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Protocol Summary for IRB: Cross-Cultural Cognitive Behavioral Group Therapy: Evaluating the effectiveness of a manualized cognitive behavior group therapy treatment for the management of menopause symptoms in a mood and anxiety disorder population.

Introduction

The population of women in the age range for peri- and early post-menopause is growing rapidly. There are approximately 52.816-million females in the United States between the ages of 40-64 (U.S. Census Bureau, 2012). The female population for minorities has expanded at a higher rate than for white females. The Hispanic population grew 43% from 2000 to 2010, compared to 5% for non-Hispanics and 1% for white females (Richard-Davis, & Mellons, 2013). An estimated 58% to 93% of American females have reported vasomotor symptoms such as hot flashes/flushes and night sweats during the menopause transition; these symptoms are more frequent during the peri- and early post-menopausal years (Thurston, Joffe, Soares, & Harlow, 2006). The terms hot flashes and hot flushes are used interchangeably as both terms were used in the literature cited in this protocol.

Over the past decade, several studies have provided empirical evidence that peri- and early post-menopausal women are at risk for major depressive episodes (Bromberger, Kravitz, Chang, Cyranowski, Brown, & Matthews, 2011). Women in the late stages of peri-menopausal transition are vulnerable to depressed mood (Woods, Smith-DiJulio, Percival, Tao, Mariella, & Mitchell, 2008). Overall, studies consistently have supported a window of vulnerability for women in the midst of menopausal transition, with or without a prior history of depression (Freeman, 2010).

While Hormone Therapy (HT) has been the "gold standard" for treating vasomotor symptoms, there has been a decline in using HT due to its potential long-term effects. Treatment based on selective serotonin re-uptake inhibitors (SSRI's) has been found to be efficacious, but not without unwelcomed side effects. Therefore, there is a growing need to explore non-medication treatment options. To date, studies that have examined mindfulness and cognitive behavioral therapy (CBT) have indicated that combining these therapies may be at least moderately effective in reducing the frequency and bother of vasomotor symptoms, with some studies revealing secondary gains such as a decrease in depressive symptoms. There have been few studies that have examined the effectiveness of cognitive-behavioral group therapy (CBGT), with no studies examining the effectiveness of CBGT where the majority of the female participants suffer from major depressive disorder or bipolar disorder. Furthermore, the potential impact of race/ethnicity has not been pursued in studies examining the effectiveness of CBGT, as these studies have been focused predominantly on white females.

Studies using SSRI's, SNRI's, and gabapentin to reduce hot flash frequency and vasomotor symptoms (i.e., severity or bother or interference) have shown a reduction in frequency and severity ranging from 21 to 61% (Joffe et al., 2014; NAMS, 2015; Shams et al., 2013). Clonidine has been found to be more effective than placebo but less effective compared to SSRI's, SSNRI's and gabapentin (NAMS, 2015).

More consistent results have been found with Paxil (paroxetine), Lexapro (escitalopram), Celexa (citalopram), venlafaxine (Effexor) and (Pristiq) desvenlafaxine compared to (Zoloft) sertraline and (Prozac) fluoxetine (NAMS, 2015) with escitalopram showing the most effective compared to all other SSRI's (Shams et al., 2013).

Gabapentin has shown higher efficacy compared to SSSRI's and SNRI's at 62.2% at 300mg/day (Allameh, Rouholamin, & Valaie, 2013) and the effects of gabapentin at 2400 mg/day are comparable to the first line treatment estrogen (NAMS, 2015). Most trials were conducted between 8-12 weeks. Therefore, in order to reduce the possibility of any reductions in hot flash bother, frequency, or interference being a result of SSRI's, SNRI's, gabapentin or clonidine, participants will be recruited after being stable on such medications for 8-12 weeks.

Many factors can lead to increased bother and the severity of vasomotor symptoms. These factors may include race/ethnicity, upsetting life events, body mass index (BMI), and negative views of the peri- and post-menopause developmental milestone (Bromberger, et al. 2011; Thurston, et al. 2006). The majority of women view menopause as normal. Yet a subset of women view menopause negatively. These negative attitudes toward menopause have been linked to increased menopausal symptoms (Rendall, Simonds, & Hunter, 2008).

Various studies have looked at how the frequency, severity and bother of menopause vasomotor symptoms influence quality of life. Few studies have applied daily life interference as an outcome measure. The literature has supported BMI and stressful life events as factors contributing to the severity of vasomotor symptoms as well as negative attitudes towards menopause.

