Psycho-Oncology
Psycho-Oncology **24**: 1159–1166 (2015)
Published online 9 March 2015 in Wiley Online Library (wileyonlinelibrary.com). **DOI**: 10.1002/pon.3794

A randomised controlled trial of a brief cognitive behavioural intervention for men who have hot flushes following prostate cancer treatment (MANCAN)†

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†The copyright line for this article was changed on 17 April 2015 after original online publication.

Received: 10 July 2014
Revised: 2 October 2015
Accepted: 2 November 2015

Abstract

***Objective*: Hot flushes and night sweats (HFNS) are experienced by up to 80% of prostate cancer patients undergoing androgen deprivation therapy (ADT). This study evaluates the effects of a guided self-help cognitive behavioural therapy (CBT) intervention on HFNS problem-rating (primary outcome), HFNS frequency, mood and health-related quality of life (secondary outcomes) in patients undergoing ADT.**

***Methods*: Patients reporting treatment-induced HFNS were randomly assigned to CBT ($n = 33$) or treatment as usual (TAU) ($n = 35$), stratified for cancer type. The CBT intervention included a booklet, CD plus telephone contact during a 4-week period. Validated self-report questionnaires were completed at baseline, 6 weeks and 32 weeks after randomisation. The primary outcome was HFNS problem rating (perceived burden of HFNS) at 6 weeks after randomisation. Potential moderators and mediators were examined. Data analysis was conducted on a modified intention-to-treat basis.**

***Results*: Compared with TAU, CBT significantly reduced HFNS problem rating (adjusted mean difference: −1.33, 95% CI −2.07 to −0.58; $p = 0.001$) and HFNS frequency (−12.12, 95% CI −22.39 to −1.84; $p = 0.02$) at 6 weeks. Improvements were maintained at 32 weeks, but group differences did not reach significance. There were significant reductions in negative HFNS Beliefs and Behaviours following CBT, but not in mood or quality of life.**

***Conclusions*: Guided self-help CBT appears to be a safe and effective brief treatment for men who have problematic HFNS following prostate cancer treatments. Further research might test the efficacy of the intervention in a multicentre trial.**

Introduction

Prostate cancer is the most common cancer among men in the United Kingdom and the second leading cause of cancer related death in men in the Western world [1]. Androgen deprivation therapy (ADT) is prescribed to inhibit cancer progression [2] but is associated with debilitating side effects, including hot flushes and night sweats (HFNS), that affect up to 80% of men having ADT [3,4]. HFNS are not well understood; reductions in androgen levels are believed to alter the function of brain neurotransmitters, leading to disruption of the thermoregulatory system in the hypothalamus [4,5]. If left untreated, HFNS are associated with sleep disturbance, distress and reduced quality of life [6,7], and reduced treatment adherence [4,5]. The symptoms tend to be frequent [8,9] and can persist for several years [10].

There are few safe and effective treatments for men with HFNS. A systematic review of treatments for HFNS in prostate cancer patients concluded that diethylstilbestrol, megestrol acetate and medroxyprogesterone are the most effective treatments, but all have side-effects that are not well tolerated [4]. With an increasing number of prostate cancer patients being diagnosed [11], there is a pressing need for safe, acceptable and effective treatments to help prostate cancer survivors manage HFNS.

There is evidence that cognitive behavioural therapy (CBT) is a safe and effective intervention for reducing the impact of HFNS and improving psychosocial functioning for menopausal women [12] and breast cancer survivors [13,14]. This relatively brief intervention is effective when delivered in groups and in a guided self-help format [12–15], and is based on a cognitive model of HFNS [16]. To our knowledge CBT has not yet been investigated in prostate cancer patients undergoing ADT who are experiencing troublesome HFNS.

MANCAN is a randomised controlled trial of guided self-help CBT compared with treatment as usual (TAU). We hypothesised that guided self-help CBT would be more effective than TAU in reducing HFNS problem-rating (the extent to which HFNS are bothersome and interfere with life) [17,18]. Secondary outcomes include the effects on HFNS frequency, sternal skin conductance monitoring [19], mood and quality of life. The trial was funded by Prostate Cancer UK and registered with the

UK Clinical Research Network (UKCRN; Trial ID: 10904). Ethical approval was obtained from South East London 2 Research Ethics Subcommittee, reference: 11/LO/1114. The authors have no conflicts of interests.

