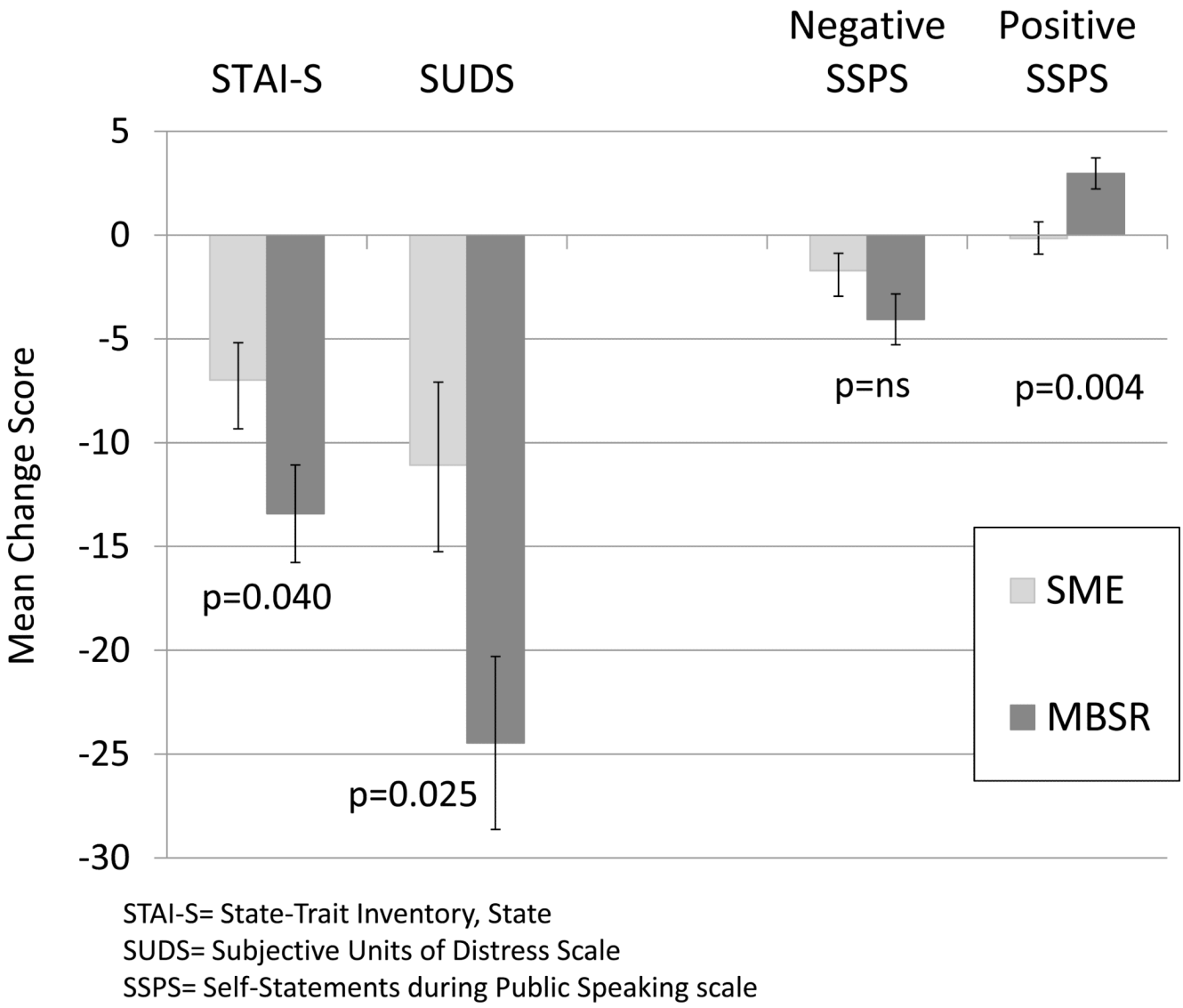

Figure 4.
Stress Reactivity Task Score Changes

Table 1

Demographic and Clinical Characteristics of Patients with GAD who Completed at Least One Treatment Session

	MBSR	SME	p-value
Characteristic	**(N=48)**	**(N=41)**	
Sex: N (%)			0.67
Male	25 (52)	19 (46)	
Female	23 (48)	22 (54)	
Race: N (%)			0.95
White	40 (83)	36 (88)	
Black	3 (6)	3 (7)	
Asian	4 (8)	2 (5)	
Other	1 (2)	0	
Age (years): Mean (SD)	41 (14)	37 (12)	0.18
Medication use (Stable SSRI or benzodiazepines, N(%)	9 (18)	8 (20)	1.0
Comorbid Depression, current, N(%)	5 (10)	6 (15)	0.75
Comorbid Panic Disorder, current, N(%)	3 (6)	4 (10)	0.7
Comorbid Social Anxiety Disorder, current, N(%)	13 (28)	12 (30)	1.0

Table 2

T-Tests of Main Clinical Outcome Measures of Anxiety in Patients with GAD

	Baseline		**Endpoint**		**Within group comparison**	
Hamilton Anxiety Scale	*mean*	*SD*	*mean*	*SD*	*t(df)*	*P*
MBSR	21.46	7.35	13.65	7.01	5.33(47)	<0.0001
SME	22.12	5.89	16.27	7.26	4.01(40)	<0.0001
Clinical Global Impression- Severity	*mean*	*SD*	*mean*	*SD*	*t(df)*	*P*
MBSR	4.54	0.97	3.15	1.11	7.6(47)	<0.0001
SME	4.38	0.98	3.58	1.28	3.8(39)	0.0002
Beck Anxiety Inventory	*mean*	*SD*	*mean*	*SD*	*t(df)*	*P*
MBSR	16.01	8.81	9.10	7.11	4.7(40)	<0.0001
SME	14.31	8.19	11.33	5.65	2.6(39)	0.012

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