Chronic fatigue syndrome

Health and impairment, treatment and prognosis

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Dissertation for the degree doctor medicinae (dr.med.)

at the University of Bergen

2008

ISBN 978-82-308-0584-8
Bergen, Norway 2008

Scientific environment

The research work in this thesis has been done and supervised at the Stress and Health Research group, initially at the Department of Biological and Medical Psychology, Faculty of Psychology; presently at Unifob Health, University Research Bergen and Research Centre for Health Promotion (HEMIL), University of Bergen.

The total thesis has been done within the institutional framework and supervision of the doctorate program, Faculty of Medicine, University of Bergen,
and the thesis is presented through the Section of Psychiatry, Department of Clinical Medicine, University of Bergen.

I dag såg eg
tvo månar,
ein ny
og ein gamal.
Eg har stor tru på nymånen.
Men det er vel den gamle.

(Olav H. Hauge; Dråpar i austavind, 1966)

Acknowledgements

First: thanks to all my patients in Haugesund who participated patiently during the months and years of questionnaires, interviews, lab-tests, bicycling, group sessions, body awareness sessions, medication and placebo, exercise diary, sleep diary, follow-up consultations and more questionnaires and questions……
This thesis would never have materialized without you and your cooperation.
The experience I have gained in meeting the pain and burden of your fatigue has challenged my own illness perceptions and improved my clinical competence.

The clinical work included in this thesis was carried out through my years at the Psychiatric Clinic in Haugesund, and I am grateful for the help from many people in Haugesund Hospital. There would have been no clinical trial or research work without the endless help and support of Synnøve Fagerland and Anne Økland as my special forces, and the efforts of Marlene Rødeseike and Ingrid Gismarvik who were co-workers in the trial and the research. Thank you all so much.
A special thank to my colleagues and friends Bjørn Bøe and Haldis Økland Lier for your interest and encouragement, and to Ole Johan Hovland from the years in Haugesund and later co-author; thanks so much for your help and cooperation.
During the early phases of research planning, I sought advice from colleagues and researchers, and I wish to thank Egil Martinsen and Ian Hickie for valuable advice.

The idea of studying chronic fatigue was mine alone, but the whole research project, plan and progress would never have been conceived, delivered and kept alive without the help from my supervisors Holger Ursin and Hege R. Eriksen. Through these years, from Årstadvollen to BBB to Vektertorget, from IBMP to Halos to Unifob Health, from idea to research to thesis: you have been there, guiding and supporting, patiently pushing and impatiently pulling. I am most grateful and indebted.
Thanks for providing resources and facilities essential to this work, from yourselves, IBMP and Unifob Health. Thanks for generosity, inclusion, fun and laughter.

The IBMP – Institute of biological and medical psychology - was my base camp trough most of the time with this research, with Vivian Fosse as the origo: Thank you so much. Thanks to Linda Sandal for help with compiling, designing and printing questionnaires. And to Nina - Nina Konglevoll: without you this work would never have been completed; I am so grateful for your help and endless efforts, willingness and pleasant company. A special thank to Torill Tveito for your help and being an always available partner, and for assistance and co-authorship in our first paper on neurasthenia. At IBMP I also met Erling Svensen, who has been an inspiring research partner during these years, along with Liv Magnussen, Silje Reme and Anette Harris: Thanks for including me and for your cooperation and support.
A most special thank to Stein Atle Lie for essential help and support in statistical analyses, and for your cheerful competence.
Thanks to Bente Groth and her staff at Unifob Health for providing good research facilities and a new base camp, with generous helpfulness and quizy lunch-hours.

Special thanks to Keith Petrie for including me in his international network of researchers, for the marvellous meetings in the Pacific and encounters with fatigue experts; thanks for input from Rona Moss-Morris, Trudie Chalder, Simon Wessely, Peter White and Michael Sharpe. It has brought a sense of fatigue coherence.

My director Hans Olav Instefjord at Division of Psychiatry, Haukeland University Hospital has been granting me opportunities and time to complete this thesis: I am most grateful for your support and encouragement.

Thanks to my parents for genetic load and education of positive outcome expectancy, and to my father for his ambitio-curious impatience in seeing me complete this thesis.
A warm gratitude to my sons Erlend, Ivar and Lars for your interest and emotional support; it has been a source of inspiration.
And through it all: thanks and loving gratitude to my wife and best friend Merete, for being there, for patience, enthusiasm, support and love.

Bjarte Stubhaug
Bergen/ Haugesund, January 24th, 2008

Introduction

Try not to know all the answers,
but to understand all the questions. *(Eastern proverb)*

On Thursday April 29, 1869, in The Boston Medical and Surgical Journal, dr. George Beard, neurologist and lecturer on nervous diseases in the University of New York, published an "Original Communication" with the headline *"Neurasthenia, or Nervous Exhaustion"*[17]. This was the starting point of a history of chronic fatigue that has been and still is chronically intriguing - and confusing.

George Beard is quoted to have said; *"Fatigue is the Central Africa of medicine, an unexplored territory which few men enter".*

I have had the fortune to enter this territory and have done so with interest and a sincere wish of exploring this exciting field of medicine. After many years as a clinician and consultant in psychiatry, my professional interests focused gradually more on psychosomatics and stress medicine, and the illnesses of chronic fatigue seemed particularly fascinating. When meeting with professor Holger Ursin nearly 10 years ago, having invited myself to discuss a possible minor research project on stress and chronic fatigue in a sabbatical period *(-"there is no minor research except research being performed by minor researchers"*), a minor suddenly became major, and there I was – on a long and winding road to systematic research and doctoral thesis – and here I am now.

A major source of motivation has been the professional interest and wish to explore and understand. As important has been recognizing the need of knowledge and competence in this field, to meet and treat patients in need.
If any supreme goal for this work, it has been to contribute to improving the competence and care in meeting patients with chronic fatigue.

Abstract

Chronic fatigue syndrome (CFS) has been known as “neurasthenia” for more than hundred years and is today often called ME (myalgic encephalopathy), CFS/ME. The illness is characterized by excessive, prolonged and disabling fatigue, pain and somatic complaints, with functional and mental impairment and with major consequences in occupational and social life. Several case definitions with varying criteria are used for CFS. The prevalence is 0.5 % in a general population; the average length of the illness is more than 5 years, and rate of work disability is high. Prognosis is varying; few patients recover totally, but most patients improve substantially over 2-5 years.

The objectives in this thesis were to investigate a clinical population with neurasthenia and chronic fatigue syndrome, by assessing subjective health complaints, functional impairment and work disability, by examining treatment effects of specific interventions, by studying long-term illness course and by analyzing the comorbidity of depression and personality patterns.

72 patients with ‘neurasthenia’ were compared with a reference population of 1000 patients in general practitioners’ waiting-rooms. Patients with neurasthenia had more prevalent and more severe subjective health complaints than the reference population of patients, longer periods of sick leave and higher rates of work disability.
The patients with neurasthenia/ CFS went through a 6 months randomised clinical trial of mirtazapine, placebo and a comprehensive cognitive-behavioural intervention (CCBT) program of CBT, body awareness therapy and graded exercise. By 3 months the CCBT program had better effect on fatigue symptoms and clinical global severity than mirtazapine medication or placebo alone. By combining the interventions, the combination of CCBT followed by mirtazapine had significantly better effect on fatigue severity by 6 months than placebo or the opposite sequence of initial medication followed by CCBT. Generally, the whole group with neurasthenia and CFS showed substantial clinical improvement after the treatment interventions.

In a 5 years follow-up study of this patient group, half of the patients reported a substantial reduction in fatigue symptoms, and diagnoses tended to shift from CFS towards neurasthenia and unspecific chronic fatigue during the follow-up period. Sudden onset, severity of fatigue at the initial phase of illness and slow improvement predicted a poor prognosis. Long-term course seemed more dependent of illness characteristics than of time-limited treatment interventions.

The prevalence of personality disorders was found equal to non-clinical populations (13%) in CFS patients; the mean personality score was at an average level, indicating low general personality pathology. CFS patients had a clinical personality profile similar to that of somatoform disorder, with elevated scores of somatisation and health concerns and low scores of self-esteem and perfectionism.

The findings in this thesis support the view of CFS as a severe illness with extensive health complaints and severe impairment. The findings also indicate that psychiatric symptoms and personality disorders are low in CFS. Although the prognosis of a full recovery in CFS seems poor, the effect of a comprehensive treatment intervention is generally good, and most patients improve gradually.

List of publications

1. Stubhaug B; Tveito TH.; Eriksen HR.; Ursin H. (2005):
   "Neurasthenia, subjective health complaints and sensitization"
   Psychoneuroendocrinology 30(10), 1003-1009

2. Stubhaug B; Lie SA; Ursin H; Eriksen HR (2008)
   "Cognitive–behavioural therapy v. mirtazapine for chronic fatigue and neurasthenia: randomised placebo-controlled trial"
   The British Journal Of Psychiatry (2008) 192: 217-223

3. Stubhaug B; Lie SA; Ursin H; Eriksen HR
   "Illness course in chronic fatigue syndromes.
   A 5 years follow-up study"
   S*ubmitted*

4. Stubhaug B; Hovland OJ; Lie SA; Ursin H; Eriksen HR
   "Personality disorders and personality profiles in chronic fatigue syndrome"
   S*ubmitted*

Contents

CHRONIC FATIGUE SYNDROME:

HEALTH AND IMPAIRMENT, TREATMENT AND PROGNOSIS

1. Introduction, background

1.1 Fatigue, chronic fatigue and Chronic Fatigue Syndrome (CFS)

1.1.1 The concept of Fatigue

Although widely used and convenient both in everyday life and in medical descriptions, fatigue is a problematic concept, in the sense that a strict or precise definition is very difficult. Most people "know" what it means, but the meaning of the term is still vague and difficult to operationalize. Fatigue is essentially a subjective experience, and is difficult to separate from normal experiences of tiredness, sleepiness, overstrain or exercise exhaustion. The symptom of fatigue could be described as a pervasive sense of tiredness or lack of energy that is not related exclusively to exertion [164]. This type of fatigue is not alleviated by rest and must be distinguished from weakness, malaise and temporary tiredness that occur as a direct result of excessive physical or mental exertion. In order to qualify fatigue as pathological, many researchers have described the subjective experience of fatigue as a continuum rather than a categorical entity [205,206,249]. Although no clear cutoff exists between normal and abnormal fatigue, assessment using unique qualifiers may help distinguish between severity and duration of fatigue illness. Many attempts have been made to develop such qualifiers in defining and assessing fatigue [76,277]. The nature of fatigue still remains complex, comprising clearly different components and wide dimensions. A comprehensive analysis of fatigue [249] shows the need for considering fatigue in terms of a number of components, the principals being fatigue as behaviour, fatigue as a feeling, and fatigue as an internal state or mechanism, in addition to which the environment of the fatigued person and the demands upon them must always be specified.

Table 1: The dimensions of fatigue

Fatigue is described by six different dimensions, each with several components that can express, explain, influence or measure fatigue.

Behaviour	e.g. work-out, endurance, relation to rest
Feeling state	Mental or physical; severity and quality
Affective and evaluative	pleasant/ unpleasant, anxiety/ depression
Cognitive/ motivational	e.g. enthusiasm, aversion
Mechanism	physiology, biochemistry, psychology
Context	physical factors: temperature and noise; social stressors; cultural context

(adapted from Wessely, Hotopf, Sharpe: Chronic Fatigue and its syndromes) [249]

1.1.2 Chronic fatigue and Chronic Fatigue Syndrome

Most clinicians and researchers distinguish normal fatigue and prolonged fatigue from both chronic fatigue and Chronic Fatigue Syndrome (CFS) [205]. Prolonged fatigue is often defined as disabling fatigue that lasts at least one month. If this degree of fatigue is persisting and lasts more than 6 months, it is called chronic. Since there is no common standard for measurements of such fatigue or cutoff for normal/ pathological fatigue, chronic fatigue cannot be more clearly defined. Depending on the specific case definition, a disabling and chronic fatigue condition is considered CFS if fulfilling specific criteria or case definitions [11,15,126,164,196], see Appendices: Case definitions (chapter 8.1). Yet, many clinicians and researchers argue that fatigue as a clear-cut symptom is not necessarily a *sine qua non* for the CFS illness, since accompanying symptoms like cognitive dysfunctions, general malaise and functional impairment are as essential elements of the illness as fatigue itself [38,187].

The descriptions and dilemmas of case definitions are elaborated and discussed further in chapter 1.2.5 in this thesis.

1.1.3 The history of fatigue

Fatigue is an old term for the condition of weakness, tiredness and lack of energy, being described through history, both in ancient stories and saga-telling and in literature and medical records [211]. It has been described both as a symptom of or accompanying another medical condition, like infections, wounds and cancer, as well as psychological conditions like trauma or bereavement reactions. The Icelandic saga historian Snorre Sturlason (1179-1241) described states of fatigue in the Viking era more than thousand years ago, both as an exhaustion reaction after war and use of weapons [221,222] and as a bereavement reaction in the ancient Egil's saga [97].

People in the seventeenth century referred to an illness called "the vapors", characterized by great fatigue and ill-explained general malaise. As early as 1698, John Pechey (London 1698) [175] described "vapors" as the *"most frequent of all Chronical Diseases"... "wonderfully various that they resemble almost all the Diseases poor Mortals are subject to".* Vapors, he points out, affect all parts of the body, especially the back.

One of the earliest medical descriptions was from the English physician, Sir Richard Manningham, who in a textbook in 1750 described symptoms of a disease he called "febricula", or "little fever", which sound similar to what we today call CFS [71]. The illness presented with a profound sense of lassitude, accompanied by a bewildering variety of constitutional complaints, but few objective, clinical findings: *"The symptoms of the febricula, or little, low, continued fever are these…transient chilliness…a mist before the eyes, listlessness, with great lassitude and weariness all over the body…little flying pain… and sometimes the patient is a little delirious and forgetful…" (Manningham 1750)[72].*

Manningham also noted the association of this condition with stressful life events.

"Febricula" never got a medical recognition, but the condition never disappeared…

The rise and fall of Neurasthenia

The modern history of fatigue started in 1869, when the term and diagnosis *neurasthenia* was introduced in medical literature for the first time, both by the neurologist George Beard [17] and even earlier by the psychiatrist van Deusen [236]. Beard was the one to be recognized for the description of the term, and it created a new paradigm of fatigue illness, as unexplained and mysterious fatigue suddenly got its physiological explanation, in Beard's elaboration of neurasthenia. The somatic explanation offered was "nerve weakness" based on a "hypersensitivity" of the nervous system, in accordance with contemporary neurological state-of-knowledge [17]. Beard himself was convinced that the causal aetiology of this illness was to be found in pathophysiological processes in the central nervous system (CNS):

..the central nervous system becomes dephosphorized, or, perhaps, loses somewhat of its solid constituents; probably also undergoes slight, undetectable, morbid changes in its chemical structure, and, as a consequence, becomes more or less impoverished in the quantity and quality of its nervous force" (Beard, 1869).