Vasomotor symptoms, which can last up to 10 years post-menopause (Freeman, Sammel, & Sanders, 2014), are most frequent in the peri- and early post-menopausal years. Vasomotor symptoms are the leading reason for mid-life women to seek medical treatment (Thurston, et al. 2006). Due to the cardiovascular and breast cancer risks of treating vasomotor symptoms with hormone therapy, the efficacy of cognitive behavioral and behavioral treatments have received increasing attention(Ayers, Smith, Hellier, Mann, & Hunter, 2012; Carmody, Crawford, & Churchill, 2006; Carmody, Crawford, Salmoirago-Blotcher, Leung, Churchill, & Olendzki, 2011; Thurston, Ewing, Low, Christie, & Levine, 2014).

Vasomotor symptoms have been found to be correlated with depressive symptoms and negative affect (Gibson, Thurston, Bromberger, Kamarck, & Matthews, 2011), as well as depression and psychological distress (Bleil, Adler, Pasch, Sternfeld, Gregorich, Rosen, & Cedars, 2012). Other factors that have been found associated with depressed symptoms during menopause developmental milestones are negative beliefs about menopause, upsetting life events, BMI, severity of bother from vasomotor symptoms and susceptibility based on race/ethnicity.

Most studies related to the relationship between menopause and depression have been based primarily on non-clinical samples or compared women with and without a history of depression (Thurston, et al. 2006). The studies that have used non-clinical samples assessed for mood symptoms with few assessing for major depressive disorder (Bromberger, et al. 2011).

Hunter and Mann (2010) developed a cognitive model for menopausal vasomotor symptoms and opined that the trigger for hot flashes (i.e. Estrogen withdrawal) is detected by the body. This detection is matched with cognitive schemas and behaviors based on beliefs and experiences. Negative beliefs are associated with more physical and emotional problems. Rendall, Simonds & Hunter (2008) found a significant link between women's prior tendency toward negative beliefs and their association between menopause and negative life consequences. These women have been found to be less likely to view menopause as a "new phase of their lives" (p. 166) (Rendall, et al., 2008). Psychological interventions, combining psycho-education, relaxation and cognitive therapy, have resulted in reductions in self-reported frequency of hot flushes.

Weight gain is common during menopause transition and tends to increase vasomotor symptoms. High or increased physical activity has been found to decrease depressive and vasomotor symptoms in women with a history of depression compared to those without a history of depression (Bromberger, et al. 2011). The Thurston et al. (2014) pilot study demonstrated a negative correlation between lower BMI, body fat and reduced vasomotor symptoms. A longitudinal, community-based study by Green and Santoro (2009) found that vasomotor symptoms were more common in females with higher BMI's and in African-American and Hispanic women.

Studies have demonstrated mixed conclusions regarding the impact of race differences on vasomotor symptoms, depression and anxiety. Some studies support the view that African-American females tend to be more depressed and anxious, with more psychological distress and vasomotor symptoms, compared to white females and exhibit more total, physical and psychosomatic symptoms than white, Asian-American and Hispanic groups (Im, 2009). Reports from a cross-sectional survey showed that after controlling for age, education and financial problems, African-American women reported more vasomotor symptoms compared to Caucasian females. Caucasian females reported more psychosomatic symptoms compared to other racial groups (Avis et al, 2001). Most symptoms varied by ethnicity.

Looking at the differences in hot flash beliefs, and using the hot flash belief scale is a true frontier and has virtually not been studied for women diagnosed with depressive and anxiety disorders. However, the very limited data shows the differences in coping style between White and Black females. Even though African American females tend to experience VMS more frequently than Caucasian females, they obtain information about menopause symptoms more from family, whereas, Caucasian females obtain information from the media and tend to discuss these symptoms with their physicians more than African American females (Grisso et al., 1999).

Helping women to manage menopausal symptoms in culturally compatible ways is important to their health and well-being (Richard-Davis, & Mellons, 2013). Understanding the differences in symptom manifestation and beliefs about the menopausal transition can potentially enhance treatment.

Studies that have examined the occurrence of major depressive disorder during peri- or early post-menopause transition have been mixed regarding the risk for mood symptoms across cultures. There is a recognition that an overlap of symptoms exist between Major Depressive

Disorder (MDD) and symptoms experienced during the menopause transition that needs to be addressed with assessment strategies (Clayton, & Ninan, 2010).

