ORIGINAL ARTICLE

The Role of Sleep Quality and Fatigue on the Benefits of an Interdisciplinary Treatment for Adults With Chronic Pain

Rocío de la Vega, PhD*,†; Melanie Racine, PhD‡; Elena Castarlenas, PhD†,§,¶; Ester Solé, PhD†,§,¶; Rubén Roy, MSc†,§,¶; Mark P. Jensen, PhD*; Jordi Miró, PhD†,§,¶; Douglas Cane, PhD**

*Department of Rehabilitation Medicine, University of Washington, Seattle, Washington U.S.A.; †Unit for the Study and Treatment of Pain – ALGOS, Universitat Rovira i Virgili, Tarragona, Spain; ‡Department of Clinical Neurological Sciences, Schulich School of Medicine & Dentistry, Western University, London, Ontario Canada; §Department of Psychology, Research Center for Behavior Assessment (CRAMC), Universitat Rovira i Virgili, Tarragona, ; ¶Institut d'Investigació Sanitària Pere Virgili, Universitat Rovira i Virgili, Tarragona, Spain; **Pain Management Unit, Nova Scotia Health Authority, Halifax, Nova Scotia Canada*

■ **Abstract**

Background: Interdisciplinary chronic pain treatment is effective for reducing pain intensity and pain-related disability, and for 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 4-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 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 improvements in disability were 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, suggesting that interventions including elements that effectively target sleep and fatigue may enhance the efficacy of interdisciplinary chronic pain programs. This possibility should be evaluated in future research. ■

Key Words: chronic pain, cognitive behavioral therapy, sleep, fatigue, depression

Address correspondence and reprint requests to: Jordi Miró, PhD, Departament de Psicologia, Universitat Rovira i Virgili, Carretera de Valls, s/n, 43007 Tarragona, Spain. E-mail: jordi.miro@urv.cat.

Submitted: April 25, 2018; Revised October 19, 2018; Revision accepted: November 9, 2018

DOI. 10.1111/papr.12746

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 during treatment.[15] Sleep quality and fatigue, which are often comorbid with pain, are potential mechanisms that may underlie the benefits of multidisciplinary treatment, and therefore warrant investigation.[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 highlighted the negative effects of 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 severe fatigue[21]; in turn, fatigue has been 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] However, evidence regarding the association between fatigue and some other outcomes, including disability and pain, remains limited.

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.

METHODS

Participants

The sample was composed of 125 adult patients with chronic pain being treated in an interdisciplinary pain treatment program in Halifax, Canada. The majority of patients (53%) reported significant pain in more than 3 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 years (standard deviation [SD] = 10.28), and the majority (76%) were women. The average pain duration was 10.49 years (SD = 11.72) and mean pain intensity was 6.35 (SD = 1.52) on a 0 to 10 scale at baseline. Details about marital status, education, and work status are reported in Table 1.

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

Table 1. Description of the Study Sample (*N* = 125)

Variable	%	*n*	Mean (SD)	Range
Age, years		125	54.4 (10.3)	25.5 to 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.

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 scale 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 4 fatigue items of the PROMIS-29 Health Survey, 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 alphas = 0.78 and 0.79, respectively).

Pain Intensity. The PROMIS-29 average pain scale (range 0 to 10) was used to assess pain intensity. The 0 to 10 numeric rating scale is widely used to measure pain intensity, and 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 interferes with what they normally do in 7 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 consecutive patients who attended a 4-week interdisciplinary cognitive behavioral therapy (CBT) chronic pain management program in Halifax, Nova Scotia, Canada. The treatment consisted of 3-hour sessions 3 times per week for a period of 4 weeks, and was administered in group format. During these sessions, patients received psychoeducation about the physiology of pain, sleep hygiene, and communication with others; learned to set relevant and realistic goals; and were trained in relaxation, activity pacing, and coping strategies.

Participants were provided with information about sleep in 2 sessions. The first session provided information about sleep architecture, environmental factors affecting sleep, sleep hygiene (ie, 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 (eg, 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 4-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 were actively suicidal. All the measures were administered during the first week of treatment (pre-treatment), and at 4 weeks upon the completion 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 were not overlapping (different questionnaires were administered to different participants).