Methods

Design and participants

Guided self-help CBT and TAU control group were compared in a randomised controlled trial. The study design is described in the trial protocol [20]. Prostate cancer patients were recruited by nurse specialists and medical staff from oncology and urology clinics in London, UK, between April 2012 and October 2013. Inclusion criteria were: English-speaking men over 18 years old, undergoing ADT and having problematic HFNS [score >2 on the Hot Flush Rating Scale (HFRS) [21] for at least 1 month and a minimum weekly frequency of 10]. Exclusion criteria were: undergoing current radiation therapy, chemotherapy and having medical/psychiatric conditions that would affect ability to participate.

Procedures

Potentially eligible patients were screened by telephone (by ES); those meeting the criteria were sent study information and baseline questionnaires. Following consent and return of questionnaires, they attended a short clinical interview (with ES), and the Sternal Skin Conductance (SSC) monitor (see measures) was fitted for 48 h; at the end of the interview they were informed of their group allocation (CBT or TAU) (see Figure 1).

At a second assessment interview 6 weeks later (with OY) (post-treatment), participants completed questionnaires, reported any health or medication changes in the previous 6 weeks and wore the SSC monitor again for 48 h. At 32 weeks after randomisation (6 months follow-up), postal questionnaires were completed. At the end of the study, TAU participants were offered the guided self-help CBT off trial.

Randomisation and blinding: Computer software (Rand.exe version 6) was used to assign men randomly to the CBT or TAU groups, stratifying for cancer type (i.e. local or locally advanced vs. metastatic). A researcher (OY) generated the randomised allocation list in sealed envelopes at the beginning of the trial. The patients and the clinical psychologist (ES) could not be blind to group allocation; however, the researcher (OY) remained blind to group allocation throughout the trial, carried out 6-week and 32-week assessments and performed all data entry. To check whether the researcher was successfully masked, he estimated which group participants had been allocated to after the post-treatment assessment. Masking was reasonably successful with the allocation of 61% being correctly identified and equal proportions from CBT and TAU groups. An independent researcher (EG), also masked to group allocations, performed the statistical analyses.

The intervention: The guided self-help CBT treatment, based on interventions developed by Hunter and colleagues [12,13,22,23], is a 4-week intervention consisting of a booklet [20] containing:

i) information about causes of HFNS, the CBT model and factors affecting HFNS, such as modifying triggers, e.g. caffeine (Week 1),
ii) cognitive therapy for overly negative thoughts and beliefs about HFNS, and behavioural strategies, e.g. using paced breathing and relaxation, to reduce stress and manage HFNS (Week 2),
iii) CBT strategies for managing sleep and NS (Week 3),
iv) suggestions for maintaining changes in the context of prostate cancer (Week 4).

The intervention which was effective for women with HFNS was adapted for men, being informed by a qualitative study [24], and was piloted on 12 prostate cancer survivors who provided feedback on content and how much guidance they required, for example the term 'hot sweats' was preferred to 'hot flushes'.

At the end of the assessment those randomised to CBT were given the booklet and a CD with relaxation/paced breathing exercises by a clinical psychologist (ES). Guiding consisted of a telephone call (average 30 min; range 20–40 min) from the clinical psychologist 2 weeks into treatment to provide support and discuss individual goals and progress. TAU included access to clinical staff, and cancer information and support services, which provided information and advice about HFNS.

Measures

Sociodemographic and clinical information were obtained from baseline questionnaires and the clinical interview. Health economics questions, adapted from Beecham & Knapp [25], included number of consultations at primary and secondary care and treatments used at post-treatment and follow-up.

Primary outcome was HFNS problem-rating at 6 weeks post-randomisation using the Hot Flush Rating Scale (HFRS) [21]; problem-rating or interference is associated with help-seeking and quality of life [17] and is recommended as the most appropriate outcome measure in clinical trials [18]. HFNS problem-rating score is the mean of three items (assessing the extent to which flushes are problematic, distressing and interfere with daily life) rated on 10-point scales where higher scores indicate more bothersome HFNS. A change of 2 points is considered clinically relevant in studies of women [12,13]. At baseline, internal consistency was high (Cronbach alpha $=0.87$).

