Chronic widespread pain and fibromyalgia from the perspective of rehabilitation
Aspects of clinical assessment and management

Dissertation from the University of Copenhagen 2017

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Ulla Wewer, Head of Faculty

List of original publications


### Table of Contents

**Abbreviations** ........................................................................................................................................ 5  
**Preface** .................................................................................................................................................... 6  
**Overview and purpose of the thesis** ........................................................................................................ 8  

1. **Introduction** ......................................................................................................................................... 9  
   The clinical concept of chronic widespread pain (CWP) and fibromyalgia ........................................... 9  
   CWP and fibromyalgia in the rheumatologic context .............................................................................. 9  
   Clinical features and case definition of fibromyalgia ............................................................................. 11  
   Natural course, long-term prognosis and healthcare utilization in CWP and fibromyalgia ............... 14  

The biology of fibromyalgia ....................................................................................................................... 15  
   Pain models and conceptualization of pain ............................................................................................ 15  
   Pain processing ....................................................................................................................................... 16  
   Pain hypersensitivity and sensitization ................................................................................................. 17  
   Abnormal pain processing in fibromyalgia .......................................................................................... 18  
      Tender points as a clinical marker of pain hypersensitivity ................................................................ 18  
      Evidence of abnormal cerebral pain processing ............................................................................. 19  
      Evidence of abnormalities in descending pain modulation ............................................................. 19  
      Evidence of abnormalities in neuroendocrine, autonomic and immune functioning ..................... 20  
   The link between fibromyalgia and other chronic pain states ............................................................. 22  
      Fibromyalgia in the spectrum of central sensitivity syndromes ................................................... 22  
      Fibromyalgia in the spectrum of neuropathic pain .......................................................................... 23  
      Fibromyalgia in the spectrum of inflammatory pain .................................................................... 25  
      Fibromyalgia in the spectrum of affective disorders ..................................................................... 25  

Disability in CWP and fibromyalgia ......................................................................................................... 26  

Assessment of patients with CWP and fibromyalgia ............................................................................... 28  
   Assessment of chronic pain patients – aspects of measurement structure and instrumentation .......... 28  
   Evaluation of disease severity from the rheumatologic perspective – the OMERACT initiative ......... 30  
   Evaluation of disease severity using the ICF as a theoretical framework for assessment ................. 30  
   Assessment of functional ability from the perspective of rehabilitation ......................................... 33  
   Assessment of depression in chronic pain populations ...................................................................... 33  

Management of patients with CWP and fibromyalgia ............................................................................. 35  
   Management of patients with fibromyalgia according to existing guidelines .................................... 35  
      Pharmacological intervention ........................................................................................................... 35  
      Non-pharmacological intervention .................................................................................................. 36  
      Multi-component therapy ............................................................................................................... 38  
   Between patient heterogeneity and clinical implications .................................................................. 39  
      Identification of patient subgroups in fibromyalgia ...................................................................... 40  
      Identification of predictors of multi-component treatment outcome in fibromyalgia ................... 41  
   Rehabilitation perspective in management and outcome assessment .............................................. 43
2. Patients and methods

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study setting and study population</td>
<td>46</td>
</tr>
<tr>
<td>Participants</td>
<td>46</td>
</tr>
<tr>
<td>The CWP cohort</td>
<td>48</td>
</tr>
<tr>
<td>Assessment and instrumentation</td>
<td>48</td>
</tr>
<tr>
<td>Observation-based assessment of functional ability</td>
<td>48</td>
</tr>
<tr>
<td>The IMPROvE study</td>
<td>50</td>
</tr>
<tr>
<td>The rehabilitation program</td>
<td>51</td>
</tr>
</tbody>
</table>

3. Own study results and discussion of clinical implications

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical assessment</td>
<td>53</td>
</tr>
<tr>
<td>Tender points as a marker of clinical disease severity</td>
<td>53</td>
</tr>
<tr>
<td>Assessment of functional ability</td>
<td>58</td>
</tr>
<tr>
<td>Validity of self-rating depression scales in patients with CWP</td>
<td>61</td>
</tr>
<tr>
<td>Outcome of rehabilitation and predictors of functional outcome of rehabilitation</td>
<td>62</td>
</tr>
</tbody>
</table>

4. Concluding comments and research perspectives

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>The clinical concept of CWP and fibromyalgia</td>
<td>70</td>
</tr>
<tr>
<td>Clinical assessment of patients with CWP and fibromyalgia</td>
<td>71</td>
</tr>
<tr>
<td>Management of patients with CWP and fibromyalgia</td>
<td>72</td>
</tr>
</tbody>
</table>

5. Dansk resumé

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference list</td>
<td>76</td>
</tr>
<tr>
<td>Appendix 1</td>
<td>93</td>
</tr>
<tr>
<td>Appendix 2</td>
<td>97</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>ACR</td>
<td>American College of Rheumatology</td>
</tr>
<tr>
<td>ADL</td>
<td>Activities of Daily Living</td>
</tr>
<tr>
<td>AMPS</td>
<td>Assessment of Motor and Process Skills</td>
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<td>BDI</td>
<td>Beck Depression Inventory</td>
</tr>
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<td>BOCF</td>
<td>Baseline Observation Carried Forward</td>
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<td>CNS</td>
<td>Central Nervous System</td>
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<td>Cuff Pressure Algometry</td>
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<td>CSQ</td>
<td>Coping Strategy Questionnaire</td>
</tr>
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<td>CSS</td>
<td>Central Sensitivity Syndromes</td>
</tr>
<tr>
<td>CWP</td>
<td>Chronic Widespread Pain</td>
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<td>EMA</td>
<td>European Medicines Agency</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>FIQ</td>
<td>Fibromyalgia Impact Questionnaire</td>
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<td>fMRI</td>
<td>functional Magnetic Resonance Imaging</td>
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<td>GAD-10</td>
<td>Generalized Anxiety Disorder Inventory</td>
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<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
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<td>HPA-axis</td>
<td>Hypothalamic-Pituitary-Adrenal axis</td>
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<td>HRQoL</td>
<td>Health-Related Quality of Life</td>
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<td>IASP</td>
<td>International Association for the Study of Pain</td>
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<td>IBS</td>
<td>Irritable Bowel Syndrome</td>
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<td>ICF</td>
<td>International Classification of Functioning, Disability and Health</td>
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<td>IMMPACT</td>
<td>Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials</td>
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<td>ITT</td>
<td>Intention-To-Treat</td>
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<td>MCS</td>
<td>Mental Composite Score</td>
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<td>MDD</td>
<td>Major Depressive Disorder</td>
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<td>MDI</td>
<td>Major Depression Inventory</td>
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<td>MPI</td>
<td>Multidimensional Pain Inventory</td>
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<td>MRS</td>
<td>Magnetic Resonance Spectroscopy</td>
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<td>MUS</td>
<td>Medically Unexplained Symptoms</td>
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<td>6-MW</td>
<td>6 Minute Walk</td>
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<td>NSAID</td>
<td>Non-Steroidal Anti-Inflammatory Drugs</td>
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<td>OMERACT</td>
<td>Outcome Measures in Rheumatology Clinical Trials</td>
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<td>PAG</td>
<td>Periaqueductal grey</td>
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<td>PCS</td>
<td>Physical Composite Score</td>
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<td>PDQ</td>
<td>Pain Detect Questionnaire</td>
</tr>
<tr>
<td>PET</td>
<td>Positron-Emission Tomography</td>
</tr>
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<td>PGIC</td>
<td>Patient Global Impression of Change</td>
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<td>PROMIS</td>
<td>Patient-Reported Outcomes Measurement Information System</td>
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<td>PSEQ</td>
<td>Pain Self-Efficacy Questionnaire</td>
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<td>RLS</td>
<td>Restless Leg Syndrome</td>
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<td>RVM</td>
<td>Rostral Ventromedial Medulla</td>
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<tr>
<td>SLE</td>
<td>Systemic Lupus Erythematosus</td>
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<tr>
<td>SNRI</td>
<td>Selective Serotonin Noradrenalin Reuptake Inhibitor</td>
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<td>SPECT</td>
<td>Single-Photon Emission Computed Tomography</td>
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<tr>
<td>SSRI</td>
<td>Selective Serotonin Reuptake Inhibitor</td>
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<td>TCA</td>
<td>Tricyclic Antidepressants</td>
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<td>TMD</td>
<td>Temporo Mandibular Disorder</td>
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<td>TP</td>
<td>Tender Point</td>
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<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
Preface

This thesis is based on my clinical and experimental work carried out from 2007, where I was employed as a consultant rheumatologist at the Department of Rheumatology and the Parker Institute, Frederiksberg Hospital. A position specifically dedicated to the clinical management of patients with chronic widespread pain (CWP) and fibromyalgia, and advancement of clinical research related to this patient population. This unique position, emphasizing a longstanding tradition at Frederiksberg Hospital for engaging in patients with fibromyalgia, has made it possible to bridge clinical work with clinical research and thus offered the best possible and inspiring working conditions.

My interest in the field of pain and rehabilitation was aroused many years ago, when Dr. Bente Danneskiold-Samsøe introduced me to the work with survivors of torture. This introduction ended up being a long and dedicated professional involvement that not only has shaped my career path, but has also introduced me to many committed and knowledgeable people from whom I have learned a lot. Bente Danneskiold-Samsøe has been an inspiration and never failing support throughout this professional engagement, as well as in my current work with patients with CWP and fibromyalgia, and for this, I am truly grateful. I would also like to thank Dr. Henning Bliddal, Head of the Parker Institute for continuous support and encouragement, and for making this thesis possible.

Rehabilitation of patients with CWP and fibromyalgia is an interdisciplinary area in both practice and research. Being a member of a devoted and skilled interdisciplinary team around these patients at the Department of Rheumatology has not only been motivating, but also brought up issues of clinical relevance that has contributed to formulate the research questions and outline of this thesis. For good collaboration and support, I also thank Dr. Hanne Slott Jensen, Head of the Department of Rheumatology, and my other colleges and coworkers at the department.

The facilitating, multidisciplinary research environment provided by the Parker Institute has been a precondition for the conduction of clinical research related to this patient population and creation of this thesis. Thus, I would like to give thanks to all of my coworkers and colleges at the Parker Institute for invaluable support and inspiration throughout the years. Thanks to Claus Bomhoff, for assistance with fund raising and support in several other ways. Especially, I want to direct my gratitude to my closest coworkers and members of my research team at the Parker Institute; Cecilie Bülow, Elisabeth Bandak, Marianne Rasmussen, Robin Christensen, Anders Stockmarr, Anders Jespersen and Eva Wæhrens for sharing this field of research, each of you providing the necessary knowledge and areas of expertise. My sincere gratitude to Eva Wæhrens, my closest colleague and co-author, for sharing your enthusiasm and knowledge about rehabilitation and assessment of functional ability, and for introducing me to the universe of the Assessment of Motor and Process Skills (AMPS) in particular. For many years of inspiring and close collaboration on chronic post-torture pain and for always taking an interest in the progress of my current line of research, I also thank Dr. Amanda Williams. I deeply appreciate your constructive support, professional collaboration and the friendship you both have offered me. I also wish to thank Dr. Bengt Sjölund and Dr. Robert Bennett for the helpful discussions and critique during the final phases of writing the thesis. Finally yet importantly, I want to thank all the patients for their support and keenly participation in all of the studies presented in this thesis.
The studies presented in this thesis would have been impossible to perform without the generous support of The Oak Foundation, Aase og Ejnar Danielsens fond, The Schioldann Foundation, The Danish Rheumatism Association, The A.P. Møller Foundation for the Advancement of Medical Science, Minister Erna Hamiltons Legat for Videnskab og Kunst and Støtteforeningen for Gigtbehandling og Forskning ved Frederiksberg Hospital.

Kirstine Amris

Allerød, November 2015
Overview and purpose of the thesis

Pain is the major clinical feature in rheumatologic diseases, and research advances over the past 40 years have greatly increased our understanding of the complex mechanisms involved in the experience of pain. We now know that uncontrolled and prolonged pain can alter both the peripheral and central nervous system through processes of neural plasticity and central sensitization, and that pain can become a disease in its own right. Considering chronic pain as a brain disease, with alterations in neural networks affecting multiple aspects of brain function, structure, and neurobiology has challenged our current diagnostic labels, and position on pain problems inherent in most rheumatologic disorders. Fibromyalgia, by many considered the prototypical 'central' pain disorder, has been pivotal in this development and highlighted that changes in brain activity may manifest as chronic pain, even in rheumatic disease traditionally classified as peripheral inflammatory disorders. The term 'central pain' was originally introduced to describe the condition in individuals who developed pain following an apparent lesion in the central nervous system (CNS). More recently, the term has been expanded to describe any CNS dysfunction or pathologic condition that may be contributing to the development or maintenance of chronic pain. A marker of 'central' pain is the occurrence of multifocal pain in conjunction with other centrally mediated symptoms, such as fatigue, sleep disruption, cognitive difficulties and emotional distress.

Chronic widespread pain (CWP) is the term used to characterize persistent, widespread musculoskeletal pain, for which no apparent tissue-based pathology can be identified. CWP is prevalent in the background population and represents a major clinical challenge due to the complexity of the disorder. Apart from pain and other centrally mediated symptoms, CWP is strongly associated with disability affecting daily life activities, incapacity for normal employment and poor social participation, and incurs high direct medical costs as well as significant indirect costs, e.g. sick leave and disability compensation. Fibromyalgia is the best characterized subset of patients presenting with CWP and while no single etiology has been identified, contemporary research has provided persuasive evidence for the role of augmented central pain processing in terms of sensitization of nociceptive neurons and ascending spinal tracts accompanied by dysfunction of descending pain inhibitory pathways. Although there is a plethora of publications describing varied treatments for fibromyalgia, including pharmacological therapy addressing central pain modulation, present symptom-based therapeutic approaches have demonstrated limited impact. Even though outcome studies indicate statistically significant improvement in some key outcome domains, effects are on average limited, and a substantial proportion of patients do not demonstrate sustainable, clinically meaningful benefits. Furthermore, there is no generally accepted classification for the degree of disease severity in this patient population, or definitions of what patients (and clinicians) would consider a substantial response to treatment or 'patient acceptable symptom state' given the current treatment possibilities.

It is well recognized that persistent pain influences all aspects of a person's functioning: physical, emotional, interpersonal, and vocational. Still, the focus of available clinical guidelines for the management of fibromyalgia has mostly addressed treatment as an implement to control symptoms, rather than focusing toward maintaining and improving functioning and optimal social integration. There is a need for a more suitable approach for assessing and classifying patients with CWP and fibromyalgia as well as research efforts that can guide management design and development of
strategies for improving outcome. Rooted in a bio-psychosocial paradigm, rehabilitation is concerned with limitations of functioning and disability associated with health conditions and with the complex interaction with personal factors and the environment. In this way, rehabilitation can be defined as a health strategy that ‘aims to enable people with health conditions experiencing or likely to experience disability to achieve optimal functioning in interaction with the environment’. Because of the inherent complexity, rehabilitation is an interdisciplinary area in both research and practice. The unique feature of rehabilitation is the focus on human functioning, disability and health, while in the biomedical approach the emphasis is on diagnosis and treatment of disease. Acknowledging the substantial negative impact of CWP on the individual’s daily life activities and social participation, moving towards a more rehabilitation-oriented paradigm may benefit this patient population.

Thus, the overall purpose of the present thesis was to contribute to an evidence-based development of the clinical practice related to the management of patients with CWP and fibromyalgia from the perspective of rehabilitation. Specific research aims were to identify valid assessment methods and instruments for the assessment of disease severity in this patient population, and to evaluate the effectiveness of a two-week, group-based rehabilitation program tailored for patients with CWP and fibromyalgia based on the identified instruments. A further aim was to identify outcome predictors of rehabilitation in patients with CWP and fibromyalgia that might guide future intervention matching and development of strategies for improving effectiveness of interventions. The thesis also reviews aspects of pain physiology and abnormal pain processing in fibromyalgia, definition, classification and diagnosis of fibromyalgia, and the linkage between fibromyalgia and other chronic pain states and emotional distress, as well as current guidelines for its management in order to describe the patient population studied and to expand and summarize the current knowledge on these aspects.

1. Introduction

The clinical concept of chronic widespread pain (CWP) and fibromyalgia

CWP and fibromyalgia in the rheumatologic context

In clinical rheumatologic practice, chronic musculoskeletal pain is often classified according to pain distribution and categorized as localized, regional, or widespread. Several definitions of CWP have been suggested. According to the American College of Rheumatology (ACR), CWP is defined as pain present in at least 3 body quadrants and the axial skeleton, which has persisted for at least 3 months (1). Although the ACR definition of CWP has been used in epidemiologic studies, it has been criticized for being too inclusive and not reflecting the concept of truly diffuse and widespread pain. A more stringent definition of widespread pain, for use in epidemiologic studies, has therefore been proposed stipulating pain in at least two sections of two contralateral limbs, and in the axial skeleton (2). Dependent on the definition of CWP applied, the reported prevalence in epidemiologic studies ranges from 4.7% to 13.5% with a male-female ratio of 1:3 (3;4). Chronic regional pain is found in 20-25% of the population (5;6).

CWP has been shown to differ from localized and regional pain not only in the distribution of pain. Individuals with generalized pain report a higher illness burden; higher pain intensity, fewer pain-free
periods, more pronounced pain-related interference with everyday life, and higher levels of psychological distress (7-10). An association between CWP and mechanical hyperalgesia assessed by threshold testing or tender point counts also seems well established. There is evidence of increasing numbers of tender points with increasing number of painful body segments (11) and lowered pressure pain thresholds in CWP compared to pain-free individuals (12;13).

Fibromyalgia is a characterized subgroup of patients presenting with CWP and widespread mechanical hyperalgesia at ≥ 11 tender point sites. These characteristics are enshrined in the 1990-ACR criteria (1), that have been the cornerstone for research studies of the past two decades. Using the ACR criteria, the prevalence of fibromyalgia has been reported to range from 0.5% to 4% in the population with a male-female ratio of 1:9 (14;15). Contemporary research in subjects fulfilling 1990-ACR criteria has provided persuasive evidence for augmented central pain processing in terms of sensitization of nociceptive neurons and ascending spinal tracts accompanied by dysfunction of descending pain inhibitory pathways (16;17). The underlying pain mechanisms in subjects with CWP and fewer than 11 tender points are less well described. Only about 20% of individuals reporting CWP related to the musculoskeletal system meet the ACR tender point criteria (11) and there is no clear clinical diagnosis for the remaining 80%. Available evidence support that CWP associated with multiple tender points, i.e. fibromyalgia, is associated with more severe symptoms and pain-related interference with everyday life compared with CWP and fewer tender points (18). It has been suggested that CWP and fibromyalgia are part of a continuum of pain in the general population (figure 1) that differ more in quantitative than qualitative measures, and that the pain in both conditions is central rather than peripheral in nature (19).

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**Figure 1** Theoretical model illustrating a possible pain continuum from localised pain to fibromyalgia in the background population.
Clinical features and case definition of fibromyalgia

Clinicians face challenges in discriminating between rheumatologic and non-rheumatologic disorders with similar manifestations and in discriminating among rheumatologic disorders with shared features. Thus, the development of criteria for use in routine clinical care and clinical research has been a priority. Classification criteria are standardized definitions that are primarily intended to create well-defined, relatively homogeneous cohorts of patients for clinical research and may therefore not capture all physician assigned diagnoses. They are not intended to capture the entire spectrum of possible patients, but rather to capture the majority of patients who share key features of the condition (i.e. high specificity at the expense of sensitivity). Although classification criteria may provide some framework to assist in diagnosis, and are frequently used that way, the goal of classification criteria differs from the intent of diagnostic criteria. Diagnostic criteria are set of signs, symptoms, and tests for use in routine clinical care to guide the care of individual patients. Diagnostic criteria are in general broad and should reflect the all possible different features and severity of a disease (heterogeneity) with the goal of accurately identifying as many individuals with the condition as possible (i.e. high sensitivity while preserving acceptable specificity). It may be difficult to capture the full range of disease presentations using any single set of criteria and the distance between diagnostic and classification criteria on this continuum depends on various factors. Compared with classification criteria, diagnostic criteria appear to be more impacted by practice setting, and the performance characteristics of diagnostic criteria may vary substantially due to differences in disease prevalence and the severity and manifestations of disease in different settings. Given that the majority of rheumatic diseases are multisystem disorders with poorly understood etiology; they tend to be heterogeneous in their clinical presentation and do not have a single clinical, laboratory, or imaging feature that may serve as a gold standard, there are only a few validated diagnostic criteria in rheumatology (20). Classification criteria are critically important for advancing research, allowing the conduct of clinical and epidemiological studies with well-defined patient populations. The process of diagnosis, however, requires consideration of features of an individual patient, beyond those represented in a set of classification criteria. Unfortunately, the existing criteria for rheumatic diseases are not always correctly applied. Based on the aforementioned concerns regarding the challenges in developing diagnostic criteria with consistent performance properties, the ACR has recently announced that it will provide approval only for classification criteria and will no longer consider funding or endorsing diagnostic criteria (20).

In clinical practice, the diagnosis of fibromyalgia has been given to individuals characterized by CWP, mainly perceived in deep somatic tissues, and widespread deep tissue hyperalgesia, for which no apparent tissue-based pathology can be identified. The painful tissues involved are not accompanied by tissue inflammation or other structural changes detectable at physical examination, and blood tests and routine diagnostic imaging of peripheral tissue structures such as joints and tendons are reported to be normal (21). The typical patient is female in her 40’s or 50’s with years of ill-defined musculoskeletal pain. Onset of symptoms is usually gradual, but occasionally there may be a sudden onset following an identifiable event, such as medical illness, a mentally stressful incident, or physical trauma. Disturbed, non-restorative sleep, fatigue, and cognitive alterations, all symptoms inherent in chronic pain disorders, are often a prominent feature of the clinical picture, as well as various symptoms related to internal organ systems (22). In clinical populations of fibromyalgia, however, different clusters of patient groups with regards to symptom reporting and symptom severity levels
have been identified, suggesting a considerable heterogeneity across patients (23). Despite few tissue-based objective findings, fibromyalgia is often associated with considerable pain-related functional disability, even when compared to other severe and disabling medical conditions (24;25).

Genes exert significant control in human pain perception and twin studies indicates heritability around 50% for migraine, tension-type headache and CWP, around 35% for back and neck pain, and around 25% for irritable bowel syndrome (26). Evidence also exists for a strong familial component in the development of fibromyalgia. Fibromyalgia has been observed to cluster in families (27) and twin studies indicate that also the symptoms known to be associated with fibromyalgia seem to have a strong genetic background (28). While no individual gene has been identified, there is increasing evidence of a polygenic effect, with polymorphism of genes affecting serotonergic, catecholaminergic and dopaminergic systems playing a role (27;29).

Over the years, various criteria have been proposed in an attempt to compensate for the lack of physical and biological markers specific to fibromyalgia. The American College of Rheumatology (ACR) classification criteria from 1990 (1) represent a consensus definition based on clinicians’ descriptions of the clinical picture of the disorder. Developing these criteria, primarily intended for research purposes, tender points were found to be the most powerful discriminator, being able to separate fibromyalgia from other painful rheumatic disorders. Introduced in the clinical context, however, 1990-ACR criteria introducing a cutoff at 11 tender points have been criticized for placing diagnosis at the far end of a severity spectrum, and for ignoring other important key symptoms (30-32).

Diagnostic, symptom-based criteria omitting the tender point examination and expanding the definition of fibromyalgia to include symptoms other than pain have therefore been suggested in 2010 (Figure 2) (32;33). A diagnosis based on these diagnostic criteria, which are not formally adopted by the ACR, depends on the patients’ reporting of the distribution of pain (0-19 widespread pain index (WPI)) together with the physicians’ subjective assessments of the presence and severity of the patient’s associated symptoms; fatigue, sleep, cognition, and related somatic symptoms scored on a 0-3 scale (0-12 symptom severity score (SS-score)), and thus still rely on clinical grounds. Patients satisfy the proposed 2010-criteria by either having a WPI ≥ 7/19 pain sites and SS-score ≥ 5/12 or a WPI ≥ 3/19 pain sites and SS score ≥ 9/12, introducing a cutoff of 12. Elimination of tender points and the requirement of a widespread pain distribution have altered the case definition of fibromyalgia (34). Using the 1990-ACR classification criteria as the gold standard, the suggested diagnostic criteria correctly identify about 81% of the cases in a rheumatologic setting (32). Applied in a large population based sample, the symptom-based diagnostic criteria modified for survey research resulted in a prevalence of fibromyalgia of 2.1% with an even male-female ratio (35). Alternative diagnostic criteria employing a combination of pain distribution and symptom reporting, including 3 diagnostically germane symptoms (stiffness, tenderness to touch, and environmental sensitivity) has been suggested in 2014 and validated in a clinical sample of chronic pain patients. Comparing these criteria with the 1990-ACR classification criteria provided a sensitivity of 81%, a specificity of 80%, and a correct classification of 80% (36).
Figure 2. The 2010 diagnostic criteria for fibromyalgia. Diagnose is based on a widespread pain index (WPI) with a theoretical score ranging from 0-19 and a symptom severity score (SS-score) ranging from 0-12 setting the cutoff for diagnosis at a total score of 12.

Previous guidelines for the management of fibromyalgia have mostly addressed treatment options rather than providing an overall approach to the clinical concept of fibromyalgia. In recent interdisciplinary guidelines, independently developed in Canada (37), Germany (38-46) and Israel (47), updated directions for the definition, classification and clinical diagnosis of fibromyalgia are accounted for. Reviewing these guidelines, Fitzcharles et al. concluded that the guidelines showed remarkable consistency regarding the clinical concept of fibromyalgia, acknowledging that fibromyalgia is neither a distinct rheumatic nor mental disorder, but rather a cluster of symptoms not
explained by another somatic disease (48). All three guidelines define fibromyalgia by the 1990-ACR classification criteria and recommend that the 2010 diagnostic criteria may be used to validate a clinical diagnosis of fibromyalgia (48). The Canadian guideline states that fibromyalgia is a clinical construct of pain and other symptoms that cannot be explained by some other illness (37). The Israeli guidelines define fibromyalgia as a central hypersensitivity syndrome (47), whereas the German guidelines classify fibromyalgia as a functional somatic syndrome, defined by a typical cluster of symptoms and the exclusion of a somatic disease which sufficiently explains the symptoms (40). Both the Canadian and the German guidelines identify fibromyalgia as a continuum disorder and not a discrete disorder (37;40). In all three guidelines, however, it is emphasized that fibromyalgia can coexist with a diagnosis of another somatic disease (e.g. inflammatory rheumatic disease) or mental disorder (e.g. depression) (37;40;47).

