

# Chapter 7

General Discussion

This thesis provides insight into (i) predictors of the outcome of multidisciplinary treatment and (ii) cognitive mechanisms (of change) that determine the outcome of multidisciplinary treatment in CWP patients.

## **Predictors of the outcome of multidisciplinary treatment**

Predictors of the outcome of multidisciplinary treatment are discussed in Chapters 2 and 3. The systematic review in Chapter 2 shows that a higher level of depression predicts poor outcome of treatment in FM patients (moderate evidence). Poorer outcome of treatment is also predicted by Minnesota Multiphasic Personality Inventory (MMPI) disturbance and pain profiles, strong beliefs in fate, and high disability (weak evidence). In contrast, better outcome is predicted by Multidimensional Pain Inventory (MPI) adaptive copers and dysfunctional profiles, a worse baseline status, and high levels of pain (weak evidence). In addition, female gender and the presence of fatigue both predict a better treatment outcome (inconclusive evidence). Finally, there is inconclusive evidence for several other predictors of the outcome of treatment. The findings of our own study in Chapter 3 show that a higher level of anxiety, negative illness beliefs (i.e. less belief in personal control and a stronger belief in negative consequences of the illness), a higher level of pain and of fatigue, a lower level of education, and female gender all predict a poorer outcome of multidisciplinary treatment in patients with CWP.

Chapter 2 and 3 suggest that not all patients with CWP benefit from multidisciplinary treatment. CWP patients form a heterogeneous group and multidisciplinary treatment may not fulfil their individual needs. A multidisciplinary treatment program tailored to the needs of the individual patient may improve the outcome of treatment. Patients with pronounced emotional problems (i.e. higher levels of depression or anxiety) and negative illness beliefs respond less well to multidisciplinary treatment. To improve the outcome of multidisciplinary treatment, these patients may need better management of their depressive symptoms and anxiety and more specific attention to their negative illness beliefs. With regard to this, a number of suggestions for improving multidisciplinary treatment can be made. One possibility is to offer these patients a stepwise approach<sup>1</sup> by treating their depressive symptoms, anxiety, and negative illness beliefs first, prior to the start of multidisciplinary pain rehabilitation. Another possibility is to provide multidisciplinary treatment in a flexible manner (e.g. modular based)<sup>2</sup> and tailor the multidisciplinary treatment to the specific needs and individual characteristics of patients. Depending on the needs of the patient the multidisciplinary treatment can then be composed of a number of modules, or additional components can be added to an existing multidisciplinary program. For example, a subgroup of patients may need additional modules such as treatment of depression, anxiety, or negative illness beliefs. When there is no option to adapt the treatment program, selection of more suitable patients (i.e. patients with less emotional problems and more positive illness beliefs) might improve the effectiveness of a multidisciplinary treatment. Currently the focus of multidisciplinary pain rehabilitation in CWP is usually on cognitive and behavioral components of pain and disability, instead of on depression and anxiety. Furthermore, altering illness beliefs is seldom structurally embedded in standard multidisciplinary treatment. Our results suggest that depressive symptoms,

anxiety, and negative illness beliefs have to be taken into account when planning treatment of CWP patients.

Our results underline the need for careful assessment of emotional problems (i.e. depressive symptoms and anxiety disorders). In this respect, computer adaptive testing systems (like the Patient Reported Outcomes Measurement Information System (PROMIS))<sup>3,4</sup> might be useful in assessing patients' reported problems in CWP. A Dutch-Flemish translation of PROMIS has recently become available<sup>5</sup>. Additionally, computer adaptive testing will potentially lighten the respondent burden and assessment load for patients, clinicians, and therapists<sup>6</sup>.