Data Analysis

For descriptive purposes, we first computed numbers and percentages for the categorical variables, and means and SDs for the continuous variables. Pre- to post-treatment changes in the outcomes were evaluated using paired *t*-tests, Cohen's *d* was computed to determine effect sizes. A change by 0.5 SDs or higher was deemed a clinically meaningful change. 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 (ie, sleep quality and fatigue severity) to assess normality of variables, and by computing the Durbin-Watson statistic and the variance inflation factors (VIFs) for the predictors to test multicollinearity issues. We then conducted 3 linear multiple regression analyses, 1 for each of the criterion variables: 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 (ie, 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 1 (ie, 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 version 20 for Mac (IBM Corp., Armonk, NY, U.S.A.) was used for all data analyses.

RESULTS

Pre- to post-treatment improvements were statistically significant for all the outcome variables, with small (Cohen's $d < 0.2$) to moderate (Cohen's $d > 0.2$ but < 0.5) effect sizes. The PROMIS measures that were used in this study do not have minimally important difference cutoff points.[33] Therefore, to help understand how meaningful the observed changes were, 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]; that is, we classified individuals who made a 0.5 SD or greater improvement in their outcome scores as demonstrating clinical improvement on that outcome. Using this criterion, only sleep quality showed a meaningful

improvement after treatment (0.9 SD), on average across the whole sample; all other improvements were below the identified reference, that is, around 0.4 SD on average for the sample as a whole. These improvements are consistent with those reported in other samples.[31] After treatment, some participants showed meaningful improvements for pain intensity (36%), disability (35%), depressive symptoms (45%), sleep (63%), and fatigue (18%). Some participants presented worsening in the treatment outcomes as well, ranging from 3% on fatigue to 23% on sleep. See Table 2 for details.

Regarding the regression analyses, the distribution of the data (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 for kurtosis for pain intensity, which was 2.5; for the rest of the variables, *Z* scores were under 1.5). The Durbin-Watson statistic was adequate, being between 1.9 and 2.5; the VIF was lower than 10 (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 (ie, 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); that is, baseline pain intensity and changes in sleep and fatigue explained more than half of the variance of pain intensity after treatment. Both the changes in sleep and fatigue made statistically significant independent contributions to the prediction of the change in pain intensity ($\beta = -0.24$ and 0.25, $P < 0.01$); that is, a greater decrease in sleep and fatigue was associated with a greater decrease in pain intensity (ie, the more sleep and fatigue decreased with treatment, the more pain decreased). See Table 3.

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 ($\beta = 0.27$, $P < 0.01$), 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 significantly 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 ($\beta = 0.26$, $P < 0.01$). In summary, only baseline pain intensity and changes in pain intensity at post-treatment (and not changes in fatigue or sleep) predicted changes in disability; the more pain decreased, the more disability decreased). See Table 4.

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 ($\beta = 0.16$, $P < 0.05$). In other words, changes in depressive symptoms were partially explained by the whole model, but only changes in fatigue made an independent contribution (ie, the more fatigue decreased, the more depressive symptoms decreased). See Table 5.

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-

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*	Meaningful Improvement (%)	No Change (%)	Meaningful Worsening (%)
Pain intensity	6.33 (1.55)	5.99 (1.66)	2.80 (109)*	0.20	36	46	18
Disability	43.41 (12.32)	39.55 (13.67)	5.28 (106)**	0.30	35	56	9
Depression	60.13 (9.31)	56.21 (9.65)	7.47 (122)**	0.67	45	49	6
Sleep	59.40 (7.47)	51.11 (8.68)	6.27 (123)**	0.56	63	14	23
Fatigue	63.31 (7.38)	60.09 (7.56)	5.62 (124)**	0.50	18	79	3

*$P < 0.01$; **$P < 0.001$.

