Chapter 6

Fatigue in Patients with Chronic Widespread Pain participating in Multidisciplinary Rehabilitation Treatment: A Prospective Cohort Study

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Abstract

Purpose. To explore the associations between (improvement in) fatigue and (improvement in) clinical and cognitive factors in patients with chronic widespread pain (CWP), participating in multidisciplinary rehabilitation treatment.

Methods. Data were used from baseline, 6 and 18 months of follow-up during a prospective cohort study of 120 CWP patients who completed multidisciplinary rehabilitation treatment. Cross-sectional and longitudinal relationships were analyzed between fatigue, clinical (i.e. pain, interference of pain and depression) and pain related cognitive factors (i.e. negative emotional cognitions, active cognitive coping, and control and chronicity beliefs).

Results. Higher levels of pain, interference of pain, depression, negative emotional cognitions, and negative control and chronicity beliefs were associated with a higher level of fatigue. Improvement in depression was related to improvement in fatigue.

Conclusions. In CWP patients, worse clinical status, and dysfunctional pain-related cognitions are associated with a higher level of fatigue. Our results suggest that improvement in depression might be a mechanism of improvement in fatigue. Furthermore, improvement in fatigue seems to be independent of improvement in pain related cognitions. Targeting fatigue in multidisciplinary pain treatment may need specific strategies.

Implications for rehabilitation

- Improvement in depression may be a mechanism of change to improve the level of fatigue in CWP.
- Improvement in dysfunctional (pain related) cognitions seems to be independent of improvement in fatigue
- Targeting fatigue in multidisciplinary treatment may need specific strategies (e.g. additional interventions focusing on reducing fatigue and specific attention to improvement of sleep).

Introduction

In addition to pain, fatigue is a prominent symptom in patients with chronic widespread pain (CWP)[1,2]. Fatigue is defined as an internal and subjective feeling of tiredness that may or may not be related to activity[1]. Chronic widespread pain (CWP) is defined as pain that is present in two contralateral quadrants of the body and in the axial skeleton, which must have been present for at least 3 months[3]. A subcategory of patients with CWP also fulfills the criteria of fibromyalgia (FM)[3]. In a study of Wolfe et al.[2] clinically significant fatigue was reported in at least 76% of fibromyalgia (FM) patients, in contrast to 41% of patients with osteoarthritis and rheumatoid arthritis. Fatigue has been found to be a strong predictor of overall health status and work dysfunction[2]. A study of Bennett et al.[4] in patients with FM revealed that pain and fatigue are two clinical features which patients would most like to see improved. Although fatigue is a major concern in CWP patients, in comparison to pain it has received much less attention in research[5].

Fatigue is a complex multidimensional phenomenon. In patients with CWP, a higher level of fatigue has been associated with the presence of more co-morbid medical conditions[6,7], higher level of pain[8], higher tenderpoint count[9], more stiffness[10], decreased physical functioning[11], depression[12,13], sleep disturbance[14], reduced sleep quality[2,13,15], and negative interpersonal events (i.e. negative daily events) [16]. In patients with chronic pain, it is known that cognitive factors (e.g. negative illness beliefs, maladaptive cognitive coping) are associated with more pain, disability and depression[17]. Whether these cognitive factors are also associated with fatigue in CWP is unclear. Preliminary evidence for an association between a higher level of catastrophizing and a higher level of fatigue in patients with chronic illnesses, including FM, was found in a review of Lukahati et al. [18].

Mechanisms of change in fatigue in CWP are largely unknown. In their review, Fisbain et al. [8] found evidence that increase in pain is related to increase in fatigue in chronic pain patients. Other studies show that increases in stiffness[10], depression[19,20] and negative affect and a decrease in positive affect[21] are also associated with an increase in fatigue.

The primary aims of our previous research were to establish predictors[22] and mechanisms of change[23] of the outcome measurements of multidisciplinary treatment specified by the recommendations of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) (i.e. pain, interference of pain with daily living, depression and global perceived treatment effect)[5]. The outcome fatigue is not included in these consensus recommendations. However, because of the high levels of fatigue observed in our patients, the high levels of fatigue found in literature in these patients, small body of knowledge about fatigue and the demand from patients, we think this subject definitely needs more exploration.

Multidisciplinary rehabilitation treatment in chronic pain (i.e. FM[24]) and low back pain[25]) has been found to reduce fatigue, although fatigue is usually not the focus of treatment. The factors and mechanisms of change associated with (improvement in) fatigue in multidisciplinary rehabilitation treatment are unclear. This study explores whether (improvement in) fatigue is associated with

(improvement in) clinical and cognitive factors addressed in the multidisciplinary treatment of CWP. Based on previous research it is hypothesized that an improvement in clinical factors, such as pain and depression is associated with improvement in fatigue in patients with CWP[2,8,13]. In a previous study we found that improvement in negative emotional cognitions, active cognitive coping and control and chronicity beliefs were related to improvement of the outcome (i.e. pain, interference of pain, depression, and global perceived effect) of multidisciplinary rehabilitation treatment in CWP[23]. We now hypothesize that improvement in these cognitions is also related to improvement in fatigue in CWP. A better understanding of factors associated with (improvement in) fatigue in the multidisciplinary treatment of CWP patients will help to direct multidisciplinary treatment.

The aim of this study was to explore the associations between (improvement in) fatigue and (improvement in) clinical and cognitive factors in patients with chronic widespread pain (CWP), participating in multidisciplinary rehabilitation treatment.