Natural course, long-term prognosis and health care utilization in CWP and fibromyalgia

The core symptoms seen in individuals with fibromyalgia; widespread pain, fatigue, sleep disturbance, cognitive impairment, and emotional distress, occur over a wide continuum in the background population (15) and any classification of disease severity based on symptom reporting depends on the criteria and thresholds used. As of today, there is no generally accepted classification for the degree of disease severity in patients with fibromyalgia. Furthermore, the majority of the research in the field has been cross-sectional and only a few long-term follow-up studies of subjects with fibromyalgia have been carried out (49-53). The overall result from these studies is one of generally continuing high levels of self-reported symptoms and distress for most patients. In a study by Walitt et al., 1,555 subjects with fibromyalgia diagnosed in a rheumatologic setting were followed semiannually with detailed outcome questionnaires for up to 11 years. Overall, fibromyalgia symptom severity worsened in 35.9% and pain in 38.6%. About 25% reported at least moderate improvement of pain over time (52). A similar poor prognosis for recovery has been reported in a seven year follow-up study of a population based sample of individuals with CWP (54).

Although findings are somewhat inconsistent across studies, mortality is reported to be increased in subjects with chronic pain (55). A recent systematic review and meta-analysis, including 10 studies, indicated a modest association between chronic pain and mortality, particularly cancer mortality (56). Restricting the analysis to studies evaluating CWP and mortality resulted in an increase in the size of the pooled estimates for all-cause, cancer and cardiovascular disease mortality, but these remained non-significant. Adjustment for confounders led to attenuation of the relationship between all-cause mortality and chronic or widespread pain, indicating that lifestyle and socio-demographic factors may have an important role. Further, there was a large heterogeneity between studies. This included inconsistency in the definition of CWP applied, pain duration and follow-up time, as well as considerable variability in the type and number of factors adjusted for between studies. Eight of the studies were carried out in population-based cohorts and two were clinical cohorts. Both clinical cohorts reported no significant increased risk of mortality for patients diagnosed with fibromyalgia according to 1990-ACR criteria, but supported an elevated risk of suicide compared to the background population (57;58).
Several studies have documented that fibromyalgia patients have high lifetime and current rates of utilization of all types of medical services (59-63). The diversity of symptoms associated with fibromyalgia probably contributes to the lengthy and expensive processes patients undergo in order to get a diagnosis. In an internet-based survey, conducted in a large sample of patients with fibromyalgia, it was shown that over 75% have seen more than three healthcare providers prior to obtaining a diagnosis and 25% more than six healthcare providers prior to diagnosis (22). In a study of 2,260 newly diagnosed fibromyalgia patients, the average number of healthcare visits during the year prior to diagnosis was 25 (64). Studies like these demonstrate that fibromyalgia continues to present a challenge for healthcare professionals as well as for patients. An area of contention still seems to be the benefits or harms of the diagnostic label ‘fibromyalgia’. However, studies have shown that a definitive diagnosis will provide reassurance, facilitate management and reduce health care utilization, with cost reduction further augmented by early diagnosis (64-66). Prolonged and excessive healthcare utilization with referral to multiple specialists and repeated imaging and laboratory investigations should therefore avoided.

The biology of fibromyalgia

Pain models and conceptualization of pain

Various models of pain have evolved throughout history and perhaps the most influential model that continues to influence our understanding of pain is Descartes’ model, separating body and mind. Contemporary research, however, have demonstrated that our pain system is highly integrated and that pathological pain states may involve central pain processing defects as well as changes in neuroimmune, neuroendocrine and autonomic nervous system regulation, probably promoted by a complex interaction between genetic vulnerabilities and environmental factors.

In spite of this increased knowledge, chronic pain is frequently included in the category of ‘medically unexplained symptoms’ or ‘functional disorders’ with reference to lack of identifiable tissue-based pathology (67). This view stems from a simplistic, unidimensional biomedical model of pain, in which the experience of pain is equated with peripheral stimulation and physiological processing of noxious stimuli (nociception) and the pain experience assumed to be directly proportional to the extent of observable tissue damage. Alternatively, the psychogenic view suggests pain is a physical manifestation of psychological problems in the absence of any apparent tissue based explanation. Modern pain models have discarded this conceptualization of pain as a purely sensory or psychological phenomenon and proposed multidimensional pain models, which integrate motivational-affective and cognitive-evaluative components with sensory-physiological ones. Accordingly, the International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage”. This definition emphasizes the inherent subjectivity of pain, with both sensory and affective dimensions, that are usually, but not necessarily, associated with tissue damage.

Further, it is well recognized that persistent pain influences all aspects of a person’s functioning: physical, emotional, interpersonal, and vocational. This has led to the development of bio-psychosocial models, which have attempted a wide integration of physical, psychological and social-contextual factors contributing to the total experience of pain (68). The bio-psychosocial view has been
instrumental in the development of multidisciplinary and multimodal treatment regimes for chronic pain, acknowledging chronic pain as a specific disease in its own right (68;69).

**Pain processing**

Modern concepts of pain processing are based on the spinal gate control theory formulated by Melzack and Wall in 1965, which highlighted the modulation of incoming sensory information at the spinal level. Prior to this, the prevailing view on pain processing was of a largely passive, one-way, non-modulated neural relay system (pain pathway) linking sensory inflow generated in primary afferents with those parts of the brain that lead to the conscious awareness of painful sensations. As of today, substantial clinical and experimental evidences has proven the existence of multiple ascending and descending neural pathways related to pain perception.

The processing of pain involves a system of mechanisms that encode and transmit the pain signal along the ascending pathways, from the point of noxious stimulation in the periphery to higher centers in the brain. Briefly, pain processing can be divided into four main processes: nociception, transmission, modulation and perception. **Nociception**, the initial processing of pain, refers to the activation of specialized sensory neurons (nociceptors), which transduces noxious stimuli (mechanical, thermal, or chemical stimuli) into a depolarizing sensor potential. **Transmission** is the process whereby the signal of nociceptor activation (action potentials) is conducted to secondary sensory neurons in the dorsal horn of the spinal cord and from there to the brainstem and higher cortical areas.

Ascending nociceptive information is not conveyed passively and non-modulated to the brainstem and higher cortical areas. Pain is continuously subject to **descending modulation** controlled by the state of the organism, the context (threat, safety) and other ongoing demands. Cortical (prefrontal cortical areas) and brainstem structures involved in descending pain modulation, which plays a crucial role for homeostasis and pain control, directly project to and modify the responses of spinal and medullary dorsal horn neurons to incoming somatosensory stimulation (70). Engagement of descending modulation can facilitate, as well as inhibit pain (Descending Noxious Inhibitory Control/ Conditioned Pain Modulation). The periaqueductal grey (PAG) in the midbrain and the rostral ventromedial medulla (RVM) are two important areas of the brain involved in descending inhibitory modulation. Both these centres contain high concentrations of opioid receptors and endogenous opioids, and compose part of the endogenous pain inhibitory circuit. Descending pathways projecting to the dorsal horn are monoaminergic, utilising noradrenalin and serotonin as neurotransmitters. While activation of spinal noradrenergic receptors exerts a strong antinociceptive effect, the effect of spinal serotonin can be either inhibitory or facilitatory, depending on the receptor subtype activated (72). The existence of a descending pain modulatory system provides targets for many centrally acting analgesics.

**Perception** is the response by the brain to nociceptive input. Neuroimaging studies have consistently demonstrated several brain areas as having a major role in pain processing and together these brain areas are commonly referred to as the ‘pain matrix’ (73). At least two major neural circuits have been identified. The first is a lateral spinothalamic ascending nociceptive pathway, which performs a sensory-discriminative function (the sense of the intensity, location, quality and duration of the pain) and includes the ventral posterior nuclei of the thalamus and the somatosensory cortex.
The second is a medial spinothalamic pathway, which involves the brainstem, the ventral medial nuclei of the thalamus, the limbic system, and the frontal cortex. The medial pain system plays a crucial role in the motivational-affective and cognitive-evaluative aspects of pain processing, memory for pain, and the autonomic-neuroendocrine responses (74;75). Several studies have indicated functional as well as structural changes of the pain matrix in the context of chronic pain states, including fibromyalgia (74).

**Pain hypersensitivity and sensitization**

Acute pain plays a protective role as it motivates the individual to withdraw from damaging situations, to protect a damaged body part while it heals, and to avoid similar experiences in the future. Chronic pain lacks these survival advantages and instead imposes a persisting stress on these protective and adaptive systems. Normally, pain is produced only by intense stimuli that are potentially or actually damaging to tissue (physiological pain). Physiological pain is caused by activation of a specific system of high-threshold peripheral and central neurons that respond only to stimuli approaching or exceeding harmful intensity. In contrast to this, pathological pain is the response to tissue injury and inflammation (inflammatory pain), damage to the nervous system (neuropathic pain), or alterations in the function of the somatosensory system. Both spontaneous pain without any apparent peripheral stimulus and hypersensitivity to peripheral stimuli may occur.

Clinically, *pain hypersensitivity* is characterized by increased responsiveness to noxious stimuli, which produce an exaggerated and prolonged pain (*hyperalgesia*), and lowered receptor thresholds, with pain elicited by normally non-painful stimuli (*alodynia*). Increased responsiveness of peripheral and central neurons (pain hypersensitivity) in the presence of tissue injury and inflammation is a normal response (neuroplasticity) that ensures healing – an adaptive response. However, pain hypersensitivity may persist long after an injury has healed or occur in the absence of any injury. In this case, pain provides no benefits, and is a manifestation of maladaptive pathological change in the nervous system (76).

*Peripheral sensitization* refers to an increased responsiveness and reduced threshold of nociceptive neurons in the periphery. Such changes in the response characteristics of peripheral nociceptors, conveying input from the peripheral tissues to the central nervous system, contribute to the pain hypersensitivity found locally at the site of tissue injury and inflammation. It arises due to the action of inflammatory mediators released in the damaged tissues, and generally requires ongoing peripheral pathology for its maintenance (70).

*Central sensitization* refers to an enhancement in the function of neurons and circuits in the central nervous system caused by increased membrane excitability and synaptic efficacy, as well as reduced descending inhibitory modulation. Because central sensitization results from changes in the properties of neurons in the central nervous system, the pain is no longer coupled, as acute nociceptive pain is, to the presence, intensity, or duration of noxious peripheral stimuli. Instead, central sensitization produces pain hypersensitivity by changing the sensory response elicited by normal inputs, including those that usually evoke innocuous sensations. Thus, central sensitization represents a major functional shift in the somatosensory system from high-threshold nociception to low-threshold pain hypersensitivity (76). Experimentally, central sensitization is characterized by pain hypersensitivity,
expansion of receptive fields, and increased pain intensity during and after repeated stimuli (temporal summation and sensory after effects).

**Abnormal pain processing in fibromyalgia**

While no single etiology has been identified, contemporary research, in subjects fulfilling 1990-ACR criteria, has provided persuasive evidence for the role of augmented central pain processing in terms of sensitization of nociceptive neurons and ascending spinal tracts accompanied by dysfunction of descending pain inhibitory pathways (16;17). In support of this notion, the most consistently detected objective abnormalities have been those involving pain processing systems, e.g. altered stimulus-response functions and summation of pain stimuli in experimental pain testing (77), as well as alterations in central pain processing visualized by functional neuroimaging (78;79).

**Tender points as a clinical marker of pain hypersensitivity**

Nociceptive afferent fibers can be found in muscles as dense innervations of vascular structures, and nociceptive input from muscles is very powerful in inducing central sensitization. It has been shown that experimentally induced acute muscle pain may cause hyperexcitability of neuronal responses, including hyperalgesia in superficial and deep tissues as well as remote pain, indicating involvement of central summation and sensitization mechanisms (80). Mechanical hyperalgesia is a characteristic feature of so-called ‘tender points’ and, although an imperfect measure, manual tender point examination has been considered a primary clinical identifier of pain hypersensitivity (16;81). There is strong evidence for a generalized lowering of pressure pain thresholds in fibromyalgia (82;83), and the mechanical hyperalgesia found in patients with fibromyalgia is not restricted to tender points, but appears to be widespread (15;84). Experimental pain studies have shown that patients with fibromyalgia cannot detect sensory stimuli at lower levels than healthy controls, but that the threshold at which these stimuli cause pain or unpleasantness is reduced (85). These findings have also been demonstrated when stimuli are given in an unpredictable random fashion suggesting that psychological factors such as hypervigilance play a minor role in modulating this hyper-responsiveness to various stimuli such as mechanical pressure, heat, cold and electrical stimulation (83). Studies have also demonstrated an increased temporal summation of painful stimuli applied to the skin or muscles in patients with fibromyalgia when compared to healthy controls (86). The results of such studies support the role of central sensitization mechanisms in the generation of widespread pain and pain hypersensitivity in patients with fibromyalgia. It is still debated, however, whether the maintenance of central sensitization requires persistent peripheral noxious input from deep somatic tissues, including a potential role of input from latent and active myofascial trigger points (87-89).

Whereas chronic degenerative muscle disorders are not painful, inflammatory myopathies may result in sensitization of muscle nociceptors and elicit pain. Hypoxia in combination with muscle activity as well as energy depletion can also cause pain. Thus, a large number of studies have examined muscle morphology (90-94), muscle microcirculation (91;95-98), and muscle energy metabolism (99-103) in patients with fibromyalgia. The muscle biopsy studies have shown that there are no specific changes conclusive for fibromyalgia (104). However, changes in the muscles, such as the observed mitochondrial changes, a change in the intramuscular microcirculation and/or a change in muscle energy metabolism might sensitize muscle nociceptors. As tonic impulses from nociceptive fibers can induce short- and long-term plastic changes in dorsal horn neurons, this could be the peripheral
Excitatory drive, responsible for maintaining central sensitization and pain hypersensitivity in fibromyalgia (16).

Evidence of abnormal cerebral pain processing

Neuroimaging techniques such as single-photon emission computed tomography (SPECT) and functional magnetic resonance imaging (fMRI) have provided further objective evidence of altered cerebral processing of painful stimuli in patients with fibromyalgia (78;79). One group of studies has evaluated the hallmark of tenderness in fibromyalgia, by using fMRI to demonstrate augmented sensitivity to painful pressure. These studies have demonstrated that in response to an equivalent pressure stimulus, patients with fibromyalgia showed increased activity in several pain related brain areas when compared to normal controls. Furthermore, that mild pressure applied to subjects with fibromyalgia elicited subjective pain and cerebral responses similar to the responses seen in normal subjects when twice as much pressure was applied (105). Another group of studies has evaluated the association of neural activation patterns with psychological variables such as depression and pain catastrophizing. Results from these studies indicate that, in patients with fibromyalgia, neither the extent of depression nor the presence of comorbid major depression modulates the sensory-discriminative aspects of pain processing, but seems to be associated with the magnitude of pain-evoked neuronal activations in brain regions associated with affective pain processing (106). Pain catastrophizing, independent of the influence of depression, was also found to be significantly associated with increased activity in brain areas related to heightened emotional, but not sensory, responses to pain (107). Abnormalities in some of the same brain regions have also been observed using magnetic resonance spectroscopy (MRS). For example, evidence of increased glutamatergic activity in the insula of fibromyalgia patients that correlated with measures of clinical pain (108). The insula is considered a limbic related structure and strongly involved in both pain and emotional processing. Together these studies suggest that pain in fibromyalgia is a result of sensory amplification, rather than just affective processing.

In addition to functional abnormalities, more studies have indicated significant regional reductions in gray matter density in the brains of fibromyalgia patients (78;79). Similar structural changes have been observed in other chronic pain states, such as chronic low back pain, as well as stress-related disorders. It has been speculated that structural changes may contribute to the impaired pain regulation, cognition, sleep and neuroendocrine function often described in patients with fibromyalgia (109). It is not clear, though, whether persistent pain is the cause of these morphological changes or whether altered brain morphology predisposes to the development of chronic pain. Either way, such findings underline the potential of chronic pain to be a neurodegenerative disease.

Evidence of abnormalities in descending pain modulation

Dysregulation of descending pain pathways, due to inadequate activity in the inhibitory pathways, excessive activity in the facilitatory pathways, or both, may contribute to the development and maintenance of pain hypersensitivity in fibromyalgia. Evidence for the role of abnormalities in descending pain pathways comes from experimental testing of conditioned pain modulation (110) and neuroimaging studies demonstrating reduced connectivity of descending pain inhibitory networks (111). Serotonin and noradrenalin are the principal neurotransmitters in the descending pain modulatory pathways, where they act by inhibiting the release of excitatory amino acids such as glutamate. Compromised neurotransmission in pain inhibitory descending systems are therefore
further supported by studies demonstrating low levels of monoamine metabolites in the cerebrospinal fluid from patients with fibromyalgia relative to healthy controls (112).

The monoaminergic system is closely linked to the opioidergic system, which is the most well-known anti-nociceptive pathway in the central nervous system. Activation of descending pain inhibitory pathways leads to opioid release in the spinal dorsal horns, where the analgesic effect is mediated. Evidence suggests altered opioid signaling in fibromyalgia, including decreased mu-opioid binding potential evaluated by positron-emission tomography (PET) imaging, a finding that may explain why opiate medications are often ineffective in reducing fibromyalgia pain (113). The role of descending facilitatory pathways in fibromyalgia has been less well addressed.

**Evidence of abnormalities in neuroendocrine, autonomic and immune functioning**

Although not entirely consistent across studies, abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis, autonomic nervous system and immune system are reported in patients with fibromyalgia. These abnormalities include insufficient glucocorticoid signaling, increased sympathetic and/or reduced parasympathetic tone and activation of innate immune inflammatory pathways. Such patterns of stress-immune system imbalance may provide physiological feedback to the brain, promoting the development of chronic pain, as well as maladaptive responses to stress (Figure 3).

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**Figure 3.** The complex interaction between endocrine, immune and emotion regulation systems and the pain signaling system.
Reduced HPA activity with decreased cortisol production, both at baseline and in response to a variety of stressors, has been reported in patients with fibromyalgia and other chronic pain disorders, including visceral pain syndromes (114). Further, in the context of chronic pain the diurnal rhythm of the HPA axis has been demonstrated to be flattened (115-117). Normalization of the cortisol slope, paralleling improvement of pain related symptoms, has been reported in patients with fibromyalgia enrolled in multidisciplinary rehabilitation (118).

The HPA axis is closely linked with the autonomic nervous system, which is involved in modulating sleep, mood, pain and cardiovascular activity. Disturbances in autonomic nervous system balance have been frequently reported in patients with fibromyalgia and may contribute to symptom development. Several authors have identified sympathetic hyperactivity as a component of the stress response that both precipitates and perpetuates fibromyalgia symptoms such as fatigue, sleep disturbance, anxiety, depression, gastrointestinal complaints and vasomotor instability, including orthostatic intolerance (119).

Such abnormalities in HPA axis and autonomic nervous system functioning may further contribute to disease pathology by perpetuating neuroimmune dysregulation and facilitating neurogenic inflammation. A consistent finding demonstrated in several studies appears to be elevations of excitatory neurotransmitters, especially substance P in the cerebrospinal fluid of patients with fibromyalgia relative to healthy controls (120;121). Much like the monoamine and opioid projections, the substance P system is present in several cortical and limbic regions involved in the stress response and the regulation of emotion and pain. The sensory function of substance P is thought to be related to the transmission of pain information into the central nervous system, and altered substance P transmission and subsequent dorsal neuron horn sensitization has been implicated in the pathogenesis of both fibromyalgia and neuropathic pain (122;123). Furthermore, substance P appears to occupy a key position in the bidirectional communication between the brain and the body. The release of substance P seems to be promoted by elevations of proinflammatory mediators, and C-fibers are also capable of retrograde release of substance P into peripheral tissues i.e. skin, muscle, and joints, which then contributes to ‘neurogenic inflammation’ mediated by proinflammatory substances, especially IL-8 (109). This reiterative loop may amplify and perpetuate chronic pain.

Elevated serum levels of IL-8 and TNF-alpha, correlating with clinical disease manifestations such as the reporting of pain and stiffness, have been demonstrated in patients with fibromyalgia (124;125). Enhanced inflammatory activity may be a widespread phenomenon in fibromyalgia, as proinflammatory cytokines e.g. TNF-alpha, IL-1 and IL-6 have been demonstrated in skin biopsies from fibromyalgia patients, but not in healthy controls (126).

Accumulating evidence also suggests that alterations in neuron-glia cell relationships may be of fundamental importance in the pathogenesis of chronic pain (127). Traditionally, glia cells have been viewed as a passive support matrix for neurons, but are increasingly recognized as playing an active role in neurotransmission through regulation of synaptic strength and plasticity. Recent research indicates that almost all classes of monoamine and cytokine receptors are expressed on glial cell membranes, and that glia cells themselves synthesize and release neurotropic factors, as well as pro-inflammatory cytokines. Altered neuron-glia cell interactions have been implicated in the genesis of neuropathic pain and may play a role in fibromyalgia. Supporting the notion of glia cell involvement in
fibromyalgia, high levels of IL-8 in the cerebrospinal fluid of fibromyalgia patients have been reported in a recent study (128).

**The link between fibromyalgia and other chronic pain states**

**Fibromyalgia in the spectrum of central sensitivity syndromes**

Influential in the development of the new symptom-based diagnostic criteria is the argument that fibromyalgia is best understood as part of a poly-symptomatic distress continuum and not as a categorical disorder (35). A contrary opinion is that fibromyalgia is both a categorical disorder and the end of a continuum of pain processing (17). Fibromyalgia has long been recognized to be associated with a larger spectrum of clinical entities, all characterized by the lack of obvious structural pathology at clinical examination (129). These overlapping conditions, which include several chronic regional and visceral pain syndromes such as irritable bowel syndrome (IBS), temporomandibular disorder (TMD), restless legs syndrome (RLS), tension headache, migraine, painful bladder syndrome, chronic pelvic pain, and various regional myofascial pain syndromes, have had many names, including functional somatic syndromes, medically unexplained symptoms (MUS), somatoform disorders, bodily distress disorders, etc. Also the term *central sensitivity syndromes* (CSS) (130), has been proposed as a common denominator, reflecting the hypothesis of central pain and/or sensory amplification as a unifying pathophysiological mechanism. In addition to pain and sensory amplification, other shared mechanisms may include neuroimmune, neuroendocrine, and autonomic nervous system dysfunction. Such disorders are probably the result of complex interactions between genetic susceptibility, peripheral pain generators, dysfunctional pain/sensory processing, psychological factors and environmental triggers combining and leading to a variety of signs and symptoms that cluster into the individual syndromes (Figure 4).

This underlying neurobiological connection may not only explain why patients with, for instance, visceral pain syndromes sometimes develop widespread pain hypersensitivity, but may also provide a rationale as to why these syndromes overlap with one another, as well as the co-occurrence of sleep alterations, fatigue, mood disturbance and cognitive impairment. The prevalence of fibromyalgia in patients with IBS is reported to be of around 40%, in tension-type headache 30%, in migraine 16%, and in painful bladder syndrome of about 15%. Furthermore, epidemiological studies have demonstrated that 75% of patients with fibromyalgia meet the TMD criteria, whereas 18% of TMD patients meet the fibromyalgia criteria (114).
Model explaining the development of Central Sensitivity Syndromes

![Diagram showing the model proposed by Yunus et al.](image)

**Figure 4.** The model proposed by Yunus et al. explaining the development of central sensitivity syndromes, reflecting the hypothesis of central pain and/or sensory amplification as a unifying pathophysiological mechanism.

**Fibromyalgia in the spectrum of neuropathic pain**

Mechanism-based pain classification refers to the classification of pain according to pathophysiological mechanisms presumed to be responsible for its initiation and/or maintenance. This concept has been introduced in the clinical setting in order to provide a more suitable approach for examining and classifying patients, with the ultimate goal of obtaining better treatment results (131). Nociceptive pain, neuropathic pain, and centrally mediated pain (i.e. augmented central pain processing) have been suggested as clinically meaningful mechanism-based classification of musculoskeletal pain (132). In the absence of any diagnostic gold standards, this approach is based on the assumption that mechanism-based classification of pain can be done clinically, based on identifiable and discriminatory patterns of symptoms and signs assumed to reflect the underlying pathophysiology.

The definition of neuropathic pain was revised in 2008, restricting the term ‘neuropathic pain’ to those pain conditions with a primary etiology clearly related to ‘injury or disease of the somatosensory system’, separating neuropathic pain from pain disorders characterized primarily by enduring abnormalities in central pain processing (133). However, despite obvious differences, including the spatial distribution of pain, there are striking phenotypic similarities between neuropathic pain and pain in fibromyalgia, namely how patients express their abnormal sensory perceptions and in particular the quality of their pain. Besides spontaneous pain in the muscles and joints, patients with
fibromyalgia often report hypersensitivity of the skin to mechanical or thermal stimuli, and burning or pricking sensations as well as neuralgic pain attacks. Several studies, applying instruments developed to assess pain qualities traditionally associated with neuropathic pain have demonstrated such neuropathic features in fibromyalgia, as well as that the presence and number of tender points are associated with neuropathic pain symptoms (134-136). Current scientific evidence suggests that both neuropathic pain and pain conditions characterized primarily by augmented central pain processing, such as fibromyalgia, may share similar and very complex neurobiological underpinnings including abnormalities in limbic, neuroendocrine, autonomic nervous system and immune functioning, in addition to sensitization of pain transmitting neurons. Given that these neurobiological underpinnings give rise to clinical symptoms, it is not surprising if centrally mediated pain and neuropathic pain may share common clinical features.