With no medical evidence to support his theory, some cautiousness seemed needed: *.."I admit that this view is speculative, but I feel assured that it will in time be substantially confirmed by microscopical and chemical examinations of those patients who die in a neurasthenic condition".*

Neurasthenia soon proved to be a much needed and attractive explanation for unexplained – and often ill-defined – conditions in its time. Throughout the next decades, the use of the term and by definition the prevalence of Neurasthenia increased almost epidemically [212].

Four different uses of the term emerged during the late 1800's [211]:

First, and mainly, neurasthenia was chronic fatigue. Chronic fatigue was and remained being the primary or "essential" symptom in neurasthenia, its *"cardinal characteristics being an inordinate sense of physical or mental fatigue"*.
The manifestations of neurasthenia most often described was "neuromuscular

weakness" or …*"unusually rapid exhaustion mainly affects the mental activities; the power of attention becomes quickly exhausted and the capacity for perception is paralysed* [249]. Fatigue in neurasthenia was not relieved by rest. Patients with neurasthenia were *"speedily exhausted in the process of moderate exercise"*, and…*"prolonged and severe mental effort"* was equally impaired [249].
Studying these and many other quotations from that time clearly indicates that neurasthenia was directly comparable to modern descriptions of chronic fatigue syndrome. It seems relevant to bear this in mind when discussing the contemporary questions concerning classification and differentiation of fatigue illnesses.

The second aspect was the equation of neurasthenia with depression or mild melancholia. Overlapping symptoms like lack of energy, reduced activity, mental fatigability and sleep disturbances, and the absence of diagnostic criteria, made the distinction between neurasthenia and melancholia difficult. This is still the case [67].

A third tradition for the use of neurasthenia was the neurasthenic symptoms in men under "stress", mainly in working-class males in farming or industrial labour [211]. At that time, neurasthenia in this sense was considered a male equivalent to female hysteria, and many clinicians and researchers considered these the same disorder, with the mechanism of irritability supposed to underlie both. Some physicians interested in social reform began from 1890 on diagnosing neurasthenia among working-class men whose health complaints until those days had been considered non-medical and which had been offered no medical care. This represented a way of "medicalizing" these people and their complaints, often representing somatoform complaints caused by "stress", overload and poverty [211]. This approach and use of "neurasthenia" directed for the first time medical attention to psychosomatic symptoms in men and provided explanations for stress-related exhaustion. It seems fair to say that modern concepts of burnout and 21st-century's models of exhaustion depression [18,78,147] are in debt and display close resemblance to this concept and use of neurasthenia more than a hundred years ago.

The fourth main tradition in using the term neurasthenia was to see it as a synonym for general nervousness and evolving psychosis, a mixture of mood disorders, anxiety disorders and obsessive-compulsive disorders, combined with somatoform symptoms. It gradually became synonymous with "pan-nervousness", which was a term so wide as to include anything and differentiate nearly nothing. Descriptions of neurasthenia as *"... a diagnostic wastebasket"* and *"...a mob of incoherent symptoms borrowed from the most diverse disorders"* [211] served to undermine its legitimacy.

The diagnosis came to be used quite liberally, to cover a multitude of obscure nervous affections of the most varied and opposing character [193]. From being a popular diagnosis both to patients and physicians, the popularity of neurasthenia gradually decreased by the turn of the 19th century, both because of this diversity and incoherence in use of the diagnosis, and because it no longer offered the comfort of an acceptable diagnosis for unexplainable symptoms. Also, the development of medical knowledge created increasing discomfort with Beard's increasingly archaic model of "deficiency of nervous strength", which was found over-simplistic in absence of explanations of potential disturbances in the neural substrate [72]. There was also an increasing awareness of the psychological aspects of behavioural antecedents of neurasthenia and the sequelae of the condition. Pierre Janet (1903) introduced *Psychasthenia*, whose main core was obsessive-compulsive states. Psychiatry rising as a medical discipline of its own also incorporated some of the conditions within the neurasthenia spectrum, especially the "neurotic" depression, and left neurasthenia with only the ill-defined and unexplained fatigue. The fall of Beard's neurasthenia was dramatic.

Although declining in popularity and prevalence, neurasthenia still continued to be used throughout the 20th century, mainly with the connotations of unexplained chronic fatigue accompanied by various somatic complaints. Internationally, neurasthenia certainly survived, and it is still an official diagnosis in the WHO International Classification of Diseases (ICD-10 – 10th edition)[264]. In 1999, The World Psychiatric Association (WPA) had an international group of psychiatrists

examining the use and meaning of neurasthenia throughout the world, and a consensus report and statement was made concerning the relevance and usefulness of the term [266]. The main conclusion was that neurasthenia was still alive.

The criteria for the diagnosis of neurasthenia in ICD-10 [265] are: either persistent and distressing complaints of feelings of exhaustion after minor mental effort or of fatigue and bodily weakness after minor physical effort, accompanied by one or more of the following symptoms: muscular aches and pains; dizziness; tension headaches; sleep disturbance; inability to relax; and irritability. There should be an inability to recover trough rest, relaxation or entertainment; the duration should exceed 3 months, and there should be no organic mental disorder, affective disorder, panic disorder or generalized anxiety disorder.

Many researchers have advocated the revival of neurasthenia for clinical use, although the battle of terminology in the Western world since long seems lost to chronic fatigue syndrome (CFS) [115,244,253,272]. Other researchers have pointed out that though neurasthenia seemed to disappear, the clinical conditions and disorders which it comprised still exist, and reappear in new terms and diagnoses, often with psychological labels [225].

Chronic fatigue syndrome, CFS

Having abandoned the model of constitutional and unexplained nervous weakness, there was from late 1800's a search for medical explanations corresponding to contemporary medical knowledge. Already in the early 1900s, the concept that chronic fatigue could follow infections, such as influenza and typhoid, was established and widely accepted [249]. The mechanisms by which an infection could produce post-infectious prolonged fatigue, was still mysterious.

During the twentieth century, several outbreaks of fatigue with unknown aetiology as an principal symptom were reported [72,211,249], all together more than 60 reports, with varying quality in their descriptions [148]. One of the first to be reported, and one to

serve as a template for later explanations of chronic fatigue, was the occurrence in the 1930's of brucellosis, or undulant/ Mediterranean fever. It is a bacterial infection spreading from animals to humans, with characteristics signs of an infection, like high fever, aches and pains, chills and malaise. Long-lasting fatigue following brucellosis was called chronic brucellosis, and the infection served as an accepted explanation for the chronic fatigue, even for some people who had never been infected but had all the symptoms, like muscular aches and pains, fatigue, irritability and mild depression.

Chronic brucellosis illustrated dilemmas and unresolved questions highly relevant even today. Is the persisting fatigue a result of the obvious infection; is it caused by an simultaneous occult infection being precipitated by the first; is it due to possible postinfectious mechanisms (a concept that developed later); could it be an expression and symptom of psychiatric disorders like depression – having fatigue as a common symptom - or could it be seen as somatisation of psychological complaints, attributing the cause of fatigue to a somatic disease?

Chronic brucellosis came to be used in the 1940's and 50's as a label for ill-defined fatigue and somatoform and somatising illness, but it never became a wide-spread or fashionable illness, sharing its destiny with theories of chronic fatigue that appeared and disappeared in the decades to follow, like reactive hypoglycaemia in the 1960's, total allergy syndrome and chronic candidiasis of the 1970's. Only by the rediscovery of infectious and post-infectious mechanisms and the distribution of information through modern media did the mysterious fatigue illness start to rise like neurasthenia once did [249].

Epidemic outbreaks of mysterious fatigue were reported from the 1930's, the first in 1934 in Los Angeles General Hospital, among the employees at the hospital. It was labelled neuromyasthenia, muscle weakness caused by neurological pathology - presumed to be an atypical poliomyelitis infection. Other labels to be used were Icelandic (or Akureyri) disease – due to the local occurrence in Iceland - atypical poliomyelitis, or myalgic encephalomyelitis. The latter was coined in 1956 after an

outbreak of endemic fatigue among the nursing and medical staff in Royal Free Hospital in London in 1955 [183]. The term myalgic encephalomyelitis (ME) came to be the standard label in the public and patient groups in England in the years to follow.

In USA, there were also several reports of similar outbreaks of epidemic fatigue [23,148], although few are described in detail. The label of neuromyasthenia came to be the dominating term in USA, with a clear assumption of a causal nervous infection.
In 1984, in Lake Tahoe, Nevada, USA, and its surrounding communities, a severe outbreak of fatigue illness was reported [13]. The symptoms of the Lake Tahoe outbreak included prolonged fatigue, abrupt onset of symptoms, severe pain and prominent cognitive disorder [148]. In many patients affected at Lake Tahoe, Epstein-Barr virus (EBV) antibodies were detected, and a causal explanation of definite organicity by post-infectious mechanisms was claimed. After this outbreak, the term Chronic Epstein-Barr Virus infection fatigue was being used, soon to be renamed as post-viral chronic fatigue syndrome or just chronic fatigue syndrome, CFS, with the addition in the US of a "immune deficiency" syndrome, CFIDS.

By the late 1980's, the illness of severe and prolonged fatigue was being known to the public, and there was an increasing pressure on the medical authorities to recognize the illness as an entity of it own. In 1988, the Center of Disease Control (CDC) in USA suggested and published a working case definition of CFS [118], later to be revised and replaced by the 1994 CDC case definition [92] (see Appendices, 8.1). In this case definition, CFS is defined as an unexplained, persistent or relapsing chronic fatigue of new or definite onset; it is not the result of ongoing exertion; it is not substantially alleviated by rest; and it results in substantial reduction in previous levels of occupational, educational, social or personal activities. Additional requirements are the concurrent occurrence of four or more of specified symptoms: impairment in short-term memory or concentration, sore throat; tender cervical or axillary lymph nodes; muscle pain, multijoint pain without joint swelling or redness; headaches, unrefreshing sleep; and postexertional malaise lasting more than 24 hours.

Since then, the term Chronic Fatigue Syndrome (CFS) has been accepted as the most common term for unexplained, severe chronic fatigue, and the CDC case definition has been the most widely used case definition internationally [124,164,257]. Still, other case definitions of CFS has been suggested and are being used, as the British/ Oxford case definition [207] and the Australian case definition [196].

Despite efforts to reach consensus about case definitions and research criteria and resolve ambiguities in the CFS case definitions, interests have been conflicting and the discussions are ongoing [125]. Advocates of CFIDS and postviral chronic fatigue (PVCF) in USA and myalgic encephalomyelitis (ME) in Britain have fought for more exclusive case definitions, emphasizing the explicit organicity by infection-precipitation and the extensively functional impairment beyond fatigue symptoms alone [171,210]. In 2003, a Canadian group proposed a case definition aiming at integrating the wider case definition of CFS and the somewhat stricter concept of ME, in a ME/CFS working case definition [38]. Although being used in research, it has not been recognized as the ultimate solution to an unambiguous case definition [39].

In 2007, the National Institute for Health and Clinical Excellence (NICE) in London published guidelines for diagnosis and management of CFS/ ME, based on a consensus work of professionals and patients, in an attempt to provide updated clinical recommendations for clinical use [11,165]. Although welcomed by most professionals as a useful tool in improving diagnosis and management of CFS/ ME [254], it is still being opposed by some patients, who have made an official lawsuit against NICE for a judicial review of the guidelines.

Like neurasthenia in its time, the contemporary chronic fatigue syndrome certainly is an illness of extraordinary controversy and accompanying engagement.

This thesis deals with a clinical population being defined initially by the wide criteria of neurasthenia (ICD-10)[265] , which also includes CFS. The possible differentiation between neurasthenia and CFS, therefore, is highly relevant for the thesis. Studies having compared neurasthenia and CFS show that these diagnoses are overlapping and that the clinical populations are comparable [88,114].

(See Appendices 8.1: Case definitions, for description of neurasthenia, CFS-CDC and CFS-Oxford)

1.1.4 Medical Unexplained Symptoms; pathoplasticity

As a parallel academic discussion to those of neurasthenia and CFS case definitions, the question of labelling the medically unexplained symptoms that persist through all revisions of classification systems and case definitions have been raised but not resolved. The term Medically Unexplained Symptoms (MUS) has been used increasingly, although still debated and explored [12]. The validity and stability of the term has been challenged [145], and the associations to the diagnosis of somatoform disorder, the concepts of alexithymia, somatisation and psychological mechanisms have been studied [12,112,141,146,192]. Medically unexplained symptoms (MUS) have no stringent criteria or case definition, and as a medical term have thus been subject to sometimes professionally ambiguous use [166,167] or categorization depending on medical speciality [204], although working case definitions have been suggested and tested for interrater-reliability [188]. An additional aspect of making the diagnosis of MUS is the influence of the doctor-patient relationship in the decision-making [166]. Since CFS by its definition is medically unexplained, it is sometimes included in the case definitions of MUS, partly depending on the discretion of the clinician, but most often CFS is excluded from MUS, along with Irritable Bowel Syndrome (IBS), fibromyalgia and other syndromes with operationalized case definitions. Still, this is a gray zone of unresolved dilemmas and borders. Researchers and clinicians have called for a comprehensive model and a biopsychosocial approach in analyzing and managing the challenges with medically unexplained symptoms [12,29,33,62].

The term subjective health complaints (SHC) has also been suggested as a useful term in describing such unexplained symptoms, assigning no cause or attribution to the complaints, which would be a better term than symptoms, implying an underlying disease [80,230].

Also, the term functional somatic disorders have been used for many of these syndromes, including CFS, IBS, fibromyalgia and Multiple Chemical Sensitivity (MCS) as well as war syndromes [6,131,134,168,250]. One implication of the term has been that "functional" disorders essentially represent mainly psychological conflicts or disguised psychiatric disorders. This contributes to the scepticism among patients towards being labelled "functional"[251], and to the dynamics in the medical establishment and in the culture of making a diagnosis [131].

In the classifications systems of ICD-10 and DSM-IV, these "unexplained" conditions have been lumped together in undifferentiated categories of "somatoform" disorders [5,264], but revision of these classifications are soon to come, based on critical analyses of the somatoform and "unexplained" concept [12,37,57,142,145,154,217,224,237]. Possibly, a new classification system will also bring and facilitate a more comprehensive view of these "unexplained" conditions [217].

Historians of medicine have described a universal "pool" of unexplained symptoms or illnesses since ancient times, often referred to as a "psychosomatic pool" [211]. These illnesses have the characteristics of varying and changing appearances and labels, transient explanations and attributions, and often show a characteristic pattern of rise and fall in prevalence and popularity.

This process of fluctuations and change in illness labels and explanations has been called "pathoplasticity" – a plasticity in the presenting features of an illness; a tendency to illness attribution and illness presentation changing with fashion, media-mediated medicine and popular knowledge [211]. Such changes are often characterized by subjectively based knowledge opposing evidence-based medicine and research. In this process, the influence of the media is instrumental, by presenting fragmented medical knowledge and by generalizing from the individual and from the subjective illness.

