ORIGINAL ARTICLE

Hypertension Analysis of Stress Reduction Using Mindfulness Meditation and Yoga: Results From the Harmony Randomized Controlled Trial

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BACKGROUND
The HARMONY study was a randomized, controlled trial examining the efficacy of an 8-week mindfulness-based stress reduction (MBSR) program for blood pressure (BP) lowering among unmedicated stage 1 hypertensive participants.

METHODS
Participants diagnosed with stage 1 hypertension based on ambulatory BP were randomized to either immediate treatment of MBSR for 8 weeks or wait-list control. Primary outcome analysis evaluated whether change in awake and 24-hour ambulatory BP from baseline to week 12 was significantly different between the 2 groups. A within-group before and after MBSR analysis was also performed.

RESULTS
The study enrolled 101 adults (38% male) with baseline average 24-hour ambulatory BP of $135 \pm 7.9/82 \pm 5.8$ mm Hg and daytime ambulatory BP of $140 \pm 7.7/87 \pm 6.3$ mmHg. At week 12, the change from baseline in 24-hour ambulatory BP was $0.4 \pm 6.7/0.0 \pm 4.9$ mm Hg for the immediate intervention and $0.4 \pm 7.8/-0.4 \pm 4.6$ mm Hg for the wait-list control. There were no significant differences between intervention and wait-list control for all ambulatory BP parameters. The secondary within-group analysis found a small reduction in BP after MBSR compared with baseline, a finding limited to female subjects in a sex analysis.

CONCLUSIONS
MBSR did not lower ambulatory BP by a statistically or clinically significant amount in untreated, stage 1 hypertensive patients when compared with a wait-list control group. It leaves untested whether MBSR might be useful for lowering BP by improving adherence in treated hypertensive participants.

CLINICAL TRIALS REGISTRATION
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Hypertension is a major risk factor for cardiovascular disease.[1] Recent improvements in the control of blood pressure (BP) have been associated with an increase in the use of antihypertensive medications[2] and subsequent improvement in cardiovascular outcomes.[3] Nonetheless, more than one-third of hypertensive patients remain uncontrolled.[4] The diagnosis of hypertension and the use of antihypertensive medications have also been associated with increased psychological stress.[5] BP reactivity to stress has been associated with greater carotid intima-media thickness.[6] Situational stressors such as job strain have also been associated with higher BP,[7] with a possible gene and job strain interaction.[8,9] An enhanced response to acute mental stress has been associated with an increased risk for future cardiovascular events.[10] The mechanism for this is not yet known but may be a combination of direct physiologic effects, such as stimulation of the sympathetic nervous system, and behavioral changes leading to reduced adherence to drug therapy.

Stress reduction and relaxation therapies have been reported to have a BP-lowering effect.[11–13] Cognitive behavioral therapy (CBT) has been reported to reduce BP by 6/4 mm Hg.[14] Epidemiologic studies have shown that reducing BP by 5 mm Hg can reduce stroke mortality by 14%, coronary heart disease mortality by 9%, and total mortality by 7%.[15] Adding CBT to traditional care after a cardiovascular event lowered the rate of recurrent acute myocardial infarctions by 45% and mortality by 28% over an 8-year period. Although BP change was not reported, improvements in cigarette consumption and lipid status were found.[16]

Individualized stress management programs such as CBT have demonstrated efficacy in BP lowering.[14] However, group therapies such as mindfulness-based stress reduction

(MBSR) have yet to be tested in this setting. MBSR is a stress reduction program theorized to help individuals learn about their relationship with their thoughts, emotions, sensations, and behaviors and may be a more efficient alternative to individualized programs because it is a standardized group therapy now widely available in major health centers.[17,18] Observational studies have shown BP lowering with MBSR.[19,20] A recent small, randomized controlled trial studying MBSR specifically for BP lowering in older medicated hypertensive black patients reported a 22 mm Hg reduction in systolic BP, but with only 10 subjects per group, these findings must be considered hypothesis generating.[21]

We have used a wait-list randomized controlled trial design with ambulatory BP as the primary outcome measure to determine whether MBSR can effectively lower BP in untreated hypertensive participants. The study design is similar to that of Linden *et al.* who found that individualized CBT lowered systolic BP by 6 mm Hg.[14] Building on our previous work, we studied untreated hypertensive participants to reduce the potential for confounding associated with individuals making changes in drug therapy during the trial.[22,23]

