Journal of Psychosomatic Research 78 (2015) 427–432

Contents lists available at ScienceDirect

Journal of Psychosomatic Research

The role of insomnia in the treatment of chronic fatigue

Håvard Kallestad [a,b,*], Henrik B. Jacobsen [c,d,e], Nils Inge Landrø [c,e,f], Petter C. Borchgrevink [c,d,e], Tore C. Stiles [d,f,g]

[a] Norwegian University of Science and Technology, Department of Neuroscience, Trondheim, Norway
[b] St. Olav's University Hospital, Department of Østmarka, Trondheim, Norway
[c] St. Olav's University Hospital, Hysnes Rehabilitation Center, Trondheim, Norway
[d] St. Olav's University Hospital, National Competence Center for Pain and Complex Disorders, Trondheim, Norway
[e] Norwegian University of Science and Technology, Department of Circulation and Medical Imaging, Trondheim, Norway
[f] University of Oslo, Department of Psychology, Oslo, Norway
[g] Norwegian University of Science and Technology, Department of Psychology, Trondheim, Norway

ARTICLE INFO

Article history:
Received 21 August 2014
Received in revised form 26 November 2014
Accepted 30 November 2014

Keywords:
Fatigue
Insomnia
Cognitive therapy
Stress

ABSTRACT

Background: The definition of Chronic Fatigue Syndrome (CFS) overlaps with definitions of insomnia, but there is limited knowledge about the role of insomnia in the treatment of chronic fatigue.
Aims: To test if improvement of insomnia during treatment of chronic fatigue was associated with improved outcomes on 1) fatigue and 2) cortisol recovery span during a standardized stress exposure.
Methods: Patients (n = 122) with chronic fatigue received a 3.5-week inpatient return-to-work rehabilitation program based on Acceptance and Commitment Therapy, and had been on paid sick leave > 8 weeks due their condition. A physician and a psychologist examined the patients, assessed medication use, and SCID-I diagnoses. Patients completed self-report questionnaires measuring fatigue, pain, depression, anxiety, and insomnia before and after treatment. A subgroup (n = 25) also completed the Trier Social Stress Test for Groups (TSST-G) before and after treatment. Seven cortisol samples were collected during each test and cortisol spans for the TSST-G were calculated.
Results: A hierarchical regression analysis in nine steps showed that insomnia improvement predicted improvement in fatigue, independently of age, gender, improvement in pain intensity, depression and anxiety. A second hierarchical regression analysis showed that improvement in insomnia significantly predicted the cortisol recovery span after the TSST-G independently of improvement in fatigue.
Conclusion: Improvement in insomnia severity had a significant impact on both improvement in fatigue and the ability to recover from a stressful situation. Insomnia severity may be a maintaining factor in chronic fatigue and specifically targeting this in treatment could increase treatment response.

Introduction

Chronic Fatigue Syndrome (CFS) is a condition primarily characterized by persistent and profound fatigue of at least six months duration (1). It causes substantial disruption to the individual's daily function. The fatigue has to be unexplained and not the result of ongoing exertion, and not substantially alleviated by rest. In addition to fatigue, the diagnostic criteria require the concurrence of four or more of the following symptoms: muscle- and joint-pain, headache, sore throat, impairment in memory or concentration, unrefreshing sleep, and postexertional fatigue lasting more than 24 h. The prevalence rates for CFS vary depending on the definition and the criteria used. Community and primary care studies have reported the prevalence to be between 0.2% and 2.6% (2).

Cognitive Behavior Therapy (CBT) has been shown to be an effective treatment of CFS (3). A meta-analysis of 1371 patients in 13 studies found that the mean between-group effect size for CBT compared to placebo was $d = 0.48$, which corresponds to a medium effect size. Although these are promising results, there is still room for improvement. It is therefore important to better understand the maintaining factors involved in CFS that could be potential therapeutic targets.

One factor that could be involved in the maintenance of CFS is insomnia. Insomnia can be defined as the subjective experience of disturbed or non-restorative sleep that gives rise to daytime impairment despite adequate opportunity and circumstances for sleep (4,5). Despite its high prevalence, insomnia is often overlooked in clinical settings (6), and it is underdiagnosed in patients with CFS (7).

CFS and insomnia have overlapping features. Between 87% and 95% of patients meeting criteria for CFS report non-restorative or

* Corresponding author at: Håvard Kallestad Norwegian University of Science and Technology, Department of Neuroscience, Medisinsk Teknisk Forskningssenter, 7489 Trondheim Norway.
E-mail address: havard.kallestad@ntnu.no (H. Kallestad).

http://dx.doi.org/10.1016/j.jpsychores.2014.11.022

unrefreshing sleep (8). On the other hand, fatigue is a core symptom of insomnia (5,9). Like in insomnia, CFS is more associated with subjective experience of sleep disturbance rather than objective measures of poor sleep (10). Impairment in memory or concentration is a symptom of both insomnia and of CFS (1,5). It is possible that a proportion of the fatigue CFS patients experience may be related to poor sleep quality and insomnia, whereas others have suggested that insomnia symptoms in CFS are secondary to pain and depression (11).