Upsetting life events have been found to be a strong predictor of initial major depressive episodes in mid-life females. Experiencing at least two upsetting life events have been found to increase depression by more than five times in mid-life females (Bromberger, et al. 2011). No studies were found comparing White and African-American females where group CBT was used as an intervention to improve vasomotor symptoms and quality of life.

Research examining menopause in chronically mentally ill women is sparse. No studies were found that used Group CBT for mid-life women with chronic and relapsing major depression. There were two studies found that conducted an assessment of chronically mentally ill women (major depressive disorder, bipolar disorder, and schizophrenia) and their quality of life (Friedman, Sajatovic, Schuermeyer, Safavi, Hays, West, Ignacio, & Blow, 2005; Sajatovic, Friedman, Schuermeyer, Safavi, Ignacio, Hays, West, & Blow, 2006). One study was found that assessed how menopause affected chronic mental illness and mental illness of family members (Sajatovic, Rosenthal, Plax, Meyer, & Bingham, 2003).

Results from cognitive and behavioral therapies have been promising (Ayers, et al., 2012; Carmody, et al., 2006; Carmody, et al., 2011; Thurston, et al., 2014). Few studies have attempted to examine CBGT, combining cognitive restructuring, psycho-education and slow-paced/deep breathing (Ayers, et al, 2012; Keefer, & Blanchard, 2005) with other studies combining cognitive restructuring, progressive muscle relaxation, psycho-education and group discussion as the CBT intervention (Alder et al., 2006). It is expected that participants will receive intrinsic benefits, physiological benefits (i.e., reduction in problematic hot flashes and night sweats) and improved ability to regulate emotions. The MENOS 1 study investigated the effectiveness of CBGT on women with breast cancer (Mann et al., 2012). The trial compared outcome measures from the treatment group (CBT group therapy for 90 minutes for 6 weeks) and usual care group. Hot flashes and night sweats (HFNS) problem ratings were significantly reduced in the CBT group compared to the usual care group at 9 and 26 weeks after randomization. Group CBT also improved mood, sleep and overall quality of life.

The MENOS 2 study compared the effectiveness of group CBT, self-help CBT and no treatment group on well women (Ayers, Smith, Mann & Hunter, 2012). HFNS problem ratings were significantly reduced in the CBT group and self-help group compared to the no treatment group at 6 weeks and 26 weeks after randomization. There were no significant differences in problems ratings in the CBT group compared to the self-help CBT group. There were no differences found in reduction of HF frequency for all 3 arms. However, the CBT group had significantly less frequent NS at 6 weeks compared to the self-help and no treatment group. Group CBT also improved mood, sleep and overall quality of life.

In the MENOS 1 and MENOS 2 studies, participants learned how to reduce stress (which can trigger and exacerbate hot flashes), identify and modify behaviors that increase the severity of hot flushes and identify negative automatic thoughts that lead to maladaptive coping and challenge these beliefs with the aim of utilizing adaptive strategies (Hunter & Smith, 2015).

Study Design & Objectives

Objectives: The general objective of this study is to advance insight into non-pharmacological treatments for maturing women that impact psychological health and wellbeing of women adapting to menopause, a natural but often challenging developmental milestone. This exploratory study proposes to expand the knowledge in the menopausal literature and evaluate the effectiveness of CBGT in reducing problematic vasomotor symptoms, reducing daily interference and improving quality of life. The study will include two homogenous peri- or post-menopausal cohorts (African-American and Caucasian) with major depressive disorder or bipolar disorder. Anxiety disorders tend to be co-morbid with depressive disorders. Therefore, women with or without anxiety disorders will be included in this study.