Materials and methods

Design. This study uses data from a longitudinal observational study on predictors of multi-disciplinary treatment outcome[22, 23]. The baseline measurements took place before the start of a multidisciplinary treatment program (T0). The second and third assessment were performed 6 months (T1) and 18 months (T2) after baseline, respectively. The estimated number of patients for inclusion was 120, allowing to establish a statistically significant correlation of $r > 0.20$[26] between the dependent and independent variables. To deal with dropout of patients the number of inclusion was extended to 138 patients. The ethical review board of Reade in Amsterdam approved this study. Written informed consent was obtained from each subject.

Patients and procedure. Patients with chronic pain were referred by rheumatologists and general practitioners to the rehabilitation physician to assess their problems and to evaluate eligibility for participation in the multidisciplinary pain program. Patients with chronic pain were referred by rheumatologists and general practitioners to the rehabilitation physician to assess their problems and to evaluate eligibility for participation in the multidisciplinary pain program. During this consultation patients were also screened for their eligibility to participate in the study. Inclusion criteria for the study were: (i) age between 18 and 75 years (ii) a diagnosis of CWP according to the criteria of the American College of Rheumatology (ACR)[3]; (iii) eligible for multidisciplinary treatment according to the criteria of the Dutch Consensus Report of Pain Rehabilitation[27], as assessed by both a rehabilitation physician and a psychologist. These criteria require patients to experience restrictions in daily living (e.g. sports or work) and/or psychosocial functioning. Exclusion criteria were: (i) pain resulting from known specific pathology (e.g. rheumatoid arthritis or Morbus Bechterew); (ii) not eligible for multidisciplinary pain treatment because of a somatic disorder, social problem and/or psychiatric disorder (e.g. major depression), or because the patient was currently involved in a legal procedure of conflicting interest, was currently receiving pain treatment elsewhere, was not motivated for behavioural change as judged by the rehabilitation physician and/or psychologist; (iii) insufficient control of the Dutch language to complete questionnaires; and (iv) refusal to provide informed consent.

A consecutive series of patients was included in the study. Recruitment took 14 months. The baseline measurements were integrated into the existing intake at our centre. Participants were contacted by telephone to inform them that the follow-up measurements were sent. Patients were asked to return the measurements by post within two weeks. After two weeks patients were phoned by the researcher of the study and a reminder was send if the questionnaires were not sent back on time to collect the data.

Intervention. All participants participated in the multidisciplinary treatment program. The main goal of the multidisciplinary treatment program was to teach patients to cope with pain and to reduce the interference of pain in their daily lives. The program included education about neuro-physiology and medication management, cognitive behavior therapy (CBT), the acquisition of pain management skills (e.g. goal setting, structuring of daily activities, pacing strategies, and ergonomics), physical training (e.g. exercise), relaxation training, and assertiveness training. The components of the multidisciplinary treatment were in line with the core elements of multidisciplinary treatment in CWP[28, 29]. Patients were asked to make a personalized plan taking into account their individual needs and requirements. Treatment was tailored to the patients' personal goals and was performed in groups and on an individual basis. A treatment protocol formed the basis of the content of the intervention. The content of the group and individual treatment was generally comparable. However, the intensity of the components and length of the treatment was tailored to the patients' needs. Group treatment consisted of seven consecutive weeks of treatment, seven hours a week and was divided into two sessions a week of multidisciplinary treatment. Individual treatment was offered during a period of four to six months with a variable frequency per patient. There was an opportunity for two post-treatment appointments to evaluate the personal goals. The multidisciplinary team involved rehabilitation physicians, physiotherapists, occupational therapists, psychologists, and social workers. The multidisciplinary team discussed the treatment progress of patients during regular team meetings.

Outcome measure. *Fatigue* was assessed with the subscale of the Fibromyalgia Impact Questionnaire (FIQ) (visual analog scale 100 mm). The FIQ has been widely used with diverse chronic pain samples, and has good psychometric properties[30].

Clinical factors. *Pain* was assessed with the Numerical Rating Scale Pain (NRS) (range 0 to 10). The endpoints of the scale are no pain and worst possible pain. A higher score indicates a higher level of fatigue. Adequate psychometric properties have been documented[31].

Interference of pain in daily living was assessed with the subscale 'interference of pain in daily living' of the Multidimensional Pain Inventory[32]. The MPI consists of 13 empirically derived scales that measure different pain-related aspects. The subscale interference assesses patients perceptions about how pain interferes with their daily lives. A higher score means more interference of pain in daily life. The MPI has been widely used in diverse chronic pain samples and has good psychometric properties[32].

Depression was assessed with the Beck Depression Inventory II (BDI-II). The BDI-II is a self-reported measure that assesses cognitive, affective, and somatic symptoms of depression[33,34]. The 21 questions are rated from 0 to 3 in terms of intensity. A higher score on the BDI-II (range 0-63)

indicates more depressive symptoms. The BDI-II has been shown to have adequate psychometric properties[35].

Cognitive factors. The cognitive variables described below are arranged according to the three cognitive domains found in our previous study[36], i.e. negative emotional cognitions, active cognitive coping, and control and chronicity beliefs. All cognitions within these domains concern pain related cognitions, with the exception of general self-efficacy beliefs.

