RIJKSUNIVERSITEIT GRONINGEN

# FIBROMYALGIA:
## towards an integration of somatic and psychological aspects

PROEFSCHRIFT

ter verkrijging van het doctoraat in de Geneeskunde
aan de Rijksuniversiteit Groningen
op gezag van de Rector Magnificus Dr. F. van der Woude
in het openbaar te verdedigen op
woensdag 1 november 1995
des namiddags te 3.00 uur precies

door

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geboren op 21 augustus 1959
te Groningen

en

des namiddags te 4.00 uur precies

door

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geboren op 5 april 1960
te Nunspeet

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ISBN-nr : 90-9008771-0
Druk : Krips repro Meppel
Lay-out : Janny Havinga-Wever

Dit onderzoek en de uitgave van het proefschrift werd mede mogelijk gemaakt door financiële ondersteuning van het Nationaal Reumafonds, Stichting Werkgroep Interne Reumatologie en de Stichting Revalidatie Voorzieningen Friesland

# Contents

# Een woord van dank

In 1986 is met het opstarten van een pilot-study een begin gemaakt met het onderzoek naar diverse facetten van het fibromyalgie syndroom, waarvan dit proefschrift een logische afsluiting vormt. Mede dankzij een vruchtbare samenwerking tussen de afdeling Revalidatie (hoofd: prof. W.H. Eisma) en de onderafdeling Reumatologie (hoofd: prof. dr. M.H. van Rijswijk) van de Interne Kliniek van het A.Z.G. kon dit fibromyalgie-onderzoek plaatsvinden, alsmede door de financiële steun van het Nationaal Reumafonds.

Grote inspirator en eerste promotor van dit onderzoek was prof. dr. M.H. van Rijswijk, die wij willen bedanken voor zijn ondersteuning, zijn enthousiasme en inhoudelijke begeleiding. Hij was degene die de vaart erin hield als vertraging dreigde en hij wist op welhaast onnavolgbare wijze organisatorische problemen op te lossen.

Prof. W.H. Eisma zorgde ervoor dat het onderzoek grotendeels op de afdeling revalidatie kon worden uitgevoerd, met alle praktische consequenties van dien. Al eerder droeg hij als opleider in belangrijke mate bij aan de vorming tot revalidatiearts van A.C.E. de Blécourt. De drie promotores, de hoogleraren van Rijswijk, Eisma en Klip (prof. dr. E.C. Klip, hoofd afdeling Medische Psychologie) danken wij voor hun kritische opstelling, hun nuttige tips en hun motiverende inzet tijdens de vervaardiging van dit proefschrift en het onderzoek dat daaraan vooraf ging.

Uiteraard konden we dit onderzoek niet getweeën tot stand brengen. Herman Bolhuis en Niels de Voogd hebben als psychomotorische therapeuten/psychologen de behandeling uitgevoerd, zoals is omschreven in hoofdstuk 14. Mia Oosterveen nam, als maatschappelijk werkende, de echtpaargesprekken voor haar rekening. Mia, Herman en Niels, met jullie samen te werken was voor ons een groot genoegen. Niels de Voogd was tevens de groepsbehandelaar van de psycho-educatie groepen, zoals beschreven in hoofdstuk 15. Niels de Voogd en Maerian de Jong willen we bedanken voor de hulp bij het verwerken van de gegevens.

Het MRI-onderzoek kon niet worden uitgevoerd zonder de hulp van Rienhard Wolf, Richard Kamman en Eduard Mooyaart en de gastvrijheid van de afdeling Radiodiagnostiek van het AZG.

Henk Bruggers heeft met veel enthousiasme en inzet de data verzameld van de diverse hormonale stress-testen en vragenlijsten, zoals beschreven in hoofdstuk 5.

Derk Jan Birnie heeft als klinisch psycholoog in de eerste fase van het onderzoek een belangrijke en initiërende rol gespeeld, daar waar het de psychologische invalshoek betrof.

Janny Havinga-Wever droeg zorg voor de lay-out van het proefschrift en heeft dit op uitmuntende wijze gedaan. De hoeveelheid werk die dit met zich mee heeft gebracht mag beslist niet worden onderschat.

Tenslotte: dit onderzoek zou uiteraard niet hebben kunnen plaatsvinden zonder de medewerking van de fibromyalgie patiënten, maar ook de reumatoïde artritis patiënten en de patiënten met chronische lage rugklachten, alsmede een aantal "gezonde vrijwilligers" bij het MRI-onderzoek. Voor al de deelnemende patiënten geldt: we

hebben veel van u geleerd en we hopen dat onze inspanningen bij zullen dragen aan een beter inzicht in het fibromyalgie syndroom.

# Preface

In this dissertation several aspects of the fibromyalgia syndrome will be highlighted and the results of the clinical studies we performed will be presented. Fibromyalgia can be seen as a variant of a chronic pain syndrome. In the fibromyalgia syndrome somatic and psychological symptoms are intertwined, and it is therefore we chose to join our forces in the effort to unravel the mysteries of the fibromyalgia syndrome.

Chapters 1, 2, 3, 8, 10, 13 summarize the knowledge thusfar published in the literature. Chapter 1 gives a general introduction to the fibromyalgia syndrome and how the concept of the fibromyalgia syndrome evolved during the years.

Chapter 2 describes the search for a somatic explanation of the syndrome. A great variety of supposed abnormalities have been published. In retrospect the conclusion must be that it is very unlikely that the key to the puzzle of the fibromyalgia syndrome will be found in a defect or dysfunction of an organic system. The search started at the end-organ, the muscle, but gradually moved away to more complex theories like an abnormal pain perception.

Chapter 3 discusses the modulating and coesisting factors, like the influence of weather on fibromyalgic complaints, and the frequency of irritable bowel syndrome, Raynaud's syndrome and Sjögren's syndrome in patients with the fibromyalgia syndrome. Furthermore the related syndromes like the myofascial pain syndrome and chronic fatigue syndrome are discussed. It is assumed that these syndromes are overlapping and not separate disease entities.

Chapter 4 relates to possible abnormalities in energy metabolism in the muscle, e.g. tender points, in patients with fibromyalgia syndrome. In this study magnetic resonance spectroscopy of the phosphorus atom was used.

In chapter 5 the results of several hormonal stress tests in female fibromyalgia patients are summarized and furthermore a possible relation between abnormal stress tests and psychological profiles is studied.

In chapter 6 a study is described on the relationship between objective meteorological data and subjective complaints, like pain, fatigue and stiffness, in fibromyalgia patients.

Chapter 7 deals with the concept of tender points, as a central role in fibromyalgia syndrome, and the reliability and consistency of these tender points.

Epidemiologic data, natural history and the implications of the fibromyalgia syndrome in relation to socio-economic aspects can be found in chapter 8.

The role of psychological factors in the fibromyalgia syndrome is outlined in chapter 10. Depression and anxiety in fibromyalgia are studied in detail and psychological factors that are related with pain, the most prominent feature in fibromyalgia, are highlighted.

Chapter 13 summarizes the different therapy-regimens thusfar published. It seems there is a considerable placebo-effect in the different treatment programs. It is very important that these studies should be undertaken in a randomized, double-blind, controlled fashion. Follow-up is short in most studies.

The results of clinical studies are presented in chapters 4,5,6,7,9,11, 12,14,15 Chapter 16brings together all different aspects of the previous chapters and a model is presented where all the aspects that play a role in the presentation of this syndrome are linked together. Is the fibromyalgia syndrome a separate entity, or is it one manifestation on a spectrum of related disorders?

Somatic aspects of the fibromyalgia syndrome are studied by A.C.E. de Blécourt, who is presently working as a physiatrist at the childrens department of the rehabilitation centre "Lyndensteyn", Beetsterzwaag (Stichting Revalidatie Voorzieningen Friesland).

Psychological aspects are studied by A.A. Knipping, who works as a psychologist at the "Wilhelmina Ziekenhuis Assen" and "afdeling Revalidatie, Academisch Ziekenhuis Groningen".

Chapters 1-8and chapter 13will be defended by A.C.E de Blécourt. The chapters 9-12 and 14-16 will be defended by A.A. Knipping.

# Introduction and historical review of the fibromyalgia syndrome

A.C.E. DE BLÉCOURT, A.A. KNIPPING.

# Introduction

The fibromyalgia syndrome is a form of nonarticular rheumatism characterized by chronic and diffuse musculoskeletal aching and stiffness accompanied by exaggerated tenderness at specific anatomical sites, known as tender points (1). The symptoms are modulated by certain factors e.g., weather, physical activity, physical or mental stress, and sleep quality. Other symptoms are fatigue and a disturbed sleep, not seldom accompanied by headache and symptoms of irritable bowel syndrome.

Since some or many of these findings may be secondary to various underlying disorders such as rheumatoid arthritis (RA), trauma, significant osteoarthritis (OA), infection and hypothyroidism, the term primary fibromyalgia was employed to describe a distinct entity. The condition was called primary when an underlying related condition was absent.

Between 1970 and 1990 several sets of criteria for the diagnosis of fibromyalgia have been proposed (Yunus, Campbell, Smythe) (1,2,3), summarized in table 1 . Wolfe (4,5,6) attempted to summarize these movements through the years and put forward his own ideas and findings concerning this patient group. Bengtsson et al. (7) already did the same in describing the clinical and laboratory findings of her patient group. They also compared this group with a rheumatoid arthritis group on the different items. Their fibromyalgia group expressed a more intense feeling of illness than did the rheumatoid arthritis patients, although on objective measures one would expect the opposite.

The Multicenter Criteria Committee in defining the American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia (8) proposed to abolish the distinction between primary and secondary-concomitant fibromyalgia at the level of diagnosis, because the two were essentially indistinguishable with the study variables used, and the proposed criteria worked equally well in both groups. These ACR 1990 criteria are now worldwide acknowledged and comprise 1) widespread pain in combination with 2) tenderness at 11 or more of 18 specific tender point sites (table 1 ). It should be noticed that these criteria are designed for classification criteria and not meant for diagnostic purposes.

Table 1
CRITERIA FOR DIAGNOSIS OF PRIMARY FIBROMYALGIA SYNDROME
(YUNUS, 1981)

| | | |
|---|---|---|
| 1. Obligatory criteria | A | Presence of generalized aches and pains or prominent stiffness, involving 3 or more anatomic sites, for at least 3 months |
| | B | Absence of secondary causes, e.g., traumatic (due to repetitive or more direct trauma), other rheumatic (including degenerative), infective, endocrine or malignant, with normal laboratory tests (CBC, ESR, rheumatoid factor, ANA, muscle enzymes) and röntgenograms |
| 2. Major Criteria | | Presence of at least five typical and consistent tender points. |
| 3. Minor Criteria | A | Modulation of symptoms by physical activity |
| | B | Modulation of symptoms by weather factors |
| | C | Aggravation of symptoms by anxiety or stress |
| | D | Poor sleep |
| | E | General fatigue or tiredness |
| | F | Anxiety |
| | G | Chronic headache |
| | H | Irritable bowel syndrome |
| | I | Subjective swelling |
| | J | Numbness |

All primary fibromyalgia patients must satisfy the 2 obligatory criteria, as well as either the major criterion plus at least 3 minor criteria. If the patient has only 3 or 4 tender points, then 5 minor criteria are suggested.

## CRITERIA OF CAMPBELL (1983)

1. A questionnaire to define possible fibromyalgia.
   Items on this questionnaire:

   1 Exercise makes me feel better.

   2 I sleep well at night.

   3 I feel well rested when I get up in the morning.

   4 I wake up frequently at night.

   5 I tire easily.

   6 I am too tired during the day to do what I want to do.

   7 I have pain in neck and shoulders.

   8 I am stiff in the morning.

   9 I have pain in my muscles and joints.

   10 I ache in the morning.

   11 Pain wakes me up at night.

   12 Heat (such as heating pads) helps my pain.

   13 My pain is affected by weather.

   14 I have more pain when I am emotionally upset.

   15 My pain is worsened by noise.

   Patients are asked to answer these questions on a 4-point scale: Never, Sometimes, Often, and Almost Always. The diagnosis of possible fibromyalgia required: 1) Questions 7 or 9: Often or Almost Always + 2) Questions 8 or 10: Often or Almost Always + 3) Question 3: Never or Sometimes + 4) Questions 1, 12-15 (any 2): Often or Almost Always.

2. Objective tenderness at dolorimeter pressures of less than 4 kg/1.54 $cm^2$ in at least 12 of 17 tender point localisations.

## CRITERIA OF SMYTHE (1980)

1. Widespread aching of more than 3 months' duration.
2. Local tenderness at 12 of 14 specified sites.
3. Skin roll tenderness over the scapular region.
4. Disturbed sleep, with morning fatigue and stiffness.
5. Normal laboratory findings.

CRITERIA OF WOLFE ET AL. (1990), ACR CRITERIA

1. History of widespread pain.
   Pain is considered widespread when all of the following are present: pain in the left side of the body, pain in the right side of the body, pain above the waist and pain below the waist. In addition axial skeletal pain must be present.
2. Pain in 11 of 18 tender point sites on digital palpation.
   These 18 sites (9 bilateral) are:

- Occiput, bilateral, at the suboccipital muscle insertions.
- Low cervical, bilateral, at the anterior aspects of the intertransverse spaces at C5-C7.
- Trapezius, bilateral, at the midpoint of the upper border.
- Supraspinatus, bilateral, at origins above the scapula spine near the medial border.
- Second rib, bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces.
- Lateral epicondyle, bilateral, 2 cm distal to the epicondyles.
- Gluteal, bilateral, in upper outer quadrants of buttocks in anterior fold muscle.
- Greater trochanter, bilateral, posterior to the trochanteric prominence.
- Knee, bilateral, at the medial fat pad proximal to the joint line.

# Historical review of previous designations

Various forms of nonarticular rheumatism under a variety of names have been described, and particularly in the last century.
Gowers in 1904 (9), in "A Lecture on Lumbago: It's Lessons And Analogues", was the first to use the general term "fibrositis" to indicate the then generally held belief that these varied clinical conditions were the result of a proliferation or inflammation of subcutaneous and muscular fibrous tissue. Gowers based the term "fibrositis" on the marked tenderness he had found to be associated with regional pain syndromes. He did not describe diffuse body pain, only asymmetrical regional pain syndromes. He gave great importance to the distinction between spontaneous pain and sensitiveness. The sensitive sites were asymptomatic at rest and produced distress only when punched, or when muscle action caused tension in hypersensitive tendinous structures connecting tissue to bone (10). Gowers also described the concepts of pain amplification, posttraumatic syndromes, lack of inflammatory products, failure of salicylates, help by distraction and gentle manipulation, counterirritation and cocaine injections. He even mentioned sleep disturbance and exhaustion as consequences of pain. The term "fibrositis" has persisted in the literature despite the failure of several authors to show reproducible and consistent changes in structure of these connective tissues.
Simons gave an extended historical review on muscle pain syndromes (11,12).

Depending upon which characteristics the authors wished to emphasize, many names have been applied to these painful clinical conditions: fibrositis, fibrositis syndrome, interstitial myofibrositis, Muskelschwiele (German for muscle callus or welt), myogelosen (muscle gelling or myogeloses), Muskelhärten (muscle hardening), muscular rheumatism, non-articular rheumatism, or Weichteilrheumatismus (soft-tissue rheumatism), myofascial (pain) syndrome, myofascitis, or trigger points, and myalgia or myalgic spots. The most extensive literature was published in Germany in the 19th century. After the turn of the century the original fibrositis literature appeared in Great Britain. Approaching mid-century a distinctive American contribution appeared.

Fibrositis is the one term most used in all English language literature to identify this painful condition of muscles. From the articles by Simons we can learn that the thoughts and beliefs on pathogenesis evolved from an interstitial myositis, together with a similar inflammatory process in the connective tissue of adjacent fat, fasciae, and especially nerves, to inflammation of fibrous tissue of the muscle. Bacterial infection was presumed to cause the connective tissue hyperplasia.

As mentioned before Gowers introduced in 1904 the term "fibrositis", in a paper on lumbago that included muscular fibrositis of the arm. He characterized muscular rheumatism in general (and lumbago specifically) as an inflammation of fibrous tissue of the muscle. He hypothesized that the inflammation in lumbago originated behind the sacrum and spread to involve the fibrous sheath of the sciatic nerve to produce the pain distribution. He did not consider it an ordinary inflammation because of the absence of regular "inflammatory products". However the term "fibrositis" had been established for many years to come. Gowers deliberately chose not to use the word "myalgia" for the affection he wanted to describe, because its analogy with "neuralgia" suggested unexcited and spontaneous pain. Aggravating or precipitating factors included exposure to cold, and acute and chronic muscular overstrain. Gowers did not mention any palpable findings, but attributed the pain to hypersensitivity of the muscle spindle.

# Supposed clinical pathological correlations

Simons mentioned the description of patchy, inflammatory changes in "white fibrous tissue" biopsies from areas of nodular soft tissue in patients complaining of "chronic rheumatism" by one of the earlier investigators. As a specific diagnosis "fibrositis" was often argued. It became increasingly apparent to multiple observers that the finding of soft tissue nodules depended on the desire of the examiner to appreciate their presence. Such nodules were often absent in patients with chronic rheumatic complaints, and similar subtle soft tissue nodules were frequently present in normal or symptom-free individuals.

Early in the twentieth century chronic articular rheumatism (rheumatoid arthritis) was

renamed as articular fibrositis, in distinction to myo-fibrositis (muscular rheumatism), and neuro-fibrositis or fibrositis of the nerve sheaths associated with pain in the distribution of the nerve. Myo-fibrositis was then defined as an "acute or chronic inflammatory change in the interstitial fibrous tissues of a striated or voluntary muscle, the parenchymatous elements of which are only secondarily implicated". This was considered the muscular manifestation of a process that applied equally to the connective tissue of fat, fascia and neural sheaths. Bacterial infection, familial predisposition, occupation (increased incidence with more physical labour), exposure to drafts or chilling and exercise beyond tolerance were considered significant predisposing factors.

A few years later, again according to Simons, an American publication emerged where the symptoms of muscular pain, stiffness and exhaustion were associated only occasionally with palpable nodules. Laboratory blood findings were normal. Muscle biopsies showed fibroblastic activity and mild degenerative changes in chronic cases. Other investigators produced pain by injecting hypertonic saline into deep structures of themselves and other volunteers and observed that the experienced pain was referred, nearly always distally, to deep tissues in a vaguely demarcated distribution determined chiefly by the segmental nerve supply. The referred pain might also be accompanied by referred tenderness and by muscle spasm. They noted that segmental reference of pain was characteristic of deep pain origin and not seen in cutaneous pain, and that deep somatic structures gave rise to segmental referred pain. They also noted that the referred sensations might have qualities of numbness and tingling as well as aching. These findings can be related to the concept of tender points. During the years more papers with different biopsy findings were written, possibly as a result of the frustration of no confirmatory biopsies in the studies earlier performed. Simons concluded that these either obtained negative results or found other diagnosable conditions. The doubts as to the anatomical validity of the fibrositis concept, raised by these papers, were even more intensified, when it was found that the pressure sensitive ("trigger points") palpable nodules associated with low back pain symptoms, were located within the distribution of pink fat. Postmortem studies showed a common pattern of fat herniation and pedunculation through adjacent fascial planes.

At the same time substantial evidence was presented for a neurogenic mechanism in at least some cases. A controlled EMG-study on patients with proven herniated disease showed spontaneous isolated motor unit action potentials firing at 8-12 per second in tender muscle, but not in adjacent non-tender muscle. Pressure on the tender muscle markedly increased EMG-activity, but pressure on adjacent non-tender muscle had no effect. These findings meant that nerve root pressure could induce a condition of hyperirritability of the muscle that involved spinal anterior horn cells and gave the appearance of typical fibrositic lesions. Some palpable nodules were attributed to muscle contraction (spasm), which contributed to the pain but did not fully account for it. The sustained contraction of part of a muscle was supposed to lead to increased

irritability and pain sensitivity and eventually to pathological changes.
In his journey through the years Simons mentions a publication of just after World War II where a very clear and detailed presentation of typical findings in fibrositis is presented, e.g. myalgic spots, in specific muscle throughout the body. The most common associations included headache, shoulder pain, forearm and hand pain, pleurodynia, sciatic pain and a painful knee. Four features were considered evidence of reflex activity originating from the myalgic spot itself: widespread referred pain, deep hyperalgesia in that same area, edema of involved tissues, and stiffness or wasting of muscles. Reflex effects were therefore implicated in both the origin and clinical expression of the myalgic lesions of fibrositis.
Still, there was no agreement on which pathophysiological findings really were related to the fibrositis syndrome. The concept that the palpable findings and the pain were caused by muscle spasm was not in concordance with the finding in one patient that severe fibrositic pain induced by sustained activity was quite independent of the rate of motor unit-activity.
In the review of Simons a description of the fibrositis syndrome emerged in the late sixties, and included four essential features: exquisite point tenderness of the muscle, a palpable "rope" in the muscle, increased dermographia, and reduction of pain by ethyl chloride spray. At this time, after studies with EMG, it was concluded that the "rope" was not due to muscle contraction, e.g.spasm, but must have an other cause, like localized edema.

# Fibromyalgia: a clinical entity?

Actually Smythe was one of the first of the new generation who looked closer in to the concept of fibrositis or fibromyalgia. Another group, under leadership of Simons and Travell, was still most interested in the myofascial pain syndrome. These two conditions are very hard to discriminate, and looking at the published papers, in particular those before 1970, it is often very hard to tell which condition is under consideration. In 1989 there was a first serious effort to bring more clearness with regard to those two overlapping syndromes, by means of an international symposium on myofascial pain and fibromyalgia in Minneapolis, USA. Here a lot of questions were raised, and only a few answers were obtained. At the second world congress, three years later in 1992 in Copenhagen, Denmark, an official document was made up at the end of the congress and is known as "The Copenhagen Declaration" on fibromyalgia. In this document the results of a consensus conference held by several international experts on fibromyalgia are summarized. During this consensus conference several questions regarding the different aspects of the fibromyalgia syndrome are addressed.

Myofascial pain syndrome is characterized by trigger points in muscle. A trigger point is defined (by Travell) as circumscript tenderness, a localized twitch or fasciculation on stimulation by pressing or pinching that portion of the muscle which contains the trigger area, and referred pain produced by pressure on the trigger point (see chapter 3).

From 1970 onwards there has been an increasing interest in the concept of fibromyalgia, concluding in numerous papers on different topics and implications of the fibromyalgia syndrome. The reason we prefer to speak of fibromyalgia, and not fibrositis, is the fact that there has never been substantial proof of an infection or inflammation of fibrous tissue. Therefore the term fibrositis is confusing and not justified.

A consensus about the existence of the fibromyalgia syndrome has not been reached, and there is still lot of discussion on this topic known, but it is increasingly accepted that this syndrome is a definable clinical entity, of sufficient uniformity to be diagnosable by clinical criteria. The discussion is more and more focused on the possible peripheral or more central origin of the pain. It seems the central theory gains the most favourable support (see chapter 2).

However, most physicians do agree they see these patients in their practices with these complaints, as fit in with our diagnosis fibromyalgia. The problem of this group of patients is to find an adequate treatment.

During the last years a number of articles (editorials, reviews) have been published in leading journals in rheumatology or general internal medicine or in pain management. An example of this is an editorial written by Mufson and Regestein (13). They favour the concept of a generalized pain-modulation disorder. They distinguish a primary fibromyalgia syndrome, a fibromyalgia syndrome with comorbid psychiatric disorder

and thirdly a psychiatric disorder with fibromyalgia-like symptoms. The background of these authors is psychiatry. Regarding treatment possibilities the authors state that a firm therapeutic alliance is essential. The patient should be made an active participant in the treatment plan. A model of rehabilitation in which active rehabilitation with patient participation and physical exercise is pursued, rather than a passive curative approach, will help the patient to become a partner in treatment and this will linger the frustration and anger that often arises when the patient expects the doctor, or other health professionals, to render immediate cure. We can certainly support this point of view.
In a review article by Cohen and Quintner (14) the fibromyalgia syndrome is addressed as a problem of tautology. They criticize the concept in which the diagnostic criteria convey no pathophysiological insight and where these criteria have been, in the authors' opinion, validated via a circular argument in which the evidence on which the construct (concept) is based is taken as proof of its veracity. The authors suggest an alternative approach to the clinical presentation of the fibromyalgia syndrome, namely via secondary hyperalgesia. Cohen published another article on this last subject together with Arroyo (15).

# Inappropriate stress coping

Another review was written by Lorentzen (16), from the department of rheumatology of the university of Copenhagen, Denmark. The title is stimulating to the readers "Fibromyalgia : a clinical challenge". Point of view of this author is that fibromyalgia is not a disease entity, but the symptoms often reported by fibromyalgia patients supposedly reflect difficulties in coping with various types of environmental stress. Lorentzen sees this as the key in the process and therefore that identification of these environmental factors and subsequently early intervention should have high priority. The experienced stress may lead to sleep disturbances, fatigue and a low level of physical activity and fitness. This again may lead to muscle pain and tenderness. The syndrome becomes chronic because of the vicious circle one ends up in. Lorentzen makes some critical remarks on the concept of fibromyalgia. Fibromyalgia syndrome contains an unusually large and heterogenous number of symptoms and this makes it very difficult to assume a common pathogenetic factor. Also the high percentage of women overall and especially between 40 and 50 years old in the western countries finds Lorentzen remarkable. The examination of tender points is also disputable, when one exerts to much pressure on palpation everyone can become a fibromyalgia patient. The nature of the heterogeneous symptoms in fibromyalgia could indicate a psychosomatic component. Lorentzen makes a comparison between fibromyalgia syndrome and the major epidemic of localized fibromyalgia in Australia in 1980. The epidemic was ended when a jury rejected compensation for a patient (see chapter 8). It is very difficult to assess the severity of the syndrome, and also the estimation of the

degree of work disability. Furthermore he states that every effort should be made to counteract the patients' disability and working incapacity.

# A non-disease?

A critical sound was earlier made by Hadler (17). The main topics of his critics are that the name fibrositis implies certain pathophysiologic insights which are not valid and proven. Following this, the patients may get the believe that they have this illness with the suggested patho-anatomic derangement and this, Hadler believes, is in many cases counterproductive towards relieve of symptoms and recovery. Hadler said that labelling of a non-disease can cause patients to perceive themselves as ill, and he illustrates this with a number of references. However he acknowledges the existence of patients with these fibromyalgic symptoms, and apart from calling them a "name", he manages these patients in the same way as the other colleagues do, with attention to physical fitness, repeated reassurance as to the absence of progressive damage, interventions to decrease psychologic stresses when possible.
A very intriguing title emerged in an article in 1990, written by three Swedish authors of the department of Rheumatology of the university hospital of Lund (18): "Does primary fibromyalgia exist?" The authors re-examined 21 of 25 consecutive patients that were diagnosed with fibromyalgia, during a five-year period in a tertiary care day-ward for pain syndromes. Fifteen of these patients fulfilled criteria for fibromyalgia, but all patients had either psychiatric disturbance or thyroid dysfunction. Four patients that were not seen for follow up developed other diseases, two neurological disease, one rheumatoid arthritis and one hypothyroidism. Six patients were not classified as fibromyalgia on follow-up, but also had other diagnoses. The authors conclude from their results that none of the 25 patients, earlier on diagnosed as (primary) fibromyalgia, had at follow-up primary fibromyalgia. They hypothesize that it could be possible that a day ward specializing in pain syndromes does not have a single case of primary fibromyalgia during a 5-year period, and also they suggest that an underlying disease could be neglected by accepting primary fibromyalgia as a separate entity. In their study most patients were occupied as manual workers, mostly cleaners, and this could indicate that occupational load could be important for the development of symptoms. Actually none of the patients had returned to work. This article brings forward other outcomes and conclusions than most other studies. What can we make of it? The distinction between primary and secondary fibromyalgia is no longer made, although any treatable concomitant disease should be treated effectively. The patient group described in the article is probably a very selected group, on a tertiary care day-ward, where a great deal of psychiatric symptoms, e.g. diseases, could be expected.