Chapters 2 and 3 have opposite findings with respect to the direction of the relationship of the pain, fatigue, and gender predictors. Chapter 2 finds that a higher level of pain is related to better physical functioning (weak evidence). In addition, the presence of fatigue is related to lesser impact of FM (inconclusive evidence) after treatment. In contrast, the results of our own study described in chapter 3 show that less pain and fatigue at baseline is related to a better global perceived treatment effect. The reasons for these opposite findings are unclear and hard to explain. A detailed interpretation of these finding would be speculative and hypothetical. Clearly, in future more research is needed to better understand the influence of symptoms on the outcome of multidisciplinary treatment. In addition, Chapter 2 finds that female gender predicted a better outcome (inconclusive evidence) of multidisciplinary treatment in contrast to the findings in Chapter 3. Since our study population only included five men, it is possible that the finding described in Chapter 3 might not be generalizable to all men suffering from CWP. The role of gender on the outcome of multidisciplinary treatment requires further investigation.

Finally, in view of our finding that the level of education predicts treatment outcome, it might be worthwhile to adjust multidisciplinary treatment to the cognitive ability of the patient. In line with other studies in FM patients<sup>7,8</sup>, our findings might be explained by low health literacy: low educational status is correlated with low health literacy in patients with chronic diseases<sup>9,10</sup>. In our clinical experience, patients with a lower level of education have difficulty in fully understanding the information presented and in applying the information in practice. Therefore, special attention should be paid to the readability of the information, the illustrations presented, and the conversation skills of the multidisciplinary team. Improvement of the accessibility of the multidisciplinary treatment program may well improve the outcome for patients with low education levels.

Chapter 2 presents (preliminary) evidence for predictors of the outcome of multidisciplinary treatment in CWP patients, but this chapter also highlights the lack of high quality studies for evaluating predictors of the outcome of multidisciplinary treatment in FM patients. Stronger adherence to international methodological guidelines (e.g. CONSORT statement)<sup>11</sup> and uniformity in measurements (e.g. as recommended in the IMMPACT core set for chronic pain)<sup>12</sup>, will help to improve the quality of studies and to make the results of different studies more comparable. In the Netherlands, the participation of pain treatment centers in the Dutch Pain database<sup>13,14</sup> would be a good starting point. In addition, to facilitate the comparison of studies and to lessen the risk of bias, a better registration of the content, duration, and intensity of multidisciplinary treatment is warranted. It may be worthwhile to make a taxonomy for multidisciplinary treatment, as has been done by Abraham et al.<sup>15</sup> for behavioral change techniques in interventions. Another option to describe the

multidisciplinary treatment in a uniform way is to develop a framework, as has done for exercise interventions for physical therapy by van der Leeden et al. 2013<sup>16</sup>.

### **Cognitive mechanisms in multidisciplinary treatment**

A wide range of cognitive mechanisms have been investigated and proposed over the years to explain the adjustment to and persistence of chronic pain. Multidisciplinary treatment in CWP addresses a variety of cognitive mechanisms. Chapter 4 shows that the cognitive mechanisms addressed in the multidisciplinary rehabilitation treatment of CWP can be categorized into three principal cognitive domains: 1) negative emotional cognitions, 2) active cognitive coping, and 3) control and chronicity beliefs. Negative emotional cognitions are characterized by negative and emotional thoughts that hinder adjustment to chronic pain. Active cognitive coping is characterized by cognitive efforts to manage or undo the negative influence of pain. Finally, control and chronicity beliefs are characterized by thoughts and expectations about the controllability and chronicity of the illness.

To our knowledge, our study is the first to purposefully explore overlap between cognitive mechanisms commonly used in the measurement and treatment of CWP. Previous studies using factor analyses investigated a broad range of constructs (e.g. pain, disability, psychological constructs) in the measurement of chronic pain and found evidence for a factor of cognitive and emotional distress<sup>17-19</sup> which is comparable to our first factor of negative emotional cognitions. In their review, the group of Keefe et al.<sup>20</sup> already stated in 2004 that there is a need to study overlap in psychological constructs (i.e. cognitive and emotional constructs) in CWP to determine the unique explanatory nature of the psychological constructs commonly used in CWP. The body of knowledge about overlap of psychological constructs in chronic pain remains, however, small, although gradually getting more attention. Recently, Campbell et al.<sup>21</sup> studied cognitive and emotional constructs related to pain in a population of patients with low back pain. Three of the domains found by Campbell et al. were consistent with those we described, which strengthens our confidence in the validity of our conclusions. In the study by Campbell, domains of "pain-related distress" (comparable to our domain of negative emotional cognitions), "cognitive coping" (comparable to our domain of active cognitive coping), and "perceptions of the future" (comparable to our domain of control and chronicity beliefs) were found. In addition, a domain of "causal beliefs" (i.e. beliefs about risk factors, immunity, etc.) was described. In our study, these latter cognitions were not included. In the study by Campbell, the domain of "pain related distress" was extended with emotional constructs like depression and anxiety.