Adaptive response to stress could be a common factor between insomnia and CFS. Sleep is important to restore the capacity to regulate emotions when exposed to negative stimuli (8,12) and could have a stress-buffering effect (13). In CFS, the ability to recover after a stressor is impaired (14) and stress exacerbates the symptoms of fatigue (15). At a physiological level, CFS patients display a flattened cortisol variation when exposed to a naturalistic stressor such as awakening (16) or in laboratory with the Trier Social Stress Task (TSST) (17). This low cortisol variability has been claimed to be a physiological expression of vital exhaustion, a mental state where the ability to adapt to stress is disrupted (18,19) and one of the biological factors contributing to the maintenance of CFS (16). Interestingly, a flattened response on the TSST has also been found to be a consequence of poor sleep quality (13). The authors of this study suggested that the stress-buffering effect of sleep is associated with improved parasympathetic tone and normalized cortisol patterns during the day (13). Improvement in insomnia severity during treatment could therefore contribute to normalizing cortisol patterns for patients with CFS. Repeated standardized stress exposures, such as the TSST before and after treatment, has been argued as an ideal study design for the investigation of such treatment effects (20).

The overarching aim of this study was to examine a possible role of insomnia in the treatment of chronic fatigue. All patients were treated for chronic fatigue with a 3.5-week intensive return-to-work (RTW) rehabilitation program based on Acceptance and Commitment Therapy (ACT) (21). Specifically, our hypotheses were that 1) improvement in insomnia severity during treatment would predict lower levels of fatigue at treatment termination when controlling for the possible confounding effects of pain intensity, depression, and anxiety. 2) Improvement in insomnia severity during treatment would predict increased changes in the cortisol recovery span on the Trier Social Stress Test for Groups (TSST-G) from pre to post treatment over and above the effects of fatigue improvement.

Method

Setting

This was a repeated measures treatment study with participants being consecutively recruited from January 2012 to June 2013 to a 3.5-week occupational rehabilitation program at Hysnes Occupational Rehabilitation Center at St. Olav's University Hospital in Trondheim, Norway.

Prior to the enrolment, the patients had all been referred from their general practitioner and thereafter examined and selected by an outpatient multidisciplinary team at St. Olav's University Hospital consisting of a physician, a psychologist, and a physiotherapist. This team evaluated whether the referred patients met the requirements for participating in the RTW-program, which were the same as the inclusion and exclusion criteria for the study. Before being evaluated at the outpatient clinic, all patients were asked to complete 18 different questionnaires (386 items) through an online self-report survey. At the end of the program and the study, the patients again completed six of these questionnaires online.

Patients

The study population consisted of patients on long-term sick leave who upon inclusion to the program gave their informed consent to join the study. The inclusion criteria were age between 18 and 60 years and to have been on sick leave for at least eight weeks due to musculoskeletal disorders, pain, fatigue and/or common mental disorders. Further they should have self-defined goals of increasing labor participation, to be adequately assessed and treated beforehand for any specific health problems, and be able to attend a rehabilitation program from 8:30 to 3:00 p.m. all weekdays.

The exclusion criteria were severe mental illness (ongoing mania, psychosis or suicidal ideation), substance abuse and addiction, pregnancy, and unexpressed difficulty functioning in a group. Moreover, patients who could not communicate in Norwegian or who needed 24-hour personal assistance were not accepted for rehabilitation. In addition to the inclusion criteria in the RTW program, the patients in the current study had to report fatigue for more than six months and score 5 or above on the Chalder Fatigue Scale (22). According to Chalder et al. (22) a score above 5 may be considered a case of chronic fatigue. Moreover, to be included in all the planned steps of analyses, the patients could not have any missing data on any of the covariates targeted in the subsequent multivariable analysis. The patients were a subsample from larger clinical trial (21).

Twenty-five of these patients were selected using a list randomization as described in another study (18). They were administered the *Trier Social Stress Test for Groups* (TSST-G) before and after treatment. The subgroup was included in the analyses to test our secondary hypothesis.

Treatment

A rehabilitation program designed to increase return-to-work was used as a multidisciplinary inpatient intervention with ACT as an overarching treatment model. Details on the rehabilitation program are published elsewhere (21). The program was group-based with up to eight participants in each group. However, the program used both group-based and individual approaches to facilitate rehabilitation. It was organized through seven-hour workdays and lasted 17 workdays. The group sessions included socialization to the ACT model and motivating the patient for change, barriers and the issue of control, consequences of attempting to control the symptoms, family and important supporters, cognitive defusion (you are not your thoughts), communication and conflict, language and staying committed to value-guided behavior. In the individual sessions the focus was on identifying the patient's goals and values, and helping the patients commit to his/her chosen values.

The therapists were coined return-to-work coordinators, trained and supervised in ACT, and targeted three areas of rehabilitation: mental training, physical training and work-related problem solving. The team of coordinators had extensive and diverse backgrounds (e.g. physical therapy, psychology, exercise physiology, medicine, nursing), and each coordinator was responsible for mentoring two or three participants through the program. There were three multidisciplinary team meetings during the inpatient stay where the coordinators discussed possible strategies for handling the participants' obstacles and possibilities with regard to returning to work.