Through history this process of changing labels, attributing old symptoms to new labels and discovering new symptoms once they have been presented and described, has been characteristic for several illnesses, mostly within this pool of medical unexplained complaints and functional somatic illnesses [250]. The symptoms and subjective complaints can be varied, often unspecific, and the causes or "attributions" seem to move from inner demons to external toxins and invisible waves [211]. The modern history of fatigue can be examined in this perspective, perhaps explaining some of the mystery and controversy of this illness [244].

The clinical work included in this thesis is a part of this complex history and comprehensive context of fatigue illness being described in this chapter. The clinical approach and research questions would be different without recognizing the history, the ambiguities in classification and the associations to related issues of medically unexplained symptoms. Also, it is a fair assumption that knowledge of the historical context of fatigue and the recognition of its complexity may contribute to empathic attitudes and respect in the clinical research encounter with patients severely disabled by chronic fatigue.

1.2 Earlier research

1.2.1 Context of CFS: Diagnosis, prevalence, comorbidity, pathophysiology

Case defintions of CFS

Several case definitions for CFS have been presented and are being used in research and clinical work. The case definitions generally accepted are the CFS- CDC (Center for Disease Control) definition of 1988 [118], later to be revised and replaced by the CFS-CDC 1994 case definition [92](see Appendices 8.1); the British CFS-Oxford case definition [207](Appendices 8.1); the Australian case definition for CFS [196] and the Canadian clinical working case definition for ME/CFS [38]. There is no general or international agreement about which case definition to use or to accept as a "gold standard", although the CFS-CDC (1994) case definition is most widely used and most often referred to in research. In a systematic review of the different case definitions [164], one conclusion is that no studies have established the superiority of one existing case definition over another. The essential characteristics likely to distinguish CFS are post-exertional fatigue not alleviated by rest and a cluster of symptoms that include chronic fatigue, sore throat, lymph node pain, post-exertional malaise, memory/ concentration problems and unrefreshing sleep [127]. These characteristic are included in the case definitions.

There is an ongoing discussion about the case definitions; researchers have pointed to the ambiguities of the existing definitions and the need for reclassification [135,137,186,218]; others - including patient groups - have called for stricter and more precise criteria identifying the allegedly specific and most severe subgroup of CFS; myalgic encephalomyelitis (encephalopathy) ME [2,38,39,210]. However, the current position in international research today seems to be the use of the terms CFS and ME as synonyms, often as CFS/ME or "CFS, often called ME" [40,43,136,165,181,254].

The issues of case definitions are relevant to the studies in this thesis, as the use of case definitions will influence the sample selection and possible selection bias. The results of the clinical studies will be discussed within the context of differentiating the patients with chronic fatigue in clinical subgroups.

Epidemiology

Many epidemiological studies have been carried out to assess the prevalence of CFS [16,42,87,114,184,245,273]. Most studies share the problem of selection bias by the use of different case definitions and inclusion criteria, by examining patients in primary or secondary or tertiary care, by community surveys or clinical studies, by the inconsistencies in sociodemographic variables like age, gender, ethnicity and industrialization, as well as inconsistencies in the inclusion of psychiatric comorbidity in the samples. The epidemiological data found in various epidemiological studies indicates a prevalence of CFS between 0.2 % - 0.7 % in the general population in Europe, Australia and USA [114,153,249]. Allowing for psychiatric comorbidity, the prevalence of CFS has been shown to be 2.5 % [248]. Studies of chronic fatigue in samples with varying ethnicity, age, gender, occupational status and use of diagnostic criteria have shown high prevalence of chronic fatigue, reaching 11-12 % from England [248] to India [184].

Several studies of chronic fatigue patients in primary care who fulfilled criteria for CFS but where neither patients nor doctors were aware of the diagnosis, indicate that the patients suffering from CFS probably outnumber and probably have different characteristic from those CFS patients who seek referral for establishing/ confirming the diagnosis. It also emphasises the role of selection bias in CFS studies [246].

The question of epidemiology, then, is a complex one, as there is no general consensus on methodology and research shows a wide range of results, possibly based on a wide spectrum of research quality and wide variation in selection criteria of the populations studied.

Comorbidity

Although being defined by specific characteristics, Chronic Fatigue Syndrome is by its nature and definition also a syndrome of varied and complex symptomatology, showing symptoms from many organ system and subjective complaints of varying intensity and duration. When fatigue is clearly accompanying and a secondary symptom to a specified medical disorder, it will exclude the diagnosis of CFS, but in many cases comorbid illness will exist and cause symptoms of varying intensity. CFS has been shown to have high rates of both somatic and psychiatric comorbidity [3], and studies have reported strong associations and high degree of overlap between chronic fatigue and fibromyalgia, irritable bowel syndrome, chronic pelvic pain, multiple chemical sensitivities and temporomandibular disorder, and have reported that chronically fatiguing illnesses were associated with high rates of many other clinical conditions [274-276]. Studies of subjective health complaints in neurasthenia have shown high levels of health complaints from all organ systems, exceeding the level found in many other chronic illnesses [120].

The distinction between overlapping conditions based on overlapping case definitions/ diagnostic criteria and comorbidity of medically different illnesses can be difficult or non-existing [134,202], and some of the research in this field is confusing because this distinction is overlooked. Studies show that somatic complaints are associated with increased social and psychiatric morbidity [138], without knowing what and which illness is primary or secondary [247]. The significance of studying temporal relationships between comorbid conditions in order to identify and treat illness has been emphasized [276]. Also, recognizing that generalised fatigue very often can be a symptom of other diseases [205], the study of comorbidity will be complex, as the "comorbid" condition might be the actual *morbus* and cause of fatigue.

The role of psychiatric illness in CFS has been studied and described extensively. Depressive and anxiety states seem to be of particular importance in CFS, most studies showing a high prevalence and comorbidity with depression, to a lesser extent anxiety disorders [3,52,75,93,214,228,247]. The role of personality pathology in CFS has been given relatively less attention. The research that does exist on this often includes

patients without formal CFS diagnosis or with unclear case definitions of chronic fatigue syndromes [32,52,110,129,252,260,262]. Associations between personality factors and fatigue states have been described, particularly associations to neuroticism [219] and negative aspects of perfectionism [152]. The combination of higher levels of perfectionism, doubts about actions, concern over mistakes and lower self-esteem has been mentioned as important in the development and perpetuation of chronic fatigue [252]. The relevance of cognitive assumptions or pre-morbid personality characteristics has also been described: conscientiousness, perfectionism and social control, creating a coping style making the person vulnerable to exhaustion in situations of inadequate competency and emotional control [223]. The tendency to catastrophizing and exaggerated somatic focus have been shown to be of importance in the related illnesses of pain and fibromyalgia [94,109], and catastrophic beliefs have been shown to impact on level of functioning in CFS [176].

Studies of personality disorders in CFS have shown high levels of personality disorder (40%) [110]. It has been hypothesised that the personalities of CFS patients may have been altered by their chronic illness [51]. It has also been suggested that any link between personality and fatigue states may in part be confounded by depression, and when examining personality factors in CFS compared to other chronic and disabling illness like Rheumatoid Arthritis (RA), there is no evidence of specific personality differences in CFS sufferers [262].

Research evidence concerning psychiatric comorbidity is thus conflicting, and the issue of psychological factors in CFS is one of the most controversial in this field. The issue of comorbidity is of great relevance, as it influences the clinical samples being studied, by allowing various degrees of comorbidity. Furthermore, the level of psychiatric comorbidity have been shown to be a strong predictor for prognosis, disability and medical utilisation [114,128,227].

Further research in this field seems needed. Comorbidity of depression and personality disorder is therefore one of the research issues in this thesis.

Pathophysiology, immune and neuroendocrine dysfunctions

The pathophysiology of chronic fatigue syndrome has been an issue of interest since the early days of Beard's Neurasthenia in 1869 [17], both among researchers and even more intensely in the public discussion and in patient groups. Numerous research findings and theories concerning pathophysiology in general and autonomic dysfunction (dysautonomia), neuroendocrinological and immunological dysfunctions in particular have been presented; some have been disproved, others not being replicated; some forgotten, others still alive but with varying evidence to support them [3,30,44,53,54,70,73,95,130,140,151,153,173,174,255].

There is evidence for immunological dysfunctions in CFS, but reviews and evaluations of the immunology in CFS have so far concluded that no consistent pattern of immunological abnormalities can be identified [50,151,182]. Preliminary evidence for a subgroup of CFS based on impaired natural immunity has been presented [213], using low natural killer cell activity (NCKA) as discriminator between subgroups of CFS. Other studies have found significant differences in cytokines and interleukins and immune T-cell activity and immune activation [216]. Overview reports emphasize the growing body of immunological and genomic evidence for immune dysregulation in subgroups of CFS, which should result in targeted therapies that impact immune function, hypothalamic-pituitary-adrenal axis regulation, and persistent viral reactivation [139].

In the field of neuroendocrinology, the main theory concerning CFS has been a mild hypocortisolism of central origin, suggesting an impaired activation of the hypothalamic-pituitary-adrenal (HPA) axis [74]. Although recent research supports a central origin of this disturbance, possibly related to premorbid stress, uncertainties remain about the primary or secondary character of the HPA- axis dysregulation. [101]. Other reports in search of consistent patterns of neuroendocrine pathology in CFS concerning cortisol response and pro-inflammatory cytokine response to stress show no conclusive evidence [100,103], although offering integrative models of interaction between stress, immune processes, proinflammatory cytokines and brain responses, including fatigue [60]. Dexamethason-suppression-test show increased suppression of

cortisol in CFS, indicating enhanced negative feedback of HPA-axis[102]. Other neuroendocrine challenge tests show that some of the HPA-dysregulation could well be secondary to behavioural correlates to CFS, like profound inactivity, deconditioning and sleep disturbances [99].

Autonomic dysfunction or dysregulation, referred to as dysautonomia, particularly affecting sympathetic activity and homeostatic regulation of the autonomic nervous system, has been suggested as a possible pathophysiological mechanism in CFS [96]. There is a fairly large research body on the association between CFS and neurally mediated hypotension as part of the dysautonomias [35]. Most findings support an association between CFS and dysautonomia, hypothesizing abnormal cardiovascular reflexes, neurally mediated hypotension and orthostatic instability as pathogenic mechanisms. Results are not consistent; other studies fail to replicate orthostatic instability, calling for a reappraisal of primary dysautonomia as essential explanatory factors in the pathogenesis of CFS [132].

In recent Norwegian studies evidence has been presented confirming altered sympathetic nerve activity among CFS adolescent patients, supporting the hypotheses of sympathetic dysfunction as essential in CFS pathophysiology [268-271]. In these studies, adolescents with CFS were found to have significant abnormalities of cardiovascular regulation in response to mild orthostatic stress, differentiating them from healthy controls [268], showing sympathetic predominance of cardiovascular regulation during very mild orthostatic stress [270]. They seemed to have increased sympathetic cardiovascular activity at rest, enhanced sympathetic cardiovascular response to orthostatic stress, but attenuated sympathetic cardiovascular response when performing isometric exercise during orthostatic stress, suggesting a possible causal relation between sympathetic dysfunction, cardiovascular dysregulation and patients' complaints [271]. Observations in these studies indicated that adolescent CFS patients had abnormal catecholaminergic-dependent thermoregulatory responses both at rest and during local skin cooling, supporting a hypothesis of sympathetic dysfunction and possibly explaining important clinical symptoms [269].

A recent review of the pathophysiology of chronic fatigue syndrome emphasizes the evidence for the involvement of the central nervous system, including a hyperserotonergic state and hypoactivity of the HPA- axis, but raises the still unresolved question of whether these alterations are a cause or consequence of CFS[50].

In summary, it seems fair to conclude that no conclusion has yet been universally proven as to the pathophysiology of CFS, neither in terms of causal pathological mechanisms nor in terms of the pathology of perpetuated chronic fatigue. In many cases of somatic diseases with fatigue as an accompanying feature, chronic fatigue can only be distinguished from CFS by its accepted attribution to somatic illness [69].

Models of sensitization mechanisms have been presented integrating theories of pathology, dysfunction, dysregulation and imbalance concerning general pathophysiology, as well as integrated with psychophysiology, negative cognitive illness perceptions and illness behaviour [24,172]. The Cognitive Activation Theory of Stress (CATS) from Ursin & Eriksen [234] has been presented particularly relevant for somatisation processes, unexplained symptoms and subjective health complaints [83,232]. (See chapter 1.2.3.)

A model presented recently in a Norwegian dissertation on CFS in adolescents suggests a unifying theory of CFS pathophysiology caused by sustained arousal [267]. This model deals with both predisposing, precipitating and perpetuating factors in CFS [182], and allows for heterogeneity of causal factors, seeing CFS as a common final pathway of different genetic, physiological, autonomic, immunological or psychological mechanisms. This theory is based on CATS and models of sustained arousal, stress mechanisms and sensitization [83,85,86,230,233].

Models of biopsychosocial dynamics have been called for and suggested by many researchers [153,156], based on the need for integrating theories of pathophysiology with psychological models such as social learning theory, stress and coping, illness cognition, and self-regulation models for explaining more carefully the predisposing, precipitating, and perpetuating factors in CFS [62].

Sensitization models

Already Beard in 1869 [17] presented theories based on some kind of sensitization in the Central Nervous System as a possible – although speculative, as Beard himself admitted – mechanism in neurasthenia. Later, several theories of sensitization mechanisms have been presented as relevant to this and other related illnesses, both concerning physiological mechanisms and cognitive processes [85,86,156,172,220,230,231,233,239].

Sensitization is defined as an increased reactivity to stimuli, and the concept has been used to describe and explain hypersensitivity reactions to external physical stimuli by neural sensitization [19,20]. It is also a concept that may be used for more complex cognitive functioning involved in fear reactions, anxiety and pain-avoidance [24]; the concept has been expanded by integrating sensitization of afferent impulses with psychological processes, explaining a wider range of "unexplained" responses [230]. In clinical contexts, the mechanisms of sensitization processes could contribute to the understanding of excessive fatigue reactions by this model of increased reactivity and amplification in the nervous system, including neuroendocrine, psychophysiological and immune systems, as well as in cognitive systems of appraisal and behavioural responses. Such sensitization can be thought to result both from infectious/ postinfectious/ immunological processes [108], from sustained arousal of any physiological system [85,86,233], as well as from sustained cognitive arousal caused by rumination and negative assumptions [25,26], health worries and anxiety [27,83,226,234,239].

This model of sensitization expands earlier theories of somatosensory amplification [14], which sought to explain the increased sensitivity to somatic sensations in some patients with unexplained severity of complaints, their interpretation of such sensations amplifying the somatic complaint and the clinical presentation and illness behaviour.

In a slightly different paradigm of explaining the complex interaction between bodily signals, emotions and appraisal of somatic sensation, the concept of interoception offers a model for psychosomatic processes, including models of how psychophysiological sensitization might amplify interoception of sensations like general malaise and fatigue [36,55,56,157,185,258]. In exploring and understanding chronic fatigue syndromes, these models seem relevant.