METHODS

Participants

The study population consisted of men and women with known unmedicated stage 1 hypertension based on screening automated office BP measurements. Eligible participants were aged 20 to 75 years with mean awake ambulatory systolic or diastolic BP ≥ 135/85 mm Hg or mean 24-hour ambulatory BP ≥ 130/80 mm Hg. BP was required to be <160/100 mm Hg on both office and ambulatory measurements. Participants were naive to antihypertensive medication for at least 6 months before the baseline screening visit.

Participants were recruited from referring physicians, advertisements in local newspapers, and posters at local hospitals. Study subjects were not given incentives for participation in the study but were reimbursed for parking. The wait-list control methodology enabled all participants to receive the MBSR intervention. The study was approved by the Research Ethics Boards at Sunnybrook Health Sciences Centre and Toronto General Hospital and was carried out according to the principles of Good Clinical Practice, the Declaration of Helsinki, and the Tri-Council Policy Statement on ethical conduct for research involving humans.[24,25]

Study design and intervention

The HARMONY study was a randomized, prospective, 2-arm, wait-list controlled trial. The safety of the wait-list methodology for stage 1 and 2 hypertensive participants has been previously demonstrated.[14] In placebo-controlled studies of stage 1 and 2 hypertension, one can expect approximately 14% of participants on placebo to discontinue the study for BP being too high.[26] Participants were allocated in a 1:1 ratio to either immediate intervention or to wait-list control. The intervention was an 8-week MBSR program that was completed during the initial 12-week period. The

primary outcome measure was change in awake and 24-hour ambulatory BP from baseline to 12 weeks. Details of the methodology of this trial have been previously reported and are summarized below.[27]

The objective of this study was to determine whether an 8-week MBSR therapy program could lower ambulatory BP among untreated participants with stage 1 hypertension. We hypothesized that individuals who received MBSR therapy would have a significant reduction in ambulatory BP. The primary outcome analysis compared change in awake and 24-hour ambulatory BP from baseline to 12 weeks between subjects randomized to immediate treatment and to wait-list control. Secondary outcome analyses included within-group BP change from pre- to post intervention, as well as persistence of effect of the MBSR on BP 24 weeks from baseline. The within-group analysis provided greater power to detect a BP-lowering effect from MBSR. Additional secondary analyses evaluated effects on nighttime BP using the above-mentioned analyses. Finally, exploratory analyses evaluated correlations between amounts of MBSR homework practiced, class attendance, and BP change and the existence of sex/gender effects.

Potential participants were screened by research staff using an automated office BP measurement device (BpTRU Limited, Coquitlam, BC, Canada). Study eligibility was based on ambulatory BP monitoring to confirm the diagnosis of stage 1 hypertension and provided the baseline BP measure for the study (Spacelabs Model 90207; Spacelabs Medical, Redmond, WA). Additional office BP readings were obtained for safety monitoring purposes. These were performed at regular scheduled study visits or monthly if a participant was deemed to be at higher risk. Research staff were trained on proper BP measurement procedures. Cuff sizes appropriate for subjects' arm circumference in the nondominant arm were used. Ambulatory BP was measured at 15-minute intervals during the day (7:00 AM to 11:00 PM) and at 30-minute intervals at night (11:00 PM to 7:00 AM). Results were adjusted to reflect participant's awake and asleep times. Laboratory tests and electrocardiograms were also obtained to rule out target organ damage and diabetes. All participants were closely monitored and received standard recommendations for lifestyle adjustments for BP management and control in accordance with recommendations from the Canadian Hypertension Education Program.[28] This was to ensure that all subjects received care according to best Canadian BP practices.[28] This included information on smoking cessation, exercise, and restricting sodium and alcohol consumption. This health information was delivered in the format of face-to-face communication as well as printed information from the Canadian Hypertension Education Program and the Heart and Stroke Foundation of Ontario. Lifestyle therapy is indicated for people with stage 1 hypertension and no underlying risk factors.[28] All HARMONY participants fell into this category. Participants whose BP remained uncontrolled were advised to start therapy after the study.[29]

