The role of sleep quality and fatigue on the benefits of an interdisciplinary treatment for adults with chronic pain

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Abstract

Background: Interdisciplinary chronic pain treatment is known to be effective for reducing pain intensity and pain-related disability, and improving psychological function. However, the mechanisms that underlie these treatment-related benefits are not yet well-understood. Sleep problems and fatigue are modifiable factors often comorbid with chronic pain. The goal of this study was to evaluate the role that changes in sleep quality and fatigue might have on the benefits of an interdisciplinary chronic pain treatment.

Methods: A total of 125 adults with chronic pain participated in a four-week interdisciplinary pain management program. Measures of depression, sleep disturbance, fatigue, pain intensity, and physical function were administered at pre- and post-treatment. Three regression analyses were conducted to evaluate the contribution of pre- to post-treatment improvements in fatigue and sleep disturbance to the pre- to post-treatment improvements observed in pain intensity, disability, and depression, while controlling for demographic characteristics (age and sex) and pain intensity.

Results: Changes in fatigue and sleep disturbance, made independent and significant contributions to the prediction of treatment-related benefits in pain intensity; improvements in depressive symptoms were predicted by improvements in fatigue, and

improvement in pain-related disability was only predicted by pre-treatment and pre- to post-treatment decreases in pain intensity (one of the control variables).

Conclusions: In addition to sleep, fatigue emerged as a key potential mechanism of multidisciplinary chronic pain treatment-related improvements (pain intensity and depressive symptoms), suggesting that interventions including elements which effectively target improvements in sleep and fatigue may enhance the efficacy of interdisciplinary chronic pain programs. This possibility should be evaluated in future research.

Keywords: chronic pain; Cognitive Behavioral Therapy; sleep; fatigue; depression

1. Introduction

Chronic pain is a common condition worldwide [1–3] and is considered a significant public health priority [4]. It often has negative effects on general health, physical function, and psychological well-being [5,6], and represents an important economic burden in terms of both direct and indirect costs [7].

Chronic pain does not respond well to standard biomedical procedures, including analgesic medications [8,9]. Given the current "opioid crisis," where the negative individual and social effects of chronic opioid use are being increasingly recognized [10], the availability of additional safe and efficient chronic pain treatments is critical. Interdisciplinary chronic pain treatments, which usually involve tapering patients *off* of opioid analgesics, have been found to be effective as evidenced by studies showing that they result in decreases in pain intensity and pain-related disability, and improvements in psychological function [11–13].

However, the mechanisms that underlie the benefits of these treatments are not yet well understood. To address this knowledge gap, there has been a call for research to better understand these underlying mechanisms using longitudinal study designs [14]. Identifying the modifiable factors that are associated with treatment outcomes is useful to better understand what are the possible mechanisms of treatment effects and to pinpoint the treatment components that should be emphasized [15]. Sleep problems and fatigue are modifiable factors that are often comorbid with chronic pain [16].

Sleep quality is known to be related to pain intensity, mood and disability in individuals with chronic pain [17,18]. Sleep disturbances reliably predict subsequent

pain and can contribute to its chronification, pain-related disability and depression [18]. A recent review examining the nature of these relationships in prospective and experimental studies has concluded that sleep and pain can influence each other in a bidirectional way—that is, sleep quality influences pain and vice versa [19]. A recent review [20] also highlights the negative effects of the poor sleep quality on impulse control, attentional capacity, and decision making. All of these are elements that could influence an individual's ability to understand and follow treatment recommendations, which, in turn, could impact treatment success.

Fatigue is also a common condition that is comorbid with sleep problems and other function domains in individuals with chronic pain. For example, poor sleep quality has been shown to be related to more fatigue [21] and fatigue has been, in turn, found to be associated with worse health-related quality of life, greater physical disability and more depressive symptoms in diverse samples such as patients with arthritis, irritable bowel syndrome, and chronic widespread pain [22–25]. Thus, it would be reasonable to hypothesize that treatment-related improvements in fatigue might also be associated with improvements in numerous outcome domains, including disability and depression.

Given these considerations, the aim of this study was to evaluate the role that changes in sleep quality and fatigue might have in predicting the benefits of an interdisciplinary chronic pain treatment program. We hypothesized that treatment-related improvements in both sleep quality and fatigue severity would contribute to pre-to post-treatment decreases in (1) pain intensity, (2) pain-related disability, and (3) depressive symptoms. Specifically, we hypothesized that greater improvements in sleep

quality and greater decreases in fatigue severity would be associated with greater reductions in pain intensity, disability and depressive symptoms.

