

Does Cognitive Behaviour Therapy for insomnia reduce clinical levels of  
fatigue, anxiety and depression in cancer patients?

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## Abstract

### Objectives

This secondary analysis of data from a RCT explores associations between common symptom clusters and evaluates pre to post-treatment changes in clinical levels of these symptoms following Cognitive Behaviour Therapy for insomnia (CBT-I).

### Methods

Baseline data from 113 participants with insomnia were explored to establish rates of and associations between clinical levels of fatigue, anxiety and depression across the sample. Effects of CBT-I on this symptom cluster was also explored by examining changes in pre to post fatigue, anxiety and depression levels.

### Results

At baseline, the most common symptom presentation was insomnia+fatigue and 30% of the sample reported at least three co-morbid symptoms. Post CBT, those experiencing clinical insomnia and clinical fatigue decreased. There were no changes in anxiety rates from baseline to post-treatment in the CBT group, and modest reductions in rates of those with clinical depression. Seven individuals (9.6%) from the CBT group were completely symptom-free at post-treatment compared with 0% from the TAU condition. Chi-square analysis revealed a significant relationship between group allocation and

changes in symptoms of insomnia and fatigue. No such relationship was found between group allocation and mood variables.

### Conclusions

These findings confirm the high rate of symptom co-morbidities among cancer patients and highlight strong associations between sleep and fatigue. CBT for insomnia appears to offer generalised benefit to the symptom cluster as a whole and specifically, is effective in reducing fatigue, which exceeded clinical cut-offs prior to implementation of the intervention. This has implications for the diagnosis/management of common symptoms in cancer patients.

Key Words: Sleep; cancer; oncology; fatigue; anxiety; depression

## Introduction

Disturbed sleep is a common and distressing problem affecting more than one-third of cancer patients both during and after completion of active treatment <sup>1,2</sup>. Despite its prevalence, insomnia is frequently rationalised as a transient side-effect of diagnosis-related stress or cancer treatment <sup>3-5</sup>. Incidence data show however, that more than one quarter of cancer patients with sleep disturbance experience chronic insomnia, which fails to remit even when active cancer treatment has ceased <sup>4</sup>.

Sleep disturbance is often associated with other symptoms like fatigue, anxiety and depression <sup>5-9</sup>. Portenoy et. al. demonstrated that this cluster was highly prevalent (40-80%) across different tumour types <sup>10</sup>, and recent work by Liu et al. found that the presence of pre-treatment symptom clusters in breast cancer patients was associated with poorer sleep, increased fatigue and lower mood during active treatment <sup>11</sup>. Therefore each symptom seems to maintain and exacerbate the others, resulting in further impairment to quality of life.

Such inter-relationships have also been studied in the general population. For example, psychiatric epidemiology indicates that insomnia is an independent risk factor for the development of first episode depressive disorder in adults of all ages <sup>12</sup>. Similarly, people with cancer and insomnia report decreased functioning, more pain and higher levels of fatigue than those sleeping well <sup>13,14</sup>. Sharma et al. <sup>15</sup> found that nearly a third of patients attending a Regional Cancer Centre reported sleep problems of clinical

significance which were strongly associated with symptoms of emotional distress. The nature of these associations requires further study.

Implementing a programme of Cognitive Behaviour Therapy for insomnia (CBT-I) in cancer patients yields generalised improvements in other symptoms including fatigue, quality of life and daytime functioning<sup>16,17</sup>, suggesting that these symptoms share common pathways<sup>8,18,19</sup>.

The aims of this paper are: (i) to report on the rates of and associations between co-morbid clinical symptoms of insomnia, fatigue, anxiety and depression in a sample of cancer patients, (ii) to investigate potential generalised effects on these symptoms following CBT-I and (iii) to assess the clinical significance of any such improvement.