Table 3. Hierarchical Regression Analysis Predicting T2 (Post-Treatment) Pain Intensity

Variables	R^2	F	F_{change}	β
Step 1. Pain intensity T1	0.507	110.16	110.16*	
Pain intensity T1				0.71*
Step 2. Sociodemographic variables	0.507	36.06	0.02	
Sex				−0.01
Age				−0.01
Step 3. Sleep and fatigue T1	0.514	21.77	0.68	
Sleep quality T1				0.04
Fatigue severity T1				0.61
Step 4. Sleep and fatigue T2	0.610	22.60	12.51*	
Sleep quality T2				−0.24*
Fatigue severity T2				0.25*

*Significant at $P < 0.01$. *B*, change in the outcome per 1 unit of change in the predictor; *F*, how much variability the model can explain relative to how much it cannot explain; R^2, percentage of the variance explained by the model.

Table 4. Hierarchical Regression Analysis Predicting T2 (Post-Treatment) Pain-Related Disability

Variables	R^2	F	F_{change}	β
Step 1. Disability T1	0.678	189.43	189.43*	
Disability T1				0.82*
Step 2. Sociodemographic variables	0.680	62.30	0.27	
Sex				−0.03
Age				−0.04
Step 3. Sleep, fatigue, and pain T1	0.739	40.21	6.48*	
Pain intensity T1				0.26*
Sleep quality T1				0.09
Fatigue severity T1				0.02
Step 4. Sleep, fatigue, and pain T2	0.804	37.29	8.94*	
Pain intensity T2				0.27*
Sleep quality T2				−0.12
Fatigue severity T2				0.06

*Significant at $P < 0.001$. *B*, change in the outcome per 1 unit of change in the predictor; *F*, how much variability the model can explain relative to how much it cannot explain; R^2, percentage of the variance explained by the model.

Table 5. Hierarchical Regression Analysis Predicting T2 (Post-Treatment) Depressive Symptoms

Variables	R^2	F	F_{change}	β
Step 1. Depressive symptoms T1	0.683	227.97	227.97*	
Depressive symptoms T1				0.83*
Step 2. Sociodemographic variables	0.686	75.58	0.49	
Sex				0.04
Age				0.04
Step 3. Sleep, fatigue, and pain T1	0.699	39.17	1.56	
Pain intensity T1				−0.01
Sleep quality T1				0.12
Fatigue severity T1				−0.10
Step 4. Sleep, fatigue, and pain T2	0.751	32.91	8.83*	
Pain intensity T2				0.10
Sleep quality T2				−0.14
Fatigue severity T2				0.16*

*Significant at $P < 0.05$. *B*, change in the outcome per 1 unit of change in the predictor; *F*, how much variability the model can explain relative to how much it cannot explain; R^2, percentage of the variance explained by the model.

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; that is, half of the changes in fatigue were explained by demographics, baseline levels of fatigue, and changes in sleep quality. In addition, we found that improvements in sleep quality independently contributed significantly to decreases in fatigue ($\beta = -0.37$, $P < 0.001$); that is, the more sleep improved, the more fatigue improved. See Table 6.

DISCUSSION AND CONCLUSIONS

Interdisciplinary chronic pain programs have been shown to be effective for improving a variety of important outcome domains (ie, disability, pain intensity, psychological function).[35,36] However, the specific factors that contribute to these benefits are not yet well understood. More knowledge regarding the factors that contribute to positive outcomes with multidisciplinary treatment could help to identify the treatment mechanisms that underlie positive outcomes. To the extent that treatment can be modified to target those mechanism factors identified, treatment efficacy could improve.

In this study, we found that treatment-related improvements in fatigue and sleep, 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] These results support the potential utility of the sleep-specific component of the treatment program examined here for reducing pain and improving function. The result also supports the investigation of the beneficial effects of

Table 6. Hierarchical Regression Analysis Predicting T2 (Post-Treatment) Fatigue

Variables	R^2	F	F_{change}	β
Step 1. Fatigue T1	0.400	81.20	81.196*	
Fatigue severity T1				0.63*
Step 2. Sociodemographic variables	0.407	27.42	0.717	
Sex				0.04
Age				−0.08
Step 3. Sleep quality T1	0.418	21.40	2.401	
Sleep quality T1				0.12
Step 4. Sleep quality T2	0.493	22.97	17.406*	
Sleep quality T2				−0.37*

*Significant at $P < 0.05$. *B*, change in the outcome per 1 unit of change in the predictor; *F*, how much variability the model can explain relative to how much it cannot explain; R^2, percentage of the variance explained by the model.

sleep interventions, such as teaching sleep hygiene techniques or cognitive behavioral therapy for insomnia (CBT-i)[38] as potential pain treatments in and of themselves.