The physiological mechanism that causes hot flashes is unknown but appears "to be associated with the rate of change of plasma oestrogen, which influences the thermoregulatory system via the hypothalamus" (Hunter & Smith, 2015, p. 5). The prevalence of hot flashes is thought to be associated with rapid estrogen withdrawal. The physiological mechanism for vasomotor symptoms is related to small fluctuations in core body temperature superimposed on an extremely narrow thermoneutral zone (TMZ). Hot flashes are triggered when the core body temperature rises above an upper threshold, causing sweating. When the core temperature decreases below the lower threshold of the TMZ, shivering occurs (Freedman 2005).
The intervention will follow a manualized CBGT treatment developed by Hunter & Smith, 2015 aimed to reduce problematic vasomotor symptoms, stress, problems with sleep and enhance well-being. The CBGT will occur weekly for 6 weeks. Each week the CBGT is for 90 minutes. The underlying premise of CBGT is to promote stress coping and emotional regulation. This in turn will improve physiological regulation. For instance, improved stress coping decreases anxiety and allows women the opportunity to regulate their emotions and behaviors, potentially resulting in less physiologic lability. In addition, there is evidence to suggest that mood and stress and vasomotor symptoms are related to problems with memory and concentration. Problems with vasomotor symptoms, mood, memory and stress impact quality of life (Hunter & Smith, 2015). These symptoms will be assessed on the pre and post intervention. It is uncertain if the outcomes will be significant, which is why the research is being conducted. Since we are measuring each construct (i.e., hot flushes, daily life interference, quality of life), we will be able to test these theories.

<u>Specific Aims and Exploratory Hypothesis</u>
A manualized cognitive behavior group therapy treatment for vasomotor symptoms developed by Hunter and Smith (2105) has been found to significantly reduce hot flashes and night sweats for well women and women with breast cancer. The vasomotor symptoms of the participants were natural, surgically induced or followed medical procedures. Although not diagnosed with bipolar disorder, major depressive disorder or anxiety disorders, CBGT also reduced depressive and anxiety symptoms in these populations. However, the feasibility and effectiveness of this manualized treatment has not been studied for women who meet DSM-V criteria for bipolar disorder or major depressive disorder, with or without an anxiety disorder. In addition, no studies were found comparing Black and White females where group CBT was used as an intervention to reduce problematic vasomotor symptoms, quality of life and decrease daily interference.

Specific Aims:

1. Evaluate the feasibility of a manualized Cognitive behavior group therapy treatment for vasomotor symptoms for Black and White females diagnosed with bipolar disorder or major depressive disorder, with or without an anxiety disorder.
2. Evaluate the effectiveness of a manualized Cognitive behavior group therapy treatment for vasomotor symptoms for Black and White females diagnosed with bipolar disorder or major depressive disorder, with or without an anxiety disorder.
3. Describe the characteristics for Black and White females diagnosed with bipolar disorder or major depressive disorder, with or without an anxiety disorder on the Hot Flush Frequency and Problem Rating Scale (HFFPRS), Hot Flash Daily Interference Scale (HFRDIS), Hot Flash Belief Scale (HFBS), Menopause Representation Questionnaire (MRQ), Montgomery Asberg Depression Rating Scale (MADRS), Perceived Stress Scale-10 (PSS-10), Snaith-Hamilton Pleasure Scale (SHAPS), Young Mania Rating Scale (YMRS), Structured Interview for the Hamilton Anxiety Rating Scale (SIGH-A) and the Short-Form Couple Conflicts (CTS2S).
4. Describe the following descriptive characteristics for Black and White females diagnosed with bipolar disorder or major depressive disorder, with or without an anxiety disorder: race/ethnicity, age, marital status, socioeconomic status, smoking status, average weekly alcohol and caffeine consumption, education, BMI, menopause status (early, late peri-menopause, early, late post-menopause) and dosages and number of weeks on SSRI's, SNRI's, gabapentin or clonidine.

This study will also explore which independent variables are significant predictors of change in problematic hot flashes and night sweats, hot flash daily interference (HFDIS), and menopause quality of life (MRQ) for peri- and post-menopausal Black and White females diagnosed with DSM-V bipolar disorder or major depressive disorder, with or without an anxiety disorder from baseline to post-treatment (6 weeks of Cognitive Behavioral Group Therapy). Examining which variables significantly contributes to the outcome variables will help direct non-pharmacologic treatment interventions and inform relevant psychoeducation for this population.

It is expected that CBGT will reduce problematic hot flashes and night sweats (as measured via the hot flash frequency and problem rating scale), reduce daily interference (as measured on the hot flash daily interference scale), and improve quality of life (as measured on the MRQ). It is expected that strong negative beliefs about hot flashes and night sweats will be associated with more vasomotor symptoms and strong positive beliefs about vasomotor symptoms will be associated with significantly fewer vasomotor symptoms. The beliefs about vasomotor symptoms will be measured on the HFBS.