A better understanding of the uniqueness and overlap of cognitive mechanisms may help to direct both assessment and treatment in chronic pain. Both our study and the study of Campbell offer a good starting point. These results indicate that it may be meaningful to investigate on a wider scale whether negative emotional cognitions, active coping styles, control and chronicity beliefs constitute principal domains of cognitive mechanisms in CWP. However, in view of the diversity (e.g. not all cognitive mechanisms were included in our analysis) and complexity of cognitive mechanisms in CWP, it is as yet too early to formulate a new and integrative model of cognitive mechanisms in CWP.

Replication, confirmatory analyses, and longitudinal studies will be needed to further validate the grouping of different cognitions into a limited set of domains and to work towards a theoretical foundation of principal cognitive domains in CWP.

Chapter 5 examines cognitive mechanisms of change of the outcome of multidisciplinary treatment. Our results reveal that improvement in negative emotional cognitions seems to be a key mechanism of change in multidisciplinary treatment of CWP. Improvement in active cognitive coping and improvement in control and chronic timeline beliefs may also constitute mechanisms of change, although the evidence is less strong.

Despite the theoretical considerations and empirical evidence for the importance of addressing a large number of cognitive mechanisms during multidisciplinary treatment of CWP, the effect of treatment is limited. It may be that the content of the multidisciplinary treatment needs to be more focused, as it now covers a broad spectrum of cognitive mechanisms. In the literature it is unclear which cognitive mechanisms are most important to target. The results described in Chapter 5 show that improvement in negative emotional cognitions is consistently associated with a better outcome of the multidisciplinary treatment. These findings can be used to tailor treatment so as to address more directly the key cognitive mechanisms of change that underlie beneficial treatment outcome. Our results suggest that multidisciplinary rehabilitation in CWP should focus more on improving negative emotional cognitions.

Chapter 5 also shows that cognitions are still changing in the long term. These findings may have consequences for the planning of treatment. After-care sessions or booster sessions may further improve treatment outcome. There may be a role for primary care givers in this. Further studies are needed to (i) clarify the impact of changes of cognitions in the long term and (ii) learn how to sustain improvements of cognitions in the long term.

## **Fatigue in chronic widespread pain**

In Chapter 6 we consider the associations between (change in) clinical and cognitive factors, and (change in) fatigue, in CWP patients participating in a multidisciplinary rehabilitation treatment. We show that both worse clinical status and dysfunctional cognitions are associated with a higher level of fatigue in CWP. In addition, our results suggest that improvement in depression is related to an improvement in the level of fatigue. We have not found evidence that an improvement in pain related cognitions improves fatigue levels during multidisciplinary treatment of CWP patients.

Literature reports that 76% of the patients with CWP complain about clinically significant fatigue<sup>22</sup>. Given the size of this problem, and the relevance for patients<sup>23</sup>, more attention should be paid to the treatment of fatigue. The present findings show that improvement in depression may be a mechanism of change to improve the level of fatigue. By contrast, improvements in other clinical and cognitive mechanisms of the multidisciplinary treatment are not related to an improvement in fatigue levels. This suggests that lowering fatigue levels may need specific strategies. Additional interventions focusing on altering specific fatigue related cognitions and gradually increasing the level of physical activity (as is done for Chronic Fatigue syndrome (CFS))<sup>24</sup> may be needed to lower

the level of fatigue in CWP. In addition, improvement of sleep, cognitions about sleep, and specific attention to sleep hygiene, may be worthwhile<sup>25</sup>. Further research is needed to explore the associations and mechanisms of change of fatigue in patients with CWP, eventually leading to more specific targets for treatment of fatigue.