Negative emotional cognitions. Negative emotional cognitions were assessed with three questionnaires. Three subscales of the Revised Illness Perceptions Questionnaire (IPQ-R) were used to assess the illness beliefs; 1) *consequences* - expected effects and outcome of the illness; 2) *coherence* - patient's logical and complete understanding of the illness; and 3) *emotional representations* - negative emotional reactions like anger and fear related to the illness. Items in these scales are rated on a 5-point Likert scale ranging from "strongly disagree" to "strongly agree". High scores indicate 1) more consequences (range 6-30), 2) lower coherence (range 5-25), 3) more emotional reactions (range 6-30). The validity and reliability of the IPQ-R have been documented[37-39].

The Dutch General Self-efficacy Scale (DGSS) was used to measure *general self-efficacy beliefs.* General self-efficacy is defined as a broad and stable sense of personal competence to deal effectively with a variety of stressful situations[40]. The DGSS consists of 10 items, which are answered on a four point scale, ranging from "not at all true" to "exactly true", with a higher score (range 10 to 40) indicating a higher self-efficacy. The psychometric properties of the DGSS have been documented[41, 42].

The Dutch adaptation of the Coping Strategy Questionnaire (CSQ) was used to assess the cognitive coping style *catastrophizing* - having negative thoughts and ideas about the impact of pain. The subscale catastrophizing consists of 6 items and per item the subject indicated to what extent this particular coping strategy was utilized. A higher score indicate that the subject uses the coping style more often. The validity and reliability of the CSQ have been documented[43].

Active cognitive coping. Four subscales of the Dutch CSQ, described above, were used to assess the active cognitive coping styles *denial of pain sensations* - denying that the sensations are painful and that they influence daily activities, *positive self statements* - telling yourself that you can handle the pain, regardless of its severity, *reinterpreting pain sensations* - visualizing something which is not compatible with the true pain experience, and *diverting attention away from pain sensations* - thinking of something to distract your attention away from the pain. Each subscale consists of 6 items and per item the subject indicated to what extent this particular coping strategy was utilized. A higher score indicates that the subject uses a particular coping style more often. For the description of the scale see above.

Control and chronicity beliefs. Control and chronicity beliefs were assessed with the use of two questionnaires. The IPQ-R, described above, was used to measure the illness beliefs: *timeline* - chronic timeline expectancies of the illness, *timeline cyclical* - expectancies on the variability of the illness, *personal control* - extent to which patients believe they can control the illness, and *treatment control* - belief in treatment and recommended advice. Higher scores on personal control (range 6 to

30) and treatment control (range 5 to 25) demonstrate positive beliefs about the controllability of the illness. High scores on timeline (range 6 to 30) and timeline cyclical (range 4 to 20) demonstrate strongly held beliefs about the chronicity of the illness, and the cyclical nature of the illness.

The Dutch CSQ, described above, was used to assess the cognitive coping style *perceived control over pain*- controllability of the pain. A higher score indicate that the subject used the coping style more often.

Statistical analyses. Descriptive statistics were used to tabulate the main baseline characteristics of the study population and mean scores of the dependent and independent variables at baseline (T0), 6 months (T1) and 18 months of follow up (T2). Because of the longitudinal design of the study with repeated measurements over time the data was analyzed using generalized estimating equations (GEE) statistics. GEE is a longitudinal regression technique which enables to correct for dependency of (repeated) observations within individuals over time by choosing a "working" correlation structure[44]. Fatigue was the dependent variable; the independent variables included clinical factors (i.e. pain, interference of pain and depression) and cognitive factors (i.e. negative emotional cognitions, active cognitive coping, control and chronicity beliefs). First, the development over time in clinical and cognitive factors and in fatigue (between T0-T1, T1-T2 and T0-T2) were modeled, using an exchangeable correlation matrix[44]. Second, to evaluate the cross-sectional associations between clinical and cognitive factors and fatigue at baseline (T0), 6 months (T2) and 12 months (T2) of follow up, we added these cognitive factors to the model including their interaction with the time dummies. Uni- and multivariable analyses were performed. In the univariable analyses the separate variables within a clinical or cognitive domain were analysed. In the multivariable analyses the variables were analysed per group (i.e. clinical variables, negative emotional cognitions, active cognitive coping and control and chronicity beliefs). Third, to evaluate whether improvement in clinical and cognitive factors were related to an improvement in fatigue, changes in clinical and cognitive factors from baseline (T0) to T1 and from T1 to T2 were related to changes in fatigue during the same time intervals (model of change, see Figure 1). The change scores were calculated for the independent variables and dependent variables by subtracting the T0 scores from the T1 scores, and the T1 scores from the T2 scores. To investigate the model of changes an independent correlation matrix was deemed most appropriate[44]. All analyses were adjusted for age and gender. All analysis were carried out in SPSS 18.0 (SPSS Inc., Chicago, IL, USA) and an alpha of 0.05 was used in all statistical tests.