Second, for the prediction of changes in pain-related disability, only pain intensity was significant. One possible explanation for the lack of association between changes in sleep or fatigue and changes in disability may be that improvements in sleep and fatigue might need to be sustained over time to influence disability. This would suggest that looking at changes over a longer period might produce a different result. New studies with longer follow-ups should 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[39] 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 et al.[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 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 null findings with respect to sleep as a contributing factor to some of the treatment outcomes. Additional research, with larger sample sizes and using measures of sleep disturbance with greater reliability, would help evaluate the reliability 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 remains unexplained variance, suggesting that variables other than sleep quality and fatigue may predict treatment outcomes. For example, pain beliefs, catastrophizing, and coping have all been identified as potential mediators of interdisciplinary pain treatment efficacy.[40] Future research investigating other potential predictors and mediators of outcomes are needed, so as to help evaluate their relative importance.

Considering the association between fatigue and treatment outcomes, it appears that effective treatments can potentially benefit people with pain and fatigue comorbidity. Moreover, the findings from this study showing an association between improved sleep and improved fatigue suggest that treatments which target improved sleep may also benefit fatigue; research to evaluate this possibility is warranted. Unfortunately, other highly effective interventions for treating fatigue have yet to be identified. In a recent review evaluating the efficacy of treatments for chronic fatigue syndrome,[41] limited benefits were found for some pharmacological (eg, rintatolimod and rituximab) and nonpharmacological (eg, counseling, behavioral, and rehabilitation programs) approaches. However, the effect sizes associated with these treatments are weak. Moreover, research on treatment approaches for fatigue in individuals with chronic pain, specifically, is scarce. Additional work is needed to develop and evaluate effective treatments for fatigue, including treatments that could then be incorporated into interdisciplinary pain treatment programs.

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 in pain intensity and related disability. Thus, it is also possible that changes in these medications also had effects on sleep changes. Finally, although this study represents a longitudinal design, it is still a correlational study. Consequently, based on the study findings, we cannot draw conclusions regarding the directions of any causal associations between sleep, fatigue, and other treatment outcomes. Additionally, participants were receiving different treatment interventions at the same time, making it difficult to

determine what were the specific mechanisms responsible for improvement in sleep and fatigue. To evaluate the potential causal influence of fatigue on pain intensity, depressive symptoms, and pain-related disability, future longitudinal studies and true experiments are needed to identify predictors of treatment outcomes, and to examine treatment mechanisms.

Despite the study's limitations, the findings provide important new evidence regarding the associations between sleep, fatigue, and other treatment outcomes. The findings indicate that improvements in fatigue and sleep quality were significantly associated with treatment improvements across the outcomes studied. Future research is needed to further understand the causal role of fatigue and sleep in relation to treatment outcomes in individuals with chronic pain, the findings of which can inform treatment development and improve treatment effectiveness.

CONFLICTS OF INTEREST

The authors declare no financial or other relationships that might lead to a conflict of interest related to this study.

SOURCE OF FUNDING

This work was partly funded by grants from the Spanish Ministry of Science and Competitiveness (MINECO; PSI2014-60180-JIN; PSI2015-70966-P; PSI2016-82004-REDT), Universitat Rovira i Virgili (PFR Program), and Obra Social de CaixaBank. J.M. is supported by the Institució Catalana de Recerca i Estudis Avançats (ICREA-Acadèmia) and Fundación Grünenthal. R.V. is supported by a Beatriu de Pinós Postdoctoral Fellowship (2014 BP-A 00009) granted by the Agency for Administration of University and Research Grants (AGAUR). M.R. is supported by The Earl Russell Chair in Pain Research, Western University, London, Ontario, and by a bequest from the estate of Mrs. Beryl Ivey to Dr. Warren R. Nielson.