Overall Design: This is a 6-week cross-cultural study to test efficacy of CGBT treatment for 60 menopausal participants with major depressive disorder or bipolar disorder, with or without an anxiety disorder. The intervention will be delivered in groups of 5 to 10 participants per group of both race/ethnicities in an outpatient setting during a 6–week time period. The participants will be assessed on the degree of hot flash problem rating, hot flash related daily interference, and menopause quality of life at screening, baseline, and post-treatment. These are the outcome variables. Participants will be assessed using the following predictor variables at the same time points: BMI, level of perceived stress (PSS-10), severity of depression (MADRS), severity of

anxiety (SIGH-A), Snaith-Hamilton Pleasure Scale (SHAPS), Young Mania Rating Scale (YMRS), and hot flash beliefs. Severity of couple's conflict will be assessed using the CTS2S.

In addition, at the end of the study intervention, a questionnaire will be given to the participants to illicit feedback about the interventions. The purpose is to collect qualitative feedback that may be useful in future studies.

All participants will be seen for screening and treatment at University Hospitals Cleveland Medical Center, Mood Disorders Program 10524 Euclid Avenue, 12th Floor, Cleveland, Ohio 44106.

Target Subject Population

Participants: This study will recruit women in early or late peri-menopause transition or early or late post-menopause with problematic HFNS and diagnosed with bipolar disorder or major depressive disorder with or without an anxiety disorder. The age range will be 40-65, including both African-American and Caucasian females. Early, late peri-menopause and early, late post-menopause are defined by The North American Menopause Society (NAMS), Menopause Practice guidelines, stages of reproductive aging. Early peri-menopause is operationalized as variable cycle length or ≥7 days in length of consecutive cycles. Late peri-menopause is operationalized as ≥ 60 days of amenorrhea. Early post-menopause is defined as up to six years after the final menstrual cycle. Late post-menopause is defined as 6 years after the final menstrual period and the remaining lifespan. With respect to the age range, below 40 indicates premature menopause. The average age of the final menstrual cycle is 51 years old and approximately 25% between 50-55 experience natural menopauses (North American Menopause Society, 2014). Sixty women will participate in the CBGT.

Inclusion Criteria.

1. Self-identified as African-American or Caucasian females between 40-65 experiencing the early, late peri-menopause or early or late post-menopause stages of reproductive aging defined by The North American Menopause Society (NAMS, 2014), Menopause Practice guidelines, stages of reproductive aging. There are situations in which menopause status will not be able to be determined, such as with women who have had a hysterectomy. However, if the potential study participant meets all other inclusion criteria, then she can be enrolled in the study.
2. Diagnosed with current or lifetime bipolar disorder or major depressive disorder as assessed by the MINI.
3. Menopause symptoms can be natural or surgically induced.
4. Willing to remain on current dose of psychotropic medications until the study has concluded.
5. Experiencing one or more hot flashes and/or night sweats per day.
6. Willing to have the 6 CBGT interventions audio recorded.
7. English speaking and capable of understanding and complying with study protocol and requirements.
8. Montgomery-Asberg Depression Rating Scale (MADRS) total score > 7
9. Women stable on psychotrophic medications for ≥ 8 weeks.

Medication regimens to treat their DSM-V diagnoses will be encouraged to continue in order to determine if the CBGT accounted for any change in symptoms.

Exclusion Criteria.

1. Unwilling or unable to comply to study requirements.
2. Women diagnosed with schizophrenia, schizoaffective, borderline personality disorder, and/or active psychosis, as confirmed by MINI.
3. Diagnosed with active substance use disorder within past 12 months as confirmed on the MINI.
4. Women currently taking HT for Vasomotor Symptoms (VMS).
5. Participants experiencing acute mania as defined by a Young Mania Rating Scale (YMRS) score > 15
6. Serious suicidal risks judged by the investigator or having score equal or greater than 4 on MADRS item number 10 at screening or baseline.
7. Participants being treated with chemotherapy and/or tamoxifen.
8. Women who are not self-identifying as either African-American or Caucasian.

Study Specific Procedures

Screening: After Informed Consent is obtained, the participants will be evaluated by the MINI International Neuropsychiatric Interview (MINI) for DSM-V Axis I diagnoses. The participants must be evaluated by the following clinician rated measurements: Montgomery Asberg Depression Rating Scale (MADRS), the Structured Interview for the Hamilton Anxiety Rating Scale (SIGH-A), the Young Mania Rating Scale (YMRS) and the Perceived Stress Scale-10 (PSS-10). In addition, the subject will complete the Quick Inventory of Depression Symptomatology-Self Report (QIDS-SR16). The clinician will gather demographics, take BMI measurements and document menstrual cycle patterns based on interview guidelines from the North American Menopause Society (NAMS).