# Chronic pain syndrome

In 1988 appeared a review article by McCain and Scudds (19). The authors presented a classification model of different chronic musculoskeletal pain syndromes and they hoped this would be a starting point for epidemiological studies outlining the similarities and differences between these clinically observable and different musculoskeletal syndromes. Although the authors tried to identify homogeneous patient's groups, they also stated that there are patients that might fit more than one of the descriptions of the different disorders. Visualizing this overlapping they designed the Venn diagram.

In 1991 a review article appeared, divided in two parts, which aimed at an understanding of the fibromyalgia syndrome. First part concerned medical and pathophysiological aspects and the second part concerned more the psychological and phenomenological aspects of the fibromyalgia syndrome (20,21).

Still earlier, in 1986, Bennett (22) published an editorial "Fibrositis: Evolution of an enigma". He pointed out that there was at that time a widespread acceptance of fibrositis by North American physicians, and that it became recognized as being one of the most common rheumatic complaints with a clinical prevalence between 6 and 20%. Furthermore he emphasized the importance of the differentiation between general fibrositis (fibromyalgia) and local fibrositis (myofascial pain). He commented on several reports on possible pathogenetic mechanisms published earlier. At that time Bennett saw a crucial role in the stage 4 sleep disturbance and he created an etiological paradigm for fibrositis (fibromyalgia). He hypothesized that many initiating factors, like joint pain or trauma or even the use of caffeine and alcohol, could lead to a final common pathway leading to the induction of a stage 4 sleep anomaly. Fibromyalgia is a syndrome, rather than a disease entity, but it can be recognised as a clinical entity.

Not only in the English language papers on fibromyalgia are found. Houvenagel wrote an editorial (23) giving an overview concerning different aspects and theories of fibromyalgia. In his references he mentioned the well-known Anglo-American publications next to a few French publications. The name used in earlier years in the french areas is "Le syndrome polyalgique idiopathique diffus". In the late eighties the name fibromyalgia is also emerging in the French publications.

To emphasize the current interest in the fibromyalgia syndrome one could find several journal issues which are totally filled with articles on fibromyalgia. Giving fibromyalgia and its consequences in daily life a place is extremely difficult. Following the WHO classification from disease to impairment to disability and finally handicap is one line that is very difficult to follow in fibromyalgia. In the real sense of the word there is no disease, but there is pain (impairment) which leads to disabilities and many fibromyalgia patients surely feel handicapped. The sequence of impairment, disability and handicap is well known in rehabilitation medicine and treatment programs try to interfere as early as possible in the process of this triad. To

measure disability in fibromyalgia, however, is a very difficult task (see also chapter 8).

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# Somatic aspects of fibromyalgia

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# Pathogenesis

Many papers have been written on possible pathophysiological mechanisms of the fibromyalgia syndrome. An early etiologic theory attributed the syndrome to inflammation of fibrous tissue (chapter 1). But in the absence of consistent histologic evidence for inflammation in the areas of tenderness, the theory upholding an infectious etiology has fallen from favour (1).
The past years have marked a clear resurgence in the number of investigators studying the fibromyalgia syndrome and in the number of articles published about it. But the factors responsible for initiating and perpetuating the symptoms are still unknown.
In this chapter the different ideas on pathophysiology of the fibromyalgia syndrome, primarily orientated on somatic aspects, will be summarized. Psychological factors in fibromyalgia syndrome will be reviewed in chapter 10. This does not imply that we believe there is a strict separation between possible somatic and psychological aspects in fibromyalgia, on the contrary.
Through the years one can see that the ideas on pathophysiology of the syndrome have changed. In the beginning most studies looked for a disease, e.g. dysfunction of the end organ, the muscle. This evolved to more complex mechanisms like immunologic problems, neuromuscular abnormalities, microcirculatory changes, sleep cycle disturbances, chronic virus infections, and finally neuro-immuno-endocrinologic abnormalities. The symptoms of the fibromyalgia syndrome are more and more thought to be of central origin, in stead of resulting from peripheral pathology.
The last part of this chapter will describe aspects of aerobic capacity in fibromyalgia.

# Studies on muscle pathology

## Muscle-biopsy findings

The pain of the fibromyalgia patients is often localized in muscle tissue and tender points play an important role in classifying a patient as a fibromyalgia patient. So logically the first generation of researchers focused on the muscle to find abnormalities in fibromyalgia patients (see chapter 1). Brendstrup (2) found increased staining for acid mucopolysaccharides, edema, increased nuclei and mast cells. Miehlke (3) described also an increase in acid mucopolysaccharides, mast cells, increased nuclei, and dystrophic changes, connective tissue proliferation and distortion of mitochondria. In a publication of Fassbender (4) he mentions swollen mitochondria, moth eaten myofilaments, irregularity of sarcomeres and increased glycogen.
Bengtsson (5) found degeneration and regeneration, inflammatory infiltrates, moth eaten, red ragged fibres, type II-fibre atrophy, myofibrillolysis, glycogen deposits, and abnormal and increased mitochondria. Henriksson (6) describes similar results.

In 1989 on the first international symposium on myofascial pain and fibromyalgia Awad postulated his theory that the fibrocyte and mast cell produce too many polysaccharides. So he assumed there is an overproduction and not a decrease in breakdown of the mucopolysaccharides. He supposed that the increased amount of acid mucoplysaccharides in the fibrositic nodules constitutes a space-occupying lesion that produces a mass effect, and that this phenomena is what one feels on palpation; fibrositic nodule and/or swelling of the muscle (7). These studies were not performed in a blinded and controlled fashion, which makes the outcomes less reliable.
A study of Kalyan-Raman, Yunus and Masi (8) was not blinded and not controlled either. In this study they described frequent abnormalities in the trapezius muscle by electron microscopy, but in a later study, which was performed in a controlled and blinded way (9), these results were not significant if compared with those of normals. In this last study trapezius muscle biopsy was carried out in 21 patients with primary fibromyalgia syndrome and 11 healthy controls, and assessed blindly by electron microscopy. Common findings in both the fibromyalgia and control group were mild myofibrillar separation, papillary projections and subsarcolemmal accumulation of glycogen and they found no statistically significant difference between the two groups. However a relatively small number of patients and controls participated and that this leaves the possibility open of subtle but significant ultrastructural changes in fibromyalgic muscle. A larger number of patients would have been more ideal for this study. These findings suggest that the changes mentioned before may be physiological in the trapezius muscle. One study of local blood flow measurement in the trapezius muscle did not reveal any abnormality (10), which makes the theory of chronic muscle spasm and local fibre ischemia as a pathogenetic factor in fibromyalgia unlikely.
A combination of Danish and English researchers (11) compared biopsies of quadriceps muscle of 48 patients with fibromyalgia and 24 patients with myofascial pain, for "rubber band" morphology, and the isokinetic strength of the quadriceps muscle was also tested. Patients were matched for age, sex, smoking and drinking habits and they found a significant difference in biopsy score between these two matched groups. The examiner was blinded to the diagnosis. Isokinetic muscle strength did not differ between the two groups, and was not related to the biopsy score. "Rubber band" morphology was blindly graded on a biopsy score scale from 0 to 2. In 63% of fibromyalgia patients these morphological changes were found, and in only 29% of the myofascial patients. The noted constrictions were not created by membrane structures because during the process of muscle preparation the membranes were chemically removed. A theory is that these "rubber bands" are an artefact due to contraction of the muscle. This could be caused during the process of needle biopsy and the manipulation thereafter. Another theory concerning the origin of these "rubber bands", was already described by Bartels and Danneskiold-Samsoe (12), namely an abnormally developed reticular network between the cells. In this study the authors reported on histological abnormalities in muscle from patients with certain types of

"fibrositis". They compared muscle biopsy specimens of 13 patients with fibromyalgia with those of 7 healthy controls. They could not detect differences in electrical charges on the contractile proteins with a microelectrode technique, but microscopical examination of fibromyalgiac muscle showed muscle fibres connected by a network of reticular or elastic fibres which were absent in normal muscle and they thought that these fibres might be the cause of the disorder. The network of elastic fibres connects the muscle fibres and forms constricting bands around the fibres in a way that creates pulls between neighbouring cells whenever one cell contracts. If the examiners were blinded towards the diagnosis of the patient is not mentioned, which makes the results hard to interpret.

Drewes et al. (13) did a blinded histo-immuno-chemical and ultrastructural study in quadriceps muscle biopsies from fibromyalgia patients and normal controls. With light microscopy they found no evidence of abnormal mitochondrial deposition and no sign of myofibrillar or interstitial abnormalities. With histochemical techniques they did not find an abnormal distribution of type I, IIa and IIb fibres and they did not see "moth-eaten" or ragged red fibres in the biopsies, in contrast with the findings of Henriksson (6). With immunoenzymatic techniques they did not find evidence of inflammatory myopathy. Ultrastructural examination with electron microscopy showed various (discrete) degenerative changes, but these were non specific and can be found in other diseases as well, such as a variety of rheumatic diseases, as well as in older people.

One of the latest published studies of muscle biopsies in fibromyalgia came from Lindh et al. (14). With light microscopy they did not find abnormal histopathological findings, not in a patient group nor in a control group. Eleven patients and 19 healthy controls participated in this study, but if the analysis was performed in a blinded way was not mentioned.

Chemical analysis of biopsies of tender points in the trapezius muscle of fibromyalgia patients showed a decrease in high energy phosphates and an increase in low energy phosphates (15), which could be due to hypoxia. Biopsies from tender points in 15 fibromyalgia patients were compared with biopsies from non-tender points in 6 other fibromyalgia patients and biopsies from tender point localisations in 8 healthy controls. In the fibromyalgia patients they found in the tender points a decrease of levels of adenosine triphosphate, adenosine diphosphate, and phosphoryl creatine, and an increase in the levels of adenosine monophosphate and creatine. If the analysis of the biopsies was performed by a blinded examiner is not mentioned. Another remark concerns the in vitro-situation of this study. Later in vivo studies showed there was no abnormality in energy metabolism (see below).

Carnitine levels in muscle biopsies of fibromyalgia patients were studied by Bengtsson et al. (16). Clinical syndromes associated with carnitine deficiency have been recognized with muscular symptoms such as weakness and fatigue. Carnitine acts as a carrier of activated fatty acids across the inner mitochondrial membrane and

is also important in other metabolic processes. The content of carnitine Bengtsson et al. found in the muscle of fibromyalgia patients was normal. However, this was an open, uncontrolled study.
The conclusion after reading and analyzing the above mentioned studies, especially the blinded and controlled studies of Yunus and Drewes, must be that it is highly unlikely that there are specific and consistent abnormalities in the muscle tissue in fibromyalgia.

## In vivo muscle studies of energy metabolism

Hypoxia has been demonstrated in the tender points of fibromyalgia muscles by use of multipoint oxygen electrode (17). In this study (with a healthy control group, but not a blinded examiner) they made an incision through the skin over a tender point in the trapezius muscle, and the fascia was opened. The cause of the hypoxia found, however, remains unknown. However these results are not replicated by other investigators.
In a study we performed (18) we were not able to confirm the findings of lowered high energy phosphates of Bengtsson et al. (15); on the contrary we found an increase in high energy phosphates measured in tender point area in the trapezius muscle using 31P-Magnetic Resonance Spectroscopy, 31P-MRS (see chapter 4). The importance of 31P-MRS in the study of fibromyalgia was earlier on outlined by Kushmerick (19), where he stated that this method is an excellent tool to investigate and document issues involved in muscle diseases, including fibromyalgia.
Jacobsen et al. (20) also studied with help of 31P-MRS energy metabolism of skeletal muscle in patients with fibromyalgia. They performed 31P-MRS in painful calf muscle in 12 patients with fibromyalgia and in 7 healthy controls, during rest, aerobic and anaerobic exercising conditions, and post-exercise recovery. Resting values of Pi/PCr were normal in the patients. Patients and controls had similar rates of Pi/PCr and pH changes during work and recovery. However the controls were able to change their Pi/Pcr and pH more than the patients due to a greater workload reached. Statistical significance was reached only for the anaerobic static exercise, namely a higher Pi/PCr in the controls. The differences may be attributed to the lower power output in the patients. Jacobsen et al. concluded that patients with fibromyalgia have a reduced voluntary capacity for work, but normal biochemical response to work and recovery.
The subject of a supposed defect in energy metabolism as a pathogenetic factor in fibromyalgia is then highlighted in an editorial by Wortmann (21), and two studies, one by Simms et al. (22), the other by Jubrias et al. (23). In the last two articles 31P-MRS was used, like in our own study. In the study of Simms et al. 13 patients and 13 matched controls were studied in rest, at performing fatiguing exercise and during recovery. Patients and controls were carefully selected for matching for level of

aerobic fitness. Two muscles were studied using 31P-MRS, trapezius muscle and tibialis anterior muscle. In this study no statistically significant differences were found between the two groups in the muscle metabolic parameters, with other words no evidence for a metabolic alteration in energy metabolism. In the study of Jubrias et al. 11 patients and 10 healthy controls performed exercises with both arms, and underwent also 31P-MRS, this time at the most muscular portion of the underarm at rest, and 20 minutes following the exercise program. In this last study follow-up measurements were made, to see if there were prolonged effects after muscle-exercises, because measurements were repeated every 24 hours for 4 days in a row. Neither in this study an association between abnormal muscle energy metabolism and having fibromyalgic complaints could be found.

The conclusion of the in vivo studies is that there is no substantial evidence for abnormalities in energy metabolism in fibromyalgia. Number of persons participating in these studies was however relatively small.

## Analysis of blood samples

Eisinger (24) reported on possible glycolysis abnormalities in fibromyalgia. Although more evidence has been put forward against biochemical abnormalities in fibromyalgia (see above), Eisinger does not take these studies into account. He studied 3 different patients' groups and a healthy control group (among them 25 fibromyalgia patients and 36 controls). In this study laboratory studies were performed on pyruvate levels in whole blood, pyruvatekinase, 2-3 diphosphoglycerate, glyceraldehyde phosphodes-hydrogenase and adenosine triphosphate in erythrocytes, and lactate at rest and after ischemic exercise and lactico deshydrogenase isoenzymes in plasma and serum. This study did not examine glycolysis directly in muscle tissue itself. Compared with other patients groups there was an increase in pyruvate levels and decreased lactate production in fibromyalgia and decreased adenosine triphosphate and muscular iso-enzymes of lactico deshydrogenase.

Biochemical changes in patients with fibromyalgia were also subject of study by Norregaard et al. (25). They looked for biochemical changes in relation to a maximal exercise test, in particular abnormal changes in potassium and lactate. Compared with a matched control group (both groups 15 persons) they found no differences in potassium levels and neither any significant changes in lactate concentration. These results are in contrast with those of Eisinger.

Danneskiold-Samsoe and coworkers (26) measured plasma myoglobin concentration in fibromyalgia patients before and after massage of painful muscles. The physiotherapist that gave all the massages knew which muscles were painful, and this means there was no blinded procedure in applying the massage. They found a significant increase after the massage, with a maximum after three hours. Normal levels of myoglobin in plasma were found when muscles without tenderness and pain were treated with massage. These findings suggested a leak of myoglobin from the muscle fibres in tender and painful muscles in patients with fibromyalgia. The authors measured the size of the tension areas and they found a positive correlation between the size of muscle tension areas and the increase in plasma myoglobin concentration. Repeated massage treatment was followed by a gradual decline in the increase of plasma myoglobin to a level not differing from that reached by massage of a comparable muscle mass without muscle pain and tension. The increase in myoglobin plasma concentration is according to the authors not due to mechanical destruction of muscle tissue, because the plasma changes decrease after repeated massage treatment and no changes were observed when normal muscles were massaged. If patients were freed of their pain after repeated massage treatment is not told. What to conclude from this study is not evident.

Aarflot et al. (27,28) described a study on the relationship between chronic musculoskeletal complaints and serum acid. The study design was cross-sectional and part of the National Health Screening Service county studies in Norway. A self administered questionnaire specially designed for evaluating various aspects of

musculoskeletal complaints was used. All persons with chronic musculoskeletal complaints had significantly higher s-urate means than the persons without these complaints. Their statistical analyses showed that the s-urate odds ratio for chronic complaints rose in a linear manner across these s-urate levels. Persons with gout were excluded from this analysis. The calculations were adjusted for 12 other independent variables that may interfere with uric acid, like for instance antihypertensive treatment. In this study however persons with elevated s-urate accounted for only a small proportion of those with chronic complaints. The fact that the authors found a relationship does not make this a causal one, as they acknowledged themselves. But the significant rise in prevalences of chronic complaints across s-urate levels indicates a dose-response relationship.
Persons with musculoskeletal complaints during the last twelve months were asked to check their actual sites of complaints in one or more of nine predefined regions from the body. Persons with five of more regions were considered to have widespread pain, i.e. complaints. Among persons with such complaints the authors tried to characterize the ones with the highest serum uric acid levels. The authors choose the minor criteria and three modulating factors from Yunus as explanatory variables. Persons with chronic widespread weather dependent complaints had the highest values. The authors hypothesized that uric acid may exert an effect on musculoskeletal tissues with modification by weather factors, or that uric acid may interfere with pain modulation mechanisms. These hypotheses should be formally tested in future studies.
The studies of analysis of blood samples do not bring forward any new ideas on the pathophysiology of fibromyalgic complaints; however the link between uric acid level and fibromyalgic complaints is interesting and warrants further research.

## Skeletal scintigraphy

Yunus et al. (29) explored multiphase skeletal scintigraphy in 16 fibromyalgia patients in a blinded study. The purpose was to detect possible subclinical synovitis and uptake abnormalities at tender point sites. Their results showed no unexpected outcomes, so no abnormalities at tender point sites, or synovitis or arthritis signs were found. The scintigraphy assessor should assess the scintigraphic findings blindly of fibromyalgia patients and matched normal controls. In the study however no controls were assessed, which was not known to the assessor. They skipped the controls because no abnormalities were found in the fibromyalgia group and the authors found that further assessment of a control group would not bring any more information. From a methodological point of view this seems not the entirely right thing to do. To avoid fibromyalgia patients with concomitant osteoarthritis which might confound bone scan results, patients older than 40 years were excluded in this study.

# Immunologic factors

## Anti nuclear antibodies (auto-antibodies)

Caro (30,31) published about the high incidence of immunofluorescent detection of IgG at the dermal-epidermal junction in patients with fibromyalgia. Because of the clinical finding of reticular skin discoloration, observed in many fibromyalgia patients during physical examination, the authors started their search for IgG at the dermal-epidermal junction. Control groups of patients with a variety of rheumatic diseases (but without fibromyalgia) and of normal persons were included. The assessor of the skinbiopsies was blinded towards the diagnosis. An explanation for the IgG deposition at the dermal-epidermal junction could be an increased vascular permeability caused by an immune-related disorder. If this positive skin immunofluorescence is causally related to fibromyalgia or represents an epiphenomenon remains an open question. Caro performed also other laboratory investigations, like IgM rheumatoid factor, ANA, anti-DNA antibody, anti-RNP and anti-Sm antibody, anti-Ro and anti-La antibody and also circulating immune complexes. These laboratory findings were normal in the twenty-five fibromyalgia patients, except one positive RF and two patients with a low titer of ANA.

Dinerman (32) evaluated 118 consecutive patients with fibromyalgia, screening the prevalence of Raynaud's phenomenon, sicca symptoms, ANA, low complement and IgG deposition at the dermal-epidermal junction. Of these 118 patients an unselected group of 36 patients underwent skin biopsies and only 4 of these 36 had a positive finding of immunoglobulin deposits at the dermal-epidermal junction. Fourteen percent of the total group had at least one positive antinuclear antibody test. Seven percent had at least one low C3. A positive history of Raynaud's phenomenon was found in 30% and 18% had sicca symptoms. The 35 patients with a history of Raynaud's phenomenon had a significantly higher prevalence of sicca symptoms, positive ANA or low complement compared to the other 83 patients (who did not have a history of Raynaud's phenomenon). This leads the authors to conclude that a subset of patients with fibromyalgia may have features suggestive of a systemic connective tissue disorder. There was no control group in this study included, so the conclusions of this study are premature.

Eneström (33) found deposits of IgG, localized to collagen bundles/extracellular matrix components, in skin biopsies from 25 patients with fibromyalgia. None of these patients demonstrated a positive lupus band. In a control group of healthy persons biopsies were negative, but in two other patients' groups, rheumatoid arthritis (RA) and SLE, a dermal fluorescence intensity was found, although lower than in the fibromyalgia group. Eneström has no explanation for the presence of IgG in dermal tissue in fibromyalgia patients.

Bengtsson (34) compared a group of 223 patients with fibromyalgia with a group of

255 blood donors with respect to the occurrence of different autoantibodies. Sera were analyzed for the presence of antibodies directed against cell nuclei (ANA), smooth muscle, mitochondria and other tissue antigens. The occurrence of serum autoantibodies in patients with fibromyalgia did not differ significantly from the reference group. Screening for autoantibodies in patients with primary fibromyalgia syndrome and a matched control group was also performed by Jacobsen et al. in (35). This study only included women (20 patients and 19 controls). Fifty-five percent of the patients had anti-smooth muscle antibodies and 40% had anti-striated muscle antibodies. In the control group there were no muscle antibodies found. Other autoantibodies tested, like anti-parietal cell antibodies, anti-adrenal cortex antibodies, antimicrosal antibodies, anti-thyroglobulin antibodies, granulocyte specific ANA, anti-neutrophil cytoplasmic antibodies and sarcolemma antibodies, showed no difference in frequency between the groups tested. No differences either in Rheumatoid Factor (RF), IgM, IgA, anti-nuclear antibodies (HEP-2 cells, granulocyte specific), anti-DNA and anti-ENA antibodies. In conclusion the authors state that their findings indicate autoimmune responses in some fibromyalgia patients against antigens of the "diseased" tissue itself. These results are in contrast with those of Bengtsson (see above). Patients were in both studies selected from a rheumatology department and mean age was about the same. However, study population of Bengtsson was much larger. In the group of Bengtsson patients with a positive RF, however, were excluded, which makes it difficult to compare the two populations.

Bridges (36) addressed also the role of antinuclear antibodies and clinical features of connective tissue disease in relation to fibromyalgia. He therefore retrospectively studied serologic and clinical findings, and follow-up of 173 patients with fibromyalgia. An ANA-titer of 1:80 or greater was considered as positive. Of the total group there was in 85 an ANA testing performed, which was in 33% of these cases positive. Then comparisons were made between the ANA-positive group, the ANA-negative group and the group who did not have an ANA testing. Forty of 173 patients had one clinical finding suggestive of a connective tissue disease. This is however not further explicated. There were no significant differences found among any of the three groups and the proportion of clinical findings and neither was there a relationship between the hight of the ANA titer and clinical findings. With a mean follow up period of three years of 159 patients, none of these patients developed a definite connective tissue disease. What happened to the other 14 patients is not mentioned. These results suggest that ANA testing in patients with fibromyalgia does not bring valuable clinical information. This information should be further analyzed in a prospective study, in a randomized fashion with inclusion of a control group.

Yunus et al. (37) performed a controlled study for antinuclear antibodies and connective tissue disease features in 192 fibromyalgia patients and 80 healthy controls. They concluded that the prevalence of ANA and of connective tissue disease features (Raynaud's phenomenon and dry mouth) was similar in patients with

fibromyalgia and healthy controls, with the exception of subjective dry mouth. ANA was positive in 11.3% of the female patients and in 10.0% of female controls. Patients that complained of a dry mouth all had a negative Schirmer's test. Among patients, connective tissue features did not correlate with positive ANA titers.
Klein et al. (38) studied the clinical relevance of antibodies against serotonin and gangliosides in patients with fibromyalgia. In order to evaluate whether patients with fibromyalgia suffer from an auto-immune disorder, they tested sera from 50 fibromyalgia patients for non-organ-specific and organ-specific antibodies. Compared to healthy controls common antibodies against nuclei, mitochondria and microsomes were not increased in patients, only antithyroid and anti-keratin antibodies were slightly higher in the patient group. Seventy-four however had antibodies against serotonin and gangliosides. This could be interesting because in other rheumatic disorders such as RA, polymyalgia rheumatica and collagen diseases, there is an absence of anti-serotonin antibodies. These antibodies may belong to the group of antireceptor antibodies, knowing that gangliosides are an important component of the serotonin receptor. In the future it remains to be determined whether these antibodies are of pathogenetic relevance, interfering with serotonin binding and thereby inducing symptoms associated with fibromyalgia. The involvement of serotonin in the pathogenesis of fibromyalgia is suggested by several other authors, see below.

## Cytokines and lymphocyte subpopulations

Wallace et al. (39) reported on cytokines and immune regulation in patients with fibromyalgia. They performed an extensive laboratory investigation on 16 fibromyalgia patients and 55 healthy controls. Complete blood cell count, erythrocyte sedimentation rate, RF and ANA titers as well as the muscle enzymes were normal or negative. Other test were lymphocyte mitogenic stimulation, lymphocyte enumeration, flow cytometric quantisation of CD2, CD4, CD5, CD20, HNK1, CD8, Leu-7, Leu-7Br, κ-light chain and λ-light chain subsets of lymphocytes and CD4:CD8 ratios of peripheral blood. Alpha-interferon, γ-interferon, IL-1β, IL-2 and IL-2 receptor were assessed, and tumour necrosis factor α. Identifying humoral immunity they examined IgG1, IgG2, IgG3, IgG4. Circulating immune complexes were in addition assessed, and next Epstein-Barr virus antibodies. In the fibromyalgia group the average CD4:CD8 was elevated, which was primarily due to increased mean percentages of $CD4^+$ lymphocytes. This is said to be a non-specific finding. Analysis of the cytokines showed no significant differences in the two groups, neither did the IgG levels. Titers of antibodies to Epstein-Barr virus were not different in fibromyalgia patients and controls matched for age and sex. Circulating immune complexes were normal. In lymphocyte subsets or measurements of mitogenic stimulation were not any differences either. These findings are in contrast with those of Hernanz et al. (40). Hernanz compared lymphocyte subpopulations in 65

fibromyalgia patients and 56 healthy controls. They measured T cells, B cells, T helper/inducer cells, T cytotoxic/suppressor cells, interleukin (IL) 2 receptor, activation inducer molecule marker, transferrin receptor and intercellular adhesion molecule 1. Furthermore the CD4/CD8 ratios were estimated (T helper/inducer cells-T cytotoxic/suppressor cells ratio). Most lymphocyte subpopulations were not significantly different between the patient and control group, however the IL-2 receptor was significantly decreased in the fibromyalgia group as well as the tendency to a decreased cellular activation inducer molecule in the fibromyalgia group. The authors think that a defect in protein kinase C activation pathway could be the primary cause of the lower level of activation, which is found in the decreased levels of peripheral blood lymphocytes with IL-2 receptor (CD25) and activation inducer molecule marker (CD69) in patients with fibromyalgia, and also by the defect in IL-2 secretion found by Hader (see below). If these findings have a relation with symptoms in fibromyalgia has as yet to be established.