Assessments

Psychological and medical examination

A licensed clinical psychologist assessed the presence of comorbid mental disorders using the Structured Clinical Interview for DSM-IV (SCID-I) (23). A physician reviewed the participants' medical records and assessed current medication.

Fatigue

The Chalder Fatigue Scale was used to assess levels of fatigue (22). It is an 11-item self-report questionnaire assessing both mental and physical fatigue. Each item has four response categories scored bimodally 0–0–1–1. (e.g., 0 = better than usual; 0 = no more than usual; 1 = worse

than usual; 1 = much worse than usual). Cut-off score of five or above indicates chronic fatigue, lasting for six months or more. This questionnaire has been shown to be highly reliable and valid (22).

Pain

To assess level of pain, one item from the Short Form-8 (SF-8) describing average pain intensity the last 7 days on a 6-point Likert scale from 1 = no pain to 6 = very strong pain was used (24). This item has been validated as a self-report measure of pain in a large Norwegian cohort (25).

Depression and anxiety

The Hospital Depression and Anxiety Scale (HADS) was used to assess the levels of depression and anxiety. The HADS is a 14-item self-report questionnaire with 7 items describing depressive symptoms and 7 items describing anxiety symptoms (26,27) and has been found to be valid for use in patients with Chronic Fatigue (28).

Insomnia

The Insomnia Severity Index (ISI) was used to assess the levels of insomnia symptoms (29). The ISI is a seven-item self-report questionnaire measuring the nature, severity and impact of insomnia symptoms the past two weeks. The items are: 1) difficulty falling asleep, 2) difficulty maintaining sleep, 3) early morning awakenings, 4) satisfaction/dissatisfaction with sleep pattern, 5) interference of sleep problems with daily functioning, 6) sleep problems being noticeable by others and 7) levels of distress/worry caused by the sleep problems. Each item is rated by using a 5-point Likert scale (e.g., 0 = no problem; 4 = very severe problem) giving a total score ranging from 0 to 28. The ISI has shown to have very good reliability and validity (29,30) and is recommended as an outcome measure for insomnia in clinical trials (31).

Trier Social Stress Test for Groups (TSST-G)

A subgroup of patients were administered the TSST-G before and after treatment. The TSST-G, as described in von Dawans et al. (32), was used to create psychosocial stress among the participants. The TSST-G is an experimental test designed to trigger mental stress among participants under controlled conditions. TSST-G is a performance task consisting of high levels of socio-evaluative threat and uncontrollability in a group format. The test consists of a *preparation phase* where the patients are instructed to prepare an application for a job of their choice in front of an expert panel. The *exposure phase* is a public speaking task (mock job interview) and mental arithmetic task (serial subtraction) in front of a panel of two evaluators. A *recovery phase* then follows where the patients are given an opportunity to share thoughts and reflections considering the experience. Each session lasts approximately 2.5 h including the 50 min preparation phase, 30 min exposure phase and 60 min recovery phase. Both pre-treatment and post-treatment sessions took place between 14:30 h, 16:30 h and/or 19:30 h in order to control for diurnal variation in cortisol secretion. These timeslots have been validated with regard to diurnal variation in previous studies (33).

Cortisol sampling

Seven saliva samples were collected during the TSST-G. One was taken during the preparation period, two during the experiment, and four were taken during the recovery phase. Purpose-designed polyester salivettes produced by Sarstedt Inc., Rommelsdorf, Germany, were used to collect the samples and have been used in several previous studies (32,34). After sampling the salivettes were stored at −20 °C before being analyzed at the Department of Medical Biochemistry at St. Olavs Hospital, Trondheim. The samples were thawed, centrifuged and analyzed on Modular E170 from Roche using an electrochemiluminescence immunoassay (ECLIA) method. The assay used for determination of cortisol in saliva had an interassay variability of 7.9% at 12 nmol/L.

Cortisol recovery after the TSST-G

In the current experiment, we studied the cortisol change from immediately after the exposure phase until the end of the recovery phase. That is, we assessed the change in cortisol levels in the fourth saliva sample and the seventh saliva sample as a measure of how the patients recovered from the exposure phase. This was calculated for the pre-treatment TSST-G and the post-treatment TSST-G. A variable describing the pre to post treatment change in cortisol recovery span after the TSST-G was then calculated as described in previous studies (35). This variable was used in the statistical analysis.

Autonomic and psychological stress response

Continuous recording of heart rate was measured using a wireless chest heart rate transmitter and a wristwatch recorder (Polar RS800TS, Polar Electro, Finland). This was used as a measure of task engagement and sympathetic arousal. Additionally, the participants completed Visual Analog Scales (VAS) 10 min before, and 3 times during the exposure phase of the TSST-G on the domains of avoidance, anxiety, and tension. A previous study from the same patient sample found that changes in heart rate and VAS scales during the test confirmed substantial autonomic and psychological activation (17).

Ethics

The study was approved by the Regional Ethical Committee for Research in Health in Trondheim, Norway.

Statistics

A cut-off of ISI > 14 was used to determine patients with clinically significant insomnia symptoms and a cut-off of ISI < 8 was used to determine patients who were normal sleepers.