Whereas the central nervous system has been extensively studied in patients with fibromyalgia, only few studies have focused on peripheral nervous involvement (137;138). However, findings from recent studies indicates the possibility of involvement of small fiber neuropathy in subsets of patients (139-142). In a study by Uceyler et al., the function and morphology of small nerve fibers in patients with fibromyalgia were examined by quantitative sensory testing, pain-related evoked potentials, and quantified nerve fiber density in skin punch biopsies, and compared to findings in patients with major depression and healthy controls (142). Fibromyalgia patients showed increased scores on neuropathic pain questionnaires, and the majority had pathological findings in more than two small fiber tests. The observed neurophysiological and psychophysiological hypo-function was morphologically paralleled by reduction in dermal unmyelinated nerve fiber bundles, whereas myelinated nerve fibers were spared. These findings point towards a possible pathological process involving peripheral C-fibers in fibromyalgia, and the authors argued that pain in fibromyalgia should be classified accordingly (142). Caro et al. also reported reduced epidermal nerve fiber density in skin punch biopsies at both the calf and thigh in patients with fibromyalgia as compared to healthy controls. Calf epidermal nerve fiber density was inversely correlated, although weakly, with serum levels of interleukin-2 receptor (IL-2R). The authors concluded that these findings suggest that small fiber neuropathy is likely to contribute to the pain symptoms of fibromyalgia; that pain in this disorder arises, in part, from a peripheral immune-mediated process; and that measurement of epidermal nerve fiber density may be a useful clinical tool in fibromyalgia (139). Microneurography provides a direct means of recording the action potentials of C fibers and to test whether C nociceptor function is abnormal. In a recent study by Serra et al., microneurography was used to record C nociceptors of 30 female patients meeting the 1990-ACR criteria for fibromyalgia compared with recordings from 17 female patients with small fiber neuropathy and nine female controls (143). The study showed that the majority of fibromyalgia patients had abnormal C nociceptors. Many mechanoinsensitive, normally silent nociceptors exhibited hyperexcitability resembling that in small fiber neuropathy, but high activity -dependent slowing of conduction velocity was more common in fibromyalgia patients and constituted a unique feature. The authors concluded that abnormal peripheral C nociceptor ongoing activity and increased mechanical sensitivity might contribute to the pain and tenderness constituting the defining features of fibromyalgia (143). Even if small fiber neuropathy only is found in a subset of patients, thinking of fibromyalgia in the spectrum of neuropathic pain seems reasonable, since the pathogenesis of this pain condition has more in common with neuropathic pain than the typical nociceptive musculoskeletal pain disorders.
Fibromyalgia in the spectrum of inflammatory pain

Increasing evidence supports the contention that central pain mechanisms may play an important role in rheumatologic diseases, traditionally considered peripheral inflammatory entities (144). Although peripheral mechanisms of nociception significantly contribute to the generation of pain in these disorders, the contribution of spinal, as well as supraspinal, mechanisms to pain generation is probably essential. Inflammation sensitizes polymodal nociceptors. This peripheral sensitization induces hyperexcitability of nociceptive neurons in the central nervous system (central sensitization) and the two together generate the features of pathological pain, allodynia and hyperalgesia, confined to the inflamed tissues. Furthermore, pro-inflammatory cytokines, such as TNF-alpha and IL-6 not only promote and maintain inflammation, they also contribute to the generation and maintenance of inflammatory pain by acting at nociceptive neurons in the central nervous system (70). Increased responsiveness of peripheral and central neurons (pain hypersensitivity) in the presence of tissue injury and inflammation is a normal response. The key question is whether augmented central pain processing persists in subsets of patients and leads to chronic pain states in which pain is no longer coupled to the presence of ongoing peripheral inflammation.

With earlier initiation of disease-modifying therapies and the development of targeted immune-modulating agents, disease remission or minimal disease activity has become the target of treatment in patients with inflammatory diseases. However, on a population level, mean pain ratings have remained the same for the past 20 years, in patients with rheumatoid arthritis for instance, and a substantial subgroup of patients continues to report moderate to severe pain levels (145). Furthermore it has been shown that rheumatoid arthritis leads to widespread pain and pain hypersensitivity (i.e. fibromyalgia) in 10-20 % of patients (146;147) and that this phenomenon is associated with poorer outcome of the disease (147). A comparable high prevalence of fibromyalgia has been reported in patients with other established autoimmune or rheumatic disease, e.g. psoriatic arthritis, spondyloarthritis, Systemic Lupus Erythematosus (SLE), and Sjögren's disease (148). If central pain mechanisms do play a significant role in pain processing and persistent pain in subgroups of patients, strategies in addition to inflammatory disease suppression are required to adequately treat the pain.

Fibromyalgia in the spectrum of affective disorders

There is considerable evidence supporting the activity of mechanisms of psychological distress in amplifying pain, compromising adaptation to pain, and acting as a stressor, thereby causing worsened distress. Further, a prior history of psychological trauma, anxiety and depression is significantly predictive of onset of chronic pain later in life (149;150). The common denominator for chronic pain, anxiety, and depression is the central nervous system. All three are conditions of the central nervous system, particularly of a persistently altered central nervous system, with shared patterns of dysregulation in circuitries involved in modulating emotion, pain, and stress responses. Analogous candidate genes have been evaluated in patient populations with chronic pain and with depression (151), and immune mechanisms, including pro- and anti-inflammatory cytokine activity, are areas of investigation in both conditions (109). Neuroimaging studies also support the pain/depression interface by demonstrating overlapping functional changes in areas of the pain matrix involved in emotional and cognitive aspects of pain processing as well as structural changes, such as hippocampal and gray matter atrophy in both conditions (152). When viewed as separate diagnostic entities they
clearly exist in complicated bidirectional relationships, such that depression may give rise to altered pain processing, and alterations in pain processing may promote affective states conductive to the development of depression (109).

Several studies support the association between CWP and depression (7;153). In fibromyalgia, the lifetime prevalence of depressive symptoms is reported to be 90%, and 30-86% for major depressive disorder (154). This association of fibromyalgia with depression is, however, most prominent in tertiary care samples and dependent upon criteria for depression (155). The high occurrence of depression in fibromyalgia has led to many years of debate as to whether the conditions are most parsimoniously considered as separate illnesses with high comorbidity, or as differential symptom presentations of a single underlying condition. Some has argued that fibromyalgia should be classified as an affective spectrum disorder (154;156); others that fibromyalgia is best understood as part of a poly-symptomatic distress continuum, where distress is operationalized as some combination of somatic symptoms and symptoms of anxiety and depression (35). Furthermore, available evidence suggests that coexistence of depressive symptoms in patients with fibromyalgia is associated with increased pain intensity, more functional disability, and poorer health-related quality of life (157), as well as poor treatment results (158).

The core symptoms of fibromyalgia, including pain and fatigue, are also possible symptoms of depressive disorders. Among patients with depressive disorders, 30-60% report pain (159) and in a clinical study, it was shown that 13% of patients with Major Depressive Disorder (MDD) also fulfilled the 1990-ACR criteria for fibromyalgia (160). It has been suggested that the proneness of patients with MDD to develop chronic pain results from a deficit in pain inhibition (109). In a study comparing patients with fibromyalgia and MDD, in their respective responses to thermal noxious stimuli, it was shown that hyperalgesia was present in both conditions but was more pronounced in fibromyalgia, and that deficiency in descending pain modulation seemed to be specific to fibromyalgia (161). Despite a partial overlap in symptoms and possible shared neuroendocrine mechanisms, evidence supports the proposal that MDD and fibromyalgia are distinct and separable diagnostic entities and should not be regarded as variants of the same disease (162). Depression is prevalent in many chronic diseases, including pain conditions with objectively confirmable pathology, such as neuropathic pain, where the prevalence of MDD is reported to be of about 30% (163).

**Disability in CWP and fibromyalgia**

Fordyce (1976) originally introduced the concept of operant pain behavior and argued that pain behavior should be the focus of treatment rather than pain per se or the presumed underlying cause of pain. He recognized the limitations of continuing to treat chronic pain as if it was acute, emphasizing that ‘when pain continues for an extended period of time, there are ample opportunities for pain behaviors to come under the influence of environmental contingencies’ (68). The early work of Fordyce and colleagues was at once novel and controversial. Critics voiced their concerns that behavioral treatments might only be effective in training stoicism, and were not dealing with the underlying problem. In response, Fordyce pointed to the literature indicating at best a modest association between pain and disability, and that treatments aimed at reducing pain often had no significant effect on level of disability (164). According to Fordyce, the disability had to be targeted
directly, in order to be treated effectively. Fordyce’s prominent work has continued to influence research and theory on behavioral dimensions of pain, and has been pivotal in the development of biopsychosocial models of pain and modern pain management. Fordyce stressed the need for a functional analysis of pain behavior and the identification of systematic interactions between occurrence of pain behaviors and environmental factors as an alternative to intra-psychic explorations (165). By moving the primary focus of unexplained ‘chronic pain from the intra-psychic realm (psychopathology) to the wider social context in which pain occurs, Fordyce paved the way for new ways of addressing pain-related disability. Behavioral outcome domains defined by Fordyce: decreased pain behavior, increased activity level, increased well-behavior (e.g. return to work), and decreased pain-related healthcare utilization could broadly be encompassed under the rubric of improved adaptation or coping. However, modern pain psychology mandates the consideration also of cognitive and emotional factors and processes, whether at a perceptual or neurophysiological level. Since 1976 a wide range of more pain-specific cognitive constructs, such as catastrophizing, self-efficacy, pain-related fear, and acceptance and readiness for change have emerged within the pain literature and prompted further development of cognitive-behavioral models for the treatment of pain and pain-related disability.

CWP and fibromyalgia carries a high level of disease burden, including disability affecting daily life tasks and social participation. In an internet-based survey, conducted in a sample of 1,735 women aged 31-78 years and diagnosed with fibromyalgia, the average woman reported having less functional ability related to activities of daily living than the average, community-dwelling woman in her eighties. More than 90% of the women reported having difficulty doing heavy household tasks; more than 60% reported difficulty doing light household tasks, and 25% reported having difficulty taking care of personal needs and bathing (25). However, pain interference with functional ability is complex and research suggests a significant heterogeneity and differences in for example adaptation to pain across different subgroups of patients (166). There is now ample evidence that patients with chronic pain are quite heterogeneous and have different combinations of biological, cognitive, behavioral and affective contributions to their experience of pain and disability (69). Based on such factors, the person may choose to ignore the pain and continue working, socializing, and engaging in previous levels of activity or may choose to leave work, refrain from all activity, and assume the sick role. In turn, this interpersonal role is shaped by responses from significant others that may promote either the healthy and active response or the sick role.

Thus, pain-related interference with functioning, whether it relates to basic ADL-tasks or more complex life domains such as work, does not occur directly because of a particular pain diagnosis or pain generator. Some individuals are able to accomplish adjustments on their own; others require assistance to accommodate their lives. The never-ending search for the cause of pain, combined with delayed active intervention, has probably been an important factor in leading to preventable long-term disability in many individuals and greater costs for society. In support of this notion, Henriksson et al., using semi-structured interviews found that in women with fibromyalgia the seemingly discrepancy between the patients’ perception of illness and the lack of objective findings produced increased distress and maladaptive pain coping. The women felt rejected, misunderstood, and disbelieved, which prevented them from dealing with their life situation in a constructive manner. Lengthy periods of medical investigation with negative outcomes was reported to provoke anxiety, and the women experienced further loss of ability to perform valued activities, lack of physical fitness and loss of future opportunities (167).
Work disability is a serious concern in patients with CWP and fibromyalgia at both the individual and societal level and incurs significant indirect medical costs, e.g. sick leave and disability compensation (24;168). It is reported that among fibromyalgia patients encountered in tertiary care settings, approximately half are employed at the time of referral, 15% in a full-time position, and 25% are receiving disability compensation (169). However, only a limited number of studies are available to provide meaningful directions for intervention. Most of the existing studies are conducted on selected patient populations; mainly females between 30 and 60 years of age, excluding participants with pending social welfare litigation, and few data are available on the socioeconomic outcomes of intervention, including changes in patients’ work status (170). The following predictors of work disability have been identified in a longitudinal multicenter survey: pain, self-reported functional ability, and unmarried status (168). Furthermore, in a Finnish twin cohort study, the burden of fibromyalgia-associated symptoms was shown to strongly predict early retirement due to disability (171). Work-related variables like heavy workload or low decision authority, previously identified as risk factors for early retirement, as well as education and social class, had only marginal effect in this study. The authors concluded that one possible explanation was that subjects with fibromyalgia had already chosen occupational tasks suited for their health condition, or that patients with the most severe symptoms had already been selected out of the workforce at baseline (171). Although working patients with fibromyalgia have generally less severe symptoms and better quality of life than those unemployed, it cannot be inferred that remaining in the workforce improves health status (172). Early intervention and individual adjustments in the work situation matching the level of ability, however, may improve retention in employment (24;169).

Prolonged litigation in fibromyalgia-based disability claims in relation to welfare payments is unfortunately more the rule than the exception. The latter difficulty seems to arise from a continued prejudice and skepticism regarding the validity of the diagnosis of fibromyalgia and a continued misconception that pain and pain-related disability should be documented based on the extent of observable tissue pathology. The individual patient’s concept of illness as well as the perceived attitude of the healthcare system strongly affects global well-being. Well-defined criteria for disability in patients with fibromyalgia, based on standardized assessment methods, therefore seem important. Observation-based assessment of the ability to perform activities of daily living (ADL) may reflect disease impact, as described later, but has not yet been related to work prognosis in patients with fibromyalgia.

**Assessment of patients with CWP and fibromyalgia**

**Assessment of chronic pain patients – aspects of measurement structure and instrumentation**

CWP presents a unique challenge to clinical practice, as well as outcome research, due to its complexity and the central importance of patient-reported information. There is broad agreement that the assessment of patients with chronic pain should occur within a multidimensional framework, and many instruments have been applied to assess the impact of pain on patients’ lives. Ideally, such instruments should be reliable and validated for use in chronic pain populations, provide relevant information to all clinicians to formulate a treatment plan, allow for evaluation of the outcome of intervention and be sensitive enough to detect change at both group and individual levels. In recent years, several initiatives have been launched to establish international consensus on the conceptual framework and scope of assessment of chronic pain to increase consistency and comparability across
patients and clinical trials. Working groups have been formed within the pain field (the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), the field of rheumatology (the Outcome Measures in Rheumatology Clinical Trials (OMERACT)) and rehabilitation. Recommendations from these working groups range from which domains to assess to endorsement of specific assessment tools (173-175). Self-report instruments provide the ‘gold standard’ in assessing pain outcomes because they reflect the inherently subjective nature of pain. However, many of the self-report instruments currently used to assess the domains of relevance have been developed and validated for use in other patient populations. It is plausible to suspect that adopted instruments are suitable for use in for example patients with CWP and fibromyalgia, but support of this suitability needs to be based upon performance within this specific patient population. Reliability, validity, and responsiveness can be condition or context specific, and are not invariant properties of an assessment tool. The benefits of adapting core outcome domains in clinical research on chronic pain, including CWP and fibromyalgia, would therefore be augmented by the identification and development of optimal instruments for assessing them.

A critical consideration in evaluating existing instruments used for outcome assessment, as well as when developing new or improved instruments, is how much change represents a clinically important difference. Depending on the specific outcome, clinical importance and meaningfulness can be assessed by patients, clinicians, significant others, and representatives of society at large (176). Such individual-level criteria make it possible to conduct responder analyses that classify each trial participant as improved, stable or worse, and provide a basis for evaluating and comparing the impact of interventions on patient-reported symptoms, functioning, well-being, and overall health-related quality of life. Methods for determining criteria for important change have been classified as either ‘anchor based’ or ‘distribution based’ (177). Anchor-based methods relate changes in scores or measures to a standard that is different from the specific measure itself, for example a global improvement item completed by the patient as the anchor for within-person changes during the course of the trial. Distribution-based methods use statistical parameters associated with the specific measure itself (e.g. effect size, standard error of measurement) to interpret the magnitude of changes in the measure’s scores over time (176;178;179). A 0.5 effect size (i.e. one-half the standard deviation) has been reported to be a reasonable criterion to use when evaluating important changes in patient reported outcomes, including pain and physical and emotional functioning (178). Important concerns about the effect size criterion for identifying important difference involve the fact that the standard deviation is specific to a particular sample and that the reliability of patient-reported outcomes can be modest (i.e. substantial error). Further, it has been demonstrated that the level of change in for example pain that is considered clinically important is influenced by baseline pain, and may also vary by age, the patient’s clinical condition, and prior treatment response (180). Definitions of clinically important changes may therefore vary by population and context (181). Kouil et al, evaluating the relationship between the patient’s perception of treatment gain (improvement, satisfaction and usefulness) and patient-reported pre-post changes in the core outcome domains of pain, fatigue, functional disability, and negative mood during a tailored multidisciplinary intervention program for patients with fibromyalgia, found only a moderate relationship, particular with regard to psychological functioning. The authors concluded that the patient’s perception of treatment gain and pre-post changes in self-reported outcomes assess different aspects and should not be used interchangeably (182).
Evaluation of disease severity from a rheumatologic perspective – the OMERACT initiative

The Outcome Measures in Rheumatology Clinical Trials (OMERACT) initiative was established to resolve the problem of measurement variability in rheumatic diseases, including fibromyalgia, by defining core data sets that should be collected and reported in randomized controlled trials. Based on consensus processes by clinicians and patients (175;183) and confirmatory processes by analyses of clinical trials (184;185), a core domain set for fibromyalgia assessment in clinical trials and practice was established and ratified by the OMERACT. Domains considered essential to assess included pain, tenderness, fatigue, patient global assessment of change, ‘multidimensional’ function, and sleep disturbance. Other important domains included depression, cognitive dysfunction, stiffness and anxiety (185). Following development of the core domain set for fibromyalgia, the OMERACT working group has progressed toward the development of a fibromyalgia responder index based on these domains, utilizing outcome indices from archived randomized clinical trials (186).

Acknowledging that there is no clear algorithm that defines disease activity or treatment decisions based on disease activity, nor are there objective markers that define thresholds of severity or response to treatment, the approach used in the development of responder indices and disease activity scores for rheumatoid arthritis represented explorative models for the work (186). The aim was to combine key symptom and function domains into a responder definition, using the most commonly applied self-report instruments across fibromyalgia clinical trials; primarily the Fibromyalgia Impact Questionnaire (FIQ) (187) and the SF-36 (188;189).

Explorative candidate responder definitions included four different levels of overall improvement in fibromyalgia symptoms; ≥ 20% (FM20), ≥ 30% (FM30), ≥ 50% (FM50) and ≥ 70% (FM70). Two definitions performed best in the analyses. Both definitions included ≥ 30% reduction in pain scored on either a numeric rating scale or a visual analog scale and ≥ 10% improvement in physical functioning evaluated by the physical functioning subscale of the SF-36. The definitions differed in that one (≥ 30% improvement in fibromyalgia; FM30 short version) included ≥ 30% improvement in sleep or fatigue, while the (FM30 long version) required ≥ 30% improvement in two of the following symptoms: sleep, fatigue, depression, anxiety, or cognition (190).

In the analysis of both versions across clinical trials, the response rate was ≥ 15% for each medication and was significantly greater than placebo. The FM50 and FM70 candidate definitions had few responders across all of the medications and were excluded from further analyses (190). Consensus on the appropriateness of the proposed responder definitions has been obtained from the OMERACT (186), but studies are still needed to explore their usefulness in future clinical trials, including non-pharmacological interventions. Further studies concerning valid assessment methods for the evaluation and monitoring of disease severity are at present carried out within in the auspices of the fibromyalgia OMERACT working group.

Evaluation of disease severity using the ICF as theoretical framework for assessment

The World Health Organization’s (WHO) International Classification of Functioning, Disability and Health, known more commonly as the ICF, provides a standard language and framework for the description of functioning, disability, and health and may therefore serve as a reference when defining clinical disease severity (191). The unit of classification in the ICF is categories that are systematically grouped within the following domains: the domain of the body (body functions and structures), the domain of activity (execution of tasks) and the domain of participation (involvement in life situations). The ICF is not an assessment tool; rather it provides a conceptual framework within which to classify
aspects of individuals' functioning. Thus, the ICF may serve as a framework on which tools for assessing functioning, disability, and health may be based, and to which such tools can be mapped. The broad framework puts assessment in context and provides the focus for selecting relevant aspects of functioning, disability, and health for assessment. This means that the focus of assessment can be on some or all the different parts of the ICF; the body domain, activity domain, or domain of participation, but considering the effects on the individuals' functioning.

![Diagram of the ICF model](image)

**Figure 5. Interactions between the components of the International Classification of Functioning, Disability and Health (ICF) (191).**

Rooted in a bio-psychosocial paradigm, the ICF conceptualizes disability and functioning as outcomes of interactions between health conditions (diseases, disorders and injuries) and contextual factors. Among contextual factors are external environmental factors (for example, social attitudes, healthcare systems, legal and social structures, as well as climate, terrain and so forth); and internal personal factors, which include gender, age, coping styles, social background, education, profession, past and current experience, overall behavior pattern, and other factors that influence how disability is experienced by the individual. Figure 5 identifies the three domains of human functioning classified by ICF: the body functions and structures of people (physiological functioning of the body including psychological function), and impairments thereof; the activities of people (functioning at the level of the individual) and the activity limitations they experience; the participation or involvement of people in all areas of life, and the participation restrictions they experience (functioning of a person as a member of society); and the interaction with contextual factors (personal and environmental factors), which affect these experiences and may act as facilitators or barriers. Thus, according to the ICF model, disability is an umbrella term for impairments, activity limitations, and participation restrictions.
referring to the negative aspects of interaction between an individual with a given health condition and that individual's contextual factors (191).

Persistent pain may be classified as a significant deviation from normal function of the somatosensory system - a severe sensory impairment - that enables the use of the ICF to describe pain-related activity limitations and participation restrictions (192). As illustrated in Figure 6, impairments, activity limitations and participation restrictions interact in an integrated manner with the contextual factors of the individual and accounts for the complex clinical presentation seen in patients with long-standing pain.

From a clinical stance, it makes more sense to define targets for assessment and management by deriving them for the ICF approach; assessing the pain category and its characteristics (the sensory impairment) as well as the activity limitations and participation restrictions in that individual in his or hers context, and to focus pain management on those persons who are distinctly limited and restricted by their pain. Based on the ICF, international recommendations for the assessment of a number of musculoskeletal pain disorders have been developed (193), including definition and validation of ICF core sets for patients with CWP (173). ICF core sets represent a selection of ICF categories relevant for specific conditions and serve as standards for the multidimensional assessment of patients for clinical encounters and trials. Efforts to validate the ICF core set for CWP based on statistical models.
(194;195), and from the patient perspective using focus group methodology (196) as well as content comparison with frequently applied assessment instruments are reported in the literature (197;198).

**Assessment of functional ability from the perspective of rehabilitation**

Although functioning is considered a core outcome domain in clinical pain research, there are different understandings of the term functioning and no consensus on which assessment tools to use. In most studies addressing patients with CWP and fibromyalgia, self-reporting of functional ability using generic or disease specific questionnaires or performance-based evaluations, assessing body functions (e.g. muscle strength) or aspects of mobility (e.g. walking ability), seems to be the gold standard (199;200).

According to the ICF, human functioning and its complementary notion disability are understood as experiences of people in the context of their personal resources, in relation to health conditions and in interaction with the environment (191). This means that disability is not a static condition, but an experience that involves some or all the different parts of the ICF; impairment at the body level, limitations in activities, and restrictions in participation. The focus of rehabilitation is human functioning and knowledge about the determinants of disability is critical in order to provide goal-directed rehabilitation and obtain improvements in functional ability. Consequently, there is a need of psychometrically robust assessment tools that are able to capture the impact of chronic pain on more complex aspects of functioning than the underlying body capacities in individuals with CWP.

Questionnaire-based, self-reporting of functional ability evaluates the amount of perceived difficulty, which may be related to other factors associated with the pain problem, including patients’ pain-related beliefs and ability to adjust to chronic pain. Supporting this notion, studies on chronic pain populations have demonstrated a poor agreement between self-report and observation-based assessment, and the influence of pain and psychological distress variables on self-reported functioning (201-204). Observation-based assessment of functional ability could therefore prove a valuable addition to questionnaire-based assessment in the clinical setting - to determine the nature and extent of disability, assist setting goals and plan for interventions focused on improving functional ability - and in clinical trials focusing on functional outcomes.

**Assessment of depression in chronic pain populations**

Consideration of the relationship between depression and chronic pain cannot be contemplated without clear conceptualizations of each, and how to evaluate or assess them. Depression is a broad and heterogeneous diagnosis. Central to the concept of depression is depressed mood and/or loss of pleasure in most activities. The assessment of emotional functioning in patients with chronic pain, however, is challenging because common symptoms of depression – such as fatigue, sleep disruption, memory and concentration deficits, and reduced activity – overlap with clinical features of chronic pain. It is unclear whether the presence of such symptoms in patients with chronic pain (and other medical disorders) should be considered evidence of depressed mood, or whether the assessment of mood in these patients should emphasize symptoms that are less likely to be secondary to somatic disorders.
There are two main approaches to the evaluation of depression in clinical and research contexts. One approach is categorical, whereby a patient’s symptoms (derived from an interview) are summed and if they meet a criterion number, the person concerned is judged to be depressed. This is also known as a diagnostic approach using established classification systems, for example the ICD-10, DSM-IV, or the recently revised DSM-5 criteria (205). A formal diagnosis using the ICD-10 classification system requires at least four out of ten depressive symptoms, whereas the DSM-IV and DSM-5 system requires at least five out of nine for a diagnosis of major depression. Both diagnostic systems require at least one (DSM-IV, DSM-5) or two (ICD-10) key symptoms (low mood, loss of interest and pleasure, or loss of energy) to be present at sufficient severity for most of every day. The other main approach to evaluating depression regards it as a dimension, ranging from low to high, and everyone can be located at some point along this dimension according to severity or number of symptoms checked on a self-report scale. Cut points may be used on these scales to equate with diagnosed depression or categorize the severity of depression. However, widely used self-report questionnaires, designed to identify and quantify symptoms of depression, are developed and validated for use in normal and/or mental health populations. Several authors have therefore pointed out that somatic items included in these instruments may compromise measurement properties and risk inflation of the total score by somatic complaints unrelated to mood, when applied in chronic pain populations (206;207).