## Methods

### Experimental Design

This is a secondary analysis of data from 113 patients, derived from a randomised controlled clinical effectiveness trial of CBT-I versus treatment as usual (TAU) for insomnia in cancer patients<sup>16</sup>. CBT comprised five, small group sessions across consecutive weeks, following a manualised protocol. TAU represented normal clinical practice; the appropriate control for a clinical effectiveness study. The trial conformed to a pragmatic, two-centre design comparing CBT-I with TAU. Major assessments were at baseline, post-treatment and follow-up 6 months later (6-month assessment is not reported due to missing data). Suitable participants were randomly allocated to either CBT-I or TAU by means of a centralised computer-based registration/randomisation service available within the Cancer Research UK

Clinical Trials Unit, Glasgow. The study was stratified for centre, existing treatment for insomnia and tumour type using the minimisation method. A 2:1 treatment allocation, in favour of the intervention, was selected because this would make more efficient use of available CBT-I sessions and would minimise the time a patient had to wait before being able to start a CBT-I course, thereby reducing patient dropout. Due to the nature of the intervention, it was not possible to blind participants or therapists to allocation. No adverse events were reported with either CBT-I or TAU. Full details of CBT therapists, integrity-fidelity of treatment allocation and attrition rates are provided in the attached Consort diagram or can be found in Espie et al. (2008)<sup>16</sup>.

#### Recruitment of Participants

Participants (18 yr.+) were attending follow-up oncology clinics at either the Glasgow Beatson Oncology Centre (BOC) or Aberdeen Royal Infirmary (ARI). Included participants had been diagnosed with either breast, prostate, bowel, or gynaecological cancer and had satisfied diagnostic criteria for chronic insomnia, defined as mean value > 30 minutes for the complaint of delayed sleep-onset latency (SOL) and/or wake time after sleep onset (WASO), insomnia occurring 3 or more nights per week for at least 3 months and affecting daytime function <sup>20,21</sup>. Participants had also scored 5 or more on the Pittsburgh Sleep Quality Index (PSQI) <sup>22,23</sup>, a psychometrically robust instrument that identifies clinically significant sleep disturbance. Thus acute insomnia and transient side-effects associated with cancer treatment were excluded. Participants had completed anti-cancer therapy (radiotherapy/

chemotherapy) by  $\geq 1$  month and had no further anti-cancer therapy planned (excepting adjuvant hormone therapy for breast and prostate patients). Participants were excluded if they had acute illness, estimated prognosis  $< 6$  months, another sleep disorder, confusional problems or untreated and unstable psychiatric disorder (screening procedures did not identify anyone with untreated/unstable psychiatric disorder so therefore, no-one was excluded on the basis of their psychiatric history).

Potential participants were notified of the study by posters/leaflets in clinic waiting areas, by mailing information to those attending upcoming clinics or directly by staff upon attendance at clinics. All participants provided written informed consent and their medical consultant agreed to their participation. The protocol was approved by local NHS research ethics committees.

Insert Table I

## Measures

We conducted a secondary analysis of sleep-onset latency (SOL) and wake time after sleep onset (WASO), anxiety and depression and fatigue (severity and interference), using a ten day Sleep Diary <sup>24</sup>, the Hospital Anxiety and Depression Scale (HADS) <sup>25</sup> and the Fatigue Symptom Inventory (FSI) <sup>26</sup>.

Sleep diaries are the staple tool of insomnia assessment practice and offer a valid, relative index of sleep disturbance when used as repeated measures.<sup>27</sup> Participants were trained to complete sleep diaries using established criteria for accurate completion <sup>28</sup>. The HADS has been validated

for use in cancer patients to screen for anxiety and depressive symptoms <sup>29,30</sup>. It is a particularly useful measure for assessing mood in sleep research, as unlike many other anxiety/depression questionnaires, the HADS does not contain a sleep-specific item. The FSI is also recommended for use with cancer patients, as a brief measure with good validity and internal consistency <sup>26,31</sup>. Median values for these scales (and subscales) are presented in Table I.

In order to understand poly-symptomatic associations between insomnia and clinical level symptoms of fatigue, anxiety and depression, baseline data were re-analysed to isolate only those participants scoring beyond recognised clinical cut-offs for insomnia and at least one other domain. Therefore, 'anxiety' refers to HADS anxiety scores of  $\geq 11$  <sup>29,30</sup>, 'depression' refers to HADS depression scores of  $\geq 11$  <sup>29,30</sup> and 'fatigue' refers to fatigue severity and/or interference scores of  $\geq 3$  on the FSI <sup>31,32</sup>. Applying these criteria<sup>1</sup> to the data meant that 37 participants, who were included in the analyses for the original trial, were excluded from this secondary analysis. This means that the proportions presented in the results section relates only to patients who presented with comorbidity at baseline.