2. Materials and Methods

Participants

The sample was composed of 125 adult patients with chronic pain being treated in an interdisciplinary pain treatment program in [BLINDED]. The majority of patients (53%) reported significant pain in more than three locations. Low back pain (13%) and pain in the cervical region and/or shoulders (7%) were the other most frequently reported locations. The mean age of the participants was 54.37 (SD = 10.28), and the majority (76%) were women. The average pain duration was of 10.49 years (SD = 11.72) and mean pain intensity was of 6.35 (SD = 1.52) on a 0-10 scale at baseline. Details about marital status, education and work status can be found in Table 1.

[Insert Table 1 about here]

Measures

Demographic variables. Information about the demographic characteristics of the sample was collected using a questionnaire completed by patients at the beginning of treatment.

Fatigue severity. The Patient-Reported Outcomes Measurement Information System (PROMIS®) was developed to improve and unify the measurement of patient-reported outcomes. The PROMIS-29 Health Survey [26] subscales were used to collect information about several of the variables included in the study, including fatigue severity. The PROMIS-29 scales scores have shown good psychometric properties in

diverse samples, including many with chronic pain, such as patients with rheumatoid arthritis, osteoarthritis, fibromyalgia syndrome, and systemic lupus erythematosus [27].

The PROMIS-29 Fatigue scale T-score, computed from the four fatigue items of the PROMIS-29, was used as the measure of fatigue. The alphas for the baseline and post-treatment PROMIS-29 Fatigue scores in this sample were 0.91 at both time points, indicating excellent internal consistency.

Sleep disturbance. The PROMIS-29 Sleep Disturbance scale T-score was used as the measure of sleep quality. The internal consistency for the PROMIS-29 baseline and post-treatment Sleep scales in this sample were moderate (Cronbach's alpha = 0.78 and 0.79, respectively).

Pain intensity. The PROMIS-29 Average Pain scale (range 0-10) was used to assess pain intensity. The 0-10 NRS is widely used to measure pain intensity, it has been found to provide valid and reliable measures of pain intensity in a variety of samples [28].

Depressive symptoms. The PROMIS-29 Depression T-score was used as the measure of depressive symptoms. The internal consistency coefficients of the baseline and post-treatment scores (Cronbach's alphas = 0.94 in both cases) indicated excellent internal consistency reliability for this scale in the current sample.

Pain-related disability. The Pain Disability Index (PDI) [29] is a 7-item questionnaire that was developed to assess pain-related disability; it has shown good psychometric properties in studies with chronic pain patients [30]. With the PDI, respondents are asked to rate how much pain is interfering in doing what they normally

do in seven categories: family and home responsibilities, recreation (hobbies and sports), social activity (activities with friends), occupation (work, housework or volunteering), sexual behavior, self-care (independent daily living), and life-support activity (eating, sleeping, breathing). Interference with each activity domain is rated using 0 to 10 scales, with 0 indicating "*No disability*" and 10 indicating "*Worst disability*". The internal consistency coefficient of the baseline and post-treatment scale scores (Cronbach's alpha = 0.83 and 0.86, respectively) indicated good reliability in the current sample for this measure.

Procedures

Participants in this study were recruited from those who attended a four-week interdisciplinary CBT chronic pain management program in [BLINDED]. The treatment consisted of three sessions per week of three hours duration that were administered in group format. During these sessions, patients received psychoeducation about the physiology of pain, sleep hygiene, and communication with others; learnt to set relevant and realistic goals, and were trained in relaxation, activity pacing and in coping strategies.

Participants were provided with information about sleep in two sessions. The first session provided information about sleep architecture, environmental factors affecting sleep, sleep hygiene (i.e., establishing a consistent wake time, improving sleep efficiency, and reducing or eliminating daytime napping), and the role of circadian rhythms and sleep drive. The second session provided information and demonstrations

of strategies for adapting sleep positions to better manage ongoing pain (e.g., use of pillows and bolsters to provide support and reduce pain).

The management of fatigue was addressed primarily in the sessions on activity pacing. There, participants were encouraged to employ activity pacing strategies to manage both pain and fatigue. Information about the use of adaptive equipment and ergonomics was also presented in other sessions and was identified as strategies to conserve energy and reduce fatigue.