DOI: 10.1002/pon

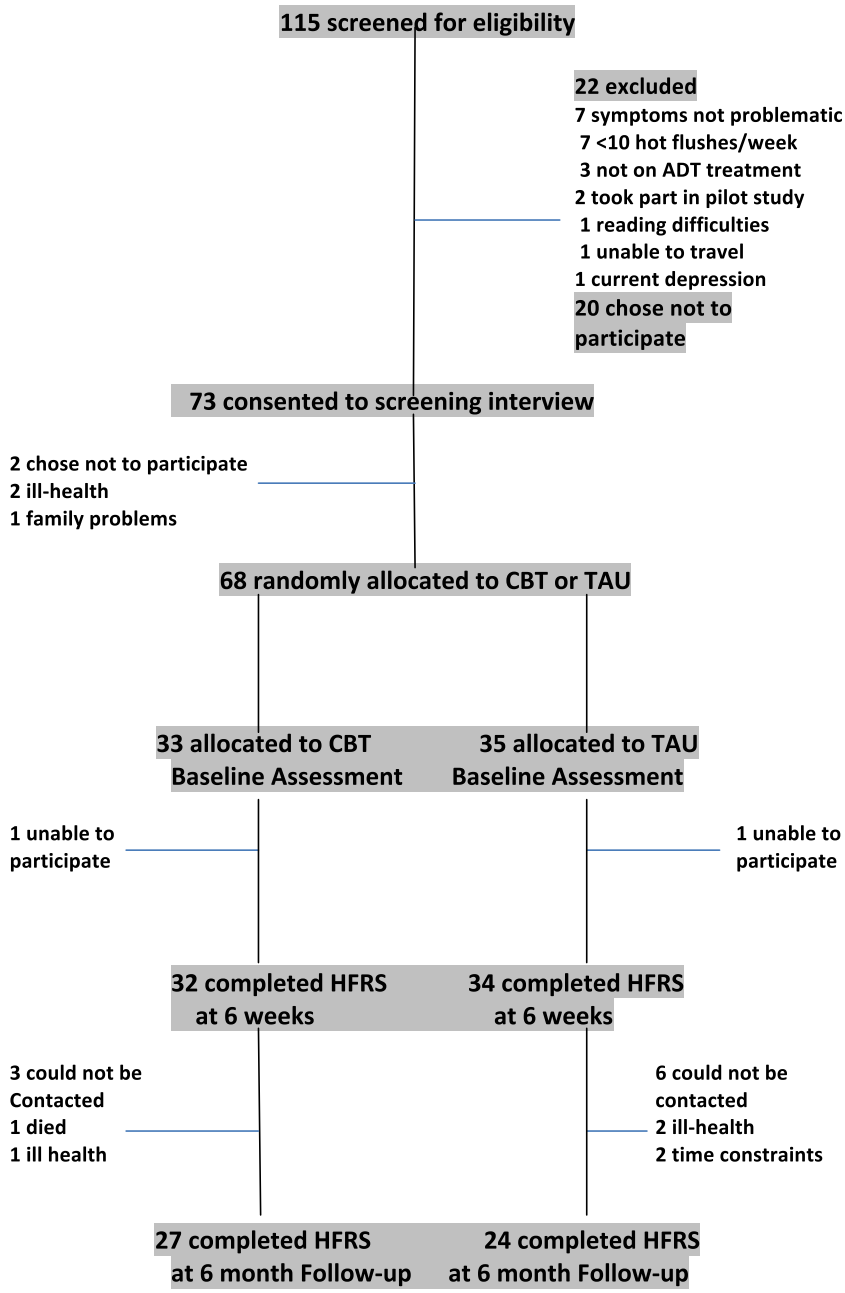

Figure 1. CONSORT diagram showing patient flow through the trial CBT = cognitive behavioural treatment, TAU = treatment as usual, HFRS = Hot Flush Rating Scale

Secondary outcomes included: HFNS problem-rating (HFRS) at 32 weeks; depression and anxiety, as assessed by the Hospital Anxiety and Depression Scale (HADS) [26]; HFNS weekly frequency in the past week, as assessed by the HFRS [21]; quality of life using the EORTC QLQ-C30 [27] and the EORTC QLQ-PR25 [28] prostate cancer-specific measure at 6 and 32 weeks.