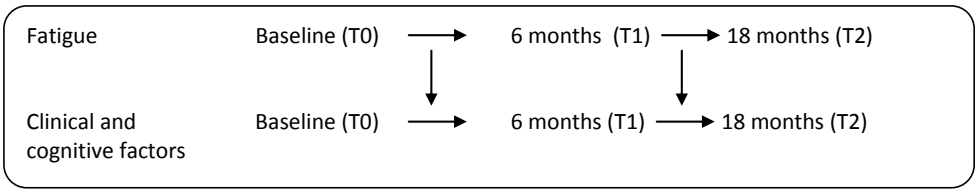

Figure 1. Model of change

Results

Study population. Information about the patient flow throughout the study is presented in Figure 2. Of 361 patients screened by the rehabilitation physician, 165 patients fulfilled the inclusion criteria for this study. Of these patients, 138 consented to participate in the study. Of these 138 participants, 133 participants provided data at T0; 120 participants provided data at T1; and 114 participants provided data at T2. The patient characteristics are shown in Table 1. Subjects were predominantly women, middle aged, and of Dutch ethnicity. In addition, patients scored high on both fatigue (median 8.29 (IQR) 7.25-10.00) and pain intensity (mean 6.08 (SD) 2.08) and had moderate symptom scores for depression.

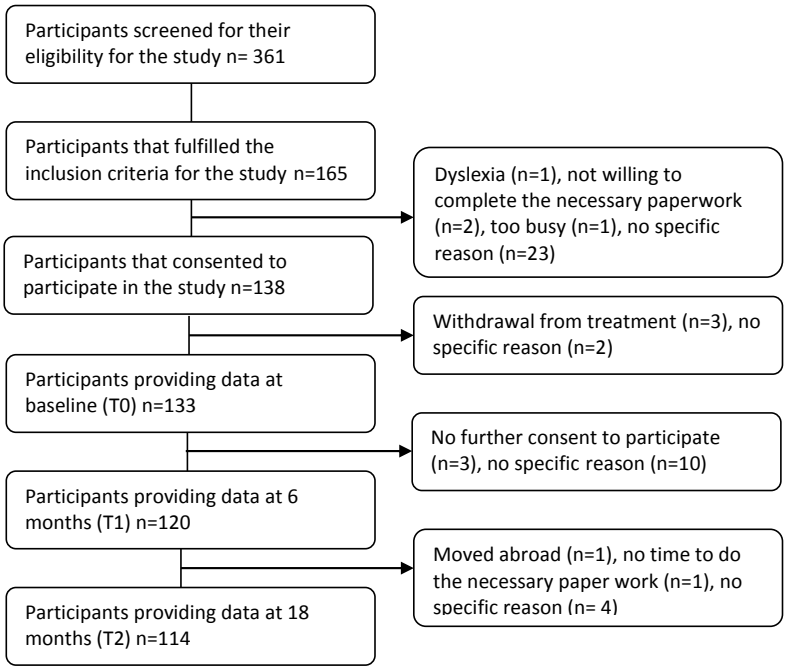

Figure 2. Flowchart

Change in fatigue, and clinical and cognitive factors. The mean changes in fatigue, clinical and cognitive factors are presented in Table 1. Over the 18 month (T0-T2) study period, a significant improvement in fatigue was found. With respect to the *clinical factors*, significant improvements were found in "interference of pain" between T0-T1 and T0-T2, and for "depression" over all time periods (T0-T1, T1-T2 and T0-T2). In addition, significant improvements were found for the *cognitive factors* "negative emotional cognitions" (i.e. emotional representation, coherence, general self-efficacy and catastrophizing) and "control and chronicity beliefs" (i.e. perceived control, personal control, treatment control, timeline, timeline cyclical), in particular between T0-T1 and T0-T2.

Table 1. Patients characteristics and changes in fatigue, clinical and cognitive factors

	T0 (n= 120)	T1 (n=120)	T2 (n=114)	*P* value T0-T1	*P* value T1-T2	*P* value T0-T2
Patient characteristics						
Female (%)	95.0					
Age, mean (SD)	45.04 (10.30)					
Partnership, Yes (%)	50.8					
Ethnicity (%)						
Native	70.8					
Western non native	12.5					
Non western non native	16.7					
Education (%)						
Primary	17.6					
Secondary	49.6					
High	32.8					
Outcome						
Fatigue (FIQ), median (IQR)	8.29 (7.25:10.00)	7.75 (7.00:9.00)	7.66 (7.00:9.00)	.13	.45	**≤.001**
Clinical factors						
Pain (NRS), mean (SD)	6.08 (2.08)	6.08 (1.89)	5.81 (2.33)	.96	.21	.20
Interference (MPI), mean (SD)	4.07 (1.06)	3.87 (1.13)	3.79 (1.29)	**.01**	.10	**.002**
Depression (BDI-II), mean (SD)	20.79 (8.86)	17.61 (9.53)	16.62 (9.97)	**≤ .001**	**.05**	**≤ .001**
Cognitive factors						
Negative emotional cognitions						
Consequence (IPQ), mean (SD)	20.93 (4.36)	20.95 (4.28)	20.59 (4.56)	.96	.10	.16
Emotional representation (IPQ), mean (SD)	19.15 (4.66)	18.02 (4.72)	17.62 (5.33)	**.01**	.23	**≤.001**
Coherence (IPQ), mean (SD)	14.99 (4.81)	13.63 (4.42)	13.50 (4.76)	**≤.001**	.54	**≤ .001**
General self-efficacy (DGSS), mean (SD)	2.93 (.61)	2.99 (.63)	3.03 (.58)	0.19	.15	**.01**
Catastrophizing (CSQ), mean (SD)	23.85 (11.04)	19.80 (12.12)	18.25 (12.19)	**≤ .001**	.10	**≤ .001**
Active cognitive coping						
Reinterpreting pain (CSQ), median (IQR)	10.00 (5.00; 20.00)	12.00 (6.00: 19.00)	9.50 (4.00: 19.30)	.52	.58	.92
Positive self-statements (CSQ), mean (SD)	36.11 (11.44)	35.06 (11.41)	34.76 (12.01)	.27	.92	.23
Denial of pain (CSQ), mean (SD)	28.64 (13.17)	27.50 (11.91)	26.76 (12.84)	.36	.53	.14
Diverting attention (CSQ), mean (SD)	21.16 (12.45)	20.10 (11.42)	19.29 (12.10)	.27	.61	.13
Control and chronicity beliefs						
Perceived control (CSQ), mean (SD)	8.20 (4.53)	9.37 (4.63)	8.73 (4.75)	**.01**	.23	.27
Personal control (IPQ), mean (SD)	18.56 (4.31)	19.19 (4.69)	18.43 (4.69)	.10	**.05**	.76
Treatment control (IPQ), mean (SD)	16.17 (2.93)	14.63 (3.41)	13.97 (3.83)	**≤ .001**	**.05**	**≤ .001**
Timeline (IPQ), median (IQR)	23.00 (12; 30.00)	24.00 (12.00; 30.00)	25.00 (9.00; 30.00)	**.002**	.99	**.01**
Timeline cyclical (IPQ), mean (SD)	15.29 (3.21)	14.92 (3.33)	14.70 (3.76)	.11	.42	**.04**