Participants were expected to practice at home and to include the new skills in their daily routines. The treatment was administered by an interdisciplinary team of psychologists, physiotherapists, and occupational therapists. The inclusion criteria were having chronic pain and a willingness to attend the four-week interdisciplinary program. Patients were excluded from treatment if they did not evidence the physical tolerance needed to participate in the program, were significantly cognitively impaired, or actively suicidal. All the measures were administered during the first week of treatment (pre-treatment), and at 4 weeks at the conclusion of the program (post-treatment). Before answering the questionnaires, the study procedures were reviewed and institutional approved was obtained; all participants received an explanation of the study and provided written informed consent. The treatment is fully described in a previous article [31]. An additional article [32] using data from the same program has been published, however, the research questions were different and the samples are not overlapping (different questionnaires were administered to different participants). This is the first paper examining the relationship between sleep, fatigue and the treatment outcomes.

Data analysis

For descriptive purposes, we first computed numbers and percentages for the categorical variables, and means and standard deviations for the continuous variables. Next, we evaluated the suitability of the data for the planned regression analyses by examining the skewness and kurtosis of the distributions of the predictor variables (i.e., sleep quality and fatigue severity) to assess normality of variables, and by computing the Durbin-Watson statistic and the variance inflation factors (VIF) for the predictors to test multicollinearity issues. We then conducted three, linear multiple regression analyses, one for each of the criterion variables; that is, post-treatment levels of (1) average pain intensity, (2) depressive symptoms, and (3) disability, controlling for demographic variables (sex and age). In step 1 of the first analysis predicting change in average pain intensity, we entered pre-treatment average pain intensity. In step 2, we entered sex and age to control for their potential effects on the model. In step 3, we entered pre-treatment levels of sleep quality and fatigue, to control for the baseline levels on these variables. In step 4 we entered post-treatment levels of sleep quality and fatigue. Because baseline measures of sleep quality and fatigue were entered in a previous step, the entry of these variables in step 4 represents residuals (i.e., changes scores) of these variables; thus, significant effects at this step can be interpreted as an indication that change in the predictor is associated with change in pain intensity. In the second and third regression analyses (predicting change in disability and depressive symptoms, respectively), we entered pre-treatment levels of the criterion variables in step one (i.e., pre-treatment disability when predicting post-treatment disability, and

pre-treatment depressive symptoms when predicting post-treatment depression. As we had in the first regression, in step 2 we entered sex and age, to control for their effects. In step 3, we entered pre-treatment levels of average pain intensity along with pre-treatment levels of sleep quality and fatigue. In step 4 we entered post-treatment levels of average pain intensity along with post-treatment levels of sleep quality and fatigue. IBM SPSS 20 for Mac was used for all data analyses.

3. Results

Pre- to post-treatment improvements were statistically significant for all the outcome variables, with small to moderate effect sizes. The PROMIS measures that were used in this study do not have a minimally important difference cut-off poinst [33]. Therefore, in order to understand the extent to which the changes observered might be meaningful, we followed the recommendations of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) for patient reported outcomes without established minimally important change cutoffs, and used a 0.5 SD as the point of reference [34]. Using this criterion, only sleep quality showed a meaningful improvement after treatment (0.9 SD), on average; all other improvements were below the identified reference, around 0.4 SD. These improvements are consistent with those reported in other samples [31]. See Table 2 for details.

[Insert Table 2 about here]

Regarding the regression analyses, skewness and kurtosis were adequate to perform the planned analyses (Z scores were under the recommended cut point of 1.96 in all cases except from the kurtosis for pain intensity that was 2.5, for the rest of the

variables they were under 1.5). The Durbin-Watson statistic was adequate, being between 1.9 and 2.5, the variance inflation VIF was lower than 10 (the maximum VIF was 1.7) and the tolerance was higher than 0.6 in all cases, indicating that multicollinearity among the predictors would not bias the results. In short, the data met the requirements for the planned analyses.

Change in pain intensity. Consistent with the study hypotheses, the regression analysis predicting improvement in pain intensity (i.e., T2 pain intensity controlling for T1 pain intensity) showed that pre- to post-treatment changes in pain intensity were partially explained (61% of the variance) by pre-treatment pain intensity and pre- to post-treatment changes in sleep and fatigue (step 4 of the model). Both the changes in sleep and fatigue made statistically significant independent contributions to the prediction of the change in pain intensity (β = -0.24 and 0.25, $p < 0.01$); that is, a greater decrease in sleep and fatigue was associated with a greater decrease in pain intensity. See Table 3.