At the end of this visit, participants who continue to meet all inclusion criteria and no exclusion criteria will be seen for a baseline visit. All qualifying participants will be asked to record The Hot Flush Weekly Diary for one week prior to Baseline visit.

During the study period, research staff and the primary investigator will be available to answer questions or concerns.

Baseline: All participants will be asked to complete the following self-rated assessments: Hot Flush Frequency and Problem Rating Scale (HFFPRS), Hot Flash Belief Scale (HFBS), Menopause Representation Questionnaire (MRQ), Hot Flash Related Daily Interference Scale (HFRDIS), Snaith-Hamilton Pleasure Scale (SHAPS), Quick Inventory of Depression Symptomatology-Self Report (QIDS-SR16) and the Short-Form Couple Conflicts (CTS2S) scale within 2 days before or the day of the first group session. All participants will also be evaluated by clinician-rated assessments using the Montgomery Asberg Depression Rating Scale (MADRS), the Structured Interview for the Hamilton Anxiety Rating Scale (SIGH-A), the Young Mania Rating Scale (YMRS), and the Perceived Stress Scale-10 (PSS-10) within 2 days

before or the day of the first group session. All participants will be weighed at baseline. Baseline assessments can be done in person, via e-mail, or over the phone.

Study Interventions (week 0 through week 5):
Cognitive-Behavioral Group Therapy (CBGT)
The CBGT intervention will be delivered in groups of 5 to 10 participants including both African American and Caucasian females in an outpatient setting during a 6–week time period. Treatment groups will start their first session when a minimum of 5 participants are conveniently enrolled, and each session will last for 1.5 hours. CBGT intervention will be facilitated by the primary investigator. The principal investigator will have periodic conference calls with Dr. Myra Hunter to review the conduct of the group sessions and to discuss any concerns/questions. Dr. Hunter originally created the manual, and her role is serving as an advisor of this study.

Hunter & Smith's manual was developed from research studies on well-women and women with breast cancer (Alder et al., 2006; Mann et al., 2012). Permission has been given by Myra Hunter, PhD to use this manual in the proposed study. The six sessions are outlined in the manual entitled: Managing Hot Flushes with Group Cognitive Behaviour Therapy: An Evidenced-Based Treatment Manual for Health Care Professionals (Hunter & Smith, 2015) as follows:

Session 1: Psycho-education and the cognitive behavioural model
Session 2: Stress management, improving wellbeing and identifying precipitants
Session 3: Managing hot flushes using a cognitive behavioural approach
Session 4: Managing night sweats and improving sleep (part one)
Session 5: Managing night sweats and improving sleep (part two)
Session 6: Review and maintaining changes (One alteration: Open discussion about maintaining change in the context of other menopause-related issues or topics that were covered in sessions 1-5. Other related menopause issues may include topics such as weight changes, sexual functioning, and/or cognitive functioning. The group may discuss the challenges of maintaining change due to mood and/or anxiety disorders. The PI will facilitate this topic in lieu of maintaining change in the context of breast cancer. The group may chose topics for part of the final session as stated in the manual.

Study sessions will be audio recorded to assess reliability of following the treatment manual. The study sessions will be randomly reviewed by another study staff member to ensure quality control and fidelity will be verified by a checklist provided by Dr. Hunter.

End of Study (week 6): All participants will be asked to complete the same assessments completed at baseline. They will be asked to complete the following self-rated assessments: Hot Flush Frequency and Problem Rating Scale (HFFPRS), Hot Flash Belief Scale (HFBS), Menopause Representation Questionnaire (MRQ), Hot Flash Related Daily Interference Scale (HFRDIS), Snaith-Hamilton Pleasure Scale (SHAPS), Quick Inventory of Depression Symptomatology-Self Report (QIDS-SR16) and the Short-Form Couple Conflicts Scale (CTS2S). All participants will also be evaluated by clinician-rated assessments using the Montgomery Asberg Depression Rating Scale (MADRS), the Structured Interview for the Hamilton Anxiety Rating Scale (SIGH-A), the Young Mania Rating Scale (YMRS), and the Perceived Stress Scale-10 (PSS-10). All participants will be weighed at their end of study visit.