## Statistical methods

The RCT was designed to have 80% power to detect a standardized difference of 0.5 between the treatments in the primary sleep outcome measures at post-treatment. A significance level of 0.0125 was chosen to

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<sup>1</sup> In order to enhance the validity of our results, we opted to use a cut-off of 11 on the HADS. We acknowledge that this potentially reduces the possibility of identifying clinical cases of depression and anxiety and therefore, higher rates of comorbidity. However, we feel that the integrity of our results is enhanced by applying more rigorous criteria to the diagnosis of clinical mood symptoms.



adjust for multiple comparisons. These criteria implied recruiting 204 participants. In practice, slow recruitment meant that a total of 150 patients were randomly assigned, giving 80% power to detect a slightly larger standardized difference of 0.59.

## Results

Descriptive analysis of baseline data across the entire sample (n=113) showed that alongside clinical levels of insomnia, 76 participants (67%) also reported levels of fatigue that reached or exceeded clinical cut-offs. This was the most common symptom profile. The next most common presentation was 'insomnia + fatigue + anxiety', reported by 20 individuals (18% of the total sample). 6 participants (5%) scored above clinical cut-offs for all symptoms and 'insomnia + fatigue + depression' also accounted for 5% of the sample. The least common symptom presentations were 'insomnia + anxiety' (3 participants), 'insomnia + anxiety + depression' (2 participants) and 'insomnia + depression', accounting for 3%, 2% and 0% of the sample respectively.

Insert Figure I

In order to explore whether CBT had any effect on the presence or absence of clinical level symptoms between baseline and post treatment, the percentage of individuals who met clinical cut-offs for each symptom was calculated. The number of people experiencing clinical level insomnia at post

treatment was reduced by 52% in the CBT group, compared with a 17.5% reduction in TAU. The rate of clinical levels of fatigue was extremely high across both treatment arms at baseline (90.4% CBT, 90% TAU). However, CBT-I resulted in a 10.9% reduction in rates of fatigue compared with a 2.5% increase in at post treatment in the TAU group. There was no change in anxiety rates from baseline to post treatment in the CBT group, and a 5% increase in those with anxiety at post treatment in the TAU group. The majority of participants were not depressed at baseline (90.4% CBT, 92.5% TAU) and CBT reduced the rate of those with clinical levels of depression by 5.5% compared with an increase of 5% in TAU. Importantly, 7 individuals (9.6%) from the CBT group were completely symptom-free at post treatment (compared to 0% in TAU). Further inspection of baseline data from this 'symptom-free' group show that all 7 individuals had both clinical level insomnia and clinical level fatigue. No one had clinical level anxiety but 1 person had clinical level depression. Although this group is small, the pattern of symptom change indicates that CBT may be of some benefit when treating clinical level insomnia and fatigue.

Insert Table II

Change data (baseline to post treatment) were calculated for each of the four variables of interest, in order to compare differences in symptom trajectories (symptom remission vs. maintenance of baseline presentation) between treatment arms. In this case, 'symptom remission' refers to the

presence of a symptom exceeding clinical cut-offs at baseline which is then below this cut-off at post treatment. 'Maintenance' refers to either a symptom exceeding clinical cut-offs at baseline which is still beyond this cut-off at post treatment, or a symptom below clinical cut-offs at baseline which is still below this cut-off at post treatment.

### Insomnia

At post treatment, 52% of the CBT group showed insomnia remission, compared with only 17.5% of the TAU group. Chi-square analyses were conducted to test the significance of this 'symptom trajectory\*group allocation' relationship. Results show that there was a significant association between treatment group allocation and post-treatment change in insomnia symptoms [ $X^2(1, N=113) = 12.875, p<0.001$ ].

### Fatigue

17.4% of the CBT group showed fatigue remission at post treatment, compared with 2.6% of TAU group. Fatigue symptoms were maintained in 82.6% of the CBT group and 97.4% of the TAU group. Chi-square analysis confirms a significant association between treatment group allocation and post-treatment change in fatigue [ $X^2(1, N=107) = 5.002, p=0.03$ ] (using Fishers exact test).