It is possible that sensitization models can provide a common theory integrating many overlapping theories and models, and although not explaining unexplainable illness it might be a psychobiological starting point for exploring more detailed mechanisms of illness processes and phenomenon not yet understood.

This thesis leans on the models of sensitization in the discussions and interpretations of empirical findings in the clinical studies.

1.2.2 Health and impairment

Both chronic fatigue (CF) and CFS are associated with significant disability and dysfunction at home and at work. Studies and reviews have demonstrated that the burden of chronic fatigue is comparable to other severe, chronic disorders, both in terms of subjective experience and functional disability [195].

The health impairment and total burden of fatigue illness can hardly be measured exactly, both because of inconsistent use of inclusion criteria and consequent heterogeneous clinical population in most studies, and because burden of illness is in the end a subjective experience influenced by vulnerability and stress in the individual's life, independent of illness. Psychosocial support, depression, cognitive illness perceptions and catastrophic beliefs all influence the experience of and the actual disability in chronic fatigue syndrome [176,227,238].

Assessing health is in itself complicated, and methodological dilemmas are legio. In research literature of chronic fatigue, health impairment is partly assessed by functional disability and health-related quality of life, partly by number of comorbid diagnosis or clinical syndromes, and sometimes by number of symptoms or complaints. There are few comparative studies as to which assessments are most accurate or correlate the most. Recent studies have reported that the number of bodily symptoms show a linear correlation to health-related quality of life and outcome [123]. A scoring system for subjective health complaints (SHC)[82] have been used to measure health complaints both in the general population and in clinical groups, and studies have correlated subjective health complaints to functional status and work disability [81,104,121]. A comparison of subjective health complaints in neurasthenia compared to illnesses like Irritable Bowel Syndrome (IBS), Low Back Pain (LBP), Whiplash Associated Disorder (WAD) as well as comparing to the general population and a population on disability pension has been done [120], showing that patients with neurasthenia had greater total load of subjective health complaints than most other groups, particularly on "pseudoneurological" symptoms [5], but also on complaints from all other organ systems [82].

As for occupational disability, research shows fatigue itself to be a strong predictor for subsequent work disability [235]. In a major systematic review of disability in CFS the majority of patients represented in the studies reported employment status to be unemployed [195]. The evidence suggests that some individuals with CFS have cognitive or affective impairments on neuropsychological tests, but results are not consistent. Depression of greater severity is associated with unemployment, but no other impairment appeared to be consistently associated with disability or work outcomes. No specific interventions have been proven to be effective in restoring the ability to work. No specific patient characteristics have been identified as best predictors of positive employment outcomes in CFS patients. Generally, the assessment of disability in CFS is associated with the same limitations as in most CFS research, concerning consistent methodology, selection criteria and measures [194].

Health impairment is closely associated with health-related quality of life, and most studies in this field report both on health complaints and quality of life. The assessment of health impairment is varying some with the clinical population, but shows generally an extreme impairment of health and health-related quality of life [31,107,113,201,248].

An additional burden of illness in CFS is the subjective experience of not being taken seriously by the physicians and the medical system; the subjective complaints not being recognized as a medical illness, the illness being questioned as a psychological disorder, or just the experience of being ignored or faced with lack of knowledge or competence of CFS. The identities of CFS patients are challenged when the legitimacy of their illness is questioned. This significant burden adds to a loss of previously established identity and makes the patient more vulnerable than just suffering from the symptoms [144].

We know of no previous Norwegian study examining disability and subjective health complaints in patients with chronic fatigue syndrome or reporting long-term outcome by health impairment. A Scandinavian study from Denmark [6] of 5 years follow-up confirmed earlier research of extensive disability in CFS patients.

The issues of subjective health complaints, health impairment and functional disability are important elements of the research in this thesis, both in discussions of the characteristics of chronic fatigue syndromes and in assessing outcome and improvement.

1.2.3 Treatment and prognosis

During the last 15 years, an increasing number of studies have examined the effect of various treatment interventions in CFS, chronic fatigue and neurasthenia. "Neurasthenia" seems to identify and include most patients with CFS [88], and "neurasthenia" and "chronic fatigue" are often used synonymously in selection criteria or descriptions of clinical populations [114,149,208,266]. However, the opposite is not true: CFS seems to represent a smaller and more severely impaired group of patients. This is to be expected from the case definition; CFS is more specific and requires more accompanying symptoms than criteria for neurasthenia, as well as requiring functional impairment per se (see Appendices 8.1).

The effects of treatment and prognosis would thus be expected to vary with the case definitions being used for sample selection, as research shows [133]. As the definition becomes more stringent the prognosis appears to worsen. Systematic reviews of effect of different treatment interventions have been published, concerning most interventions considered generally acceptable. Conclusions from these reviews are the main basis of clinical recommendations for the management of CFS, as have been published in many countries [165,169,196].

Systematic reviews of all interventions for treatment and management of Chronic Fatigue Syndrome demonstrate mixed results in effectiveness [43,257]. There is a wide range of treatment designs and outcome measures, and the data are of too inconsistent quality to perform robust meta-analyses. Interventions of graded exercise therapy (GET) and cognitive behavioural therapy (CBT) have shown positive results and also scored high on validity assessment [65,66,180,189,203]. For pharmacological interventions,

including antidepressant medication, the overall evidence in CFS has been inconclusive, and no systematic effects have been proven [10,43,257]. A Norwegian systematic review of treatment effects in CFS concluded that only CBT and Graded Exercise have shown systematic effects [169]. The evidence is often weak, and the most severely patients are not examined. These conclusions are very much in line with the underlying conclusion in the British NICE-report [11], providing systematic guidelines for the management and treatment of CFS/ ME.

In studies in primary care comparing effect of counselling programs to cognitive behavioural therapy, results show that counselling with evidence-based knowledge of CFS was as effective as CBT [190] . This is also confirmed by studies showing that education and counselling increase and sustain exercise in CFS patients [177,178], also by 2 years follow-up. CBT seems easier to "sell" to patients, effect of GET and CBT seems equal on the least severely fatigued patients, but short-term programs of 3 months seem to be too short for the most disabled patients [189].

The present state of research evidence for effective treatment with single interventions in chronic fatigue syndromes could be summarized by saying that CBT and graded exercise have been found effective, mainly on functional impairment, less on fatigue symptoms [43]. Evidence is weak, however, and all reviews recommend further research, preferably with more homogeneous clinical populations, with stringent criteria, and with high quality in methodology, design and assessment. Combination treatments, i.e. combining different types of interventions have rarely been studied systematically in chronic fatigue syndrome.

The research evidence suggests that high-quality interventions studies are still needed, and that the effect of combination therapy would be of special relevance. A combination of interventions is tested in the clinical trial included in this thesis.

1.3 Summary of research relevant to the thesis

Patients with chronic fatigue seem to have significantly higher risk of having other illnesses and more severe functional disability than most other clinical groups and reference populations. The concurrent diagnoses and syndromes in CFS have been investigated, but subjective health complaints have not been studied. There is no clear evidence whether CFS patients have distinctly specific health complaints, if the subjective health complaints are similar to those of other illnesses or the general population, or if the health complaints are mainly more of the same…
The study of health characteristics and subjective health complaints seems relevant.

Research concerning effective treatments for CFS shows that cognitive-behavioural interventions and graded exercise have effect, but evidence has been weak and the effects on fatigue, mental and physical function show varying results. Educational programs seem to be as effective as the more costly CBT, which can be offered to a few patients. Although CFS is an illness with evidently complex aetiology and complex pathophysiological processes and with frequently accompanying disorders like sleep disturbances and depression, few treatment studies have been done to examine combination treatment with different interventions. Comprehensive treatment programs combining interventions proven effective have rarely been investigated with adequate research quality.

Illness course and prognosis in CFS have generally been found to be poor, but varying. Most patients improve, but few seem to recover. Analysis of improvement and illness course in clinical subgroups or by illness characteristics show varying results. Few systematic long-term follow-up studies have been done.

Studies of comorbidity with psychiatric illness and personality disorders in CFS show conflicting results and give reasons to different interpretations, as well as background for controversies of psychological or somatic cause of CFS. There is no general consensus as to what extent personality disorders or personality factors are of importance in chronic fatigue syndromes. Further research seems needed.

Generally, in research of neurasthenia and chronic fatigue syndromes the questions and dilemmas of sample selection and selection bias are unresolved. A wide variety of inclusion criteria is being used, sometimes inclusion by discretion; assessments are based on subjective reports and complaints without objective findings, and the quality of research methods are varying widely, making general interpretations difficult.

In this thesis, it has been a main objective in the clinical studies to adhere to recognized research methods of high quality, in order to contribute to further evidence-based knowledge in the field of chronic fatigue. It has also been a goal to address clinically relevant issues in this field, both issues that need confirming or replicating and dark holes that need more knowledge.

2. Aims and research questions

Based on earlier research on neurasthenia and Chronic Fatigue Syndrome, these problem areas and research issues are identified, constituting the empirical basis for the present thesis:

Research question 1:

- What are the health characteristics of patients with chronic fatigue in terms of general health and subjective health complaints, functional impairment and work disability? *(paper 1)*

Research question 2:

- Would a comprehensive treatment program combining earlier proven effective element have positive effect, and would a combination with an antidepressant medication give added effect? *(paper 2)*

Research question 3:

- What is the illness course after a systematic treatment intervention, during 1 – 5 years follow-up? *(paper 3)*

Research question 4:

- What is the prevalence of personality disorders in our clinical population of CFS, and is there a specific pattern of personality factors in CFS, compared to a reference population? *(paper 4)*
  Are there associations between personality factors and long-term improvement? *(paper 4)*

3. Methods

3.1 Material

In the study of neurasthenia and subjective health complaints (paper 1), patients were recruited through a screening process after a systematic distribution of questionnaires to all patients in waiting rooms of general practitioners in the local area of Haugesund Hospital on the West coast of Norway, urban and rural areas, March – May 1999. 1075 patients filled in questionnaires on subjective health complaints, neurasthenia, coping strategies, together with demographic information, illness history and lifestyle. The group of responders was considered to be representative for a normal patient population in general practice. Responders, who fulfilled screening criteria of neurasthenia and/or scored 2-3 (scale 0-3) on the "tiredness" item on Subjective Health Complaints (SHC, see Instruments), were invited to clinical interviews. Out of 1075 total responders, 106 fulfilled screening criteria for neurasthenia. 92/ 106 had given consent for further interviews, 16 proved not to fulfil criteria of neurasthenia by telephone interview, 6 were unwilling to interviews. 70 patients met for clinical interviews for establishing the diagnosis of neurasthenia (ICD-10: F 48.0; see Appendices 8.1), bringing referral from their GP. 28 patients fulfilled inclusion criteria for the study. Patients were also referred directly from the general practitioners (GPs) in the region (total population 90.000) to the psychosomatic outpatient clinic, for evaluation of neurasthenia and chronic fatigue syndrome. 44 patients fulfilled inclusion criteria for the study.

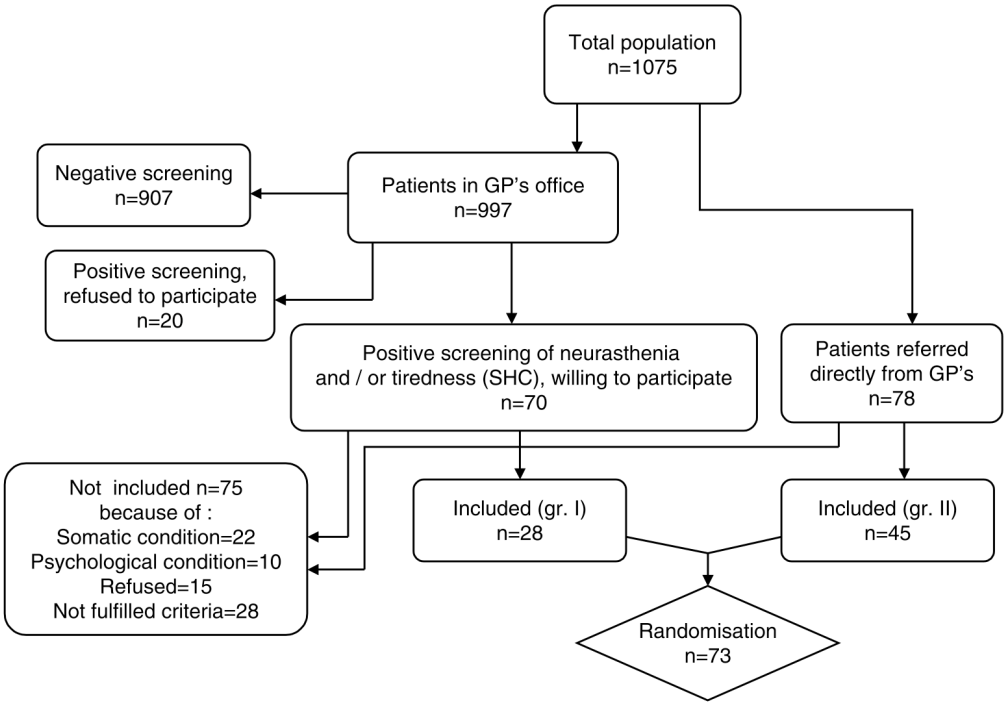
(See flow chart A /fig 1).

Hence, the neurasthenia group (paper 1) consisted of two groups of patients: one group was selected from the patients having completed the screening questionnaires and one group was directly referred to treatment for fatigue from GPs in the area. The groups did not differ on most of the demographic or outcome variables. However, the group of patients referred for treatment had slightly higher level of education,

modestly lower physical fitness, fewer of them did physical exercises regularly and they had more weeks of sick leave during the last year (31 versus 18 weeks).

During the interviews, the diagnosis of neurasthenia was confirmed, and possible reasons for exclusion were ruled out. The interviews and the evaluation were based on an experienced clinical judgment from one and the same interviewer (BS).
The group of neurasthenia patients (n=72) later went on to randomization and a treatment program (paper 2).