## Interleukines

Hader et al. undertook a study (41) regarding the IL-2 secretion in patients with fibromyalgia. In this study they investigated IL-2 secretion by T-cells and by their isolated CD4+ T cells in 12 fibromyalgia patients compared with 10 healthy controls. Number of patients in this study was low. The authors thought that IL-2 might be involved in the symptoms of fibromyalgia and therefore Hader et al. investigated whether stimulated T cells from fibromyalgia patients differ from normal T cells in their ability to secrete IL-2. They found that IL-2 secretion by fibromyalgia patient cells was indeed altered in that a higher concentration of mitogen was needed for maximal stimulation, and that the time of peak IL-2 secretion was shifted from 24-48 hours to 48-72 hours.

## Immunogenetic factors

HLA-antigens in the fibromyalgia syndrome were studied by Hoerven et al. (42). They found no significant association between primary fibromyalgia syndrome and alleles of the HLA system. Both class I (A,B,C) and II (DR) were determined in 60 patients and in over 150 healthy controls. In an earlier study by Burda (43) HLA antigens class I (A,B,C) and class II (DR) were also determined. They found in 67% of the fibromyalgia patients a DR4 and in a normal control group this percentage was 30. In other class I and II antigens they did not find a significant difference between controls and the fibromyalgia group.

The outcomes of the different studies on immunologic factors are not the same, and are sometimes contradictory. Overall there is no hard proof that there are consistent

immunologic abnormalities in fibromyalgia or that fibromyalgia is (or will develop into) a (auto-immune) connective tissue disorder.

# Neuromuscular factors

Increase of neurogenic inflammation in fibromyalgia was described by Littlejohn et al. (44). They studied mechanically (with a swab stick) and chemically (with capsaicin) induced flares (dermatographia) quantitatively in 13 patients with fibromyalgia and in 14 control subjects. The authors found earlier and more flare responses after chemical triggering in the fibromyalgia group. However, there was a wide range of responses in both groups, and the observer was not blinded towards the diagnosis. The flare or vasodilatation is thought to be a neurogenically mediated axon reflex response and the authors suggest that exaggerated neurogenic inflammatory responses in patients with fibromyalgia reflect increased activity of polymodal nociceptors of unmyelinated primary afferent nerves. They hypothesize that this increased receptor activity may contribute to the pain and tenderness in fibromyalgia patients. In one of the earlier criteria sets dermatographia was part of the criteria and can therefore be seen as part of the syndrome. The result of this study brings no new information.

## EMG studies

Elert et al. (45) studied electromyography (EMG) activity during short pauses between active contractions in 10 patients with fibromyalgia and found an increased activity during these pauses, compared with 10 healthy physiotherapists. At rest no increased or pathological EMG activity has been found, but it is often suggested that increased muscle tension is an etiological factor of fibromyalgia. The fibromyalgia patients had a rapidly developing perception of fatigue in their shoulder muscles and the maximum of this fatigue was reached after only 20 to 30 contractions. The test consisted of 100 maximal isokinetic shoulder flexions using a isokinetic dynamometer. The group of healthy controls never reached the maximum level of perception of fatigue. The EMG amplitude ratios of the trapezius muscle and the deltoid muscle were significantly higher in the patients. The signal amplitude ratios in the controls decreased during the initial contractions, followed by a stable level, while the patients had nearly constant ratios throughout the test. The authors hypothesized that this could be a consequence of the rapidly increasing perception of fatigue or pain that the patients said to experience throughout the test. Weak points in this study are the choice of a fit control group of physiotherapists and the fact that the perception of fatigue was only a subjective feeling of the patients.
Baeckman et al. (46) found prolonged relaxation times in 15 fibromyalgia patients, compared with 11 healthy controls. The main aim of study of Baeckman was to assess

whether the (muscle) fatigue in fibromyalgia patients is of central of peripheral origin. They measured maximal voluntary hand grip strength and various contraction characteristics in the adductor pollices muscle after electrical stimulation of the ulnar nerve, and after a regional sympathetic blockade of the forearm with guanethidine. In the patient group a lower hand grip strength was found than in the controls, with and without guanethidine blockade. However the developed force after nerve stimulation did not differ between patients and controls. As stated before a lower muscle relaxation rate was found in the fibromyalgia group, but this rate increased in the patient group during the sympathetic blockade. The control group had no sympathetic blockade. Baeckman thinks her findings indicate both a central and peripheral origin of muscle dysfunction. The maximal voluntary contraction was lower in fibromyalgia patients, where the contraction force after electrical stimulation was not lower, which is a support of the theory of a suboptimal central activation of motor units. Another explanation could be that the patients did not fully cooperate and did not give their best in the voluntary contraction. So this seems a weak argument for the central hypothesis. The changes in relaxation parameters are according to the authors supportive for the involvement of peripheral mechanisms. The increase of relaxation rate after guanethidine blockade might be the result of an increased microcirculation and/or increased temperature. This seems highly speculative.

Zidar et al., among whom also Baeckman (47), found no significant changes in quantitative EMG and muscle tension in painful muscles in 22 fibromyalgia patients, compared with these findings in 9 healthy controls. So this ruled out an important loss of motor units and also ruled out overt muscle fibre degeneration in fibromyalgia. Neither were they able to find any electrically detectable muscle activity in muscles where the patients felt pain during the examination. This ruled out the factor of muscle tension as a pathogenetic factor in fibromyalgia, according to the authors. Muscle tension can not be seen as the ongoing factor in maintaining the pain in fibromyalgia patients. Svebak et al. (48) also tested the hypothesis that increased levels of muscle tension are present in fibromyalgia and these should cause algogenic substances to accumulate in the muscle due to increased metabolic activity. This hypothesis was tested using surface-EMG while performing a perceptual-motor video task, and also before and after this task. Analyzing the EMG activation no differences could be detected between a patient and control group. Their results confirm the findings from the above mentioned study; no evidence is found to support a role for high muscle tension in fibromyalgia.

Further study with EMG was performed by Vitali et al. in (49). In this study the presence of clinical and electromyographic features of neuromuscular hyperexcitability and of the commonly associated neurovegetative disturbances were investigated in 49 fibromyalgia patients and in 33 patients with RA. Neuromuscular hyperexcitability is characterized by a large number of different symptoms including motor, sensory, psychological and visceral disturbances. Neurovegetative distur-

bances, like palpations, shortness of breath and dizziness are often associated with the neuromuscular hyperexcitability and have been ascribed to the same metabolic alterations of normocalcemic tetany at different levels of the neurovegetative system. Their results showed that neuromuscular hyperexcitability did frequently occur in the fibromyalgia group, significantly more than in the control group of RA patients. Neurovegatative disturbances were also far more common in the fibromyalgia group. The assessment of neuromuscular hyperexcitability is a vague point in their study, and the symptoms of neurovegetative disturbances were reported by the participating persons (subjective assessment). Trying to explain their findings the authors hypothesize that a coexistence of a chronic hyperventilation syndrome in some of the studied fibromyalgia patients could be possible, but there is no substantial proof for that.

In a study of Elam et al. (50) no evidence was found for muscle sympathetic nerve overactivity in patients with fibromyalgia. In this study muscle nerve activity was recorded in the peroneal nerve of 8 fibromyalgia patients and of 8 healthy controls.

The theory of altered nociception in the pathogenesis of fibromyalgia was subject of study by Arroyo and Cohen (51). They investigated the nociceptive status with nonnoxious electrocutaneous stimulation. Perception threshold and pain tolerance were studied in the upper limbs of patients with fibromyalgia and in healthy controls. Their results showed no differences in perception threshold between the two groups, but there was a strong reduction in pain tolerance in the fibromyalgia group. This was accompanied by spread and persistence of dysesthesia (both subjective symptoms). Considering their results the authors suggest that the upper limbs of fibromyalgia patients may be regions of secondary hyperalgesia. Secondary hyperalgesia is characterized by an increased pain response to mechanical stimuli and occurs in undamaged tissue neurally related to a site of for instance an injury or inflammation. There is no known site of injury or inflammation in fibromyalgia. The authors suggest a state of activation and sensitization of specific nociceptive afferents. The abnormal afferent function may be related to altered central excitability. They hypothesize that fibromyalgia may be an example of altered central nociception and perhaps associated with peripheral nociception. However the relevant mechanisms of this theory are to be identified and in subsequent studies tested. For the time being it is just another theory without any proof of its veracity.

# Microcirculatory changes

Bennett et al. (52) published a paper in which they commented on the symptoms of Raynaud's syndrome in patients with fibromyalgia and a healthy control group. In the study they utilized the Nielsen test, digital photoplethysmography and did measurements of platelet α-2 adrenergic receptors. Twenty-nine female patients were questioned and examined. Forty-one percent had an abnormal Nielsen test (abnormal

cold-induced vasospasm) and 11% had elevated levels of platelet α-2 adrenergic receptors. There was a positive correlation between the percentage of change in finger systolic pressure on cooling and the number of α-2 adrenergic receptors. There was poor correlation between Raynaud's syndrome symptoms and an abnormal Nielsen test result. The authors hypothesize that a subgroup of patients with fibromyalgia syndrome have an up-regulation of α-2 adrenergic receptors as a cause of their exaggerated reaction to cold. This study shows that 12 of 29 unselected patients with fibromyalgia had objectively measurable vasospasm. Remarkably however, there was no correlation between the patient's self report of symptoms suggestive of vasospasm and the results of objective measurements.

The article by Grassi et al. (53) describes the capillary permeability in 13 fibromyalgia patients, compared with 9 healthy controls, which are small numbers. In their study they found indications for a lowered transcapillary diffusion and an earlier and more rapid interstitial clearance of Na-fluorescein, that was earlier on injected. The authors hypothesize that in fibromyalgia patients there is a decrease in capillary flow or a disturbance in the regulation of the capillary pressure causing a lower transcapillary transfusion of the tracer (Na-fluorescein) and its earlier and more rapid interstitial clearance. They found support for a supposed widespread hypotension in fibromyalgia, in the results of Bennett, mentioned above. Bennett reported a >20% decrease in finger blood pressure after cooling in 41% of a fibromyalgia patient group.

In a study of Vaeroy et al. (54) the authors tried to document circulatory changes due to sound stimuli and to cooling with associated pain, and study the possible association between pain in fibromyalgia and involvement of the sympathetic nervous system in the pathogenesis of fibromyalgia. Twenty-seven patients and 29 healthy controls underwent an auditive stimulation test and a hand cold pressor test at 10 and 4°C. The microcirculatory changes observed indicated that the vasoconstrictory responses are less in patients with fibromyalgia than in normal controls. This could indicate altered sympathetic nervous activity in patients with fibromyalgia and that the cutaneous manifestations often interpreted as Raynaud's phenomenon should be reconsidered, according to Vaeroy. Their tests were not sufficient to initiate a Raynaud's phenomenon in the patients with fibromyalgia, although the patients had described such symptoms in a questionnaire.

The same group published another article (55) about electrodermal and microcirculatory activity in 27 patients with fibromyalgia during baseline, after acoustic stimulation and in cold pressor tests. Twenty-nine healthy subjects served as a control group. This is the same study population as mentioned above. Compared to the controls, the patient group showed a significantly larger overall increase in the skin electrical conductance and less vasoconstriction during acoustic stimulation and cold pressor tests, see also above. The authors interpreted these findings again as an altered sympathetic nervous activity in fibromyalgia patients with an increased activity of cholinergic and decreased activity of adrenergic components of the

peripheral sympathetic nervous system.

Again, the conclusions of the different studies do not point in the same direction. There seems to be no abnormal muscle tension present in fibromyalgia. An abnormal reaction to cold with vasospasm is observed in fibromyalgia, but there has been no relation established between these vasospasm and the subjective experiences of Raynaud-like phenomena in these patients.

# Sleep pathology

## Sleep anomaly-EEG sleep studies

Moldofsky was one of the first researchers of the new generation, together with Smythe (56), and he reported on a study on musculoskeletal symptoms and non-Rapid Eye Movement (nREM) sleep disturbances in patients with fibromyalgia and healthy subjects (57). Moldofsky suggested that an internal arousing stimulus induces the sleep anomaly in fibromyalgia patients and thus would impair the restorative function of the nREM sleep and may lead to developing symptoms. Moldofsky then hypothesized that a disorder of serotonin metabolism serves as a basis for both the electroencephalography (EEG) sleep disturbances and the symptoms in fibromyalgia. Following this there were more publications from his hand concerning sleep physiology and fibromyalgia. He also found that normal sedentary subjects who were exposed to noise stimuli disrupting stage 4 nREM sleep had a similar α-EEG sleep anomaly, musculoskeletal pain and mood symptoms (58). Another term he used for the fibromyalgia syndrome was a rheumatic pain modulation disorder. Moldofsky et al. (57,59) found that patients with fibromyalgia syndrome exhibit an α(7,5-1 Hz)-EEG nREM sleep anomaly. They proposed that the α-frequency occurring in EEG sleep is an indicator of an arousal disturbance. This physiologic arousal disorder in sleep is related to the subjective experience of nonrestorative sleep commonly seen in patients with fibromyalgia, and is associated with a variety of psychological, environmental, or physiologic agents that disturb sleep. Sleep physiology and symptoms of 9 patients with fibromyalgia secondary to a febrile illness were compared 9 patients with fibromyalgia who did not attribute their symptoms to a febrile illness and to healthy controls. Both patient groups showed the same α-EEG nREM sleep anomaly, had similar observed tender points and self ratings of musculoskeletal pain. Moldofsky et al. concluded from these results that patients with postfebrile fibromyalgia have a nonrestorative sleep disorder characteristic of patients with fibromyalgia syndrome and share similar symptoms with patients who have a chronic fatigue syndrome. One could also conclude from these results that a febrile illness does not cause fibromyalgia, that there is no postfebrile fibromyalgia, and that these are just two independent variables. In another study (60) he compared

nonrestorative sleep and symptoms after a febrile illness in patients with fibromyalgia and chronic fatigue syndrome, see also chapter 3. Both disorders are common in young and middle-aged women. Patients complain of unexplained persisting or relapsing fatigue and diffuse myalgia that are intensified with minimal exertion.
Furthermore Moldofsky studied sleep related myoclonus in fibromyalgia (61). In a number of patients with fibromyalgia he had found this myoclonus and he wanted to know if fibromyalgia patients with this sleep related myoclonus differed from other fibromyalgia patients without myoclonus, in specific aspects of sleep physiology and in clinical aspects. Thirty-three consecutive patients with fibromyalgia underwent sleep recordings. Sleep related myoclonus was established by polysomnography. Twenty-one patients showed no evidence for sleep related myoclonus, where the other 12 patients did. In all patients an α-EEG sleep anomaly was present. The 12 patients with sleep related myoclonus were older, had later onset of illness, showed disrupted sleep with periodic involuntary leg movements that were related to fatigue, and α-EEG sleep related to fatigue and pain, as rated by the patients themselves. Moldofsky stated that his data do not suggest that sleep related myoclonus in older fibromyalgia patients is a consequence of fibromyalgia at a younger age, because both groups showed the same duration of illness. If sleep related myoclonus was a consequence of fibromyalgia one would expect a longer duration of illness in the older fibromyalgia group with sleep related myoclonus than in the group with only fibromyalgia. The fibromyalgia group with sleep related myoclonus is seen as a subgroup. Caffeine containing substances, alcoholic beverages and tricyclic antidepressant medication tend to increase sleep related myoclonus and should perhaps be avoided in these fibromyalgia patients. The possibility that the sleep related myoclonus is a concomitant disorder in the elderly (fibromyalgia patients) is not discussed. Patients without fibromyalgic complaints but with sleep related myoclonus should be included in a future study to unravel the relation between the myoclonus and fibromyalgia.
Another investigator on sleep and other symptoms in fibromyalgia was Jennum et al. (62). They evaluated sleep architecture and self reported complaints in 40 female fibromyalgia patients and in 10 age and sex matched healthy controls. Study instruments were a clinical examination, a questionnaire and polysomnography. They found that the percent arousal time and arousal index were significantly higher among the fibromyalgia patients compared to the controls. No other differences were found in sleep architecture and they conclude that these are minor polysomnographic findings. No differences were found in nREM, REM latencies, nREM stages 1-4 and REM sleep, or in sleep related muscle cramps. The higher occurrence of arousals is partly explained, according to the authors, by respiratory abnormalities. No association between fibromyalgia and sleep apnea was found. However insomnia, tiredness, mood, cognitive disturbances and muscular pain were all more commonly reported by the patient group, which does not come as a surprise; they are part of the syndrome. The authors suggest that there may be a relation between sleep fragmentation and

some of the complaints, like insomnia, in fibromyalgia patients. These results are in so far in concordance with those of Moldofsky that they also show a higher amount of arousal time in the fibromyalgia patients compared with the control group.
One of the latest studies published on sleep and fibromyalgia came from Branco et al. (63). Ten patients and 14 healthy controls underwent polysomnography and for each individual the δ- and α-activity and α-δ ratio across sleep cycles were studied. These authors found, like others did before, an increased incidence of α-EEG nREM sleep, and also abnormalities in the sleep cycle organization. The α-δ ratio increased progressively in successive sleep cycles in the patient group compared with the control group. All the patients in the study had complaints of insomnia, but that again is part of the syndrome. The controls were selected if they did not have sleep complaints. The patients had an increased percentage of wake and 2nREM and marked reductions of 4nREM and of REM sleep. There were no significant differences between sleep cycle durations between the patient and control group. It would be interesting to find persons with insomnia but without fibromyalgic complaints, and compare these to fibromyalgia patients in regard to sleep cycles and polysomnography.
Another study on α-like EEG activity in nREM sleep and fibromyalgia came from Horne and Shackell (64). They think the evidence for a causal link between nREM sleep, α-activity and musculoskeletal symptoms is not conclusive. They compared the sleep EEGs of fibromyalgia patients and healthy controls, with special interest in the qualification, quantification and location of forms of α-like activity during nREM sleep. Both the (selected) fibromyalgia group and control group said that they were good sleepers. This surely does not look like a random fibromyalgia population. Although there was a trend for the fibromyalgia group to show more α-activity in nREM sleep, this did not reach significance for any of the sleep stages. According to Horne the overlap in distribution of nREM α-like activity in sleep between the two groups is indicative that there is not a direct relation with musculoskeletal symptoms.

The conclusion of these studies is that an α-EEG sleep anomaly in patients with fibromyalgia is established by several authors. However, if fibromyalgia is caused by sleep anomalies, or that fibromyalgia and sleep anomalies are both the result of another, still unknown, factor, needs to be established.

## Sleep apnea

A relationship between sleep, sleep apnea and fibromyalgia was suggested by Molony et al. in (65). They examined 11 male sleep apneics, of which 3 met the criteria of fibromyalgia. This is more than was expected in nonrheumatologic patients. However in examining female fibromyalgia patients for sleep apnea symptoms there was no significant evidence found of occult sleep apnea compared to healthy controls. Molony

did find in a blinded sleep physiology study of 7 fibromyalgia patients an increased frequency of arousals from sleep.
Alvarez Lario et al. (66) found no association between fibromyalgia and sleep apnea syndrome. They studied 30 patients (27 male, 3 female) with sleep apnea syndrome and only one of these 30 met the criteria of the fibromyalgia syndrome. This would come down to 3%, where the estimated prevalence of fibromyalgia in the population of a general medical clinic is 6%, according to the authors. The authors forget to mention that their patient group consisted mainly of men, and therefor a comparison with other populations, where this is not the case, is not very worthful. Fibromyalgia patients are predominantly female. Neither did they find a significant correlation between number of tender points and the various sleep parameters that were studied in this study group of patients with sleep apnea syndrome. The authors conclude that deprivation of sleep does not produce a fibromyalgia syndrome by itself. The fibromyalgia sleep alterations that are described are only part of a larger complex and the cause of this complex, called fibromyalgia, is multifactorial.
Disdier (67,68) addressed the possible relation between narcolepsy-cataplexy and fibromyalgia. The narcolepsy and chronic disturbance of night sleep could precede the fibromyalgic complaints by many years, according to the author. A possible link is seen in serotonin, which is thought to play a role in nREM sleep and in sensitivity to pain. However no substantial research is conducted on this subject and therefore the suggested relationship remains highly speculative.

# Infection

## Virus

Interest in a viral genesis of the fibromyalgia syndrome came along with the interest in the chronic fatigue syndrome, surely because of the many similarities between the two syndromes, see also chapter 3. However further viral research has not demonstrated a specific agent to be the cause of chronic fatigue syndrome or fibromyalgia. Until recently, the diagnosis fibromyalgia syndrome, like chronic fatigue syndrome, was viewed with doubt and scepticism. In the absence of definite structural pathology some authors have suggested that patients have primarily a non organic disorder (such as somatoform disorder) that was otherwise labelled as postinfectious neuromyasthenia, chronic Epstein-Barr syndrome, postviral fatigue, chronic fatigue syndrome, or fibromyalgia syndrome. In the past years a considerable amount of papers emerged concerning possible viral infection in relation to fibromyalgia.
Leventhal et al. (69) described 3 patients developing fibromyalgia symptoms after acute parvovirus B19infections. A causal relationship is of course not proven with this report, but they suggest a more careful search for viral infections, especially in

patients with fibromyalgia whose symptoms appear to be post flu-like.
Berg (70) reported also on fibromyalgia syndrome in relation with parvovirus B19 infection. He compared 15 female patients with a history of a viral prodromes preceding the fibromyalgia complaints, with 11 female patients without such a history. Berg et al. used a control group of healthy women as well. Serum IgM and IgG anti B19-antibodies were measured by ELISA-techniques. They found no positive IgM levels, not in the patients and not in the healthy control group. The prevalence of a prior B19 infection was the same in the total patient group compared with the healthy control group. No differences were seen between the patient group with a positive history of viral ongoing before the fibromyalgia complaints, and the patient group with a negative history regarding viral prodromes. So Berg's data do not support the suggestion that parvovirus B19 plays a pathogenetic role in patients developing fibromyalgia.
Several authors have suggested that an Epstein-Barr virusinfection may be associated with unexplained persistent fatigue (71,72). Buchwald (73) followed 50 fibromyalgia patients in an academic rheumatology practice with frequently reported symptoms thought to be typical of the so called chronic Epstein-Barr virus infection, but not of fibromyalgia, namely recurrent sore throat, recurrent rash, chronic cough, recurrent adenopathy and recurrent low-grade fevers. In more than half of these fifty patients the illness had begun suddenly, with what seemed to to be a viral syndrome. However in these patients there were no significant differences in antibody titers to Epstein-Barr virus, compared with another patient group (non-fibromyalgia) without complaints of chronic fatigue, and a second group with a 1 chronic illness (non-fibromyalgia as well). These 2 control groups were very heterogenous in regard to the medical diagnosis, which makes the results of the comparison hard to interpret. All participating persons in this study were patients with frequent contacts in the health care system.
Simms et al. (74) reported on the fibromyalgia syndrome in patients infected with human immunodeficiency virus. In this study patients with human immunodeficiency virus (HIV)infection were evaluated for rheumatic disease using a standard questionnaire and examination. Patients with fibromyalgia were compared with HIV-infected patients without fibromyalgia and with fibromyalgia patients without known risk factors for HIV infection. Thirty-seven of 140 patients with HIV infection had musculoskeletal symptoms and 15 of those 37 were found to have either definite or probable fibromyalgia, which means 11% of all HIV-infected patients. Only 3 of 37 patients had arthritis, only 2% of all HIV-infected patients. Fibromyalgia patients with HIV infection had a longer duration of HIV infection and more frequently reported past depressed mood than HIV-infected patients without fibromyalgia. Compared to other fibromyalgia patients with no known risk behaviour for HIV, known HIV-infected patients with fibromyalgia were more commonly male and reported current depressed mood more frequently. At first sight this does not come as

a surprise when one realises that HIV infection has a high frequency among male homosexuals. However the study population had intravenous drug use as the most common risk factor for HIV infection, but in that population there also were more men. Explanations for the high rate of fibromyalgia in HIV-infected patients are suggested: intravenous drug may confound the association of fibromyalgia and HIV infection, but there is no scientific proof of this hypothesis. Or the association between HIV and fibromyalgia may be related to depression. A third explanation mentioned is the role of chronic infection. But the existence of a chronic infection in fibromyalgia is disputable. The association between HIV and fibromyalgia based on depression seems the most likely hypothesis. Fibromyalgia was found in those HIV patients who were infected for the longest time, which means they had the longest stressful experience of knowing they had a fatal disease coming up.

A few years earlier Buskila et al. (75) had reported on the prevalence of fibromyalgia in HIV infection. His group compared patients with HIV, patients with psoriatic arthritis and patients with RA using tender point count. Nearly 30% of the HIV group met criteria for fibromyalgia based on the existence of a minimum number of tender points. In the psoriatic group this percentage was 24, in the RA group the prevalence of fibromyalgia was 57%. Analysis of the HIV group with tender points (fibromyalgia positive) showed significantly more myalgia and arthralgia. There was no relation with age, duration of HIV infection, stage of HIV disease or zidovudine therapy. However in this study the criterium of chronic widespread pain was not taken into account in establishing the diagnosis of fibromyalgia, and this makes it questionable if we can speak of prevalence of fibromyalgia in this study.

## Bacterial infection

In the beginning of the nineties Lyme disease became a topic of more interest (76-80). Lyme disease is a multisystem inflammatory disorder caused by Borrelia burgdorferi and the infection is spread by the bite of an infected tick. The clinical expressions of Lyme disease have been divided into three stages. The third or chronic stage occurs months to years after the initial tick bite and may be expressed by oligoarthritis. Nonspecific symptoms such as headaches, fatigue and arthralgia can occur during any of the 3 stages.

Dinerman (77) looked closer into Lyme disease associated with fibromyalgia. The suggestion that Lyme disease may be associated with fibromyalgia came from a publication of Sigal (81). Dinerman reported on clinical courses, laboratory findings and results of treatment in 15 patients who had Lyme disease associated or followed by fibromyalgia. These 15 patients were recruited from a total group of 287 patients with Lyme disease, of which 8% (22 patients) had fibromyalgia, according to the authors, associated with Lyme disease. Diagnostic criteria for both Lyme disease and fibromyalgia were the golden standards at that time, Centres for Disease Control and American College of Rheumatology criteria respectively. Some of these 15 patients developed fibromyalgia symptoms, and also memory difficulties and debilitating fatigue, after early Lyme disease, the others developed those symptoms during the course of Lyme arthritis. The signs of Lyme disease resolved after intravenous antibiotic treatment in almost all cases. The fibromyalgia symptoms however persisted in 14 of the 15 patients after the antibiotic treatment. Dinerman concludes from these observations that Lyme disease may trigger fibromyalgia, but the antibiotic treatment of Lyme disease is not effective in lingering the fibromyalgia symptoms in the same patients. But this assumption seems open for debate; perhaps it is just a coincidence that some persons with Lyme disease also develop fibromyalgic complaints. This could explain that the treatment for Lyme disease was ineffective in regard of the fibromyalgic complaints.