### Anxiety

Anxiety remission at post treatment was noted in 5.8% (CBT) and 5.6% (TAU) of cases respectively. The majority of both groups maintained their baseline anxiety scores at post treatment (94.2% CBT, 94.4% TAU). No

significant associations were found between treatment allocation and anxiety symptom change [ $\chi^2(1, N=105) = 0.003, p=1.00$ ] (using Fishers exact test).

### Depression

8.5% of the CBT group showed depression remission at post treatment, compared with 0% of the TAU group. As with anxiety, the majority of those in the CBT group (91.5%), maintained their baseline depression scores at post treatment (compared with 100% of the TAU group). No significant associations were found between treatment allocation and depression symptom change [ $\chi^2(1, N=109) = 3.398, p=0.09$ ] (using Fishers exact test).

Overall, we can conclude that there is a significant relationship between group allocation (i.e. CBT or TAU) and changes in clinical levels of insomnia and fatigue. No such relationship was found between group allocation and mood variables.

### Worsening of symptoms

Whilst calculating change score data from the CBT group, we discovered that in a small number of cases, symptoms seemed to worsen at post treatment (characterised by post treatment data exceeding clinical levels when baseline data had not). Given that this finding was not isolated to the TAU group, we decided to analyse these individuals separately. Given that all participants had baseline insomnia scores that exceeded clinical cut-offs, it was not possible for insomnia to worsen at post treatment (according to our criteria). Also, it is not surprising that insomnia-related symptoms would worsen in the TAU group over time. Therefore, only those people with

worsening symptoms of fatigue, anxiety and depression following CBT is examined. Of the 8 people, 4 reported worsening fatigue, 2 reported worsening anxiety and 2 reported worsening anxiety + depression.

## Discussion

All participants in our original trial of CBT versus TAU met criteria for clinical insomnia<sup>16</sup>. However less than a quarter of them (n=37) were troubled by sleep problems alone, with the majority (n=113) experiencing other co-morbid symptoms like fatigue, anxiety and depression. Further analysis of this symptom cluster revealed that clinical fatigue was the most common co-morbid symptom, experienced by the majority of participants at baseline. Almost a third of participants in this study presented with three or more co-existing symptoms which exceeded clinical cut-offs. These findings are consistent with previous evidence of the high prevalence of symptom clusters in cancer patients<sup>5-9</sup>.

At baseline, anxiety was more prevalent than depression across both groups, although the number of participants experiencing clinical levels of either symptom was small. Findings from a large prospective study examining symptoms in early breast cancer patients over 5 years, also reported higher levels of clinically significant anxiety than depression (14.4% vs. 3.1%)<sup>29,30</sup>. Our data indicates a relatively small association between clinical insomnia and mood disturbance, which is in contrast to numerous studies reporting high rates of co-morbidity between insomnia and depression and insomnia and anxiety in cancer patients<sup>8,9,11,15</sup>. However, the current study applied strict

clinical cut-offs for identifying those with depression and anxiety which may explain this reduced prevalence. Low levels of clinically meaningful anxiety and depression in this sample may also be due to the time since diagnosis in our sample (median of approximately 2 years), as initially high levels of distress after diagnosis and during treatment would be expected to decrease over time. Insomnia is commonly viewed as an expected consequence of depression or anxiety, but this low insomnia-mood association indicates that the majority of participants (67%) in this study experienced chronic insomnia without any significant clinical mood disturbance. It is therefore important that mood and sleep symptoms are recognised as distinct disorders and measured and treated in their own right.

Our CBT-I intervention, delivered primarily to treat sleep disturbance, resulted in a significant reduction in insomnia prevalence at post treatment compared to the TAU group. However, further exploration of the data reveals that treating insomnia with CBT offers additional benefits to the symptom cluster as a whole. Participants receiving CBT-I also experienced significant reductions in fatigue, and 10% of the CBT-I group no longer met clinical criteria for any symptoms post-treatment. None of the participants in the TAU group were symptom free at post treatment, indeed symptoms often worsened in this group at post treatment assessment. This suggests that improvements in the CBT-I group did not occur simply as an artefact of natural symptom reduction over time, but as a direct result of the intervention.

