A randomised controlled trial of cognitive behaviour therapy for women with problematic menopausal hot flushes: Trial protocol.

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ARTICLE SUMMARY

Article focus

- There is a need for safe and effective, non-hormonal treatments for menopausal symptoms, i.e. hot flushes and night sweats.

- This protocol paper outlines the design of a randomised controlled trial of self management psychological interventions for menopausal hot flushes and night sweats.

- The RCT aims to evaluate the effectiveness of Group cognitive behaviour therapy (CBT) and Self-Help CBT verses no treatment control in managing frequency and problem rating of hot flushes and night sweats.

Key messages:

- This is a trial protocol

- The study is the first study to use both self-report and physiological measures to examine the effectiveness of two forms of cognitive behaviour therapy for menopausal symptoms.

- If this treatment is successful the interventions can be made widely available to women using manualised training sessions for health professionals, publication of the self help book and educational sessions for women.

Strengths and limitations of this study:

Strengths - the study uses both self report and physiological outcome measures and aims to recruit a diverse sample of menopausal women from a range of backgrounds.

Limitations - may recruit women with only very severe hot flushes thereby reducing

generalisability   to   menopausal   women   or   population   as   a   whole.

ABSTRACT

Objectives Hot flushes and night sweats (HF/NS) are experienced by 60-70% of menopausal women and are problematic for approximately 20-25%. Potential health risks associated with hormone replacement therapy (HT) have led to a significant decline in HT use. There is therefore a need for safe, effective and evidence-based alternative treatments for menopausal symptoms. Previous exploratory work suggests that cognitive behaviour therapy (CBT) is acceptable and effective for women with HF/NS during natural menopause and following breast cancer treatment. This randomised controlled trial compares the effectiveness of Group CBT and Guided Self-Help CBT with no treatment control in reducing HF/NS Problem Rating and Frequency at post treatment (main outcome) and at 6 months post randomisation.

Methods and Analysis

120 women, with 10 or more HF/NS a week for a month are recruited from GP surgeries and the local community of South London. They are randomised to either four weeks of Group CBT, four weeks guided Self-Help CBT or no treatment control. Participants attend a clinical interview, and complete baseline questionnaire measures of HF/NS Problem Rating and Frequency (primary outcomes), mood, quality of life, self-esteem, hot flush beliefs and behaviours, optimism and somatic amplification and undergo 24-hour sternal skin conductance monitoring (SCC - physiological measure of HF/NS) (secondary outcomes). Post-treatment measures (SSC and questionnaires) are collected six to eight weeks later and follow-up measures (questionnaires and a use of medical services measure) at six months post-randomisation.

Ethics and Dissemination

Ethical registration was granted by Kings College London Research Ethics Committee (ref: PNM/08/09-42). All participants provide written informed consent. If

treatment is successful, a Group CBT training manual and training sessions for health professionals, and a Self-Help CBT book will be published. Other CBT delivery options will also be examined (including Computerised Self-Help CBT and Group CBT workshops).

Trial Registration

Current Controlled Trials ISRCTN57302613

INTRODUCTION

Menopausal symptoms - hot flushes and night sweats (HF/NS) - are experienced by 60-70% of women in Western cultures, and are troublesome for approximately 20-25%, who seek medical help.[1] Hormone replacement therapy (HT) is an effective treatment for HF/NS, but there are concerns about its safety following the publication of prospective trials[2, 3] associating HT use with increased risks of breast cancer and stroke. As a result HT use has fallen in the UK from 30 to 10% between 2002 and 2005.[4] Many women prefer non-medical treatment options for these symptoms,[5] consequently there is an urgent need for the development of safe, acceptable and effective non-medical treatments to help women to manage menopausal symptoms.[6]

The aetiology of HF/NS is not clearly understood, but they appear to be associated with the rate of change of plasma oestrogen, which influences the thermoregulatory system via the hypothalamus.[7] Hot flushes are also more prevalent following rapid withdrawal of oestrogen, for example, following surgical menopause or adjuvant chemotherapy for breast cancer.[8] Alterations in estrogen levels (but not absolute oestrogen levels) and neurotransmitters, such as norepinephrine and serotonin, and their subsequent impact on thermoregulatory homeostasis, have been widely implicated in the pathogenesis of HF/NS.[9-11] Freedman[12] proposes that there is a narrowed thermoneutral zone in women who have HF/NS suggesting that small elevations in core body temperature such as changes in ambient temperature or other environmental triggers can activate HF/NS.[13, 14] There is some evidence that the thermoneutral zone is narrowed by elevated brain norepinephrine[12, 15] and general levels of stress.[14] Hot flushes are often associated with social embarrassment,

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anxiety, discomfort and reduced health-related quality of life[16] whereas night sweats are associated with sleep problems and fatigue.