A related issue to the evaluation of depression in pain patients concerns the concept of depression in this context. Typically patients with depression encountered in psychiatric settings display hopelessness, worthlessness, and suicidal thoughts. The focus of depression in the context of pain seems to focus more on low mood, somatic symptoms, and the consequences of disability (208;209). A need for new models describing the complex interaction between depression and chronic pain, and a reconsideration of what constitutes depression in the presence of chronic pain, has therefore been pointed out by several authors (206;208;210). However, such new models cannot be derived without the use of valid and reliable assessments of depression in chronic pain populations. The notion of a common core of pain-related somatic symptoms contributing to high scores on depression rating scales in chronic pain patients is supported by a study analyzing the factor structure of the Beck Depression Inventory (BDI) in a large sample of chronic pain patients (210). In this study, two factors emerged. Factor 1 consistently included items reflecting negative evaluations of the self, on which most patients scored relatively low. Items loading on factor 2 were predominantly concerned with somatic and physical function, on which most patients scored at least moderately. Based on these findings, Morley et al. concluded that the factor structure meant that despite relatively high total BDI scores in the sample, the content of the scores showed relatively little of the cognitive beliefs characterizing depressed patients without chronic pain. Further, that ‘the BDI cannot measure depression in chronic pain patients, but instead may be a useful tool for considering components of cognitive, affective and behavioral distress’ (210).

Instruments omitting somatic and some cognitive items (guilt, suicidal thoughts), such as the widely used Hospital Anxiety and Depression Scale (HADS) (211), have been developed specifically to assess anxiety and depression in individuals with somatic illnesses, and are recommended for use in chronic pain populations (212). However, psychometric studies indicate that although the HADS may be a clinically useful scale of emotional distress, its ability to differentiate between the constructs of anxiety and depression is unclear, which means that its use needs to be targeted to more general assessment of distress (213).
Few studies have specifically considered what changes in scores on self-report depression scales would constitute important improvement in clinical pain trials. Based on its extensive use in pain research and responsiveness to changes in clinical pain trials, the BDI is recommended by the IMMPACT group for evaluation of depression in clinical pain research (174). Three different approaches have been suggested to determine clinically important changes in BDI scores (176). One is to consider a patient to have shown important improvement when the BDI score falls into the ‘normal’ range. However, given what may be limited effects of existing pain interventions on emotional functioning, requiring normal levels of depression as an outcome appears to be too conservative (208). A second approach would be to consider that important change has occurred when a patient shifts to a less severe category of depression. Shifts between categories of depression may be a relatively arbitrary criterion of important change, especially when pain clinical trials do not specifically target emotional functioning. Finally, based on the existing literature, applying one-half of a standard deviation could be considered a reasonable estimate of clinically important change (176).

Management of patients with CWP and fibromyalgia

Management of fibromyalgia according to existing clinical guidelines

Throughout the years, several professional organizations have published evidence-based clinical guidelines for the management of fibromyalgia (37-47;214-216), and reviews reporting on consistencies and differences across guidelines are available (48;217). Recognizing, that currently there is no cure for fibromyalgia, symptom-based management aiming at symptom reduction and maintenance of optimal function is recommended by most of these guidelines, and ideally management should include both non-pharmacological and pharmacological treatment strategies (37;39;47). There is, however, limited information on the effectiveness of combination of non-pharmacological and pharmacological interventions in this patient population (218).

Pharmacological interventions

All recommendations for the pharmacological treatment of fibromyalgia now propose classes of medications, such as antidepressants and anticonvulsants, which target central pain processing mechanisms (219-221). Several of these drugs have been tested in controlled trials for their efficacy in fibromyalgia, and meta-analyses have been written on most of these interventions (222-228). Generally, these meta-analyses have revealed that overall effect sizes are modest; a minority of patients will have substantial benefit (patient reported pain relief of 50% or greater), and more will have moderate benefit (patient reported pain relief of 30% or greater). Many will have no or trivial benefit, or will discontinue because of adverse events. However, it appears that even moderate reductions in pain may lead to considerable increase in self-reported quality of life and other outcome domains in this specific patient population (229;230).

It is well documented that serotonin noradrenalin reuptake inhibitors (SNRIs) are effective in some patients with fibromyalgia. These antidepressants reduce pain, fatigue, and improve sleep and quality of life in patients obtaining clinical benefits (222;223). They work by inhibiting the reuptake of serotonin and noradrenalin in the central nervous system - the principal neurotransmitters in the descending pain modulatory pathway - and may therefore be effective in conditions characterized by loss of descending pain inhibitory activity (231). The U.S. Food and Drug Administration (FDA) has
approved two SNRIs, duloxetine and milnacipran, for the treatment of fibromyalgia. The data on tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) are based on early studies and generally with small sample sizes. Study design has improved considerably over the years and primary endpoints have changed with more emphasis on global health status rather than focusing on any single symptom. There are some evidence that amitriptyline does improve sleep and give moderate pain relief to some patients with fibromyalgia, but most will fail to achieve beneficial outcomes (225). SSRIs are poor agents to provide analgesia in most pain conditions, including fibromyalgia (17).

The αsδ ligands, gabapentin and pregabalin, are anticonvulsants used in the treatment of neuropathic pain (232). Meta-analysis of the trials with gabapentin and pregabalin also showed effects on reduction of pain, improved sleep, and quality of life in some patients with fibromyalgia (224;227;228). Gabapentin and pregabalin bind potently to the αsδ subunit of voltage-gated calcium channels in neurons, reducing depolarization-induced calcium influx at the nerve terminals and, consequently, the release of several excitatory neurotransmitters including glutamate, noradrenalin, and substance P (232). These compounds may therefore be effective in conditions characterized by central sensitization, as well as decreased activity in descending pain modulatory pathways. Pregabalin was the first drug to receive FDA approval for the treatment of fibromyalgia in the USA.

Tramadol has been shown to have some beneficial effects in fibromyalgia (233). It acts centrally and inhibits serotonin noradrenalin reuptake, while also binding to the mu-opioid receptor. The use of opiate analgesics in chronic musculoskeletal pain is, however, controversial and a recent prospective cohort study indicate that opioid use, including tramadol, is associated with negative health related outcomes in fibromyalgia (234). Other analgesics, including NSAIDs, are reported to be ineffective in the treatment of pain in fibromyalgia (17). As for other chronic pain conditions there is a lack of head-to-head trials comparing efficacy and side effects of medications used in the treatment of fibromyalgia. In one study comparing the drugs licensed by the FDA for fibromyalgia - duloxetine, milnacipran, and pregabalin – adjusted indirect comparisons indicated no significant differences in 30% pain relief and dropout rates due to adverse events for these three drugs. Side effect profiles, however, differed (235). No medications, including the FDA-licensed drugs, have gained European Medicines Agency (EMA) approval, thus creating a significant trans-Atlantic difference in the pharmacological management of fibromyalgia. However, based on the modest effect of currently available drugs, high prevalence of adverse effects, and poor record of continued use, pharmacological intervention as the sole strategy for the management of fibromyalgia should be discouraged.

Non-pharmacological interventions

No single non-pharmacological treatment strategy has been demonstrated to outperform others, and patient education/psychoeducation, exercise activity, and psychological intervention, either as single interventions or combined in a multimodal approach, are recommended, depending on the severity and complexity of the clinical condition (37;39;47). However, there are no studies at hand to validate the recommendation of a scaling of the treatment intensity based on case severity or guide the needed duration of therapy or follow-up in ‘difficult to treat’ patients. The importance of including relapse prevention strategies in multidisciplinary pain treatment programs in order to increase the likelihood of maintained or even increased gains after treatment have been emphasized, but little research has examined this aspect (69).
Coping with symptoms includes the acceptance of symptoms and of some activity limitations as well as continuous self-management (169). Non-pharmacological intervention strategies with active patient participation and patient education, encouraging self-management (e.g. physical activity and stress reduction), are therefore recommended by evidence-based guidelines to be an integral component of the therapeutic plan for the management of fibromyalgia (37;39;47).

Exercise approaches to fibromyalgia recommended by clinical guidelines mainly include physiotherapy (37;46;47). Several exercise reviews have been published evaluating the effectiveness of aerobic (land or water-based), strength, and flexibility training and various combinations of these exercise modalities. There is high quality evidence that supervised, moderate aerobic land- and water-based exercise has medium-sized positive effects on pain, small to medium-sized positive effects on global wellbeing and medium-sized positive effects on physical performance (aerobic fitness) if provided at a frequency of two to three times a week for at least four to six weeks (236;237). The evidence for effect of strengthening and flexibility exercises is less clear as studies are rated as low quality (236). Based on the available evidence (rated as low quality) it is suggested that moderate- and moderate to high resistance training for 16 to 21 weeks improves functioning, pain, tenderness and muscle strength in women with fibromyalgia (236;238). No information on the effect of aerobic and resistance training in males with fibromyalgia is available. The evidence (rated as low quality) also suggests that eight weeks of aerobic exercise is superior to moderate-intensity resistance training for improving pain in fibromyalgia (238). However, there are several limitations of exercise studies in fibromyalgia. Fundamental to application of exercise as an intervention is the requirement that exercise must be well tolerated by individuals with fibromyalgia. Attrition rates are reported to be high in most studies (range 13-44%) and adherence to both exercise intensity and frequency is rarely well documented (236;237). Information on adverse effects is variable, with some studies reporting vague effects (e.g. increased stress) and others attributing high attrition rates to exacerbations of typical signs and symptoms of fibromyalgia (236). It has been argued that prolonged exposure to a high-intensity exercise regime is not well tolerated and may have an adverse effect on functioning, whereas exercising at a low-intensity level is well tolerated and may be associated with improved functioning as adherence continues (239). It is therefore recommended that in the clinical context, the amount and intensity of exercise programs should be adapted to the individual level of physical fitness and the training volume gradually progressed (237). Finally, the exercise literature on fibromyalgia is hampered by the lack of agreement on how to assess outcomes of interest. In a Cochrane review on exercise for treating fibromyalgia, Busch et al. reported the use of more than 100 tests and instruments, including eight for pain, nine for cardiovascular fitness and 13 for physical function (236). Such diversity is likely to undermine the consistency and comparability across studies.

Activity and participation are core aspects of occupational therapy and referral for occupational therapy becomes appropriate when a person experience problems related to performance of ADL tasks of importance to his or her everyday life. Although it is well documented that CWP and fibromyalgia are associated with substantial limitations in activity and societal level functioning, no studies have evaluated the effectiveness of occupational therapy provided as a single treatment modality for this patient population.

Psychological treatments are designed to treat pain, distress and disability, and are in common practice either on their own or, more typically, as an essential component of multimodal treatment regimes. In general, psychological treatments for chronic pain are reported to be most effective when
incorporated with other treatment components, such as physical exercise or patient education. Although psychological treatments appear to be important components of rehabilitation programs for chronic pain patients, not all patients benefit equally. In a recent Cochrane review on the effectiveness of psychological therapies for chronic pain, updating and extending the 2009 version, 35 randomized controlled trials (4,788 participants) provided data. Two main classes of treatment (cognitive behavioral therapy (CBT) and behavior therapy) were compared with two control conditions (treatment as usual; active control) at two assessment points (immediately following treatment and six months or more following treatment) on four outcomes: pain, disability, mood and catastrophic thinking. The review reported that overall there is an absence of evidence for behavior therapy, except for a small improvement in mood immediately following treatment when compared with an active control. CBT had small positive effects on disability and catastrophizing, but not on pain or mood, when compared with active controls. CBT had small to moderate effects on pain, disability, mood and catastrophizing immediately post-treatment when compared with treatment as usual/waiting list, but all except a small effect on mood had disappeared at follow-up. The authors concluded that 'CBT is a useful approach to the management of chronic pain and that there is no need for more general RCTs reporting group means. Rather, different types of studies and analyses are needed to identify which components of CBT work for which type of patient on which outcome/s, and to try to understand why'

A comparable small benefit on pain, negative mood and disability, as well as differential treatment responses are reported from systematic reviews evaluating the effectiveness of CBT, used either alone or in combination with other treatment modalities, in the management of fibromyalgia. Psychological interventions such as traditional CBT, group therapy sessions or motivational interviewing in order to help patients to cope better with pain are recommended by the Canadian and German guidelines, whereas the Israeli guideline place more emphasis on medical treatment combined with aerobic physical exercise. Acknowledging differential treatment responses to psychological interventions, the German guideline recommends that psychological intervention in fibromyalgia may be applied in the following clinical constellations: maladaptive disease management (e.g. catastrophizing, avoidance behavior) and/or relevant modulation of the symptoms due to stress and/or interpersonal problems and/or comorbid mental disorder.

Multi-component therapy
In the fibromyalgia literature, the term ‘multi-component therapy’ is used synonymously with ‘multidisciplinary therapy’ and described as the combination of at least one educational or other psychological intervention and at least one exercise therapy, although there is no accepted formal definition. Ideally, such care should be delivered by a team of healthcare professionals with expertise in a variety of physical, psychological and educational strategies, rather than rely on contact with a single healthcare professional. Multidisciplinary teams involved in the management of patients with fibromyalgia most often include rheumatologists, psychologists or psychiatrists and physiotherapists. Other possible team members are social workers and occupational therapists. The fibromyalgia literature does not outline a unifying theoretical framework for the conceptual description of multi-component therapy that can serve as a reference for delivery of interventions or how best to lead and coordinate the multidisciplinary team effort across professions. Levels of multidisciplinary team care can be divided according to levels of cooperation. In interdisciplinary team care, the team members work towards shared goals (what does the multidisciplinary team want to
achieve with its intervention program?) and monitoring of treatment progress is ensured through interdisciplinary team meetings. In multidisciplinary team care, different professionals work with the same individual, but within their own professional capacities (what does the assigned health professional want to achieve with his or her intervention?) and often without knowledge about each other’s practices (244).

Multi-component/multidisciplinary therapy is recommended by clinical guidelines for fibromyalgia patients with high disease impact who do not respond to mono-component pharmacological or non-pharmacological treatment (37;39). However, the number of controlled studies providing high quality information on the effectiveness of multi-component therapy, defined as delivery of at least two treatment modalities, is limited and knowledge is lacking in several areas (38;170;218). Most studies are conducted on selected patient populations; mainly females between 30 and 60 years of age, excluding participants with comorbid depression/anxiety disorder and pending social welfare litigation, and only few data are available on the socioeconomic outcomes, including changes in patients work status (38;170). Furthermore, there are conflicting results of systematic reviews regarding the short- and long-term effectiveness of multi-component treatment in fibromyalgia (38;170;218). It is reported that the positive effects on key symptoms and health-related quality of life decline with time, and that there is no convincing evidence for a sustainable long-term effect (170;245). In most of the studies, self-reported outcomes are the gold standard, and the effectiveness estimates based on averages and not individual patient responses. The organizational aspects of care delivery (e.g. multidisciplinary or interdisciplinary approach) and the theoretical foundation for applied interventions, are rarely described (170).

Between-patient heterogeneity and clinical implications

Current evidence based recommendations for the management of patients with fibromyalgia, including pharmacological treatment, are based on disease classification. However, fibromyalgia is not a homogenous entity, and several interacting factors, including neurobiological, psychosocial, cognitive and environmental factors, may add to this variability (157;166;246;247), and influence outcome of standardized intervention programs (248;249). Large inter-individual differences in response to drug interventions are likewise reported (250). Recognizing a large disparity in individual patient responses has moved outcome research within fibromyalgia from a focus on average responses to responder analyses; reporting the proportion of patients achieving clinically meaningful outcomes (190;250). Rather than requiring clinicians to make inferences about individual patients from group means, the responder approach may assist clinical decision-making, but still there is a need to determine how best to use the treatment options we have. Matching treatment to patients’ characteristics may potentially enhance clinical outcomes and thereby the effectiveness of available interventions.

A potential for treatment matching and differential response to the same intervention also seems to apply for pharmacological therapy. Pharmacological studies have generally evaluated pain in fibromyalgia as a global and uniform symptom, but different mechanisms of pain amplification may be present in different clusters of patients. Such a pathophysiological heterogeneity may explain, why randomized controlled trials investigating the efficacy of centrally acting drugs, often report generally modest treatment outcomes and poor responder rates. A more suitable approach for subgrouping
patients therefore seems necessary in order to better select drugs targeting particular mechanisms in individual patients. Identification of responders' profiles based on comprehensive information about disease characteristics and pain phenotyping based on somatosensory profiles, using specific pain questionnaires, has been suggested for future pain clinical trials in fibromyalgia (136).

**Identification of patient subgroups in fibromyalgia**

Several attempts have been made to define fibromyalgia subgroups primarily based on clinical characteristics (251). As early as 1996, Turk et al., using cluster analyses of Multidimensional Pain Inventory (MPI) data, classified patients with fibromyalgia into three subgroups (dysfunctional, interpersonally distressed, and adaptive copers) (166), and demonstrated differential responses across subgroups to multidisciplinary intervention (249). Later Thieme et al. showed that these three subgroups were characterized by different levels of comorbid anxiety and depression (157). Giesecke et al., using cluster analyses based on psychological variables (anxiety, depression), cognitive variables (catastrophic thinking, control over pain), and pressure pain sensitivity (dolorimetry), found three different subgroups: one group who exhibited extreme tenderness but low levels of distress, an intermediate group who displayed moderate tenderness and moderate distress, and a third group with low levels of tenderness and high levels of distress (246). Hurtig et al. subgrouped fibromyalgia patients by quantitative sensory testing (i.e. thermal pain thresholds) using cluster analyses and identified two subgroups. Subgroups showed clinical differences in pain intensity, number of tender points, and sleep quality. Cold pain threshold was especially linked to these clinical aspects (252).

A consistent pattern of clustering, with subgroups characterized by high, intermediate, and low levels of symptom reporting, has also been derived in studies using generic and disease specific assessment questionnaires, such as the FIQ and SF-36 (253;254), and internet-based surveys of large population based samples (23). In the study by Wilson et al, patient-reported healthcare utilization, functional status, and perceived social support and work disability were associated with levels of symptom reporting (23). More recently, Rehm et al., using hierarchical cluster analyses based on questionnaire-derived somatosensory descriptors of neuropathic pain as well as the extent of comorbid depression, revealed five distinct subgroups of fibromyalgia patients showing a characteristic clinical profile. Four subgroups of patients suffered from severe sensory disturbances in various combinations and had no pronounced comorbid depression. In one subgroup, however, severe comorbid depression dominated the clinical picture. The authors concluded that differences in pathophysiological mechanisms of pain generation may be attributed to each subgroup, and suggested that subgrouping can be used to tailor optimal pharmacological treatment strategies for the appropriate patient (136).

Only few studies have attempted to define fibromyalgia subgroups based on observation-based measures. Auvinet et al., using gait analysis, identified five distinct subgroups based on cluster analyses of gait markers (stride frequency, stride regularity) and found differences across groups in self-reported core symptoms of fibromyalgia (255).

Although such studies substantiate the notion of a disease severity spectrum and considerable heterogeneity within fibromyalgia populations, longitudinal studies of patients with fibromyalgia using clinically relevant subgroups to direct interventions and predict outcome are still missing. In a recent Swedish study, including 2,784 patients (709 men and 2,075 women) with chronic musculoskeletal pain collected from the Swedish Quality Register for Pain Rehabilitation, it was shown
that the number of persons with dysfunctional MPI profiles decreased after rehabilitation. Those with other MPI profiles had less full-time sick leave one year later than those with dysfunctional profiles, indicating that leaving the dysfunctional profile is a prognostic sign long-term. Furthermore, the gender differences observed in this study suggested the need to tailor rehabilitative strategies differently for men and women (256).

**Identification of predictors of multi-component treatment outcome in fibromyalgia**

Prognostic factor research aims to discover and evaluate factors that might be useful as modifiable targets for interventions or predictors of differential treatment responses (257). It is a fundamental component of 'stratified medicine', which refers to the targeting of pharmacological and non-pharmacological interventions according to the biological or clinical risk characteristics shared by subgroups of patients (258). Identification of predictors of differential treatment responses could assist tailor the therapeutic decision for specific patients and maximize benefit compared with offering generic multi-component intervention programs to patients with fibromyalgia.

Few empirical studies aiming at identifying outcome predictors for multi-component treatment in fibromyalgia are, however, available. In a recent systematic review by Rooij et al., the lack of high quality studies within this field was emphasized and the authors concluded that no strong evidence was found for any predictor of multi-component treatment outcome based on the existing studies (158). Studies were included in the review if the intervention comprised as a minimum two treatment modalities delivered by at least two different professional disciplines and had a longitudinal study design with a least one follow-up assessment. Outcomes were categorized into five outcome domains: pain, physical functioning, mental functioning, global treatment effect, and others (quality of life, social functioning, vitality, general health, return to work). Only 14 studies met the inclusion criteria, eight prospective cohort studies and six randomized controlled trials, one of which only provided psychological and educational treatment modalities (259). Most of the studies concerned outpatient programs delivered in a group format and with an intensity ranging from 12 to 120 hours (158). A weak to moderate evidence for a poorer outcome in several outcome domains predicted by higher levels of depression, was generated by two of the included cohort studies (260;261). However, identifying predictors of change in uncontrolled studies does not make it possible to distinguish between prognostic factors associated with the natural course of the disease and predictors of successful treatment outcome. Supporting an influence of the study design, most of the included controlled studies pointed towards a weak evidence for better treatment outcomes predicted by worse baseline status, and higher levels of pain and disability (Table 1) (262-266).

The review by Rooij et al. suggested that the benefits of intervention depended not only on patient characteristics, but also on the content of the intervention program (158). In a systematic review of available randomized controlled trials, providing an overview of the effectiveness of multidisciplinary treatments of chronic pain, Scascighini et al. found that fibromyalgia and chronic back pain patients tended to profit more substantially than patients with diverse chronic pain diagnoses. Compared with other mono-disciplinary treatments, moderate evidence of higher effectiveness for multidisciplinary interventions was shown. No evidence was found that treatment variables, such as duration or program components, were influential for the success of the intervention.
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study design and number of patients</th>
<th>Intervention</th>
<th>Outcome assessment</th>
<th>Outcome and predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Keel P et al. 1998</strong></td>
<td>RCT</td>
<td>Referred: 55 Selected: 32 Participated: 32 Completed: 27</td>
<td>Setting: rheumatology clinic Content: treatment arm 1: exercise, information, self-control strategies, relaxation; treatment arm 2: discussion, relaxation Form: outpatient, group therapy Disciplines: treatment arm 1: PT, Psy, Ps; treatment arm 2: PT, Psy</td>
<td>4 months after baseline</td>
</tr>
<tr>
<td><strong>Thieme K et al. 2003</strong></td>
<td>RCT</td>
<td>Referred: ? Selected: 63 Participated in the study: 63 Participated in the treatment arm: 40 Completed: 38</td>
<td>Setting: rheumatology clinic Content: education, medication management, increase in activity, OPT, reduction of interference and pain behavior Form: inpatients, group therapy Disciplines: Ps, PT, N, Rh</td>
<td>15 months after baseline</td>
</tr>
<tr>
<td><strong>Lemstra M et al. 2005</strong></td>
<td>RCT</td>
<td>Referred: 82 Selected: 82 Participated in the study: 79 Participated in the treatment arm: 43 Completed: 35</td>
<td>Setting: non-clinical Content: dietary, massage, pain/stress management, exercise Form: outpatient, group therapy Disciplines: ET, PT, Ps, Rh</td>
<td>15 months after baseline</td>
</tr>
<tr>
<td><strong>Hammond A et al. 2007</strong></td>
<td>RCT</td>
<td>Referred: 183 Selected: 183 Participated in the study: 183 Participated in the treatment arm: 97 Completed: 71</td>
<td>Setting: community leisure centers Content: education, exercise Form: outpatient, group therapy Disciplines: OT, PT</td>
<td>Unclear 4 or 8 months after baseline</td>
</tr>
<tr>
<td><strong>Lera S et al. 2009</strong></td>
<td>RCT</td>
<td>Referred: 171 Selected: 107 Participated in the study: 83 Participated in the treatment arm: ? Completed: 68</td>
<td>Setting: hospital fibromyalgia unit Content: multidisciplinary treatment: discussion, individual medical treatment, exercise; treatment arm 2: multidisciplinary treatment + CBT Form: outpatient, group therapy Disciplines: PT, Ps, Rh, RP</td>
<td>Post-treatment 36.5 h, 4 months, 14 sessions</td>
</tr>
</tbody>
</table>


**Table 1.** Predictors of outcome of multidisciplinary treatment (defined as the delivery of at least two different treatment modalities by at least two different professional disciplines) and explored in a randomized controlled trial design (158)
The authors concluded that future studies should more specifically focus on differential effects of treatment components and patient variables, allowing the identification of subgroups, which most probably would profit from multidisciplinary pain programs (248). Whether treatment matching promotes clinical effectiveness remains to be clarified, as no studies on fibromyalgia using outcome predictors to direct the design of the intervention or allocation of patients are available.

**Rehabilitation perspective in management and outcome assessment**

Rehabilitation is rooted in a bio-psychosocial paradigm and can be conceptualized as a ‘health strategy’ that aims to enable individuals with different health conditions that are experiencing disabilities to achieve and maintain the best possible functioning in their environment (267). The basis for the definition of rehabilitation understood as a health strategy is the WHO’s integrative model of human functioning, disability and health – the ICF – in which a person's functioning and disability is conceived as a dynamic interaction between health and contextual factors (268). In this way, rehabilitation differs from the bio-medically founded concept of treatment, where the emphasis is on pathology and consequences of disease, and the aim of treatment to cure or interfere with the disease process. The medical model views disability as a problem of the individual directly caused by disease, trauma or other health condition, which requires medical care in the form of individual treatment. Management of the disability is aimed at cure, or at the individual’s adjustment and behavioral change.