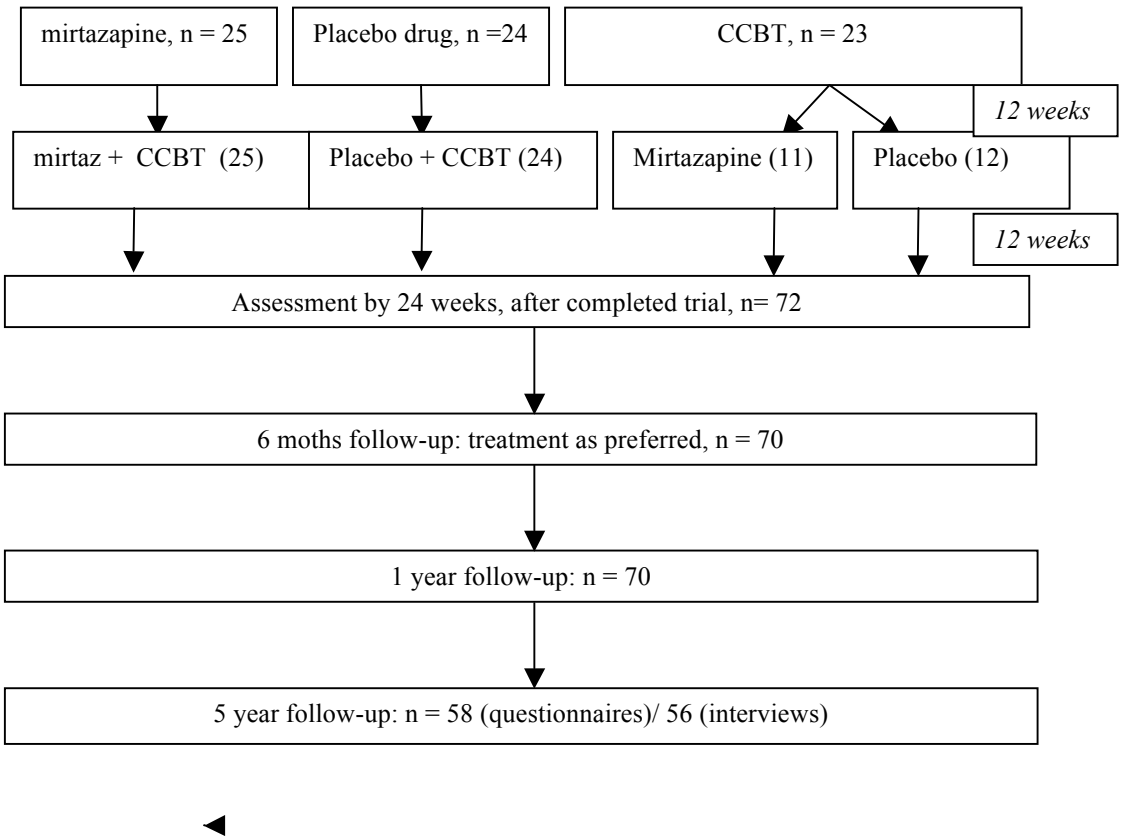
Fig. 1: Flow chart A



The clinical study population were 72 patients with chronic fatigue complaints, fulfilling ICD-10-research criteria of Neurasthenia, F48.0 [265]. Illness definition was operationalized by examining ICD-10 criteria. The included patients satisfied the ICD-10-criteria, allowing for mild depressive or anxiety symptoms clinically evaluated to be independent of or secondary to fatigue symptoms. The criteria for Chronic Fatigue Syndrome, using CDC-criteria and British/Oxford-criteria, [92,207] were also examined in the included patient population of neurasthenia (n=72). 65/72 patients fulfilled case definition by British/ Oxford criteria; 29 patients fulfilled CDC-case definition.

The interviews and assessments were done by SCAN [263] structured interview schedules, check-lists for neurasthenia and CFS-case definitions (Appendices, 8.1), in addition to medical evaluation and laboratory investigations.

Fig.2: Flow chart B (treatment study)



72 patients fulfilled the 24 weeks treatment program (paper 2), (fig 2; flow chart B). 13 patients had a premature discontinuation; for these patients the data from last observation carried forward (LOCF) were used in end-of-treatment analysis.

All study participants were invited to follow-up investigations; 70 patients (97 %) met for follow-up studies at 6 months and 1 year. 58 patients (81 %) responded at 5 years follow-up (2007) by completing questionnaires, 56 (78 %) completed interviews and diagnostic evaluation (paper 3).

62 patients from the study population fulfilling CFS case definitions of CFS- Oxford or CFS-CDC (excluding patients with neurasthenia non-CFS) provided data for assessment of personality disorders by SCID-II interviews; 53 patients completed the Personality Assessment Inventory (PAI) questionnaire, providing data for analysis of personality factors (paper 4). The study population was further divided into exclusive categories of CFS-CDC (n=28) and CFS-Oxford non-CDC (n=34), for analysis purposes.

3.2 Design of clinical trial

Treatment intervention study

A three-armed randomised clinical trial of mirtazapine medication, placebo drug and a comprehensive cognitive treatment program (CCBT) was conducted to investigate treatment effect in the patient group with chronic fatigue diagnosed with neurasthenia (n=72) and chronic fatigue syndrome (n=65/ 72), at an outpatient specialist psychosomatic clinic. The CCBT program was compared to mirtazapine and placebo for 12 weeks, followed by a 12 weeks treatment regimen with a mixed crossover-combination design. Assessments were done by 12 and 24 weeks.

The protocols and design adhered to the standards of the CONSORT statement of randomised clinical trials [4].

Follow-up study

Patients met for interviews and completed questionnaires at 6 months, 1 year and 5 years after end of treatment program, with no systematic treatment in the follow-up period. Symptoms, functional impairment, clinical severity and improvement were evaluated by self-report questionnaires, structured interviews and clinical assessment.

3.3 Instruments

Data in paper 1 were collected and measured by a compiled questionnaire consisting of Norwegian versions of various questionnaires, covering a broad range of factors including demographic variables, physical and psychological variables at work, factors related to work organizing and leadership, social support and family relationships, and individual coping resources.

Further data from the clinical study group (n=72) were collected by another compiled questionnaire measuring illness perceptions, illness management, illness behaviour and coping factors.

Structured clinical interviews were used for diagnostic assessment;
SCAN [261] for psychiatric diagnosis and evaluation; SCID-II [90] for evaluation of personality disorders. The Personality Assessment Inventory (PAI) [159] were used to assess personality factors. Clinical checklists for case definitions of CFS (CFS-CDC; CFS- Oxford) were used to assess CFS *(see Appendices 8.1)*.

For outcome measurements in the clinical trial and follow-up study, both self-reported questionnaires and clinical assessments were used. The specific questionnaires and assessments instruments are described in the following section.

Specific instruments and questionnaires

General health: Subjective health complaints

Subjective health complaints were measured by the Subjective Health Complaints Inventory (SHC) [82], consisting of 29 items on subjective somatic and psychological complaints experienced during the last 30 days. This questionnaire has been tested and has satisfactory validity and reliability [82]. Severity was scored on a four-point scale, from 0 – no complaints, to 3 – severe complaints. Five sub scales were

computed, allergy (5 items), flu (2 items), musculoskeletal pain (headache, neck pain, upper back pain, low back pain, arm pain, shoulder pain, migraine, and leg pain) (8 items), gastrointestinal problems (heartburn, epigastric discomfort, ulcer/non-ulcer dyspepsia, stomach pain, gas discomfort, diarrhoea, and constipation) (7 items), and "pseudoneurology" [5] (palpitation, heat flushes, sleep problems, dizziness, anxiety, and sadness) (6 items). The SHC has been tested and used in studies of the general population, in Low Back Pain, Irritable Bowel Syndrome, Whiplash Associated Disorder and other chronic illnesses, as well as in studies of comorbidity and health-related life quality [104,120-122,229].

Coping: CODE

Coping was measured by the Instrumental Mastery Oriented Coping Factor from the CODE [84] coping and defence questionnaire. The questionnaire has satisfactory reliability and validity. Instrumental mastery oriented coping (22 items) (active problem solving, avoidance and passive expectancy, and depressive reaction pattern) implies an instrumental, active, goal-oriented coping style, with strategies like direct intervention, considering different solutions to the problem, and considering the problem a challenge [84]. To get a high score on this factor, the score on active problem solving must be high, and the score on avoidance and passive expectancy and depressive reaction pattern must be low. Instrumental mastery oriented coping is the coping variable in the demand/coping model [79].

Fatigue

Fatigue was assessed by the Chalder Fatigue Scale [41]; a self-rating scale developed to measure severity of physical and mental fatigue. The scale consists of 11-items, being rated 0-3 in severity. The scale has been found to be reliable and valid in chronic fatigue syndrome, showing a high degree of internal consistency [162]. Principal components analyses indicated a two-factor solution (physical and mental fatigue) [162].

Clinical Global Impression

Clinical Global Impressions (CGI) [98] –dimensions of Severity of Illness (CGI-S) and Improvement (CGI-I) were used; rated on a 7-point scale. Severity of illness is rated within last week; global improvement is rated since admission to the study. CGI-Severity was assessed by clinical assessment, CGI-Improvement was based on patients' self-reports.

Quality of life

Health related quality of life was measured by the generic health status measure SF-36 (Short Form 36-items) for health situations during the last 4 weeks [150] . SF-36 is a generic QoL scale consisting of 36 items describing eight dimensions [243], aggregated to one physical and one mental health component [242]. Adjusted SF-36 scores were calculated. The mean is 50, and a deviation of ten points from the mean represents one standard deviation.

Illness Perception

The Revised Illness Perceptions Questionnaire (IPQ-R) [163] was used to measure patients' illness perceptions. It has demonstrated good reliability and validity across several illness groups and includes eight cognitive dimensions.

Cardiorespiratory fitness

Cardiorespiratory fitness was assessed by the Åstrand-Rhyming test (indirect test of maximal oxygen uptake (VO_{2max}) [9]; the test was performed on an ergometer bicycle [9].

Depression

Depression was assessed by Hamilton Depression Scale 21 items (HAMD-21), rating symptoms of depression by a 21-item rating scale [105,106], indicating the level of depression.

Personality Assessment

A Norwegian version of the Personality Assessment Inventory (PAI)[158,160,161] (back translation to English approved by Leslie C. Morey and Psychological Assessment Resources (PAR)) was used. The Norwegian version had been used in studies of cognitive schemas in psychiatric outpatients [119]. The Personality Assessment Inventory (PAI) is a multiscale inventory that is widely used in clinical settings [161,241]. PAI is an objective inventory of adult personality that assesses psychopathological syndromes [158,160]. It consists of 22 scales measured by 344 items. The 22 scales are organized into four categories that include validity scales, clinical scales, treatment scales and interpersonal scales. Its validity has been tested and compared to MMPI-2, showing good validity and producing few invalid profiles [22].

In assessing specific personality factors relevant to research questions the following PAI-scales and subscales were used [161]:
Exaggerated somatic focus: Scale for somatic complaints (PAI-SOM), (subscales conversion SOM-C, somatisation SOM-S, health worries SOM-H); Doubts about actions, concern over mistakes: anxiety scale, cognitive subscale (ANX-C); Tendency to catastrophizing: anxiety scale, affective (ANX-A) and physiological subscale (ANX-P); Perfectionism: anxiety-related disorder scale, obsessive-compulsive subscale (ARD-O); Low self-esteem: mania scale, grandiosity subscale (MAN-G); Inadequate social control: dominance interpersonal scale (DOM); Inadequate competency: depression scale, cognitive subscale (DEP-C).

Structured psychiatric interview and assessment: SCAN

SCAN (Schedules for Clinical Assessment in Neuropsychiatry)[263] was used in the diagnostic process in assessing psychiatric disorders and symptoms. SCAN is a structured clinical interview for ICD-10 diagnosis [264]; it has been found to have good validity and reliability [1,200]. The interviewer was trained in use of SCAN.

Assessment of personality disorders: SCID-II

SCID-II [90] is a structured clinical interview for DSM-IV axis-II diagnosis. The instrument has been found to have good validity and test-retest reliability [197,259]. The interviewers were trained for SCID interviews.

Safety assessments (paper 2)

Safety assessments during the intervention study included a full clinical examination prior to inclusion in the trial; spontaneously reported adverse events and measurements of vital signs and weight at each scheduled efficacy evaluation, in addition to laboratory tests. Adverse events were coded in MedDRA system [28], using Preferred Term (PT) as unit of registration. There were defined procedures for immediate reporting in case of serious adverse events.

3.4 Statistical methods

SPSS (SPSS inc. Chicago, USA) version 11.5 for MS-Windows was used for the statistical analyses in paper 1. ANOVA and binary logistic regression statistics were used to analyze differences in subjective health complaints in the two populations of general help-seeking population and neurasthenia population.

Analyses in paper 2 and 3 were done with a mixed model for normally distributed continuous data for the outcome measures; using PROC MIXED in SAS for Windows, version 8 (paper 2) and 9.1 (paper 3). To account for the repeated measures for the individuals, individual were entered in a mixed model for repeated measures, with an unstructured covariance structure (paper 2) and an autoregressive (AR1) covariance structure (paper 3). Other variables were entered as fixed effects. Other analyses were done in SPSS version 13 for Windows (paper 2) and 14.01 (paper 3).

Analyses in paper 4 were done with a mixed model for normally distributed continuous data for the outcome measures; using SPSS version 14.0 for Windows. To account for correlation between the different measures for the individuals, a variance component model was used. Other variables were entered as fixed effects. Descriptive statistics and other analyses were also done using SPSS.

3.5 Ethics

The study was approved by the Regional Ethic Committee and the Norwegian Data Inspectorate. The trial was registered with the Norwegian Social Science Data Services (NSD) prior to any patient inclusion. All participants had received written information about the trial and had given formal consent about participation, including new formal consent about the follow-up study.

4. Results and summary of the papers

Paper 1

Neurasthenia, subjective health complaints and sensitization

***Background**:* Neurasthenia and chronic fatigue syndromes are prevalent and disabling illnesses. There are few studies of general health and comorbidity in these patients.

Objectives: To study general health and health complaints, functional disability and coping and illness variables in patents with neurasthenia.

***Methods**:* Patients (*n*=997) visiting general practitioners in an area in Western Norway completed a battery of questionnaires related to subjective health complaints and fatigue. 78 other patients were referred directly to the hospital for neurasthenia. After screening the selected sample with questionnaires and interviews, a total of 72 patients were included as 'neurasthenia' patients satisfying the ICD-10 diagnosis. These patients were compared with the remaining 1003 patients.

***Results**:* Patients with neurasthenia had more prevalent and more severe subjective health complaints than the reference population of patients. Sickness leave periods were significantly longer. Patients with neurasthenia reported low levels of instrumental coping and poor physical fitness. The overall high score on subjective complaints from all organ systems could indicate a general sensitization of the afferent inputs from their psychophysiological systems. The lower level of coping could be maintaining ruminating cognitive perceptions. A rumination process may maintain the expectancies and the sustained activation, and be part of the neurobiological foundation for the sensitization process.

Having examined health and impairment in patients with chronic fatigue, a clinical challenge would be to design and study the effect of treatment interventions.

Paper 2

Cognitive–behavioural therapy v. mirtazapine for chronic fatigue and neurasthenia: a randomised placebo-controlled trial

Background: Single interventions in chronic fatigue syndrome have shown only limited effectiveness, with few studies of comprehensive treatment programs.

Objectives: To examine the effect of a comprehensive cognitive behavioural treatment program (CCBT) compared to placebo-controlled mirtazapine medication in patients with chronic fatigue, and to study the combined effect of the comprehensive treatment program and medication.

Methods**:** A three-armed randomised clinical trial of mirtazapine medication, placebo drug and a comprehensive cognitive treatment program (CCBT) was conducted to investigate treatment effect in a patient group with chronic fatigue diagnosed with Neurasthenia (n=72) and Chronic Fatigue Syndrome (CFS, n=65/ 72), referred to a specialist clinic. The CCBT program was compared to mirtazapine and placebo for 12 weeks, followed by a 12 weeks treatment regimen with a mixed crossover-combination design. Assessments were done by 12 and 24 weeks, by self-report questionnaires and clinical assessments.