T0= baseline, T1= follow up at 6 months, T2= follow up at 18 months. Values are means and SD= standard deviation, medians and IQR= interquartile range, or percentages. *P* values are analysed with GEE statistics, to correct for dependency of repeated measurements. Bold formatted numbers are *P* values ≤ 0.05. BDI-II= Beck Depression Inventory, CSQ= Coping Scale Questionnaire, DGSS= Dutch General Self efficacy Scale, FIQ= Fibromyalgia Impact Questionnaire, IPQ= Illness Perception Questionnaire, MPI= Multidimensional Pain Inventory, NRS= Numerical Rating Scale.

Associations of fatigue with clinical and cognitive factors. At baseline, the univariable analyses showed a limited number of significant associations between clinical and cognitive factors and fatigue (Table 2). At 6 (T1) and 18 (T2) months of follow up, worse scores on all three *clinical factors* (i.e. pain, interference of pain and depression) were significantly related to a higher level of fatigue (Table 2). In addition, *negative emotional cognitions* (i.e. consequences, emotional representations, illness coherence, general self-efficacy, catastrophizing) and *negative control and chronicity beliefs* (i.e. perceived pain control, personal control, treatment control, timeline and timeline cyclical) were also significantly associated with a higher level of fatigue at 6 (T1) or 18 months (T2) in univariable analyses (Table 2).

Table 2. Univariable associations of fatigue with clinical and cognitive factors at every time point

	Fatigue		
	T0	**T1**	**T2**
	β (95% CI) *P* value	β (95% CI) *P* value	β (95% CI) *P* value
Clinical factors			
More pain (NRS)	.17 (.05 to .30) **.01**	.32 (.18 to .47) < **.001**	.23 (.03 to .43) **.02**
More interference of pain (MPI)	.31 (.02 to .61) **.03**	.71 (.45 to .96) < **.001**	.67 (.43 to .91) < **.001**
More depression (BDI)	.02 (-.01 to .05) .23	.08 (.06 to .11) < **.001**	.08 (.05 to .10) < **.001**
Negative emotional cognitions			
More consequences (IPQ)	.06 (.003 to .12) **.04**	.15 (.08 to .21) < **.001**	.15 (.08 to .22) < **.001**
More emotional representations (IPQ)	.02 (-.03 to .08) .44	.04 (-.02 to .09) .24	.11 (.05 to .16) < **.001**
Less illness coherence (IPQ)	.05 (-.01 to .10) .10	.06 (-.01 to .13) .09	.10 (.04 to .16) **.001**
Low self-efficacy (DGSS)	.04 (-.42 to .51) .85	.55 (.12 to .99) **.01**	.75 (.26 to 1.2) **.003**
More catastrophizing (CSQ)	-.003 (-.03 to .02) .78	.03 (.01 to .06) **.002**	.04 (.02 to .07) **.001**
Active cognitive coping			
Less reinterpretation of pain (CSQ)	.01 (-.01 to.03) .27	.02 (-.01 to.05) .25	-.01 (-.03 to .03) .75
Less positive self-statements (CSQ)	.001 (-.02 to .02) .93	.01 (-.02 to .03) .46	-.02 (-.04 to .01) .19
More denial of pain (CSQ)	-.01 (-.03 to .01) .42	-.002 (-.03 to .02) .87	.01 (-.01 to .04) .25
Less diverting attention (SCQ)	.02 (-.004 to .03) .12	-.02 (-.04 to .01) .22	-.01 (-.04 to .01) .26
Control and chronicity beliefs			
Less perceived pain control (CSQ)	.01 (-.05 to .08) .64	.01 (-.06 to .08) .82	.08 (.01 to.14) **.02**
Less personal control (IPQ)	.06 (-.01 to.12) .08	.10 (.05 to .16) < **.001**	.12 (.06 to .19) < **.001**
Less treatment control (IPQ)	.06 (-.02 to .14) .11	.10 (.03 to .16) **.004**	.07 (-.01 to .15) .08
Stronger timeline (IPQ)	.02 (-.05 to .10) .54	.10 (.02 to .18) **.01**	.11 (.03 to .18) **.01**
Stronger timeline cyclical (IPQ)	-.06 (-.13 to .01) .09	-.09 (-.17 to -.01) **.02**	-.03 (-.11 to .05) .40

β; regression coefficient adjusted for age and gender, 95% CI of β, Negative β indicates: associations of clinical and cognitive factors with a lower level of fatigue. Positive β indicates: associations of clinical and cognitive factors with a higher level of fatigue. Bold formatted numbers are P values ≤ 0.05. BDI-II= Beck Depression Inventory CSQ= Coping Scale Questionnaire, DGSS= Dutch General Self efficacy Scale, FIQ= Fibromyalgia Impact Questionnaire, IPQ= Illness Perception Questionnaire, MPI= Multidimensional Pain Inventory, NRS= Numerical Rating Scale.

