

Summary

Chronic widespread pain (CWP) is characterized by widespread musculoskeletal pain, fatigue, and poor sleep. A subcategory of patients with CWP also fulfill the criteria of fibromyalgia (FM). The etiology of CWP remains unclear, but there is a growing body of evidence suggesting that a process of central sensitization plays a part. Central sensitization is manifested by hypersensitivity to both noxious and non-noxious stimuli. CWP is associated with impaired physical and emotional functioning and may result in work dysfunction, reduced social functioning, and lower quality of life.

Multidisciplinary treatment programs are recommended for patients with CWP and associated problems. The multidisciplinary treatment commonly involves a (rehabilitation) physician, a physiotherapist, an occupational therapist, a psychologist, and a social worker and acts through changes in physiological processes (e.g. through exercising and aerobic fitness) and psychological processes (e.g. altering cognitive mechanisms). Positive effect of multidisciplinary treatment in FM have been reported. The effects of multidisciplinary treatment are, on average, however, limited. This might be explained by CWP patients being a heterogeneous group. It is likely that the outcome of multidisciplinary treatment depends on the combination of patient and treatment characteristics. Furthermore, there is still much unknown about the mechanisms of multidisciplinary treatment. Altering cognitions is supposed to be one of the mechanisms of multidisciplinary treatment of CWP. The (cognitive) mechanisms of change of multidisciplinary treatment effects are, however, only partially understood.

Chapter 1 provides an overview of the background and treatment of CWP. The first aim of this thesis was to investigate which pre-treatment characteristics (predictors) are associated with the outcome of multidisciplinary treatment in patients with CWP (**Chapters 2 and 3**). The second aim of this thesis was to gain a better insight into the cognitive mechanisms of multidisciplinary treatment (**Chapters 4 to 6**).

In **Chapter 2**, predictors for the outcome of multidisciplinary treatment in patients with CWP and FM were identified in a systematic review of the literature. Fourteen studies on FM generated evidence for predictors of five outcome domains: pain, physical functioning, emotional functioning, global treatment effect, and a residual category. Although we found six studies that were of high methodological quality, no strong evidence was found for any predictor of treatment outcome, and the level of evidence was generally weak. This was mainly due to predictors being only examined in one study. In addition, there was moderate evidence that a higher level of depression predicted poorer treatment outcome in patients with FM. Finally, for several predictors, the level of evidence was found to be inconclusive. From the results of the systematic review it can be concluded that there is insufficient knowledge about predictors of the outcome of multidisciplinary treatment. This is regrettable, as more knowledge about predictors of the outcome of multidisciplinary treatment will help to differentiate between patients who are likely to benefit from multidisciplinary treatment and those who are not. Treatment efficacy will likely improve when treatment is tailored to the specific needs of patients, or when more eligible patients are selected for multidisciplinary treatment. Further research on predictors of multidisciplinary treatment outcome is needed.

Chapters 3 to 6 use data from a prospective cohort of CWP patients at the Reade center for rehabilitation and rheumatology. This cohort study was designed to answer the research questions described in this thesis. The most important inclusion criteria for the study were 1) the presence of

CWP according to the American College of Rheumatology (ACR) classification criteria: pain for at least three months, present in at least two contralateral quadrants of the body, above and below the belt, and in the axial region (thoracic and/or spine); and 2) indication for multidisciplinary rehabilitation treatment. The main goal of the intervention was to teach patients to cope with pain and to reduce the interference of pain in daily living. The treatment was performed in groups and on an individual basis. Patients were assessed at baseline (before treatment), at 6 months, and at 18 months. The measurements carried out in this study were in line with the consensus core set recommendations of outcome measures in the evaluation of clinical trials in chronic pain (i.e. pain, interference of pain with daily living, depression, and global perceived effect). In addition to this, relevant prognostic factors and cognitive factors were identified.