The target of rehabilitation is human functioning. The assessment of functioning in rehabilitation relies on the integrative model on human functioning, disability and health as defined in the ICF (Figure 5). The goal of the assessment is to understand or describe a person's experience of disability in relation to impairments and/or in relation to interaction with environmental and personal factors (269). In the framework of the ICF, an individual's functioning in a specific domain (i.e. body, activities, and participation domains) is viewed as a dynamic interaction or complex relationship between the health condition and contextual factors (i.e. environmental and personal factors). These interactions are specific and not always in a predictable one-to-one relationship. The interaction works in two directions; the presence of disability may even modify the health condition itself. To infer a limitation in activities (e.g., reduced performance in activities of daily living) from one or more body impairments (i.e., the biomedical status of the body and its functions) or a restriction in participation (e.g., work disability), may therefore not be reasonable. Likewise, one may experience activity limitations and restrictions in participation without evident body impairments. Two constructs, 'performance' and 'capacity', are used in the ICF to describe the activities and participation domains. These constructs provide a way of indicating how the environment influences a person's activities and participation, and how environmental change may improve a person's functioning. 'Capacity' relates to what an individual can do in a 'standardized' environment (this often involves some kind of clinical assessment). 'Performance' relates to what the person actually does in his or her current (usual) environment. The gap between capacity and performance reflects the difference between the impacts of current and uniform environments, and thus provides a useful guide as to what can be done to the environment of the individual to improve performance. The environment provides the context for the performance, and the various features of the environment can provide opportunities, limits or constraints, challenges, and important physical and social supports.
Rehabilitation is a continued process and rehabilitation goals can shift from input intended to minimize impairment to more complex interventions that are designed to encourage active participation and prevent further disability (268). The rehabilitation strategy includes biomedical approaches, approaches that build on and strengthen the resources of the person, approaches that provide a facilitating environment, and that develop performance in interaction with the environment. Body level or impairment interventions are primarily medical or rehabilitative, and attempt to prevent or ameliorate limitations in activity or societal level functioning by correcting or modifying intrinsic functions or structures of the body. Other rehabilitative treatment strategies and interventions are designed to increase capacity levels. Interventions that focus on the actual performance context of an individual may address either capacity-improvement or else seek environmental modification, either by eliminating environmental barriers or by creating environmental facilitators for expanded performance of actions and tasks in daily living (269). Because of its inherent complexity, rehabilitation is an interdisciplinary area in both research and practice. The training of professionals has a focus on different parts of the ICF that complement each other in the interdisciplinary effort; physicians focus on health condition/disease and body function and structure, whereas the social worker has more of a focus on the environmental factors and participation, the physiotherapists on body function and activity, while the occupational therapist focuses on activity and participation.

Intervention programs applying a rehabilitation strategy are typically based on an interdisciplinary approach and delivered in a coordinated iterative problem-solving and patient-centered process (268). A structured approach to rehabilitation involves the following: identifying the problems and needs most relevant to the patient; relating the problem to modifiable impairments, personal and environmental factors; selecting appropriate measures to follow-up the result of the intervention; planning implementing and coordinating interventions; treating impairments, compensating for impairments, activity and participation limitations by addressing environmental factors, addressing personal factors, and preventing further disability (269). This process is described in terms of a rehabilitation cycle and involves the following steps: assessment, assignment, intervention, and evaluation (270). The assessment step includes the identification of patients’ problems, the definition of the overall long-term goal (e.g., re-integration into prior work or living situation), the definition of assigned intervention program goals, and the intervention targets for each professional. The assignment step refers to the assignment of health professionals and the assignment of interventions to the intervention targets. Different interventions provided by different professionals may be applied to the same intervention target. The evaluation step refers to the evaluation of intervention target achievement and ultimately the intervention program goals. The key to a successful rehabilitation management is the understanding of the relationship between the selected intervention goals, which are normally at the level of activities and participation, and the impaired body functions, psychosocial and environmental factors. Vocational counseling is often an integrated part of rehabilitative efforts and successful management of work disability usually requires an early intervention that includes both mobilization of patient resources and adjustments in the work situation matching the level of ability. Ideally, the rehabilitation process therefore also include continuity and coordination across sectors, and the present challenge seems to be how to implement optimal rehabilitation interventions between health and social services (244).

A prerequisite for defining a patient’s problems and for evaluating the effects of rehabilitation are standardized assessments of relevant parameters and endpoints. Further, a clear understanding of
the outcomes of interventions is required to be able to judge the effectiveness of interventions and to be able to judge the efficiency of intervention programs. Important dimensions that should be considered when evaluating clinical outcomes of rehabilitation not only include the proportion of the treated patient sample that demonstrated significant therapeutic improvement, but the clinical meaningfulness in the patient's natural environment of the therapeutic changes that were obtained in the clinical setting. The ICF and the ICF core sets, which are short lists of ICF categories relevant for specific conditions, are recommended to serve as a common standard for multidisciplinary assessment and outcome evaluation within rehabilitation (271-273). As aforementioned, international recommendations for the assessment of a number of musculoskeletal pain disorders have been developed based on the ICF (193), including definition and validation of ICF core sets for patients with CWP (173), but they do not indicate how to evaluate them. The assessment tools used in outcome evaluation should capture the core interventions of the rehabilitation program addressing: body structure and function (impairment), activity limitation and participation restriction and have the potential to reflect the combined interventions of rehabilitation teams.

The ICF core set for CWP was developed to reflect the complex functional problems encountered by patients with CWP and also the crucial influence of patients’ surroundings and life situations on their functioning and health (173). The brief ICF core set for CWP includes 10 categories from the domain of body functions, 10 categories from the activity and participation domains, and six categories from environmental factors. The substantial representation of environmental factors, reflects the growing awareness of the important influence of patients’ surroundings and life situations (274). This may in particular apply to patients with fibromyalgia, where social support and relationships and external attitudes can serve as either a barrier or facilitator and may therefore influence fibromyalgia outcome (275). Validation of the ICF core set for CWP from the perspective of fibromyalgia patients using focus groups support their applicability in this patient population, as well as the significant influence of negative attitudes of social support and health care systems adding to the burden of pain and disability (198). Since personal factors have not yet been classified in the ICF, and therefore lack standardization (276), it is difficult to address central issues such as pain beliefs and coping strategies in the current version of the ICF core sets (173).

Limitations in activity and restrictions of participation may, indeed, be most relevant to patients with CWP and fibromyalgia (183), and are frequently referred to in the literature under the umbrella term Health-Related Quality of Life (HRQoL) or ‘multidimensional’ functioning, where considered relevant and selected by the group of experts (185). Evaluation of the outcome of rehabilitation is generally accomplished through the assessment of individuals’ functional status and there is a large number of tools available that assess activity limitation (197;198;277). The scope of participation restriction is far wider, and is concerned with social roles and expectations outside the treatment setting. HRQoL is important because it incorporates multiple domains and generally involves patients’ own perspectives. However, there is no clear relationship between HRQoL dimensions and the ICF constructs of impairment, activity limitation and participation restriction. In fact, these constructs may overlap in HRQoL instruments rather than evaluating them as independent domains (197). Generic HRQoL instruments are mostly epidemiologic tools and as such intended to measure change in large populations (189). As yet there is no empirical evidence about whether HRQoL tools can measure clinically meaningful change longitudinally in individual patients. There are ongoing initiatives that might assist further standardization of outcome assessment within rehabilitation, such as the Patient-
Reported Outcomes Measurement Information System (PROMIS). PROMIS is a US National Institutes of Health initiative that has produced a large self-reported item bank for physical, mental and social health. Efforts to describe the content of the PROMIS at the item level using the ICF have been reported, and suggest that the PROMIS-ICF mapped items may provide a basis for users to evaluate the ICF-related content of specific PROMIS instruments and to select PROMIS instruments in ICF-based assessment applications (278).

2. Patients and methods

Study setting and participants

Participants

The thesis encompasses two separate study populations: the CWP cohort and participants from the first phase of the IMROvE study (Table 2).

<table>
<thead>
<tr>
<th>Paper</th>
<th>Number of subjects</th>
<th>Gender</th>
<th>Study population</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>81</td>
<td>76 females, 5 males</td>
<td>CWP cohort</td>
</tr>
<tr>
<td>II</td>
<td>271</td>
<td>271 females</td>
<td>CWP cohort</td>
</tr>
<tr>
<td>III</td>
<td>257</td>
<td>257 females</td>
<td>CWP cohort</td>
</tr>
<tr>
<td>IV</td>
<td>257</td>
<td>257 females</td>
<td>CWP cohort</td>
</tr>
<tr>
<td>V</td>
<td>263</td>
<td>263 females</td>
<td>CWP cohort</td>
</tr>
<tr>
<td>VI</td>
<td>192</td>
<td>192 females</td>
<td>IMPROvE study</td>
</tr>
<tr>
<td>VII</td>
<td>192</td>
<td>192 females</td>
<td>IMPROvE study</td>
</tr>
</tbody>
</table>

Table 2. Overview of subjects included in the studies comprising this thesis.

All of the participants were adults, primarily females, with CWP diagnosed according to the ACR-1990 definition of widespread pain (i.e. reporting of pain axially and in minimum 3 body quadrants) and referred for rehabilitation at the outpatient clinic at Department of Rheumatology, Frederiksberg Hospital. In addition to CWP, the majority of participants also fulfill the 1990-ACR criteria of 11 or more tender points, i.e. the classification criteria for fibromyalgia.

Evaluated in an ICF framework, participants are characterized by a high level of symptom burden and substantial disability, although a considerable individual variability is present as indicate by the observed wide range in scores on key outcome instruments (Table 3). Still, the average person referred for rehabilitation averages over 100 months of pain duration, demonstrates extensive limitations in ADL task performance and a potential need of support for community living. Only about 21% are part of the workforce at the time of referral, 82% report a change or permanent disability from usual working activity due to the pain condition, 25% are on long-term sick leave, and 34% are receiving some sort of social welfare payment.
<table>
<thead>
<tr>
<th>Demographics</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>45.5</td>
<td>9.7</td>
<td>46.5</td>
<td>20.4-71.5</td>
</tr>
<tr>
<td>Symptom duration (months)</td>
<td>122</td>
<td>102</td>
<td>85.0</td>
<td>6-540</td>
</tr>
<tr>
<td>Body mass index (BMI)</td>
<td>26.9</td>
<td>5.5</td>
<td>16.9-45.7</td>
<td></td>
</tr>
<tr>
<td>Changes or permanent disability from usual working activity</td>
<td>82%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Applied for permanent disability pension at some stage</td>
<td>25%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently holding a position or enrolled in education</td>
<td>21%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently on long-term sick leave</td>
<td>25%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently receiving social benefits/social services of some sort</td>
<td>34%</td>
<td></td>
<td></td>
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<tr>
<td>Body</td>
<td></td>
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</tr>
<tr>
<td>Muscle strength UE (PTQ extension Nm)</td>
<td>84.9</td>
<td>36.9</td>
<td>86.3</td>
<td>7-199</td>
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<tr>
<td>Muscle strength UE (PTQ flexion Nm)</td>
<td>40.2</td>
<td>18.4</td>
<td>39.2</td>
<td>5-85</td>
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<tr>
<td>Grip strength, maximal (N)</td>
<td>175.0</td>
<td>82.2</td>
<td>172.0</td>
<td>8-408</td>
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<tr>
<td>Vitality (SF-36)</td>
<td>21.9</td>
<td>17.3</td>
<td>20.0</td>
<td>0-75</td>
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<tr>
<td>Fatigue (FIQ)</td>
<td>8.0</td>
<td>1.9</td>
<td>8.6</td>
<td>1.3-10</td>
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<td>Restedness (FIQ)</td>
<td>7.6</td>
<td>2.3</td>
<td>8.3</td>
<td>0-10</td>
</tr>
<tr>
<td>Wellbeing (SF-36)</td>
<td>55.6</td>
<td>20.6</td>
<td>56.0</td>
<td>0-100</td>
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<tr>
<td>Wellbeing (FIQ)</td>
<td>7.4</td>
<td>2.7</td>
<td>7.1</td>
<td>0-10</td>
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<tr>
<td>Anxiety (FIQ)</td>
<td>4.5</td>
<td>3.4</td>
<td>4.3</td>
<td>0-10</td>
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<tr>
<td>Anxiety (GAD-10)</td>
<td>19.2</td>
<td>9.8</td>
<td>18.0</td>
<td>1-50</td>
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<td>Depression (FIQ)</td>
<td>3.8</td>
<td>3.4</td>
<td>3.0</td>
<td>0-10</td>
</tr>
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<td>Depression (MDI)</td>
<td>21.6</td>
<td>10.7</td>
<td>20.0</td>
<td>3-50</td>
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<tr>
<td>Bodily pain (SF-36)</td>
<td>24.1</td>
<td>15.0</td>
<td>22.0</td>
<td>0-84</td>
</tr>
<tr>
<td>Pain intensity (FIQ)</td>
<td>7.1</td>
<td>1.9</td>
<td>7.5</td>
<td>0-10</td>
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<td>Muscle stiffness (FIQ)</td>
<td>6.3</td>
<td>2.8</td>
<td>7.0</td>
<td>0-10</td>
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<td>Tiredness mobility (Mob-T)</td>
<td>1.7</td>
<td>1.6</td>
<td>1.0</td>
<td>0-6</td>
</tr>
<tr>
<td>Pain Detection Threshold (PDT KPa)</td>
<td>12.2</td>
<td>7.5</td>
<td>10.4</td>
<td>0.3-46.2</td>
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<tr>
<td>Pain Tolerance Threshold (PTT KPa)</td>
<td>31.7</td>
<td>14.7</td>
<td>28.5</td>
<td>9.2-86.7</td>
</tr>
<tr>
<td>Activity and participation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMPS ADL ability motor (logits)</td>
<td>1.07</td>
<td>0.50</td>
<td>1.07</td>
<td>0.4-2.82</td>
</tr>
<tr>
<td>AMPS ADL ability process (logits)</td>
<td>1.09</td>
<td>0.35</td>
<td>1.09</td>
<td>0.12-2.18</td>
</tr>
<tr>
<td>Walking speed (6-MW m/s)</td>
<td>449.7</td>
<td>114.4</td>
<td>461.2</td>
<td>95-712</td>
</tr>
<tr>
<td>Activity limitations (FIQ)</td>
<td>5.2</td>
<td>2.2</td>
<td>5.7</td>
<td>0-9</td>
</tr>
<tr>
<td>Physical functioning (SF-36)</td>
<td>42.9</td>
<td>20.0</td>
<td>40.0</td>
<td>0-95</td>
</tr>
<tr>
<td>Role physical (SF-36)</td>
<td>9.7</td>
<td>21.0</td>
<td>0.0</td>
<td>0-100</td>
</tr>
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<td>Role emotional (SF-36)</td>
<td>45.1</td>
<td>43.3</td>
<td>33.3</td>
<td>0-100</td>
</tr>
<tr>
<td>Social functioning (SF-36)</td>
<td>48.0</td>
<td>26.5</td>
<td>50.0</td>
<td>0-100</td>
</tr>
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<td>Days of sick leave pr. week (FIQ)</td>
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<td>1.7</td>
<td>0.0</td>
<td>0-6</td>
</tr>
<tr>
<td>Work ability (FIQ)</td>
<td>6.6</td>
<td>2.5</td>
<td>7.35</td>
<td>0-10</td>
</tr>
<tr>
<td>Personal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catastrophizing (CSQ)</td>
<td>15.9</td>
<td>8.4</td>
<td>15.0</td>
<td>0-36</td>
</tr>
<tr>
<td>Perceived control over pain (CSQ)</td>
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<td>1.4</td>
<td>3.0</td>
<td>0-6</td>
</tr>
<tr>
<td>Ability to decrease pain (CSQ)</td>
<td>2.3</td>
<td>1.2</td>
<td>2.0</td>
<td>0-6</td>
</tr>
<tr>
<td>Global</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIQ total</td>
<td>61.3</td>
<td>18.5</td>
<td>61.6</td>
<td>2.9-97.4</td>
</tr>
<tr>
<td>SF-36 PCS</td>
<td>27.0</td>
<td>6.7</td>
<td>26.8</td>
<td>8.8-50.7</td>
</tr>
<tr>
<td>SF-36 MCS</td>
<td>40.7</td>
<td>12.0</td>
<td>40.9</td>
<td>14.9-66.6</td>
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<tr>
<td>General health (SF-36)</td>
<td>31.6</td>
<td>18.2</td>
<td>30.0</td>
<td>0-97</td>
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**Table 3.** Baseline characteristics and key outcome ICF variables in 271 female patients referred for rehabilitation (the CWP-cohort)
The CWP cohort
The first part of the thesis, aiming to identify valid assessment methods and instruments for the evaluation of disease severity in patients with CWP and fibromyalgia, is based on data from the CWP cohort. The CWP cohort comprises 289 patients (274 females and 15 males) diagnosed with CWP according to the 1990 ACR criteria and consecutively enrolled in the rehabilitation program at the Department of Rheumatology, Frederiksberg Hospital from March 1 2007 to February 28 2009. In this two-year period, a comprehensive baseline and 1-year follow-up assessment was conducted on all patients using several self-report and observation-based assessment instruments and data stored in a clinical database. The analyses and results presented in paper I to V are based on cross-sectional baseline data from this study population.

Assessment and instrumentation
The WHO International Classification of Functioning, Disability and Health (ICF) (191) was used as a conceptual framework for organizing the multidimensional assessment and several self-report and observation-based assessment tools was identified based on the literature and implemented to cover ICF-categories included in the brief ICF core set for CWP (173). However, many of the identified instruments overlap and contain a mixture of impairments and activity, for example the SF-36. A few ICF categories encompassed in the brief ICF core set for CWP were not covered by the applied instruments in particular categories related to interpersonal relations. An overview of the applied instruments and alignment with ICF-categories is presented in Table 4, and a detailed description of the instruments and assessment methods in Appendix 1.

Observation-based assessment of functional ability
To determine the nature and extent of ADL task performance problems and document change, there is a need for instruments that can be used to obtain linear measures of ADL ability. Furthermore, as ADL evaluations based on observation are rarely used in studies of chronic pain patients it was considered of great importance to supplement self-reporting of ADL ability with observation-based measures. The ‘Assessment of Motor and Process Skills’ (AMPS) is an individualized, observation-based evaluation of functional ability, developed to establish the extent of an individual’s ability to perform and complete familiar and relevant activities of daily living (279). The AMPS measurement model is based on Rasch analysis and therefore provides equal-interval linear measures of ADL ability. The AMPS has been standardized on more than 100,000 persons between 3 to 100 years of age internationally and cross-culturally (279) and has demonstrated stability over repeated measurement, as well as sensitivity to changes in ADL task performance in women with CWP (280).

When the AMPS is administered, the person chooses and performs two relevant and familiar ADL tasks of appropriate challenge. During each ADL task performance, a trained and calibrated occupational therapist observes 36 ADL skills and rates the person’s performance of each skill on a 4-point ordinal scale. The ordinal ADL scores are then converted into two overall linear ADL ability measures; one for ADL motor ability (moving self and objects) and one for ADL process ability (organizing and adapting actions), by Rasch-based computer-scoring software that adjusts measures to account for rater severity, skill item difficulty and ADL task challenge. The resulting ability measures are expressed in logistically transformed probability units (logits). The overall ADL motor ability measure is an indication of how much clumsiness, effort or fatigue the person was observed to demonstrate when moving him- or herself and task objects. The overall ADL process ability measure is
an indication of how timely and well organized (efficient) the person was observed to be when choosing and using task objects and organizing the spatial-temporal actions of the task performance.

The AMPS ADL ability measures can be interpreted from a norm-referenced perspective. Age norms, based on means and 95% confidence intervals are available for healthy adults and different age groups. Furthermore, the ADL ability measures of the AMPS can be interpreted from a criterion-referenced perspective, using a criterion of competence. ADL ability measures below the 2.0 logits cutoff on the ADL motor scale and below the 1.0 logits cutoff on the ADL process scale indicate ADL skill deficits that reflect diminished quality of ADL task performance. Studies support both ADL motor ability and ADL process ability as having utility as indicators of the need for assistance, and that ADL ability measures <1.5 logits on the ADL motor scale and <1.0 logits on the ADL process scale indicate that the person is likely to need assistance for community living (281;282). Finally, changes in AMPS ADL ability measures of at least 0.30 logits have been reported to represent a clinically meaningful change (279).

<table>
<thead>
<tr>
<th>ICF Core Sets for CWP</th>
<th>Instruments in this study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body functions</strong></td>
<td></td>
</tr>
<tr>
<td>Emotional functions</td>
<td>GAD-10, MDI, SF-36, FIQ</td>
</tr>
<tr>
<td>Sensation of pain</td>
<td>FIQ, SF-36, PDQ, CPA, TPC</td>
</tr>
<tr>
<td>Exercise tolerance functions</td>
<td>Mob-T</td>
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<tr>
<td>Psychomotor functions</td>
<td>AMPS motor</td>
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<tr>
<td>Control of voluntary movement functions</td>
<td>FIQ, SF-36</td>
</tr>
<tr>
<td>Energy and drive functions</td>
<td>Mob-T, SF-36, FIQ, MDI</td>
</tr>
<tr>
<td>Sleep functions</td>
<td>FIQ, MDI</td>
</tr>
<tr>
<td>Content of thoughts</td>
<td>CSQ, MDI, GAD-10</td>
</tr>
<tr>
<td>Muscle power functions</td>
<td>Grippit, LIDO Multi Joint</td>
</tr>
<tr>
<td>Attention function</td>
<td>GAD-10, MDI</td>
</tr>
<tr>
<td><strong>Activity and participation</strong></td>
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</tr>
<tr>
<td>Carrying out daily routines</td>
<td>AMPS, SF-36, FIQ</td>
</tr>
<tr>
<td>Handling stress and other psychological demands</td>
<td>CSQ, GAD-10, MDI</td>
</tr>
<tr>
<td>Family relationships</td>
<td>SF-36</td>
</tr>
<tr>
<td>Remunerative employment</td>
<td>FIQ, SF-36, BIQ</td>
</tr>
<tr>
<td>Intimate relationships</td>
<td></td>
</tr>
<tr>
<td>Walking</td>
<td>6-MW, SF-36, FIQ</td>
</tr>
<tr>
<td>Recreation and leisure</td>
<td>SF-36</td>
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<tr>
<td>Solving problems</td>
<td>AMPS process, CSQ</td>
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<tr>
<td>Lifting and carrying objects</td>
<td>AMPS motor, SF-36</td>
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<tr>
<td>Doing housework</td>
<td>AMPS, FIQ, SF-36</td>
</tr>
<tr>
<td><strong>Personal and environmental factors</strong></td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td>BIQ</td>
</tr>
<tr>
<td>Immediate family</td>
<td>BIQ</td>
</tr>
<tr>
<td>Health professionals</td>
<td>BIQ</td>
</tr>
<tr>
<td>Individual attitudes of immediate family members</td>
<td>BIQ</td>
</tr>
<tr>
<td>Social security services, systems and policies</td>
<td>BIQ</td>
</tr>
<tr>
<td>Individual attitudes of friends</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Instruments classified according to the ICF Core sets for CWP
**Interdisciplinary rehabilitation and evaluation program for patients with chronic widespread pain (the IMPROvE study)**

The second part of the thesis, aiming to evaluate the effectiveness of the rehabilitation program tailored for patients with CWP and to identify predictors of differential treatment responses, is based on data from the IMPROvE study. The design of the overall IMPROvE study, which included two phases conducted by a multidisciplinary research team, is presented in Figure 7.

**Figure 7.** The IMPROvE study: study diagram and timing of measurements.
The first phase of the IMPROvE study was designed as a randomized, controlled, single-centre trial, with two groups evaluating the functional and psychological outcomes of the two-week, group-based rehabilitation program tailored for patients with CWP (Clinical-Trials.gov identifier: NCT01352052). Based on a priori sample size calculation, the intention-to treat (ITT) population comprised 192 patients randomized 1:1, stratified by baseline level of functional ability as measured with the Assessment of Motor and Process Skills (AMPS), to either treatment or a waiting list control group. Co-primary outcomes were the AMPS ADL motor and ADL process ability measures and the SF36 Mental Composite Score (MCS) evaluated at 6-months follow-up. Efficacy was evaluated on an ITT basis using a non-responder imputation with baseline observations carried forward (BOCF). Participants included in the analyses were all females fulfilling the ACR-1990 criteria for fibromyalgia (1), consecutively recruited from the outpatient clinic and enrolled in the IMPROvE study. Eligible patients were ages ≥18 years, without sever concurrent psychiatric disorders not related to the pain disorder or uncontrolled rheumatic or medical disease capable of causing CWP. All patients enrolled in the IMPROvE study underwent a comprehensive baseline and follow-up assessment, which included several self-report instruments and observation-based assessments. Patients completed the Fibromyalgia Impact Questionnaire (FIQ), the SF-36, the Major Depression Inventory (MDI), the General Anxiety Disorder inventory (GAD-10), the Coping Strategy Questionnaire (CSQ), the PainDetect Questionnaire (PDQ), and the Pain Self-Efficacy Questionnaire (PSEQ). In addition to the AMPS, observation-based assessments included a manual tender point examination, measurements of maximal isokinetic knee muscle strength, maximal grip strength, a 6-minute walk test (6-MW), and measurement of pressure pain thresholds using cuff pressure algometry (CPA).

Participants receiving immediate attention in phase one of the study were offered continuation in an open label study with follow-up at two years, acting as control group in the second phase of the IMPROvE study. Participants randomized to the control group received no treatment during the first phase of the study, but were offered the same two-week rehabilitation program at the end of the waiting list plus an additional 16-week mono-component intervention of either individualized physiotherapy or occupational therapy in the second phase of the study (Figure 7). Only results from the first phase of the IMPROvE study are reported on in this thesis.

The rehabilitation program
A non-residential two-week rehabilitation program specifically tailored for patients with CWP and fibromyalgia has been part of the rheumatology service at the Copenhagen University Hospital of Frederiksberg for several years. The rehabilitation program is group-based with eight patients participating in each group. Participants with a confirmed diagnose of CWP or fibromyalgia are consecutively enrolled in the rehabilitation program from a waiting list, only divided by gender. The capacity at the department of rheumatology allows for the treatment of 21 groups of eight patients per year. Based on the referral pattern, only one group per year consists of males.