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. R.V. wrote the first draft and conducted the data analyses. D.C. collected the data.

REFERENCES

1. Nahin RL. Estimates of pain prevalence and severity in adults: United States, 2012. *J Pain*. 2015;16:769–780.
2. Schopflocher D, Taenzer P, Jovey R. The prevalence of chronic pain in Canada. *Pain Res Manag*. 2011;16:445–450.
3. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain*. 2006;10:287–333.
4. Goldberg DS, McGee SJ. Pain as a global public health priority. *BMC Public Health*. 2011;11:770.
5. Lapane KL, Quilliam BJ, Benson C, Chow W, Kim MS. Impact of noncancer pain on health-related quality of life. *Pain Pract*. 2015;15:333–342.
6. Calati R, Laglaoui Bakhiyi C, Artero S, Ilgen M, Courtet P. The impact of physical pain on suicidal thoughts and behaviors: meta-analyses. *J Psychiatr Res*. 2015;71:16–32.
7. Gaskin DJ, Richard P. The economic costs of pain in the United States. *J Pain*. 2012;13:715–724.
8. Enthoven WT, Roelofs PD, Deyo RA, van Tulder MW, Koes BW. Non-steroidal anti-inflammatory drugs for chronic low back pain. *Cochrane Database Syst Rev*. 2016;2:CD012087.
9. Chaparro LE, Furlan AD, Deshpande A, Mailis-Gagnon A, Atlas S, Turk DC. Opioids compared to placebo or other treatments for chronic low-back pain. *Cochrane Database Syst Rev*. 2013;8:CD004959.
10. U.S. Department of Health & Human Services. The U.S. Opioid Epidemic 2017. https://www.hhs.gov/opioids/about-the-epidemic/index.html (accessed December 7, 2018)
11. Scascighini L, Toma V, Dober-Spielmann S, Sprott H. Multidisciplinary treatment for chronic pain: a systematic review of interventions and outcomes. *Rheumatology*. 2008;47:670–678.
12. Kowal J, Wilson KG, Geck CM, Henderson PR, D'Eon JL. Changes in perceived pain severity during interdisciplinary treatment for chronic pain. *Pain Res Manag*. 2011;16:451–456.
13. Kitahara M, Kojima KK, Ohmura A. Efficacy of interdisciplinary treatment for chronic nonmalignant pain patients in Japan. *Clin J Pain*. 2006;22:647–655.
14. Kazdin AE. Understanding how and why psychotherapy leads to change. *Psychother Res*. 2009;19:418–428.
15. Kazdin AE. Mediators and mechanisms of change in psychotherapy research. *Annu Rev Clin Psychol*. 2007;3:1–27.
16. Karaman S, Karaman T, Dogru S, et al. Prevalence of sleep disturbance in chronic pain. *Eur Rev Med Pharmacol Sci*. 2014;18:2475–2481.
17. Bonvanie IJ, Oldehinkel AJ, Rosmalen JGM, Janssens KAM. Sleep problems and pain: a longitudinal cohort study in emerging adults. *Pain*. 2016;157:957–963.
18. Naughton F, Ashworth P, Skevington SM. Does sleep quality predict pain-related disability in chronic pain patients? The mediating roles of depression and pain severity. *Pain*. 2007;127:243–252.
19. Finan PH, Goodin BR, Smith MT. The association of sleep and pain: an update and a path forward. *J Pain*. 2013;14:1539–1552.

20. Pilcher JJ, Morris DM, Donnelly J, Feigl HB. Interactions between sleep habits and self-control. *Front Hum Neurosci*. 2015;9:284.

21. Togo F, Natelson BH, Cherniack NS, FitzGibbons J, Garcon C, Rapoport DM. Sleep structure and sleepiness in chronic fatigue syndrome with or without coexisting fibromyalgia. *Arthritis Res Ther*. 2008;10:R56.

22. Campbell RCJ, Batley M, Hammond A, Ibrahim F, Kingsley G, Scott DL. The impact of disease activity, pain, disability and treatments on fatigue in established rheumatoid arthritis. *Clin Rheumatol*. 2012;31:717–722.