Upon achieving study entry participants were randomized to 1 of 2 study arms by sealed envelope method using a permuted block design. Sealed envelopes were not opened until the participant's eligibility was confirmed with ambulatory BP results. Patients were not blinded to their randomization to immediate intervention or wait-list control status. The

study coordinator was not blinded to randomization status when processing the ambulatory blood pressure monitoring (ABPM). Staff members who instructed MBSR were not informed of participants' randomization status. Participants randomized to immediate intervention were schedule to begin the 8-week MBSR program within 4 weeks of their baseline visit (Figure 1), whereas those randomized to wait-list control began the 12-week wait-list period. All participants returned 12 weeks after baseline for a second 24-hour ambulatory BP monitoring, which represented the 12-week primary outcome time point for the study. Participants randomized to immediate intervention began their post-MBSR 12-week follow-up, whereas those randomized to wait-list control began the MBSR program within 4 weeks of the second ambulatory BP monitoring. All subjects returned 24 weeks after baseline for a third 24-hour ambulatory BP recording. At this point, participants randomized to immediate intervention closed out of the study, whereas those randomized to wait-list control completed their post-MBSR 12-week follow-up period. After this 12-week follow-up period, wait-list control participants completed a fourth ambulatory BP monitoring visit and closed out of the study.

The MBSR program used in this study was designed in 1979 by Jon Kabat-Zinn. MBSR is a multicomponent group intervention that provides systematic training in mindfulness meditation as a self-regulation approach to stress reduction and emotion management.[30] MBSR focuses on 4 major therapeutic elements: formal meditation, informal mindfulness practice, psycho-education activities, and self-monitoring/reflection exercises. These therapeutic elements are explored through activities including but not limited to, gentle stretching and mindful yoga, a meditative body scan, mindful breathing, and mindful walking. "MBSR works as both an acute and preventive treatment as it provides participants with strategies for working with the challenges and stressors in their lives."[27,31] By bringing mindfulness to life stressors, MBSR participants may more clearly see the full context of a situation, access a broader range of emotional responses, and cope with stressful situations more effectively.[18]

