

Chapter 1

General Introduction

Chronic widespread pain

Chronic widespread pain (CWP) is defined as pain that is present in at least two contralateral quadrants of the body and in the axial skeleton, which must have been present for at least 3 months according to the American College of Rheumatology (ACR)¹. A subcategory of patients with CWP also fulfil the criteria of fibromyalgia (FM)¹. According to the ACR criteria (1990), patients with FM have, in addition to CWP, at least 11 of 18 painful tender points. Tender points are characterized by a heightened and painful response to pressure (i.e. allodynia). In 2010, new diagnostic criteria for fibromyalgia have been proposed². These preliminary criteria include the importance of recognition of somatic symptoms, cognitive problems and the extent of symptoms². In contrast to the ACR criteria of 1990¹, the criteria of 2010² do not require a tender point examination and provide a severity scale for characteristic fibromyalgia symptoms.

The population prevalence of CWP in western countries has been estimated at 4.2% - 13.3% and for FM at 0.7 - 3.3³. In the Netherlands, the population prevalence of CWP has been estimated at 5.2%⁴, which would imply that this concerns more than 800.000 persons. Estimated prevalence rates in chronic pain varies depending on how chronic pain is defined and how the survey questions are asked. CWP is more prevalent in women than in men^{5,6}.

The aetiology of CWP remains unclear, but there is a growing body of evidence suggesting that a process of central sensitisation plays a part. Central sensitization refers to an increased excitability of the central nervous system⁷⁻⁹. Central sensitization is manifested by hypersensitivity to both noxious (i.e. hyperalgesia - an increased response to a stimulus which is normally painful) and non-noxious stimuli, (i.e. allodynia - pain due to a stimulus which does not normally provoke pain). Literature suggests that genetic^{3,10}, biological¹¹, psychological factors¹² and environmental^{3,10} are all involved in the development of central sensitisation. Central sensitisation results in symptoms such as pain and fatigue^{8,13,14}. Chronic pain is strongly associated with mood disorders (e.g. depression and anxiety)¹⁵. The relationship between chronic pain and depression is bidirectional: chronic pain predicts depression¹⁶ and depression predicts chronic pain¹⁷. CWP is associated with impaired physical functioning^{18,19} (see Figure 1).

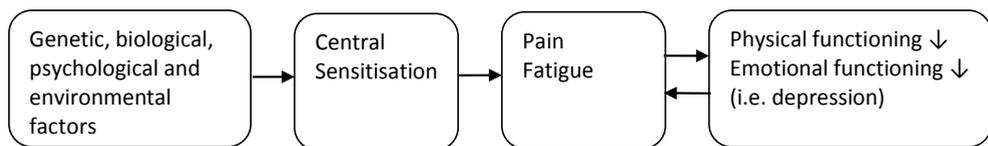


Figure 1. Mechanisms and factors contributing to central sensitization, which results in symptoms of pain and fatigue. CWP is associated with reduced physical and emotional functioning.

CWP and its associated problems affect various dimensions of life. Patients experience difficulties in carrying out activities of daily living (ADL)¹⁸⁻²⁰, may have difficulties with spouses^{21,22}, experience restrictions in social life, work²³, and quality of life^{4,25,26}. It is found that CWP is associated with a

reduced quality of life more than in other chronic diseases (e.g. osteoarthritis and rheumatoid arthritis)^{25,26}. The complexity of symptoms and associated problems makes CWP a challenge to treat for clinicians and therapists.

Treatment of chronic widespread pain

A variety of treatment strategies are available for patients with CWP, ranging from mono-therapy (e.g. pharmacological interventions) to multidisciplinary treatment. In CWP, multidisciplinary treatment has been found to have more positive effects than a mono-disciplinary treatment²⁷. Therefore, the complex problems of CWP patients can best be managed by a multidisciplinary approach²⁸⁻³⁰. In primary care, disciplines (e.g. general practitioners, physical therapists/remedial therapists and psychologists³¹) should collaborate in order to devise an optimal treatment for the patients. When treatment in primary care does not progress/is less successful or when more care is indicated, patients can be referred to a specialized rehabilitation centre (secondary care) for multidisciplinary treatment by a specialized team. Multidisciplinary treatment programs typically approach pain and disability as an interaction of physiologic, psychological and social factors and not solely as a biomedical problem^{30,32}. The multidisciplinary team works synergistically and achieves a better result than each member individually and separately could accomplish³³.