Possible moderators included age, marital status, level of education, ethnicity, cancer type, BMI, as well as the Constructed Meaning Scale (CMS) [29], the Emotional Control subscale of the Barriers to Help Seeking Scale [30], the Somatosensory Amplification Scale [31] and Revised Life Orientation Test (LOT-R) [32]. Potential mediators included the Hot Flush Beliefs and Behaviour Scale-for Men scale (HFBBS), developed to assess men's cognitive appraisals (beliefs) and behaviours in relation to their HFNS [33] with three subscales (Negative HFNS beliefs/behaviours, Calm acceptance and Humour/openness, scored 1–6) and frequency of HFNS using 48-h ambulatory SSC monitoring [19,34,35]. Questions about self-efficacy and treatment expectations were asked prior to randomisation.

DOI: 10.1002/pon

Adherence to CBT was measured by the number of booklet chapters read and the number of times relaxation/paced breathing were practised each week, recorded at the end of treatment. Adverse events were recorded in both groups.

Statistical analysis

A total sample size of 50 (25 in each group) was needed to provide 90% power to detect a clinically significant difference in mean HFNS problem rating of 2 points, for the comparison of CBT to TAU at 6 weeks post-randomisation, allowing for baseline value (estimated to have a mean of 5 and SD of 2.4) and a HFNS problem rating baseline-to-outcome correlation of 0.4 on analysis of covariance with two-sided 5% significance levels. Analyses were conducted on a modified intention-to-treat basis; missing values were replaced by the average scores of completed items, in the same scale for each individual, provided that at least 50% of the items in that scale had been completed. Analyses of covariance were carried out for each variable separately, comparing baseline scores with (a) 6-week and (b) 32-week scores, with group (CBT vs. TAU) as fixed factor and baseline scores as covariates and Bonferroni adjustment for multiple comparisons. Statistical analyses are reported with adjusted mean differences (standard errors; SE), and two-sided 95% CIs. SPSS (version 18.0) was used for all statistical analyses.

Results

One hundred and fifteen men expressed interest in the study and 68 met inclusion criteria and were randomised (Figure 1). Withdrawal rates were minimal at 6 weeks, and complete data were available for 66 participants for the primary outcome measure (HFNS problem-rating). Baseline demographics and clinical characteristics were broadly similar in both treatment groups (Table 1). The sample had a mean age of 69 years, range 49 to 83 years. They tended to be mainly of white ethnicity (74%), married/cohabiting (74%), unemployed/retired (78%) and 48% of men had received education beyond 16 years. Comorbidity was common; additional medical conditions included cardiovascular (e.g. high blood pressure 44.2%), haematological (e.g. cholesterol, diabetes 32.6%) or musculoskeletal (e.g. joint pain 16.3%) problems. Cancer diagnosis included localised (50%), locally advanced (19%) and metastatic cancer (31%) (Table 1). On average the men had been on their current ADT regime for 16 months (range 2–74 months). Baseline anxiety and depression scores (HADs) were 5.17 (SD = 5.17) and 4.10 (4.10), respectively (25% scored above the cut-off for depression and 20.6% for anxiety) and Global QOL (EORTC) was 69.19 (SD = 17.23).

At baseline HFNS were frequent with a weekly average of 54.47 (SD = 41.34), range 9 to 280, average duration of 4 (range 2 to 10) min and were rated as moderately problematic, with average scores of 4.68/10 (SD = 2.20).