MBSR was delivered by 2 trained therapists to groups of 25–30 individuals. It consisted of 10 sessions over 9 weeks (introduction, 8 weekly 2.5-hour sessions, and a 6-hour session/silent retreat). Participants agreed to complete 45 minutes of homework meditation practice per day, which included practicing the various techniques learned during formal class. Homework logs were distributed on a weekly basis to track both class attendance and number of minutes spent practicing MBSR each day.
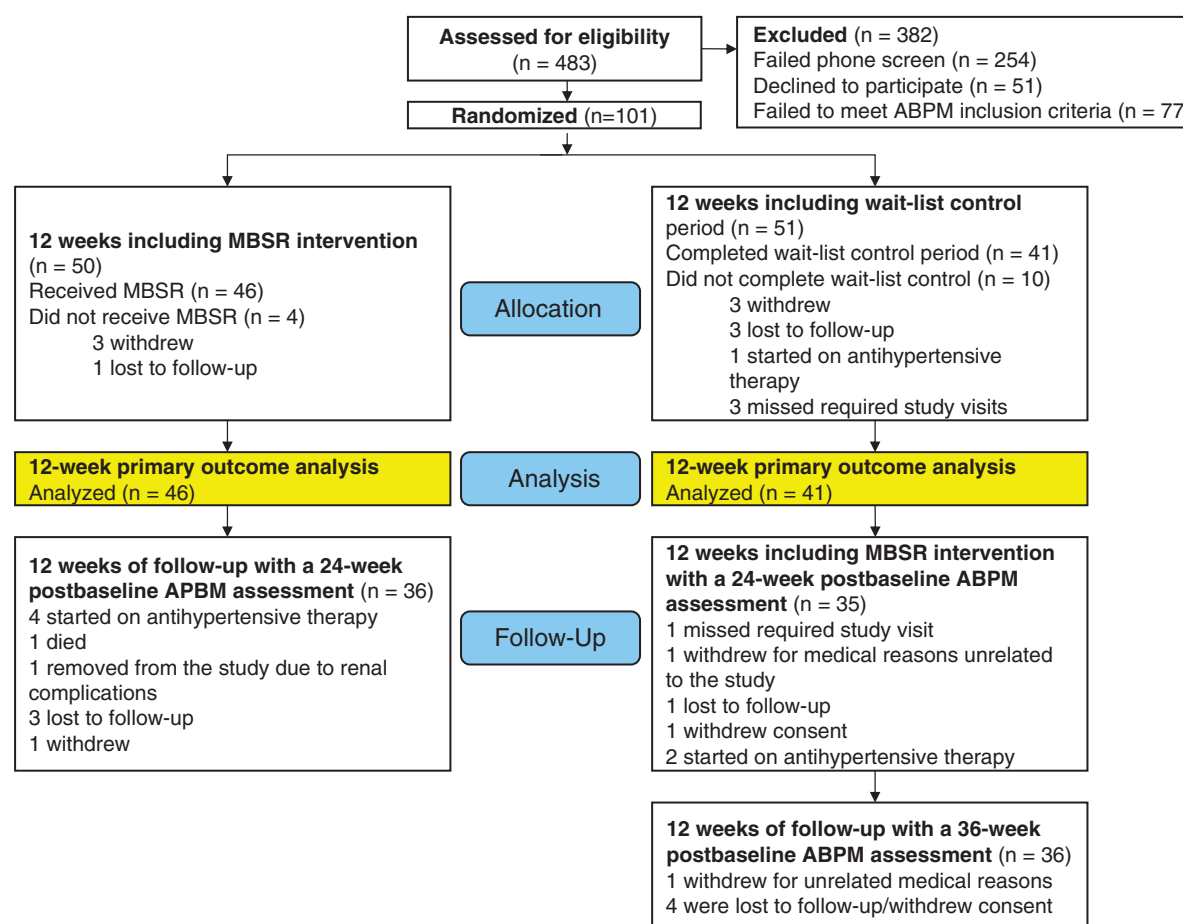
Figure 1. HARMONY study CONSORT diagram. Abbreviations: ABPM, ambulatory blood pressure monitoring; MBSR, mindfulness-based stress reduction.

Statistical methods

The HARMONY study was designed using 2 treatment arms and multiple BP measurements over time. It was determined that a sample size of 50 subjects per arm would provide sufficient power to detect a difference of 6 mm Hg on systolic 24-hour ambulatory BP assuming an attrition rate of 25%.[27] Repeated measures analysis of variance was used for the primary between-group and secondary within-group analysis. For the primary analysis, data were analyzed according to a grouping variable (GROUP) with two levels (immediate treatment vs. wait-list control) by TIME with 2 levels (baseline and 12-weeks after baseline). The secondary analysis examined within-participant BP change over 3 time points (baseline, postintervention, and study close) collapsing across the GROUP factor and using pairwise TIME contrasts. Statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC). Baseline comparisons were evaluated using t tests and McNemar tests of independence.

RESULTS

Participant flow

A total of 101 subjects were randomly allocated to the immediate treatment (intervention) group or to the wait-list control group (Figure 1). Four hundred eighty-three individuals who expressed an interest in the program were screened, with 254 excluded after a telephone interview. The most common reason for exclusion was current or recent antihypertensive therapy. Of the remaining 229 participants, 51 declined to participate and 77 did not have stage 1 hypertension on ambulatory BP monitoring. The remaining 101 participants were enrolled into the study.

Participant study flow can be observed in Figure 1. Fifty participants were randomized to immediate intervention, with 46 completing the MBSR intervention program and 12-week ambulatory BP monitoring. Full data were not available for 4 patients—3 because of early withdrawal from the study and 1 because of losss to follow-up. Fifty-one participants were randomized to the wait-list control group, with 41 completing the wait-list period and 12-week ambulatory BP monitoring. Full data were not available for 10 patients—3 withdrew from the study, 3 were lost to follow-up, 3 were started on antihypertensive medication, and 1 missed the 12-week ambulatory BP monitoring visit. The most common reason for withdrawal was time and/or travel constraints. Ambulatory BP data for those started on antihypertensive therapy were censored from the point of antihypertensive initiation onward.