Acknowledging a substantial chronicity in the referral population, the rehabilitation program has been designed to help patients to adopt sufficient coping skills and greater responsibility for self-management, and places emphasis on compensating for activity limitations and participation restrictions, and prevention of further disability. A routine baseline assessment of all patients is part of
the rehabilitation program and includes evaluation with several standardized questionnaires and assessment of ADL ability evaluated with the AMPS.

An interdisciplinary team consisting of a rheumatologist, a psychologist, nurses, and occupational and physical therapists delivers the interventions in the two-week, group-based rehabilitation program, which has a daily time schedule between three and five hours; in total 35 hours. A structured working process with a planned team conference every second week is inherent in the interdisciplinary set up. Prior to the team conference, the rheumatologist prepares and presents a written resume focusing on the bio-psychosocial situation of each of the eight group members, and specific issues pertaining to the group are discussed in order to adjust the content of the rehabilitation course within the frames of the scheduled program. Given the considerable proportion of patients presenting with work-related disability and issues pertaining to prolonged litigation in fibromyalgia-based disability claims, the inclusion of social workers in the interdisciplinary team and initiatives promoting coordination and continuity across the health and social sector would be desirable, but has not yet been possible to integrate within the frames of the current rehabilitation program. Pharmacological treatment of individual patients is also beyond the scope of the rehabilitation program, due to its group format and lack of resources to provide regular, individual checkups.

The rehabilitation program itself is based on an interactive, participatory approach and comprises a combination of presentations and group discussions, as well as instructions during physical exercise and performance of ADL tasks. A two-hour session with the participants and their spouses/significant others conducted by the psychologist and the rheumatologist, and a 30-minute individual consultation with the rheumatologist at the end of the program, is included. The educational part of the program provides information about CWP and fibromyalgia, theories of pain perception, bio-psychosocial models of pain and pain management, active self-management of pain and stress, sleep hygiene, and cohabitation and sexuality. Group discussions facilitated by the psychologist are focused on shared experiences of living with chronic pain, cognitive flexibility and individual strategies for behavioral changes, and existentialistic reflections.

The overall aim of the physiotherapy sessions is to encourage a continued engagement in physical activity/training as part of an active pain self-management strategy, and to introduce participants to various forms of training. Physical therapy sessions include group discussions of participants’ prior experiences with supervised/unsupervised training, and prior and present level of activity, information about the principles of graded exercise and activity pacing, as well as supervised training sessions; aerobic exercises, pool exercises, balance training and proprioceptive exercises adapted to the functional level of participants, and relaxation exercises. The overall aim of the occupational therapy sessions is to increase participants’ abilities to perform everyday life tasks, including ADL tasks that the participant wants to, needs to or is expected to perform. Group discussions are focused on participants’ experienced pain related interference with ADL task performance, and how to solve these problems through adapting the environment or modifying the task in order to increase participation in and performance of ADL tasks (adaptive and compensatory intervention strategies). Participants are introduced to the AMPS and the obtained AMPS ADL ability measures across the group are discussed. Practical, supervised ADL-exercises, including introduction to the use of various aid devices, takes place at the department of occupational therapy where there are accesses to training facilities such as a fully equipped kitchen, computer work place, and ergonomic furniture. The weekly
time schedule and headlines for the content of individual sessions in the rehabilitation program is presented in Appendix 2.

Finally, participants are routinely offered a four-hour, 1-year follow-up session together with their group (one hour with the nurse, one hour with the rheumatologist, two hours with the psychologist). The individual sessions are based on group discussions of issues raised by individual group members, but with a focus on experienced treatment gains and implementation of adaptive pain management strategies. Aside from this, the continued routine care and support of patients are managed by their primary care physicians.

3. Own study results and discussion of clinical implications

Clinical assessment

Tender points as a marker of clinical disease severity

Manual tender point (TP) examination has been considered a primary clinical identifier of pain hypersensitivity, linking fibromyalgia features to augmented central pain processing. Still, the utility of TP examination for classification purposes, and as a marker of clinical disease severity in patients reporting CWP is the subject of contemporary debate. A quite variable association between the TP count and clinical disease severity has been reported (81;283-286). In these studies, clinical disease severity has been defined in different ways and only a minority has included patients with CWP and fewer than 11 TPs (18;287), or disease variables derived from observation-based assessment. Further, it has been argued that TPs are linearly related to fibromyalgia variables and distress, and that there is no discrete enhancement or perturbation of disease severity associated with high levels of TPs (30). Two of the studies [I, II] in this thesis aimed at evaluating the rationale for a continued used of manual tender point examination in the clinical assessment of patients with CWP, including as a marker of clinical disease severity.

The objective of the first study [I] was to evaluate self-reported somatosensory symptoms of neuropathic pain in patients with CWP using the painDetect questionnaire (PDQ) (288) and to assess the relationships between PDQ-score, TP-count, and pressure-pain thresholds (PPT) measured with CPA. Eighty-one patients (6 males, 75 females), out of whom 79 % fulfilled the 1990-ACR classification criteria for fibromyalgia, were included in the study. The study showed that pain in patients with CWP display neuropathic features, and that the presence and number of tender points are associated with neuropathic pain symptoms. Frequently reported pain qualities were burning pain, paresthesias, pain attacks (electric shocks), thermally evoked pain and deep tissue hyperalgesia, reported by 86% of the patients (Figure 8).
Figure 8. The profile of self-reported somatosensory symptoms obtained with the PDQ in the study population of patients with CWP (N=81). The figure illustrates the proportion of patients reporting the presence of clinically relevant somatosensory symptoms defined as a symptom severity score ≥3 on a 6-point Likert scale [1].

Seventy-five percent of the patients had a PDQ-score above 18 indicating a predominantly neuropathic pain component being present and the majority of these patients (80%) also met the ACR tender point criteria of 11 or more TPs. Pressure pain thresholds measured with cuff pressure algometry (CPA) (82) were significantly lower in this subgroup, supporting the ability of the PDQ to identify patients characterized by pain hypersensitivity. Furthermore, significant correlations between neuropathic pain score on the PDQ, VAS intensity values for pain, TP-count and pressure pain thresholds measured with CPA were found in this study, whereas no correlation with questionnaire-derived scores of depression, anxiety or pain catastrophizing was noted.

The PDQ is a symptom-based assessment tool primarily composed of questions regarding the presence and severity of positive somatosensory signs that traditionally are ascribed to neuropathic pain. However, applied in a CWP/fibromyalgia population the PDQ classifies these conditions as neuropathic, i.e. having clinical features that are non-nociceptive. Current scientific evidence suggests that both neuropathic pain and fibromyalgia are characterized by central sensitization and may share similar and very complex neurobiological underpinnings (109). Given that these neurobiological underpinnings give rise to clinical symptoms, it is not surprising if CWP/fibromyalgia and neuropathic pain may share common clinical features. Thus, the study results indicate that the PDQ may be applied as a screening tool for assisting identification of a primarily central pain component in patients with chronic widespread musculoskeletal pain. The results also support the notion that fibromyalgia, as defined by the dual 1990-ACR criteria, represents the upper end of a physiological pain severity
spectrum (a severe sensory impairment) characterized by the presence of widespread pain hypersensitivity and other clinical manifestations of central sensitization expressed as total score on the PDQ. These findings have been confirmed in other studies reporting an identical pattern of PDQ-derived somatosensory symptoms of neuropathic pain in a large sample of patients with fibromyalgia (134;136) as well as the relationship between neuropathic pain symptoms and number of TPs (135;289).

In the second study [II], relationships between outcome variables included in the ICF measurement framework (Table 3) and TP-count were analyzed with logistic regression in a continuum model, allowing the TP-count to depend on the included ICF variables, and two regression models carried out for a TP-count threshold level, varying between 1 and 17. One model type was carried out for each single covariate, with only the given covariate considered as an explanatory variable (the univariate/marginal model). The other model simultaneously considered all covariates in a multiple logistic regression model (the multivariate/full model). These two models were used in order to uncover whether the covariate was associated to a TP-count above each TP-count threshold, either marginally/in its own respect, or in full/considered simultaneously with other covariates.

TPs were assessed both for number and severity of mechanical hyperalgesia as described in the 1990-ACR guidelines (1). Digital pressure of approximately 4 kg was applied at each of the 18 predefined TP sites, and the patient's pain response at each site was scored as 0 = no pain, 1 = mild pain (complaint of pain without grimace, flinch or withdrawal), 2 = moderate pain (pain plus grimace or flinch), 3 = severe pain (pain plus marked flinch or withdrawal). As the primary goal of this study was to evaluate the relationships between mechanical hyperalgesia and disease severity, a mild pain response (i.e. 1 as recommended by the ACR for classification purposes) was considered potentially ambiguous and the cutoff response was therefore set at ≥ 2.

The three different models showed different strength of relationship between variables and number of TPs. In the first model (the continuum model), none of the included variables from the ICF-measurement framework reached a significance level above 0.05 with the TP-count established at either of the TP-count pain response cutoffs (1 and 2, respectively). Setting the TP-count pain response cutoff at 1, threshold analysis in the univariate/marginal model revealed only a few scattered significances in the higher end of the TP-count threshold spectrum and the multivariate/full model did not function for a TP-count established at a pain response cutoff at 1. With the TP-count pain response cutoff set at 2, TP-count thresholds ≥ 8 were associated with a large number of consistently significant covariates related to pain and pain-related interference with everyday life. The first group of covariates to enter the model was PROs mainly related to pain, fatigue, stiffness and functioning followed by observation-based measures of muscle strength and walking ability, which appeared at a TP-count threshold of 11. The last group of covariates, entering the model at a TP-count threshold at 15, were psychological distress variables (anxiety, depression) and self-reported wellbeing measured with the SF-36. None of these variables appeared as significant explanatory factors at lower TP-count thresholds and pain catastrophizing and pain self-efficacy variables never entered the model. At TP-count thresholds of 1-7 only a few significant covariates were seen and only the ADL motor ability measure of the AMPS was consistently significant.
A notable feature of the results of the univariate/marginal model with the TP-count pain response cutoff set at 2 was that as the TP-count threshold increased, all covariates were either consistently non-significant, only scattered significant, or reached a threshold from where they became consistently significant. This was in contrast to the analysis with the TP-count pain response cutoff set at 2 in the multivariate/full model, where all covariates were considered simultaneously. Here threshold analyses indicated a shift in explanatory variables similar to the shifts in the univariate/marginal model and at the same thresholds. However, whereas the results in the marginal model were more consistently significant, the behavior of the full model suggested a change in explanatory variables. At lower TP-count thresholds covariates related to functioning (the ADL motor ability measure of the AMPS, muscle stiffness, social functioning and work interference) seemed to show the strongest and most consistent relationship with number of TPs. Equivalent to the univariate/marginal model, the next shift in the full model took place for the TP-count threshold of 11; the strongest and most consistent relationship now seemed to be with pressure pain threshold measured by CPA. The last shift took place at the TP-count threshold of 15; here psychological distress variables including ability to reduce pain, pressure pain tolerance measured with CPA, and self-reported tiredness related to mobility entered the model. The latter has been shown to be an early indicator of later disability and use of social and health services among elderly (290).

Figure 9. Number of significant covariates versus tender point count (TPC) thresholds, varying between 1 and 17. Analyzed in a univariate regression model a large number of variables linked to pain and pain-related functional interference appeared as consistently significant explanatory factors from a TPC threshold at 8, indicating a perturbation of clinical disease severity at this threshold [II].
Thus, the result of the study showed that patients with CWP encountered in the clinical setting exhibit a positive relationship between the number of TPs and severity of the clinical pain condition through a TP-count threshold rather than a TP-count continuum. Provided the requirement of a moderate or greater pain response at palpation (TP score ≥ 2), the major shift of disease severity occurred at a TP-count of ≥ 8, above which a large number of variables linked to pain and pain-related interference with everyday life became consistently significant explanatory factors. A graphic representation of this relationship is seen in Figure 9, which provides a direct visualization that the disease severity does not vary much for TP thresholds less than 8, indicative of a pronounced shift in disease severity at this threshold. A similar relationship was not observed if the TP-count in individual patients was based on a TP cutoff set at mild tenderness at clinical examination (TP score < 2), suggesting that a hyperalgesic pain response at palpation should be required in order for TPs to be considered a primary identifier of pain hypersensitivity.

It is noteworthy that in the univariate/marginal model only the ADL motor ability measure of the AMPS was consistently significant throughout the entire range of TP-count thresholds and that a significant relationship between TP-count and self-reported physical functioning was only demonstrated from a TP-count threshold at 8 and above. This finding emphasizes that self-reported and observation-based assessment of functioning may evaluate different aspects of functional ability and the AMPS may prove to be a sensitive and valuable core instrument in the outcome assessment of patients with CWP, particularly at the lower end of the TP spectrum. Contrary to the findings in the univariate/marginal model, self-reported level of pain and fatigue never entered the full model as significant explanatory factors. Pain reduction following treatment has been reported to parallel improvements in other outcomes in patients with CWP, including self-reported physical and social functioning, sleep, and interference with work (229). The interaction between TP-count, pain intensity and functional ability is probably multifaceted. The results of this study indicate that functional ability, whether related to ADL performance or working ability in the multivariate context provides a stronger correlation to number of TPs than level of pain.

Evaluated in an ICF-measurement framework covering core set categories identified for the multidimensional assessment of CWP, the negative impact on scores and measures obtained in the body domain and domains of activity and participation was substantial. Although a wide range of scores on key outcome instruments was observed, patients with a high TP-count reported higher levels of clinical pain, muscle stiffness, tiredness, fatigability and interference with functional ability than patients with a lower TP-count. Setting the TP-count threshold at eight yielded significant group differences in observed ADL task performance as measured with the AMPS, and observation-based assessment of body functions, including measures of pressure pain thresholds, muscle strength and walking ability. No in-between group differences were observed in psychological distress variables or pain self-efficacy variables at this TP-count threshold level, indicating that the pain condition itself and not concomitant psychological distress more likely explained the observed between-group difference of disease impact. These findings are at odds with the affective spectrum disorder hypothesis (30) and support the proposal that the presence and spread of pressure pain hyperalgesia influences the expression of clinical symptoms in CWP.

Using a TP cutoff at eight, based on the requirement of a moderate or greater pain response at clinical examination would assist the identification of patients with CWP and a more severe pain
condition, which could be labeled as fibromyalgia. A similar TP-count threshold of eight has been observed in a study evaluating discriminating clinical features between psoriatic arthritis and fibromyalgia (291), and it has previously been demonstrated that significant decreases in isokinetic maximal voluntary muscle strength only is found in patients with nine or more TPs (292). In further support of our study results, tenderness was included in the inner core set by the OMERACT working group as an essential domain to measure in all fibromyalgia trials. This endorsement was based on analyses of data from ten studies involving four different pharmacological agents, all of which have shown efficacy in fibromyalgia. Patients Global Impression of Change (PGIC) was used as a surrogate measure of overall improvement and was the dependent variable in multivariate regression analyses, against which other identified domains were regressed. Tenderness was retained in the model, as a domain separate from pain, contributing to the variance in PGIC in all studies where it was assessed (185).

In conclusion, a continued use of the manual TP examination in the assessment of patients presenting with widespread musculoskeletal pain is recommended, both for classification purposes and as a clinical marker of pain hypersensitivity and abnormal pain processing. Manual TP-examination should be performed in all patients presenting with multifocal pain in order to assist in advancing a more individualized and pain mechanism focused management. The PDQ, being an easily applied screening tool, may further assist identification of patients with a primarily central pain component in the clinical setting.

Assessment of functional ability in patients with CWP and fibromyalgia

Two of the studies in this thesis [III, IV] aimed at further validation of the AMPS used in the clinical assessment of patients with CWP, and as a potential mean to classify disease severity in this patient population.

The objective of study III was to evaluate the extent of performance difficulties encountered by women with CWP when performing familiar and relevant activities of daily living as measured by the AMPS, and to evaluate the relationship between self-reported and observation-based measures of functional ability in the study population. Two-hundred-fifty-seven women with CWP (mean age 45.5 years), out of whom 77% fulfilled the tender point criteria of ≥ 11 tender points based on a requirement of a moderate or greater pain response at palpation, were evaluated with the AMPS.

The study showed that the observed extent of ADL performance difficulties was substantial, even when compared to other severe and disabling medical conditions including stroke, rheumatoid arthritis, depression, and heart failure. Only 5% of the study population had ADL ability measures comparable to age norms (Figure 10) and a mean ADL motor ability measure corresponding to the lower limit of healthy seventy to eighty-year old women. Supporting the notion of a positive relationship between the number of TPs and severity of the clinical pain condition, a significantly lower mean ADL motor ability measure was obtained in women with ≥ 11 TPs, whereas no group difference was present in the mean ADL process ability measure. Analyzed from a criterion-referenced perspective, 81.3% of the participants had ADL ability measures below the 1.5 ADL motor cutoff and 41.6% below the 1.00 ADL process cutoff, indicating increased effort and/or inefficiency during ADL task performance as well as a potential need of assistance for community living. Thus, in the majority
of the women, the observed performance difficulties appeared to be dominated by motor skill deficits, i.e. increased effort and fatigability during ADL task performance. This finding seems to be in accordance with other studies reporting impaired functioning measured at the body level, e.g. reduced muscle strength and muscle endurance (283;293-295), as well as increased levels of perceived exhaustion and pain during muscle work compared to healthy controls (296).

![Figure 10](image-url) Mean age ADL motor and ADL process ability measures in healthy subjects and study participants of the age range 20.4 to 71.5 years. The obtained mean age ADL motor and ADL process ability measures in the study population were all below age mean of healthy subjects of corresponding age, and the mean age ADL motor ability measure below the 1.5 logit competence cutoff, indicating individuals with potential need of assistance in everyday life in all age groups [III].

These findings are also in accordance with studies investigating how women with fibromyalgia perceive the impact of the disease on everyday life. Henriksson et al. (169), using diaries, found that daily life tasks, especially those related to motor performance, took longer time and caused frequent pauses and rest periods. Arnold et al. (183) found, based on focus group interviews, that the ability to complete self-care and household tasks was severely limited and placed a burden on spouses who had to take on a greater share in household chores. The authors stressed that the degree of effort required to complete an ADL task is an important aspect of functioning and argued the need for better instruments to measure these aspects of functioning. It seems that the AMPS is able to capture these aspects of ADL task performance difficulties encountered by women with CWP and verify patients’ verbalized concerns of increased effort and fatigue, decreased efficiency and need for assistance. In further support of the applicability of the AMPS in this patient population are the findings in study II. Here only the ADL motor ability measure of the AMPS entered the regression model as a consistently significant explanatory variable throughout the entire range of TP-count thresholds, suggesting that the AMPS may be a sensitive and valuable core instrument in the outcome assessment of patients with CWP, particularly at the lower end of the TP spectrum.

The physical functioning subscales of the FIQ (187) and SF-36 (188;189) are the most commonly used self-report tools, when assessing functional ability in patients with CWP and fibromyalgia (199).
Both instruments were included in study III in order to assess the relationship between self-report and observation-based assessment of functional ability in this patient population. Despite the fact that these self-report instruments and the performance-based ADL ability measures of the AMPS concern similar ADL tasks, the obtained level of agreement was low. Such discrepancy, has also been demonstrated in patients with e.g. inflammatory rheumatic diseases (297;298), supporting that instruments based on observation and self-report assess different aspects of functioning.

The objective of study IV was to evaluate relationships between observed functional ability, specified as ADL motor and ADL process ability as measured with the AMPS, and key outcome variables included in the ICF measurement framework (Table 3). Furthermore, to evaluate if relationships between ICF-variables and measures of observed functional ability differed from those obtained for self-reported functional ability on the FIQ and SF-36. The study showed that neither self-report of functional ability using standardized questionnaires nor surrogate measures of functioning obtained at the body level can substitute for observation-based assessment of ADL ability in patients with CWP. Only moderate relationships between AMPS ADL ability measures and observation-based measures of body functions, e.g. hand and knee muscle strength and measures of mobility (6-MW test) were observed. Also the composite scores of the FIQ and SF-36, often used as a surrogate measure of overall disease severity or symptom burden in patients with fibromyalgia, showed a weak relationship with the ADL ability measures of the AMPS, indicating that perceived health and observed activity limitations are not directly related.

Further supporting that the AMPS provides a more accurate and psychometrically robust measure of ADL ability in CWP populations, the results of study IV demonstrated a significant contribution from pain and psychosocial variables to the variability in self-reported functional ability, but not to the variability in the ADL ability measure of the AMPS. The influence of the patients’ psychosocial profile did in particular apply to the variability of self-reported functional ability on the FIQ, where almost 55% of the variability was explained by pain and psychosocial variables, and where no observation-based measures entered the regression model as significant explanatory factors. Such contribution from pain and psychosocial variables to the variance in self-reported functional ability evaluated with the currently most widely used functional assessment questionnaires are likely to influence their usefulness in studies focusing on functional outcomes and other important interrelationships between pain and functional ability. Although there seems to be considerable evidence supporting that, for example, co-existence of depressive symptoms in patients with fibromyalgia is associated with increased pain and disability (157) and that significant pain relief leads to improvement in physical and social functioning (229;230), it should be noted, that these associations have mainly been evaluated based on self-reporting of functional ability.

In conclusion, self-reported functional ability and observation-based assessments obtained at the body level cannot substitute for observation-based assessment of ADL ability in CWP populations. They measure different aspects of functioning and offer distinct and supplementary information. Patients’ perception of functional ability may be related to other factors associated with the pain problem, including patients’ pain-related beliefs and ability to adjust to chronic pain. It is recommended to include valid observation-based assessment tools, such as the AMPS, in the clinical assessment of patients with CWP and future clinical pain and rehabilitation studies addressing functional outcomes in this patient population. Recognizing that everyday life problems are
substantial in patients with CWP and that the AMPS seems able to capture how women with CWP perceive the impact of the disease on everyday life, it is also suggested that the AMPS – from the perspective of rehabilitation - may be used to classify disease severity in this patient population.

The validity of self-rating depression scales in patients with CWP – own results

The Major Depression Inventory (MDI) (299) is one of the most commonly used self-rating depression scales in Denmark (300). The MDI is criterion based and provides a potential depression diagnosis according to ICD-10 (and DSM-IV) criteria, and a severity score for monitoring the condition. The MDI is recommended by the Danish National Board of Health for routine screening and diagnostic assessment of depression in high-risk categories of primary care patients, including individuals with chronic pain conditions (301). Further, the MDI has been used in clinical studies on chronic pain populations (302;303). The psychometric properties of the MDI has been evaluated in mental health (304-306) as well as population-based samples (307) using clinician-assessed diagnosis of depression as the validity index. Adequate sensitivity and specificity of the MDI algorithm for depression are reported in clinical samples of depressed patients (304), but have found to be low in population-based samples (307). MDI cut points rather than the diagnostic algorithm have therefore been proposed for population-based studies (307).

The psychometric properties of the MDI applied in chronic pain populations have never been evaluated and most of the available studies on mental health and population-based samples are based on a classical test theory paradigm. Rasch measurement models are increasingly used in psychometric studies based on item response theory and allow detailed analyses of an instrument’s rating scale structure and of further aspects of validity and reliability. This includes examination of unidimensionality, i.e., fit of individual scale items to a unidimensional model indicating assessment of a single construct (depression), as a prerequisite for measurement. The internal validity of the MDI has previously been evaluated in a smaller sample of depressed patients, based on item response theory (Rasch analysis, Mokken analysis) as well as classical psychometric testing (principal component analysis) (306). The study supported acceptable unidimensionality of the MDI scale, but with suboptimal fitting of two somatic items (sleep, appetite) in the Rasch analysis and the lowest factor loading of these items in the principal component analysis (306).

The objective of the fifth study [V] in this thesis was to evaluate the psychometric properties of the MDI when used to identify and quantify the depression severity among females with CWP, based on Rasch analysis; further, to explore relationships between MDI scores and other widely used measures of emotional functioning in this patient population. Two-hundred-sixty-three females diagnosed with CWP and referred for rehabilitation completed the MDI as part of baseline evaluation. Rasch analysis was applied to this dataset. The study showed that although the MDI has demonstrated adequate psychometric properties when applied in mental health and background populations, the instrument demonstrated insufficient psychometric properties when applied in a clinical sample of female patients with CWP and fibromyalgia. The Rasch analysis revealed substantial problems with the rating scale properties (threshold disordering) as well as lack of unidimensionality (misfit of items related to sleep, appetite, and bad conscience) suggesting a serious threat to the validity of the inherent diagnostic algorithm and depression severity scores provided by the instrument in this patient population.
The MDI classified 32% of the study population with major (moderate, severe) depression based on conventional cut points versus 23% when using the ICD-10 algorithm. However, the obtained hierarchical order of item difficulty in the Rasch analysis (i.e. the scale items position on a continuum from less difficult to more difficult) showed a characteristic pattern, which differed from the symptom endorsement pattern obtained with the MDI in a sample of patients with different states of depression (306). In our sample, the more difficult items (i.e. the least endorsed items) were mainly items related to depressed mood and negative view of oneself, whereas the easier items (i.e. the most endorsed items) were related to lack of energy, poor sleep, difficulty concentrating and loss of interest in daily activities. This finding is in accordance with the findings by Morley et al (210) and supports that the relatively high scores on the MDI and other self-rating depression scales, rather than pertaining to depressed mood and negative view of oneself, are primarily related to a common core of pain-related somatic items in chronic pain patients. The results of such psychometric studies emphasize the need for careful consideration when interpreting questionnaire-derived scores of depression implemented in clinical and epidemiological research, dedicated to discerning the nature of the relation between depression and chronic pain. This may in particular apply to patients with fibromyalgia, as the observed symptom endorsement pattern on the MDI showed a substantial overlap with the aggregate of symptoms suggested as the core of the newly proposed symptom-based diagnostic and survey criteria for this pain condition (32;35).