Primary outcome

There was a significant difference between groups in the primary outcome, HFNS problem rating, at 6 weeks after randomisation (adjusted mean difference of −1.33, 95% CI −2.07 to −0.58; $p = 0.001$) with a greater reduction from baseline in the CBT group compared to the TAU group and a large effect size (Table 2, Figure 2). The change in problem rating from baseline was −1.81 (SD 1.94) in the CBT group, compared with −0.57 (SD 1.74) in TAU group, representing to a 40% reduction in the CBT group and a 12% reduction in the TAU group; 41% of the CBT group had a two-point reduction in HFNS problem rating compared to 23% of those allocated to TAU.

Secondary outcomes

There was a significant difference between groups in HFNS frequency at 6 weeks (adjusted mean difference −12.12, 95% CI −22.39 to −1.84; $p = 0.02$) with greater reductions from baseline in the CBT group compared to the TAU group (Figure 3), with a 36% reduction in the CBT group and 16% for TAU, and a medium effect size (Table 2). At 32 weeks the CBT group maintained their improvements in HFNS problem rating (CBT 41% and TAU 31% reductions from baseline) and frequency (CBT 42% and TAU 20% reductions from baseline), but group differences were not significant. When HFNS were considered separately, there were significant group differences in frequency of hot flushes at 32 weeks (Table 2). No significant group differences were observed for depressed mood, anxiety (HADS) or quality of life (EORTC QLQ-C30 Global QOL) at 6 or 32 weeks (Table 2).

CBT was more effective than TAU in reducing HFNS problem rating regardless of BMI (normal vs. overweight/obese), educational level (16 years or less vs. more than 16 years) or cancer type (locally and locally advanced vs. metastatic). There were too few numbers in each category to analyse ethnicity (white vs. non-white) or marital status. The group difference in the primary outcome, HFNS problem rating at 6 weeks, remained significant (adjusted mean difference of −1.38, 95% CI −2.16 to −0.60; $p = 0.001$) when we adjusted for baseline HADs scores, cancer type, age, BMI, educational level and employment. Baseline self-efficacy and treatment expectations, CMS, EC, SAS and optimism (LOT-R) (Table 1) did not moderate HFNS problem-rating outcomes at 6 weeks.

HFNS beliefs and behaviours

There were significant group differences in HFNS Beliefs and Behaviour subscales (see Table 2), the CBT group

DOI: 10.1002/pon

Table 1. Demographic and clinical baseline characteristics (*N* (%) or mean (SD) with *p* values for between group comparisons)

	CBT ($n = 33$)	TAU ($n = 35$)	*p* Values
Age at randomisation [years]	67.97 (7.65)	69.71 (7.90)	0.36
Ethnic origin			
White	28 (85%)	22 (63%)	0.08
Black	5 (15%)	12 (34%)	
Other		1 (3%)	
Married/living with partner	25 (76%)	25 (71%)	0.89
Educated beyond 16 years of age	16 (49%)	16 (46%)	0.90
Employed	9 (27%)	6 (17%)	0.48
Mean body mass index (kg/m^2; SD)	26.40 (3.79)	27.74 (3.63)	0.16
Cancer type			
Localised	16 (49%)	18 (51.5%)	0.91
Locally advanced	7 (21%)	6 (17%)	
Metastatic	10 (30%)	11 (31.5%)	
Time since prostate cancer diagnosis [months]	24.76 (20.70)	29.57 (34.48)	0.49
Previous treatment history:			
Prostatectomy	10 (30%)	8 (23%)	0.49
Radiotherapy	23 (70%)	18 (51%)	0.19
Current hormonal therapy:			
Luteinizing/gonadotropin-releasing hormone agonists			
Goserelin (zoladex)	23 (70%)	23 (66%)	
Leupropelin (prostap)	2 (6%)	5 (14%)	
Triptorelin (de-capeptyl)	2 (6%)	2 (6%)	
Anti-androgens			
Cyproterone acetate (cyprostat)	1 (3%)	0	
Bicalutamide (Casodex)	5 (15%)	5 (14%)	
Receiving other treatments for HFNS at baseline:			
Red clover	3 (9%)	1 (3%)	
Fish oils	1 (3%)	0	
Ginseng	0	1 (3%)	
Evening primrose	0	1 (3%)	
Self-efficacy in carrying out treatment	3.51 (1.08)	3.40 (0.93)	0.20
Treatment expectations	3.09 (1.19)	3.05 (0.82)	0.18
Somatosensory Amplification Scale	2.47 (0.60)	2.47 (0.59)	0.99
Revised Life Orientation Test	15.96 (4.14)	16.05 (4.18)	0.91
Constructed Meaning Scale	32.18 (6.46)	31.48 (6.29)	0.65
Emotional Control—Barriers to Help Seeking Scale	1.71 (0.76)	2.10 (0.82)	0.06