Results**:** By 12 weeks, treatment effect was significantly better in the group initially receiving the comprehensive treatment program (Fatigue Scale ($p=0.014$); Clinical Global Impression ($p=0.001$)). By 24 weeks, the treatment group initially receiving CCBT 12 weeks followed by mirtazapine 12 weeks showed significant improvement, compared to other treatment groups (Fatigue Scale ($p<0.001$) and Clinical Global Impression ($p=0.002$)). Secondary outcome measures showed overall improvement, but no significant differences between treatment groups.

Conclusion**:** Multimodal interventions with initial cognitive-behavioural therapy, body awareness therapy and exercise followed by mirtazapine antidepressant medication seem to have positive treatment effects in chronic fatigue syndrome. The

findings indicate that initial non-pharmacological "priming" by a cognitive-oriented treatment program prior to medication gives the best treatment effect.

The results of a 6 months intervention program showed general improvement on fatigue symptoms and severity. Since neurasthenia and CFS represent a chronic illness, it seemed of relevance to study the further illness course; if improvement continued and whether the long-term illness course differed within the patient group.

Paper 3

Illness course in chronic fatigue syndromes. A 5 years follow-up study

***Background**:* A six months randomized clinical trial in patients with chronic fatigue syndrome (CFS) and neurasthenia showed positive effect of a comprehensive cognitive-behavioural treatment intervention combined with mirtazapine. There are few previous studies of time-limited treatments or studies of long-term course of CFS based on different case definitions.

***Objectives**:* 1) To examine the long-term effect of treatment interventions and examine if the initial treatment effects were sustained. 2) To study the illness course and diagnostic stability in subgroups of chronic fatigue patients based on different case definitions (neurasthenia, CFS-Oxford and CFS-CDC).

Methods: Patients with chronic fatigue syndrome (CFS) and neurasthenia (n=70) were examined by interviews and questionnaires at 6 months, 1 year, and 5 years after a systematic treatment program. Fatigue symptoms, clinical severity, health-related quality of life, subjective health complaints and depression were recorded.

***Results**:* Improvement in fatigue symptoms in the treatment period continued during the follow-up period, but the difference between treatment groups were not sustained. Half of the patients showed a substantial reduction in fatigue symptoms during the follow-up period, irrespective of the specific treatment received previously. Patients fulfilling the case definition of CFS-CDC reported more debilitating symptoms of fatigue and showed poor prognosis, and represented the most consistent group with chronic fatigue. Patients on antidepressant medication at 5 years follow-up showed the greatest improvement on fatigue symptoms from baseline.
Sudden onset, severity of fatigue at the initial phase of illness and slow improvement predicted a poor prognosis. Diagnoses tended to shift from CFS towards the less serious condition of neurasthenia and unspecific fatigue through the follow-up period.

Conclusion: The specific effects of a time-limited treatment intervention seem to be of less importance for the long-term course in CFS than the severity and characteristic of the illness itself. Findings confirmed that most patients with chronic fatigue syndrome have a substantial improvement over some years, while many patients still suffer a severe illness course. Different case definitions of CFS seem to represent different parts of a fatigue spectrum; the findings support the assumption that CFS-CDC represents a distinct illness entity within the fatigue diagnoses, characterized more by global severity, functional impairment and subjective health complaints than fatigue symptoms alone Improvement of fatigue and improvement of mood seemed significantly associated.

Improvement in self-reported and clinician-assessed fatigue severity in patients using antidepressant medication at 5 years follow-up could indicate that some patients benefit from antidepressant medication on fatigue symptoms, irrespective of depressive symptoms. Findings suggest that CFS-CDC could represent the most consistent subgroup of severe CFS, needing further differentiation. Findings also suggest that both chronic fatigue illness and CFS case definitions may represent a continuum of fatigue rather than specific subgroups. This supports the argument for keeping case definitions for chronic fatigue syndrome wide, as in neurasthenia.

Keeping the question of psychiatric comorbidity in mind, concerning possible psychological components in CFS, it seemed relevant to study psychiatric symptoms and personality pathology. Major psychiatric disorders were ruled out by inclusion criteria for the study; other psychiatric symptom were evaluated trough intervention trial and follow-up (paper 2, 3). It seemed relevant to examine personality disorders and personality factors in the patient group with CFS, comparing results to previous research on this issue.

Paper 4

Personality disorders and personality factors in chronic fatigue syndrome

Background: The role of personality in CFS has not been studied extensively in CFS; previous research show varying and inconsistent results concerning the impact of personality factors on predisposition and perpetuation of CFS.

Objectives: To study the prevalence of personality disorders and patterns of personality factors in patients with Chronic Fatigue Syndrome (CFS).

Methods: Patients with CFS (n=53) were interviewed using SCID-II and fulfilled questionnaires of Personality Assessment Inventory (PAI) prior to a treatment program. Patients were examined at 5 years follow-up after treatment, recording fatigue symptoms and improvement after 5 years by self-reported Fatigue Scale.

Results: The prevalence of personality disorder was low (13 %), equal to a non-clinical sample. The mean personality score by PAI was 51 (norm T=50), indicating low average personality dysfunctions. The total patient group had a clinical profile close to that of somatoform disorder (Coefficient of Fit = .667). There were elevated scores of somatisation and health concerns and on subscales of vegetative signs of depression, and low scores of self-esteem and perfectionism. Low improvement by 5 years seemed associated with low levels of perfectionism and high levels of vegetative signs of depression.

Conclusion: Patients with CFS seem to have personality disorders or pathology equal to the average population. CFS patients have a tendency to higher levels of somatisation and somatic complaints, more vegetative signs of depression, lower self-esteem and low level of perfectionism. This could be secondary to the CFS illness, possible explained by physiological and cognitive sensitisations processes. Findings suggest that bodily sensations are exaggerated and cognitive awareness correspondingly low. Somatisation may be a function of a psychobiological "sensitisation" and CFS may be a chronic stress disorder, characterised by sustained activation. Low levels of perfectionism combined with low levels of self-esteem and perception of social control could indicate a state of helplessness and negative outcome expectancy that is corresponding well with depression.

Summary of results

Patients with neurasthenia and chronic fatigue had substantially more and more severe subjective health complaints than a reference group of average patients in primary care. Work disability was higher; sickness leave periods were significantly longer.

Improvement after 3 months treatment intervention in a clinical population of neurasthenia and Chronic Fatigue Syndrome (CFS) was significantly better in a group receiving a comprehensive treatment program of cognitive-oriented group therapy, body-awareness therapy and graded exercise (CCBT), compared to mirtazapine and placebo drug. After combining different treatment interventions for additional 3 months, the treatment group initially receiving CCBT followed by mirtazapine showed significantly better improvement by 6 months, compared to other treatment groups.

Improvement in fatigue symptoms continued after the 6 months' systematic treatment interventions, but the differences between the initial treatment groups disappeared. Half of the patients showed a substantial reduction in fatigue symptoms during a 5 years follow-up period, and diagnoses tended to shift from CFS towards neurasthenia and unspecific fatigue through the follow-up period. Patients with CFS-CDC represented the most consistent diagnostic group, reported more debilitating symptoms of fatigue and had a poorer prognosis. Patients on antidepressant medication at 5 years follow-up showed the greatest improvement from baseline. Sudden onset, initial severity of fatigue and slow improvement predicted a poor prognosis.

Patients with CFS seem to have personality disorders or personality pathology equal to the average population, with a personality profile similar to patients with somatoform disorder. CFS patients have a tendency to higher levels of somatisation and somatic complaints, more vegetative signs of depression, lower self-esteem and low level of perfectionism. Low improvement by 5 years seems associated with low levels of perfectionism and high levels of vegetative signs of depression.

5. Discussion

5.1 Discussion of results

Research question 1: What are the health characteristics of patients with chronic fatigue in terms of general health and subjective health complaints, functional impairment and work disability? (Paper 1)

The main finding in paper 1 was that patients with neurasthenia (including CFS) had substantially more subjective health complaints and more functional and work disabilities than the general patient group in GP's waiting room. This finding confirms the view of neurasthenia and chronic fatigue syndrome as a severe and incapacitating illness [3,34,182]. The comorbidity of symptoms and complaints from all organ systems raises the question whether neurasthenia/ CFS is an illness characterized by general sensitization of afferent impulses and an increased cognitive preoccupation with these sensory inputs [19,24,156,233]. This increased sensitivity and the possible sensitisation is discussed further in Paper 4.

Research question 2: Would a comprehensive treatment program combining earlier proven effective element have positive effect, and would a combination with an antidepressant medication give added effect? (Paper 2)

Systematic treatment programs for 6 months showed clinically significant positive effects in the majority of patients. The lack of any non-treated control group makes it difficult to fully evaluate these effects; the improvement found could be caused by time and illness course alone. This may be an unreasonable assumption, given the fact that most patients had several years' duration of illness with no substantial improvement.

A comprehensive cognitive behavioural treatment intervention (CCBT) had significant better effect than the antidepressant medication mirtazapine alone or placebo. Adding mirtazapine to CCBT had added effect on improvement, and this combination showed greater effect than the opposite sequence of intervention (mirtazapine followed by CCBT). These findings indicate that the effect of a comprehensive intervention program with emphasis on illness perceptions and body awareness is clinically effective, and that such a program might have a "priming effect" on the compliance and effect of medication. This group of patients has generally a sceptical attitude towards psychotropic medication [21,217] and showed an unusual level of side effects from medication. Therefore, medication (antidepressants, sleep regulating medication) to patients with chronic fatigue should be offered following an initial intervention focusing on illness perceptions, body awareness and careful exercise.

Research question 3: What is the illness course after a systematic treatment intervention, during 1 – 5 years follow-up? (Paper 3)

Following the systematic interventions reported in paper 2, half of the patients with CFS improved substantially over the 5 years. However, the CFS-CDC subgroup seemed to be a more consistent diagnostic group than other subgroups with chronic fatigue, with the poorest outcome after 5 years, showing little if any improvement. This group also differed from other groups before treatment and had greater severity in symptom load and functional impairment. The majority of patients fulfilling the CFS-Oxford diagnosis by baseline improved during the 5 years. At the 5 years follow up most patients no longer qualified for this diagnosis, but had "moved" to neurasthenia or did not fulfil any diagnosis of chronic fatigue.

Depression symptoms also improved substantially during the follow-up period. The prevalence of depression, defined by cutoff levels on Hamilton Depression Scale [111], was high at baseline; more than half of the patients had a depression score indicating mild clinical depression. At 5 years follow-up only 6 % of patients had this level of

depression scores. There was no association between level of depression and fatigue illness severity. There was, however, a significant association between improvement in fatigue symptoms and reduction of depression scores. Patients using antidepressant medication by the 5 years follow-up examination had less fatigue symptoms and less functional impairment than patients who did not use antidepressant medication. The findings indicate that antidepressant medication could have a positive effect on chronic fatigue, independent of depression and antidepressant effect, by effect on different levels and mechanisms [123,170].

The results indicated that the long-term effect of a time-limited intervention program is of less importance than specific features of the chronic fatigue illness. These features might again represent different subgroups of chronic fatigue syndromes, showing different prognosis and potential for treatment effect. The characteristics predicting poor outcome and prognosis and low improvement corresponded with the subgroup of patients fulfilling the CFS-CDC case definition, with a significantly higher frequency of precipitating infections and sudden onset of fatigue illness. Although there was variation in baseline and outcome variables also within the CFS-CDC group, supporting the need for resolving ambiguities in the CDC case definition and validity of assessment instruments [218], our findings did support the notion of a specific, more disabled and severely ill group of patients within CFS. This seem to be a group more congruent with the case definitions of myalgic encephalomyelitis (ME)/ CFS [38,39], supporting the call for re-evaluation of the case definitions of chronic fatigue syndromes.

Research question 4: What is the prevalence of personality disorders in our clinical population of CFS, and is there a specific pattern of personality factors in CFS, compared to a reference population? - Are there associations between personality factors and long-term improvement? (Paper 4)

Personality disorders and personality factors were examined in patients fulfilling case definitions for chronic fatigue syndrome (CFS) (CFS-CDC and CFS-Oxford). There was no evidence of the high prevalence of personality disorders (DSM) and patterns of specific personality factors in patients with CFS reported by others [110]; the prevalence of personality disorders was similar to what has been found in the general population. As for specific personality factors, there was no signs of increased levels of negative perfectionism or obsessive-compulsive factors, as has been described earlier [152,252]. However, the CFS patients reported lower self-esteem and lower experience of self-assertion and social control. This could be interpreted as a feeling of helplessness and negative outcome expectancy, being consistent with a mild level of depression. The self-concept cluster was stable, indicating that the moderately negative cognitive assumptions about health and helplessness were more state-dependent of the fatigue illness than trait-dependent of the individual.

The personality "profile" was similar to a reference group of somatoform disorder. The CFS patents had clinically and statistically higher levels of somatisation than the average reference population. This may be a function of a psychobiological "sensitization", both by chronic physical complaints and by cognitive processes of rumination and perseveration of thoughts and worries about the illness. Intervention strategies aiming at increasing body awareness and appraisal of bodily sensations could be effective in modifying the tendency to somatisation and health worries.

The prevalence of depression symptoms, low level of self-esteem and perceived social control could be interpreted as secondary to having a severe and long-lasting illness like CFS. There were no differences in personality factors between the CFS-CDC and CFS-Oxford groups, in spite of significantly different severity and illness course in these two groups.

5.2 Issues in interpretation of results and context of CFS

The empirical work and results constitute the core research of this thesis, along with the discussions of the results in this section. However, there are some issues concerning the concept and construction of chronic fatigue syndrome that need to be discussed in a broader context beyond the specific research questions and papers. These issues pertain to the major objectives of this thesis, concerning health and impairment, treatment and prognosis, and deal with aspects of classification and sample selection, with the concept of comorbidity and with the pathophysiological mechanisms that represent the ambiguities and unexplained questions in this field. The question of CFS being a somatic or psychiatric illness also needs being discussed, as well as the chronically unexplained questions of chronic fatigue.

In the following chapters, these issues are discussed and brought into the wider interpretation of the empirical research issues and discourse of CFS.

5.2.1 Fatigue classification in the clinical sample

In the clinical studies in this thesis, it was decided to use neurasthenia (ICD-10: F48.0) as the primary selection and inclusion criterion, regardless of whether case definitions of CFS were fulfilled. In doing so, we wanted to include patients within the spectrum of chronic fatigue illness, but still with defined criteria that could be operationalized, as was possible with the ICD-10 diagnosis of neurasthenia, using ICD-10 research criteria [265]. However, we also assessed if the case definitions for CFS-CDC [92] and CFS-Oxford [207] were fulfilled, to be able to analyze and compare CFS from neurasthenia, as well as comparing the two clinical populations corresponding to the case definitions. For purposes of analysis and differentiation, we wanted to compare non-overlapping groups, and thus divided our patient population into CFS-CDC, CFS-Oxford non- CDC, and neurasthenia non-CFS.