[Insert Table 3 about here]

Change in pain-related disability. Regarding the prediction of pre- to post-treatment change in pain-related disability, changes in pain intensity were significant in predicting the changes in disability (β = 0.27, $p < 0.01$), accounting for 80% of the variance (along with the rest of the variables included in the model). However, neither change in sleep nor change in fatigue predicted change in pain-related disability. Interestingly, both pre-treatment pain intensity and pre- to post-treatment decrease in

pain intensity did predict decreases in pain-related disability (β = 0.26, p < 0.01). See Table 4.

[Insert Table 4 about here]

Change in depressive symptoms. Finally, in the third model, along with pre-treatment depressive symptoms, changes in sleep, fatigue and pain intensity accounted for 75% of the variance, although only changes in fatigue made a statistically significant independent contribution to the prediction of changes in depressive symptoms (β = 0.16, p < 0.05). See Table 5.

[Insert Table 5 about here]

Predicting fatigue changes as a function of sleep changes. Given the results showing a general lack of strong associations between changes in sleep and outcomes (described above), we examined in a post-hoc regression analysis the association between changes in sleep and changes in fatigue. In this analysis, with post-treatment fatigue as the dependent variable, we entered pre-treatment levels of fatigue in step 1, sex and age in step 2, pre-treatment sleep in step 3, and post-treatment sleep in step 4. This model explained 49% of the variance in fatigue. In addition, we found that improvements in sleep quality independently contributed significantly to decreases in fatigue (β = -0.37, p < 0.001). See Table 6.

[Insert Table 6 about here]

4. Discussion and conclusions

Interdisciplinary chronic pain programs have been shown to be effective for improving a variety of important outcome domains (i.e., disability, pain intensity,

psychological function) [35,36]. However, the specific factors that contribute to these benefits are not yet well understood. Increasing our knowledge regarding the factors that explain treatment outcomes would allow us to better appreciate not only how pain treatments have their benefits, but also to identify those factors to target more intensely in order to maximize treatment improvements. In the analyses presented here, we found that treatment-related improvements in fatigue and sleep disturbance, were significantly associated with some of the outcomes examined, over and above any benefits associated with demographic factors. First, for the prediction of changes in pain intensity, changes in both fatigue and sleep were significant. These findings are consistent with the body of research supporting the role that sleep quality has in influencing pain intensity [19], including results from interdisciplinary pain treatment studies [37]. They also support the inclusion of sleep specific interventions, such as teaching sleep hygiene techniques or CBT-i, as part of multicomponent interventions for individuals with chronic pain.

Second, for the prediction of changes in pain related disability, only pain intensity was significant. One possible explanation may be that a reduction in pain intensity can have an immediate effect on disability, while improvements in sleep and fatigue might need to be sustained over a period of time to influence disability. This would suggest that looking at changes over a period longer than four weeks might produce a different result. New studies with longer follow-up periods would be needed in order to test this possibility.

Third, for the prediction of improvements in depression, only fatigue was significant. Consistent with our findings, in a prospective study with patients with chronic widespread pain, Rooij and colleagues [38], also obtained results showing that improvements in fatigue were associated with improvements in depression after a multidisciplinary rehabilitation treatment. In line with these results, in a cross-sectional study, Naughton and colleagues [18] found that despite showing a concurrent association with depression and pain-related disability, sleep disturbance was no longer associated with disability when controlling for depression and pain.

Another interesting finding was the fact that treatment-related improvements in sleep quality predicted improvements fatigue. This finding may explain why in some of the analyses sleep *per se* was not predictive of changes in specific outcomes. However, it is also possible that the moderate sample size of the current study and/or the lower reliability of the measure of sleep disturbance used here might have contributed to the negative findings with respect to sleep as a contributing factor of some of the treatment outcomes. Additional research, ideally with larger sample sizes and using measures of sleep disturbance with greater reliability, would help evaluate the stability of the current findings.

The moderate-to-large percentage of the variance explained by the models including pain intensity, sleep and fatigue (specifically: 61% for pain intensity, 80% for disability and 75% for depression), indicates that, although pre- to post-treatment changes in fatigue, sleep and pain intensity are significantly associated with the treatment effects for all the outcome domains studied, there are also other variables

that have shown independent associations with treatment outcomes. For example, pain beliefs, catastrophizing and coping have all been identified as potential mediators of interdisciplinary pain treatment efficacy [39]. Future research should consider examining all of these factors in the same study, so as to help evaluate their relative importance.