In **Chapter 3** we describe our study of potential predictors of the outcome of multidisciplinary rehabilitation treatment of CWP. For this study we made use of the data from baseline and 6 month follow-up measurements of our prospective cohort of 120 CWP patients. We evaluated eight hypotheses about the relationship between the selection of patients, nature of treatment, and predictive value of a potential predictor of the outcome of multidisciplinary treatment. The results of this study show that psychological distress (i.e. anxiety) is associated with a poorer treatment outcome. Furthermore, we found that negative illness beliefs (negative beliefs about personal control and consequences of the disease); more pain and fatigue; and socio-demographic characteristics, such as female gender and lower level of education, are related to a poorer outcome of multidisciplinary treatment of CWP. In addition, for all outcome measures, higher baseline values (i.e. indicating a worse health status) are associated with a greater improvement in outcome. This study contributes to the knowledge on predictors of the outcome of multidisciplinary treatment as we found some new predictors to be added to those identified in Chapter 2.

In **Chapter 4** the interrelationships and overlap of cognitive mechanisms addressed in the multidisciplinary treatment are studied. In research, as well as in the diagnostics and treatment of CWP, the identification of cognitive mechanisms plays an important role. The relationships between cognitive mechanisms are, however, diverse and complex and it is unclear whether the cognitive mechanisms identified in patients with CWP are unique or whether there is overlap in these mechanisms. Factor analysis was used to study the associations between various cognitive mechanisms. The results show that out of a large number of measurements of cognitive mechanisms, three domains can be distinguished: 1) *negative emotional cognitions* - "negative and emotional thoughts that hinder adjustment to chronic pain", 2) *active cognitive coping* - "the cognitive efforts of a person to manage or undo the negative influence of pain", and 3) *control beliefs and chronicity beliefs* - "thoughts and expectations about the controllability and chronicity of the illness".

Chapter 5 describes the relationship between improvement in negative emotional cognitions, active cognitive coping, and control and chronicity beliefs, and outcome of multidisciplinary rehabilitation treatment in patients with CWP. For this study, the data of 120 CWP patients at baseline, 6 months, and 18 months were analyzed. The results show that improvements in negative emotional cognitions are associated with improvements in all outcome domains, in particular with improvement in interference of pain with daily life and depression (between baseline and 6 months and 6 and 18

months). In addition, improvements in active cognitive coping are associated with improvements in interference of pain with daily life (between baseline and 6 months). Finally, improvements in control and chronicity beliefs are associated with improvements in pain and depression (between 6 and 18 months). Our findings show that improvements in negative emotional cognitions are consistently associated with a beneficial treatment outcome, while the two other domains show less consistent results. Therefore, improving negative emotional cognitions seems to be a key mechanism to improve the results of multidisciplinary rehabilitation treatment of CWP.

Finally, in **Chapter 6** we describe our findings with respect to the associations between (change in) clinical and cognitive factors, and (change in) fatigue in CWP patients participating in a multidisciplinary rehabilitation treatment, using the data from Chapter 5. Fatigue is a prominent symptom in patients with CWP and is perceived as a major problem by patients. We expected that the same mechanisms as found in Chapter 5 would play a role in the treatment of fatigue. A high level of fatigue was found in our patients. Over the 18 month study period, a significant improvement in fatigue was found, but this change was not clinically relevant. In CWP patients a worse clinical status (i.e. higher levels of pain, interference of pain and depression) and dysfunctional pain related cognitions (i.e. negative emotional cognitions, and negative control and chronicity beliefs) were associated with a higher level of fatigue. The results suggest that improvement in depression is a mechanism of improvement in fatigue. Other mechanisms in the multidisciplinary rehabilitation of CWP were not related to the improvement of CWP. Targeting fatigue in multidisciplinary rehabilitation treatment of CWP may need specific strategies. Additional interventions focusing on reducing fatigue and improving sleep might be worthwhile.

The main results of this thesis are summarized and discussed in **Chapter 7**. The implications of our findings for clinical practice and directions for further research regarding the multidisciplinary treatment of CWP are provided.