The operationalized depression domain in the MDI is conceptualized as comprising a set of symptoms covering the ICD-10 and DSM-IV symptoms of depression. However, a very strong association between the MDI score and scores of anxiety and general mental wellbeing obtained with other self-report instruments was observed in this study indicating that rather than being a score of the domain of depression, the MDI score reflects a more general score of emotional distress, in patients with CWP. The Rasch analysis supported the possibility of developing the MDI into a psychometrically sounder version, providing linear measures of an undimensional construct in patients with CWP. Whether this construct should be equated with depression as understood in psychiatric settings is debatable.

In conclusion, from the perspective of the Rasch rating scale model, the MDI demonstrated insufficient psychometric properties when used to identify and quantify the severity of depression in a clinical sample of female patients with CWP and fibromyalgia. It is therefore recommended not to use the inherent diagnostic algorithm or depression severity scores provided by the instrument to assess depression in this patient population. Depending on the specific objective of the study, supplemental analyses could be conducted to separately examine non-somatic and somatic aspects of emotional functioning, applying a Rasch adapted version of the instrument.

Outcome of rehabilitation and predictors of functional outcome of rehabilitation in fibromyalgia

In January 2015, the Danish Health and Medicines Authority issued the first national clinical practice guideline addressing the diagnostic assessment and management options for patients with CWP (308). Like other recently published recommendations, also this guideline points out that optimal management requires prompt diagnosis and timely intervention aiming at improving pain-related
disability and health related quality of life, which often requires a multidisciplinary approach. Even though evidence-based recommendations are provided by the guideline for a number of individual pharmacological and non-pharmacological treatment modalities, just as important for the treating healthcare professional is the general principles of management and how individual therapies fit together into an overall plan of management. Currently, there are no official recommendations or directions on how to coordinate the clinical care for this patient population across healthcare professionals and across specialist and primary care setting. Although prevention and early intervention could hold promise for reduction in the extent of disability, only few intervention programs specifically addressing this patient population are available in the Danish healthcare system and long waiting lists rather the rule than the exception. Supporting the need of such specialized care, the newly updated German guideline for the management of fibromyalgia recommend instigation of coordinated, multidisciplinary rehabilitative efforts in the following cases: ‘when participation in the work force is at risk, when participation in social life or ability for self-sufficiency is at risk, or recommended therapeutic modalities are unavailable or insufficiently effective’ (39). Chronic pain among primary care patients is associated with substantial economic burden for the health care system and work force and it has been demonstrated that the costs tend to increase as pain causes more limitations in a patient's daily activities (309). This underlines the need for and potential benefits of improving chronic pain management through specific intervention strategies targeting the impact of pain on daily functioning.

The last two studies included in this thesis (VI, VII) reporting on the first phase of the IMPROvE study, aimed at evaluating the effectiveness of the interdisciplinary rehabilitation program as delivered in the clinical setting, and to identify predictors of differential treatment responses based on post hoc exploratory analyses. In contrast to most other studies in this field, the a priori defined primary outcome was not self-reported, but observed improvements in functional ability as measured by the AMPS. This decision was based on the aforementioned validation of the AMPS as a valuable core instrument in the assessment of ADL ability in this patient population, and an intervention program strategy focusing on increasing participants’ functional ability and pain coping through patient education and adjustment in everyday life. Both domains of the AMPS; the ADL motor ability measure and the ADL process ability measure were considered primary outcomes. The SF-36 Mental Composite Score (MCS) was included as an additional co-primary outcome, in order to address mental functioning as an outcome of intervention. Responders were defined as those patients who achieved an improvement of at least 0.3 logits on the AMPS ADL motor or ADL process scale during the study period, which is reported to represent a clinically meaningful change (279). An improvement of at least 6 points on the SF-36 MCS was considered to reflect a clinically meaningful change, based on one-half standard deviation obtained in a clinically matching sample of 271 women from the CWP-cohort (Table 3).

In study VI, 192 females, all fulfilling the 1990-ACR criteria for fibromyalgia, were consecutively recruited from the outpatient clinic and randomized to either immediate participation in the rehabilitation program or a waiting list control group. The rate of attendance in the intervention group was high; 100% in 53% of the patients (i.e. no days missed), and 87.5% of the patients attended five or more days, indicating that the rehabilitation program in general was well accepted by the patients. The results of the study showed that even in fibromyalgia patients presenting with longstanding pain and a
substantial disability established over many years, the two-week, group-based rehabilitation program resulted in observable improvements of functional ability in a subgroup of patients. Primary endpoints in the randomized controlled trial were partly achieved with a statistically significant improvement in mean ADL motor and ADL process ability measures in the intervention group compared to the waiting list control group at 6-months follow-up (Table 5).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Rehabilitation group</th>
<th>Control group</th>
<th>Group Difference (95% CI)</th>
<th>P-value1</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPS ADL motor logits</td>
<td>0.23 (0.15 to 0.31)</td>
<td>0.02 (-0.05 to 0.10)</td>
<td>0.20 (0.09 to 0.31)</td>
<td>.0003</td>
</tr>
<tr>
<td>AMPS ADL process logits</td>
<td>0.07 (0.02 to 0.12)</td>
<td>-0.13 (-0.18 to -0.08)</td>
<td>0.20 (0.12 to 0.27)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>SF-36 MCS</td>
<td>2.29 (0.41 to 4.18)</td>
<td>1.15 (-0.73 to 3.03)</td>
<td>1.14 (-1.52 to 3.81)</td>
<td>.40</td>
</tr>
<tr>
<td>AMPS ADL process responder, no. (%)</td>
<td>17/96 (18%)</td>
<td>9/95 (9%)</td>
<td>8.2% (0.2% to 16.3%)</td>
<td>.045</td>
</tr>
<tr>
<td>AMPS ADL motor responder, no. (%)</td>
<td>35/96 (36%)</td>
<td>24/95 (25%)</td>
<td>11.2% (0.4% to 22.0%)</td>
<td>.041</td>
</tr>
<tr>
<td>SF-36 MCS responder, no. (%)</td>
<td>26/96 (27%)</td>
<td>26/95 (27%)</td>
<td>-0.3% (-9.1% to 8.6%)</td>
<td>.95</td>
</tr>
<tr>
<td>SF-36 PCS</td>
<td>1.35 (0.27 to 2.43)</td>
<td>0.78 (-0.30 to 1.86)</td>
<td>0.57 (-0.95 to 2.10)</td>
<td>.46</td>
</tr>
<tr>
<td>SF-36 PCS responder, no. (%)</td>
<td>26/96 (27%)</td>
<td>22/95 (23%)</td>
<td>3.9% (-5.4% to 13.2%)</td>
<td>.41</td>
</tr>
<tr>
<td>SF-36 physical function</td>
<td>1.10 (-1.34 to 3.55)</td>
<td>1.58 (-0.87 to 4.03)</td>
<td>-0.48 (-3.94 to 2.99)</td>
<td>.79</td>
</tr>
<tr>
<td>FIQ total</td>
<td>-1.28 (-3.90 to 1.33)</td>
<td>-1.37 (-4.01 to 1.28)</td>
<td>0.08 (-3.64 to 3.80)</td>
<td>.96</td>
</tr>
<tr>
<td>FIQ VAS pain</td>
<td>0.07 (-0.31 to 0.44)</td>
<td>-0.14 (-0.52 to 0.24)</td>
<td>0.21 (-0.32 to 0.74)</td>
<td>.44</td>
</tr>
<tr>
<td>GAD-10 anxiety score</td>
<td>-0.78 (-2.01 to 0.46)</td>
<td>-0.54 (-1.80 to 0.72)</td>
<td>-0.24 (-2.00 to 1.53)</td>
<td>.79</td>
</tr>
<tr>
<td>MDI depression score</td>
<td>-1.73 (-3.19 to -0.27)</td>
<td>-0.47 (-1.96 to 1.01)</td>
<td>-1.26 (-3.34 to 0.82)</td>
<td>.23</td>
</tr>
<tr>
<td>CSQ pain catastrophizing score</td>
<td>-1.80 (-2.89 to -0.70)</td>
<td>-0.47 (-1.57 to 0.63)</td>
<td>-1.32 (-2.88 to 0.23)</td>
<td>.096</td>
</tr>
<tr>
<td>PSQ pain self-efficacy score</td>
<td>3.10 (1.37 to 4.82)</td>
<td>1.48 (-0.25 to 3.22)</td>
<td>1.61 (-0.84 to 4.06)</td>
<td>.20</td>
</tr>
</tbody>
</table>

Values are Means (95% CI) unless otherwise noted.  
1Continuous outcomes analysed using analysis of covariance (Difference between means); Dichotomous outcomes analysed using Chi-square tests comparing proportions responding (Risk Difference).

Table 5. The IMPROvE study; change from baseline in primary and secondary outcomes in the ITT-population (N=192)
However, responder analyses demonstrated large inter-individual patient variability and that a clinically meaningful improvement in AMPS ADL ability measures only was obtained in a subset of patients. No improvement in patient-reported primary or secondary outcomes, including scores of self-reported functional ability on standardized questionnaires, was observed at 6 months post intervention.

The performance difficulties encountered by the women in our study population appeared to be dominated by ADL motor skill deficits, and it was within this domain that most patients achieved a clinically meaningful improvement: less observable effort and fatigability during ADL task performance. Clinically relevant improvements in ADL ability were observed in participants presenting both with substantial and less substantial ADL disability at baseline. There might be several reasons for these results. Interventions that are adaptive and compensatory in nature, such as teaching patients to use energy saving techniques targeted at reducing the amount of effort and fatigue when performing daily life tasks, could be argued to mainly affect ADL motor ability. Secondly, some energy saving techniques, like pausing to take a break, result in lower scores in some ADL process skills, due to “less efficient” use of time. In other words, adaptations to reduce effort or fatigue might be at the cost of reduced efficiency, which is reflected in the ADL process ability measures of the AMPS. Both the ADL motor ability and the ADL process ability measure have utility as indicators of independence in the community. Studies suggests that the ADL motor ability scale may be more accurate than the ADL process ability scale in predicting the need for assistance in patients with musculoskeletal pain, and propose the following ADL motor competence cutoffs; $\geq 1.5$ logits: independent ADL task performance but demonstrates increased effort and fatigability, $1.0$ logit to less than $1.5$ logit: in possible need of minimal assistance, $< 1.0$ logit: in possible need of moderate to maximal assistance (282). A clinically meaningful improvement of 0.3 logits may therefore be sufficient to raise the functional status of a given individual from one competence level to another, and thereby support a continued engagement in increasingly challenging ADL tasks. Given the considerable ADL motor disability observed in our study population and an intervention focusing on patient education and adjustment in everyday life, that is requiring participants to make a number of lifestyle changes, analyses over even longer time horizons seem warranted and may reveal further benefits of the intervention. It could also be speculated that patients characterized by such substantial disability, as the individuals attended in our outpatient clinic, might gain from a more comprehensive rehabilitation program or ‘add on interventions’ individualized to address specific needs of individual patients. The second phase of the IMPROvE study (Figure 7), not reported on in this thesis, was designed to address some of these questions, including the effect of graded intervention models (add on physiotherapy or occupational therapy) and the long-term outcome of the rehabilitation program evaluated at 2-years-follow-up.

The results of the study also indicated a decline in ADL process ability during the 6-months intervention period in patients allocated to the waiting list. Process skills are essential for an efficient and independent ADL task performance. When problems in ADL motor skills occur, there is an increased demand on the ADL process skills that reflect the underlying organizational and adaptive capacities of the individual (e.g. ability to use cognitive compensation, ability to use alternative or compensatory strategies). Concomitant influence on process skills by for example increased pain, distress or environmental barriers may decrease the capacity to adapt to or compensate for ADL motor skill deficits and places the individual at even higher risk for loosing independence (279).
Patients with chronic pain often face long waiting times to access specialized, multidisciplinary pain services, which seems unfortunate as the results of this study indicates that this may contribute to further functional loss in these patients.

Cognitive-behavioral models of chronic pain theorize an important role for pain-related beliefs and coping responses in patient’s adjustment to chronic pain and subsequent development of pain-related disability (67;245;310). These associations, however, have mainly been investigated using self-reported assessment of functional ability, i.e. addressing patients’ perception of their level of disability and not their actual performance. This may explain why this study found a significant improvement in functional ability as measured with the AMPS, despite the lack of clinically relevant improvements in self-reported measures traditionally linked with functional outcome, e.g. catastrophic thinking and pain self-efficacy, at 6-months follow-up. It may also be that the belief patterns in patients with long-standing pain recruited from tertiary care settings are not easily changed and that the rehabilitation program was not therapeutically sufficient to induce such changes. The multidisciplinary rehabilitation program was specifically designed to enhance functional ability and contained only few elements of cognitive-behavioral treatment provided at a group level. It could therefore be assumed that a prolonged and more individually tailored rehabilitation program, designed to help patients re-conceptualize their views of their problems, might have been more appropriate to increase patients’ self-efficacy beliefs and their perceived level of disability. Almost all psychological interventions for chronic pain have been shown to be effective, at least for some individuals, but the emphasis of treatment probably need to be individualized and address specific maladaptive beliefs or reinforce more appropriate ones to initiate major changes in belief patterns.

Furthermore, the study also supported the lack of association between self-reported symptom burden and observed ADL ability in this patient population. In line with other studies reporting that there is no convincing evidence for a sustainable long-term effect of rehabilitation on key symptoms and health-related quality of life (170;245), this study could not demonstrate improvement in patient-reported pre-post changes in the core outcome domains of pain, fatigue, and negative mood as an outcome of rehabilitation. However, the level of symptom reporting seems to be fairly stable over time in patients with fibromyalgia (52) and one can speculate about the factors that affect the quality of life of patients with chronic pain. It has been suggested that perhaps we have underestimated the complexity of behavioral changes and the social and psychological influences that maintain disability in chronic pain patients (250). Patients with pending social welfare litigation are most often excluded from clinical trials and knowledge about the influence of this social stressor on outcome in fibromyalgia patients are therefore limited (170). The reported work disability in our patient population was high and almost half had pending social welfare litigation at the time of enrolment. Post hoc analyses revealed no differences in baseline characteristics in patients with and without a pending social welfare application, including baseline measures of AMPS ADL motor and process ability. However, in the ITT population (n=102) without a pending social welfare application, a significant larger proportion of patients obtained a clinically relevant improvement in ADL motor ability measures, indicating a better treatment response in this subgroup. Few studies have used the AMPS as a predictor of work-related outcome (311;312). In one study, assessing the work performance of vocationally disabled individuals in Belgium, it was suggested that an AMPS ADL motor ability measure below 2.5 logits combined with an ADL process ability measure below 1.2 logits was insufficient for regular employment (312). None of the patients in our study population was above
the 2.5 logits on the AMPS ADL motor scale at 6-months follow-up. This suggests that return to regular employment hardly is a realistic treatment goal in most fibromyalgia patients managed in tertiary care settings, and underlines the importance of a timely and coordinated work rehabilitation effort. Although not reflected in any of the patient-reported outcomes, this study finding also indicates that pending social litigation may be a social stressor, which contributes to the maintenance of disability in patients with fibromyalgia and impede the functional outcome of rehabilitative efforts in this patient population.

Stratifying patients into streams of care matching based on identified predictors of outcome of rehabilitation may further ensure optimized treatment outcomes. Although functioning is considered a core outcome domain in fibromyalgia (185), only few studies have explored predictors of physical functioning as an outcome of multi-component therapy in this patient population (158). In the aforementioned review by Rooji et al., which included 14 studies evaluating predictors of outcome of multi-component therapy in fibromyalgia, only five studies addressed predictors of physical functioning as an outcome of intervention (158). Outcome assessment was solely based on self-report of physical functioning (260;261;266;313;314) and only one study applied a randomized, controlled trial design (266) (Table 1). The review reported weak evidence for poorer outcomes for physical functioning being associated with higher baseline levels of depression and for better outcomes for physical functioning being associated with worse baseline status and high pain intensity (158).

The last study included in this thesis (VII) was based on an exploratory analysis of outcome data from the IMPROvE study. The goal of the study was to explore if any of the baseline variables predicted differential treatment effects when the outcome of interest was defined as a clinically meaningful improvement in AMPS ADL ability measures at the 6 months follow-up. Seventy-four (38.7%) of the 191 participants included in the overall ITT-population could be classified as AMPS responders, i.e. obtained an improvement of ≥ 0.3 logits in the AMPS ADL motor ability measure and/or ADL process ability measure during the study period. For both groups combined (intervention and waiting list control group), being an AMPS responder was associated with a lower reported intake of weak analgesics, better self-reported social functioning and less bodily pain assessed with the SF-36, higher pressure pain thresholds measured with CPA, and a lower AMPS ADL motor ability measure at baseline. These five variables identified in the bivariate analyses as being associated with the outcome at a significance level of 0.05, together with the randomization stratification variable, were included as covariates in all subsequent logistic regression models.

Analyses based on these logistic regression models, one for each potential predictor, showed that out of the 52 baseline variables analyzed, only four had potential predictive value as assessed by evaluating their interaction with group allocation (i.e. treatment group): intake of weak analgesics (P= .013), intake of strong analgesics (P=.017), total score on the PDQ (P=.032), and score of current pain on the PDQ (P=.036). To further describe the nature of interactions, adjusted Odds Ratios (ORs) with corresponding 95% confidence intervals (95% CI) were calculated for the association between treatment group and the outcome, separately for each high/low subgroup corresponding either to the binary predictor variables or obtained by dichotomizing the continuous predictor variables at the median. The results of the stratified exploratory analyses suggested that patients participating in the rehabilitation program were significantly more likely to achieve a clinically meaningful improvement in observed functional ability (compared to those assigned to the waiting list) for specific subsets of
patients, including those who had a low intake of weak and strong analgesics, a high total score on the PDQ, and a high score of current pain on the PDQ (Table 6).

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>Predictor variable “low” at baseline</th>
<th>Predictor variable “high” at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intake of weak analgesics</td>
<td>25.55</td>
<td>2.92-223.7</td>
</tr>
<tr>
<td>Intake of strong analgesics</td>
<td>5.70</td>
<td>1.85-17.54</td>
</tr>
<tr>
<td>PDQ total score</td>
<td>1.28</td>
<td>0.47-3.48</td>
</tr>
<tr>
<td>PDQ current pain</td>
<td>1.30</td>
<td>0.48-3.48</td>
</tr>
</tbody>
</table>

* Values are the adjusted (for the covariates) odds ratios and corresponding 95% CIs; for the last 2 predictors “low” corresponds to below the median and “high” to at or above the median

**Table 6.** Subgroup specific odds ratios for the association between treatment group and having clinically significant improvement in AMPs ADL ability measures at 6 months post treatment.

The strongest predictor of having a positive treatment outcome was found to be the baseline intake of weak analgesics (mainly acetaminophen). Among those with a low intake of weak analgesics at baseline, the OR for the association of treatment with the outcome was 25.55 (95% CI: 2.92-223.77) as compared to an OR of 1.45 (95% CI: 0.68-3.08) for those with a high intake. Based on the general safety profile of acetaminophen, it seems unlikely that a high occurrence of drug-related side effects may have impeded functional gains in the group of participants with a high intake of weak analgesics. Prospective cohort studies in patients with fibromyalgia do support the association of opioid use, including tramadol, with negative health-related and functional outcomes (234), which possibly could be ascribed to the profile of side effects in these drug classes. Consistent with this, an initial low intake of strong analgesics (opioid medications including tramadol) seemed to predict a better functional outcome of intervention (OR=5.70 for participants with a low intake vs. OR=0.87 for participants with a high intake at baseline). Baseline intake of NSAIDs or other centrally acting drugs (antidepressants and anticonvulsants) showed no association with the functional outcome and no interaction with treatment allocation.

The main objective of pain rehabilitation programs is not to cure pain, but emphasizes self-control and self-management of symptoms, which requires patients to make a number of lifestyle changes and to engage in active coping strategies. However, research suggest that people vary in their readiness to adopt a self-management approach to their pain as an alternative to traditional medical interventions, and that patients’ own beliefs and expectations concerning how their pain should be managed may have an important influence on treatment outcomes (315-317). The current study did not include an assessment of patients’ readiness to adopt a self-management approach to chronic pain, including patients’ beliefs in medical cure for pain and the importance of medication as a treatment for pain.
Still, it could be speculated that patients with a low intake of analgesics are generally more inclined towards engagement in active pain coping strategies, promoting more positive outcomes of rehabilitative interventions focusing on increased self-management, and improvement of functional ability through adjustment in everyday life. This hypothesis needs to be tested in future studies. Identification of patients’ pre-treatment beliefs that may interfere with adherence to self-management and outcome of rehabilitation would permit targeting of patient education and structuring interventions to take advantage of important characteristics of patients that may enhance functional outcomes (318). Further, the results of the study underline the need for controlling for medication in outcome studies focusing on non-pharmacological interventions.

Patients' baseline level of pain and pain-related interference with functioning are reported to influence the outcome of multi-component therapy in patients with fibromyalgia (158). The results of the exploratory analysis from this study, suggested that not only the level of pain, but also patients’ clinical pain phenotype may influence the functional outcome of the intervention. The results indicated that among patients with a high score of current pain and total score on the PDQ, those treated were more likely to achieve a better functional treatment outcome than the controls. Thus, the results of the exploratory analysis suggested that patients with more pronounced clinical signs of central sensitization were more likely to benefit from the treatment by achieving a positive functional outcome of intervention. This finding was further supported by an observed borderline predictive value of the pressure pain threshold measured with CPA (P=.058), where an initial low pressure pain threshold seemed to predict a better functional outcome of intervention (OR=3.50 (95% CI: 1.17-10.47) for participants with a low pressure pain threshold vs. OR=1.53 (0.60-3.89) for participants with a high pressure pain threshold at baseline). Perceived muscle fatigue during exhaustive muscle contraction is prominent in fibromyalgia and studies indicate that this may be of central rather than peripheral origin (296). Exercise therapy, most often administered by physiotherapists, is recommended either alone or as an integrated part of multi-component therapy for patients with fibromyalgia (37;46). Occupational therapy was a core modality in the current interdisciplinary rehabilitation program, and was focused on adaptive and compensatory intervention strategies targeted at reducing the amount of effort and fatigue when performing daily life tasks. This could be argued to mainly affect ADL motor ability and in particular match the needs of patients with a more pronounced pain hypersensitivity and fatigability.

Although several psychosocial, cognitive and behavioral factors have been reported to be predictive of functional outcomes for many pain syndromes, this study did not support a predictive value of study participants' baseline levels of self-reported or observed functional ability, psychological (depression, anxiety, mental wellbeing) or cognitive (catastrophizing, pain self-efficacy) factors, or overall symptom burden. In most studies on fibromyalgia, outcome assessment has been based on self-report, including self-reporting of functional ability. This may explain why this study, investigating predictors of observed ADL-ability as an outcome of rehabilitation, could not demonstrate such relationships. Taken together these findings seem to support advancement of pain mechanism-orientated management of patients with CWP and fibromyalgia, rather than graded intervention models based on case severity defined by the level of overall symptom reporting.

In conclusion, even in fibromyalgia patients presenting with a substantial disability established over many years, the two-week, group-based rehabilitation program resulted in observable
improvement of ADL ability as measured with the AMPS at 6-month follow-up. However, responder analyses demonstrated large inter-individual patient variability and post hoc analyses indicated that pending social welfare litigation influenced the response rate. The improvement in AMPS ADL ability measures was not reflected in any patient reported outcomes, including self-reported functional ability on standardized questionnaires. The post hoc exploratory predictor analyses suggested that several subgroups of patients, specifically those with a low baseline intake of weak and strong analgesics, and more pronounced clinical signs of central sensitization, may have the most clinical benefit from rehabilitation when the outcome of interest is improvement in observed functional ability. It is recommended that the identified predictors may be used to direct the allocation of patients to rehabilitation programs targeting these characteristics, that is, rehabilitation programs developed for patients with widespread pain and pain hypersensitivity that focus on adaptive and compensatory intervention strategies. The results also suggest that patients’ pre-treatment beliefs and readiness to engage in active pain coping strategies may interfere with functional outcomes of rehabilitation programs. A next step will be to determine whether knowledge of these outcome predictors may assist to inform future designs of better tailored rehabilitation programs that take into account individual patients’ baseline characteristics in order to increase both the cost-effectiveness and the clinical effectiveness of interventions. Earlier intervention aiming at prevention of, or at least minimization of, long-term disability should also be prioritized.

4. Concluding comments and future research perspectives

This thesis has attempted to provide an overview of areas that contribute to the understanding of the clinical concept of CWP and fibromyalgia, as well as aspects of clinical assessment and management of this patient population from the perspective of rehabilitation. Considering the complexity of chronic pain states characterized by widespread pain and pain hypersensitivity, it is not surprising that many questions remain unanswered and that many avenues of research that may have clinical implications still need to be pursued. The following main conclusions and suggestions for future research directions were developed:

The clinical concept of CWP and fibromyalgia

During the past decade, there has been a vast expansion of knowledge regarding the underlying neurophysiological mechanisms involved in development of chronic pain, and research has provided persuasive evidence for the role of augmented central pain processing in fibromyalgia. Yet the legitimacy of fibromyalgia as a diagnosis in its own right and the relationship between fibromyalgia and CWP without authenticated tender points is a subject of debate. Population-based studies have conclusively demonstrated that CWP is very common, it is sometimes accompanied by tenderness, distress and other somatic symptoms – and when this does occur, CWP is more likely to be persistent than transient and to lead individuals to seek medical care. The 1990-ACR classification captures only of about 20% of individuals with CWP and there is no clear clinical diagnosis for the remaining 80%. Manual tender point examination used for classification purposes in the clinical context, although linking fibromyalgia features to augmented central pain processing, has therefore been questioned.

The studies included in this thesis supported a continued use of the manual tender point examination in the assessment of patients presenting with widespread musculoskeletal pain, both for
classification purposes and as a clinical marker of pain hypersensitivity and abnormal pain processing. It could be demonstrated that patients with CWP encountered in the clinical setting exhibit a positive relationship between the number of tender points and severity of the clinical pain condition through a tender point count threshold, and that the major shift in disease severity occurred at tender point count of ≥ 8. Using a tender point cutoff at eight, based on the requirement of a moderate or greater pain response at clinical examination would assist the identification of patients with CWP and a more severe clinical pain condition, which could then be labeled as fibromyalgia. It should be noted that, just as for fibromyalgia, criteria for many other rheumatic and medical diseases are arbitrary. Whatever the medical position on fibromyalgia, the care of patients is essential. Rigidly adhering to a tender point criterion in routine clinical practice should be avoided, in order to instigate timely and relevant intervention.