reporting less negative HFNS Bel/Beh about hot flushes (adjusted mean difference −0.92, 95% CI −1.34 to −0.51; $p = 0.0001$) and more Humour and Openness (0.56, 95% CI 0.10 to 1.01; $p = 0.02$) compared to the TAU group 6 weeks after randomisation. Reduction (more than one point difference) in negative HFNS Bel/Beh (adjusted mean difference 1.61 CI 2.49 to 0.73; $p = 0.001$) was associated with improvement in HFNS problem rating at 6 weeks. This effect was not significant for Humour and Openness (0.10 CI −0.91 to 1.11).

SSC monitoring

Forty-four men wore the SSC monitor; at 6 weeks there was little change in 48-h rate of HFNS measured by sternal skin conductance, but there was considerable variability in response (Table 2).

Treatment adherence was generally good

The majority (88%) read either all (69%) or more than half of the booklet (19%); 79% used the relaxation CD, and 76% practiced paced breathing, at least once a week. At 6 weeks, a significantly greater reduction in HFNS problem rating was reported by men who read all of the booklet compared to those who read less (adjusted mean difference of 2.78, 95% CI 2.19 to 3.37; $p = 0.01$). No significant differences were found between men who practised the relaxation/paced breathing more or less than once a week.

Adverse events, medication changes and use of health services

Two cases of adverse events unrelated to the intervention were reported: one participant passed away before the 32-week assessment because of metastatic cancer and

DOI: 10.1002/pon

Table 2. Effect of treatment on hot flushes and night sweats measures: HFNS problem rating, frequency and Beliefs and Behaviours Scale; HADs and Global QOL (EORTC). SSC = Sternal Skin Conductance