To test if there was a difference before and after treatment on the included variables, we conducted paired samples t-tests. Cohen's effect sizes were calculated using the equation $(m_{post} - m_{pre})/SD_{pooled}$.

In order to test the hypothesis that improvement in insomnia severity during treatment would predict lower levels of fatigue at treatment termination, independently of changes in pain, depression and anxiety, we conducted a hierarchical regression analysis in 9 steps. The dependent variable was level of fatigue post treatment. In step 1 we entered age, in step 2 we entered gender, in step 3 we entered level of fatigue pre treatment, in step 4 we entered pain intensity pre treatment, in step 5 we entered level of depression and anxiety pre treatment, in step 6 we entered level of insomnia severity pre treatment, in step 7 we entered level of pain intensity post treatment, in step 8 we entered levels of depression and anxiety post treatment, and in step 9 we entered level of insomnia severity post treatment. When entering the independent variables in this order, the regression model tests how improvement from pre to post therapy in pain, depression and anxiety, and insomnia severity predicts improvement in levels of fatigue, independently of level of the variables entered previously in the regression analysis.

In order to test the hypothesis that insomnia improvement will increase changes in the cortisol recovery span from pre to post treatment, over and above the effects of reduction in levels of fatigue, we conducted another hierarchical regression analysis in two steps. The dependent variable was the pre to post treatment change in the cortisol recovery after the TSST-G. Because patients have a flattened cortisol response pre treatment, a negative value will represent a favorable outcome where the cortisol recovery is larger after treatment than pre treatment. In step 1 we entered change in fatigue from pre to post treatment. In step 2 we entered change in insomnia severity from pre to post treatment. We used change variables in this analysis rather than pre and post therapy variables because the number of patients was limited.

Because it is possible that the change in cortisol recovery is a marker of how stressed the patients initially become in the test, rather than

their recovery after the stressor, we also repeated the above regression analysis but we also controlled for peak levels of cortisol after the stressor in step 1. In step 2 we entered improvement in fatigue, and in step 3 we entered improvement in insomnia.

Results

Descriptive data

A total of 279 patients were offered treatment in the inclusion period, and 188 of these patients reported chronic fatigue. Of the 188 patients with chronic fatigue, 144 patients (76.7%) had complete datasets on all items before and after treatment. From the SCID interview, a total of 22 patients (15.3%) were diagnosed with a comorbid mental disorder before treatment. These 22 patients were excluded from the analyses in order to obtain a pure sample of patients with chronic fatigue without comorbid mental disorders. The final sample for analyses was therefore 122 patients. These patients were between 22 and 61 years old and had a mean age of 44.0 (SD = 8.9). There were 98 females (80.3%) and 24 males (19.7%)

Before treatment, 42 patients (34.4%) had clinically significant insomnia symptoms, whereas 23 patients (18.9%) had insomnia after treatment. Before treatment, 31 patients (25.4%) were normal sleepers, whereas 51 patients (41.8%) were normal sleepers after treatment.

See Table 1 for levels of fatigue, insomnia, pain, depression and anxiety before and after treatment. There was a significant improvement on all variables.

Hypothesis testing 1: Improvement in insomnia will predict improvement in fatigue over and above the effects of improvement in pain, depression and anxiety

A summary of the hierarchical regression analysis testing predictors of fatigue post treatment is shown in Table 2. The regression model explained 34% of the variance in level of fatigue post treatment (Adjusted $R^2 = 0.34$).

Improvement of pain was not associated with improvement in fatigue, as seen in step 7 of the regression analysis, whereas improvement in levels of depression and anxiety was significantly associated with improvement in fatigue as seen in step 8.

Improvement in insomnia severity, entered in the final step, was significantly associated with improvement in fatigue after controlling for age, gender, fatigue pre treatment, improvement in pain, and improvement in depression and anxiety. Improvement in depression and anxiety remained significant in the final step.

Hypothesis testing 2: Improvement in insomnia will predict improvement in cortisol recovery over and above the effect of improvement in fatigue

A summary of the hierarchical regression analysis testing improvement in cortisol recovery is shown in Table 3. The regression model explained 44% of the total variance in improvement in cortisol recovery.

Improvement in fatigue was significantly associated with improvement in cortisol recovery when entered in the first step. Improvement in insomnia was significantly associated with improvement in cortisol recovery when entered in the second step. Improvement in fatigue remained significant in the second step.

The results remained the same for the association between improvement of insomnia and improvement in cortisol recovery when we conducted the regression analysis and controlled for initial peak levels of cortisol.

Discussion

In this study we found that improvement in insomnia predicted levels of fatigue post treatment in the treatment of patients with chronic fatigue. The results suggest that insomnia improvement has a

Table 1
Changes in the clinical variables for 122 patients with chronic fatigue before and after 3.5 weeks of Acceptance and Commitment Therapy for chronic fatigue.