In the multivariable analyses the associations between clinical factors and fatigue predominantly remained statistically significant, whereas only some associations between the cognitive factors and fatigue remained statistically significant (Table 3).

Table 3. Multivariable associations of fatigue with clinical and cognitive factors for every time point separately

	Fatigue		
	T0	**T1**	**T2**
	β (95% CI) *P* value	β (95% CI) *P* value	β (95% CI) *P* value
Clinical factors			
More pain (NRS)	.19 (.04 to .34) **.01**	. 19 (.03 to .36) **.02**	.07 (-.11 to .24) .47
More interference of pain (MPI)	.19 (-.14 to .52) .26	.30 (-.06 to .66) .10	.51 (.17 to .84) **.003**
More depression (BDI)	-.003 (-.03 to .03) .85	.06 (.02 to .09) < **.001**	.04 (.001 to .07) **.05**
Negative emotional cognitions			
More consequences (IPQ)	.06 (-.01 to .13) .09	.14 (.07 to .20) **<.000**	.10 (.03 to .18) **.01**
More emotional representations (IPQ)	-.004 (-.10 to .09) .93	-.06 (-.12 to .01) .07	.04 (-.04 to .11) .36
Less illness coherence (IPQ)	.05 (-.02 to .12) .15	.02 (-.05 to .08) .57	.03 (-.04 to .09) .40
Low self-efficacy (DGSS)	-.07 (-.57 to .43) .77	.26 (-.18 to .69) .25	.10 (-.39 to .59) .70
More catastrophizing (CSQ)	-.01 (-.04 to .01) .32	.02 (-.003 to .05) .09	.01 (-.02 to .04) .56
Active cognitive coping			
Less reinterpretation of pain (CSQ)	-.001 (-.03 to.03) 1.00	.04 (.004 to .08) **.03**	.01 (-.03 to .04) .78
Less positive self-statements (CSQ)	-. 01 (-.04 to .01) .32	.02 (-.01 to .05) .13	-.01 (-.04 to .03) .63
More denial of pain (CSQ)	-.01 (-.04 to .02) .56	.01 (-.02 to .04) .60	.01 (-.02 to .04) .71
Less diverting attention (SCQ)	.02 (-.01 to -04) . 16	-.04 (-.07 to -.01) **.01**	-.01 (-.04 to .02) .57
Control and chronicity beliefs			
Less perceived pain control (CSQ)	.01 (-.06 to .07) .85	-.02 (-.09 to.04) .48	.05 (-.01 to .12) .09
Less personal control (IPQ)	.05 (-.02 to .11) .19	.07 (-.01 to .15) .08	.07 (.03 to. 12) **.001**
Less treatment control (IPQ)	.03 (-.05 to .10) .52	.05 (-.03 to .13) .19	.03 (-.05 to .11) .47
Stronger timeline (IPQ)	.02 (-.05 to .09) . 56	.08 (-.01 to .17) .08	.07 (-.01 to .14) .08
Stronger timeline cyclical (IPQ)	-.06 (-.14 to .01) .10	-.10 (-.17 to -.02) **.01**	-.01 (-.09 to .06) .71

β; regression coefficient adjusted for age and gender, 95% CI of β. Negative β indicates: associations of clinical and cognitive factors with a lower level of fatigue. Positive β indicates: associations of clinical and cognitive factors with a higher level of fatigue. Bold formatted numbers are P values ≤ 0.05. BDI-II= Beck Depression Inventory CSQ= Coping Scale Questionnaire, DGSS= Dutch General Self efficacy Scale, FIQ= Fibromyalgia Impact Questionnaire, IPQ= Illness Perception Questionnaire, MPI= Multidimensional Pain Inventory, NRS= Numerical Rating Scale.

Associations of changes in fatigue with changes in clinical and cognitive factors. No associations were found between improvement in pain and interference of pain, and improvement of fatigue between T0-T1 and T1-T2 in univariable analyses. Improvement in depression between T0-T1 and T1-T2 was significantly associated with improvement in fatigue over the same time intervals (Table 4). Also in multivariable analysis improvement in depression between T0-T1 was significantly associated with improvement in fatigue between T0-T1 (Table 5). Hardly any of the changes in cognitive factors were significantly associated with change in fatigue. Only less belief in consequences and less use of the coping style 'diverting attention' over T0-T1 were associated with improvement in fatigue (Table 5). In multivariable analyses both relationships remained statistically significant.