Baseline data

Data for all subjects were included as part of the intent-to-treat analysis. All subjects had stage 1 hypertension and were untreated for at least 6 months before study entry. The mean baseline 24-hour ambulatory BP for all 101 participants was $135 \pm 7.9/82 \pm 5.8$ mm Hg; mean awake ambulatory BP was $140 \pm 7.7/87 \pm 6.3$ mm Hg; and mean nighttime ambulatory BP was $122 \pm 11.1/71 \pm 7.4$ mm Hg. There were no significant baseline differences between the treatment arms (Table 1).

Primary outcome

There was no significant difference in the changes in 24-hour ambulatory BP from baseline to week 12 of the primary outcome period between the group randomized to immediate intervention ($-0.4 \pm 6.7/0.0 \pm 4.8$ mm Hg) vs. the group randomized to wait-list control ($-0.4 \pm 7.8/-0.4 \pm 4.6$ mm Hg) (Table 2). There was also no significant difference between groups in the changes in awake and nighttime ambulatory BP from baseline to 12 weeks during the primary outcome period. No significant between-group differences were found in lifestyle or anthropomorphic measurements at the 12-week primary outcome period between the 2 arms (data not shown).

Secondary outcome

A within-group analysis of 87 participants found a small but significant decrease of 1.8 ± 6.9 mm Hg for 24-hour systolic BP ($P = 0.01$) and 2.1 ± 7.1 mm Hg for awake systolic BP ($P = 0.01$) from pre- to postintervention (Table 3). Persistence of effect 12 weeks after the intervention in 66 participants with available data found very small BP changes; none achieved statistical significance (Table 3).

Exploratory outcomes

There were no significant correlations between or within groups for all ambulatory BP parameters with respect to minutes of MBSR homework completed or number of MBSR classes attended vs. change in ambulatory BP. Analyses of sex/gender effects revealed an interaction for the significant within-group finding, wherein 24-hour systolic BP decreased in female subjects by 1.8 ± 6.0 mm Hg but increased in male subjects by 1.9 ± 8.3 mm Hg ($P = 0.02$).

Harms/adverse events

One subject enrolled in the control group died at week 21. She was seen for a routine BP safety visit the day before death when her average seated office BP was 146/96 mm Hg. Later that day, she developed a severe headache but did not inform the study coordinator. The following day she was found comatose, and a computed tomography scan revealed an acute intracerebral hemorrhage. This serious adverse event was reviewed by Research Ethics Boards at both institutions as well as the study sponsor and study investigators. The review concluded that the study was not related to the subject's death. All parties agreed that the HARMONY study should continue to enroll participants; however, a new safety amendment was added to specify that mandatory monthly office BP should be monitored and a routine inquiry about headaches should be done at all study visits. There were no other serious adverse events or minor adverse events.

DISCUSSION

In this study, MBSR did not significantly lower ambulatory BP when compared with BP change in a wait-list

Table 1. Baseline demographic data

Characteristic	Immediate intervention	Wait list
No.	50	51
Male sex, %	36	37
Age, y	57 ± 12	55 ± 11
BMI, kg/m^2	28 ± 4.6	27 ± 5.1
24-h systolic BP, mm Hg	135 ± 8.4	134 ± 7.4
24-h diastolic BP, mm Hg	83 ± 6.2	82 ± 5.3
Family history of hypertension, %	60	65
Family history of premature coronary heart disease, %	23	33
Education postsecondary or greater, % yes	82	90
Number of MBSR classes attended out of 8	6 ± 1	6 ± 2
Homework per day, min	30 ± 15.4	32 ± 15.2
Working, %	85	77
Standard alcohol drinks ≥ 10/week, %	19	22
Regular use of relaxation techniques at baseline, %	10	24
Proportion of subjects exercising vigorously at baseline, %	63	70
Proportion of subject exercising moderately at baseline, %	89	94
White race, %	78	88

Data are reported are mean ± SD for continuous variables. *P* = nonsignificant for all between-group comparisons. Vigorous exercise was defined as any weekly vigorous aerobic exercise lasting ≥20 minutes. Moderate exercise was defined as any weekly moderate exercise lasting ≥30 minutes.

Abbreviations: BMI, body mass index; BP, blood pressure; MBSR, mindfulness-based stress reduction.