## **Methodological limitations and implications for future research**

Some methodological considerations underlying the study will be discussed below and suggestions for future research will be proposed.

**Population and intervention.** The studies described in this thesis were conducted in only one multidisciplinary outpatient rehabilitation center. Although the characteristics of the study population were comparable to other CWP samples described in literature<sup>26,27</sup>, and the content of our multidisciplinary pain program was comparable to other evidence based treatment programs<sup>28,29</sup>, it might be possible that the results are not generalizable to other rehabilitation settings. Multicenter studies are needed to investigate the generalizability of the results.

In addition, the intensity and length of the intervention were not standardized in our study. This may hinder the reproducibility of the intervention. Remarkably, little research has been done about the influence of treatment intensity on multidisciplinary treatment response. Additional studies are necessary to develop a greater understanding of the influence of treatment intensity on mechanisms of change and multidisciplinary treatment outcome in patients with CWP.

**Directionality of the relationships.** The study design does not allow drawing conclusions regarding causal relationships. A correlational study design was used and the directionality of the relationships was based on theoretical and clinical reasoning. It is, therefore, possible that improvement in, for example, cognitions occurred because of reductions in emotional or physical functioning, rather than the other way around, as hypothesized in our study (Chapter 5). The same caution should be taken into account when interpreting the results from Chapter 6: it is possible that improvement of depression occurred because of reductions in fatigue, rather than the other way around, as hypothesized in the study. Experimental studies are needed to establish causal relationships.

**Natural course versus treatment effect.** The data of our study were collected through a prospective cohort. We did not include a control group and are thus not able to conclude whether changes in outcome measurements are the result of the multidisciplinary treatment. Our research design does not allow us to distinguish between predictors of natural course of a disease and predictors of successful treatment. Whether a distinction in predictors exists can only be studied in randomized controlled trials investigating the effectiveness of multidisciplinary treatment in patients with CWP. The same limitation applies to the evaluation of mechanisms of change of the outcome of treatment. Evaluating mechanisms of change in uncontrolled studies does not enable distinguishing 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 the disorder and mechanisms of successful treatment in CWP.

However, in clinical practice, treatment effect is always a sum of the effects of natural course and of treatment. The conclusions of the studies are therefore useful for clinical practice.

**Mechanisms of change in multidisciplinary treatment.** The treatment encompasses a wide range of strategies, including education, cognitive behavioral therapy, relaxation, the acquisition of pain management skills, and physical training. It is not possible to determine exactly which component of treatment is critically responsible for the favorable effects of treatment. Future intervention studies are needed to determine if improvement in cognitive mechanisms is responsible for the positive effects of treatment. Moreover, it is still unclear how cognitive changes can be achieved<sup>30,31</sup>. To improve the efficacy of multidisciplinary treatment, future research focusing on identifying and distinguishing the components and mechanisms (specific and nonspecific) that are responsible for the cognitive changes is needed.

### Implications for future research from a clinical perspective

The preceding section addresses the implications for future research from a methodological perspective. In this section, the direction for future research will be discussed from a clinical perspective. Considerations from both perspectives are needed to design new studies.

Preliminary evidence has been presented for several predictors of the outcome of multidisciplinary treatment in CWP. Future studies should focus on both replication and deepening of our results. For example, for use in clinical practice the development of cut-off scores for predictors is warranted. In addition, future studies should focus on understanding what kind of multidisciplinary treatment works for which type of CWP patient. Next, randomized control trials are needed to examine the effectiveness of multidisciplinary treatment tailored to the specific characteristics of patients.

To evaluate patient reported problems the development of computer adaptive testing systems may be worthwhile. Computer adaptive systems will potentially lighten the assessment load for patients, clinicians, and therapists<sup>6</sup>, and may increase the efficiency in the selection process for multidisciplinary rehabilitation in CWP.

