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Cognitive behaviour therapy for menopausal symptoms following breast cancer treatment: Who benefits and how does it work?

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ABSTRACT

Objectives: Cognitive behaviour therapy (CBT) has been found to reduce the impact of menopausal symptoms, hot flushes and night sweats. This study investigates the moderators and mediators of CBT for women who had problematic menopausal symptoms following breast cancer treatment.
Study design: Analysis of 96 patients with breast cancer induced menopausal symptoms recruited to the MENOS1 trial; 47 were randomly assigned to Group CBT and 49 to usual care. Questionnaires were completed at baseline, 9 and 26 weeks post randomisation. Potential moderators and mediators, including sociodemographic, clinical and psychological factors, of the treatment effect on the primary outcome were examined.
Main outcome measure: Hot Flush Problem Rating.
Results: CBT was effective at reducing problem rating at 9 weeks regardless of age, BMI, time since breast cancer diagnosis, menopausal status at time of diagnosis, or type of cancer treatment (radiotherapy or chemotherapy or endocrine treatment). The treatment effect was significantly greater in women not receiving chemotherapy, those with higher levels of psychological distress at baseline and for non-white women. Beliefs about control/coping with hot flushes were the main mediators of improvement in problem rating following CBT. Beliefs about hot flushes in a social context, depressed mood and sleep problems were also identified as mediators.
Conclusions: These findings suggest that CBT is widely applicable for breast cancer patients who are experiencing treatment related menopausal symptoms, and that CBT works mainly by changing beliefs and improving mood and sleep.

1. Introduction

Hot flushes and night sweats (HFNS) are commonly reported by women who have had breast cancer but are challenging to treat [1]. Between 65% and 85% of women treated for breast cancer report having HFNS, 60% rate them as severe, and these symptoms impact on quality of life, sleep, and mood [2,3]. Chemotherapy or adjuvant endocrine treatments can result in rapid reduction of oestrogen concentrations, which in turn induce or exacerbate HFNS. Hormone replacement therapy is generally contraindicated because it can increase the likelihood of recurrence, and, if left untreated, HFNS can reduce adherence to endocrine therapy [4,5]. A Cochrane review of non-hormonal medical treatments concluded that selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), clonidine and gabapentin are mild to moderately effective in reducing the frequency of HFNS in women with a history of breast cancer [6] but side-effects were often reported [8]. Non-medical treatments tend to be preferred by breast cancer survivors [4] but non-pharmacological therapies, such as vitamins, herbal remedies, in general, do not have a strong evidence base [7].

There is increasing awareness that multidisciplinary approaches are needed [8], and growing evidence from three recent randomised controlled trials that cognitive behaviour therapy (CBT) can effectively reduce the impact of HFNS for women who have had breast cancer [9,10] and for well women during the menopause transition [11]. The three trials used group CBT (four to six weekly sessions of CBT; 8 h in total) developed by Hunter and colleagues. The MENOS1 trial [9,12] is an RCT of CBT ($n = 47$) versus treatment as usual (TAU) ($n = 49$) targeted at improving HFNS in breast cancer survivors. At 9 weeks after randomisation HFNS problem rating scores were significantly lower in the CBT group compared to usual care (adjusted mean difference [AMD] = −1.67, 95% CI −2.43 to −0.91, $p < .001$), an effect that was maintained at 26 weeks (AMD = −1.76, 95% CI −2.54 to −0.99); relating to standardised mean differences of $d = 1.19$ and $d = 1.07$, respectively [9].

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A recently conducted gap analysis of UK breast cancer research highlighted the need for the development of effective theory-based interventions for treatment-related symptoms experienced by breast cancer survivors, with analysis of moderators and mediators and identified components [13]. This paper reports on planned analyses of the MENOS1 study to consider moderators and mediators of the treatment effect – that is, to identify for whom CBT works and how. The MENOS1 study included a relatively heterogeneous sample, involving women of different menopausal stages at diagnosis and on different treatments. While there is evidence that CBT is effective for women with HFNS, who were premenopausal when diagnosed with breast cancer [10], we do not know whether CBT can be confidently offered to different subgroups of women, for example those who had had chemotherapy or were having endocrine treatments. Similarly, does educational level, age or ethnicity influence CBT outcomes? In addition, while the main reports determined efficacy of CBT for breast cancer patients, neither considered the mechanisms by which CBT works [14]. Based on a cognitive model of HFNS [15] we hypothesised that CBT works by changing overly negative beliefs concerning HFNS and by helping women to use more adaptive behavioural strategies, which reduce the perceived impact of HFNS rather than their frequency.