Kaplan et al. (82) compared patients with Lyme encephalopathy with fibromyalgia patients and with nonpsychotically depressed patients using several memory tests and Minnesota Multiphasic Personality Inventory (MMPI) and Beck Depression Inventory (BDI). Study purpose was to determine the impact of psychological factors, particularly somatic concerns, depression, and anxiety, upon memory impairment in patients with Lyme encephalopathy by comparing them with patients with fibromyalgia and nonpsychotic depression. The symptoms in these illnesses may be similar, according to the authors. The Lyme encephalopathy group had statistically significant memory deficits on two of the three used memory-tests, compared with the two other groups. The fibromyalgia group scored significantly higher on the MMPI scale which is most sensitive to somatic concern than the other two groups. The depressed group scored higher than the Lyme group on the scales most sensitive to depression and anxiety. The fibromyalgia group did not differ significantly from

either the depression or Lyme patients on the depression scale or anxiety scale of the MMPI. All three patients groups complained about memory problems, but only the Lyme group had quantifiable deficits. The subjective memory difficulty in the fibromyalgia group and in the depression group is, according to Kaplan, due to psychological distress. These results show that these 3 patients groups can be recognized as separate entities and that there is no objective evidence for memory impairment in fibromyalgia.
As is stated by Hsu and Sigal (79) persistent musculoskeletal pain, chronic fatigue, mild cognitive difficulties, dysesthesias or headaches are often incorrectly ascribed to features of Lyme disease, and this in spite of the absence of objective evidence of prior or ongoing infection. Because of the fear of treatment failure and/or progression to later manifestations, patients and physicians are urged to diagnose the patients. They found in a group of 800 patients who supposedly had chronic Lyme disease, in retrospect in 77 persons the symptoms of fibromyalgia (approximately 10%). Approximately 20% of patients with later manifestations of Lyme disease recall no history of tick bite or erythema chronicum migrans of the first stage of the Lyme disease (78). The symptoms of early Lyme disease can be adequately treated in most instances with oral antibiotics, later disease symptoms require more aggressive antibiotic therapy. Lack of response to therapy has led to fear and anxiety about the disease, and the suspicion of an overshoot of antibiotic therapy was suspected. Lightfoot et al. made a cost-effectiveness analysis of empirical parenteral antibiotic treatment of patients with chronic fatigue and myalgia and a positive serologic result for Lyme disease but without classical manifestations. They conclude that the risks and the costs of this therapy exceeds the benefits. Just in case the value of the anxiety of the patient about leaving a positive test untreated exceeds the cost of such therapy, is such a therapy cost-effective.
Sigal (76) attacks the incorrect diagnosis of Lyme arthritis in paediatric and adolescent fibromyalgia. He again urges to be careful in diagnosing chronic Lyme disease, especially in areas where anxiety about Lyme disease is great. There is frequent concern in areas endemic for Lyme disease that any medical complaint after Lyme disease is due to persistent infection. Physicians may respond to persistence of symptoms by prescribing more antibiotics, thus perpetuating the impression of a chronic, debilitating disease that is refractory or resistant to therapy. The lack of response to antibiotics then causes concerns about so called resistant or refractory Lyme disease. Apprehension and anxiety may then have contributed to the persistence of the fibromyalgia symptoms, especially fatigue and musculoskeletal complaints.

Analyzing the different reports and studies on a possible virus or other invader in the etiology of the fibromyalgia syndrome, the conclusion must be there is no ground to hold this theory upright. In the absence of active inflammation, a role of ongoing infection is unlikely.

Goldenberg (80) addressed also the question: "Do infections trigger fibromyalgia", and came to the same conclusion. Goldenberg makes a shift from the medical model to a more psychosocial-related model. This psychosocial model of illness emphasizes an individual's adaptation to stressful events. The anxiety and preoccupation that goes with chronic infections such as Lyme disease are thought to lead to avoidance behavior and inactivity, sleep disturbances, mood disturbances, tense muscles and decreased exercise tolerance. So, rather than the existence of a direct causal relationship between fibromyalgia and infection or other so called triggers, infection may be one of many events that promote a maladaptive behavior pattern which secondarily leads to fibromyalgia. When these assumptions are true, Goldenberg continues with the remark that these observations indicate that these common syndromes, e.g. fibromyalgia and chronic fatigue syndrome, fit best into an interactive biopsychological model of illness. Biobehavioral research, like studies of neuroendocrine and immune function, is therefore more likely to be productive than searching for a single infectious etiology or isolated tissue abnormality.

# Neurohormonal (immuno-endocrinologic) factors

## Thyroid function, altered hypothalamic-pituitary-adrenal axis

Stress might well be an important factor in fibromyalgia, but there are no data available on whether stress determines the aches and pain of the fibromyalgia patient, or vice versa (83). A subgroup of fibromyalgia patients presents depression and also a high stress score. Ferraccioli et al. (83) studied the endocrinologic profiles of fibromyalgia patients, because in chronic benign pain-patients with depressive disorders, neuroendocrinologic abnormalities have been observed (for instance dexamethasone (DXT) suppression test). They studied thyroid stimulating hormone (TSH), prolactine (PRL) and cortisol profiles in 24 patients with fibromyalgia, 11 with RA and 12 with chronic low back pain. Study parameters were age, duration of symptoms, erythrocyte sedimentation rate (ESR), number of tender points, VAS, McGill Pain Questionnaire, Zung Depression Inventory (ZDI) and Stress Symptoms Score (SSS).

No differences were found between basal levels of T3, T4, TSH, PRL and cortisol between the three groups. A thyroid releasing hormone (TRH)-test was performed, with an infusion of 200 µg of TRH, and the TSH- and PRL-response were evaluated. No differences were found for TSH and PRL between the fibromyalgia group and the chronic low back pain group. Compared with normal controls all three patients groups showed higher PRL-response 15 or 30 minutes after the TRH-injection.

A blunted TSH response was the commonest hormone finding, especially in the RA group, in the absence either of hyperthyroidism or of any relationship with cortisol levels. A subset of fibromyalgia patients presented several endocrinological

abnormalities, being cortisol non-suppression to DXT and a hyperprolactinaemic response to TRH. These findings, although in a lower degree were also found in the two control groups.
A significantly higher SSS was observed in cortisol resistant vs nonresistant, while there was no difference in patients with a blunted TSH or hyper-PRL response to TRH in fibromyalgia. These findings suggest a close link between stress and hypercortisolemia. The fibromyalgia group scored higher on the ZDI than both other patients groups, but no relation with any of the neuroendocrinologic data was found. These findings, especially the non-suppression of cortisol to DXT are in contrast with those of Hudson (84), who found a normal dexamethason suppression test in fibromyalgia.
Carette and coworker (85) assessed the prevalence of fibromyalgia in 100 patients with subclinical or biochemical primary hypothyroidism. Only in 5% a diagnosis of fibromyalgia could be made, where nearly 20% (19 patients) reported pain and stiffness. However 5 of these 19 patients were not assessed to evaluate the fibromyalgia criteria. Carette concluded that fibromyalgia is uncommon in patients with primary hypothyroidism, although the frequent occurrence of complaints of pain and stiffness is suggestive of fibromyalgia. The thyroid function in fibromyalgia was studied by Neeck et al. (86). They injected TRH in 13 patients with fibromyalgia and in 10 healthy controls. The basal thyroid hormone levels were in both groups within the normal range. After the TRH-injection the fibromyalgia group responded with a significantly lower secretion of thyrotropin and thyroid hormones than the controls and a significantly higher increase of prolactin. The authors suggest that the blunted response of TSH to TRH may be the consequence of enhanced secretion of cortisol.
Other suggestions of altered reactivity of the hypothalamic-pituitary-adrenal axis in patients with fibromyalgia came from Griep et al. (87). They performed a DXT suppression test, a corticotropin-releasing hormone test and an insulin-induced-hypoglycaemia test in 10 fibromyalgia patients and in a 10 healthy controls. In the DXT suppression test there was no escape from suppression in patients or controls. The corticotropin- releasing hormone test induced a significantly higher ACTH release in the patient than in the control group, but the cortisol response was not different in both groups. The basal levels of ACTH were not different either in both groups. In the insulin-induced-hypoglycaemia test all patients and controls had a symptomatic hypoglycaemia. The ACTH and cortisol response showed according to the authors the same pattern as in the corticotropin-releasing hormone test. The authors stated that they found an altered reactivity of the hypothalamic-pituitary-adrenal axis in the fibromyalgia group, with a hyperreactive pituitary ACTH release and a relative hyporesponsiveness of adrenal corticosteroid output in reaction to corticotropin-releasing hormone and to insulin-induced-hypoglycaemia. The authors hypothesized that their findings indicated a relative adrenal insufficiency in fibromyalgia, which could explain the reduced aerobic capacity and impaired muscle

performance seen in fibromyalgia patients. Crofford et al. (88) reported as well on alterations in the hypothalamic-pituitary-adrenal axis in fibromyalgia patients. They found a low 24-hour urinary free cortisol, with however normal peak and elevated trough plasma cortisol levels in a fibromyalgia group, compared with a control group. Furthermore they found indications of adrenal hyporesponsiveness, because the cortisol response to corticotropin-releasing hormone was significantly decreased. In the same year Griep et al. (89) reported on possible further disturbances in neuroendocrine reactivity. They investigated the pituitary release of growth hormone and PRL. Ten patients and a 10 healthy controls had an insulin-induced hypoglycaemia test. At several times glucose, growth hormone and prolactin were measured. In the patient group there was a significantly lower basal level of growth hormone, whereas the basal PRL levels were higher. The authors found a hyperreactivity of the growth response in the fibromyalgia group, following hypoglycaemia. The prolactin response actually did not differ between the patient and control group.
Diurnal hormone variation in 20 fibromyalgia patients was studied by McCain and Tilbe (90). Plasma cortisol levels, growth hormone, prolactin, ACTH and TSH were measured (peak and through levels). As a control group served a group of 20 RA patients. In the fibromyalgia group there was a loss of diurnal variation in plasma cortisol levels and one third of the fibromyalgia patients had an abnormal dexamethason suppression test. In the other hormone levels no differences were found between the two patient groups. McCain suggested that there could be an alteration in the pituitary hypothalamic axis with respect to cortisol secretion in the patients with fibromyalgia and this could be the result of experiencing chronic pain. This explanation seems not very plausible, because patients with RA experience chronic pain as well.
It is very difficult to summarize the results from the different neuroendocrinologic studies. Furthermore they do not agree on all points. What is the role of cortisol and could a relation with stress be put forward beyond any reasonable doubt? To unravel the mystery of stress is an enormous task, but could very well be the key to the puzzle of fibromyalgia and other related syndromes. Abnormal reactions in the hypothalamic-pituitary-adrenal axis are described by several researchers, although study-populations were small.

## Imipramine and serotonine (precursors)

Kravitz (91) tried to find a link between depression and fibromyalgia by examining imipramine-binding in patients of both groups and in healthy controls. Imipramine-binding is a biochemical indicator of serotonin-uptake. As Kravitz stated it has been established that central serotonin activity regulates pain, sensitivity and sleep. Both of these symptoms, pain and disturbed sleep, go (almost always) together in fibromyalgia

patients. Logically the association between a disturbed serotonin metabolism or a relative serotonin deficiency and fibromyalgia is made. On the other hand depression too is linked with disturbances in serotonin metabolism. In their study Kravitz et al. tried to determine whether imipramine-binding in 10 fibromyalgia patients, who were at the time not depressed, differed from the levels found in 14 patients with a currently active major depression (with no fibromyalgia), and also to examine the direction of this difference compared with 10 controls, e.g. higher or lower levels of imipramine binding in the 2 patient's groups than in the control group. The fibromyalgia patient group consisted of only women, the depressed and the control group consisted of women and men. The results showed that women with fibromyalgia have significantly lower imipramine-binding levels than women with depression. But these levels were not significantly different from the levels found in depressed men or in the control group (women or men). So these results do not support a connection between fibromyalgia and a serotonerg dysfunction. However the study sample sizes were small. Definite conclusions can not be made.
Moldofsky and Warsh (92) reported on an inverse relationship between tryptophan concentration and the severity of musculoskeletal pain. Tryptophan is an essential amino acid and a metabolic precursor of serotonin synthesis. Serotonin was already known to be a neurotransmitter with a role in the regulation of deep, restorative sleep and in the interpretation of painful stimuli. Russell et al. (93) tried to find answers to the following questions, brought forward by the findings of Moldofsky et al. Is tryptophan the only amino acid which varies inversely with the severity of symptoms in fibromyalgia and is the total serum tryptophan abnormally low in fibromyalgia, even though the free plasma tryptophan is within range? Russell studied the total serum amino acid pool. They found in 20 patients with fibromyalgia significantly lower levels of total serum tryptophan, compared with 20 pain-free controls, as well as 6 other amino acids: alanine, histidine, lysine, proline, serine, and threonine. These findings support the serotonin deficiency hypothesis as a pathogenetic factor in fibromyalgia, but also imply a more generalized defect in amino acid homeostasis among fibromyalgia patients. In later publications Russell addressed this same issue (94,95). He examined platelet 3H-imipramine uptake receptor density (in 22 fibromyalgia patients) and serum serotonin levels (in 9 fibromyalgia patients). The results showed that mean serum serotonin levels in the fibromyalgia group were lower than in a matched healthy control group and that the binding of 3H-imipramine was higher, but this binding normalized after treatment with ibuprofen and alprazolam. The authors stated that this change in platelet 3H-imipramine binding correlated with improvement of certain clinical measures, like tender point index and physicians global assessment score of disease severity, in the treated group of fibromyalgia patients. The examiner however probably was not blinded towards the diagnosis, which means introducing an observer-bias.
In a controlled study by Yunus et al. (96) the hypothesis of a decreased plasma

tryptophan and/or its transport in fibromyalgia was tested. They measured plasma tryptophan and its transport ratio in 29 patients with fibromyalgia and in 30 pain-free controls. The transport ratio of tryptophan was found to be significantly decreased in fibromyalgia, compared with the controls. Plasma tryptophan was not significantly lower in the fibromyalgia group, but there was a trend to significance. Not only tryptophan was examined, also 21 other amino acids were analyzed. Plasma histidine and serine levels were found to be significantly lower in the fibromyalgia group compared with the controls (see also the study of Russell above). The authors concluded that a decreased brain serotonin level, which may possibly be reflected by a decreased transport ratio of plasma tryptophan, could play a pathophysiologic role in fibromyalgia.

The results of these studies show an abnormality in serotonin levels and metabolism. The link with depression (and stress?) is interesting and warrants further study.

## Beta-endorphin

Yunus et al. (97) studied serum ß-endorphin levels in patients with fibromyalgia. Endorphins are endogenous opioid peptides which function as neurotransmitters and are concentrated in the brain, the spinal cord and neuronal cells. Endorphins and enkephalins are naturally occurring substrates for the opiate receptors which modulate pain. A role for these opioids in pain control has been established both in animals and man. Plasma endorphin levels have been found to be elevated in patients with chronic pain due to combined organic and emotional causes, as well as in psychiatric conditions, such as major depression and schizoaffective disorders. Cerebrospinal fluid (CSF) endorphin levels were found to be significantly higher in chronic "psychogenic pain" than in "organic pain" conditions in another study (98). Serum ß-endorphin levels were found to be decreased in various rheumatic disorders of organic etiology causing chronic pain, as compared to pain-free normal controls (99). Because fibromyalgia is commonly seen as a rheumatologic condition of unknown etiology, characterized by chronic pain, in which psychological factors may play a significant role, Yunus et al. (97) investigated the serum ß-endorphin levels in fibromyalgia patients and control subjects. They studied 44 consecutive fibromyalgia patients, 30 patients with rheumatoid arthritis (RA), and 30 normal controls. They did not find any statistically significant differences. Serum ß-endorphin levels did not correlate with clinical variables that were relevant in either fibromyalgia or RA groups. Serum levels of ß-endorphin did not significantly vary according to seasons of the year or time of the day in any of the groups. Nor was there a correlation found between ß-endorphin serum levels and self-assessed psychogenic symptoms or between these serum levels and severity of pain. Another group of investigators (100) also investigated the levels of endorphin in patients with fibromyalgia, this time in the CSF. They

stated that if CSF is in constant exchange with the nervous system, this fluid rather than plasma should have been chosen for investigation of neuropeptides related to pain. Measurements of ß-endorphin in plasma or serum give no information about endorphin in the central nervous system. Vaeroy et al. found the same CSF levels of ß-endorphin in 18 patients with fibromyalgia and in 10 healthy controls. Their conclusion was that the pain mechanisms involved in fibromyalgia are much more complicated than could be explained by a simple hypothesis of possible endorphin deficiency.

## Substance P

Vaeroy et al. (101) investigated CSF level of immunoreactive substance P (SP), and they commented on the high incidence of Raynaud's phenomenon in patients with fibromyalgia. The aim of this study was to investigate CSF levels of SP in patients with fibromyalgia, and to see whether the CSF SP level could be related to any clinical observation and in particular to the high incidence of Raynaud/Raynaud-like phenomenon. IgG deposition at the dermal-epidermal junction (30) and high prevalence (27%) of HLA B27 tissue antigen, associated with ankylosing spondylitis, suggest that fibromyalgia may be associated with the more classical inflammatory rheumatic diseases such as prodromata or subclinical expressions of these diseases (102). In later studies and publications the idea of an association with inflammatory or auto-immune (rheumatic) diseases has been abandoned. Vaeroy et al. (101) found that in 30 female patients with fibromyalgia the CSF levels of SP were significantly higher compared to normal values. Fifty-three percent of the patients reported Raynaud's phenomenon localized in their fingers, toes or both. No significant difference in CSF levels of SP was found between the group of patients with Raynaud's phenomenon and the group that did not report episodes with Raynaud's phenomenon. The presented study addressed the possibility that SP is in some way related to the diagnosis of fibromyalgia. The role of SP is hereby seen as a moderator or transmitter in forwarding of afferent pain stimuli.
Reynolds et al. (103) measured plasma levels of SP in 32 patients with fibromyalgia and in 26 sex and age matched control. They did not find any significant differences. They stated that these findings do not negate a possible role for SP as an important factor in fibromyalgia. It could be that local alterations in neurotransmitters, such as at tender point-sites, may play a role in this syndrome, but such changes, if present, are not reflected in abnormal levels of SP in plasma. Many years later Russell et al. (104) reported on elevated CSF levels of SP in patients with fibromyalgia. The authors tried to find correlations between SP levels and clinical symptoms in fibromyalgia, like tender points and standardized questionnaires. From their results they concluded that CSF levels of SP were indeed higher in fibromyalgia patients compared with controls, but that there were no strong correlations with tenderness. So there must be other

variables that play a role in the symptoms of fibromyalgia.

## Calcitonin gene related peptide

Again Vaeroy (105) investigated the cerebrospinal fluid, this time the levels of calcitonin gene related peptide (CGRP), which is thought to be a pain related neuropeptide. Vaeroy tried to find indicators for modulation of pain in fibromyalgia. CGRP may regulate the degradation of SP. The peptide is formed in nervous tissue and has been localized in both central and peripheral areas of the nervous system. CGRP has been found in small diameter sensory fibres. In the spinal horn it is colocalized with immunoreactive SP. The authors suggest that this may indicate a synergistic interaction between CGRP peptide and SP in sensory neurons. However no correlation between the CSF content of CGRP and SP was found.

Regarding the above mentioned studies no firm conclusions can be drawn. It is not clear if there is a relation between SP levels and complaints.

## Miscellaneous

Russell et al. (106) studied the CSF fluid biogenic amine metabolites in fibromyalgia and RA. These researchers found low levels of the metabolites of serotonin, norepinephrin and dopamine in the CSF fluid in 17 fibromyalgia patients compared to those of 12 healthy controls. There could be a metabolic defect in fibromyalgia and these results indicate that this defect may be located at a neuroregulatory level.
Yunus (107) published the results of a controlled study of plasma and urinary catecholamines in 30 fibromyalgia patients and 30 controls. In this controlled study they were not able to find any significant differences in those catecholamines (epinephrine, norepinephrine and dopamine) between fibromyalgia patients and controls, and neither a correlation between catecholamine levels and any clinical features or psychologic measures that were assessed in these patients. These results are in contradiction with those described above, although Russell studied CSF levels and Yunus urinary and plasma levels of cathecholamines. Russell expected low levels of the measured metabolites caused by a serotonin deficiency, whereas Yunus expected high levels of the metabolites caused by an increased sympathetic activity. This last assumption is not very valid, according to Yunus himself.
Disdier (108) reported on one patient that developed fibromyalgia syndrome after hypophysectomy for Cushing's disease. It is hypothesized that the hypophysectomy may have played a role in disturbing the endorphin secretion and pain modulation. This theory needs of course to be further analyzed in a randomized, controlled and blinded study.
Levels of somatomedin C in fibromyalgia patients were studied by Bennett et al.

(109) and Ferraccioli et al. (110). Bennett and coworkers found significantly lower levels of somatomedin C in 70 fibromyalgia patients (all female) compared with 55 healthy controls, age and sex matched. Bennett explained these results as an abnormality in the function of the growth hormone-somatomedin C neuroendocrine axis in fibromyalgia patients. Furthermore he hypothesized that this finding could explain the link between disturbed sleep and experienced muscle pain in these patients. During stage 4 sleep a great part of the daily secretion of growth hormone is produced.
Ferraccioli in his study tried to establish a relation between stress hormones and insulin-like growth factor. Insulin-like growth factor is seen as a very important anabolic hormone for muscles. They found that acute cortisol release or a norepinephrine release was followed by low insulin like growth factor (e.g. somatomedin C). The stressors used were an insulin-induced hypoglycaemia, and clonidine induced depression of noradrenergic tone. However these tests were not performed in fibromyalgia patients and this makes the relevance of these findings limited. Compared with a RA and osteoarthritis group the fibromyalgia group had the lowest insulin like growth factor.
Jacobsen et al. (111) found that fibromyalgia patients with low serum procollagen type III aminoterminal peptide had more symptoms, thus were more affected by their fibromyalgia, had more tender points and lesser quality of sleep than fibromyalgia patients with normal levels of procollagen type III aminoterminal peptide. The dynamic muscle strength was also lower in the first group. Fourty-five fibromyalgia patients participated in this study. Serum procollagen type III aminoterminal peptide is said to be reflecting the synthesis of tissue collagen type III and increased serum concentrations are said to be seen in inflammatory diseases, including RA. But the fact that in fibromyalgia there is a normal or lower serum concentration does not support the concept of increased fibrogenetic activity or chronic inflammation. What implications these findings should have for the fibromyalgia patients remains unclear.
Nilsson et al. (112) measured blood levels of dehydroepiandrosterone sulphate in 25 patients with polymyalgia rheumatica/giant cell arthritis and in 15 patients with fibromyalgia. These levels were significantly reduced in the first group compared with the fibromyalgia group. The authors mention that the low levels of dehydroepiandrosterone sulphate are a consistent finding in patients with certain immune-mediated rheumatological diseases, like RA or SLE, and it is suggested that this steroid may regulate immune reactions. The normal levels found in the fibromyalgia patients are further evidence for a non-immune mediated disease.
The results of these studies do not bring us any closer to the solution and possible pathogenetic pathways in the fibromyalgia syndrome.

# Other somatic aspects

A high bone turnover in fibromyalgia patients was assessed by Appelboom (113). Bone density was not significantly different from controls. These findings made the authors suggest that there is an accelerated bone metabolism in fibromyalgia patients. In the study participated 44 premenopausal women, of which 28 met the diagnosis fibromyalgia. The other 16 patients suffered from other (soft tissue) rheumatic conditions and served as the control group. There were no differences in the level of physical activities between the two groups. Jacobsen (114) found no difference in bone mass or turnover between 12 premenopausal fibromyalgia patients and 12 healthy, sex and age matched controls. Both studies had small sample sizes and study design, for instance mode of assessment, were different. A larger, randomized, controlled and blinded study should be performed to get a reliable answer on the question if a higher bone turnover is present in fibromyalgia.

Pellegrino (115) stated that fibromyalgia may be an inherited condition with a variable latent stage before clinical expression. He studied seventeen families of patients with primary fibromyalgia for evidence of inherited primary fibromyalgia. The examiner knew what he was looking for, and no controls were included in this study, which are major drawbacks in this study. Fifty-two percent of parents and siblings had characteristic symptoms and findings of primary fibromyalgia. Twenty-two percent were asymptomatic but had clinical evidence of abnormal muscle consistency to palpation without tender or trigger points. The mode of inheritance Pellegrino said was autosomal dominant. There also could be another explanation for the clustering of fibromyalgic complaints in certain families, it could be possible that siblings copy the (illness-) behavior of other family members. Inheritance is certainly not proven in this study.

A Swedish group (116) reported on eye mobility dysfunction in patients with fibromyalgia and dysesthesia. They found abnormal saccades in up to 42% of the patients in their study (total number of patients studied was 36, and a control group of 71). One could wonder why anyone would take an interest in eye motility in fibromyalgia patients. Anyhow the authors did and conclude from their findings that brain dysfunction, at the brainstem level, is commonly seen in fibromyalgia patients with dysesthesia. However for this assumption hard evidence is missing. The link with dysfunction in eye motility was laid because lesions at different locations in the brain might disturb eye motility, but this seems nothing more than speculation. The authors not only looked into eye motility in relation to fibromyalgia with dysesthesia,they also examined the neuroaudiologic system (117). The same patient group was studied as in the former study. They found in 31% a pathologic auditory brainstem response and again the authors suggest a brainstem dysfunction in a subgroup of fibromyalgia patients with dysesthesia. All patients with pathologic auditory brainstem response also had pathologic eye motor dysfunction. The authors suggest several hypotheses of the origin of the supposed brainstem lesion, but these do not bring any clarity in the matter of the pathogenesis of fibromyalgia.

# Aspects of aerobic capacity in fibromyalgia

Aerobic fitness and capacity are becoming more and more object of study in patients with fibromyalgia. Patients with fibromyalgia are not only said to have lower aerobic fitness than normal controls, this also became a treatment target, see also chapter 13. Bennett et al. (118) published about a controlled study of respiratory gas exchange and 133-Xenon clearance from exercising muscles. Twenty-five female fibromyalgia patients exercised to volitional exhaustion on a cycle ergometer. More than 80% were not physically fit, compared to known standards, assessed by maximal oxygen uptake. Compared with 25 matched sedentary controls the fibromyalgia patients attained a similar level of lactic acidosis, as assessed by their respiratory quotient and ventilatory threshold. The muscle blood flow during exercise, estimated by 133-Xenon clearance, showed a reduced 133-Xenon clearance in the fibromyalgia group. This could be due to a peripheral detraining effect. Compared to sedentary controls the fibromyalgia patients perceived their level of exertion in relation to oxygen uptake accurately. Bennett stressed that this detraining phenomenon could be of relevance in the etiopathogenesis of fibromyalgia (119). Why do fibromyalgia patients enter a spiral of habitual inactivity and what is the role of deconditioned muscles in causing the symptoms pain and fatigue? Because many patients with fibromyalgia experience more pain after physical activity, they withhold themselves from habitual activity which in the end can cause a cycle of deconditioning. Burckhardt and colleagues (120) proposed to use a modified Balke treadmill protocol to determine the aerobic capacity of women with fibromyalgia. Treadmill testing would resemble more the normal activity of walking and, apart from this, is it also weightbearing. Another argument was that bicycle riding was not a familiar activity for a lot of women. In a Dutch female fibromyalgia population this last argument would probably not be true. The modified Balke treadmill protocol keeps the speed constant and increases workload by increasing grade. Preliminary results of the use of this protocol showed a lower percentage of subjects stopping secondary to leg fatigue than in a bicycle protocol. The treadmill protocol is suggested to be a safe and effective method for determining aerobic fitness levels of women with fibromyalgia.