Table 4. Univariable associations of changes in fatigue with changes in clinical and cognitive factors

	Fatigue (FIQ) T0-T1 β (95% CI) *P* value	**Fatigue (FIQ) T1-T2** β (95% CI) *P* value
Clinical factors		
More pain (NRS)	-.01 (-.17 to .15) .91	.13 (-.05 to .30) .16
More interference of pain (MPI)	.32 (-.12 to .76) .15	.52 (-.04 to 1.08) .07
More depression (BDI)	.05 (.01 to .10) **.02**	.05 (-.001 to .10) **.05**
Cognitive factors		
Negative emotional cognitions		
More consequences (IPQ)	.05 (-.05 to.14) .33	.13 (.04 to .22) **.003**
More emotional representations (IPQ)	.02 (-.07 to .10) .70	-.03 (-.13 to .06) .53
Less illness coherence (IPQ)	.03 (-.05 to .10) .51	.02 (-.06 to .10) .68
Low self-efficacy (DGSS)	.14 (-.60 to .88) .70	.14 (-.60 to .88) .71
More catastrophizing (CSQ)	.03 (-.00 to .06) .06	.01 (-.03 to .04) .63
Active cognitive coping		
Less reinterpretation of pain (CSQ)	.00 (-.03 to. 02) .98	.01 (-.03 to.05) .59
Less positive self-statements (CSQ)	.00 (-.03 to .03) .91	.01 (-.04 to.03) .61
More denial of pain (CSQ)	.01 (-.02 to .04) .53	.00 (-.03 to .03) .96
Less diverting attention (SCQ)	-.03 (-.06 to.00) **.03**	.01 (-.03 to.06) .54
Control and chronicity beliefs		
Less perceived pain control (CSQ)	-.04 (-.10 to.03) .26	.03 (-.04 to.10) .44
Less personal control (IPQ)	.01 (-.08 to.10) .79	.01 (-.06 to.08) .81
Less treatment control (IPQ)	.05 (-.05 to.14) .30	.00 (-.10 to.10) 1.0
Stronger timeline (IPQ)	.06 (-.03 to.16) .19	.07 (-.01 to.16) .10
Stronger timeline cyclical (IPQ)	-.10 (-.24 to.04) .16	-.05 (-.15 to .03) .24

β; regression coefficient adjusted for age and gender, 95% CI of β, Negative β indicates: associations of clinical and cognitive factors with an decrease in fatigue. Positive β indicates: associations of clinical and cognitive factors with an increase in fatigue. Bold formatted numbers are P values ≤ 0.05. BDI-II = Beck Depression Inventory CSQ= Coping Scale Questionnaire, DGSS= Dutch General Self-efficacy Scale, FIQ= Fibromyalgia Impact Questionnaire, IPQ= Illness Perception Questionnaire, MPI= Multidimensional Pain Inventory, NRS= Numerical Rating Scale.

Table 5. Multivariable associations of changes in fatigue with changes in clinical and cognitive factors

	Fatigue (FIQ) T0-T1 β (95% CI) *P* value	**Fatigue (FIQ) T1-T2** β (95% CI) *P* value
Clinical factors		
More pain (NRS)	-.06 (-.20 to .09) .43	.05 (-.13 to .23) .58
More interference of pain (MPI)	.15 (-.27 to .57) .47	.52 (-.07 to 1.11) .09
More depression (BDI)	.05 (.01 to .09) **.02**	.03 (-.02 to .08) .26
Cognitive factors		
Negative emotional cognitions		
More consequences (IPQ)	.04 (-.04 to .13) .35	.14 (.05 to .23) **.002**
More emotional representations (IPQ)	-.004 (-.08 to .07) .91	-.05 (-.15 to .04) .27
Less illness coherence (IPQ)	.02 (-.06 to .09) .68	.01 (-.08 to .09) .85
Low self-efficacy (DGSS)	.03 (-.61 to.67) .94	.26 (-.57 to1.10) .54
More catastrophizing (CSQ)	.03 (-.001 to .06) .06	-.001 (-.04 to .04) .97
Active cognitive coping		
Less reinterpretation of pain (CSQ)	.02 (-.01to.05) .27	.01 (-.03 to.06) .64
Less positive self-statements (CSQ)	.01 (-.02 to.05) .47	-.02 (-.05 to.02) .43
More denial of pain (CSQ)	.01 (-.03 to .05) .59	-.002 (-.04 to .03) .91
Less diverting attention (SCQ)	-.04 (-.07 to -.004) **.03**	.01 (-.04 to .06) .63
Control and chronicity beliefs		
Less perceived pain control (CSQ)	-.03 (-.10 to.03) .29	.03 (-04 to.10) .38
Less personal control (IPQ)	-.01 (-.10 to.08) .80	-.003 (-.08 to.07) .93
Less treatment control (IPQ)	.06 (-.03 to.15) .23	-.01 (-.11to.10) .92
Stronger timeline (IPQ)	.06 (-.03 to .16) .19	.07 (-.03 to .16) .16
Stronger timeline cyclical (IPQ)	.05 (-.11 to .20) .55	-.06 (-.15 to .03) .18

β; regression coefficient adjusted for age and gender, 95% CI of β, Negative β indicates: associations of clinical and cognitive factors with an decrease in fatigue. Positive β indicates: associations of clinical and cognitive factors with an increase in fatigue. Bold formatted numbers are P values ≤ 0.05. BDI-II= Beck Depression Inventory CSQ= Coping Scale Questionnaire, DGSS= Dutch General Self efficacy Scale, FIQ= Fibromyalgia Impact Questionnaire, IPQ= Illness Perception Questionnaire, MPI= Multidimensional Pain Inventory, NRS= Numerical Rating Scale.