In the Netherlands, multidisciplinary pain rehabilitation is defined as a multidisciplinary treatment for patients with chronic pain of the musculoskeletal system, consisting of a co-ordinated combination of physical and psychosocial treatments, which are carried out under responsibility of a rehabilitation physician³⁴. It aims to teach patients how to independently deal with pain and the consequences of their illness for their daily functioning. A multidisciplinary rehabilitation program focuses on increasing or optimizing activity level, learning patients to cope with their pain in daily living and alters perpetuating factors of CWP³⁴. Although often asked by patients, treatment is not aimed at reducing pain. The multidisciplinary team commonly involves a rehabilitation physician, physiotherapist, occupational therapist, psychologists, and a social worker. The treatment encompasses a wide range of strategies including education, cognitive behavioral therapy, relaxation, the acquisition of pain management skills and physical training.

Consensus recommendations on the evaluation of outcome have been developed in order to improve the uniformity and comparability of studies on the treatment of CWP patients. There are four core outcome domains specified in the consensus recommendations of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) to evaluate CWP clinical trials³⁵. These domains include (1) pain intensity; (2) physical functioning (i.e. interference of pain with daily life); (3) emotional functioning (i.e. depression)^{1*}; and (4) ratings of overall improvement by the participant (i.e. global perceived effect) (5). The consensus recommendations of the OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trials) include outcome domains on pain,

^{1*} The measurement of depression conducted in the evaluation of the treatment in CWP represent the severity of depressive symptoms and feelings. Patients are not necessarily diagnosed with depression according the criteria of Diagnostic and Statistical Manual, Fourth/Fifth Edition (DSM-IV/V), which represent the gold standard for the diagnosis of mood disorders.

tenderness, fatigue, patient global, multidimensional function, and sleep disturbance³⁶. In this thesis we focused on the assessment of the four outcome domains defined by the IMMPACT recommendations, as well as fatigue.

Predictors of the outcome of multidisciplinary treatment

Although beneficial effects have been found for multidisciplinary treatment of CWP patients, on average the results are limited^{27,37,38}. Patients with CWP are a heterogeneous group and can differ with regard to symptoms and their physical and psychological characteristics^{39,40}. It is likely that the effect of multidisciplinary treatment depends on these factors. Treatment efficacy may improve when it is tailored to the specific needs of patients, or when eligible patients are selected for a multidisciplinary treatment program. Therefore identification of individual differences in patient characteristics and their relation to the outcome of multidisciplinary treatment is needed.

Although empirical studies are available, no systematic review of the literature has been published which summarizes the research evidence on predictors of the outcome of multidisciplinary treatment in patients with CWP and FM. We systematically summarized predictors of the outcome of multidisciplinary treatment in patients with FM and CWP (**Chapter 2**).

A limited number of studies have been carried out into predictors of the outcome of multidisciplinary treatment. Therefore, we studied a number of potential predictors of the outcome of multidisciplinary treatment, in a prospective cohort study of 120 CWP patients participating in a multidisciplinary rehabilitation treatment (**Chapter 3**). In Chapter 3, we present an analysis of the relationship between the selection of patients, nature of treatment and predictive value of a potential predictor of the outcome of multidisciplinary treatment. Patient characteristics may predict treatment outcome, depending on the selection of patients and the nature of treatment (see Figure 2). Let us assume that factor A (e.g. depression¹⁵) predicts the persistence of symptoms and disability in untreated patients. In an unselected sample of patients and with treatment not targeting factor A, factor A is expected to predict a poor treatment outcome. Conversely, in an unselected sample and with treatment targeting factor A, factor A is not expected to predict treatment outcome: because factor A is targeted during treatment, it is expected to lose its predictive value. The same reasoning applies to a sample selected for factor A. Finally, in a selected sample, with patients with factor A excluded from treatment, factor A will not predict treatment outcome: if factor A is not present, it cannot predict treatment outcome.

Based on this analytical framework, we formulated and evaluated 8 hypotheses about the potential predictors of the outcome of multidisciplinary rehabilitation treatment. The results of Chapter 3 contribute to the small body of knowledge about predictors of the outcome of multidisciplinary treatment in CWP.