Klug et al. (121) wrote about fundamental concepts of exercise and fitness which are known in healthy subjects and tried to relate this to patients with fibromyalgia doing exercises. The authors chose to narrow their scope to the form of exercise where intensity is sufficiently low, and which can be sustained for a longer period of time. This type of exercise is also known as submaximal exercise or aerobic exercise. This type of exercise seemed the most logical to choose in the fibromyalgia group because fibromyalgia patients are thought to be physically unfit (explained by their low level of activities or a condition which may reduce their capacity to exercise) and can only tolerate low intensity of exercise. Another consideration was the earlier notation of

Moldofsky that persons who exhibited a high volume of this type of exercise were immune to some of the fibromyalgia symptoms caused by sleep deprivation. A third line of thinking Klug used was that there were reports on reduced high energy phosphate levels and tissue oxygenation. As we now know this is not really the case, but at that time this theory was still held upright. Compared to other rheumatic diseases like RA and osteoarthritis patients with fibromyalgia appear to be equal, in terms of oxygen consumption. In a pilot study fibromyalgia patients engaged in a exercise training showed no improvement in pain, stiffness or fatigue scores, but the score of the severity of their fibromyalgia indicated an improvement. A control group showed no improvement. Most trained persons showed an improvement in $VO_2$ max. In regard to the supposed psychological benefits resulting from exercise, like reduction of anxiety and mild to moderate depression as well as increases in percepts of psychological well being and self concept, Klug proposed a few hypotheses. One is the monoamine hypothesis, where a link is suggested between changes in brain monoamines and increased positive affect after vigorous exercise. The second hypothesis is the ß-endorphin activity. Following acute vigorous exercise the plasma ß-endorphin levels increase, and endorphins are known to have an opiate like effect in that they alleviate pain and facilitate sensations of euphoria. A third hypothesis mentioned is the distraction hypothesis. This means that being distracted from stressful stimuli results in a more positive state. These theories should be tested in randomized, placebo controlled and blinded studies.

The reduced maximum oxygen uptake, established by Bennett et al., led Sietsma et al. (122) to examine the level and pattern of maximum oxygen uptake in response to graded exercise and defined levels of constant work rate exercise in fibromyalgia patients. Next to 14 fibromyalgia patients served 8 healthy persons as a control group. All subjects performed upright cycle ergometry exercise with measurements of respiratory gas exchange and grading of the pain using visual analog scales. The peak of maximum oxygen uptake was not different in both groups. There was a considerable variability in maximal exercise performance within the patient group, but variables of oxygen utilization during exercise were not different between the two groups. These results demonstrate no abnormalities in the overall rate and pattern of utilization of oxygen during muscular exercise in patients with fibromyalgia and no arguments for a generalized muscle ischaemia that causes pain of the fibromyalgia patient are found.

Mengshoel et al. reported (123) on muscle fatigue in early fibromyalgia. All patients in their study group were engaged in some form of labour (job) and compared with studies of healthy persons, they found normal physiological muscle fatigue responses. They only observed that the plasma catecholamine concentrations during exercise did not increase in their patient group. However this was an uncontrolled study with a small number of selected patients.

Stokes et al. (124) studied paraspinal muscle fatigue mechanisms in 14 fibromyalgia

patients and 14 controls. A standardized isometric endurance test of the paraspinal muscles was used with at the same time recording of surface integrated electromyographic (IEMG) activity. Fibromyalgia patients often complain of a generalized muscle fatigue, next to myalgia. Subject of debate is whether this fatigue is of central of peripheral origin. Central mechanisms could be due to impaired motor-unit recruitment within the brain or spinal cord, caused by poor motivation and/or pain inhibition. Peripheral mechanisms could be explained by dysfunction of the metabolic or electrophysiological or contractile apparatus in the muscle. In the fibromyalgia group the fatigue induced IEMG increases were similar with a control group during the initial 40 seconds of the test. After 40 seconds IEMG fell significantly in patients but only slightly, not significant, in controls. This decline was most obvious in patients with overweight. Their study showed normal paraspinal muscle fatigue mechanisms in patients with fibromyalgia.

Van Denderen et al. (125) studied the influence of maximum exercise in 10 fibromyalgia patients and 10 healthy sedentary controls. A bicycle and step test had to be fulfilled until exhaustion. In the fibromyalgia group the maximal workload was lower than in the control group. Furthermore they found lower levels of serum creatinekinase, myoglobin, cortisol, epinephrine and norepinephrine in the patient group and also a lower heartbeat in these patients compared to the controls under the same workload. Prior to the exercise tests there were no differences found in the various blood concentrations, these emerged after the tests. The lower (nor)epinephrine serum level and lower heartbeat under the same workload made the authors hypothesize that there might be a disturbance of the sympathetic activity in fibromyalgia, and also a disturbance of the hypothalamic-pituitary-adrenal axis. Why there were no differences found in the resting state between the patients and controls is not explained. This makes the assumptions less likely to be true. The differences after the test could also be explained by the lower workload that was performed in the patient group.

Jacobsen and coauthors (126,127) published also on a subject related to muscle function, on isokinetic and isometric muscle strength in patients with fibromyalgia. The second article reported on transcutaneous electrical muscle stimulation in these patients. In the first group maximal isometric and isokinetic strength of knee extension was measured using Cyber II (isokinetic dynamometer) in 15 fibromyalgia patients and in 15 matched healthy controls. There was a marked reduction in maximal isometric strength at different knee angles in the patient group compared with the control group. Also for the maximum isokinetic strength at different knee extension velocities there was a marked difference, with the fibromyalgia group scoring significantly lower. However these findings can be the result of a submaximal effort on the side of the patients, inspired by the fear of an increase of pain. In the study published in 1991 (127) maximum voluntary isokinetic contractions of the quadriceps muscle were performed in an isokinetic dynamometer and maximum

voluntary isometric contractions of the quadriceps muscle were performed with superimposed transcutaneous electrical stimulation. Again they found significantly lower isokinetic and isometric muscle strength in a fibromyalgia group compared with matched healthy controls. The authors tried this time to answer the question if the strength reduction during maximum voluntary contraction in fibromyalgia patients could be due to a submaximal force application. Therefore they used the twitch interpolation technique which increases the force of the muscle examined at the time only when voluntary contractions are submaximal. They found a distinct lower maximum voluntary muscle strength, indicating submaximal force application, and this time they suggest that pain inhibition on a conscious level or reflex mediated may be partly responsible for this phenomenon. This theory seems plausible.

In 1989 Jacobsen and Danneskiold-Samsoe (128) reported on the inter-relations between clinical parameters and muscle function in 44 patients with fibromyalgia, compared to 24 healthy controls. Muscle function, determined as the dynamic muscle strength measured with an isokinetic dynamometer, was found to be low in fibromyalgia patients with pronounced muscle tenderness when compared with healthy controls. The reduction in muscle function further increased with an increasing number of tender points and subjective symptoms. There were no correlations found between muscle strength and age or height in the fibromyalgia group, in contrast with positive correlations in the control group. These findings can be in concordance with the submaximal force application in the fibromyalgia group, see above.

Maximal voluntary muscle contraction in fibromyalgia patients was also studied by Lindh et al. (129). Their results indicated a lower voluntary contraction in 25 patients compared with 22 healthy controls, but with superimposed electrical stimulation submaximal values were reached. While performing a functional test, like in this case stool climbing, the EMG activity was higher then what was scored during the test with voluntary "maximal" contraction. A possible explanation, according to the authors, might be an impaired control mechanism at a supraspinal level. This seems a little farfetched. More likely patients just do not perform at the top of their abilities in a voluntary muscle contraction test. To test muscular performance in an objective way, it would be wise to let the patient perform functional activities, rather than laboratory tests with muscle contractions.

Muscle strength and aerobic capacity in fibromyalgia was subject of a study by Mengshoel et al. (1990) (130). They measured grip strength with a manometer and dynamic and static endurance work was performed by 26 fibromyalgia patients and 26 healthy persons. In the patient group normal aerobic capacity was found, but there was a significantly higher mean fatigue score as compared to the expected values (determined by Borg's rating scale for perceived exertion according to heart rate in a cycle ergometer). The grip strength in the patient group was significantly lower in the patient group, as well as the dynamic and static muscular endurance. The authors

suggest that pain and fatigue could restrict the patient's ability to perform muscle work. And again the results can be explained by submaximal effort on the side of the patients.

Grip force in fibromyalgia patients and patients with RA and healthy controls was assessed by Nordenskiöld and Grimby (131). In this study they used the Grippit device, i.e. an electronic grip force measurement instrument. The reliability of this instrument was high in RA and healthy controls, and satisfactory in fibromyalgia patients. The instrument measured both peak force and sustained force over ten seconds. The authors hypothesize that in fibromyalgia patients fatigue and pain could have an influence on muscle contraction, but also factors of a more central origin could paly a role. What this exactly means is not further explained. Perhaps they imply differences in motivation in the fibromyalgia patients.

Biochemical changes in patients with fibromyalgia were subject of study by Norregaard et al. (25), see above. They looked for biochemical changes in relation to a maximal exercise test, in particular abnormal changes in potassium and lactate. Furthermore they investigated if a few days after the exercise test an abnormal incline in plasma-creatine kinase or myoglobin could be detected. The authors used a stepwise incremental maximal bicycle-ergometer test. Compared with a matched control group they found no difference in potassium levels and neither any significant changes in lactate concentration. The patients complained of more pain two days after the exercise, but creatine kinase and myoglobin concentrations were not increased. The rise in pain after the performed exercise could be explained by an altered central stimulus modulation, which could be part of the pain perception in fibromyalgia.

The conclusion of the different studies on aerobic capacity and muscle performance in fibromyalgia is that there is no structural abnormality in muscle performance and that the basic physiological function of the muscles is normal in patients with fibromyalgia during exercise, but patients do not bring their maximal effort in the different testsituations. They are afraid their complaints will increase after a (work) performance. Fibromyalgia patients are physically unfit, but this is due to a deconditioning effect. It seems important to break through the circle of pain, deconditioning, fatigue and again pain.

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# Coexisting and modulating factors, and related syndromes

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# Introduction

In this chapter different coexisting and modulating factors will be discussed. Attention will be primarily focused on the coexistence of irritable bowel syndrome, and furthermore on the prevalence of Raynaud's syndrome in fibromyalgia, and also of Sjögren's syndrome. Next the prevalence of sexual abuse in the history of female fibromyalgia patients will be outlined. Weather-dependent complaints in fibromyalgia are addressed in chapter 6.
The second part of this chapter will summarize the related syndromes of fibromyalgia, like chronic fatigue syndrome and myofascial pain syndromes.

# Coexisting and modulating factors

In an article by Reilly and Littlejohn (1) they comment on the first presentation of fibromyalgia patients which is in their experience often with peripheral arthralgic complaints. The study included 216 consecutive new referrals to a general rheumatology clinic. 10% of these new referrals were diagnosed as fibromyalgia, of which half presented with pain in hands or wrists. Their message is that joint pain and tenderness do not necessarily mean there is joint pathology and that a mistaken diagnosis of seronegative arthritis or similar should be avoided where there is good evidence of fibromyalgia, so that fruitless and potentially dangerous therapies are withheld. We all know that at the first presentation of what turns out to be a fibromyalgia patient, we have to include rheumatoid arthritis in our differential diagnosis.
Pellegrino (2), in an anecdotal report, mentions atypical chest pain as an initial presentation of fibromyalgia.
Langevitz et al. (3) described the possible link between familial mediterranean fever (FMF) and fibromyalgia symptoms. A subpopulation of patients with FMF experience chronic lower body pain and the authors tried to determine if these chronic musculoskeletal complaints were due to FMF itself or to mechanical problems in the lower body or to other factors operative in fibromyalgia. In 93 consecutive patients with FMF a tender point count was conducted (Smythe 14 tender point count). Patients with 10 or more tender points and widespread pain were considered to have fibromyalgia. The same definition of widespread pain as was defined in the 1990 ACR criteria was used. Furthermore tenderness thresholds at 7 tender points and 5 control points were obtained. Thirty of their patients (35.5%) were found to have fibromyalgia. Dolorimeter thresholds were significantly lower in the female fibromyalgia group, both at the tender points sites and the control sites. The tenderness thresholds at control sites in the fibromyalgia group were also significantly lower than thresholds at the same sites in the patients without fibromyalgic

complaints. The authors conclude that their data suggest that the chronic experienced pain in a subgroup of FMF patients is associated in part with fibromyalgia and likely due to mechanical problems in the lower back rather than to the concomitant FMF itself. Recognition of the fibromyalgic complaints could help the patients to cope with this problem.
This report shows us that fibromyalgic complaints can coexist with other diagnoses, and that we have to be aware of this if a patient experiences widespread pain.

## Irritable bowel syndrome

In the criteria published by Yunus (4) the irritable bowel syndrome (IBS) is one of the minor symptoms in fibromyalgia, which may lead to diagnosing fibromyalgia. Campbell (5) also put emphasis on IBS in the diagnostic process. In later criteria sets for diagnosing fibromyalgia, for instance the 1990 criteria, IBS is no longer part of the diagnostic tools.
Fibromyalgia and IBS frequently coexist, and both are common conditions which account for 30% or more of referrals to rheumatology and gastroenterology clinics (6). Veale et al. (6) studied the prevalence of fibromyalgia in IBS patients and that of IBS in fibromyalgia patients, using strict criteria for diagnosis of fibromyalgia and IBS, and compared these to both normal and disease control groups. The authors said that no earlier study examined both patients groups simultaneously to evaluate the frequency with which the conditions coexist. They studied four patient groups, 20 with fibromyalgia, 20 with IBS, 20 with inflammatory arthritis, 20 with inflammatory bowel disease and also 20 normal controls (recruited from patients attending for uncomplicated fractures). Results show that 70% of the fibromyalgia group had IBS and 65% of the IBS patients had fibromyalgia. In the control groups (all patients except fibromyalgia patients) 12% had fibromyalgia and 10% IBS. So these results indicate that fibromyalgia and IBS frequently coexist, and the authors suggest a common pathogenetic mechanism for both conditions may be present. We must realize that the number of patients in this study was not very high. Romano (7) also published about the coexistence of IBS and fibromyalgia. Three hundred patients in a private rheumatology practice were studied prospectively; 100 patients fulfilled the diagnostic criteria of primary fibromyalgia syndrome (a compilation of different diagnostic sets), 100 patients with an arthritis disorder who fulfilled criteria for secondary fibromyalgia syndrome, that is patients with nonrestorative sleep, specific and reproducible tender areas and complaints of musculoskeletal pain and achiness, and a third group of 100 patients who had arthritic diseases but did not have problems with sleep, nor did they have enough myofascial tender areas to fulfil the diagnostic criteria for fibromyalgia. These 300 patients were asked for IBS-symptoms (using a questionnaire). IBS was diagnosed in 49% of primary fibromyalgia syndrome patients, in 19% of patients with secondary fibromyalgia, and in 9% with arthritic

controls. Regarding all fibromyalgia patients together (primary and secondary) IBS coexists in one third of the fibromyalgia group.
Yunus (8) performed a controlled study of primary fibromyalgia syndrome for clinical features and association with other functional syndromes, among which IBS was one. IBS was significantly more common in primary fibromyalgia syndrome, compared with RA and normal control groups.
Both syndromes occur predominantly in women and the pathogenesis of both syndromes remains obscure.
An other study for bowel dysfunction in fibromyalgia (criteria of Smythe) was undertaken by Triadafilopoulos et al. (9). They used a validated self-administered questionnaire to assess the prevalence of symptoms of bowel dysfunction and IBS in a group of 123 patients with fibromyalgia. These patients were compared with 54 patients with degenerative joint disease and with 46 normal controls. They found a high prevalence (60%) of gastrointestinal symptoms suggestive of IBS in the fibromyalgia patient group, and that these symptoms worsened during stress or disease exacerbations. In contrast, only 13% of degenerative joint disease patients and 0% of normal controls reported any symptoms of bowel dysfunction.
Prescott (10) reported on a study of clinical features of fibromyalgia in the adult Danish population. Study population was based an a national health interview survey. In this study subjective swelling, fatigue and headache were significantly associated with the number of tender points and with the diagnosis of fibromyalgia. However the symptoms like irritable bowels, morning stiffness and sleep disturbances were not related to fibromyalgia. This finding might be explained, according to the authors, by the changing of criteria sets in classifying fibromyalgia. The Yunus criteria included irritable bowel symptoms as one of the minor criteria, thus bringing in a diagnostic bias.
Also addressing the comorbidity of, among other disorders, IBS and fibromyalgia was Hudson in 1992 (11). Doing this they assessed the personal and family histories of a broad range of medical and psychiatric disorders in 33 female fibromyalgia patients. In this patient group there were high rates of migraine, IBS, chronic fatigue syndrome, major depression and panic disorder. There were also high rates of familial major mood disorder. The authors were especially focused on these disorders using a structured clinical interview comprising the symptoms and complaints of these disorders, by standard operational criteria. They found no case of somatization disorder in their patient group. If the symptoms of chronic pain would not have been attributed to the fibromyalgia, the authors mentioned, than 21% would have met criteria for somatization disorder. In most cases the associated disorders began at least 1 year before the onset of the fibromyalgia symptoms, except the chronic fatigue syndrome. The chronic fatigue syndrome almost always preceded the fibromyalgia start within a year. This last finding could suggest, according to the authors, that the current diagnostic criteria do not adequately distinguish these two disorders, or even

that these two are actually the same illness. The authors think their results are consistent with the possibility of a shared, heritable?, abnormality that is necessary, but not sufficient, for these disorders to occur. So other factors, like for instance exposure to certain viral antigens, might be necessary for the development of fibromyalgia. They also stress that their hypothesis does not imply that any of these disorders causes another.
In our study 30% of the fibromyalgia patients said they had symptoms of IBS, and 16% of the RA patients. IBS was present, in our opinion, in the presence of chronic, moderate or severe constipation and/or diarrhoea as well as moderate or severe abdominal pain related to bowel movement in the absence of an underlying organic condition, as assessed by medical history. Yunus in 1989 used the same criteria. Summarizing the results of the different studies mentioned above, there seems to be a high incidence of IBS in patients with fibromyalgia. An explanation for this coexistence can not be found in these articles, but most authors suggest there is a common pathogenetic pathway. Fibromyalgia is not a disorder with solely musculoskeletal complaints; other psychophysiological factors can be involved. Weather-dependent fibromyalgic complaints are often mentioned, see chapter 6 (12). Patients with fibromyalgia frequently report problems associated with cold: worsening symptoms in cold weather, having cold hands, and feeling colder than others. In our study (12), where we examined the subjective complaints of the fibromyalgia patients, compared with objective meteorological factors, we were not able to confirm the hypothesis that weather influences pain and other complaints in fibromyalgia patients. One year later, Hagglund et al. (13) conducted a very similar study like ours. Their study group of fibromyalgia patients reported that weather affected musculoskeletal symptoms predominantly, but they did not find any correlation between meteorological data and disease severity measures. They found a strong association between beliefs about weather and self-reported pain. The authors had to come to the same conclusion like we did: fibromyalgia patients belief that weather affects their symptoms, but is very unlikely that there are physiologic changes associated with actual weather.

## Raynaud's syndrome

Questionnaire-based studies have demonstrated a 30-53% prevalence of symptoms suggestive of Raynaud's syndrome in patients with fibromyalgia. In our study sample this was 23% in the fibromyalgia group. Different authors have studied the relationship between fibromyalgia and symptoms of Raynaud's syndrome, and these studies are discussed in chapter 2 (14-17).

## Sjögren's syndrome

Vitalli and other Italian coworkers (18), reported on fibromyalgia features in patients with primary Sjögren's syndrome. Patients with fibromyalgia often describe the presence of dry mouth and dry eyes. They compared three groups of 30 patients, one group with primary Sjögren's syndrome, one group with osteoarthritis and a third group with diabetes mellitus. Fibromyalgia features were found in 47% in the Sjögren's group, in 70% of the osteoarthritis group and only 33% in the diabetes group. In the Sjögren's group there was the highest prevalence of moderate-severe depression (also 47%). The criteria for fibromyalgia were those of Yunus (1981). The fibromyalgic pain in the Sjögren-patients appeared, according to the authors, to be closely correlated with psychopathological changes, and in particular depression. In patients with primary Sjögren's syndrome the neurotic changes might be a consequence of chronic disease state. They suggest that the Sjögren patient suffers more and experiences more impairments and disabilities than is commonly acknowledged and this might induce neurotic changes, like depression, more than is expected. The development of fibromyalgic pain could be the consequence of these psychological changes, more so than related to other disease-specific mechanisms.
The association of fibromyalgia with primary Sjögren's syndrome was prospectively studied by Bonafede et al. (19). Seventy-two fibromyalgia patients underwent a Schirmer test and those persons with an abnormal test had a minor salivary gland biopsy. Nearly 40% of a tertiary centre fibromyalgia population had a positive Schirmer test. In total 6.9% of their study sample had probable Sjögren's syndrome, and 11% possible Sjögren's syndrome (established after the biopsy). They followed these patients for a period of over 6 years and none of these patients have developed systemic complications of Sjögren's syndrome.
The relationship between fibromyalgia and Sjögren's syndrome is not clear. There is no evidence for an autoimmune basis in fibromyalgia, and an infectious etiology seems also farfetched. Maybe stress plays an important factor in developing fibromyalgic complaints in patients with Sjögren's syndrome.

## Prevalence of sexual abuse in fibromyalgia

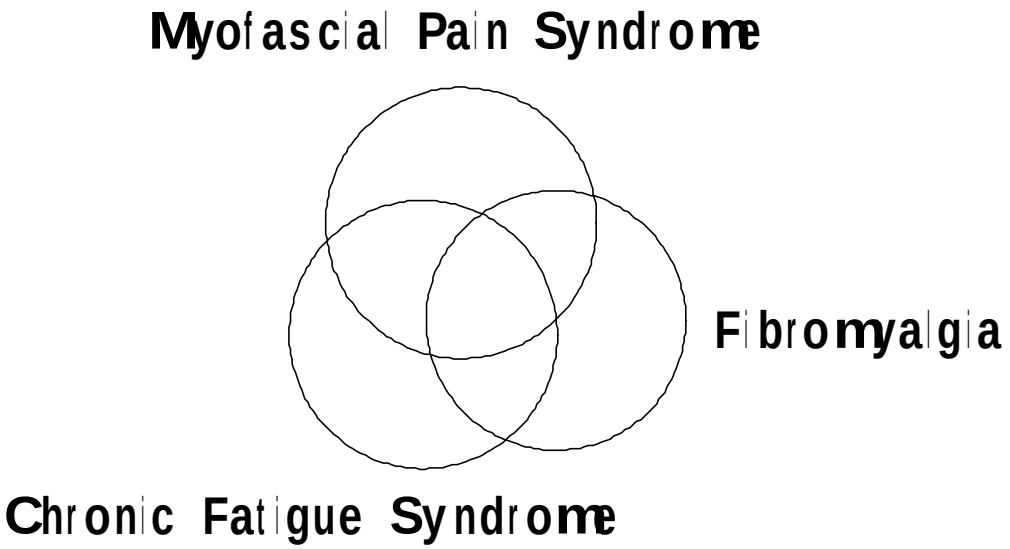
In 1995 two studies were published concerning the prevalence of a history of sexual abuse in women with fibromyalgia (20,21), by Taylor et al. and Boisset-Poiro et al. Information was gathered by the use of self-administered questionnaires, and in both studies a control group of women was present. In the study of Taylor the control group consisted of healthy controls, in the study of Boisset-Poiro of rheumatology patients (non-fibromyalgia). In the two fibromyalgia groups, as well as in both control groups the incidence of reported abuse was high (more than 50%), but no statistically significant difference was found between the patient group and control group in both studies. The authors conclude that sexual abuse does not cause fibromyalgia, but their results show that sexual abuse is correlated with the number and severity of associated

symptoms, and furthermore that abuse (not only sexual, but also physical, drug and alcohol, and eating disorders) might have an effect upon the expression and perpetuation of fibromyalgia in adult women. Hudson (22) presses on the fallacy that a found correlation between childhood (sexual) abuse and fibromyalgia does not necessarily mean that there is a causal link between the two. Both may very well be caused by the same (third) factor. Hudson states that the only thing to do to get a definite answer concerning this causality question is a prospective longitudinal study of a group of children that were sexually abused, and another, matched, group that was not, and to see if over the years a medical or psychiatric illness develops.
In these studies remarkable high numbers of sexual abuse in fibromyalgia patients came forward. The relationship between the abuse and fibromyalgic complaints could, once again, be the (psychological) stress phenomenon. Stress could represent some etiologic role in the development of the fibromyalgia syndrome.

# Fibromyalgia and related syndromes

Fibromyalgia as a separate entity is very often not recognised, but on the other hand fibromyalgia has certainly an overlap with other syndromes. It is very difficult to say if these related syndromes, like chronic fatigue syndrome, myofascial pain syndrome, female urethral syndrome, and fluid retention syndrome are distinguishable other syndromes or if their part of the same spectrum of symptoms. We tend to believe they are overlapping syndromes, especially fibromyalgia, chronic fatigue syndrome and myofascial pain syndrome (figure 1 ).

Figure 1



# Fibromyalgia and Chronic Fatigue Syndrome

Fibromyalgia and chronic fatigue syndrome are conditions which are both controversial. Both syndromes go by different names. Fibromyalgia has been known as soft tissue rheumatism, psychogenic rheumatism, fibrositis, myofascial pain syndrome etc.

Chronic fatigue syndrome is known as chronic Epstein-Barr Virus syndrome, postviral fatigue syndrome, postviral exhaustion, neurasthenia, myalgic encephalomyelitis etc, and a more popular namegiving "yuppy plague".

Chronic fatigue syndrome is characterized by chronic, debilitating fatigue lasting longer than 6 months, with exclusion of other conditions that may cause similar symptoms. Nonspecific neurological symptoms like poor concentration, visual blurring and vertigo are often mentioned by patients with chronic fatigue syndrome.

It happens that the fibromyalgia patient, with complaints of widespread pain, consults a rheumatologist, and that a chronic fatigue patient is more often seen by a neurologist. Specific musculoskeletal symptoms and signs are required for the diagnosis of fibromyalgia and severe debilitating fatigue is required for the diagnosis chronic fatigue syndrome. But actually most patients with fibromyalgia also complain about fatigue, and on the other hand patients with chronic fatigue often have musculoskeletal complaints.

Interest in a viral genesis of the fibromyalgia syndrome came along with the interest in the chronic fatigue syndrome, surely because of the many similarities between the two syndromes.

In an editorial (23) Wessely addresses the chronic fatigue syndrome and refers to neurologists. In the editorial he discusses the supposed relations between the chronic fatigue syndrome and neuromuscular disorders, and psychiatry, infection, and the immune system. Finally Wessely puts forward his idea of the concept of the chronic fatigue syndrome, in which he sees chronic fatigue as a dimensional in stead of a categorical variable. Fatigue can be seen anywhere on a spectrum from no fatigue to worst possible fatigue and there is no clear boundary to separate the normal from the abnormal. Being on the end of the spectrum could mean severe morbidity which in itself needs treatment. In the treatment of chronic fatigue Wessely sees a crucial role for rehabilitation, where a physical and psychological approach are combined. As in the fibromyalgia syndrome recognition of the complaints is very important and over investigation should be avoided. The patients with these complaints should be taken for real and the patient presenting with a psychosocial disability needs our attention and care as any other patient. This again shows the similarities between the patients with fibromyalgia and chronic fatigue syndrome.

David et al. (24) stressed as well on the possible interactions between psychological and physical influences on health, and this should be given much more attention.