Considering the findings relating the impact of fatigue on the studied domains, a highly effective approach for treating fatigue has yet to be identified. In a recent review evaluating the efficacy of treatments for chronic fatigue syndrome [40], limited benefits were found for some pharmacological (e.g. rintatolimod and rituximab) and non-pharmacological (e.g. counselling, behavioral and rehabilitation programs) approaches. However, the effect sizes associated with these treatments tended to be weak. The effect sizes associated with other treatments, such as adaptive pacing and the use of nutritional supplements as treatments for fatigue, are still unclear. Unfortunately, the research literature on treatment approaches for fatigue in individuals with chronic pain, specifically, is scarce. A meta-analysis on the effects of cognitive-behavioral treatments for fatigue in individuals with multiple sclerosis (often suffering chronic pain), found moderate positive effects of the treatment on fatigue, but only in the short-term [41]. Thus, although the current findings suggest that effectively addressing fatigue in patients with chronic pain could have important benefits and perhaps increase the overall efficacy of chronic pain treatment, there are not as yet many treatment options for achieving this. Clearly, additional work is needed to develop and evaluate effective

treatments for fatigue, including treatments that could then be incorporated into interdisciplinary pain treatment programs.

Although it was not a focus of the study, nor did we have any *a priori* hypotheses about the influence of changes in pain intensity on outcomes, it was interesting that both baseline and treatment-related improvements in pain intensity predicted response to treatment in terms of reductions in pain-related disability. The direction of the relationship with respect to baseline pain indicated that those who reported more pain at pre-treatment also reported the greatest treatment-related reductions in pain-related disability. Perhaps presenting with higher symptoms at the beginning of the treatment provided these individuals with greater opportunity for improvements relative to those with lower initial levels. Additional research in other samples would be needed to determine if this finding replicates.

This study has a number of limitations that should be considered when interpreting the results. First, only pre- and post-treatment data were collected. It is possible that we may have missed different trajectories of change that would have been identified had we been able to analyze short- or long-term follow-up data. Second, the sample size was moderate, which could have limited the power to detect the effects of changes in sleep on outcomes. Additional research is needed, ideally using studies with larger sample sizes, to help establish the reliability of the results. Sleep and pain medication intake were not assessed, because the main purpose of the study was to assess changes on pain intensity and related disability. Thus, it is also possible that changes on these medications also had effects on sleep changes after treatment. Finally,

although this study represents a longitudinal design, it is still a correlational study. We cannot conclude, based on the current findings, if changes in the outcomes produced changes in sleep and fatigue, if changes in sleep and fatigue produced changes in the outcomes, or if sleep and fatigue and outcomes have mutual causal influences. Additionally, participants were receiving different treatment interventions at the same time, making difficult to determine what were the specific mechanisms responsible for improvement in sleep and fatigue. In order to evaluate the potential causal influence of fatigue on pain intensity, depressive symptoms, and pain-related disability, a true experiment would be needed, in which individuals with chronic pain were randomly assigned to receive a treatment that effectively decreased fatigue.

Despite the study's limitations, the findings provide new important information regarding the potential role that fatigue and sleep quality may play in interdisciplinary chronic pain treatment. The findings indicate that changes in fatigue and sleep quality, were significantly associated with treatment improvements across the outcomes studied. Research is needed to determine if these findings are due to sleep and fatigue's impact on outcomes. If such research indicated that it is, then chronic pain treatment outcomes could potentially be enhanced by providing additional focus on interventions that effectively targeted fatigue.

Author contributions

All authors contributed to the conception, design and data analysis plan, discussed the results, commented on multiple versions of the manuscript and approved the final

version. [BLINDED] wrote the first draft and conducted the data analyses. [BLINDED] collected the data.

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Table 1. Description of the study sample (N = 125).

Variable	Percent	N	Mean (SD)	Range
Age, years		125	54.4 (10.3)	25.5 – 78.7
Sex				
Men	24%	30		
Women	76%	95		
Marital status*				
Married/Common-law	65%	81		
Divorced/Separated	14%	17		
Widowed	4%	5		
Never Married	15%	19		
Highest level of education*				
Primary school	8%	9		
Secondary school	27%	33		
College or University	62%	76		
Other	2%	2		
Current work status*				
Working	15%	19		
Volunteer	3%	4		
Homemaker	1%	1		
Unemployed	13%	16		
On disability	41%	51		
Retired	18%	23		
Student	1%	1		
Other	7%	8		

* Marital status information was missing for 3 participants, education for 5, and work status for 2.