It can be argued that the groups of neurasthenia and CFS-Oxford for this reason comprised only the least seriously affected patients, and as such were not representative for a clinical population fulfilling this diagnosis/ case definition. Although recognizing this, the total analyses could still be seen as representative for chronic fatigue patients including CFS patients, since through the intervention trial and follow-up study both the total group and the differences between-groups consistently have been analyzed, using the exclusive criteria for the subgroups of patients.

It can also be argued that the high prevalence of depression found at baseline in our patient population should disqualify for a "real" chronic fatigue syndrome or the diagnosis of neurasthenia in many patients. This seems insignificant for the diagnosis of CFS, as the level of depression was mild in every case, and the fatigue illness could not be explained by depression. The CFS-Oxford case definition states explicitly that mood disturbance may be part of the illness, and that occurrence of depression does not necessarily exclude the diagnosis [207] (appendices 8.1). As for the diagnosis of neurasthenia, although the research criteria excludes the presence of any mood or anxiety disorder/ diagnosis in the ICD-10 [265] (appendices 8.1), it was decided to modify the inclusion criteria to allow for mild depressive or anxiety conditions that were clinically evaluated as independent of or clearly secondary to the fatigue illness. Comorbid depressive and anxiety symptoms are the rule rather than exception in neurasthenia, and allowing clearly secondary symptoms to fatigue would be in accordance with the clinical entity and ICD-10 guidelines for neurasthenia [114], allowing mild depression as part of the condition (appendices 8.1).

5.2.2 Comorbidity of unexplained and subjective symptoms

Patients with CFS and neurasthenia have many health complaints, as the empirical results show. This thesis does not elaborate on the issues of classifying and differentiating the unexplained medical conditions or complaint-syndromes occurring in these patients and in related conditions. Chronic fatigue syndrome CFS is by its definition unexplained, and the distinction between CFS and "unexplained/ idiopathic chronic fatigue" is at best vague, at worst arbitrary. Still, this distinction is being used in research [61,155,187,199,256], implying that CFS is an "explained" illness. A way of dealing with this dilemma is the stringent use of operationalized selection criteria, although it does not resolve the main problem with the overlapping conditions and gray zones.

In the clinical studies, in the papers and in this thesis the selection criteria used are being presented, both for neurasthenia as well as CFS-Oxford and CFS-CDC. Subjective health complaints (SHC) were assessed and analyzed as a measurement of general health (health complaints) and comorbidity, in the sense of coexisting health complaints. Comorbidity of subjective health complaints between neurasthenia/ CFS and other specified syndromes has been measured, but was not analyzed or presented in these studies [120]. As the SHC-items do not correspond directly with diagnostic criteria in examining "comorbidity" by medical syndromes or diagnostic entities, an analysis of comorbidity with specific diagnoses was not made, and a direct comparison with previous studies of "medical" comorbidity was not possible. As most of these other previous studies have limited clinical significance since they report on overlapping conditions based on overlapping inclusion criteria, the use of subjective health complaints (SHC) seems as justified and – it could be argued – more relevant and useful in assessing comorbidity, morbidity and health.

5.2.3 Health and impairment assessments

The assessment of health was based on measuring subjective health complaints (SHC). This has not been done in other studies of CFS, and makes a comparison of health in our clinical population to other CFS population difficult. As SHC have been measured both in the general population and in other clinical populations with chronic illness, assessment of health and health impairment was possible. The results showing extremely high levels of subjective health complaints compared to the general population are corresponding well with other studies showing high levels of comorbidity and overlapping conditions, supporting earlier evidence that shows CFS to be a severe illness with a wide spectrum of severe symptoms [3,34,182].

Furthermore, the high levels of health complaints from all dimensions of SHC (musculoskeletal, gastrointestinal, allergy, flu, "pseudo-neurological") indicate that all physiological systems could be involved, as well as cognitive appraisal mechanisms of bodily sensations. This supports the model of chronic fatigue as an illness of general sensitization [153,156,233].

Assessment of functional impairment was based on self-reported functional status by SF-36, assessing specific domains of functioning, which in this thesis have been analyzed by the dimensions of mental and physical functioning [242]. The instrument does not cover all aspects of functional impairment or life quality, but has still been used widely in comparable clinical studies, making comparison with our studies possible. The results showing extremely low levels of physical functioning in CFS-patients are supported by other studies [31,209,227]. The relatively less – but still distinctly impaired mental functioning, indicate that mental functions are indeed impaired in CFS – especially concentration and perception of memory. However, the physical impairment exceeds by far the mental impairment. This could be interpreted as CFS primarily being a physical illness, with distinct although less severe mental and emotional symptoms, indicating that aspects of brain functions are involved.

5.2.4 Sensitization models of CFS

Although this thesis is based on empirical research and data analysis and the results will have their empirical validity of their own, the discussions of the results will need referring to theoretical concepts. In this thesis, the models of physiological and cognitive sensitization described by Ursin, Eriksen, Overmier and Brosschot [19,25,86,172,232] are the central context from which the discussions and interpretations of chronic fatigue syndrome as an end-state of complex sensitization processes originate. These models make possible a common concept of the pathophysiological and cognitive mechanisms in CFS, without dismissing related models of somatosensory amplification [14], psychobiological perspectives [191] or neuroendocrine and immunological theories of pathology [50,53,70,95]. Also, the old but revived concept of interoception [36,55,157,185] give added value to and expands the model of sensitization.

In the discussions of the empirical findings in studies and papers 1, 3, 4, the theories of sensitization are referred to, representing a possible integrative model for the physiological and cognitive hypersensitivity indicated by the empirical results. The findings of general and widespread subjective health complaints (paper 1) and the association between low self-esteem, low coping and poor improvement (paper 4) are interpreted and discussed within the model of sensitization, helplessness (stress) and sustained cognitive arousal [24,86,232,239]. It can be argued that these models and the corresponding interpretations are constructs not validated by the empirical findings, and that interpretation beyond the empirical results is speculative. Still, in this field of chronic fatigue with varying findings of multi-level pathology, models that can integrate different perspectives are called for, both as explanatory models and as a reference structure in identifying and formulating issues of new research.

It is a general interpretation of the results from the clinical studies in this thesis that sensitization processes can be involved in both the immunological and neuroendocrine dysfunctions appearing to be common aspects of CFS and in the cognitive perception and appraisal processes that seem to be part of the perceived severity of the illness.

5.2.5 Somatic, psychiatric or sensitization illness?

In summary, the empirical findings from the studies in this thesis showed and confirmed that chronic fatigue syndrome, whether fulfilling case definitions of CFS or the diagnosis of neurasthenia is a severe and incapacitating illness with extensive subjective health complaints, severe physical disability and moderate mental impairment. There was no evidence of increased psychiatric pathology, personality pathology or personality disorders in patients with CFS. Half of the patients had moderate levels of depression symptoms, clinically evaluated not to explain the fatigue symptoms, which were not associated with level of depression score.

The results indicate that CFS is a syndrome that can not be explained by psychiatric illness or personality disorders. This is in contrast to many other reports of psychiatric comorbidity [117,214,247], but is confirmed by other studies [3,67,116]. These conflicting research findings in CFS are probably due to the inherent problem in the CFS concept based on a spectrum of case definitions and selection criteria [126]. (The dilemmas of sample bias are discussed in chapter 5.4.)

As the issue of CFS being a physical or psychological illness causes controversies in the patient groups and in the public as well as in medical and clinical contexts [130,182,249], results from this study probably will be interpreted both ways. The prevalence of patients with depression scores above cutoff for depression would indicate that depression is common in CFS, although level of depression is mild; no patients had a major depression. Symptoms of depression and fatigue are partly overlapping, which could imply that we are in fact assessing part of the fatigue

syndrome when measuring depression score [67]. Depressive symptoms in CFS could also be secondary to and part of the chronic illness, as is reported in studies of depression in chronic illnesses [89,129]. As discussed in other chapters in this thesis, the findings from the studies in the thesis are taken to support the view that mild depression and perceived "stress" (paper 4) are secondary to the fatigue illness and not predisposing or explaining factors [116].

The results from the intervention trial showed that treatment actually might help people improve with CFS, which has been hard to prove consistently [43]. Our CCBT treatment program was based on interventions already proven effective, like CBT [179] and exercise [77], to which we added counselling and education [48,190] in the cognitive approach and body awareness therapy in integrating aspects of self-regulation, mindfulness and awareness of bodily sensations, limitations and potentials [143,215]. The obvious problem in analyzing the effective components of such a comprehensive program based on combination of interventions is that that all components are integrated and no intervention is subject to explicit analysis. This is a limitation in the analysis and interpretation of the study, and a different design with a larger number of participants might have resolved this by providing another kind of factor analysis. The findings from the study could, however, be taken as an indication that comprehensive multimodal treatment programs are more effecive than single interventions.

The findings showing that mirtazapine medication gave added effect to CCBT, superior to placebo, could also be interpreted as confirming the psychiatric aspect of CFS. The same goes for the finding from the follow-up study, indicating associations between improvement in fatigue symptoms, improvement in depression score and use of antidepressant medication.

So, again: somatic or psychological? Does effect of medication prove that the CFS is de facto a psychiatric disorder?

The interpretation is complex, since we have no complete understanding of the physiological mechanisms by which mirtazapine and other antidepressants have their

effect. Earlier studies of antidepressant therapy in CFS have shown no consistent effect [43,169], and there is little reason to interpret the impact of mirtazapine in our studies as an antidepressant effect. The drug was chosen mainly because its proven positive effect on sleep [7,8] and early reports of positive effect in pain and fibromyalgia, which have later been supported [91,198], and because psychotropic drugs in these categories have been shown to have effect in many of the overlapping conditions to CFS and in medically unexplained symptoms. This could be caused by complex effects on the global fatigue illness, including treating comorbid depression or anxiety symptoms, inhibition of ascending pain pathways or inhibition of prefrontal cortical areas that are responsible for "attention" to noxious stimuli [123,170]. Such a model of action would fit well with the models of psychophysiological sensitization as a possible mechanism in these illnesses [86,232], as well as with biopsychosocial models of central sensitization [156] and interoception [36].

A fair conclusion of these findings concerning questions of psychiatric pathology and effect of antidepressant medication would then be that our studies support the biopsychosocial models of chronic fatigue syndrome, integrating theories of stress, sustained arousal, sensitization and the physical awareness of the mental self [58,59].

Such a conclusion could be part of an integrative concept of CFS based on physiological and psychological sensitization processes.

5.2.6 Chronically unexplained questions

In spite of all research being done within the field of chronic fatigue syndromes, CFS and CFS/ ME, some questions still remain unexplained, although the dark territories of chronic fatigue are being reduced, as the overview of CFS in this thesis shows. Issues of causal mechanisms and pathophysiology, of immunology and neuroendocrine substrates, of predisposing, precipitating and perpetuating factors, of comorbidity and overlap with psychiatric and somatic illnesses: there is still much to learn. Although many researchers of CFS might feel like George Beard (1869):
"...I feel assured that it will in time be substantially confirmed by microscopical and chemical examinations of those patients who die in a neurasthenic condition";
still, others have called for alternative models in exploring the unexplained questions.

As much of the research in the field of chronic fatigue and CFS seem inconclusive, due to inconsistent use of diagnostic criteria, intervention methodology and outcome assessments, suggestions have been made to reconsider many of the concepts of fatigue and the research methods in the clinical field of fatigue [69]. The attempts to make case definitions unambiguous as well as find explicit biologic markers for CFS seem yet unattainable. "*The lack of a uniform definition of subjective fatigue has resulted in little advance beyond what was known about fatigue 100 years ago"* (John DeLuca, 2005)[69]. Many researchers of fatigue consider the neural mechanisms of fatigue to be essential in developing substantially new knowledge about fatigue and chronic fatigue syndromes. The study of such neural mechanisms seems yet to be in its infancy.

An alternative concept for studying and analyzing fatigue has been proposed for more sophisticated explanations of CFS: defining fatigue by primary and secondary fatigue might be one important step towards better understanding and treatment [249]. Primary fatigue can be seen as the fatigue resulting from specific biologic mechanisms, either in the brain or in the systemic physiological system. Such fatigue could be caused by disease activity, HPA-axis abnormalities, tryptophan and serotonin, cytokines or comorbid medical conditions (e.g. anemia, hypo-/hyperthyroidism). Studies have

demonstrated specific neuropathology in patients with chronic fatigue in neurological diseases, and it has been suggested that such "central" fatigue may occur due to a failure in the integration of the limbic input and the motor functions within the basal ganglia affecting the striatal-thalamic-frontal cortical system [45]. A state of pre-existing relative hypocortisolaemia might sensitise the hypothalamic-pituitary-adrenal axis to the development of persistent central fatigue after stress [46], as well as result in ion channel dysfunctions in the cell membrane, as is hypothesized as an explanatory model for chronic fatigue syndrome [47]. Furthermore, there are studies confirming explicit brain dysfunction in CFS, related to dysfunctional motor planning [63], as well as reduction in gray matter volume linked to physical activity [64].

These theories of central fatigue could constitute an expanded model of chronic fatigue syndrome, by integration of the models of sensitization [20,26,86,232,239] and interoception [36,258]. A common conclusion from these various theories is that neither of them presents conclusive evidence or a defined explanatory model, but all provide essential elements to an increasingly comprehensive model of chronic fatigue, as well as being guides to future research.

In the concept of distinguishing fatigue by its potential mechanisms [69], secondary fatigue is the fatigue caused by general mechanisms like deconditioning, psychological factors (depression, anxiety, illness perception), sleep, pain and stress. The implication of defining secondary fatigue would be to search for the underlying condition causing fatigue, being it sleep or pain or whatever, and to offer the best treatment available. According to a model of primary and secondary fatigue, it will be naive to expect even effects of any treatment in chronic fatigue syndrome, as the mechanisms underlying the fatigue might be totally different. The unexplained question is how to differentiate, in the diagnostic process as well as in therapy.

We definitely do not know all the answers in this field, but we might be on our way to raise and understand the essential questions.

5.3 Discussion of methodological issues

Fatigue and fatigue assessment

Fatigue is a difficult symptom to assess and measure objectively, as it must include – in addition to any "objective" measurement available - the subjective experience of the individual. Furthermore, as it is not the fatigue itself but the fatigue illness and the chronic fatigue syndrome that is the focus of interest in our studies, assessment of fatigue as an indicator of CFS can be problematic. Still we are left with fatigue as the core complaint and symptom, and it has been accepted research standard to base the assessment of CFS severity mainly on the assessment of fatigue. Several instruments and questionnaires have been developed for such assessments, studies testing and validating these instruments have been carried out, and recommendations have been made in guiding clinicians and researchers in which instrument to use [76].

In choosing one instrument to another, most researchers have to base their choice on evaluations and recommendations from others. In our study, we have chosen the Chalder Fatigue Scale [41] as the primary measurement for the assessment of fatigue and outcome measurement. It can be argued that other assessment scales can be more precise or appropriate in our clinical study population or that more comprehensive inventories be used. As shown in the papers in this thesis, the fatigue measurements were supplemented by assessment of function, using the Medical Outcome Survey Short-Form (SF-36)[241], as well as assessing the symptoms listed in the CFS-CDC [92] and CFS-Oxford [207] case definitions of CFS.