Non-medical treatments such as complementary therapies are popular, but in many cases there is insufficient evidence to support their efficacy.[17-19] Non-hormonal medical treatments such as Clonidine, Megace and Venlafaxine (SSRI) have been found to be effective, but are associated with side effects.[20, 21] In contrast, there is some evidence that relaxation therapy and paced breathing can reduce HF/NS.[22, 23] Anxiety and negative thoughts, associated with embarrassment, feeling out of control and being unable to cope, have also been associated with more frequent and problematic HF/NS.[24, 25] Hunter and Liao[26] developed a four session cognitive behavioural treatment (CBT), which included psycho-education, paced breathing and relaxation to reduce stress and cognitive behavioural therapy to help women manage HF/NS.[5, 26] In an initial study using a patient preference design (no treatment vs. HT vs. CBT) CBT and HT resulted in 50% reduction in hot flush frequency, whereas there were no significant changes in the no treatment group. These findings were replicated in a pilot study using CBT delivered in small groups[27] and in a recent exploratory trial of Group CBT for breast cancer treatment related menopausal symptoms.[28] However, this form of CBT has not yet been evaluated for HF/NS. A recent systematic review of psychosocial interventions for HF/NS concluded that while psycho-educational interventions are acceptable for HF/NS, further evaluation of treatment effects in high-quality randomised controlled trials are required.[29]

The use of self-help methods can be a cost-effective way of delivering treatments that have limited availability.[30] Guided self-help can also address some of the drawbacks

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previously fielded at self-help interventions (i.e. lack of social context/social support and incorrectly completed tasks). In a recent systematic review, guided self-help treatments were found to be comparable to face-to-face treatments for depression and anxiety disorders.[31]

Evaluating treatment efficacy depends on valid and reliable measures of HF/NS. Self-report measures include daily diaries recording frequency and severity of HF/NS and validated scales such as the Hot Flush Rating Scale,[32] or electronic event markers. Sternal skin conductance (SSC) monitoring is considered to be the most valid physiological index of HF/NS.[33] The sweat response seen in HF/NS produces a sudden increase in skin conductivity which tails off (i.e. like a swishy tail). The use of both subjective and physiological measures can increase our understanding of the impacts of interventions.[34] CBT may influence physiological hot flushes, women's perceptions of hot flushes, or both. 24-hour SSC hot flush monitoring has not yet been used to evaluate menopausal treatments in the UK but it has been piloted and is acceptable to women.[35, 36] Hunter and Mann[34] developed a cognitive model of HF/NS that explains how cognitive and behavioural changes might impact on HF/NS. For example, stress and stimulants (such as caffeine) may potentiate HF/NS in symptomatic women, and HF/NS may be more distressing or interfering when they are associated with negative thoughts such as embarrassment, social anxiety, feeling out of control.[34]

Current study

This trial aims to evaluate the effectiveness of Group CBT and Self-Help CBT to alleviate HF/NS in women seeking help for menopausal symptoms. It will compare Group CBT to no treatment (control) and Self-Help CBT to no treatment (control) in a

randomised controlled trial, with a 6-month follow-up. It is the first UK trial to evaluate menopause treatments using both physiological (SSC)[35, 36] and self-report measures of HF/NS.

Specific hypothesis include:

1. Group CBT and Self-Help CBT will be more effective than no treatment in reducing HF/NS Problem Rating (primary outcome) and Frequency at post treatment

2. Group CBT and Self-Help CBT will be more effective than no treatment in reducing HF/NS Problem Rating and Frequency at 6 months post randomisation.

3. Group CBT and Self-Help CBT will be more effective than no treatment in reducing physiological HF/NS at post treatment.

4. Additional analyses will examine the effects of Group CBT and Self-Help CBT on mood and quality of life and possible moderators (optimism and somatic amplification) and mediators (SSC, mood, beliefs and behaviours).