23. Novaes GS, Perez MO, Beraldo MB, Pinto CR, Gianini RJ. Correlation of fatigue with pain and disability in rheumatoid arthritis and osteoarthritis, respectively. *Rev Bras Reumatol*. 2011;51:451–455.

24. Cohen BL, Zoëga H, Shah SA, et al. Fatigue is highly associated with poor health-related quality of life, disability and depression in newly-diagnosed patients with inflammatory bowel disease, independent of disease activity. *Aliment Pharmacol Ther*. 2014;39:811–822.

25. Kato K, Sullivan PF, Evengård B, Pedersen NL. Chronic widespread pain and its comorbidities. *Arch Intern Med*. 2006;166:1649.

26. Craig BM, Reeve BB, Brown PM, et al. US valuation of health outcomes measured using the PROMIS-29. *Value Heal*. 2014;17:846–853.

27. Katz P, Pedro S, Michaud K. Performance of the PROMIS 29-item profile in rheumatoid arthritis, osteoarthritis, fibromyalgia, and systemic lupus erythematosus. *Arthritis Care Res (Hoboken)*. 2017;69:1312–1321.

28. Jensen M, Karoly P. Self-report scales and procedures for assessing pain in adults. In: Turk D, Melzack R, eds. *Handbook of Pain Assessment*. New York, NY: Guilford Press; 2001:15–34.

29. Tait RC, Pollard CA, Margolis RB, Duckro PN, Krause SJ. The Pain Disability Index: psychometric and validity data. *Arch Phys Med Rehabil*. 1987;68:438–441.

30. Tait RC, Chibnall JT, Krause S. The Pain Disability Index: psychometric properties. *Pain*. 1990;40:171–182.

31. Cane D, McCarthy M, Mazmanian D. Obstacles to activity pacing. *Pain*. 2016;157:1508–1514.

32. Miró J, Castarlenas E, de la Vega R, et al. Pain catastrophizing, activity engagement and pain willingness as predictors of the benefits of multidisciplinary cognitive behaviorally-based chronic pain treatment. *J Behav Med*. 2018;41:827–835.

33. PRISMA Assessment Center. What is the minimum change on a PROMIS instrument that represents a clinically meaningful difference? In: *Pain Intensity: A Brief Guide to the PROMIS Pain Intensity Instrument*. https://www.assessmentcenter.net/documents/PROMIS%20Pain%20Intensity%20Scoring%20Manual.pdf (accessed December 7, 2018).

34. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain*. 2008;9:105–121.

35. Eccleston C, Morley SJ, Williams AC. Psychological approaches to chronic pain management: evidence and challenges. *Br J Anaesth*. 2013;111:59–63.

36. Jensen MP, Turk DC. Contributions of psychology to the understanding and treatment of people with chronic pain: why it matters to ALL psychologists. *Am Psychol*. 2014;69:105–118.

37. Davin S, Wilt J, Covington E, Scheman J. Variability in the relationship between sleep and pain in patients undergoing interdisciplinary rehabilitation for chronic pain. *Pain Med*. 2014;15:1043–1051.

38. Trauer JM, Qian MY, Doyle JS, Rajaratnam SMW, Cunnington D. Cognitive behavioral therapy for chronic insomnia: a systematic review and meta-analysis. *Ann Intern Med*. 2015;163:191–204.

39. de Rooij A, van der Leeden M, de Boer MR, Steultjens MPM, Dekker J, Roorda LD. Fatigue in patients with chronic widespread pain participating in multidisciplinary rehabilitation treatment: a prospective cohort study. *Disabil Rehabil*. 2015;37:490–498.

40. Jensen MP, Turner JA, Romano JM. Changes in beliefs, catastrophizing, and coping are associated with improvement in multidisciplinary pain treatment. *J Consult Clin Psychol*. 2001;69:655–662.

41. Castro-Marrero J, Sáez-Francàs N, Santillo D, Alegre J. Treatment and management of chronic fatigue syndrome/myalgic encephalomyelitis: all roads lead to Rome. *Br J Pharmacol*. 2017;174:345–369.