Also, we have used a used the instrument of Clinical Global Impression (CGI) [98] to assess severity and improvement, to expand the total assessment of fatigue. This is in line with recent recommendations for identification of CFS in clinical work and research [186] .

In addition, symptoms and score of depression were assessed, by using Hamilton depression scale [105], in addition to structured psychiatric interviews of SCAN and SCID-II. This seemed relevant in evaluating a qualified differential diagnosis of

depression or any other mental disorder, as required by the diagnostic criteria of neurasthenia and case definitions of CFS. The Hamilton 21-items depression scale (HAMD-21) was used, but only the items corresponding to HAMD-17 were analyzed, as the additional/ psychotic items were irrelevant with 0 score in all patients.

C*linical assessment bias*

Some outcome measures (Hamilton depression scale, Clinical Global Impression (Severity) were assessed by the clinician (BS) involved in and responsible for the treatment interventions. These assessments could be biased, and independent assessors should be sought but were unavailable in this actual setting. The dilemma of possible assessment bias was sought resolved by correlating CGI assessments to self-reported CGI-Improvement, showing high correlations (paper 2).

Operalization of inclusion criteria

Criteria for diagnosis of neurasthenia were used for inclusion of neurasthenia; case definitions (CDC and Oxford) were used as check-lists for inclusion of CFS. These are not validated questionnaires, but they represent the criteria for CFS and the use of these is considered a sufficient operalization. Added symptom inventories and functional assessments have been developed to both validate the inclusion criteria and to assess the total burden of the illness [240]. In our study, we did not use any such instruments, but in future research we would recommend using these.

Design of the intervention study

To be able to answer the research question of comparing treatment effects of different interventions, a design of a randomised clinical trial (RCT) was chosen [4]. The specific design of the intervention trial was complex, as discussed in paper 2, which also made the interpretation of the results more complicated. Ideally, a control group receiving no medication should have been part of the study design, but we decided against it for ethical reasons. The statistically significant differences found in the study indicate that our findings are of clinical relevance for patients with chronic fatigue and CFS.

As many research studies in this field have used varying design and exhibit varying research quality [10,43,169,257], standardized designs and protocols should be used. In this thesis, the standards of the CONSORT statement [4] was used in planning the study, in the protocols, in the randomisation process and in the data analysis.

5.4 Sample selection, selection bias

The question of possible selection bias in recruiting patients to the clinical study is complicated, as the dynamics and reasons behind responding and willingness to participate are difficult to explore. Any sample based on clinical populations will be biased and differ from the general population. In the clinical material in this thesis, the patients were recruited both through screening procedures (questionnaires) and by referral from GPs to the specialist clinic. Patients from these two groups were compared, and did not differ significantly, except for higher education in referred group, lower level of physical exercise and physical fitness and longer sick leave. The clinical population is then a mixture of referred patients to specialist care and patients being selected by a general primary care survey. It can be argued that our study population thus neither represents (or could be compared to) clinical populations in primary care nor patients in tertiary specialist care. Recognizing this, our clinical population could still represent a common group of patients seen in clinical practice, and as such our findings would be clinically relevant.

Also, as both the questionnaires used for screening and the indications for referral were based mainly on fatigue symptoms, it could be argued that our sample could be biased by fatigue selection, possibly excluding patients with other dominating symptoms or with the common but poorly defined malaise feeling typical of CFS [187]. Such bias would be similar for all sample selections based on screening of fatigue symptoms, as most studies are, but could be resolved by using additional instruments or procedures to assess the illness and its functional impairments [240].
In our studies, we did not use such additional instruments, but used screening

procedures and operationalized inclusion criteria in accordance with common research standards.

In the RCT intervention study, patients were randomised to different interventions, resolving the selection question. In the inclusion process, both neurasthenia and chronic fatigue syndrome were used in establishing inclusion criteria. Since the overlap between neurasthenia and CFS has been shown to be substantial [88], it seemed justified to include both these diagnostic categories in an empirical study of chronic fatigue. Also, consistently analyzing the subgroups with neurasthenia and CFS, it was possible to differentiate the specific clinical populations with specific illness characteristics.

Our studies have no data from the most severely affected patients or patients confined to bed, which obviously leads to a bias of the patient sample, as the most severe part of the fatigue spectrum is not included in our clinical population. It can be argued that this weakens the general interpretations of our findings, and that the group of severe CFS patients being confined to bed because of their illness could comprise an entirely different illness than the one we are studying. This is a general problem and weakness in most CFS research, as these patients rarely are accessible for research carried out in hospital out-patient settings, as our studies and most studies are.

Follow-up selection bias

85 % of the patients responded to follow-up invitations and participated in follow-up. There was no sign of specific selection bias of the responders or non-responders.
82 % of the patients fulfilling CFS completed PAI questionnaires (53/65) and are included in the analysis of personality factors in CFS *(paper 4)*. There was no sign of specific selection bias in the responder sample, by analysis of demographic and clinical data.

In summary, the issue of selection bias is complex but crucial to the interpretation and discussion of the results. In some aspects, the results in the clinical studies in this thesis were different from findings in other research studies, although being supported by others. The results showing substantial clinical effect of intervention, significant long-term improvement and no psychiatric comorbidity could be an effect of the cautiousness in many CFS patients towards a study at a psychosomatic/ psychiatric clinic. Also, study participants had to accept the use of "medication"- mirtazapine or placebo drug, implicating a "risk" of using antidepressants. Many CFS patients feel stigmatized by a possible notion of CFS being related to psychiatry in any way, and it is possible that this would influence the recruitment and thus the sample selection. How this would influence the clinical profile and severity in the sample population could only be speculations. Studies have shown that many of CFS patients are particularly sceptical to psychiatry and medication and that negative attitudes towards treatment interventions influence treatment outcome negatively [49,68,217]. Possibly, our patient sample had a relatively higher proportion of patients being positive or open to treatment in a psychosomatic context including medication, influencing treatment attitudes and treatment outcome positively. If so, this could influence the results towards better outcome reports.

A factor of definite selection bias in our clinical population was the requirement that patients should meet for consultations at the hospital, being able to participate in two group session of 1,5 hours each, the session with body awareness therapy requiring a fair level of physical strength and ability to move. By this treatment design and inclusion requirements, we did not include the most severely affected patients with chronic fatigue syndrome. Quite possibly, this implicates a selection bias that would affect the treatment outcome in the study population.

6. Conclusions and implications

- Chronic fatigue syndrome seems to be an illness presenting and representing a broad spectrum of subjective complaints and functional impairment, from mild cases to severe impairment *(paper 1, 2, 3)*. None of the studies have data from the most severely affected patients or patients confined to bed.
- No significant correlation between mental or psychiatric pathology and chronic fatigue syndrome was found, neither in terms of prevalent psychiatric symptoms, personality disorders and mental dimensions of functional impairment, nor in terms of treatment effect or long-term illness course *(paper 2, 3, 4)*.
- Personality factors may be associated with illness behaviour and coping. Patients with CFS show higher levels of somatisation and physiological depressive equivalents than a non-fatigue reference population. The findings indicated that personality factors representing low social control, low skills of self-assertion and low levels of perfectionism were associated with the poorest improvement through the 5 years follow-period. The findings could both be a result of the illness and a predictor of illness course *(paper 4)*.
- Most patients with chronic fatigue syndrome show improvement through a 6 months treatment program of combined interventions. A comprehensive program of cognitive-behavioural treatment, body awareness therapy and individualized graded exercise (CCBT) followed by mirtazapine medication seemed to be most effective *(paper 2)*.
- Long-term effect of specific time-limited interventions seemed hard to prove; difference in illness severity and improvement between different treatment groups were not sustained. All patients in the study received some form of cognitive- educational and body awareness therapy, but the sample size was too small to make robust analyses of possible interaction effects between specific treatment interventions and subgroups of patients *(paper 3)*.

- Long-term course/ follow-up through 5 years showed substantially improvement in 50 % of the patients, with a corresponding shift in diagnoses from more severe case-definitions of CFS to milder case-definitions or to neurasthenia or no fatigue diagnosis *(paper 3)*.
- Prognosis seems to depend mainly on the initial severity and specific characteristics of the fatigue illness, corresponding with the most severe case definitions. Sudden onset, initial severity, severity by 1 year and slow recovery seemed to predict poor prognosis *(paper 3)*.

Implications for further research:

- Treatment programs of long duration (more than 1 year) should be established and studied systematically by evidence-based methods; combining interventions already proven effective.
- Antidepressant medication should be used for long-term treatment interventions (more than 3 months).
- Studies investigating differences within the fatigue spectrum, especially concerning physiological responses, immunological markers and illness perceptions should be designed, as well as studies exploring further the possible sensitization processes related to chronic fatigue.
- The group of severely affected fatigue patient (staying at home/in bed) should be examined systematically. Interventions based on continuing care and support should also be examined, as well as long term course and prognosis.
- Novel questions of fatigue should be asked, for direction of research efforts, identification of unexplored areas and for the mindfulness of not holding on to any fixed theory or eternal truth.

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8. Appendices

8.1 Case definitions

CFS-CDC (Centre of Disease Control)[92]

Chronic Fatigue Syndrome

A case of the ***chronic fatigue syndrome*** is defined by the presence of the following:

1) clinically evaluated, unexplained, persistent or relapsing chronic fatigue that is of new or definite onset [has not been lifelong]; is not the result of ongoing exertion; is not substantially alleviated by rest; and results in substantial reduction in previous levels of occupational, educational, social, or personal activities; and

2) the concurrent occurrence of four or more of the following symptoms, all of which must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue: self-reported impairment in short-term memory or concentration severe enough to cause substantial reduction in previous levels of occupational, educational, social, or personal activities; sore throat; tender cervical or axillary lymph nodes; muscle pain, multijoint pain without joint swelling or redness; headaches of a new type, pattern, or severity; unrefreshing sleep; and postexertional malaise lasting more than 24 hours.

The method used (for example, a predetermined checklist developed by the investigator or spontaneous reporting by the study participant) to establish the presence of these and any other symptoms should be specified.

Idiopathic Chronic Fatigue

A case of *idiopathic chronic fatigue* is defined as clinically evaluated, unexplained chronic fatigue that fails to meet criteria for the chronic fatigue syndrome. The reasons for failing to meet the criteria should be specified.

The following conditions do not exclude a patient from the diagnosis of unexplained chronic fatigue.

1. Any condition defined primarily by symptoms that cannot be confirmed by diagnostic laboratory tests, including fibromyalgia, anxiety disorders, somatoform disorders, nonpsychotic or nonmelancholic depression, neurasthenia, and multiple chemical sensitivity disorder.

2. Any condition under specific treatment sufficient to alleviate all symptoms related to that condition and for which the adequacy of treatment has been documented. Such conditions include hypothyroidism for which the adequacy of replacement hormone has been verified by normal thyroid-stimulating hormone levels or asthma in which the adequacy of treatment has been determined by pulmonary function and other testing.

3. Any condition, such as Lyme disease or syphilis, that was treated with definitive therapy before development of chronic symptomatic sequelae.

4. Any isolated and unexplained physical examination finding or laboratory or imaging test abnormality that is insufficient to strongly suggest the existence of an exclusionary condition. Such conditions include an elevated antinuclear antibody titer that is inadequate to strongly support a diagnosis of a discrete connective tissue disorder without other laboratory or clinical evidence.

CFS- Oxford Guidelines [207]

Chronic fatigue syndrome (CFS)

(a) A syndrome characterized by fatigue as the principal symptom.

(b) A syndrome of definite onset that is not life-long.

(c) The fatigue is severe, disabling, and affects physical and mental functioning.

(d) The symptom of fatigue should have been present for a minimum of 6 months during which it was present for more than 50% of the time.

(e) Other symptoms may be present, particularly myalgia, mood and sleep disturbance.

(f) Certain patients should be excluded from the definition. They include:

(i) Patients with established medical conditions known to produce chronic fatigue (eg severe anaemia). Such patients should be excluded whether the medical condition is diagnosed at presentation or only subsequently. All patients should have a history and physical examination performed by a competent physician.

(ii) Patients with a current diagnosis of schizophrenia, manic depressive illness, substance abuse, eating disorder or proven organic brain disease. Other psychiatric disorders (including depressive illness, anxiety disorders, and hyperventilation syndrome) are not necessarily reasons for exclusion.

ICD-10: F48.0 Neurasthenia

Considerable cultural variations occur in the presentation of this disorder, and two main types occur, with substantial overlap. In one type, the main feature is a complaint of increased fatigue after mental effort, often associated with some decrease in occupational performance or coping efficiency in daily tasks. The mental fatigability is typically described as an unpleasant intrusion of distracting associations or recollections, difficulty in concentrating, and generally inefficient thinking. In the other type, the emphasis is on feelings of bodily or physical weakness and exhaustion after only minimal effort, accompanied by a feeling of muscular aches and pains and inability to relax. In both types a variety of other unpleasant physical feelings is common, such as dizziness, tension headaches, and feelings of general instability. Worry about decreasing mental and bodily well-being, irritability, anhedonia, and varying minor degrees of both depression and anxiety are all common. Sleep is often disturbed in its initial and middle phases but hypersomnia may also be prominent.

Includes:

Fatigue syndrome

Excludes: asthenia NOS (R53), burn-out (Z73.0), malaise and fatigue (R53), postviral fatigue syndrome (G93.3), psychasthenia (F48.8)

Neurasthenia: *ICD-10 Research Criteria*

A. Either of the following must be present:

(1) Persistent and distressing complaints of feelings of exhaustion after minor mental effort (such as performing or attempting to perform everyday tasks that do not require unusual mental effort);
(2) persistent and distressing complaints of feelings of fatigue and bodily weakness after minor physical effort.

B. At least one of the following symptoms must be present:

feelings of muscular aches and pains; dizziness; tension headaches;
sleep disturbance; inability to relax; irritability.

C. The patient must be unable to recover from the symptoms in criterion A (1) or (2) by means of rest, relaxation or entertainment

D. The duration of the disorder is at least 3 months.

E. Exclusion clause:
The disorder does not occur in the presence of organic emotionally labile disorder (F06.6), postencephalitic syndrome (F07.1), postconcussional syndrome (F07.2), mood (affective) disorder (F30-F39), panic disorder (F41.0) or generalized anxiety disorder (F41.1)

8.2 Papers

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   "Neurasthenia, subjective health complaints and sensitization"
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2. Stubhaug B; Lie SA; Ursin H; Eriksen HR (2008)
   "Cognitive–behavioural therapy v. mirtazapine for chronic fatigue and neurasthenia: randomised placebo-controlled trial"
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3. Stubhaug B; Lie SA; Ursin H; Eriksen HR
   "Illness course in chronic fatigue syndromes.
   A 5 years follow-up study"

4. Stubhaug B; Hovland OJ; Lie SA; Ursin H; Eriksen HR
   "Personality disorders and personality profiles in chronic fatigue syndrome"