The data can be collected immediately after the end of the last study session or within 2 days of the last study session. End of Study assessments can be done in person, via e-mail, or over the phone.

The Hot Flush Weekly Diary will be collected each week.

Study Assessments

Demographics: including date of birth, race, ethnicity and smoking status
Medical and Treatment History: including date of last menstrual period, number of menstrual periods in the past year, and treatment received to treat vasomotor and/or mood symptoms.
Concomitant medication(s): we will collect concomitant medication information on all medications a participant is taking at the time of screening and within the 90 days prior to screening. Participants will be asked if there have been any changes to medications at each study session.

Participant-rated

Quick Inventory of Depression Symptomatology-Self Report (QIDS-SR16): This 16-item scale will be used to measure depression severity. This self-reported questionnaire was developed based on the DSM-V diagnostic criteria for a major depressive disorder episode.
The Hot Flush Weekly Diary: This objectively measures the frequency and intensity of daily hot flashes and night sweats. It is used one week prior to starting the intervention to gather baseline data and then weekly during the CGBT sessions.
The Menopause Representation Questionnaire (MRQ): This is a 32-item scale developed by Hunter & O'Dea (2001) to assess the cognitive appraisal of menopause. The questionnaire was derived from self-regulation theory. The MRQ consists of 2 sections (identity and beliefs sub-scales). The identity scale measures symptoms that are attributed to menopause. The greater the symptom attribution to menopause the greater menopause was viewed as having a bigger impact on their life. The items on the identity scale are scored from 0-2, with *Yes= 2, Uncertain= 1 and No=0.* Summation of scores range from 0-40. The beliefs scales consists of 6 subscales, measuring positive and negative consequences of menopause, time frame and the coping/control scale, which measures feelings of control over menopause symptoms. The belief scale items are scored on a Likert scale- *Strongly Agree (5) to Strongly Disagree (1).* Negative impact (1,4,6,10,12), relief/new phase (2,11,13) and control/coping (5,8,14,17) are used in the current study as they have higher reliability (personal communication with the author).
Hot Flush Frequency and Problem Rating Scale (HFFPRS): This is a 5-item rating scale assessing hot flush frequency and how much those hot flushes cause problems, distress or interferes with daily routine.
The Hot Flash Daily Interference Scale (HFRDIS): This is a 10-item rating scale assessing the degree to which hot flashes interfere with daily functioning in nine areas (i.e., work, social activities, leisure activities, sleep, mood, concentration, relations with others, sexuality, and enjoyment in life). The tenth item requires rating the degree to which hot flashes interferes with overall quality of life. The degree of interference is rated on a 0 – 10 point Likert scale.
The Hot Flash Beliefs Scale (HFBS): This is a 63-item measure that uses a six-point response scale, coded from 0-5 (i.e., strongly disagree, moderately disagree, mildly disagree, mildly agree, and strongly agree). This instrument was developed to assess the cognitive appraisal of women experiencing HFNS. Rendall et al. (2008) suggested that systematized use of this instrument will

provide reliable data and **"**contribute to an increased understanding of the relationship of cognitions to the experience of hot flushes and night sweats" (p.167). Systematized use can help define reasons for individual differences in response to menopausal symptoms that can potentially inform and evaluate psychological treatment interventions that will alleviate stress related to this developmental milestone.

Short-Form Couple Conflict (CTS2S): A Short Form of the Revised Conflict Tactics Scales. This is a 20-item assessment designed to assess how couples handle conflict.

Snaith-Hamilton Pleasure Scale (SHAPS): This is a 14-item assessment designed to measure hedonic experience or positive valence.

Managing Menopausal Symptoms: Evaluation of Groups: An evaluation of CGBT sessions and techniques learned. This is a short questionnaire asking participants to rate their experience of the group sessions, the effectiveness of the group sessions and the relaxation and breathing skills. The ratings are on a 5-point Likert scale.

The Perceived Stress Scale-10: This is a self-rated psychological measurement designed to measure perceived stress.

Clinician-rated

MINI International Neuropsychiatric Interview (MINI) for DSM-V: A Clinical Interview for DSM-V Axis I diagnoses.

Documentation of Menstrual Cycles: Interview based on NAMS criteria.