Variable	Pre treatment		Post treatment		Paired samples *t*-test		
	Mean	SD	Mean	SD	*t*	*P*	*d*
Fatigue	8.97	1.86	5.62	3.83	10.3	<.001	1.11
Insomnia severity	12.0	6.07	9.51	6.12	5.55	<.001	0.41
Pain	3.96	1.20	3.50	1.15	4.71	<.001	0.39
Depression and anxiety	14.9	7.11	10.5	6.25	8.14	<.001	0.66

Fatigue = sum score on the Chalder Fatigue Scale.
Pain = score on level of somatic pain from the Short-Form 8.
Anxiety and depression = sum score on the Hospital Anxiety and Depression Scale.
Insomnia = sum score on the Insomnia Severity Index.
d = effect size, Cohen's *d*.

Table 2
Summary of the hierarchical regression analysis on predictors of level of fatigue after treatment for 122 patients with chronic pain. The regression model explains 34% of the total variance in fatigue post treatment.

Step		ΔR^2	B	SE B	β	*t*	*P*
1		.04					
	Age		.09	.04	.20	2.23	*
2		.03					
	Age		.08	.04	.19	2.20	*
	Gender		1.55	.85	.16	1.82	
3		.11					
	Age		.06	.04	.14	1.66	
	Gender		1.09	.81	.11	1.34	
	Fatigue pre treatment		.70	.18	.34	3.95	***
4		.01					
	Age		.06	.04	.15	1.66	
	Gender		1.23	.82	.13	1.51	
	Fatigue pre treatment		.75	.18	.37	4.18	***
	Pain pre treatment		−.39	.28	−.12	−1.38	
5		.00					
	Age		.06	.04	.15	1.74	
	Gender		1.17	.82	.12	1.43	
	Fatigue pre treatment		.79	.19	.38	4.22	***
	Pain pre treatment		−.37	.28	−.12	−1.32	
	Depression and anxiety pre treatment		−.03	.05	−.06	−.76	
6		.00					
	Age		.06	.04	.15	1.73	
	Gender		1.17	.82	.12	1.42	
	Fatigue pre treatment		.79	.19	.38	4.18	***
	Pain pre treatment		−.37	.29	−.12	−1.29	
	Depression and anxiety pre treatment		−.04	.05	−.07	−.69	
	Insomnia pre treatment		.00	.06	.00	.05	
7		.01					
	Age		.07	.04	.15	1.76	
	Gender		1.05	.83	.11	1.27	
	Fatigue pre treatment		.79	.19	.38	4.19	***
	Pain pre treatment		−.56	.34	−.18	−1.66	
	Depression and anxiety pre treatment		−.03	.05	−.05	−.58	
	Insomnia pre treatment		−.01	.06	−.01	.13	
	Pain post treatment		.38	.35	.11	1.07	
8		.09					
	Age		.06	.04	.15	1.83	
	Gender		1.13	.79	.12	1.44	
	Fatigue pre treatment		.88	.18	.43	4.88	***
	Pain pre treatment		−.39	.33	−.12	−1.20	
	Depression and anxiety pre treatment		−.17	.06	−.03	−2.74	**
	Insomnia pre treatment		−.02	.06	−.03	−.32	
	Pain post treatment		−.02	.35	−.01	−.06	
	Depression and anxiety post treatment		.25	.07	.40	3.72	***
9		.10					
	Age		.06	.03	.14	1.81	
	Gender		1.34	.74	.14	1.81	
	Fatigue pre treatment		.90	.17	.44	5.34	***
	Pain pre treatment		−.37	.30	−.11	−1.21	
	Depression and anxiety pre treatment		−.12	.06	−.22	−2.07	*
	Insomnia pre treatment		−.20	.07	−.32	−2.91	***
	Pain post treatment		−.24	.33	−.07	−.71	
	Depression and anxiety post treatment		.14	.07	.23	2.13	*
	Insomnia post treatment		.30	.07	.48	4.21	***

Dependent variable: sum score on the Chalder Fatigue Scale post treatment.
Fatigue = sum score on the Chalder Fatigue Scale.
Pain = score on level of somatic pain from the Short-Form Health Status-8.
Depression and anxiety = sum score on the Hospital Anxiety and Depression Scale.
Insomnia = sum score on the Insomnia Severity Index.
* $p = <0.05$.
** $p = <0.01$.
*** $p < 0.0001$.

Table 3
Summary of the hierarchical regression analysis on predictors of improvement in cortisol recovery span after the Trier Social Stress Test for Groups for a random subsample of 25 patients. The regression model explains 44% of the total variance in the improvement in cortisol recovery span post treatment.

Step		ΔR^2	B	SE B	β	t	P
1		0.27					
	Fatigue reduction during treatment		−.59	.19	−.53	−3.04	.006
2		0.17					
	Fatigue reduction during treatment		−.42	.19	−.38	−2.28	.03
	Insomnia reduction during treatment		−.39	.15	−.43	−2.62	.02

Fatigue reduction = difference in the sum score on the Chalder Fatigue Scale before and after treatment.
Insomnia reduction = difference in the sum score on the Insomnia Severity Index before and after treatment.

contribution to reduction in fatigue outcomes over and above the effects of improvements in pain, depression and anxiety. Moreover, we found that this improvement in insomnia was strongly related to improved stress response for these patients over and above the effects of improved fatigue.