	CBT mean (SD)	*N*	TAU mean (SD)	*N*	Adjusted mean difference (SE)	95% CI
HFNS problem rating						
Baseline	4.54 (1.98)	33	4.81 (2.41)	35		
6 weeks	2.76 (1.53)	32	4.19 (2.20)	34	−1.33 (0.37)**	−2.07 to −0.58
					Effect size partial $Eta^2 = 0.16$	
32 weeks	2.66 (1.67)	27	3.33 (1.84)	24	−0.7 (0.43)	−1.59 to 0.16
HFNS total frequency						
Baseline	56.09 (30.16)	33	52.95 (50.07)	35		
6 weeks	36.06 (25.03)	32	44.58 (38.70)	34	−12.12 (5.14)*	−22.39 to −1.84
					Effect size partial $Eta^2 = 0.08$	
32 weeks	32.11 (24.54)	27	42.08 (54.85)	24	−12.43 (7.93)	−28.38 to 3.52
HF frequency						
Baseline	39.18 (24.21)	33	34.94 (39.56)	35		
6 weeks	25.56 (18.63)	32	27.47 (23.74)	34	−4.97 (4.06)	−13.09 to 3.14
32 weeks	19.40 (17.93)	27	29.95 (39.63)	24	−12.80 (6.17)*	−25.21 to −3.86
NS frequency						
Baseline	16.90 (14.27)	33	18.01 (13.05)	35		
6 weeks	10.50 (9.67)	32	17.11 (18.80)	34	−5.79 (2.96)	−11.71 to 0.13
32 weeks	12.70 (11.72)	27	12.12 (17.67)	24	0.66 (3.59)	−6.56 to 7.88
SSC frequency						
Baseline	29.31 (11.73)	23	27.80 (11.63)	21		
6 weeks	27.47 (9.99)	20	23.61 (11.98)	12	0.69 (3.19)	5.84 to −7.22
HF beliefs/behaviour						
Baseline	3.06 (1.00)	33	3.06 (1.18)	33		
6 weeks	1.41 (1.08)	30	2.35 (1.12)	27	−0.92 (0.20)**	−1.34 to −0.51
32 weeks	1.57 (1.17)	24	2.09 (0.98)	17	−0.49 (0.30)	−1.11 to 0.12
Calm acceptance						
Baseline	2.62 (0.78)	33	2.75 (0.97)	33		
6 weeks	3.58 (1.11)	30	3.81 (0.90)	27	−0.29 (0.16)	−0.70 to 0.21
32 weeks	4.09 (0.67)	24	3.90 (0.49)	17	0.29 (0.18)	−0.07 to 0.66
Humour openness						
Baseline	4.22 (1.04)	33	4.07 (1.37)	33		
6 weeks	3.58 (1.17)	30	3.02 (0.91)	27	0.56 (0.23)*	0.10 to 1.01
32 weeks	3.55 (1.05)	24	3.52 (0.80)	17	0.20 (0.25)	−0.31 to 0.72
HADS depression						
Baseline	4.03 (3.57)	33	4.17 (3.27)	33		
6 weeks	3.26 (3.40)	30	4.21 (3.46)	27	−0.59 (0.67)	−1.94 to 0.74
32 weeks	3.61 (3.11)	24	3.16 (2.22)	17	−0.52 (0.83)	−1.15 to 2.20
HADS anxiety						
Baseline	5.06 (2.96)	33	5.28 (3.64)	33		
6 weeks	4.70 (3.33)	30	5.14 (4.09)	27	−0.15 (0.68)	−1.21 to 1.52
32 weeks	4.15 (2.73)	24	4.83 (2.81)	17	−0.32 (0.70)	−1.75 to 1.10
EORTC global QOL						
Baseline	72.22 (17.26)	33	66.16 (16.92)	33		
6 weeks	76.19 (20.12)	30	68.26 (19.15)	27	3.61 (4.49)	−5.42 to 12.63
32 weeks	75.36 (18.54)	24	70.83 (17.59)	17	−0.97 (5.91)	−13.01 to 11.01

CBT = Cognitive Behavioural Therapy
TAU = Treatment as usual
*$p = 0.05$.
**$p = 0.001$.

another started chemotherapy, and his data was excluded from further analyses. One participant (CBT) stopped zoladex injections after his 6-week assessment, and two (TAU) reported changes between baseline and 6 weeks (one started zoladex and one radiation therapy). Between the 6 and 32 weeks, four (CBT) started new medications for prostate cancer (two casodex, one alpharadin and one zytiga). There were no significant group differences in attendance at GP, oncologist or nurse specialist between baseline and 6 weeks or between 6 and 32 weeks.

Discussion

The results of this trial suggest that CBT appears to be a safe and effective intervention to help prostate cancer patients undergoing ADT to manage troublesome HFNS. At post-

DOI: 10.1002/pon

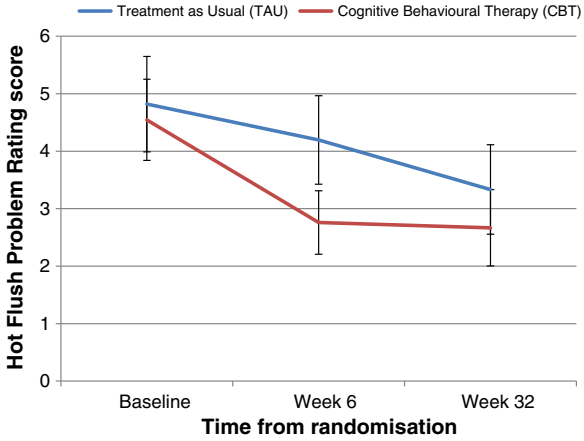

Figure 2. Changes in problem rating scores for hot flushes and night sweats in CBT and TAU groups from baseline to 6 and 32 weeks post randomisation. Error bars show 95% CI