Discussion

This study explored factors associated with (change in) fatigue in patients with CWP participating in a multidisciplinary pain program. Little is known about factors associated with (change in) fatigue in the multidisciplinary pain rehabilitation in CWP. A high level of fatigue was found in our patients: the level of fatigue was even higher than the level of pain. Such findings are frequently reported in literature[2,45]. The high level of fatigue underlines the fact that fatigue is a serious health problem in patients with CWP.

Chronic widespread pain patients with worse clinical health status (i.e. higher levels of pain, interference of pain with daily living and depression) experienced a higher level of fatigue. The results of the multivariable analyses show that these clinical factors are independently associated with the level of fatigue. These results support the fact that fatigue is a multidimensional phenomenon, that is associated with pain, physical functioning and psychological distress in patients with chronic pain[1, 46].

To our knowledge this is the first study which extensively explores the relationships between pain-related cognitions and fatigue in CWP. Pain-related dysfunctional cognitions, like negative emotional cognitions and negative control chronicity beliefs, were related to a higher level of fatigue. The results of the multivariable analysis revealed that only a limited number of cognitions were independently associated with fatigue in CWP, which demonstrates the coherence between cognitions within a cognitive domain. Cognitive behavioral models in CWP address pain related cognitions and beliefs (e.g. cognitive coping and illness and self-efficacy beliefs) as components of the experience of the severity and persistence of pain[47-49]. Our results in CWP now show that dysfunctional cognitions related to pain are, to a certain extent, related to the level of fatigue as well.

The above described associations were predominately found after 6 months and 18 months of follow up. At baseline, only a limited number of associations between clinical and cognitive factors, and fatigue were found. This might be explained by a ceiling effect of the fatigue variable at baseline (i.e. a large proportion of CWP patients reported to have a severe fatigue at baseline), making it impossible to find all associations between clinical and cognitive factors and fatigue at this time point.

A small, but statistically significant improvement in fatigue level was found after multidisciplinary treatment. Improvement in depression was associated with improvement of fatigue. The present results suggest that an improvement in depression might be a mechanism of change of an improvement in fatigue in CWP patients. Fatigue and depression frequently co-occur[20,50]. Our findings are compatible with previous findings that co-morbid mood disorders in FM have a negative impact on the severity and course of FM[19].

In contrast to both our expectations and the conclusions in the review of Fisbain et al.[8], we did not find a relationship between change in pain and change in fatigue. The cause for our inconsistent finding is unclear and can not be readily explained. Although the variance of the changes in the variables fatigue and pain is rather small, it should allow to demonstrate an association between these variables. Clearly more work will be needed to clarify this point.

The present results suggest that changes in pain related cognitions typically addressed in the multidisciplinary treatment of CWP are not related to an improvement in fatigue. Only two associations were found between changes in pain related cognitions and change in fatigue. Taking into account the multiple testing these associations might be chance findings (type 1 error). In chronic fatigue syndrome (CSF), a similar pattern has been found for fatigue related cognitions in relation to pain. Improvement in fatigue related cognitions in CSF has been shown to be effective for improving fatigue, but not for improving the level of pain in CSF[51]. This finding as well as our own finding, suggest that cognitive mechanisms of change in fatigue may be specific for fatigue.

Some limitations can be noted. Firstly, the study design does not allow to draw conclusions regarding the directionality of the relationships under study. It is possible that improvement of depression occurred because of reductions in fatigue, rather than the other way around, as hypothesized in the present study. Secondly, evaluating mechanisms of change in uncontrolled studies does not enable to distinguish between mechanisms of change of natural course of a disorder, and mechanisms of change of treatment. Randomized controlled trials with a non-treated control group are needed to

distinguish between mechanisms of the natural course of fatigue and mechanisms of successful treatment of fatigue in CWP. Thirdly, data of the presence of comorbidity was not available in our cohort. The level of fatigue might be influenced by the presence of co-morbidities in our group of patients. Fourthly, measurement error may have led to an underestimation of true relationships. Fifthly, the multiple testing may have caused us to find some false positive associations. Finally, we used a one-dimensional measurement of fatigue. More detailed information can be obtained from a multi-dimensional measurement of fatigue, which may also be more sensitive to changes in fatigue, allowing to find more individual variation in fatigue.

A better understanding of associations of fatigue in patients with CWP, participating in a multidisciplinary treatment, can help to more efficiently direct multidisciplinary treatment of CWP patients to improve this outcome. The findings of the present study suggest that reducing the level of depressive symptoms is useful in treating fatigue associated with CWP. Additional interventions focusing on reducing fatigue (i.e. altering specific fatigue related cognitions, attention for day structure and gradually increasing the level of physical activity (as is done for CSF[52])) may further improve the level of fatigue in CWP. In addition, because sleep disturbances[53-55] and reduced sleep quality[55,56] are a common problem in chronic pain patients, specific attention to improvement of sleep (i.e. improvement of, cognitions about sleep and sleep hygiene[57]) might be worthwhile. Clearly, further research is needed to optimize the treatment of fatigue in patients with CWP.

In conclusion, the results show that in patients with CWP, worse clinical health status and dysfunctional cognitions are associated with a higher level of fatigue. Our results suggest that improvement in depression might be a mechanism of improvement in fatigue. Furthermore, improvement in fatigue seems to be independent of improvement in cognitive factors. Targeting fatigue in multidisciplinary pain treatment may need specific strategies.

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