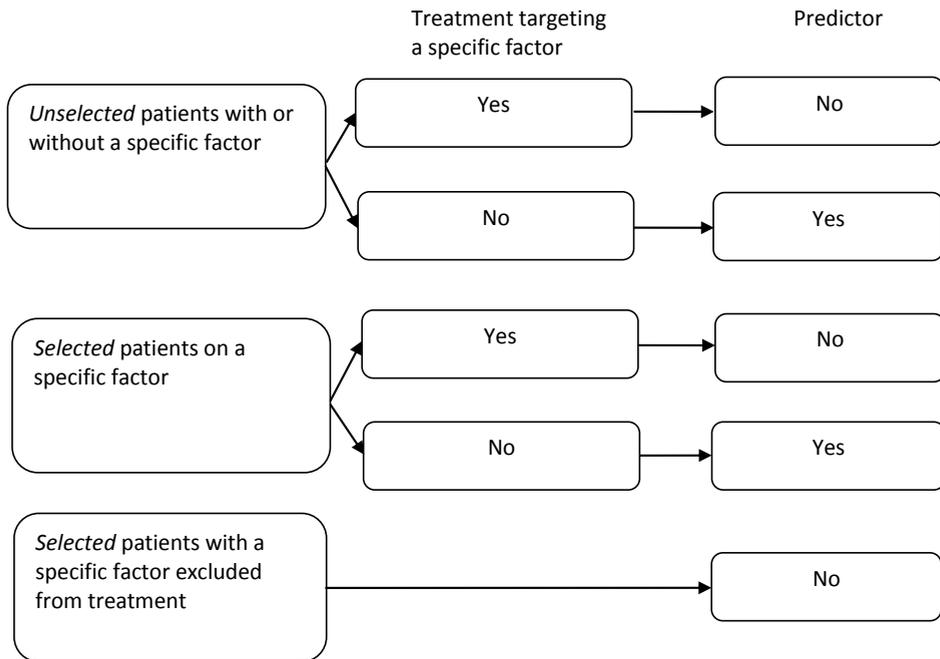


Figure 2. Schematic representation of the relationship between selection of patients, nature of treatment and predictive value of patient characteristics on treatment outcome⁴¹.

Cognitive mechanisms in multidisciplinary treatment

The multidisciplinary treatment acts through changes in physiological processes (e.g. exercising, aerobic fitness) and psychological processes (e.g. cognitive mechanisms). Altering cognitions is supposed to be one of the mechanisms of multidisciplinary treatment of CWP^{27,42,43}. A wide range of cognitive mechanisms has been proposed over the years to explain the adjustment to and persistence of chronic pain. Relevant cognitive mechanisms include self-efficacy beliefs⁴⁴, cognitive coping styles⁴⁵, fear-avoidance beliefs^{46,47} and illness beliefs^{48,49} (see Figure 3).

The cognitive mechanisms as studied in this thesis, are briefly described below.

Self-efficacy is defined as one's confidence in performing a particular behaviour and overcoming barriers to that behaviour⁴⁴. Self-efficacy beliefs may include "general self-efficacy beliefs" - i.e. a broad and stable sense of personal competence to deal effectively with a variety of stressful situations⁵⁰ and "specific illness-related self-efficacy beliefs" - i.e. confidence in being able to perform a particular behaviour or task despite of a specific illness e.g. pain⁵¹. This thesis focuses on the general self-efficacy beliefs in patients with CWP.

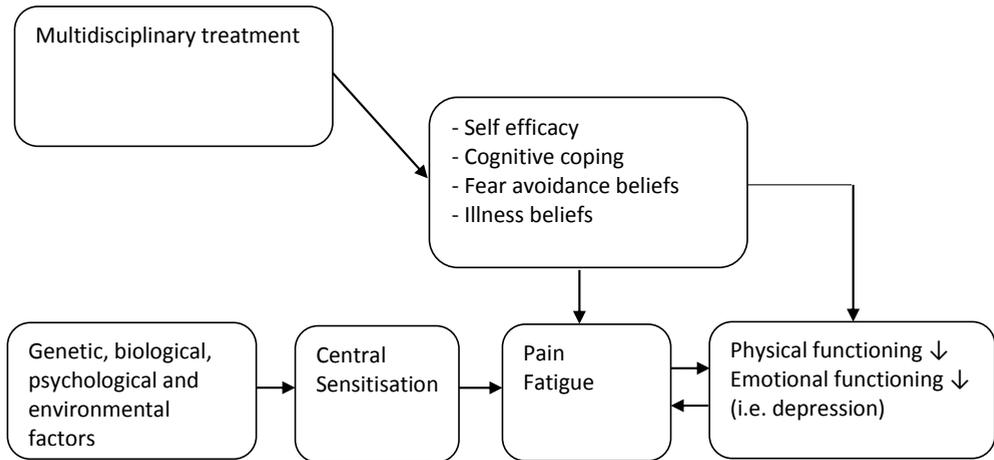


Figure 3. Cognitive mechanisms in multidisciplinary treatment affecting CWP

Coping is defined as cognitive and behavioural efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of the person⁴⁵. Coping styles can be classified as cognitive, behavioural or physiological⁵². Patients with CWP use a variety of coping styles⁵³. This thesis focuses on cognitive coping styles. Cognitive coping styles determine the functioning of the CWP patient⁵⁴⁻⁵⁶. Cognitive coping styles may include “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 of pain sensations” - visualizing something which is not compatible with the true pain experience, “diverting attention away from pain sensations” - thinking of something to distract your attention away from the pain and “praying hoping” - praying and hoping that the pain will lessen once, and “catastrophizing” - having negative thoughts and ideas about the impact of pain.