Table 2. Primary between-group analysis: baseline to 12 weeks

	Change	
	Baseline	Baseline to 12 weeks
24-h BP		
Immediate treatment	135 ± 8.4/82 ± 6.2	−0.4 ± 6.7/0.04 ± 4.9 (n = 46)
Wait-list control	134 ± 7.4/82 ± 5.3	−0.4 ± 7.8/−0.4 ± 4.6 (n = 41)
Awake BP		
Immediate treatment	140 ± 8.1/87 ± 6.7	−0.9 ± 7.0/−0.3 ± 5.3 (n = 46)
Wait-list control	140 ± 7.4/86 ± 6.0	−0.5 ± 7.6/−0.7 ± 4.9 (n = 41)
Nighttime BP		
Immediate treatment	123 ± 10.8/72 ± 6.9	0.7 ± 8.7/0.8 ± 5.1 (n = 46)
Wait-list control	121 ± 11.4/70 ± 7.8	−0.08 ± 12.2/−0.1 ± 7.5 (n = 41)

Data are reported as mean ± SD. All blood pressure (BP) measurements are in mm Hg. *P* = nonsignificant for all between-group comparisons. Numbers are for patients with complete datasets.

control group at 12 weeks. When BP readings for all study participants were combined and evaluated using within-group analyses, there was a small but statistically significant decrease in 24-hour and awake ambulatory BP between pre- and postintervention. In the exploratory analysis, this decrease in BP was related to an interaction with sex/gender, with BP decreased for female subjects and increased for male subjects. Although this finding is only hypothesis generating, it is consistent with a previous study finding published by our

group.[7] In that study, a sex-specific interaction was present between marital cohesion and job strain in women but not in men.

The HARMONY study was sufficiently powered to detect a difference of 6 mm Hg for 24-hour systolic BP between subjects randomized to immediate MBSR intervention and wait-list control.[7,14] This difference was derived from Linden *et al.* who reported a fall of 6.1/4.3 mm Hg in 24-hour BP when comparing CBT to a wait-list control.[14] Table 4 contains a

Table 3. Secondary within-patient group analysis: pooled blood pressure change over time

	Baseline to post-MBSR (n = 87)		Baseline to study close (n = 66)	
	Change	P value	Change	P value
24-h BP	−1.8±6.9/−0.7±4.5	0.01/0.18	−1.4±8.3/−0.6±5.0	0.15/0.29
Awake BP	−2.1±7.1/−0.8±4.8	0.01/0.11	−1.8±8.1/−1.2±4.9	0.07/0.05
Nighttime BP	−0.8±9.5/0.1±5.4	0.42/0.85	−0.9±11.9/0.2±7.5	0.52/0.78

Data are reported as mean ± SD. All blood pressure (BP) measurements are in mm Hg. Numbers are for patients with complete datasets

Table 4. Studies using stress reduction for blood pressure lowering

Study	Intervention	No.	HT subjects included?	% on drug	BP lowered?
Achmon et al.[32]	CBT vs. control	97	Yes	41%	Yes
Schneider et al.[38]	TM vs. LE	127	Yes	50%	Yes
Linden et al.[14]	CBT (WLCl)	60	Yes	74%	Yes
Nolan et al.[33]	BNT vs. AR	65	Yes	71%	Yes
Palta et al.[21]	MBSR vs. SS	20	Yes	90%	Yes
Jacob et al.[39]	TB vs. SE	19	Yes	100%	Yes[a]
Johnston et al.[40]	SM vs. MEx	96	Yes	0%	No
Van Montfrans et al.[41]	RT vs. NSC	35	Yes	0%	No
Blanchard et al.[42]	TB vs. control	42	Yes	0%	No
Hughes et al.[34]	MBSR vs. PMR	56	Yes	0%	No
Campbell et al.[35]	MBSR (WLC)	70	Yes	16%	No
Wenneberg et al.[43]	TM vs. CBSE	39	No	0%	No

Only studies that used a reliable method of blood pressure measurement were included in this summary. This includes standardized manual, automated office (i.e., BpTru), home, or ambulatory blood pressure.