2. Materials and methods

2.1. Study design

The design of the MENOS1 RCT, and intervention procedure, is described in detail in the trial protocol [12] and main outcome paper [9]. Recruitment took place between March 2009 and August 2010 from breast cancer clinics in London, UK. Patients having at least ten problematic HFNS per week, who had completed medical treatment for breast cancer (surgery, radiotherapy, or chemotherapy), with no evidence of other cancers or metastases were included. Those taking adjuvant endocrine treatment were eligible. Sample characteristics are shown in Table 1. Following baseline assessment they were randomised to Group CBT or TAU and reassessed after 9 and 26 weeks; Group CBT involved 6 weeks of 1.5 h of CBT in groups of 6–8 women. All participants gave written, informed consent before taking part. Ethical approval was obtained from the UK NHS Research Ethics Committee.

2.2. Measures

2.2.1. HFNS measures

The primary outcome was the HFNS problem rating (Hot Flush Rating Scale) [16] at 9 weeks after randomisation, which is the mean of three 10 point scales assessing the extent to which symptoms are problematic and interfere with daily life; 10 indicates most problematic HFNS. A difference of two points or more is regarded as clinically relevant. The scale had good reliability in the MENOS1 sample (Cronbach $\alpha = 0.89$). HFNS frequency subscale measures the total number of HFNS reported in the past week [16]. Sternal skin conductance (SSC) was included to measure physiological HFNS frequency using the Bahr SSC monitor [Simplex Scientific; Middleton, WI, USA]. A 6-cm by 6-cm monitor measured SSC every 10ýs by passing an electric current across two electrodes attached to the sternal region of the chest.

2.2.2. HFNS beliefs and behaviours

Hot Flush Beliefs Scale [17] is a 27-item scale comprising three subscales: (i) beliefs about HF in social context (e.g. everyone is looking at me), (ii) beliefs about coping/control of hot flushes (e.g. when I have a HF I think they will never end), and (iii) beliefs about night sweats and sleep (e.g. if I have NS I'll never get back to sleep). The HFNS Behaviour Scale [18] was developed using factor analysis and includes three subscales measuring, (i) positive coping behaviour, e.g. accepting HFNS, using breathing and calming responses; (ii) avoidance behaviour, and (iii) cooling behaviours, such as fanning oneself.

2.2.3. Stress and mood measures

The Perceived Stress Scale [19] includes 14 items, on a scale from 0 never to 4 very often; items are summed to form a 0–56 scale with a high score representing high stress. Subscales of the Women's Health Questionnaire (WHQ) [20] were used to measure depressed mood, anxiety and sleep problems. The WHQ was standardised on women aged 45–65 years and has been widely used to evaluate interventions for menopausal symptoms.

2.2.4. Personality measures

The Somatosensory Amplification Scale (SSAS) [21] has 10 items rated on 5 point scales measuring respondent's tendency to experience somatic sensation as intense, noxious and disturbing. *Dispositional optimism*. The Revised Life Orientation Test (LOT-R) [22] measures dispositional optimism on a 6-item scale rated on a 5 point scale. High scores indicate greater dispositional optimism.

2.2.5. Demographic and health behaviour variables

Demographic and health behaviour factors were recorded at baseline including: age, height, weight, ethnicity, education, employment status, smoking, and exercise frequency. Breast cancer treatments, use of concomitant medications and therapies were also recorded.

2.3. Statistical analysis

The moderator analysis extended the model used in the main study to test changes in HFNS problem rating over the study. This involved the estimation of linear mixed effects model with random intercepts for participant and cohort group. Time, treatment group, baseline HFNS problem rating score and age at randomisation were included in the model as covariates. A time by treatment group interaction term was also included to allow the calculation of adjusted means at individual time points. This model was extended to allow for the testing of potential moderators of the effect of CBT on HFNS problem rating at 9 weeks by including the main effect of the moderator variable, and two and three-way interactions of the moderator variable with time and treatment group. Inclusion of moderator by time by treatment group interaction terms allowed for the assessment of effect modification at 9 weeks. To aid interpretation effect sizes were calculated for the moderator effects. Effect sizes were standardised mean differences (Cohen's d) for the categorical variables and standardised regression coefficients for continuous variables (beta's). Although the study was not specifically powered to detect moderator variables, power was adequate: assuming 80% power, a medium sized moderator effect was detectable ($R^2 = 7.7$).

The original trial identified that patients receiving CBT reported significantly less depression symptoms, anxiety, stress and sleep problems at 9 weeks compared to those receiving TAU. In the present analysis, we evaluated whether HFNS beliefs and behaviours also altered over the intervention using ANCOVA to estimate the effect of treatment on the variable at 9 weeks, adjusted for the baseline level of the variable [23]. Using the variables identified as changing significantly from the original trial and analysis conducted here (HFNS beliefs and behaviours), mediation was evaluated using path models that estimated the indirect effect of treatment group on HFNS problem rating at 26-weeks through the residualised change in the potential mediator at the 9-week follow-up. Both the potential mediator at 9 weeks and HFNS problem