Whereas the pain processing system has been extensively investigated in patients fulfilling the 1990-ACR criteria, such studies are missing in patients with CWP and fewer than 11 tender points. It is reasonable to assume that the underlying pain mechanism in these individuals as well is central rather than peripheral in nature. Neuroimaging and other pain experimental studies are needed to clarify this aspect, and to examine if the nature and magnitude of aberrant central pain processing is related to clinical disease expression and supports that CWP and fibromyalgia are part of a severity spectrum of pain in the general population. Studies focusing on early intervention should also be prioritized; in order to develop healthcare strategies that identify individuals characterized by augmented central pain processing earlier, and intervene effectively before pain-related disability and maladaptive pain behaviors create therapeutic inertia.

Clinical assessment of patients with CWP and fibromyalgia

Supporting the above mentioned, patients referred to specialized pain rehabilitation programs are generally characterized by considerable chronicity. The symptom duration in the patients included in this thesis averaged 10 years and evaluated in an ICF framework patients’ exhibited a high pain-associated symptom burden as well as substantial limitations in activity and societal level functioning. Only 21% were employed or enrolled in education at the time of referral. Still, most patients had received their fibromyalgia diagnosis within the last three years, supporting that fibromyalgia continues to represent a challenge to healthcare professionals and patients, delaying timely and targeted rehabilitative efforts. Well-defined criteria for disease severity and disability in patients with CWP and fibromyalgia, based on standardized assessment methods therefore seem important.

The studies included in this thesis supported the use of the AMPS as a valuable core instrument in this patient population, both in the clinical context and for research purposes. Evaluated with the AMPS, the observed extent of ADL task performance difficulties in the overall clinical sample of 463 individuals was substantial and indicated a potential need of assistance in everyday living in individuals across all age groups. The encountered ADL tasks performance difficulties was dominated by motor skill deficits, in terms of increased effort and fatigability during ADL task performance, corroborating patients’ perceived impact of pain on daily life activities, and was more pronounced in individuals with a high tender point count. Nevertheless, a poor agreement between self-report and observation-based assessment of functional ability was demonstrated. Contrary to the ADL ability measures of the AMPS, scores of functional ability on the most widely used standardized questionnaires was significantly influenced by patients’ pain and psychosocial profile. Such
contributions from pain and psychosocial variables to the variance in self-reported functional ability are likely to influence the usefulness of generic and disease specific questionnaires in studies focusing on functional outcomes and other complex interrelationships between pain and functional ability. The clinical evaluation and evaluation of outcome of rehabilitation is generally accomplished through an assessment of the individual's functional status. The use of the AMPS, being a psychometrically robust, observation-based assessment tool, is therefore recommended both for clinical encounters and in research concerning individuals with CWP and fibromyalgia. Further, it is suggested that the AMPS – from the perspective of rehabilitation – may be used to classify disease severity in this patient population.

Future studies should evaluate the further potential of the AMPS as a mean to characterize patients with CWP and fibromyalgia across a disease severity spectrum and not only address patients encountered in specialized care that are already facing substantial disability:

1) Studies evaluating relationships between observed ADL ability as measured with the AMPS and alterations in central pain processing visualized by functional neuroimaging in individuals with CWP and fibromyalgia, and other painful rheumatic diseases.

2) Studies evaluating if the AMPS can assist early identification of individuals with clinical signs of central sensitization that are likely to develop long-term disability, e.g. if different patterns of AMPS ADL motor and process skill deficit are associated with different long-term functional outcomes.

3) Studies evaluating if the AMPS, across a disease severity spectrum, can assist treatment matching in patients with CWP and fibromyalgia, for instance, identifying patients who will benefit from interventions emphasizing adaptive and compensatory intervention strategies versus patients that might rather benefit from more restorative intervention strategies.

4) Studies evaluating the relationship between functional ability as measured with the AMPS and work prognosis in patients with CWP and fibromyalgia.

**Management of patients with CWP and fibromyalgia**

Acknowledging the substantial negative impact of CWP and fibromyalgia on the individual’s daily life activities and social participation, and moving towards a more rehabilitation-oriented paradigm, may benefit this patient population. Even in fibromyalgia patients presenting with a substantial disability established over many years, a two-week, group-based rehabilitation program resulted in observable improvement of functional ability at 6-month follow-up. However, responder analyses demonstrated large inter-individual patient variability and that only a subset of patients obtained a clinically meaningful improvement in AMPS ADL ability measures. An exploratory predictor analysis suggested that several subgroups of patients, specifically those with a low baseline intake of weak and strong analgesics and more pronounced clinical signs of central sensitization, may benefit the most from rehabilitation programs focusing on adaptive and compensatory intervention strategies.

These findings seem to support advancement of a pain mechanism-oriented management of patients with CWP and fibromyalgia, rather than graded intervention models based on case severity defined by the level of overall symptom reporting. It is recommended that patients characterized by widespread pain and pain hypersensitivity associated with limitations in activity and/or societal level
functioning are referred to specialized interdisciplinary rehabilitation programs. Ideally, the rehabilitation process should also demonstrate continuity and coordination across sectors, where the present challenge seems to be how to implement optimal rehabilitation interventions between health and social services. Development of more tailored rehabilitation programs matching individual patients’ characteristics, as indicated by the stratified predictor analyses, should be developed in order to promote both the cost-effectiveness and clinical effectiveness of interventions. The potential of the ICF to develop rehabilitation care further in the management of CWP and fibromyalgia and to stimulate research with the common goal of optimizing functioning and minimizing disability from the individual and public health perspective should be pursued. It is therefore suggested to prioritize the following research areas:

1) Studies evaluating the long-term effect of interdisciplinary rehabilitation of patients with CWP and fibromyalgia, including sustainability of obtained improvements in observed ADL ability.

2) Studies evaluating which components of interdisciplinary rehabilitation programs works for whom and which components need to be individualized to address specific needs of individual patients, including gender specific needs.

3) Studies evaluating if graded intervention models (e.g. add-on of specific individualized treatment modalities) and development of maintenance-enhancement strategies will improve the clinical effectiveness of interventions and should be included in future rehabilitation programs targeted for patients with CWP and fibromyalgia.

4) Studies evaluating if early intervention in patients with CWP and fibromyalgia may lead to increased functional gains and prevention of long-term disability.

5) Studies evaluating the functional outcome of occupational therapy specifically targeted at increasing participation in and performance of ADL tasks in patients with CWP and fibromyalgia as compared to the functional outcome of conventional exercise therapy.

6) Studies investigating the relationship between patients’ pre-treatment beliefs and readiness to adopt greater responsibility for self-management and improvement in ADL ability as an outcome of rehabilitation.

5. Dansk resumé

Smerteforskningen har gennem de seneste årtier bidraget med megen ny viden, som har øget forståelsen af de komplekse mekanismer, der er involveret i smertesansningen. Vi ved i dag at ændringer i de centrale smertesignalerende- og modulerende systemer formentlig spiller en stor rolle for udviklingen af mange kroniske smertetilstande og at der ved disse smertetilstand ikke kan påvises en årsagsforklaring ved klinisk undersøgelse af perifere væv, så som muskler, sener og led. Generaliserede smirter i bevægeapparatet (CWP), uden oplagt vævsskaderårsagsforsklaer, er hyppigt forekommende og adskiller sig fra de kroniske localiserede smertetilstande ikke alene ved smertens udbredelse, men også i den kliniske præsentationsform og konsekvenserne for det enkelte individ. Patenter med generaliserede smirter rapporterer højere smerteniveau, har færre smertefri
perioder, og ofte er smertene ledsaget af søvnforstyrrelser, træthed, hukommelses-
konzentrationsbesvær samt en betydelig nedsættelse af funktionsevnen, der påvirker den
helbredsbetingede livskvalitet og dagligdags livsførelse. Patienter med fibromyalgi er den mest
undersøgte og dermed bedst karakteriserede undergruppe af patienter med CWP. Der eksisterer
internationalt anerkendte sygdomskriterier for fibromyalgi, der primært er udviklet til forskningsbrug
af ‘the American College of Rheumatology’ (ACR) tilbage i 1990. I henhold til disse kriterier
classificeres patienten som havende fibromyalgi på baggrund af CWP af mere end 3 måneders
varighed og smertereaktion i mindst 11 af 18 forud definerede tender points ved klinisk undersøgelse.
Ikke alle patienter med CWP opfylder ACR tender point kriteriet for fibromyalgi og hos denne
patientgruppe er den kliniske diagnose mere uklar. Både ætiologi og patogene ved CWP er
ufuldstændigt kortlagt, men hos undergruppen, der opfylder ACR kriterierne for fibromyalgi, peger
forskningen på en tilgrundliggende abnorm smerteregulering, der bl.a. omfatter central sensibilisering
(søget smertefølsomhed i centralnervesystemet) og dysfunktion af de smertemodulerende systemer
(smertehændende og smertefremmende systemer). I overensstemmelse hermed har de mest
konsistente objektive fund hos fibromyalgipatienter været dem, der involverer smertesystemet, for
eksempel påvisning af generelt nedsatte tryksmertetærskler i eksperimentelle smertestudier og
ændringer i hjernens forarbejdning af smertefulde stimuli visualiseret med forskellige billeddannende
teknikker, herunder funktions MR-scanning. Symptomerne ved CWP og fibromyalgi udviser generelt
stabilitet over tid, og symptomfrihed eller egentlig helbredelse er kun meddelt kasuistisk. I opfølgende
undersøgelser, strækende sig i op til 11 år, er der rapporteret om generel symptomforværring hos ca.
36%, smerteforværring hos ca. 39% og moderate smerteforbedring hos ca. 25%. Livstidsprognosen
ved fibromyalgi synes derimod at være god.

Patienter med CWP og fibromyalgi gennemgår ofte omfattende og langvarige udredningsforløb, før
der stilles en endelig diagnose og patientgruppen medfører betydelige direkte såvel som indirekte
sundhedsudgifter, for eksempel udgifter i forbindelse med sygefravær og uarbejdsdygtighed. Dette til
trods for at litteraturen peger på, at en hurtig definitiv diagnostisk afklaring beroliger patienten, letter
håndteringen af patienten og reducerer forbruget af sundhedsudgifter. Egne undersøgelser har vist at
patienter, der henvises til behandling i specialiserede enheder, i gennemsnit har haft smertes i 10 år,
er præget af betydelig nedsættelse af funktionsevnen i almindelig dagligdags livsførelse og at kun 21% er
tilknyttet arbejdsmarkedet eller under uddannelse på henvisningstidspunktet. 463 kvinder med
CWP og fibromyalgi blev funktionsevnemålet som led i denne afhandling. Funktionsevnemålingen blev
foretaget med en standardiseret, observationsbaseret ergoterapeutisk test – Assessment of Motor and
Process Skills (AMPS) – der måler kvaliteten af en persons motoriske og procesmæssige færdigheder i
forbindelse med udførelsen af dagligdags aktivitet. Der blev påvist en betydelig nedsættelse af funktionsevnen i hele patientgruppen, som især involverede de motoriske færdigheder. Dagligdags
aktiviteter, såsom madlavning og andet hushold, er således vanskelige at udføre, medfører hurtig
udtrætning og et uforholdsmæssigt stort tidsforbrug. Graden af funktionsevnemødring blev vist at
korrelere med antallet af tender points og var således mest udtalt i undergruppen med fibromyalgi.

Diagnosen fibromyalgi eller CWP giver med baggrund i disse smertetilstandes kompleksitet og en
stor individuel variation sjældent en afklaring af, hvilken behandlingsmæssig indsats den enkelte
patient har behov for. Vurderingen af patienten i behandlingsmæssige sammenhænge bør således
baseres på en individuel helhedsvurdering, som indrager ikke blot de fysiske, men også de
psykologiske, emotionelle og sociale aspekter af smertetilstanden. Overordnet set er målet med
behandlingen at hjælpe patienten til en optimal egen håndtering af smertetilstanden, og at bedre det
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Appendix 1

Description of instruments and assessment methods

Patient reported outcomes (PRO’s)

Short-Form-36 Health Survey (SF-36)
The SF-36 is a generic, health-related quality of life instrument (188;189). It consists of 35 items, which are used to assess eight health domains; 1) limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions. One additional item assesses change of health over the past year and is not scored. Individual items are scored on Likert scales and item responses summed to produce the eight scale scores, which are then transformed linearly into a 0-100 scale, with 100 representing the best possible state of health. Two summary scores, the physical component summary (PCS) and the mental component summary (MCS), are provided and are standardized to reflect a general population mean of 50 and a SD of 10 (319). The SF-36 has been widely used in normal and diseased populations, including subjects with fibromyalgia (320).

Fibromyalgia Impact Questionnaire (FIQ)
The FIQ is a disease specific, self-report instrument developed and validated in 1991 to measure health status in patients with fibromyalgia (187). Modifications were made in 1997, 2002, and 2009, each with different scoring systems. Subscales in the original 1991 version, which was applied in this study, include physical function (10 sub-items), feel good (1 item), missed work (1 item), do job (1 item), pain (1 item), fatigue (1 item), rested (1 item), stiffness (1 item), anxiety (1 item), and depression (1 item). The physical function items use a 4-point Likert scale response set ranging from “always to never”. The feel good item response set is the number of days of the past week. The work missed item response is the number of workdays in the past week. The other symptom-based items use 100-mm anchored visual analogue scales. The score for each item, all standardized to range from 0-10, can be reported individually or summed to report a FIQ total score ranging from 0-100, with higher scores indicating more disease impact. The FIQ is one of the most widely used assessment instruments in fibromyalgia populations, having been cited in over 300 papers and recommended as a primary efficacy endpoint in fibromyalgia clinical trials (199). Adequate test-retest stability (321) and concurrent validity of the FIQ subscales, including depression and anxiety subscales, are reported (187).

Generalized Anxiety Disorder Inventory (GAD-10)
GAD-10 is a self-report instrument developed from the Hamilton 6-item anxiety scale (HAM-A) to assess the severity of generalized anxiety, but is not a diagnostic tool. It contains 10 items, each of which are scored on a 6-point Likert scale according to how much of the time the individual symptom has been present during the past 14 days; 0 representing ‘the symptom has not been present at all’ and 5 representing ‘the symptom has been present all of the time’. Scores are summed up with a theoretical score range from 0-50. Scores between 15-19 are suggested to represent mild anxiety.
disorder, between 20-29 moderate anxiety disorder, and between 30-50 severe anxiety disorder (322).

**Major Depression Inventory (MDI)**
The MDI is developed to cover both the ICD-10 and DMS-IV symptoms of depression (299). It contains 10 items, each of which are scored on a 6-point Likert scale according to how much of the time the individual symptom has been present during the past 14 days; 0 representing ‘the symptom has not been present at all’ and 5 representing ‘the symptom has been present all of the time’. Item 8 and 10 are divided into two sub-items, a and b, but only the highest score on each item is included in the overall scoring of the instrument. As a diagnostic instrument, the MDI items are dichotomized to indicate the presence or absence of each of the symptoms. In both DSM-IV and ICD-10 the items of depressed mood and lack of interest in daily activities (item 1 and 2) are considered core symptoms of depression. In ICD-10, the lack of energy (item 3) is also considered a core symptom. Consequently, for diagnostic purposes, item 1, 2 and 3 are considered significantly present at scores 4 and 5 (i.e. most of the time, all of the time). For the remaining items (item 4-10) the symptom is considered significantly present at scores 3 to 5 (i.e. more than half of the time, most of the time, and all of the time). The algorithm for DSM-IV is: items 4 and 5 are combined and only the highest score is considered. Thus, the number of items is 9. Major depression is defined as the presence of at least five of the nine items. However, either item 1 or item 2 should be among the five items. The algorithm for ICD-10 moderate to severe (major) depression is the presence of at least two of the three core symptoms (items 1-3) and at least four of the other seven items (299). As a measuring instrument, the 10 items are summed up with a theoretical score range from 0-50. A cutoff at 20 representing clinical depression (mild, moderate, severe) and 26 representing major (moderate, severe) depression have been proposed (304;307). The MDI has been validated in mental health (304;306) as well as population-based samples (307) and used in prevalence studies of major depression in the Danish background population (323).

**The Coping Strategy Questionnaire (CSQ)**
The CSQ is a self-report instrument used to evaluate one behavioral and six cognitive coping strategies (324). Scoring of items on each coping strategy subscale are based on the frequency with which they are used (0=never, 6=always) with a total score ranging from 0 to 36. In addition, there are two self-efficacy items reflecting “perceived control over pain” and “ability to reduce pain” with a score ranging from 0 to 6. Pain studies have found significant relations between both the factor scores and subscales of the CSQ and various measures of adjustment to chronic pain (325;326). In these studies, only the subscale for Pain Catastrophizing and self-efficacy items were included in the analysis.

**The Mobility-Tiredness (Mob-T) scale**
The Mob-T scale is one of four subscales of the “Measure of functional ability” developed for the elderly population (327). The Mob-T scale is used to evaluate tiredness related to performance of six mobility items. For each item, the respondents are asked to report if they get tired (0= yes, 1= no) when performing the mobility task. A simple sum score is calculated, the total score ranging from 0 to 6, with low scores indicating more tiredness related to mobility. Tiredness in mobility has been found to be an early indicator of later disability and use of social and health services among elderly (290;327).
The Pain Self-Efficacy Questionnaire (PSEQ)
The PSEQ is a self-report instrument developed to assess self-efficacy beliefs in individuals with chronic pain. It contains 10 items where patients are asked to reflect their ability to perform activities despite their pain. Items reflect a variety of tasks and activities, frequently reported as problematic for patients living with chronic pain. The patients are asked to rate their confidence in own ability to perform the different activities despite their pain, by selecting a number on a 7-point numeric scale, where 0 equals not at all sure, and 6 equals completely sure, yielding a sum score ranging from 0-60, with higher scores indicating greater pain self-efficacy. Psychometric testing of the source version, found the instrument to be reliable: Internal consistency evaluated by Cronbach’s $\alpha$ coefficient, was 0.92. Test-retest analysis with Pearson’s correlation was 0.73. Validity was evaluated by a principal factor analysis showing that the correlations ranged from 0.64 to 0.84 (328).

The painDetect Questionnaire (PDQ)
The PDQ is a patient-administered screening questionnaire developed and validated to predict the likelihood of a neuropathic pain component being present in individual patients (288). It comprises questions regarding pain intensity (VAS intensity values for current, average, and worst pain), course of pain (selection between 4 pain course patterns), subjective experience of a radiating quality of the pain (yes/no), and the presence and perceived severity of seven somatosensory symptoms of neuropathic pain scored on a 6-category Likert scale (never, hardly noticed, slightly, moderately, strongly, and very strongly). For diagnostic purposes, a validated algorithm is used to calculate a total score ranging from 0 to 38 based on the patient’s answers. A total score above 18 indicates that a predominantly neuropathic pain component is likely, whereas a total score below 12 indicates that this is unlikely. The PDQ has been applied in studies of specific sensory profiles in established neuropathic pain conditions (329) as well as in studies of clinical manifestations of central sensitization in generalized (136;330) and regional musculoskeletal pain conditions e.g. osteoarthritis (331).

Clinician reported and observation-based outcomes

Assessment of pressure pain threshold and tolerance
Pressure pain sensitivity was determined on the lower leg using computerized cuff pressure algometry (CPA). The setup consisted of a pneumatic tourniquet cuff, a computerized compressor and an electronic 10 cm Visual Analogue Scale (VAS). Double-Chambered Textile Tourniquet Cuffs (VBM Medizintechnik GmbH, Sulz, Germany) were used for pressure application (332). Measurements were carried out with the patient in supine position, and on the patient's dominant side. At all measurements a compression rate of 1.0 kPa/sec were used. To minimize bias due to summation of pain, all measurements were carried out with a time interval of 5 minutes. Following parameters were determined: Pain Threshold defined as the pressure of the cuff at the subject's first sensation of pain when applying a constantly raising pressure (Unit kPa). Pain Tolerance defined as the pressure of the cuff when the pressure is switched off by the patient due to worst tolerable pain caused by pressure stimulation (Unit kPa). Reduced pressure-pain thresholds assessed by CPA has been demonstrated in patients with fibromyalgia, and CPA is reported to be less influenced by psychological distress, indicating that this method is a more objective tool for the assessment of deep tissue pain hypersensitivity in this condition (82).
Manual tender point examination and tender point count (TPC)
Standardized, manual tender point examination was performed on all patients by experienced and calibrated raters. The 18 predefined tender points were assessed according to the 1990-ACR guidelines (1) by applying a digital pressure of approximately 4 kg at each site and the pain response to palpation, scored as 0 = no tenderness, 1 = affirmative response to questioning, 2 = spontaneous expression of tenderness, 3 = withdrawal reaction, registered at each tender point site. Tender points with a score of 1 or more were included in the overall tender point count in individual patients for classification purposes according to ACR guidelines. Studies support high inter-and intra-rater agreement of manual TP examination among calibrated raters (333).

Maximal isokinetic knee muscle strength
An isokinetic dynamometer (Lido Multi Joint II, USA) was used to measure maximal voluntary muscle strength of the dominant knee extensors and flexors. Concentric contractions were performed in all patients at an angular velocity of 60°/s and the highest value of 7 repetitions recorded as the maximal muscle strength measured in Nm (294;334;335). Published norms are available for the Danish background population (336).

The Grippit® dynamometer
Grippit® was used to measure maximal grip strength (N), as well as sustained grip strength averaged over a 10 sec period (N) (337). Grippit® has demonstrated good intra- and inter-rater reliability in healthy adults (338) as well as ability to detect changes in grip strength in patients with fibromyalgia (339).

Six-Minute Walk Test (6-MW)
The 6-MW test was standardized and performed in a hospital corridor with a length of 100 meters. Patients were given standard instructions to walk for 6 minutes at a pace that was efficient, but comfortable escorted by a physiotherapist. The distance walked in 6 minutes was recorded in meters. 6-MW testing has been applied in fibromyalgia training studies and found to be reliable in this specific population (200;340).
## Appendix 2: Weekly time schedule for the rehabilitation program

### Week 1

<table>
<thead>
<tr>
<th>Time</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Physiotherapist</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Practical exercises in hot water pool</td>
</tr>
<tr>
<td>10-11</td>
<td><strong>Nurse</strong></td>
<td><strong>Occupational therapist</strong></td>
<td><strong>Rheumatologist</strong></td>
<td></td>
<td>Nurse</td>
</tr>
<tr>
<td></td>
<td>Introduction and presentation of</td>
<td>ADL problems and strategies for problem</td>
<td>Pain physiology and biopsychosocial models</td>
<td></td>
<td>Sleep and sleep hygiene</td>
</tr>
<tr>
<td></td>
<td>participants</td>
<td>solving</td>
<td>of pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11-12</td>
<td><strong>Nurse</strong></td>
<td><strong>Practical ADL-exercises</strong> (kitchen)</td>
<td><strong>Rheumatologist</strong></td>
<td><strong>Psychologist</strong></td>
<td>Lunch break</td>
</tr>
<tr>
<td></td>
<td>Living with chronic pain; adaptive</td>
<td>Goal-setting</td>
<td>CWP and fibromyalgia</td>
<td>Living with chronic pain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>self-management strategies</td>
<td></td>
<td></td>
<td>Acceptance</td>
<td></td>
</tr>
<tr>
<td>12-13</td>
<td><strong>Lunch break</strong></td>
<td><strong>Lunch break</strong></td>
<td><strong>Lunch break</strong></td>
<td>Cognitive flexibility and strategies for</td>
<td>Nurse</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>behavioral changes</td>
<td>Plenum: recapitulation of the week</td>
</tr>
<tr>
<td>13-14</td>
<td><strong>Nurse</strong></td>
<td><strong>Physiotherapist</strong></td>
<td><strong>Rheumatologist</strong></td>
<td><strong>Psychologist/rheumatologist</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Plenum: participants experiences and</td>
<td>Principles of graded exercise and activity</td>
<td>Management of CWP and fibromyalgia</td>
<td>Significant others;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>outcome expectancies</td>
<td>pacing</td>
<td></td>
<td>lecture and plenum discussion</td>
<td></td>
</tr>
<tr>
<td>14-15</td>
<td></td>
<td>Goal setting</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>15-16</td>
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</tr>
</tbody>
</table>
### Week 2

<table>
<thead>
<tr>
<th>Time</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
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</thead>
<tbody>
<tr>
<td>9-10</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>10-11</td>
<td><strong>Physiotherapist</strong> Practical exercises - balance training - relaxation</td>
<td><strong>Occupational therapists</strong> Aid devices, legislation Evaluation/lessons learned</td>
<td><strong>Physiotherapist</strong> Practical exercises Evaluation and plans for future training</td>
<td><strong>Nurse</strong> Sexuality and cohabitation</td>
<td></td>
</tr>
<tr>
<td>11-12</td>
<td><strong>Lunch break</strong> (11:30-12:00)</td>
<td>Presentation of the AMPS and discussion of participants test results</td>
<td><strong>Physiotherapist</strong> Practical exercises Evaluation and plans for future training</td>
<td><strong>Nurse</strong> Plenum: recapitulation and evaluation</td>
<td></td>
</tr>
<tr>
<td>12-13</td>
<td><strong>Occupational therapist</strong> Ergonomic principles Practical ADL-exercises Aid devices (kitchen)</td>
<td><strong>Lunch break</strong></td>
<td><strong>Lunch break</strong></td>
<td><strong>Nurse</strong> Plenum: recapitulation and evaluation</td>
<td></td>
</tr>
<tr>
<td>13-14</td>
<td>Ergonomic principles Practical ADL-exercises Aid devices (sleep, IT)</td>
<td>Individual consultation with the rheumatologist</td>
<td><strong>Psychologist</strong> Self-management of pain and stress</td>
<td>Individual consultation with the rheumatologist</td>
<td></td>
</tr>
<tr>
<td>14-15</td>
<td></td>
<td></td>
<td>Self-management of pain and stress</td>
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<td></td>
</tr>
</tbody>
</table>