Research from the last decade on treatment of insomnia comorbid to other disorders has shown that insomnia may be a useful therapeutic target because improved insomnia can also enhance the effectiveness of other treatments beyond the effects of improved sleep quality (e.g. (36–39)). The present findings indicate that insomnia may have such a function for patients with Chronic Fatigue Syndrome. This is particularly interesting because the mean change on the insomnia severity index was lower ($d = 0.4$) than what is typically found in treatment studies using behavioral or cognitive behavioral therapy for insomnia ($d = 2.0$–2.5) (e.g. (40)). Thus, even a moderate change in insomnia severity seemed to have a robust impact on outcomes.

The established first line of treatment for insomnia is Cognitive Behavior Therapy for Insomnia (CBT-I) (41). One underlying assumption of CBT-I is that spending excessive time in bed is one of the maintaining factors of insomnia, and the core treatment component of sleep restriction requires patients to curtail the time in bed to the time spent sleeping (42). Patients with CFS may spend more time in bed than other normal controls (8), which may maintain their insomnia symptoms. The treatment provided in the current study did not have a specific focus on insomnia. However, the structured inpatient treatment did require patients to get up at the same time each morning regardless of their sleep, have structured activities during the day, and spend less time in bed than they usually do. The treatment did therefore include some of the elements of CBT-I though not presented in the rationale or structure of CBT-I. On the basis of these results it would be interesting for future studies to test if providing concurrent CBT-I would enhance the treatment outcomes for patients with CFS.

Impairment in the HPA-axis has been suggested as one of the biological factors contributing to the maintenance in fatigue and other symptoms in CFS (16). We found that improvement in insomnia was related to an improved cortisol recovery in response to a stressor. In the presence of CFS, this stress-buffering effect of sleep could be particularly important given that patients with CFS report excessive fatigue in response to stressors (15). Thus, improved sleep quality may improve the physiological response to stress for these patients and could be a potential mechanism of change in the treatment of CFS. Palesh et al. found that sleep disruption was related to a flattened cortisol response on the TSST (43). Our result is in line with this, though we found that for patients who already displayed a flattened cortisol response on the TSST, improved insomnia severity is related to having improved cortisol response. However, from the current study we do not know the direction of causality. That is, we do not know if it is improvement in insomnia that causes the improvement in cortisol recovery or if the improvement in cortisol recovery causes improved sleep. An alternative explanation would be that through the ACT treatment, the patients learned more adaptive skills for coping with stress. This could lead to both improvements in insomnia and to improved cortisol recovery.

Limitations

A major limitation of the current study is that we used self-report on the Chalder Fatigue Scale as a marker for CFS and not a clinical diagnostic assessment. Thus, the group of patients here reported were on sick leave and had self-reported severe fatigue of at least 6 months duration, but this group may not be generalizable to the group that meets the full criteria for CFS. Similarly, we used self-reported levels of insomnia on the Insomnia Severity Index (ISI) as a marker for levels of insomnia severity and not a clinical assessment of insomnia. However, the ISI is widely used in insomnia research and recommended as a standard questionnaire to assess insomnia severity and insomnia change during treatment (31).

Second, we did not include sleep diary data or actigraphy data where we can test if circadian factors have an impact on the results. Similarly, we did not have any objective measure of sleep to screen for organic sleep disorders. It is therefore possible that some of the patients who report high on insomnia severity could have sleep apnea or related sleep disorders. It is unlikely that these patients would have improved sleep quality over the duration of this intervention.

A third limitation was that the TSST was administered to a subgroup of our sample and not the entire sample. This limits the generalizability of our findings, though the sample was randomly selected and the sample size is similar to other studies using the TSST (e.g. (32)).

Fourth, not all patients were drug-free and medication could have had an effect on cortisol secretion in the TSST. However, a previous study from the same patient sample has found that neither the use of anti-depressive medication nor the use of beta-blockers had an effect on cortisol slope on the TSST (17).

Conclusion

We found that improvement in insomnia severity had a significant impact on improvement in fatigue that was independent of improvements in pain, depression and anxiety. Moreover, we found that improvement in insomnia severity was also associated with improved ability to recover after a stressful situation during the day. Insomnia severity may be a maintaining factor in chronic fatigue and specifically targeting this in treatment could increase treatment response.

Acknowledgments

The authors would like to thank the clinicians at Hysnes Rehabilitation Center for all their assistance in the collection of this data.