Kings College London Research Ethics Committee approval has been granted (Psychiatry, Nursing and Midwifery Research Ethics Subcommittee, ref: PNM/08/09-42). The trial is registered with Current Controlled Trials (ISRCTN57302613).

METHODS AND ANALYSIS

The study design and participant recruitment (completed May 2010) is shown in Figure 1. Participants are block-randomised to receive either no treatment (access to GP support) or four weekly sessions of Group CBT (herein referred to Group CBT) or a four week guided Self-Help CBT Booklet (herein referred to Self-Help CBT). The

Group CBT was developed from previous work and an exploratory trial[26, 28] and is specified in a treatment manual. Group CBT is delivered by a clinical psychologist, but is designed to be delivered by appropriately trained and supervised health professionals. Post-treatment assessment is conducted 6-8 weeks post-randomisation (1-3 weeks after 4 weeks of treatment). Follow up assessment is conducted 6 months post-randomisation. The primary outcome is Problem Rating of HF/NS (Hot Flush Rating Scale – HFRS)[32] at post-treatment assessment.

Group and Self-Help CBT will be compared to the control group separately, based on identical assumptions. A total sample size of 120, 40 in each group, will have 90% power to detect a clinically relevant difference in mean HF/NS Problem Rating of 2 points[26] controlling for baseline value (estimated to have a mean of 5 and standard deviation of 2.4), a correlation between baseline and post-treatment values of 0.4 (giving a correction factor of 0.84)[37] and a 5% two-sided significance level.

Study sample and recruitment

120 participants will be recruited from posters and leaflets placed in South London GP surgeries, menopause and breast screening clinics, a menopause website (Menopause Matters) and newspaper advertisements over an 18 month period from March 2009 to May 2010. Women opt into the study by returning a tear-off slip on the leaflet or through websites, phone or email.

Inclusion criteria:

1. English speaking women

2. Aged 18 plus

3. Have had problematic HF/NS for at least 1 month (minimum frequency of 10 or more a week).

Women are excluded if they cannot understand English or if they are currently undergoing psychiatric treatment (i.e. their psychiatric problem is the main issue for them at the time).

Procedure

Women who opt in to the study are contacted by telephone for a screening interview. A researcher conducts an eligibility check using the above criteria and explains the study, the three arms of the trial and the randomisation process. Those eligible are sent a participant information sheet, consent form, socio-demographic questionnaire and an appointment for the baseline assessment. The consent process is completed at the assessment appointment, whereby the researcher summarises the information in the participant information sheet and responds to questions about the study. Participants then provide written consent. The researcher then conducts a clinical interview covering medical history including mental health issues, menopause symptoms and treatments used, concomitant medication and therapy use and current life concerns. Participants are given a questionnaire to complete, assessing HF/NS frequency and problem rating, beliefs about HF/NS, health related quality of life, body image satisfaction, self-esteem, stress, dispositional optimism and somatic amplification. After checking that the participant has no allergy to adhesive dressings (e.g. plasters) and does not wear a pacemaker, the SSC hot flush monitor is fitted. Participants are given a magnet event marker, worn on a bracelet, and a 24-hour hot flush diary. They mark the experience of a HF/NS by passing the magnet over the monitor and noting the time and severity of the HF/NS in the diary. Participants wear

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the monitor for 24 hours, carrying out their usual daily activities and removing the monitor only to shower or bathe.

Randomisation: Women are randomised in blocks of 18-30, when sufficient participants have been assessed at baseline to enable group sizes of 6-10 participants in each arm. Participant IDs are inputted into an internet randomisation site and individually randomised to the three treatment arms in the ratio 1:1:1 by the trial coordinator. Within two weeks of randomisation, participants are informed of their group allocation and the clinical psychologist (who delivers the CBT treatment) arranges appointments to deliver the treatments. Assessments take place in the Health Psychology department of King's College London at Guy's Hospital. They are conducted by the trial coordinator and a research assistant who, for practical reasons, are not blind to group allocation. Analysis is conducted by the trial statistician, who is blind to group allocation.