Table 2. Pre- and post- treatment values of the main variables

Variable	Pre-treatment mean (SD)	Post-treatment mean (SD)	*t* (*df*)	Cohen's *d*
Pain intensity	6.33 (1.55)	5.99 (1.66)	2.80 (109)*	0.20
Disability	43.41 (12.32)	39.55 (13.67)	5.28 (106)**	0.30
Depression	60.13 (9.31)	56.21 (9.65)	7.47 (122)**	0.67
Sleep	59.40 (7.47)	51.11 (8.68)	6.27 (123)**	0.56
Fatigue	63.31 (7.38)	60.09 (7.56)	5.62 (124)**	0.50

* P < 0.01; ** P < 0.001

Table 3. Hierarchical regression analysis predicting T2 (post-treatment) pain intensity.

Variables	R^2	ΔR^2	F	F_{change}	F_{change} *P*-Value	β	β *P*-Value
Step 1. Pain Intensity T1	0.507	0.507	110.16	110.16	0.001*		
Pain Intensity T1						0.71	0.001*
Step 2. Sociodemographic variables	0.507	0.000	36.06	0.02	0.982		
Sex						-0.01	0.930
Age						-0.01	0.859
Step 3. Sleep and fatigue T1	0.514	0.006	21.77	0.68	0.510		
Sleep Quality T1						0.04	0.562
Fatigue Severity T1						0.61	0.447
Step 4. Sleep and fatigue T2	0.610	0.097	22.60	12.51	0.001*		
Sleep Quality T2						-0.24	0.007*
Fatigue Severity T2						0.25	0.004*

*p < 0.01

Table 4. Hierarchical regression analysis predicting T2 (post-treatment) pain-related disability.

Variables	R^2	ΔR^2	F	F_{change}	F_{change} *P*-Value	β	β *P*-Value
Step 1. Disability T1	0.678	0.678	189.43	189.43	0.001*		
Disability T1						0.82	0.001*
Step 2. Sociodemographic variables	0.680	0.002	62.30	0.27	0.764		
Sex						-0.03	0.676
Age						-0.04	0.521
Step 3. Sleep, fatigue and pain T1	0.739	0.060	40.21	6.48	0.001*		
Pain Intensity T1						0.26	0.001*
Sleep Quality T1						0.09	0.159
Fatigue Severity T1						0.02	0.810
Step 4. Sleep, fatigue and pain T2	0.804	0.064	37.29	8.94	0.001*		
Pain Intensity T2						0.27	0.001*
Sleep Quality T2						-0.12	0.106
Fatigue Severity T2						0.06	0.401

*p < 0.001

Table 5. Hierarchical regression analysis predicting T2 (post-treatment) depressive symptoms.

Variables	R^2	ΔR^2	F	F_{change}	F_{change} *P*-Value	β	β *P*-Value
Step 1. Depressive symptoms T1	0.683	0.683	227.97	227.97	0.001*		
Depressive symptoms T1						0.83	0.001*
Step 2. Sociodemographic variables	0.686	0.003	75.58	0.49	0.616		
Sex						0.04	0.461
Age						0.04	0.479
Step 3. Sleep, fatigue and pain T1	0.699	0.014	39.17	1.56	0.205		
Pain Intensity T1						-0.01	0.931
Sleep Quality T1						0.12	0.058
Fatigue Severity T1						-0.10	0.142
Step 4. Sleep, fatigue and pain T2	0.751	0.052	32.91	8.83	0.001*		
Pain Intensity T2						0.10	0.242
Sleep Quality T2						-0.14	0.059
Fatigue Severity T2						0.16	0.029*

*p < 0.05

Table 6. Hierarchical regression analysis predicting T2 (post-treatment) fatigue.

Variables	R^2	ΔR^2	F	F_{change}	F_{change} *P*-Value	β	β *P*-Value
Step 1. Fatigue T1	0.400	0.400	81.20	81.196	0.001*		
Fatigue Severity T1						0.63	0.001*
Step 2. Sociodemographic variables	0.407	0.007	27.42	0.717	0.490		
Sex						0.04	0.583
Age						-0.08	0.302
Step 3. Sleep quality T1	0.418	0.012	21.40	2.401	0.124		
Sleep quality T1						0.12	0.124
Step 4. Sleep quality T2	0.493	0.075	22.97	17.406	0.001*		
Sleep quality T2						-0.37	0.001*

*$p < 0.05$