References

[1] Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med 1994;121:953–9 [PubMed PMID: Medline:7978722. English].
[2] Reid S, Chalder T, Cleare A, Hotopf M, Wessely S. Chronic fatigue syndrome. BMJ (Clinical research ed) 2000;320:292–6 [PubMed PMID: Medline:10650029. English].
[3] Malouff JM, Thorsteinsson EB, Rooke SE, Bhullar N, Schutte NS. Efficacy of cognitive behavioral therapy for chronic fatigue syndrome: a meta-analysis. Clin Psychol Rev 2008;28:736–45 [PubMed PMID: Medline:18060672. English].
[4] Buysse DJ. Insomnia. JAMA Feb 20 2013;309:706–16 [PubMed PMID: 23423416. Pubmed Central PMCID: 3632369].
[5] American Academy of Sleep Medicine. The international classification of sleep disorders: diagnostic and coding manual. , xviiiWestchester, Ill: American Academy of Sleep Medicine; 2005[297 pp.].
[6] Kallestad H, Hansen B, Langsrud K, Ruud T, Morken G, Stiles TC, et al. Differences between patients' and clinicians' report of sleep disturbance: a field study in mental

health care in Norway. BMC Psychiatry 2011;11 [PubMed PMID: 22112049. Pubmed Central PMCID: 3231868].
[7] Mariman A, Delesie L, Tobback E, Hanoulle I, Sermijn E, Vermeir P, et al. Undiagnosed and comorbid disorders in patients with presumed chronic fatigue syndrome. J Psychosom Res Nov 2013;75:491–6 [PubMed PMID: 24182640].
[8] Mariman AN, Vogelaers DP, Tobback E, Delesie LM, Hanoulle IP, Pevernagie DA. Sleep in the chronic fatigue syndrome. Sleep Med Rev Jun 2013;17:193–9 [PubMed PMID: 23046847].
[9] Lichstein KL, Means MK, Noe SL, Aguillard RN. Fatigue and sleep disorders. Behav Res Ther Aug 1997;35:733–40 [PubMed PMID: 9256516].
[10] Watson NF, Kapur V, Arguelles LM, Goldberg J, Schmidt DF, Armitage R, et al. Comparison of subjective and objective measures of insomnia in monozygotic twins discordant for chronic fatigue syndrome. Sleep May 1 2003;26:324–8 [PubMed PMID: 12749553].
[11] Jackson ML, Bruck D. Sleep abnormalities in chronic fatigue syndrome/myalgic encephalomyelitis: a review. J Clin Sleep Med: JCSM: official publication of the American Academy of Sleep Medicine 2012;8:719–28 [PubMed PMID: Medline:23243408. English].
[12] Yoo S-S, Gujar N, Hu P, Jolesz FA, Walker MP. The human emotional brain without sleep—a prefrontal amygdala disconnect. Curr Biol 2007;17:R877–8 [PubMed PMID: Medline:17956744. English].
[13] Palesh O, Zeitzer JM, Conrad A, Giese-Davis J, Mustian KM, Popek V, et al. Vagal regulation, cortisol, and sleep disruption in women with metastatic breast cancer. J Clin Sleep Med Oct 15 2008;4:441–9 [PubMed PMID: 18853702. Pubmed Central PMCID: 2576311].
[14] Gaab J, Huster D, Peisen R, Engert V, Heitz V, Schad T, et al. Hypothalamic–pituitary–adrenal axis reactivity in chronic fatigue syndrome and health under psychological, physiological, and pharmacological stimulation. Psychosom Med Nov–Dec 2002;64:951–62 [PubMed PMID: 12461200].
[15] Lutgendorf SK, Antoni MH, Ironson G, Fletcher MA, Penedo F, Baum A, et al. Physical symptoms of chronic fatigue syndrome are exacerbated by the stress of Hurricane Andrew. Psychosom Med Jul–Aug 1995;57:310–23 [PubMed PMID: 7480560].
[16] Roberts AD, Wessely S, Chalder T, Papadopoulos A, Cleare AJ. Salivary cortisol response to awakening in chronic fatigue syndrome. Br J Psychiatry Feb 2004;184:136–41 [PubMed PMID: 14754825].
[17] Jacobsen HB, Bjorngaard JH, Hara KW, Borchgrevink PC, Woodhouse A, Landro NI, et al. The role of stress in absenteeism: cortisol responsiveness among patients on long-term sick leave. PLoS One 2014;9:e96048 [PubMed PMID: 24788346. Pubmed Central PMCID: 4008526].
[18] Appels A. Exhaustion and coronary heart disease: the history of a scientific quest. Patient Educ Couns 2004;55:223–9 [PubMed PMID: Medline:15530758. English].
[19] Kudielka BM, Bellingrath S, Hellhammer DH. Cortisol in burnout and vital exhaustion: an overview. G Ital Med Lav Ergon Jan–Mar 2006;28:34–42 [PubMed PMID: 19031555].
[20] Kirschbaum C. Trier social stress test. In: Stolerman IP, editor. Encyclopedia of Psychopharmacology. Berlin Heidelberg: Springer-Verlag; 2010.
[21] Fimland MS, Vasseljen O, Gismervik S, Rise MB, Halsteinli V, Jacobsen HB, et al. Occupational rehabilitation programs for musculoskeletal pain and common mental health disorders: study protocol of a randomized controlled trial. BMC Public Health 2014;14:368 [PubMed PMID: 24735616. Pubmed Central PMCID: 3996166].
[22] Chalder T, Berelowitz G, Pawlikowska T, Watts L, Wessely S, Wright D, et al. Development of a fatigue scale. J Psychosom Res 1993;37:147–53 [PubMed PMID: Medline:8463991. English].