It is hypothesized that a limited number of underlying domains can be distinguished among measurements of cognitive mechanisms in CWP. Our finding of three cognitive domains (i.e. negative emotional cognitions, active cognitive coping, and control and chronicity beliefs) offers a good starting point. Replication, confirmatory analyses, and longitudinal studies will be needed to further validate the grouping of different cognitions into a limited set of domains.

The results of Chapter 5 highlight the relationships between improvement in negative emotional cognitions and improvement of the outcome of multidisciplinary treatment. For use in clinical practice, the development of a multidisciplinary treatment protocol and training of the multidisciplinary team in diagnosing and improving negative emotional cognitions is warranted to optimize treatment outcome and to provide a structural embedding of this treatment strategy. In addition, targeting negative emotional cognitions during multidisciplinary treatment should be tested for its effectiveness in a randomized controlled trial. Furthermore, further studies are needed to (i)

clarify the long term impact of changes of cognitive mechanisms and (ii) learn how to sustain improvements of cognitions in the long term. Moreover, to improve our insight into the efficacy of the multidisciplinary treatment, extension of research on mechanisms of change (i.e. cognitive mechanisms, behavioral mechanisms, and physiological mechanisms) of the outcome of multidisciplinary treatment in CWP is warranted.

Finally, further research is needed to explore other associations and mechanisms of change of fatigue in CWP patients. Future studies should focus on the evaluation of treatments aimed at improving fatigue (e.g. treatment aimed at improving sleep, sleep hygiene, cognitions about sleep, cognitions about fatigue, day structure and activity level) in patients with CWP.

## Conclusions

**Predictors of the outcome of multidisciplinary treatment.** The results of the review suggest that CWP patients with pronounced emotional problems (i.e. depression: moderate evidence) seem to respond less well to multidisciplinary treatment. In line with this, our own study provided evidence for anxiety as a predictor of poorer outcome of treatment. These results suggest that careful assessment of emotional problems (i.e. depressive symptoms and anxiety disorders) might be worthwhile. Multidisciplinary treatment programs tailored to the need of these patients might improve the outcome of treatment. Alternatively, when there is no option to adapt the treatment program, selection of eligible patients (i.e. less pronounced emotional problems) might improve the effectiveness of a multidisciplinary treatment. In addition, a wide range of patient characteristics have been examined as predictors of the outcome of multidisciplinary treatment programs. As the evidence in support of these is preliminary and not always consistent, further research is needed to strengthen the evidence for predictors of the outcome of multidisciplinary treatment.

**Cognitive mechanisms in multidisciplinary treatment.** A limited number of underlying domains can be distinguished among measurements of the cognitive concepts of self-efficacy, cognitive coping styles, fear-avoidance, and illness beliefs. Three cognitive domains can be distinguished: negative emotional cognitions, active cognitive coping, and control and chronicity beliefs. Negative emotional cognitions are characterized by negative and emotional thoughts that hinder adjustment to chronic pain. Active cognitive coping is characterized by the cognitive efforts of a person to manage or undo the negative influence of pain. Finally, control and chronicity beliefs are characterized by thoughts and expectations about the controllability and chronicity of the illness. Improvements in negative emotional cognitions are consistently associated with a beneficial outcome of multidisciplinary treatment. Improving negative emotional cognitions may therefore be a key mechanism of change in multidisciplinary treatment. Other, less central, mechanisms of change may include improving active cognitive coping and improving control and chronicity beliefs.

**Fatigue in chronic widespread pain.** We found a high level of fatigue in our patients. Our results show that a worse clinical status and dysfunctional pain related cognitions are associated with a higher level of fatigue. In addition, the results suggest that an improvement in depression might improve fatigue associated with patients. Improvement in other clinical and cognitive mechanisms of the multidisciplinary treatment was not related to an improvement in fatigue levels. Targeting fatigue in multidisciplinary pain treatment may need specific strategies.

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