Fear-avoidance beliefs refers to the interpretation of pain as a signal for future pain and injury, resulting in pain-related fear and avoidance of activity. In low back pain, fear-avoidance has been argued to be more disabling than actually experienced pain⁵⁷ and is assumed to lead to depression and activity limitations (i.e. reduced physical functioning)⁵⁸. In FMS patients stronger fear and avoidance beliefs are associated with greater disability and depressive symptoms⁵⁹.

Illness beliefs are ideas that patients hold about their illness⁴⁸ and include beliefs on the timeline, consequences and control or cure of the illness. Perceptions of serious consequences of the illness and less personal control⁶⁰ are negatively associated with physical functioning.

This thesis aimed at a better understanding of cognitive mechanisms targeted in the multidisciplinary treatment and which improvements work for what outcome. A better understanding of the (key) cognitive mechanisms of change in the multidisciplinary treatment may provide a clearer direction

for the optimization of multidisciplinary treatment and will help to target multidisciplinary treatment at the most powerful agents of change.

In **Chapter 4** we have studied (i) the inter-relationships between self-efficacy, cognitive coping styles, fear-avoidance beliefs and illness beliefs in patients with CWP and (ii) explored the possibility of a reduction of these cognitions into a more limited number of domains. The cognitive mechanisms of self-efficacy, cognitive coping, fear-avoidance beliefs and illness beliefs comprise several operationalisations and these mechanisms are generally considered as theoretically distinct entities. Although these various mechanisms are considered conceptually separate, they might be interrelated and there might be overlap between these mechanisms (e.g. catastrophizing closely resembles emotional illness representations; and “personal control” (illness belief) closely resemble “perceived control of pain” (cognitive coping strategy)). More understanding of the overlap and uniqueness of cognitive mechanisms is worthwhile for clinicians, therapists and researchers. In addition, reduction of the number of cognitive mechanisms into a limited set of domains may help to direct multidisciplinary treatment. However, to direct multidisciplinary treatment to the most powerful cognitive mechanisms, more insight is needed into which improvements are associated with beneficial multidisciplinary treatment outcome. Using the results from Chapter 4 we studied the relationship between cognitive mechanisms of change and the outcome (i.e. pain, interference of pain, depression and global perceived effect) of multidisciplinary rehabilitation treatment in patients with CWP (**Chapter 5**).

Fatigue in chronic widespread pain

Although pain is the primary symptom of CWP, patients also often complain about fatigue. Fatigue is defined as an internal and subjective feeling of tiredness that may or may not be related to activity⁶¹. Seventy six percent of the patients with FM suffers from clinically significant fatigue compared to only 41% of patients with osteoarthritis and rheumatoid arthritis⁶². Fatigue in CWP is associated with a reduced quality of life and with work dysfunction⁶² and is often difficult to manage. Although fatigue is a serious health problem in CWP, in comparison to pain it has received much less attention in research.

Multidisciplinary treatment has been found to reduce fatigue³⁷ in FM and low back pain⁶³, although fatigue is usually not the focus of a multidisciplinary rehabilitation treatment in chronic pain. The mechanisms of change associated with diminishment of fatigue in multidisciplinary treatment of CWP are unclear. Based on previous research we hypothesized that an improvement in clinical factors, such as pain and depression, are associated with an improvement in fatigue in patients with CWP^{62,64,65}. In addition, we hypothesized that improvement in (pain related) cognitions addressed in the multidisciplinary treatment of CWP is also related to improvement in fatigue in CWP. A better understanding of mechanisms associated with (improvement in) fatigue in the multidisciplinary rehabilitation treatment of patients with CWP will help to direct multidisciplinary treatment. In **Chapter 6**, we explored (i) the associations between (improvement in) fatigue and (improvement in) clinical and cognitive factors in patients with CWP, participating in multidisciplinary rehabilitation treatment.

Aims of this thesis

The first aim of this thesis is to investigate which pre-treatment patient characteristics are associated with the outcome of multidisciplinary treatment in patients with CWP. In **Chapter 2**, we systematically summarize predictors of the outcome of multidisciplinary treatment in patients with CWP from literature. In **Chapter 3**, we studied potential predictors of the outcome of multidisciplinary rehabilitation treatment in CWP and 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 rehabilitation treatment.

The second aim of this thesis is to gain a better insight into the cognitive mechanisms of the multidisciplinary treatment. In **Chapter 4** the interrelationships and overlap of cognitive mechanisms addressed in the multidisciplinary treatment are studied. In **Chapter 5**, we evaluate the contribution of improvement in cognitive mechanisms to the outcome (i.e. pain, interference of pain, depression and global perceived effect) of the multidisciplinary treatment in patients with CWP. Finally, in **Chapter 6** we study the associations between (change in) clinical and cognitive factors, and (change in) fatigue in CWP patients participating in a multidisciplinary rehabilitation treatment. The results of this thesis are summarized and discussed in **Chapter 7**.

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