Both conditions are controversial, because of lack of objective evidence for structural pathology or disease. So it is often said that psychogenic factors play the most

important role in the etiology of these syndromes.
A lot of work has been done in investigating psychological backgrounds of fibromyalgia patients, see chapter 10. The results were contradictory, but most investigators found elevated psychological test scores in patients with primary fibromyalgia syndrome. The question which came first, the psychological symptoms or the physical symptoms, is of course not answered. Altogether should the dichotomy of organic versus functional be replaced by a multifactorial approach, as well in fibromyalgia as in chronic fatigue syndrome.

## Ideas on viral etiology of chronic fatigue syndrome and fibromyalgia syndrome

Several studies have been published on the search for a viral etiology (25-29). An anecdotal report on parvovirus B19 infections in fibromyalgia (25), and Buchwald published a study (26), in which he described the antibody titers to Epstein-Barr virus in patients with fibromyalgia. He found that these titers were not significantly different from those in age- and sex-matched healthy and unhealthy controls. Later studies did actually not find higher titers of the antibody against the Epstein-Barr virus in patients with the chronic fatigue syndrome. The association between Coxsackie B virus infection and the postviral fatigue syndrome and the assessment of immunological abnormalities associated with this syndrome, were studied by Nash et al. (27) and Miller et al. (28). Miller found no significant differences between different categories of patients according to clinical likelihood of the syndrome nor any predictive value in a fourfold rise or fall in the Coxsackie B virus IgG titre in patients between entry and review at six months. Nash et al. reported in a case report the history of a patient who met the fibromyalgia criteria according to Smythe and who had evidence of chronic infection with Coxsackie virus over a 4-year period of follow-up.
The presence of parvovirus B19 infection in chronic fatigue was subject of study by Ilaria et al. (29). Parvovirus B19 had been identified in some fibromyalgia patients, see above and chapter 2, and because the considerable overlap between chronic fatigue syndrome and fibromyalgia the authors were interested if this same virus could be involved in chronic fatigue syndrome. Bone marrow and serum samples of a selected group of chronic fatigue patients most likely to have parvoviral infection were obtained. However no evidence of clinically important parvoviral infection was found. Altogether no substantial evidence have been put forward for a viral etiology in the chronic fatigue syndrome (nor in the fibromyalgia syndrome).

## Hormonal disturbances in chronic fatigue syndrome

Sternberg (1993) (30) subscribes the importance of a variety of neuroendocrine abnormalities in rheumatologic disease and associated fatigue syndromes including the chronic fatigue syndrome. She states that now researchers have proven the interactions between the immune system and central nervous system, and vice versa. As an example of this she says that products of the immune system, such as cytokines, stimulate parts of the central nervous system (CNS), such as the hypothalamus, and thus initiate a cascade of hormonal events which results in suppression of the immune/inflammatory response through the potent anti-inflammatory/immunosuppressive effects of the glucocorticoids. And next that an interruption of this feedback loop by any means and at any point may result in susceptibility to or enhancement of inflammatory disease. Special interest is laid on abnormalities in hypothalamic-pituitary-adrenal function in which case lethargy and fatigue states can occur. This could be explained by a central adrenal insufficiency, by means of a deficiency of cortico releasing hormone (CRH) and/or cortisol, or by means of a primary adrenal insufficiency, in which there is glucocorticoid deficiency on the whole. Enhanced immune responsiveness is associated with both lethargy and fatigue states, regardless of the etiology of the hypocortisolism. Furthermore Sternberg suggests that a hyporesponsive adrenal cortex can result in increased susceptibility to disordered states of immunity, manifesting either as chronic fatigue or fibromyalgia. This theory is gaining more and more support, where an abnormal reaction to stress plays an important role. Stress influences the central nervous system and immune system.

## Trace elements in chronic fatigue syndrome

Cox et al. (31) tested the hypotheses that patients with chronic fatigue syndrome have low red blood cell magnesium and that magnesium treatment would improve the wellbeing of such patients. They did this in a case-control study and a randomized, double-blind, placebo-controlled trial. They found that patients with chronic fatigue syndrome had lower red cell magnesium concentrations than healthy controls, and in the clinical trial patients treated with magnesium claimed to have improved energy levels, better emotional state and less pain. In the control group the results were far less. Red cell magnesium returned to normal in all patients on magnesium, but in only 1 (of 17) patient on placebo. The authors suggest that these findings show that magnesium may play a role in chronic fatigue syndrome.

Lund-Olesen and Lund-Olesen (32) hypothesized in a case report, that a virus injury to the calcium channels could be a causative factor in the pathogenesis of the chronic fatigue syndrome/fibromyalgia. The authors suggest that an injury to the calcium channels will lead to larger quantities of calcium ions entering the striated muscle cells and this would result in increased muscle tone, and the cells and whole muscle,

will develop a state comparable to that following static muscular work. The authors suggest placebo-controlled studies with calcium antagonists in patients with chronic fatigue syndrome.
The study on the low red blood cell magnesium is interesting, also while it is performed in a well-designed way. The study on calcium is speculative and can not lead to any conclusions, being just one case report.

## Depression and chronic fatigue syndrome

Kendell (33) made a statement about his viewpoint of chronic fatigue, viruses and depression. According to Kendell the description of a depressive episode begins with the statement that the subject suffers from lowering of mood, reduction of energy, and decrease in activity. Capacity for enjoyment, interest, and concentration are impaired, and marked tiredness after even minimum effort is common ($10^{th}$ revision of International Classification of Disease). Apart from the absence of any reference to previous viral infection, this description is almost the same as the one for the postviral fatigue syndrome. Depressive illness are also twice as common in women as in men and are uncommon in children; both features of postviral fatigue syndrome as well. When patients with chronic fatigue are assessed psychiatrically more than half of them are found to fulfil operational criteria for psychiatric disorder.

## Sleep problems in chronic fatigue syndrome

Whelton in 1992 (34) compared sleep physiology, viral serology and symptoms in 14 chronic fatigue patients and 12 healthy controls. All patients had unrefreshing sleep and α-intrusion in nREM sleep. They found no difference in Epstein-Barr virus serology. The chronic fatigue patients had significantly more tender points than the control group, and had also more somatic complaints and depressive symptoms. The chronic fatigue patients did not have irresistible daytime sleepiness, although they complain of daytime exhaustion.
These findings are very similar to those published on the fibromyalgia syndrome.

## Treatment modalities in chronic fatigue syndrome

Treatment for the chronic fatigue syndrome has consisted of intravenous immunoglobulintreatment, as a trial. The result of this study (35) indicated that intravenous IgG is unlikely to be of clinical benefit in chronic fatigue syndrome. However, Llyod et al. (36) published a study in which they suggested that immunomodulatory treatment with immunoglobulin is effective in a significant number of patients with chronic fatigue syndrome. According to the authors this should be a support to the concept that an immunologic disturbance may be important

in the pathogenesis of this disorder. Straus (37) commented on these two studies, which have opposite conclusions. With regard to sample size and immunoglobulin dosage there were differences in these two studies, and also the study cohorts may not have been comparable.
Also other treatment modalities in the chronic fatigue syndrome are suggested, like for instance cognitive behavior therapy(38). 50 patients enroled an open trial, in which the rationale was that a distinction could be drawn between factors that precipitate the illness and those that perpetuate it. Similarities can be seen here with the fibromyalgia syndrome. Perpetuating factors can be cognitive factors like the belief that physical symptoms would mean tissue damage, but also behavioral factors such as persistent avoidance of activities associated with an increase in symptoms. The authors warn not to avoid physical and mental activity, because in their opinion this only works counterproductive. The authors have an interesting theory on the etiology of chronic fatigue syndrome: "..it is plausible that an initial ineffective trigger may begin a cycle in which both attributional and cognitive factors fuel avoidant behaviour. The initial symptoms, in particular fatigue and myalgia, engender a state of "learned helplessness" being potent, aversive and uncontrollable, and may also trigger or exacerbate the mood disorder that is found in many patients. Continuing attribution of all symptoms to a persistent, untreatable "virus", continues to increase helplessness, although preserves self esteem. Avoidant behavior, which is reinforced by the advice currently offered to patients, sustains symptoms, by decreasing activity tolerance and increasing sensitivity to any stimulation, as does associated mood disorder. Re-exposure to activity causes more symptoms, and more fear. The result is a vicious circle of symptoms, avoidance, fatigue, demoralisations and depression..". Therefore they see a chance for success when the avoidance behavior could be reduced and the perception of helplessness could be decreased and improvement of mood could be achieved.
This theory also would fit the fibromyalgia syndrome perfectly.

## Comparison between fibromyalgia syndrome and chronic fatigue syndrome

The relationship between fibromyalgia and chronic fatigue syndrome has been studied by several investigators.
Moldofsky et al. (39) have noted similar sleep disturbances in fibromyalgia and chronic fatigue syndrome. In 1989 Moldofsky (40) wrote about non-restorative sleep and symptoms after a febrile illness in patients with fibromyalgia and chronic fatigue syndromes. A febrile illness may trigger alteration in sleep-wake brain and immune functions in patients with fibrositis or chronic fatigue syndromes. In this article Moldofsky tried to find connections between sleep disturbances, immune functions, chronic fatigue and myalgia. The author stated that earlier experimental data and

clinical observations suggested a connection between the sleep-waking brain and immune system, but the contribution of disturbances in the sleep-waking brain and immune system to chronic fatigue and myalgia is as yet not clear.

In 1988 Goldenberg (41) looked for evidence for chronic viral disease in fibromyalgia and other chronic fatigue syndromes. Goldenberg gave a summary of the literature of the different syndromes and reviewed the last studies concerning the two syndromes, including their own study (42,43).

Goldenberg (42) stated that the two syndromes have similar clinical and demographic features. He found that most patients with chronic fatigue syndrome have a tender point examination similar to patients with fibromyalgia. Another point he makes is that similar pathophysiologic changes have been described in both syndromes. Single fiber electromyographic changes and reduced high energy phosphate levels in muscle have been reported in both conditions, suggesting that muscle alterations may be important. Depression is also common in both syndromes. In another publication of Goldenberg (43) he reported a high frequency of fibromyalgia in patients with chronic fatigue in an academic primary care practice. Of 27 chronic fatigue patients 19 (70%) had a tender point examination similar to those of patients with fibromyalgia, and these patients had persistent diffuse musculoskeletal pain. The other 8 patients did not have musculoskeletal pain and the tender point examination in those patients was similar to those in healthy controls.

Wysenbeek et al. (44) investigated fibromyalgia patients for chronic fatigue syndrome symptoms. This study was conducted in Israel. Only 21% (7 of 33) of the fibromyalgia patients fulfilled criteria for the chronic fatigue syndrome, which is a lower number than other authors reported. They asked however if painful glands were present, while in other studies the authors asked for swollen glands. This could explain the differences in study outcome. In conclusion Wysenbeek stated that there is a limited relationship between the two syndromes and that they do not seem to represent the same condition.

Goldenberg (45) tried to bring a synthesis between fibromyalgia, chronic fatigue and myofascial pain syndromes, for which syndromes there is an overlapping area.

A Danish group performed a 4-year follow-up study in fibromyalgia and looked closer into the relationship with the chronic fatigue syndrome (46). They wanted to investigate the common existence or later appearance of other diseases in patients that were diagnosed as fibromyalgia, and to describe the overlap between fibromyalgia and chronic fatigue syndrome. Their patients attended the department of rheumatology. In their follow-up period only 2 of 91 patients developed another somatic disease that could explain the muscle pains. The pain was generally reported to be aggravated. There was no notable decrease in muscle strength. Only one fifth of their fibromyalgia patient group fulfilled all the criteria of the chronic fatigue syndrome, including sudden onset of symptoms, fever, lymphadenitis, or pharyngitis.

A new syndrome is introduced by Buchwald and Garrity (47), in their comparison

study of patients with chronic fatigue, fibromyalgia and multiple chemical sensitivities (MCS). The authors themselves state that there are no generally agreed-on criteria for MCS, but it could be summarized as an acquired disorder triggered by exposure to diverse chemicals at doses far below those documented to cause adverse effects in humans. The demographic characteristics and specific symptoms were very similar. Seventy percent of the fibromyalgia group met the criteria for chronic fatigue and 30% of the MCS group met criteria for chronic fatigue. Health care use was highest in the fibromyalgia group (39.7 contacts in the previous year), but also high in the other two groups (MCS 23.3 contacts, chronic fatigue 22.1 contacts). The authors found no difference in health locus of control between the three groups.
Regarding all the different studies on chronic fatigue syndrome in relation with fibromyalgia syndrome, we belief these two are overlapping syndromes. How many patients fulfil both criteria sets depends on what particular criteria sets were used in the different studies.

## Fibromyalgia and myofascial pain syndromes

A clear distinction between fibromyalgia and myofascial pain syndrome was not made in the earlier days. Simons and Travell (48) were the pioneers in the field of myofascial pain syndromes, but in the beginning and middle of the eighties there still was a lot of confusion on the terminology, for instance "Fibrositis/fibromyalgia; A form of myofascial trigger point.", by Simons in 1986 (49), and even in 1989 in a publication by Fishbain (50) "DSM-III diagnoses of patients with myofascial pain syndromes (fibrositis)." Simons puts the question forward whether patients diagnosed as having fibromyalgia are only having extensive multiple myofascial trigger points aggravated by severe perpetuating factors or that fibromyalgia is a separate systemic disorder that is responsible for the symptoms or, thirdly, there could be a combination of fibromyalgia and myofascial trigger points. The different features of fibromyalgia and myofascial pain syndrome are compared with one another and the difference between tender points and trigger points is elucidated (see also chapter 7). A trigger point is always a tender spot and a tender point may, or may not, be a trigger point. This is of importance, according to Simons, because trigger points are responsive to specific treatment. Simons states that fibromyalgia and myofascial pain syndromes are almost certainly separate entities, but a considerable number of patients could have both conditions. This leaves the reader a little in the dark.
There have been a number of investigators who looked into the different aspects of each of the syndromes, for instance Sheon (51). He emphasizes the distinction between tender and trigger points. At one point Sheon asks a very interesting question, if these two disorders are really different entities or part of a spectrum of a muscular rheumatic disorder. Unfortunately this question stays unanswered. It is basically the same question that Simons in 1986 addressed. Myofascial pain syndrome can be seen

as a local form of fibromyalgia. Myofascial pain syndromes are characterized by trigger points and there is no need to have generalized pain complaints.
Durette et al. (52) evaluated needle electromyographic activity in patients with myofascial pain syndrome and in patients with fibromyalgia. They selected tender points in fibromyalgia patients, similar tender areas with pain referral, so called trigger points, and associated muscle bands and adjacent uninvolved musculature. Not in any of the muscles of the participating subjects there were spontaneous fibrillatory or positive sharp wave potentials found. Neither was their evidence of focal motorunit activity in the tender points, trigger points or associated muscle bands in either group. There were no differences found in motor unit recruitment in the sampled areas. Following these findings the authors say that no electrodiagnostic evidence of ongoing denervation or focal muscle spasm is found in association with focal myofascial pain or fibromyalgia.
Yunus et al. (53) outlined clinical features and muscle pathology in fibromyalgia syndrome and myofascial pain syndrome. Stress was laid on the pathologic changes in muscle in the fibromyalgia syndrome, namely moth-eaten appearance of type I fiber and myofibrillar lysis with glycogen and mitochondria deposition. Pathologic changes in muscle in myofascial pain syndromes are not further discussed. Yunus, however, recommended strongly further controlled studies to establish meaningful pathologic changes in muscle in fibromyalgia.
Scudds et al. (54) conducted a comparative study of pain, sleep quality and pain responsiveness in 20 patients with fibromyalgia and 18 with myofascial pain syndrome. The authors found substantial differences in overall pain and pain responsiveness between the two groups. The myofascial pain group was significantly younger than the fibromyalgia group, but there was no difference in duration of the pain complaints between the two groups. They also looked for differences in anxiety and depression on VAS-ratings, but no differences were found. The fibromyalgia group had lower generalized pain thresholds, meaning that they were more responsive to pain, and they also scored higher on mean VAS scores concerning pain intensity. No differences were found in sleep quality, measured with VAS as well. These findings still could mean that the two syndromes are part of a continuum; fibromyalgia being the more severe in experiencing pain complaints.
Jacobsen et al. (55) compared dynamic muscular endurance (DME) in fibromyalgia (36 patients) and myofascial pain syndrome (18 patients). Patient's groups were matched for sex, age, height and weight, peak torque and contractional work of the right quadriceps muscle. A Cybex II dynamometer was used to determine the DME of the right quadriceps muscle. Subjects were asked to perform repeated knee extensions with maximal strength each time (with a constant angular velocity). The DME was defined as the number of repeated knee extensions needed for the contractional work in two successive knee extensions to be equal to or below 70% of the initial value. They found a significantly lower voluntary muscular endurance in the fibromyalgia

group. In the myofascial pain group however almost none of the patients had their symptoms in the lower extremities. And how can one be sure that a patient really showed his maximal strength at the initial contraction and during the endurance test? The DME was not related to the number of subjective symptoms of the patients in this study. The patients with a lower muscular endurance, however, also had lower levels of physical activity, which may not come as a surprise. These results are hard to interpret. The impact of experiencing pain on the maximal muscle endurance can not be reliable established, and therefore these results are not very worthful.
Smythe (56) addresses the links between fibromyalgia and myofascial pain syndromes too. He urges that more attention should be given to the examination of specific sites of deep tenderness, e.g. tender points and trigger points. He clearly sees two different areas, the widespread pain syndromes and regional pain syndromes. He recommends the study of Wolfe et al. (57) (see chapter 7).

## Fibromyalgia and female urethral syndrome

A relationship between fibromyalgia and the female urethral syndrome was suggested by Wallace (58) and Paira (59). The female urethral syndrome is characterized by the presence of urinary frequency, dysuria, suprapubic discomfort and urethral pain. The urine however should be sterile. Wallace and Paira found in respectively 12 and 18% of a group of fibromyalgia patients (respectively 50 and 212 patients) also the presence of the female urethral syndrome. In a control group of patients (same number of patients) with other rheumatic conditions their were none with the female urethral syndrome. Both authors suggest that the female urethral syndrome should be taken into account in the evaluation of every patient with fibromyalgia. But what to do with the male fibromyalgia patients? Wallace remarks that the personality profiles of patients with the female urethral syndrome and patients with fibromyalgia are similar, but no direct comparisons are made. Both authors believe that the urethral syndrome might represent a form of fibromyalgia, or are overlapping syndromes. Both syndromes are said to respond to similar therapies, like cyclobenzaprine, NSAID's, aerobic exercises and swimming.
The authors hypothesize that the urethral musculature is affected in fibromyalgia and that this could explain the combination of the two syndromes. This assumption seems highly speculative, more so while the general opinion moves away from the peripheral (pathogenetic) theory.

## Fibromyalgia and fluid retention syndrome

Deodhar (60) drawes attention to the fluid retention syndrome in relation to fibromyalgia. Although this fluid retention syndrome is not well known, Deodhar thinks it is important enough that physicians are aware of the symptoms of this syndrome. Another synonym of this syndrome is idiopathic oedema and is said to be seen almost only in women. A diversity of accompanying symptoms are reported, among which fatigue, generalized weakness and bloating. This makes the possible overlap between the fluid retention syndrome and fibromyalgia clear. Fibromyalgia patients often complain of subjective swelling, but this is not seen at the physical examination. The pathogenesis of the fluid retention syndrome is thought to be an unidentified defect in the capillary walls, which makes them more permeable especially when the patient is in the upright position. Management of the fluid retention syndrome leans, as in the fibromyalgia syndrome, on careful explanation of the syndrome and acceptance of the patient's complaints. Furthermore a low carbohydrate and low salt diet. Only 4 patients are described in this study, so we have to wait for the results of a larger, controlled study before this topic can be analyzed in a proper fashion. Interesting in the light of the fluid retention syndrome, with a suspected defect in the capillary walls, is the article by Grassi et al. (61). In their study they found indications for a lowered transcapillary diffusion and an earlier and more rapid interstitial clearance of Na-fluorescein, that was earlier on injected. So they conclude there is a lowered transcapillary permeability in fibromyalgia patients, and this seems contrary to the findings mentioned above in the fluid retention syndrome.

Overlooking the studies on fibromyalgia and related syndromes the conclusion can be drawn that all these syndromes belong to the same spectrum, where different symptoms are more prominent existent in the one syndrome than in the other. It might very well be true that the effort of the physician by asking all the right questions brings forward a wide variety of symptoms that would make the patient fit in more syndromes at one time.

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# In vivo 31P Magnetic Resonance Spectroscopy (MRS) of tender points in patients with primary fibromyalgia syndrome

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Rheumatol Int 1991;11:51-54.

# Summary

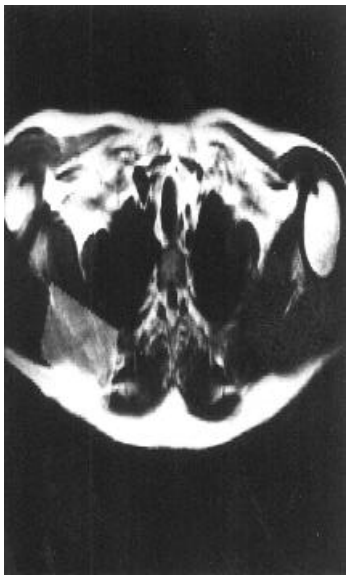
31P Magnetic Resonance-Spectroscopy was performed at the site of tender points in the trapezius muscle of patients with primary fibromyalgia syndrome. Earlier, in vitro studies have reported changes in the high energy phosphate-metabolism in biopsies taken from tender points of fibromyalgia patients.
The observed alterations could not be confirmed with in vivo Magnetic Resonance-Spectroscopy.

# Introduction

Fibromyalgia syndrome is a commonly recognised form of non-articular rheumatism, characterized by chronic musculoskeletal pain. A typical feature is the finding of so called "tender points" on physical examination (1). Tender points are defined as areas of prominent localized tenderness elicited on firm palpation of specific anatomic sites. Fibromyalgia predominantly affects women in the age group from 20 to 50 years (1). Criteria for the diagnosis of fibromyalgia according to Yunus are described in chapter 1. The American College of Rheumatology proposed new criteria for the classification of fibromyalgia in 1990 (2). These criteria are 1) widespread pain in combination with 2) tenderness at 11 or more of 18 specific tender points sites (chapter 1).
The underlying mechanism of fibromyalgia is not clear. The possible etiologic role of stress and other psychologic factors in fibromyalgia have recently been addressed (3,4). Increasing attention has also been given to a possible organic origin of the complaints (5,6). Histochemical as well as light and electron microscopic studies of trapezius muscle biopsy samples of fibromyalgia patients have shown non-specific abnormalities, and no evidence of inflammation (5). Significant histochemical abnormalities are Type II fiber atrophy and moth-eaten appearance of Type I fibers. Electron microscopy has revealed segmental muscle fiber necrosis with lipid and glycogen deposition as well as subsarcolemnal mitochondrial accumulation. Papillary projections of sarcolemnal membrane have also been described. The etiology of these abnormalities is uncertain, but it is held possible that muscle spasm and ischemia may contribute to the observed muscle changes (5).
Chemical analysis of biopsy samples from tender points in trapezius muscle has shown an alteration in the content of high energy phosphates compared to biopsies taken from identical regions in healthy volunteers (6). In particular, decreased levels of adenosine tri- and diphosphate (ATP and ADP) and phosphocreatine (PCr) have been reported, whereas levels of adenosine monophosphate (AMP) and creatine appeared to be increased. From these results the authors have concluded that pain experienced by fibromyalgia patients may be of muscular origin, and that muscle hypoxia could play an important pathogenetic role in fibromyalgia.

More evidence for the existence of abnormal oxygenation in fibromyalgia patients has been provided by Lund et al. (7), using a multipoint oxygen electrode placed on the muscle surface. They have reported abnormal or low muscle oxygenation at the site of tender points in fibromyalgia patients.
In vivo 31P Magnetic Resonance Spectroscopy (MRS) provides the opportunity to study high energy phosphate metabolism in muscle tissue (8-10). We used this non-invasive technique in order to detect metabolic differences between tender points in fibromyalgia patients and identical regions in healthy volunteers.

Figure 1
TRANSVERSE SLICE OF THE UPPER THORACIC REGION, WITH THE VOLUME OF INTEREST (VOI) OF THE RIGHT SHOULDER REGION, AT THE SITE OF THE TENDER POINT IN THE DESCENDEND TRAPEZIUS MUSCLE (SEE THE WHITE AREA IN THE PICTURE)



# Patients and Methods

Ten patients diagnosed as having fibromyalgia according to the criteria of Yunus (1981), were randomly chosen from the rheumatology outpatient clinic of the University Hospital of Groningen (NL), see table 1a . Informed consent was obtained from all patients.
Six healthy volunteers served as a control group, see table 1a.
The patients were seen in the outpatient clinic for physical, laboratory and radiological examination, followed by the 31P MRS.
The physical examination was performed by the same investigator (AB) and comprised a functional assessment of the musculoskeletal system, including stature, gait, mobility, global muscle strength (0-5), muscle tone, sensibility and myotendal reflexes. Tender points as described by Smythe (11), were charted. We considered a tender point positive when the patient complained of pain on palpation of the tender spot or when the patient, on palpation, showed signs of pain such as flinching or withdrawing. (In retrospect we were not able to see how many of our patients meet the new American College of Rheumatology criteria for the fibromyalgia syndrome, because we did not chart all the proposed 18 tender points.)
Laboratory investigation included ESR, haemoglobin level (Hb), leucocyte and platelet count, differential blood cell count, electrolytes, AF, LDH, SGOT, SGPT, Ca, P, triglycerides, cholesterol, CPK, thyroid hormone, serum protein electrophoresis, glucose, ANA (Anti-Nuclear Antibodies) and rheumatoid factor, as a screening for metabolic disorders or systemic autoimmune diseases. Urine was checked for glucose and albumen.
X-ray images of shoulders and cervical spine were made, frontal and lateral view, in search for possible anatomical causes of pain in the neck-shoulder region.
MR-Spectroscopy was performed on a 1.5 Tesla Philips whole body MR system with a 31P resonance frequency of 25,855 MHz. Preceding spectroscopy a series of transverse slices of the upper thoracic region was obtained by MR-imaging, thus facilitating the positioning of the Volume Of Interest (VOI) in the appropriate region (see figure 1 ).
Localization of the VOI, which is the area from which a spectrum is obtained, was achieved using a modified ISIS technique (Image Selected In vivo Spectroscopy). The 31P spectra were acquired using a send/receive surface coil (diameter 15 cm) which was positioned adjacent to the trapezius muscle at the site of the tender point. A standard VOI was chosen of approximately 100 $cm^3$ from which 512 signal accumulations were recorded with a repetition time of 3 s. Spectra were filtered and deconvoluted using a standard set of parameters.
Because MR-Spectroscopy in this set up does not allow absolute measurement of the concentration of the high energy phosphate metabolites, we used changes in peak area ratios. This limitation arises from many operational and technical factors. At the moment most measurements made from MR-spectra are ratios, where one peak is

compared with another (12-14).
Peak area ratios Pi (inorganic phosphate)/PCr, PCr/β-ATP and Pi/β-ATP were calculated, using time domain fitting routines (12,13). The pH was calculated from the relative distance of the Pi-peak to the PCr-peak on the PPM (parts per million)-scale on the horizontal axis.

# Results

On physical examination there were no structural disorders in stature or mobility, or neurologic disorders. Laboratory and urine tests were normal, as well as the radiological examinations.
All ten patients and the six healthy controls underwent 31P MR-Spectroscopy. The spectra obtained for fibromyalgia patients and healthy controls looked similar initially (figure 2a,b ).