Participants in the Group CBT treatment arm attend 2 hour sessions of Group CBT, once a week for four weeks. Women in the Self-Help CBT arm attend one introductory session with the clinical psychologist (to receive the booklet and discuss the treatment), and complete the booklet over four weeks, receiving a 'guiding' telephone call from the clinical psychologist 2 weeks into treatment. Participants can also contact the psychologist for unscheduled guidance during the treatment phase. Women from all three arms attend post-treatment assessments in the two weeks following the treatment phase (see Figure 1). All participants are interviewed about their use of health services and treatments, as well as any changes to lifestyle and

health during the treatment phase. They complete post-treatment questionnaires and repeat 24-hour SSC hot flush monitoring. Six months after randomisation, participants complete a follow-up questionnaire identical to the post-treatment questionnaire, plus use of health services and treatments, and changes in lifestyle and health over the previous four months since post-treatment assessment.

Group CBT: Group CBT is interactive and psycho-educational, with a focus on helping participants to develop strategies to reduce stress, apply paced breathing and cognitive and behavioural strategies during HF/NS (see Hunter et al[28] and Hunter & Mann[34] for detailed descriptions of the components of CBT for HF/NS). Sessions include information and discussion, individual goal setting and problem-solving, relaxation/paced-breathing practice (using a CD) and homework. Each session takes place at the Health Psychology department of King's College London at Guy's Hospital and is run according to protocol set out in a treatment manual, including presentation slides and handouts. A clinical psychologist has been trained to deliver the treatment and assistants also are trained to assist in the groups. Sessions are audio taped and an independent psychologist, experienced in cognitive behavioural therapy, rates 10% of the sessions for adherence to protocol using a coding sheet created for the purpose.

Self-Help CBT: Self-Help CBT comprises 4 weekly sessions of approximately 1 hour. The approach and sessions are identical to Group CBT, with participants receiving a Self-Help CBT booklet and relaxation/paced breathing CD and the same homework tasks each week. The booklet includes interactive exercises with space for participants to write relevant information. A clinical psychologist trained in the delivery of the treatment provides an information session at the beginning of

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treatment. Participants are provided with the psychologist's contact details for assistance during the 4 week programme. Two weeks into treatment participants receive a telephone call from the clinical psychologist to provide support and discuss their individual treatment goals.

Session 1 aims to engage participants by introducing them to the CBT model of HF/NS.[34] They are informed about physiological, cognitive, behavioural, and emotional components of HF/NS within an overall CBT model of menopausal symptoms and complete tasks on stressful thinking and problem solving techniques. Full body relaxation and paced breathing (slow, deep and even breathing with attentional focus on the breath) is introduced and participants practice relaxation for homework.

Session 2 introduces cognitive and behavioural aspects of hot flushes. Participants revisit the CBT model and information about psychological processes contributing to distress during a hot flush is introduced. Participants' complete tasks on thinking and behaviour during hot flushes and problem solve their unhelpful thoughts. Paced breathing and cognitive behavioural strategies to alleviate HF are discussed.

Session 3 focuses on sleep and night sweats. Participants are taught the mechanisms of sleep and cognitive processes that influence subjective judgements of sleep to address unhelpful cognitions, behaviours and anxieties about sleep.

Session 4 reviews the overall model and goals of the previous three weeks. Participants write their individual maintenance plan.

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No treatment control: Control participants do not receive CBT treatment but have access to their GP and other health care options. Treatments and services accessed during the treatment phase are logged at post-treatment assessment. The control group are offered a form of CBT off-trial at the end of the trial.

Measures

Socio-demographics

Socio-demographic variables include age, height, weight, ethnicity, number of children, education, marital status, employment status, smoking, drinking and exercise. Menopausal status (as defined by STRAW),[38] use of treatments for menopause and concomitant medications and therapies are also recorded.

Primary Outcome: Hot flush Problem Rating

Hot flush problem rating is a subscale of the Hot Flush Rating Scale,[33] calculated as the mean of three items, each measured on a 10 point scale (low to high). Items include "To what extent do you regard your flushes/sweats as a problem?"; "How distressed do you feel about your hot flushes?" and "How much do your hot flushes interfere with your daily routine?"

Secondary Outcomes

Hot flush Frequency and Severity are assessed using the following measures:

Hot Flush Rating Scale[33]: Frequency subscale

The frequency subscale of the HFRS is a retrospective recording of the number of HF/NS experienced in the previous week, e.g. "How often have you had hot flushes in the past week?" Average severity of HF/NS over the previous week is estimated for hot flushes and for night sweats separately (1=mild, 2=moderate and 3=severe).