Abbreviations: AR, autogenic relaxation; BNT, behavioral neurocardiac training; BP, blood pressure; BT, cognitive behavioral therapy; CBSE, cognitive-based stress education; HT, hypertensive; IEx, isotonic exercise; LE, lifestyle education; MEx, mild exercise; MBSR, mindfulness-based stress reduction; NSC, nonspecific counseling; PMR, progressive muscle relaxation; RT, relaxation therapy; SE, stress education; SM, stress management; SS, social support; TB, thermal biofeedback; TM, transcendental meditation; TRT, treatment; WLC, wait-list control.

[a]BP lowered in stress education group.

summary of randomized controlled trials conducted on adult subjects that tested the effects of stress reduction therapies on BP and reported the use of a reliable method for BP measurement t (either standardized manual, automated office, home, or ambulatory BP). This summary was not based upon a systematic review; however, to the best of our knowledge, it contains all of the studies comparable with the HARMONY study that were randomized, conducted on adults, and used a reliable method of BP measurement. It should be noted that HARMONY enrolled more subjects than all but one of the reported studies. A thorough systematic review to 2007 by Rainforth of different types of stress reduction therapies for BP lowering found heterogeneity among the categories of mind–body interventions and effects on BP, including a significant effect for transcendental meditation.[12]

Examining the impact of hypertension treatment status in the studies from Table 4 revealed an interesting pattern. The observation that the studies containing a high proportion of treated participants reported significant findings suggests that BP responses to stress reduction therapies may be confounded by improved adherence to antihypertensive therapy.

Among treated hypertensives, Achmon et al. reported a difference of 17/11.4 mm Hg, 17 weeks after a CBT intervention[32] and Nolan et al. reported a difference of 2.1/1.1 mm Hg after 8 weeks of behavioral neurocardiac training.[33] In contrast with these as well as other studies where a high proportion of participants were treated, studies of stress reduction on unmedicated participants have failed to report significant BP reductions (Table 4). With sponsorship from the National Center for Complementary and Alternative Medicine, an early report by Hughes et al. found no significant ambulatory BP lowering from MBSR but did find lowering of clinic BP when compared with progressive muscle relaxation among prehypertensive subjects.[34] Campbell et al. similarly found no BP lowering from MBSR when compared with a wait-list control in a cohort of women who were largely unmedicated for hypertension.[35] The baseline BP can also impact on the treatment effect. A wait-list controlled trial by Nidich[36] of transcendental meditation lowered automated BP by 2/1 mm Hg among 298 normotensive subjects, and in a subgroup of these with high normal BP the BP lowering was 5/2.8 mm Hg, demonstrating the larger effect of BP lowering with a higher BP at baseline. Taken together, this information reveals a pattern

whereby studies with a high proportion of treated participants report BP lowering from relaxation therapies, and studies of untreated participants do not report significant BP lowering. Because the HARMONY study did not enroll patients receiving antihypertensive medication, its findings cannot be extrapolated to this patient population. Future studies examining the BP-lowering effects of a stress reduction program such as MBSR on changes in adherence to drug therapy should differentiate these changes from the effects that are directly attributable to the awareness of being in a research study from those of the therapeutic treatment regimen received.[37]

A limitation of the HARMONY study was that the sample size was predicated on the expected 6 mm Hg systolic BP reduction based on Linden *et al.*[14] In that study, 74% of participants were medicated for hypertension, and this may have increased the effect size. More recent studies of stress reduction for unmedicated participants have found smaller effect sizes, as did the HARMONY study. In the HARMONY study, the baseline systolic BP SD (9 mm Hg) and rate of attrition (25%) during the 12-week primary outcome period demonstrated that neither measure exceeded the parameters used in the power analysis. The randomized wait-list control style was used to mirror the methods used by Linden *et al.*[14]

In summary, the HARMONY study demonstrated that MBSR did not lower ambulatory BP by a statistically or clinically significant amount in untreated, stage 1, hypertensive patients when compared with a wait-list control group. In the secondary analysis, a small but significant within-group decrease in BP was observed for the entire cohort from pre- to postintervention. This effect was largely confined to female subjects. The potential benefit of MBSR to improve adherence to drug therapy among treated hypertensive patients remains to be tested.

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DISCLOSURE

The authors declared no conflict of interest.

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