The most notable symptom reduction within the CBT-I group were for sleep and fatigue symptoms. The CBT-I treatment clearly improved sleep symptoms and had some effect on fatigue. It appears that participants were

more able to manage their fatigue symptoms after receiving the intervention, reducing the impact of fatigue on their quality of life. Researchers have begun to investigate the interactional relationship between disturbed sleep and fatigue in cancer patients<sup>5</sup> and further exploration of the shared and individual mechanisms of these symptoms for this group would be beneficial. There is currently no accepted gold standard treatment for cancer related fatigue although psychological and exercise interventions have shown promise<sup>33,34</sup>. It would be useful to further explore consider the role of CBT interventions in the treatment of this sleep + fatigue symptom cluster.

Although these findings were derived from a relatively large sample of cancer patients, we cannot assume that our sample is representative of the cancer population as a whole. The majority of our patients were female and breast/prostate cancer was the most common tumour type. It is therefore difficult to generalise these findings to patients with different tumour types, as it is possible that the prevalence of the symptom cluster may differ between cancer types. However, these results do provide further evidence of the development of and associations between common symptom clusters in this patient group and indicate the usefulness of CBT for reducing clinical levels of insomnia and fatigue in cancer patients.

#### Disclosures and Acknowledgements

The authors gratefully acknowledge funding support from Cancer Research UK (Ref. C8265/A3036) and from the Dr Mortimer and Theresa Sackler Foundation. The authors declare no conflict of interest.

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Table 1 – Baseline demographic and clinical information on the sample. Data are categorical or median (IR). No between-group differences.

	<b>CBT group (n=73)</b>	<b>TAU group (n=40)</b>
<b>Age (years)</b>	63 (55-69)	58 (54-66)
<b>Gender</b>		
Male	23 (32%)	12 (30%)
Female	50 (68%)	28 (70%)
<b>Civil status</b>		
Married	51 (70%)	27 (68%)
Single	8 (11%)	7 (17%)
Separated	1 (1%)	0
Divorced	7 (10%)	4 (10%)
Widowed	6 (8%)	2 (5%)
<b>Employment status</b>		
Employed	27 (37%)	18 (45%)
Unemployed	2 (3%)	1 (2%)
Retired	44 (60%)	21 (53%)
<b>Tumour site</b>		
Breast	46 (63%)	22 (55%)
Prostate	18 (25%)	9 (23%)
Bowel	8 (11%)	8 (20%)
Gynaecological	1 (1%)	1 (2%)
<b>Cancer diagnosis - screening (months)</b>	22 (9-52)	25 (10-68)
<b>Current treatment for depression</b>		
Yes	10 (14%)	7 (17%)
No	63 (86%)	33 (83%)
<b>Insomnia duration (months)</b>	30 (12-60)	27 (10-60)

**Insomnia pattern**

Constant	49 (67%)	25 (63%)
Episodic	24 (33%)	15 (37%)

**Sleep medication**

Yes	18 (25%)	6 (15%)
No	55 (75%)	34 (85%)

**PSQI**

13 (11-16)	13 (11-15)
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**Sleep**

SOL (mins)	41 (20-59)	27 (23-50)
WASO (mins)	69 (47-118)	47 (30-81)

**Fatigue**

Severity	5 (4-6)	5 (4-6)
Interference	4 (2-5)	4 (2-5)

**Anxiety**

7 (4-10)	8 (5-10)
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**Depression**

4 (2-8)	5 (2-7)
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Table II – Group allocation \* symptom present or absent at baseline (BL) and post treatment (PT)

		<b>CBT (BL)</b>	<b>CBT (PT)</b>	<b>TAU (BL)</b>	<b>TAU (PT)</b>
<b>Insomnia</b>	Absent	0%	52%	0%	17.5%
	Present	100%	48%	100%	82.5%
<b>Fatigue</b>	Absent	9.6%	20.5%	10%	7.5%
	Present	90.4%	79.5%	90%	92.5%
<b>Anxiety</b>	Absent	79.5%	79.5%	77.5%	72.5%
	Present	20.5%	20.5%	22.5%	27.5%
<b>Depression</b>	Absent	90.4%	95.9%	92.5%	87.5%
	Present	9.6%	4.1%	7.5%	12.5%
<b>Symptom free</b>		0%	9.6%	0%	0%

Figure I - Venn diagram representing baseline associations between fatigue (F), anxiety (A) and depression (D) scores across the sample (n=113).. All participants met criteria for insomnia.