24-hour hot flush diary

Women monitor their HF/NS prospectively for 24 hours. When they experience a hot flush or night sweat they note down the severity (1=mild, 2=moderate and 3=severe) and the time at which it occurred.

24-hour ambulatory sternal skin conductance and event marker

During the 24-hour diary monitoring period women wear an ambulatory SSC monitor.[39] The monitor is approximately 6x6cm, with two 8cm electrodes attached to an adhesive electrode patch by press studs. This electrode patch is attached to the sternum, two inches below the sternal notch and holds the monitor close to the body. Skin conductance is measured by passing a pulse through the electrodes every 5 seconds, indicated by a green flash of an LED on the monitor. A hot flush is defined by an increase in conductance of 2mmhos or more in 30 seconds, occurring no less than 15 minutes since the last SSC-defined HF/NS (i.e. 15 minute lock out period).[40] For each SSC-defined hot flush or night sweat, SSC level and the time at which it occurred are extracted for analysis. Women indicate that they are experiencing a HF/NS by passing a magnet near to the monitor. The magnet is worn on a bracelet.

The times at which the magnetic event marker is registered are summed to produce a 24 hour HF/NS subjective frequency.

Health related quality of life

General physical and mental health are indexed using the *General Health Survey Short Form 36* (SF-36),[41] a widely used 36 item health survey. Nine physical and mental health summary scales are constructed, with a possible range from 0 to 100, where higher scores indicate better health.[42]

Perceptions of physical and emotional symptoms are measured using the *Women's Health Questionnaire,*[43] which is standardised on samples of mid-aged women. The WHQ contains 36 items, which are scored on 4-point scales. Nine subscales are formed by counting the number of items scoring 2 or 3 and dividing by the number of items for each scale, resulting in scales from 0 to 1. The WHQ has been widely used to evaluate interventions for menopausal symptoms.[44]

Process measures

Beliefs about hot flushes and night sweats

HF/NS beliefs were measured using the Hot Flush Beliefs Scale,[45] a 27-item scale comprising of three subscales including beliefs about HF in a social context, beliefs about ability to deal with HF, and beliefs about night sweats and sleep. An additional scale is included assessing behavioural reactions to HF/NS (avoidance, safety behaviours and positive acceptance).

Perceived stress

The Perceived Stress Scale[46] measures 14 items, on a scale from 0 (never) to 4 (very often). Items are summed to form a scale from 0-56, where 0 is low stress and 56 is high stress.

Somatic amplification

Barsky, Grace and Klerman's Somatic Amplification Scale[47] is a 10 item scale measuring a general tendency toward body focus, including items such as "When someone else coughs, it makes me cough too" (1=not like me to 5=very much like me). The mean for the items is calculated to give a 5-point scale, where 5 is high somatic amplification.

Dispositional optimism

The Revised Life Orientation Test (LOT-R)[48] measures dispositional optimism on a 8-item scale including "In uncertain times, I usually expect the best" (0=strongly disagree to 4=strongly agree). Items are summed to give a total score ranging from 0-32, where high scores indicate higher dispositional optimism.

Self-esteem

Rosenberg's Self-Esteem Scale[49] measures perceived self worth on a 10-item scale. Items are scored 1-4 in the direction of negative self-esteem and scores are summed to give a total self-esteem score ranging from 10-40.

Body Image

The Multi-Dimensional Body Self Relations Questionnaire – Appearance Subscale (MBSRQ-AS)[50] is a 34-item measure which assesses attitudes towards ones body. It has five subscales – appearance orientation, appearance evaluation, overweight preoccupation, self-classified weight and the body areas satisfaction scale - and includes items such as "most people would consider me good-looking." Items are

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presented on a 5-point scale from 1=definitely disagree to 5=definitely agree and means are calculated for the different subscales.

Menopause Representation Questionnaire

The Menopause Representations Questionnaire (MRQ)[51] is a 37-item measure designed to assess women's cognitive representations (general beliefs) of the menopause with respect to identity, consequences, time-line and control/cure. Items are scored on a 5-point scale from strongly agree to strongly disagree (5-1). The identity subscale is scored from 0-2. Mean scores are calculated for the subscales.