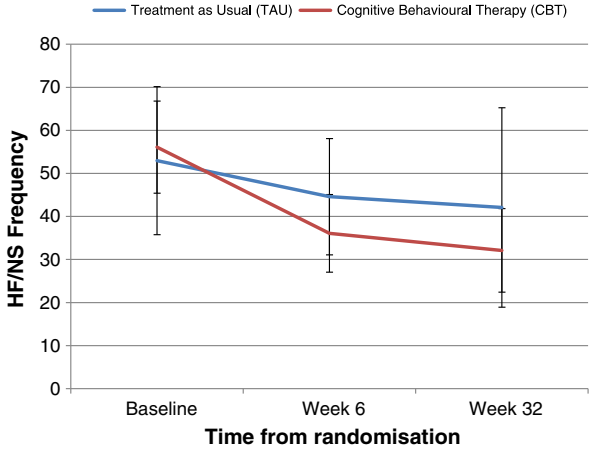

Figure 3. Changes in frequency for hot flushes and night sweats in CBT and TAU groups from baseline to 6 and 32 weeks post randomisation. Error bars show 95% CIs

treatment, the CBT group reported less problematic and less frequent HFNS than the TAU group, with clinically relevant reductions. At 32 weeks the CBT group maintained their improvement but group differences did not reach significance, largely because of some improvement in the TAU group. However, the group difference in hot flush (but not night sweat) frequency remained significant at 32 weeks.

At baseline the sample reported frequent (44–58 HFNS per week) and problematic HFNS, at levels consistent with previous studies of prostate cancer survivors having ADT [36,37]. The percentage scoring within the clinical range for depression and anxiety (HADS) (>/8) were 20% and 25% respectively, higher than that reported in a recent meta-analysis of prevalence of anxiety (15%) and depression (15%) in men undergoing treatment for prostate cancer [38], which might be because they all had HFNS—which are associated with distress [7]. Their QOL EORTC Global scores (69.19, SD = 17.23) were similar to norms for men with prostate cancer (68.4, SD = 22.2) [39]. The sample was socially mixed (based on level of education), and co-morbid health problems were common. Nevertheless, CBT was effective adjusting for baseline characteristics and regardless of BMI, educational level or cancer type. However, the intervention did not significantly reduce mood or QOL.

Adherence to the CBT was good in terms of reading the booklet and using the relaxation/paced breathing CD, and those who read the whole booklet derived more benefit. We examined potential mediators in order to understand how the treatment might be working. Although significant improvements in subjective measures were evident, no group differences in physiologically (SSC) measured HFNS were found. The concordance between subjective and physiologically (SSC) measured HFNS is relatively low in ambulatory settings [35,37], but inclusion of SSC measures can aid understanding of how treatments are working. Overall, our results are consistent with findings from a CBT trial for HFNS in breast cancer patients [13], suggesting that CBT might work mainly by affecting symptom perception and cognitive appraisal of HFNS, rather than physiological mechanisms [16,23,40]. The CBT group reported less negative HFNS beliefs and behaviours and more humour and openness compared to TAU at 6 weeks, and change in HFNS negative beliefs and behaviours (e.g. changes in beliefs about the social consequences and about sleep, and less avoidance of activities) was associated with reduction in problem-rating. Therefore the intervention appeared to be targeting cognitive and behavioural changes as intended.

Limitations include lack of an attention control arm and the sample size, particularly for the TAU group at 32 weeks; the sample size was not large enough to examine all secondary measures, nor to perform a full mediation analysis. We attempted to reduce bias by masking where possible, but it is not possible to mask participants in this type of trial. Additional variables might have affected HFNS, such as health-related behaviours, e.g. caffeine intake, and other specific health problems. Future research could test the intervention in a multi-centre trial including a range of ethnicities, as well as examine specific components of the intervention, such as paced breathing.

In terms of clinical implications, to our knowledge this is the first evaluation of a brief guided self-help CBT intervention for men with HFNS. Adherence to treatment was good, and the contact/therapist time was on average only 60 min. The CBT intervention was delivered in a hospital setting, using standardised materials (treatment booklet, CD) and could be included within survivorship support programmes.

Acknowledgements

We thank Phil Reynolds, Louisa Fleure, Gian Gargaro. This work was supported by a Prostate Cancer UK Project Award (PG10-01).

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