Montgomery-Asberg Depression Rating Scale for monitoring depressive symptoms (MADRS): This is a 10-item clinician-rated measure that queries symptoms of depression.

The Structured Interview for the Hamilton Anxiety Rating Scale (SIGH-A): This is a 14-item clinician-rated measure designed to assess the severity of anxiety.

Young Mania Rating Scale (YMRS): This is an 11-item clinician rated instrument designed to quantify severity of participant's current symptoms of mania

BMI: A standard BMI calculator will be utilized for height and weight.

Table 1: Study Procedures Schedule

	Screening	**TX(1) Baseline**	**TX(2)**	**TX(3)**	**TX(4)**	**TX(5)**	**TX(6) End of Intervention**
Weeks		0	1	2	3	4	5
Visit	1	2	3	4	5	6	7
Intervention		X	X	X	X	X	X
Clinician Rated Assessments							
Demographics and Height	X						
Weight	X	X					X
Tracking and Documentation of Menstrual Cycles	X						
MINI	X						
MADRS	X	X					X
YMRS	X	X					X
SIGH-A	X	X					X
Concomitant Medications	X	X	X	X	X	X	X
Patient Rated Assessment							
QIDS	X	X	X	X	X	X	X

PSS	X	X					X
The Hot Flush Weekly Diary		X	X	X	X	X	X
HFFPRS		X					X
MRQ		X					X
HFBS		X					X
HFRDIS		X					X
SHAPS		X					X
CTS2S		X					X
Managing Menopausal Symptoms: Evaluation of Groups							X

Medication regimens to treat their DSM-V diagnoses will be encouraged to continue in order to determine if the CBGT accounted for any change in symptoms. Changes to medications during study participation will not be permitted. All concomitant medications taken during the study will be documented, including information on the indication, dosing, and dates of administration.

Efficacy & Data Analysis

Statistical Analysis:
Descriptive statistics will be used to describe demographic and clinical variables. This includes means and standard deviations for continuous variables and number and percentages for categorical variables. Difference in outcome measures from baseline to post-treatment will be determined by a matched-pairs *t*-test. Regression analysis will be used to assess the significance of the covariates on the differences of the 3 outcome variables. The significance of the race covariate in the regression models will be of special interest to the study. Statistical significance will be based on a Type I error rate of 0.05 for all statistical tests (two-tailed). Since this is an exploratory study no adjustment will be made for multiple comparisons.

Sample size determination.
For a two-tailed test, setting $\alpha = 0.017$ to simultaneously account for the 3 outcome variables and assuming the dropout rate = 20%, a total sample size of 60 will provide at least 80% power for detecting a medium effect size (Cohen's $d = 0.5$) in difference in outcome measure from baseline to post-treatment. A total sample size of 30 using these parameters would enable the detection of a large effect size (Cohen's $d = 0.8$).
Protecting Patient Privacy: Study information is collected in a private office by the research coordinator and study doctor. Discussions regarding participant information or patient care will be restricted to private offices and involvement will be limited to study related staff.

Prior to the participation, all participants will be asked to agree to maintain the confidentiality of all members of the group by signing the ICF. Participants will be reminded of this agreement at each group session.

Protecting Data Confidentiality: Patient medical records are stored electronically, in Ambulatory EMR (aEMR), and are password protected. Only investigators and staff involved with the study have access to this information. All study participants are assigned a study ID. This ID is composed of a number, assigned sequentially, and the participant's initials. This identification code will take the place of a participants name on all study documents with the exception of the consent form, HIPAA authorization, and study participant ID log, all of which

will be stored separately from other study related documents in order to maintain patient confidentiality. All paper source documents and Case Report Forms (CRFs) will be stored in locked offices, and will only be listed with the study ID number and no identifying information. Only study staff will have access to the source documents and CRFs, including REDCap. For additional information on REDCAP, see "Digital Data Collection of Patient Assessments" section on pages 10-11. In order to provide additional confidentiality protection for this information, we will obtain a Certificate of Confidentiality from the National Institutes of Health.

Recordings of the group sessions will be audio only and participants will not be identified on the tapes. The recordings will be kept in a protected program folder on a password-protected local hard drive that will be physically located in a locked environment, the Mood Disorders Program. Only investigators and staff involved with the study have access to this information. The audio files will be kept until 7 years after the last date of service delivery (i.e. EOS visit) and will be deleted at the end of 7th year.

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