Figure 2a
31P-SPECTRUM OF TRAPEZIUS MUSCLE TISSUE IN A HEALTHY VOLUNTEER

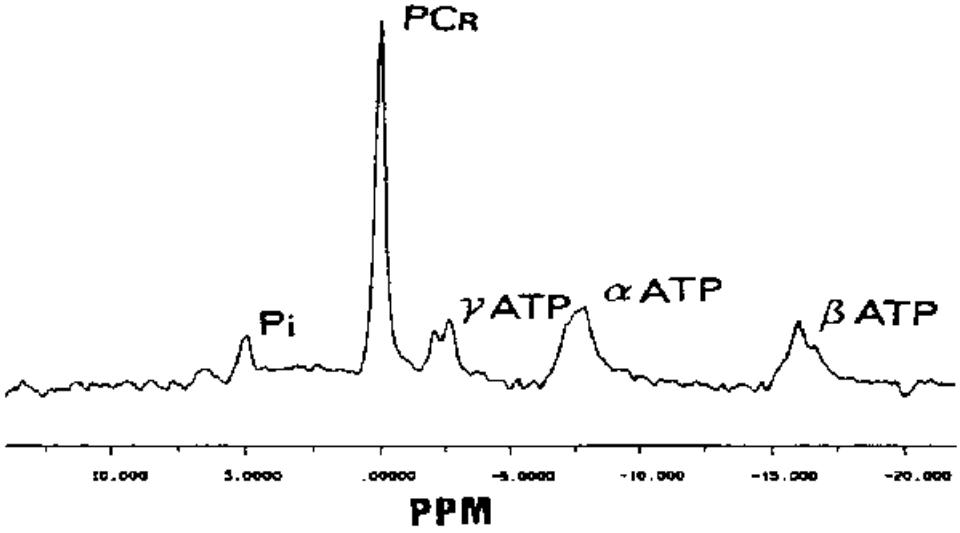
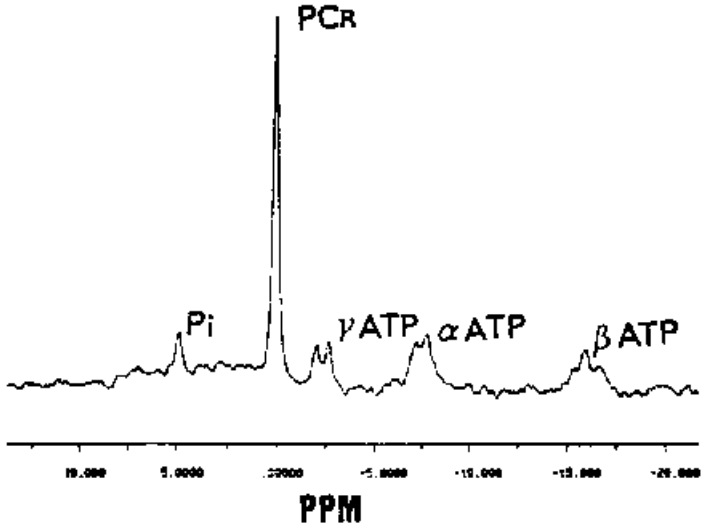


Figure 2b
31P-SPECTRUM OF TRAPEZIUS MUSCLE IN A FIBROMYALGIA PATIENT ON THE HORIZONTAL AXIS THE PEAK POSITIONS ARE GIVEN IN PPM (PARTS PER MILLION) RELATIVE TO THE POSITION OF THE PHOSPHOCREATINE PEAK




Calculations of peak area ratios Pi/β-ATP, Pi/PCr and PCr/β-ATP, as well as the pH were made (table 1b ). The ratios Pi/ßATP and Pi/PCr in the fibromyalgia patients were not significantly higher than the ratios in healthy controls, in fact these ratios were significantly lower (one tailed T-test $p<0.05$). There was no significant difference in the PCr to ßATP ratio, as well as the pH between the patient and control groups.

Table 1a

| | Patients (n=10) | Controls (n=6) |
|---|---|---|
| women/men | 9:1 | 5:1 |
| age (mean) | 37-47 (41.8) | 29-56 (43.2) |
| duration of complaints (years) | 1-11 (5.7) | - |
| number tender points | 3-13 (7.9) | - |

Table 1b

| | Patients | Controls |
|---|---|---|
| Pi/β-ATP | 0.29±0.11 | 0.39±0.09 |
| Pi/PCr | 0.14±0.03 | 0.21±0.02 |
| PCr/β-ATP | 2.01±0.68 | 2.07±0.23 |
| pH | 7.14±0.05 | 7.13±0.01 |

# Discussion

MR-Spectroscopy provides a non-invasive method of studying in vivo energy metabolism of intact muscle tissue.
It has been hypothesized by Bengtsson et al. that muscle tissue hypoxia may be of pathogenetic significance in patients with fibromyalgia syndrome. Muscle hypoxia will inevitably lead to alterations in the state of high energy phosphates, e.g. decreased levels of PCr and ATP, and an increase in the level of Pi.
If a marked change in metabolism of energy-rich phosphates in fibromyalgic muscle is present, 31P MR-Spectroscopy would be an appropriate method to detect such an alteration. The results of our study did not show a decrease in PCr and ATP or an increase in Pi in the trapezius muscle of the fibromyalgia group, compared with the trapezius muscle of healthy controls. However these results are in contrast with the findings of Bengtsson et al. We failed to show a significant decrease in high energy phosphate metabolites in trapezius muscle of fibromyalgia patients. The results of our study did not support the theory that a state of hypoxia causes the muscle complaints in fibromyalgia, providing an organic origin for the illness. Differences between our study and the study of Bengtsson et al. are that we did our measurements in a in vivo environment; chemical analysis is performed in vitro. We examined a greater volume of tissue (of the trapezius muscle) compared to the amount needed for chemical analysis.
The spectroscopy was performed in a resting state. Further research in this field should be done. As suggested by Kushmeric (15) a dynamic stress test may be needed to reveal any changes in muscle metabolism in fibromyalgia patients, because spectroscopy in a resting state might not be sufficient to reveal changes in muscle metabolism in a fibromyalgia patient. It is possible that in a resting state there is no alteration of metabolite content. However fibromyalgia patients in a resting state often do complain of pain and feelings of fatigue in their muscles, even when they have not performed any exercise beforehand.

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# Hormonal disturbances and related psychological factors in fibromyalgia

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# Introduction

The past years an increasing interest has emerged in the possible (neuro) hormonal disturbances in relation to the physical and emotional distress in patients with fibromyalgia. Yunus (1) acknowledged an aberration of the normal control mechanisms of pain as the central core of the problems in fibromyalgia syndrome. Disturbances in these control mechanisms can be divided into three levels. The first one is a functional deficiency of the inhibitory neurotransmitters at the spinal or supraspinal levels, like serotonin and norepinephrine. The second level can be recognized as the overactivity of excitatory neurotransmitters, like substance P. The third level is a hormonal dysfunction, like an abnormal hypothalamic-pituary-adrenal axis (see also chapter 2) (2-9). The different levels are not separated entities, but can very well influence one another, like for instance the role of serotonin in the hypothalamic-pituary-adrenal axis. It is known that serotonin stimulates the release of prolactin, and serotonin also has an influence on the level of substance P.
Neuroendocrinologic (hormonal) abnormalities have been described in patients with chronic pain (including fibromyalgia syndrome) and depressive symptoms. It is therefore interesting to study the possible relationship between these neuroendocrinologic abnormalities and psychological profiles in fibromyalgia syndrome.
The psychological reactions to the experience of stress are accompanied by other changes involving body state. These physiological responses appear to be dominated by activity in the autonomic nervous system and in various endocrine systems (10).
A key concept in discussing the psychological response to stress is that of "coping", and this owes much to the work of Lazarus (11). A person expe-riencing stress will remain in trouble unless and until he does something to remove the source of the problem, or reduce the distress experienced. What a person does to master the situation is commonly called coping. Coping may involve both cognitive and behavioral strategies.
Issues regarding control are especially important to health because there is extensive evidence suggesting that restrictions in control are often stress-inducing. Seligman (12) and his co-workers have systematically described the way that decreased control feelings and behaviors are associated with helplessness.
Etiology of disease have been linked to increased feelings of helplessness and lack of control (13).

# Patients and methods

Twenty female patients with fibromyalgia from the rheumatology outpatient clinic of the University Hospital of Groningen, the Netherlands, were invited to participate in this study. All patients fulfilled the 1990-ACR criteria of fibromyalgia.
All patients were tested with releasing hormones on two different days. The first day a TRH/LHRH-test (Thyrotropin Releasing Hormone/Lutein Releasing Hormone), another day a CRF/GRF-test (Corticotropin Releasing Factor/Growth Releasing Factor). Psychological test that were used were the Pijn Beheersings Vragenlijst (PBV), which gives information on the internal and external locus of pain control (14), and furthermore the State Anxiety Inventory (STAI) which is directed at the anxiety state and disposition (15).
The TRH/LHRH test was performed 10 days after the start of the menstruation in those women who were premenopausal.
The two hormone stress tests were performed under standardized circumstances. The participating women had fasted from 22.00h pm the foregoing day. The infusions were between 8.00h and 9.00h am. Blood samples were taken 15 minutes before the infusion (T=-15), just before the infusion (T=0), and 30, 60 and 120 minutes after the infusion (T=30, T=60, T=120). In the TRH/LHRH-test assessments of the levels of TSH, FT4, FT3, Prolactine, GH, FSH and LH were made. In the CRF/GRF-test levels of cortisol, ACTH, glucose and GH were assessed.
After the hormonal stress tests and the psychological tests the results of all the women were charted. To compare inter-individual variables relative intra-individual values are necessary (Qp, Ql, Qt) and these relative values give an indication of the change in the body. Next to an overview of these results a correlation analysis was performed to see if abnormal hormonal-stress-tests results correlated with scores of the psychological tests.

# Results

Mean age of the 20 women was 48.4 years (range 33-64 yrs; SD 6.8 yrs). Eleven of these twenty women were postmenopausal. Mean normal values of the hormonal stress tests are summarized, and also the number of abnormal tests in our patient group (tables 1 and 2 ).
One woman was excluded from further analysis because of a primary hypothyroidism. She had high basal TSH and high Qt, and also abnormal levels of FT4, FT3, QP, Ql and GH max.

Table 1
NORMAL VALUES HORMONAL STRESS TESTS

| | |
|---|---|
| TRH-test: | Basal TSH = 0.30 - 5.0 mE/l. After infusion it should rise with at least 4.0 mE/l. |
| | Qt(30) = (ΔTSH at 30 minutes/basal TSH) x 100% = between 500 and 909%. |
| | Basal Prl = < 700 mE/l. |
| | Qp(30) = (ΔPrl at 30 minutes/basal Prl) x 100% = between 147 and 625%. |
| | Basal GH = < 5.0 µg/l. Normal adults show no rise during TRH test. More than 50% above basal value is defined as abnormal.<br>Normal FT4 = 9.0 - 26.0 pmol/l.<br>Normal FT3 = 3.0 - 8.4 pmol/l. |
| LHRH test: | Ql(30) = (ΔLH at 30 minutes/basal LH) x 100% In premenopausaic women the range is 278-1428%. ΔLH at 30 minutes = 15- 65IE/l. Basal LH and FSH is beneath 11 IE/l in premenopausaic women and above 11IE/l in postmenopausaic ones. |
| CRF-test: | Basal cortisol is above 125 nmol/l. After infusion it should rise above 525 nmol/l.<br>Normal values after infusion = 592-732 nmol/l. Normal ACTH = 4.7 -70 pg/l.<br>Users of oral contraceptivum show values between 87 -120 pg/l. |
| GRF-test: | GH should exceed 5.0 µg/l after infusion. |

Two women had scores within the psychiatric range on the STAI (state and trait), one woman had only a very high score on the trait score, but a relatively low score on the state score. The outcomes on the PBV showed similar results like those described in the study group of Linssen, a group of 23 chronic low back pain patients (14). Correlation analysis showed no significant correlation between the physiological test results and the psychological test result (table 3 ). These results were based on the parameters of 16 patients; 1 patient was excluded because of a primary hypothyroidism and from three other women the pshychological questionnaires were not completed and could therefor not be used in the analysis.

Table 2
ABNORMAL TESTS IN 20 FEMALE PATIENTS

| Pat.nr | Qt | Qp | FT4 | FT3 | menopause | Ql | Cbas | Cmax | GHmmax |
|---|---|---|---|---|---|---|---|---|---|
| 1 | | | | | + | | | | |
| 2 | ↓ | ↑ | ↓ | ↓ | | ↓ | | | ↓ |
| 3 | | | | | | ↓ | | | |
| 4 | | ↑ | | | + | | | | |
| 5 | ↑↑ | | | ↓↓ | | | | | ↓ |
| 6 | | | | | + | | | | ↓ |
| 7 | ↑ | | | | | ↓ | | | |
| 8 | | ↑ | | | + | | | | |
| 9 | | ↑ | | | + | | | | ↓ |
| 10 | | ↑ | | | | | | | ↓ |
| 11 | ↑ | | | | | | | | |
| 12 | | ↑ | | | + | | | | ↓ |
| 13 | ↑ | ↑ | | | + | | | | |
| 14 | | ↑ | | | + | ↓ | ↓ | ↓ | |
| 15 | | | | | + | | | | |
| 16 | | ↑ | | | + | | | | |
| 17 | | ↑↑ | | | | ↓ | | ↓ | |
| 18 | ↑ | | | | + | | | | |
| 19 | ↑ | | | | | | | | |
| 20 | ↑ | | | | | | | | |

Patient 2 had a hypofunction of the thyroid gland Qt, Qp, Ql see table 1.
Cbas and Cmax: basal cortisol, and maximum level of cortisol after CRF injection
GHmax is maximum GH in CRF/GRF test.

Table 3
CORRELATION ANALYSIS BETWEEN HORMONAL AND PSYCHOLOGICAL TEST RESULTS
(* : P<0.001)

| | QT30 | QP30 | QL30 | GHMAX | STAISTA | STAIDIS | PBVI | PBVE |
|---|---|---|---|---|---|---|---|---|
| QT30 | 1.00 | -0.31 | 0.35 | 0.58 | -0.39 | -0.37 | 0.58 | -0.08 |
| QP30 | | 1.00 | 0.01 | -0.37 | -0.04 | 0.30 | 0.03 | -0.04 |
| QL30 | | | 1.00 | 0.05 | -0.38 | 0.36 | 0.04 | 0.17 |
| GHMAX | | | | 1.00 | 0.52 | 0.30 | -0.17 | -0.15 |
| STAISTA | | | | | 1.00 | 0.83* | -0.12 | 0.12 |
| STAIDIS | | | | | | 1.00 | 0.03 | -0.04 |
| PBVI | | | | | | | 1.00 | -0.32 |
| PBVE | | | | | | | | 1.00 |

# Discussion

Our study was performed without a control group. However the test results were compared with mean values of reference groups. These tests have been validated. In future studies control groups with chronic pain and a healthy control group should be included, next to the inclusion of placebo "hormonal-stress test". The response of the pituary organ was measured after hypothalamic releasing hormone was infused. Basal hormonal values and rise of hormonal levels of the pituary were assessed, but also hormonal values of the effector-organs, like thyroid gland, adrenal glands and the gonads. Basal values depend on the stimulation of the hypothalamus, feedback from the effector-hormones and the magnitude of the pituary (quantity of producing cells). Of course a combination of these mentioned factors can also change basal values.
The increase in serum TSH concentration, which was induced by TRH, seems to correlate with basal serum TSH concentration. So a low basal level predicts a lesser absolute response and the relative rise is within close limits the same (approximately 10 times basal level). Seven patients had an increased response in TSH after TRH injection. In the study of Ferraccioli (2) a blunted TSH response is reported after TRH injection, and also in the study of Neeck (5).
The only woman with an abnormal FT4, and low response in TSH after TRH injection, was excluded from this study, because she was found to have a primary hypothyroidism.
The basal levels of prolactine (PRL) were low. All testpersons reached their maximum at 30 minutes after the infusion. In two persons also an assessment was made after 15 minutes and at this point there was an even higher PRL-response. It is possible that this has been the case in other patients as well, but we do not have those results. Our results showed that some patients had a hyperprolactinemic response, and

others showed a high-normal response, at 30 minutes. Ferraccioli and Neeck found similar results (2,5).
GH in the TRH/LHRH test was more than 50% over basal level in one woman. In this woman however two times a venapunction was needed to obtain blood and this can cause a rise in GH after 30 minutes and is thought to be caused by physical injury. On the other hand a rise in GH may follow emotional stressors. The levels of GH in the CRF/GRF test showed different types of reaction. In one third of the women an explosive reaction was found, in one third a normal reaction and the last third seemed not to react.
The LH level showed an attenuated response in 3 of the 8 premenopausal women (the woman with hypothyroidism was excluded). One of the 11 postmenoupausal women showed a too low basal level of LH and LH response, with normal oestradiol and FSH.
One of the women had a too low basal level of cortisol, without elevated values of ACTH. After infusion she did not reach normal levels of cortisol, while ACTH was reacting normal. This could be suggestive of hypothalamic hypocortisolism. Still another woman also did not reach normal levels of cortisol after infusion, but she did have a normal basal level of cortisol and ACTH and normally reacting ACTH levels on CRF-infusion.
The results of the STAI showed a normal distribution. The means of the outcomes of the PBV showed no abnormalities. Both internal and external scores had a large variation.
There was no correlation between psychological stress-scores and the hormonal stress scores (physiological outcomes). Our results showed a wide variation in the various abnormal hormonal stress-scores, so it is very unlikely to find any correlation between the results of the stress-tests and psychological test scores in a limited number of patients as in our study.
However evaluating the different hormonal testresults, there are many abnormal values. In the TRH/LHRH test aberrant high response of TSH and PRL was seen in 79% of the participating women with fibromyalgia, together with abnormal low basal LH or abnormal low response of LH in 26%.
In the CRF/GRF test abnormal low basal cortisol and too little response of cortisol in 11% of the women was seen, and 26% showed abnormal low response of GH.
These results also could be found in people who live under stressful circumstances, either acute or chronic. Disorders of the hypothalamic-pituary system, like in anorexia nervosa, could also cause similar results.
A direct relationship with psychological stress is very difficult to assess; in any way we could not find correlations between the physiological and psychological stress scores used in this study. We agree however with the conclusions of recent publications (16,17) where the possibility of neurohormonal abnormalities in fibromyalgia is acknowledged, but that this knowledge does not imply that these abnormalities are a

causative factor in developing fibromyalgic complaints. We have to be very careful not to run in a blind wall, thinking that the answer to the puzzle of the fibromyalgia will be found in the finding of neurohormonal abnormalities. The relation with stress is very important, but this field needs further exploring. There is no simple "cure" for the patient suffering from fibromyalgic complaints, and we can not expect this will come. The existence of chronic pain is part of our today's world. We should focus all our attention to "care" and learn patients to cope efficiently with bodily and psychological complaints.

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# Weather conditions and complaints in fibromyalgia

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J Rheumatol 1993;20:1932-1934

# Abstract

Patients with musculoskeletal disorders, including fibromyalgia, often state that weather conditions modulate their complaints. There have been a few studies concerning this issue, but the results appear to be contradictory. We tried to relate the subjective symptoms of pain, stiffness, sleep and mood in fibromyalgia patients, to objective meteorological factors. Correlation analyses did showed no relation between the subjective complaints and the meteorological factors. The symptoms pain, stiffness and fatigue, however, showed a strong intercorrelation.

# Introduction

It is often said by fibromyalgia patients, as well as by patients with rheumatoid arthritis (RA), that certain weather conditions worsen their musculoskeletal complaints.
The effect of weather conditions on rheumatic patients has been studied incidently (1-7), but the results have been contradictory. An objective study for weather influences in fibromyalgia patients has thus far not been reported. We tried to relate the subjective symptoms of pain, stiffness, sleep and mood to objective meteorological factors.

# Patients and methods

As part of a larger study conducted at the University Hospital of Groningen on psychosocial factors in fibromyalgia syndrome and the effects of a combined treatment program of psychomotor therapy and marital counselling, fifty patients with fibromyalgia, according to the criteria of Yunus (8), were randomly selected from the outpatient clinic of rheumatology of the University Hospital of Groningen. At the start of our program the 1990 criteria study of Wolfe et al. (10) was not yet published, therefore our patients could not be selected by these latest criteria.
The fifty patients were asked to fill out a diary once a week during the period they participated in the therapy program. Therapy sessions were held with an interval of about one month, 10 times in total. During this time period patients filled out a diary once a week to compare every Wednesday at 12:00 noon. Wednesday was chosen as an average weekday. Patients had to fill out Numerical Rating Scales (NRS), ranging from 0-9, on 4 items: pain, stiffness, fatigue, and mood. In the first three items the score ranged from 0 (no problems) up to 9 (worst possible). For the item "mood" the score was the other way around: 0 for low mood, and 9 for high mood. Once a month the patients had to turn in their diary-forms.
Meteorological factors were sampled from weekly reports of the Royal Dutch Meteo-

rological Institute at Airport Eelde, which covered the living area of the participating patients, and included mean temperature (24 h; 150 cm; in degrees Celsius), mean vapour pressure (24 h; in mbar), mean relative humidity (24 h; in percentages), mean atmospheric pressure (24 h; sealevel; in mbar), mean wind speed(force) (24 h; m/s), mean cloud cover (24 h; in octal system), and rainfall (sum of 24 h; in mm). Meteorological factors from all wednesdays, and 2 preceding and successive weekdays were considered to determine wether there was a correlation between the mean scores of pain, fatigue, stiffness and mood of the total group and meteorological factors in the direct past, the present and the direct future.
The patients in this study were not informed of the aim of the study.
The 50 patients were followed over two different time periods: 25 patients from September, 1989 to April, 1990, and the other 25 patients from September, 1990 to April, 1991. The results of the 89/90 group were compared with the result of the 90/91 group. Thus the second group was a replicate study of the first group.
Analysis of the data was made by SSPS-X Pearson correlation coefficients. Results were considered significant if the correlation was significant in both groups ($p<0.05$), thus yielding an overall significance of $(0.05)^2=0.0025$.

# Results

Mean age of the group of 50 patients was 41.9 year (22-59 years). The group consisted of 45 women and 5 men. Before the start of the treatment program, 80% (n=40) of the patients had a history of indicating that weather factors influenced their symptoms of fibromyalgia. In most cases it was rain or dampness, combined with cold that exerted a negative influence. It was also frequently reported that climatic changes from fair to rainy weather negatively influenced pain. Comparing with 25 patients with RA (matched for age and sex), who were asked the same questions, 44% (11 patients with RA) said that there were influences of weather factors.
From 50 patients we obtained 32 diaries (16 of either group), which could be used for analysis.
Seventeen patients dropped out of the study, because they did not finish the combined psychomotor and marital counselling treatment program. Of these dropouts, 7 patients gave reasons that were related to the treatment program, 10 patients gave other reasons, related to their physical condition or to personal circumstances. One patient had not understood the instructions correctly, so his diary was not reliable and was omitted from further analysis. The other 32 patients finished the treatment program and filled out their diaries weekly.
In 27 (mean age 43.2 yr, 24 female, 3 male) out of the remaining 32 patients there was a history of weather influencing their complaints.
The mean painscore, measured on Wednesdays at noon for these 27 patients ranged from 4.1 to 6.1.

The means and ranges of the meteorological data are given in table 1 .
Correlation analyses of these 27 patients showed no significant relation between meteorological factors and the mean pain scores (table 2 and table 3 ). The correlation analysis between meteorological factors and the mean scores on stiffness, fatigue and mood also showed no significant relation. Comparison between the mean scores on pain, stiffness and fatigue yielded strong intercorrelations between these variables (table 4 and table 5 ).

Table 1
MEANS AND RANGES OF THE METEOROLOGICAL FACTORS (89/90 AND 90/91)

| | ranges | means |
|---|---|---|
| windspeed (m/s) | 1-24 | 9.6 |
| mean temperature ( °C) | -9-15 | 6.2 |
| relative humidity (%) | 69-99 | 89.8 |
| rainfall (mm) | 0-22 | 2.1 |
| atmospheric pressure (mbar) | 983-1041 | 1014.2 |
| cloud cover (0-8) | 0-8 | 5.5 |

Table 2
CORRELATIONS BETWEEN MEAN PAINSCORES AND METEOROLOGICAL FACTORS IN 89/90

| | ws-1 | ws0 | ws+1 | mt-1 | mt0 | mt+1 | rh-1 | rh0 | rh+1 | rf-1 | rf0 | rf+1 | ap-1 | ap0 | ap+1 | cc-1 | cc0 | cc+1 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| pain | 0.36 | 0.51 | 0.67 | -0.14 | 0.08 | 0.06 | -0.04 | 0.16 | 0.05 | 0.21 | 0.33 | 0.34 | -0.25 | -0.26 | -0.20 | 0.34 | 0.42 | 0.12 |
| p<.. | 0.04 | 0.01 | 0.00 | 0.27 | 0.35 | 0.39 | 0.43 | 0.22 | 0.41 | 0.17 | 0.06 | 0.05 | 0.12 | 0.11 | 0.17 | 0.05 | 0.02 | 0.29 |

ws = windspeed, mt = mean temperature, rh = relative humidity, rf = rainfall, ap = atmospheric pressure, cc = cloud cover. -1 = 1 day before day of painscore, 0 = day of painscore, +1 = day after day of painscore.

Table 3
CORRELATION BETWEEN MEAN PAINSCORES AND METEOROLOGICAL FACTORS IN 90/91

| | ws-1 | ws0 | ws+1 | mt-1 | mt0 | mt+1 | rh-1 | rh0 | rh+1 | rf-1 | rf0 | rf+1 | ap-1 | ap0 | ap+1 | cc-1 | cc0 | cc+1 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| pain | -0.03 | -0.06 | -0.01 | -0.18 | -0.29 | -0.28 | -0.08 | -0.19 | 0.00 | 0.09 | -0.06 | -0.04 | 0.15 | 0.08 | -0.10 | -0.16 | -0.26 | 0.06 |
| p<.. | 0.44 | 0.38 | 0.48 | 0.17 | 0.06 | 0.07 | 0.33 | 0.15 | 0.49 | 0.32 | 0.37 | 0.41 | 0.21 | 0.34 | 0.30 | 0.19 | 0.08 | 0.39 |

ws = windspeed, mt = mean temperature, rh = relative humidity, rf = rainfall, ap = atmospheric pressure, cc = cloud cover. -1 = 1 day before day of painscore, 0 = day of painscore, +1 = day after day of painscore.