Treatment evaluation

Participants randomised to Group CBT and Self-Help CBT are asked to rate the specific elements of the intervention and the sessions/booklet overall. Use of the relaxation CD, attendance and completion of homework are also being monitored for both treatment arms at each treatment week and through self-report on CBT evaluation forms. At follow-up participants are interviewed by telephone or in person using open questions to ascertain their subjective evaluation of the treatments.

Table 1: Study measures

Phase	A0 Baseline assessment	Treatment phase	A1 Post-treatment assessment	A2 Follow up assessment
Interview measures				
Medical history, menopause symptoms, concomitant medications and therapies	X			
Questionnaire measures				
Weekly diaries		X[1]		
Demographics: Age, BMI, ethnicity, parity, marital status, education, employment, smoking, drinking, exercise	X			
Hot flush rating scale	X	X[1]	X	X
Menopause representations questionnaire	X		X	X
Hot flush beliefs scale	X		X	X
Women's health questionnaire	X		X	X
Rosenberg's self-esteem scale	X		X	X
Multi-dimensional body self relations questionnaire	X		X	X
Perceived Stress Scale	X		X	X
Somatic Amplification Scale	X		X	X
SF-36	X		X	X
Life Orientation Test	X			
Use of services			X	X
CBT session evaluation		X[1]		
24 hour monitoring				
Sternal skin conductance	X		X	
24 hour diary	X		X	

Notes: [1]Completed each week for 4 weeks by those randomised to Group CBT and Self-Help CBT only

Analysis

An analysis plan has been agreed (i.e. prior to completion of data collection). A trial statistician carries out primary and secondary data analysis, and is blind to group allocation. Unless indicated, scales are calculated according to published scoring algorithms. All statistical tests are two sided (level of significance = 0.05). The outcome analyses are performed using the statistical software SPSS version 15.0. An intention to treat analysis of difference in Problem Rating HFRS between intervention and control groups (Group CBT versus no treatment or Self-Help CBT versus no treatment) is conducted using a linear mixed model, utilising fixed and random effects, allowing for the baseline measurements to control for pre-treatment differences and clinically relevant covariates. Secondary outcomes at post-treatment are analysed similarly. Follow-up data at 6 months is also explored through linear mixed models utilising repeated measures analyses, allowing simultaneous modelling of the two outcome time points. Mediation of treatment effects by hot flush beliefs and behaviours, mood, self-esteem, body satisfaction, stress, quality of life and frequency of HF/NS defined by skin conductance rises will be explored using a two stage least squared method.[52] Moderation by optimism and somatisation is also tested using multiple-group modelling.[53]

ETHICS AND DISSEMINATION

Ethical and safety considerations: some women consider the menopause a taboo subject and may be embarrassed about the topic of the questionnaires and CBT sessions (menopause, hot flushes, night sweats etc). However, we ensure that all potential participants are fully informed about study materials prior to obtaining consent and that they are given the opportunity to withdraw from the study should

they feel uncomfortable. Women will also be randomised into three groups, two active treatment groups and one no treatment group. Some participants may be disappointed that they are not receiving a potentially helpful treatment. However, we offer all no treatment participants a form of the CBT intervention at the end of the trial. We also ensure that all participants are fully aware of the randomisation procedure prior to obtaining informed consent.

The SSC monitor is attached to the skin with an adhesive electrode patch and operates with an event marker (a magnet on a bracelet). The adhesive electrode patch may cause irritation to those with skin allergies and the magnet may interfere with a pacemaker. Participants will be asked if they have skin allergies or a pacemaker prior to wearing the monitor. Those who do will not be asked to wear the monitor and this will not exclude them from the study.

We hope to disseminate the study through conferences and journal publications. If the treatment is successful we plan to produce a Group CBT training manual and training sessions for health professionals, publish the Self-Help CBT as a book, design a further study using a computerised version of Self-Help CBT and hope to examine other delivery options for the intervention (guided vs. unguided Self-Help CBT, workshops and 1 day, 2 day versions of Group CBT). If effective these interventions will enable menopausal women with problematic hot flushes and night sweats to easily access acceptable, safe alternative treatment options. These CBT based interventions can also be used to enable women to stop using HT when this is indicated.

Competing interests: The authors declare that they have no competing interests.

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