[23] First MB, Spitzer R L, Williams J B W. Structured clinical interview for DSM-IV axis I disorders. Washington, DC: American Psychiatric Association; 1995.
[24] JEea Ware. How to score and interpret single-item health status measures: a manual for users of the of the SF-8 health survey. Lincoln, RI: QualityMetric, Inc.; 2001.
[25] Landmark T, Romundstad P, Dale O, Borchgrevink PC, Kaasa S. Estimating the prevalence of chronic pain: validation of recall against longitudinal reporting (the HUNT pain study). Pain Jul 2012;153:1368–73 [PubMed PMID: 22575226].
[26] Haug TT, Mykletun A, Dahl AA. The association between anxiety, depression, and somatic symptoms in a large population: the HUNT-II study. Psychosom Med Nov–Dec 2004;66:845–51 [PubMed PMID: 15564348].
[27] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983 Jun;67:361–70 [PubMed PMID: 6880820].
[28] McCue P, Buchanan T, Martin CR. Screening for psychological distress using internet administration of the Hospital Anxiety and Depression Scale (HADS) in individuals with chronic fatigue syndrome. Br J Clin Psychol Nov 2006;45:483–98 [PubMed PMID: 17076959].
[29] Morin CM, Belleville G, Belanger L, Ivers H. The insomnia severity index: psychometric indicators to detect insomnia cases and evaluate treatment response. Sleep May 2011;34:601–8 [PubMed PMID: 21532953. Pubmed Central PMCID: 3079939. Epub 2011/05/03. eng].
[30] Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med Jul 2001;2:297–307 [PubMed PMID: 11438246. Epub 2001/07/05. Eng].
[31] Buysse DJ, Ancoli-Israel S, Edinger JD, Lichstein KL, Morin CM. Recommendations for a standard research assessment of insomnia. Sleep Sep 1 2006;29:1155–73 [PubMed PMID: 17040003. Epub 2006/10/17. eng].
[32] von Dawans B, Kirschbaum C, Heinrichs M. The Trier Social Stress Test for Groups (TSST-G): a new research tool for controlled simultaneous social stress exposure in a group format. Psychoneuroendocrinology May 2011;36:514–22 [PubMed PMID: 20843608].
[33] Kudielka BM, Buske-Kirschbaum A, Hellhammer DH, Kirschbaum C. HPA axis responses to laboratory psychosocial stress in healthy elderly adults, younger adults, and children: impact of age and gender. Psychoneuroendocrinology Jan 2004;29:83–98 [PubMed PMID: 14575731].
[34] Witteveen AB, Huizink AC, Slottje P, Bramsen I, Smid T, van der Ploeg HM. Associations of cortisol with posttraumatic stress symptoms and negative life events: a study of police officers and firefighters. Psychoneuroendocrinology Aug 2010;35:1113–8 [PubMed PMID: 20083359].
[35] Dickerson SS, Kemeny ME. Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. Psychol Bull May 2004;130:355–91 [PubMed PMID: 15122924].
[36] Taylor DJ, Lichstein KL, Weinstock J, Sanford S, Temple JR. A pilot study of cognitive–behavioral therapy of insomnia in people with mild depression. Behav Ther 2007;38:49–57.
[37] Manber R, Edinger JD, Gress JL, San Pedro-Salcedo MG, Kuo TF, Kalista T. Cognitive behavioral therapy for insomnia enhances depression outcome in patients with comorbid major depressive disorder and insomnia. Sleep 2008;31:489–95.
[38] Myers E, Startup H, Freeman D. Cognitive behavioural treatment of insomnia in individuals with persistent persecutory delusions: a pilot trial. J Behav Ther Exp Psy Sep 2011;42:330–6 [PubMed PMID: 21367359. Epub 2011/03/04. eng].
[39] Talbot LS, Maguen S, Metzler TJ, Schmitz M, McCaslin SE, Richards A, et al. Cognitive behavioral therapy for insomnia in posttraumatic stress disorder: a randomized controlled trial. Sleep 2014;37:327–41 [PubMed PMID: 24497661. Pubmed Central PMCID: 3900619].
[40] Harvey AG, Belanger L, Talbot L, Eidelman P, Beaulieu-Bonneau S, Fortier-Brochu E, et al. Comparative efficacy of behavior therapy, cognitive therapy, and cognitive behavior therapy for chronic insomnia: a randomized controlled trial. J Consult Clin Psychol May 26 2014;82(4):670–83 [PubMed PMID: 24865869].
[41] Morin CM, Bootzin RR, Buysse DJ, Edinger JD, Espie CA, Lichstein KL. Psychological and behavioral treatment of insomnia: update of the recent evidence (1998–2004). Sleep Nov 2006;29:1398–414 [PubMed PMID: 17162986].
[42] Morin CM. Insomnia: psychological assessment and management. , xviiNew York: Guilford Press; 1993[238 pp.].
[43] Pigeon WR, Moynihan J, Matteson-Rusby S, Jungquist CR, Xia Y, Tu X, et al. Comparative effectiveness of CBT interventions for co-morbid chronic pain & insomnia: a pilot study. Behav Res Ther Nov 2012;50:685–9 [PubMed PMID: 22982083. Pubmed Central PMCID: 3466363].