Table 4
CORRELATION ANALYSIS BETWEEN SUBJECTIVE SYMPTOMS YEAR 89/90

| Group 89/90 | Pain | Mood | Stiffness | Fatigue |
|---|---|---|---|---|
| Pain (mean NRS) | | 0.22 p=0.15 | 0.85* p<0.01 | 0.74* p<0.01 |
| Mood (mean NRS) | | | 0.08 p=0.35 | 0.18 p=0.20 |
| Stiffness (mean NRS) | | | | 0.77* p<0.01 |
| Fatigue (mean NRS) | | | | |

* = p<0.05

Table 5
CORRELATION ANALYSIS BETWEEN SUBJECTIVE SYMPTOMS YEAR 90/91

| Group 90/91 | Pain | Mood | Stiffness | Fatigue |
|---|---|---|---|---|
| Pain (mean NRS) | | -0.17 p=0.18 | 0.70* p<0.01 | 0.35* p=0.03 |
| Mood (mean NRS) | | | 0.15 p=0.22 | -0.63* p<0.01 |
| Stiffness (mean NRS) | | | | 0.26 p=0.08 |
| Fatigue (mean NRS) | | | | |

* = p<0.05

# Discussion

There have been few studies concerning the influence of weather factors on joint complaints. They did not agree on all points, and study-designs differed. Edstrom (1) showed that arthritic patients improved by staying in a climate chamber with constant warm temperature and moderate humidity. In this study no variations in temperature or humidity were studied. Hollander (2), however, designed a controlled climate chamber where the effects of climatic variations on rheumatic patients could be studied objectively. Especially the simultaneous variations of humidity and barometric pressure. From the results it appeared that rising the humidity combined with a fall of barometric pressure, gave a significant subjective and objective worsening of arthritis.

Rose (3) found slightly, but significantly higher incidence of rheumatic exacerbations after rain, and also before high humidity in patients with rheumatic complaints in Kent, Great Britain.

A prospective study was performed by Nyberg and Nyberg (4) in 1984. They asked 25 patients with rheumatic complaints (including 6 patients with joint or muscular pain unaccompanied by objective findings), who complained that their symptoms varied in relation to forthcoming weather changes, enabling them to forecast the weather. The predictions made by the patients were in fact not better than chance.

Patberg et al. (5) found that pain in patients with RA associates positively with temperature and with vapour pressure, negatively with relative humidity, whereas no relation was found with the solar irradiation, atmospheric pressure, and wind speed. In the report of Sibley (6) no significant correlations were found between symptoms of any patient group or individual and any included weather variable examined. In this study patients with RA and patients with osteoarthritis (OA) were included.

As has been indicated by several authors, fibromyalgia patients tend to say that a change of weather conditions does aggravate their pain (8-10). In fact this has been one of the minor criteria of Yunus et al. (8). Of 50 consecutive patients diagnosed as having primary fibromyalgia, 92% reported aggravation of their symptoms with cold or humid weather (8). In an evaluation of symptom frequency in 291 rheumatic patients and 58 healthy individuals, Wolfe et al. (9) found a history of weather influence on pain in 57% (of 155) fibromyalgia patients, in 43% (of 51) patients with RA, in 54% (of 37) patients with OA, in 38% (of 48) patients with low back pain, and in 3% (of 58) healthy controls there was a positive history of weather conditions influencing pain complaints. In the 1990 criteria study of Wolfe et al. (10) the sensitivity of the symptom pain influenced by weather change was 66.1% and the specificity 53.8%, with an accuracy of 60.3%.

Guedj et al. (7) wanted to re-evaluate the effect of weather conditions on patients with various rheumatic diseases including fibromyalgia. They conducted a prospective study in patients with RA, with other forms of inflammatory arthritis, with osteo-arthritis and with fibromyalgia. The authors did not state the selected patients were aware of the aim of the study, which may well have an influence on study-outcome. Eight of 11 fibromyalgia patients reported that a change in one or more of the weather conditions changed their pain-score. When the association between pain and meteorological variable was examined with discriminant analysis it appeared that pain in fibromyalgia was associated with barometric pressure only. Until now no study has been reported which described the effect of weather conditions in the fibromyalgia syndrome. In our study, where we examined subjective complaints compared with objective meteorological factors, we were not able to confirm the hypothesis that weather influences pain and other complaints in fibromyalgia patients. However 80% of our fibromyalgia patients stated that there was such an influence.

An explanation for this discrepancy can be found in the attribution theories (11). As

suggested by Nyberg (4) patients with pain may feel less helpless if they can relate their pain to some external condition, i.e., the weather, thus justifying it.
We must also bear in mind that this patient-group was treated during the observation period, which may have influenced the study-outcome. However, no positive effect was found on the level of pain, as measured with visual analogue scales before and after treatment.
Another complicating factor is that our study was carried out in a marine climate, where ranges in meteorological factors are small (e.g. temperature). The study was carried out in the winter-spring period, so the range of the meteorological factors is smaller than when a complete year had been used as a time period. These two factors may have led to a restriction of range, which may have lowered the correlations (12).
We found a strong intercorrelation between the symptoms pain, stiffness and fatigue. In the fibromyalgia syndrome these subjective complaints are indeed related to each other, and it may be difficult for the patient to discriminate between the different symptoms.

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# Role and consistency of tender points in fibromyalgia

## A review in literature compared with a recent clinical study

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# Introduction

A certain number of tender points is one of the major clinical findings for diagnosing the fibromyalgia syndrome. Smythe was the first in the recent literature, in 1972 (1) who pointed out that the presence of so called tender points was a diagnostic criterion for fibrositis/fibromyalgia. According to Smythe (1) local tenderness at palpation at 12 of 14 specified sites had to be present in case of fibromyalgia. Over the years there have been different sets of tender points proposed that should be required for the diagnosis fibromyalgia, and also different ideas on the examination and interpretation of tender points are put forward in the literature. In our own study we used the tender point count described by Smythe. Our study started before 1990 and therefore we could not use the tender point count of the 1990 criteria study for classification of fibromyalgia (2).

We were interested in the consistency of the total number and localization of the tender points in the fibromyalgia patient during time. Furthermore we will discuss different aspects regarding tender points, like mode of examination and identification of tender points, the concept of tender points in relation to fibromyalgia and other diagnoses, reliability of tender points and the value of tender point counts as therapy outcome variable.

# Patients and methods

As part of a larger study (chapter 14) we studied the consistency of tender points in 50 fibromyalgia patients in time. These patients were selected according to the criteria of Yunus (3) from the University outpatient clinic of rheumatology in Groningen, the Netherlands. Assessments were made at baseline (T=0), 9 months later (T=1) and 15 months after the baseline assessment (T=2). At each visit the individual tender point score was charted.

Fourteen tender points were examined, next to three control points, performed in all cases by the same investigator. Tender points (according to Smythe) were scored from 0-4, with 0=normal, no pain 1=sensitive or tender, but not painful, 2=painful, with or without light grimacing or flinching, 3=painful with marked flinch or jerking or withdrawal, 4=unrealistic response to or even before touching. Examination of the tender and control points was made by direct palpation with the index finger. A tender (and control) point was scored positive with a score of 2 or higher. Comparison of the mean tender point of the patient group was made at T=0, T=1 and T=2. Next to this, comparison of number of tender points at the three assessments in each patient was made, and the consistency of each individual tender point pro patient in the control group was analyzed. (Chi square for 2x2 contingency tables).

# Results

Our patient group in this study consisted of 45 women and 5 men, mean age was 42.6 years. Mean number of tender points at the three assessments made for the total patient group did not differ significantly. In our study group the intra-individual number of tender points did not change significantly (table 1 ).

Table 1
CORRELATION N TENDER CONTROL GROUP $T_0$, $T_1$, $T_2$

| | n tender $T_0$ | n tender $T_1$ | n tender $T_2$ |
|---|---|---|---|
| n tender $T_0$ | 1.000<br>(49 pts) | 0.5453<br>(49 pts)<br>p=0.000 | 0.5415<br>(45 pts)<br>p=0.000 |
| n tender $T_1$ | | 1.000<br>(50 pts) | 0.4633<br>(46 pts)<br>p=0.001 |
| n tender $T_2$ | | | 1.000<br>(46 pts) |

The score of each individual tender point (positive vs negative) pro patient was highly consistent in the control group as well (statistical significant $p<0.001$) (table 2 ).
Comparison of the Campbell Questionnaire with outcome "possible fibrositis" (4) and number of tender points was made. There was no statistic significant difference in mean tender point score between the patients who scored as "possible fibrositis" on the Campbell questionnaire and the patients that did not. Fifty percent of the fibromyalgia patients had an outcome of "possible fibrositis" on the Campbell Questionnaire.
Patients with a high number of tender points had significantly more positive control points. There was also a positive correlation between the number of tender points and VAS-score of pain for the total patient group.
Men had fewer tender points than women (6.5 vs 9.4, $p<0.005$). However no statistical significant difference was found in the VAS-scores of pain between men and women.

Table 2
CONSISTENCY OF TENDER POINTS IN CONTROL GROUP (14 POINTS)
NO = SCORE 0 OR 1 AT PALPATION OF TENDER POINTS LOCALISATION
YES = SCORE 2 OR 3 AT PALPATION OF TENDER POINTS LOCALISATION

| score at $T_1$<br>score at $T_0$ | NO | YES |
|---|---|---|
| NO | 124 | 83 |

| | | |
|---|---|---|
| YES | 113 | 370 |
| $\chi^2 = 84.0$, significant $p<0.001$ | | |

| score at $T_2$ / score at $T_0$ | NO | YES |
|---|---|---|
| NO | 101 | 92 |
| YES | 108 | 342 |
| $\chi^2 = 48.2$, significant $p<0.001$ | | |

# Discussion

Tender points have become more and more a topic and subject of research in the studies on the fibromyalgia syndrome. From these studies different aspects concerning the tender points can be distillated. One aspect is the mode of examination and identification of positive tender points (2,4,5,6,7). Finding a certain number of tender points during physical examination is a crucial point in classifying a chronic pain patient with wide spread pain as a fibromyalgia patient. Identifying a tender point by palpation, however, is not uniformly performed and not uniformly scored. In the study by Campbell et al. (4) a tender point was considered positive at dolorimeter pressures of less than 4 kg/1.54 $cm^2$. In the study by Wolfe et al. (2) a tender point is scored as positive when the patient on palpation indicates he or she is experiencing pain. This can be just a verbal expression of pain. Tenderness alone is not enough to make a score as a tender point. We used the same turning point in considering a localized area on palpation as a positive tender point or not, with the discrimination of tenderness and pain on palpation. In the study by Wolfe and Cathey (5) a tender point was considered positive when there was an exaggerated tenderness to palpation. Mode and force of palpation were not specified, but palpation was in all cases performed by the same examiner. Positive tenderness (positive tender point) in the study of Cott et al. (6) was defined as either a reflexive withdrawal, verbal report of pain, or both. Cott et al. found that the examination with dolorimetry showed fewer tender points than examination with hand palpation, which they thought is due to a greater force used in hand palpation. Hand palpation and dolorimetry may provide different measures of tenderness and should thus not be used interchangeable in identifying tender points in patients with fibromyalgia. Prescott et al. (7) found in a group of persons who met screening criteria for fibromyalgia (as part of a national health interview survey) that there was a significant increase in pain index with more tender points. The 18 tender points sites as defined by the ACR-1990 were used and a tender point was scored positive with at least a spontaneous verbal response, or flinch or grimace to palpation pressure of approximately 4 kg.

Comparing these different studies positive tenderness is scored differently. A verbal report of pain alone, without any physical sign, is not always considered as a positive tender point in all studies. There is no generally accepted definition when a tender point on palpation should be scored as a positive tender point.

Another very important aspect in the studies on tender points is the concept of tender points, especially in relation to fibromyalgia and compared with other diagnoses (8,5,9-18,4,19-24,26,27). Smythe (8) reviewed the past literature on the subject of tender points and already postulated at this time that an altered pain modulation, caused by biochemical factors like neurotransmitters, might play a very important role in the pathogenesis of the fibromyalgia syndrome. Wolfe and Cathey (5) did a prospective study of 1520 patients regarding the epidemiology of tender points. These patients were consecutive patients seen at an outpatient rheumatology clinic and had different rheumatic diagnoses, most frequently rheumatoid arthritis and osteoarthritis, but also nonspecific arthralgias and low back pain syndromes. Fourteen tender points, as described by Smythe (1) were examined in all these patients. They found in only 40% of all patients local tenderness, a high number of tender points was rare, women had more tender points than men, and they found more tender points with increase of age. Caucasians had more tender points than blacks or Hispanics. Correlation between tender points and other clinical data obtained was poor. There was no clinical significant association between the most common diagnoses and the number of tender points. It is not quite clear if in this group of 1520 patients a fibrositis/fibromyalgia group was identified. In 13.6% there were 7 or more tender points and in 4.3% there were 12 or more tender points.

Croft et al. (9) reported on a population study of tender point counts and pain as evidence of fibromyalgia. The population under study consisted of two general practices in England and study design was a two stage cross sectional study and study subjects were selected according to a stratified random sample. An initial questionnaire about pain classified those who could be invited for an examination of tender points. Pain, as assessed with the questionnaire was categorised into three groups (chronic widespread pain, regional pain and no pain). From all three groups persons were invited to have an interview and examination of tender points. Measures of depression, fatigue and sleep were also obtained. Their results showed that women had higher mean tender point count than men. Tender point counts were higher in those who reported pain than in those who did not report pain, and in the group with widespread pain higher than in the regional pain group. In the widespread pain group most persons did not have 11 or more tender points. They even found persons with 11 or more tender points in the no pain group. Mean symptom scores for depression, fatigue and sleep problems increased with higher tender point scores, and this finding was independent of pain complaints. These results made the authors conclude that tender points are a measure of general distress, and that they are related to pain complaints, but are separately associated with fatigue and depression. The relation

between sleep disturbance and tender point counts, even in persons with no pain, is explained by the authors by the idea that poor sleep give rise to tender points. Furthermore the authors state that high tender point counts do not define a distinct disease entity in the general population and the combination of chronic widespread pain and high tender point counts seem to be more like one end of a spectrum of pain status and tender point counts rather than a distinct entity.

Tenderness in 75 (unilateral) anatomic sites was studied by Simms et al. (10) to see if distinction between fibromyalgia patients and controls was possible. They saw 10 fibromyalgia patients and 10 healthy control persons. In the 75 sites examined were all the tender points included described by Smythe in 1972 (1), Yunus in 1981 (3) and Campbell (4) in 1983. The costochondral junction at C2 was left out, because of the overlap with two other points which were examined, namely costochondral junctions C1 and C3. The amount of pressure required with a dolorimeter to elicit intolerance was recorded in all 75 sites in the 20 subjects. The scale length went up to 6.0 kg/cm2. For each of the 75 sites a mean score was computed for the fibromyalgia patients and for controls, and these were compared by an unpaired T-test. Mean total tenderness scores were also compared. There were 19 sites that best distinguished fibromyalgia patients from controls, but only 2 of these 19 sites were earlier described tender points. The authors found that 15 of these 19 points were clustered in 4 regions, anterior shoulder, anterior chest, posterior scapula and medial knee. So they suggest it might be more useful to examine specific regions than the exact anatomic sites within these regions. The mean dolorimeter scores of all 75 sites were lower for fibromyalgia patients, but they did not conclude that in fibromyalgia there is a generally lowered pain threshold, as other investigators in later publications did. Simms et al. found a number of sites that had similar degrees of tenderness in both patients and controls, so they tend to say that fibromyalgia patients are tender at specific musculoskeletal sites. This last remark would make the distinction between fibromyalgia patients and patients who have psychogenic rheumatism (which is not nearer defined) and patients who are tender all over (not nearer defined as well).

Wolfe et al. (11) compared three sets of diagnostic criteria in three different centres. Patients included in the study were sent a questionnaire, based on the questionnaire of Campbell. Next to fibromyalgia patients also patients with rheumatoid arthritis, osteoarthritis, and low back pain participated and a control group of normal individuals. It appeared that the tender point count best separated patients with fibromyalgia from patients without fibromyalgia. No combination of questions and tender point count did better than the tender point count alone. Campbell's outcome "possible fibrositis" was met in 43% of the fibromyalgia group and in 0% of the control group. In our study group 50% of the fibromyalgia group had an outcome score of "possible fibrositis".

In another study by Wolfe et al. (12) the study object was to elucidate the distinction between trigger points in myofascial pain syndromes and tender points in

fibromyalgia. A trigger point can be defined as focal muscle tenderness which is elicited by palpation and then results in referred pain that reproduces the patient's pain problem or pain complaint. Latent trigger points do not cause a clinical complaint of pain, but when compressed can reproduce its referred pain pattern. Tender points are specific discrete areas over muscle, bone, tendon and fat that are painful to palpating pressure. To study the relationship of the two syndromes and their examinations 4 experts on myofascial pain syndromes and 4 experts on fibromyalgia studied 8 patients with myofascial pain syndrome, 7 patients with fibromyalgia and 8 healthy controls. The examinations were blinded, using standard and predefined definitions. The authors concluded that defining what a trigger point is, is an essential condition, as well as the identification of examination findings. The proportion of patients with trigger points was highly dependent on the definition of trigger point used. On the whole the examination performed by the rheumatologists and MFP experts differed and therefore the authors say that reports regarding musculoskeletal findings may be subject to variation based on the training and type of examination performed, and that reports in the literature may not be directly comparable.

The number of tender points found during physical examination is related to the total number of areas that are palpated by the examiner. It makes of course a difference if only 14 points are regarded, or that a total of 50 points are regarded. A percentage of positive tender points in relation to the total number of spots examined would be an indicator in classifying a patient as a fibromyalgia patient.

Several studies mention the difference between total number of tender points in fibromyalgia patients and other patients, mostly patients with rheumatoid arthritis. We found significantly less tender points in an age and sex matched group of patients with rheumatoid arthritis compared with our fibromyalgia group (2.7 vs 9.1), see chapter 12.

In an earlier study by Leavitt (13) in which he compared pain properties in fibromyalgia patients and rheumatoid arthritis patients, there was also a lower number of tender points in the RA group. However RA-patients with more than 4 tender points were excluded from Leavitt's study, and in the fibromyalgia group the patients had to have at least 4 tender points. Leavitt's patients were hospitalized. These differences in Leavitt's study design and our study design makes it impossible to compare the study outcomes on the tender point count in RA patients and fibromyalgia patients.

Granges et al. (14) published data about pressure pain thresholds in pain-free subjects, in patients with chronic regional pain syndromes, and in patients with fibromyalgia syndrome. They assessed 18 tender points and 4 control points in 60 patients of each of the three groups. Prior to their study they hypothesized that fibromyalgia is a disorder of pain modulation and that a change in pain threshold to pressure reflects a generalized change in the pain system affecting both tender and control points. And indeed they found a significant correlation between myalgia scores at tender points

and control points in the subjects of their study. In pain-free subjects they also found lower thresholds of pain to pressure in the tender point areas as in the control areas. With generalized lowering of the pain threshold these tender point areas become more tender and are than recognized as abnormally tender and are called a tender point. In another study by Granges (15), he reported again on pain threshold to pressure, this time in fibromyalgia patients and in pain free controls, one group of normal pain free controls and one group of exercising pain free controls. Pain threshold was significantly lower in fibromyalgia group than in the control group. Fit controls had significantly higher total myalgic scores, also on the control sites, as the unfit controls. The total myalgic score was defined as the sum of the amount of pressure required to elicit pain in the used tender points and control points. How higher the score, how more pressure was needed to elicit pain. Skinfold tenderness of the back was present in 95% of the fibromyalgia patients, in 33% of the unfit controls and was absent in the fit controls. Here again Granges underlines his hypothesis of increased multifocal tenderness to pressure and of decreased pain tolerance to pressure in fibromyalgia. He found a continuum in total myalgic scores, as a measure of pain threshold, between the lowest (fibromyalgia group) and the highest (fit controls), and the unfit controls had intermediate values. Granges stated that localized pain could not have resulted in these findings, because the same continuum appeared when comparing the values of the control points of pain free persons. Smythe (16,17) studied the relation between fibrositic and control site tenderness. They used different dolorimeters with different sizes of footplates. The dolorimeter should have an adequate length of scale. Dolorimeters with a limited scale fail to assess variations in thresholds at non-tender sites. Smythe and coworkers compared two dolorimeters with different scale and footplates. The results with the two instruments were not equal. The instrument with the larger scale and smaller diameter of footplate gave lower readings at tender sites and higher values at non-tender sites. Thresholds at fibrositic and control sites were significantly correlated and the authors see this as evidence of generally acting factors affecting tenderness.
The size of the footplate made less difference to the measured threshold than expected. In their study they found a strong relationship between control and fibrositic site tenderness. The control thresholds were twice as high as the fibrositic sites. They also looked into the relationship between the size of the footplate and the measured threshold of tenderness, and at the effect of scale length on statistical inferences. Twenty patients with a variety of rheumatic diseases participated, as well as 1 healthy person. This group of patients represented a subgroup of patients with tenderness into the range associated with fibromyalgia, a subgroup into the non-tender rang and a subgroup with intermediate values. Two control and 2 fibrositic sites were measured in each person. Their results support the correlated-control model, in which control site tenderness varies with fibrositic tenderness. Our findings with high number of tender points combined with positive control points also makes sense in the light of

the correlated-control model. One could say that our results are also indicative of the existence of generally acting factors affecting tenderness in fibromyalgia syndrome. In a study of Arroyo (18), using electrocutaneous stimulation, is also reported on disturbed central nociceptive mechanisms in the pathogenesis of fibromyalgia, where they found no differences in perception thresholds in the upper limbs of fibromyalgia patients and healthy controls, but did find a reduction in pain tolerance accompanied by spread and persistence of dysesthesia. Campbell et al. (4) found a high predicting value for the presence of multiple tender points when the questionnaire indicated possible fibrositis. In our Dutch fibromyalgia population using a translated questionnaire we could not confirm these findings. The Campbell questionnaire is a rough screening method with many false negative outcomes. The sensitivity of the questionnaire is low. Campbell demonstrated that the "fibrositis" patient had not a generally diminished pain threshold and tolerance, because similar results with the dolorimeter were found over control points in both "fibrositis" and control patients. Mikkelsson (19) studied pain threshold and pain tolerance in fibromyalgia patients and controls as well. They examined non-trigger-point (in this case non-tender point) muscle and bone with a dolorimeter. This group found highly significant differences in pressure pain thresholds and in pressure pain tolerances on both muscle and bone, i.c. lower in the fibromyalgia group, so they concluded that patients with fibromyalgia have a generalized amplification of pain sensitivity. These two studies seem contradictory; however in the Campbell-study the control group consisted of patients attending the general medical and medical subspeciality clinics (excluding rheumatology) not meeting "fibrositis" criteria, and in the Mikkelsson-study the control group consisted of healthy persons. Tunks et al. (20) found significantly lower tenderness thresholds of tender points in fibromyalgia compared to normal subjects, but there was an even larger difference on non-tender points observed between fibromyalgia and normal subjects. They suggest that the low tenderness threshold at the tender points in fibromyalgia may reflect a more generalized lowering of tenderness thresholds, seen at non-tender points as well, and in their study pain thresholds of non-tender points discriminated more significantly the group of normals from the group of patients with fibromyalgia. So the primary problem in fibromyalgia could be a diffuse lowering of pain thresholds, causing these patients to experience more pain. Scudds (21) already came to the same conclusion as Tunks. Scudds in his study determined pain threshold and pain tolerance with three different stressors in three different patient groups (fibromyalgia, RA and normal controls) at non-tender areas (to light pressure on palpation). In a further study by Smythe (22) the performance of scored palpation, a point count and dolorimetry were regarded in assessing unsuspected nonarticular tenderness in three groups of patients, 51 with rheumatoid arthritis, 50 with psoriatic arthritis and 51 with human immunodeficiency virus infection. The point count consisted of a 14-site point count, furthermore scored tenderness at 6 fibrositic and 4 control sites, and dolorimetry at the same 10 sites.

There were strong correlations among the three measures. As it turned out the scored tenderness at just 6 fibrositic sites provided as much information about the presence and severity of widespread tenderness as the other two measures. The two methods based on palpation were significantly more sensitive to differences among individuals at the distinction between tender and non-tender, than was dolorimetry. By using just palpation method different degrees of non-tenderness are not evaluated. Sites which were scored zero by palpation showed widely different thresholds of tenderness by dolorimetry, significantly associated with sex and diagnosis. Interestingly this study was not focused on tender points or tenderness in fibromyalgia.
Buskila (23) assessed in over 300 healthy schoolchildren tenderness thresholds and prevalence of fibromyalgia, according to the 1990 criteria. In this group 6.2% met fibromyalgia classification criteria (3.9% of the boys, 8.8% of the girls, which was borderline significant). Boys had higher tenderness thresholds than girls and children with fibromyalgia had lower thresholds for tenderness both at control and tender points compared to those children without fibromyalgia. The children were not selected for or excluded by symptoms of pain. In another study of Buskila (24), he reported on the assessment of nonarticular tenderness and prevalence of fibromyalgia in hyperprolactinemic women. Their results suggest that in a subset of hyperprolactinemic women fibromyalgia is very common and they found that the frequency of fibromyalgia was directly associated to the level of prolactin. Hyperprolactinemic women have lower thresholds of tenderness than women with normal prolactin levels. In their study women with fibromyalgia were more tender than the women without fibromyalgia, both in tender points and control sites. An explanation for the association is between prolactin level and fibromyalgia is not given by the authors, other than that a hyperprolactinemic response to thyroid releasing hormone is demonstrated by Ferraccioli (25). Rollman (26) commented on the different measurements of pain in fibromyalgia in the clinic and laboratory. With measurement in the clinic he meant the spontaneous, continuous, endogenous pain in fibromyalgia, measured with questionnaires or visual analogue scales. With laboratory measures he meant the elicited, acute, exogenous pain of the fibromyalgia patient, originated at the tender points. Rollman thinks that the found lowered pain threshold and tolerance at non tender spots might suggest that a distortion in the perception of generally innocuous stimuli may be a characteristic of fibromyalgia syndrome. The effect of treatment regimens on pain assessments needs to be further determined.
In an article by Smythe (27) he reported on the referred pain syndromes. He states that at exactly the same sites as the tender points described in the fibromyalgia syndrome, there is a similar tenderness in referred pain syndromes. The sites of origin of the pain are often unknown to the patients with referred pain syndromes. The points are usually gathered in a rather small area and the general symptoms of fibromyalgia, like fatigue and stiffness are absent. It seems that the subject of this article, referred pain syndromes, resembles the myofascial pain syndromes.

A third aspect in the studies on tender points is the reliability of tender points (28,20,6,29,30). A dutch physiotherapist (28) studied the reliability of tender points in fibromyalgia syndrome. Subject of study was to see if the tender point localizations of Smythe were indeed more tender than control points and if these tender points were reproducible. There were two independent observers (inter-observer reliability), and both observers conducted the tender point examination two times, with an interval of one week (intra-observer reliability). Most tender points were painful in all patients, only 4 of 13 used control points were not painful. The Spearman correlation coefficient in the inter-observer analysis was approximately 0.5, in the intra-observer analysis equal or greater than 0.5. Tunks et al. in 1988 (20) established inter-rater and test-retest reliability of use of a pressure algometer, e.g. dolorimeter. In this study a clear distinction between tender and trigger points was not made and is according to the authors still open for debate. They see as important factors in a dolorimeter the size of the surface area of contact, the material from which this surface is made and for the user of the dolorimeter it is important that he uses a constant fixed rate of application of the stimulus and direction of application. In their study they found a high inter-rater (0.85) and test-retest (0.85) reliability. Cott (6) found that interrater agreement on the absence or presence of tender points is not significantly reduced by hand palpation or dolorimetry. In a study of Yunus et al. (1989) (29) is reported that tender point sites among fibromyalgia patients were significantly consistent at an interval of 3 and of 6 weeks, compared with a baseline examination. In 1995 Tunks et al. (30) reported on the reliability of the assessment of tenderness using dolorimetry and palpation. In this study 3 blinded examiners compared 19 paired tender points and 8 paired control points in 4 matched groups (fibromyalgia, myofascial pain, pain controls and healthy controls). For dolorimetry scores good test-retest reliability was found. In ratings of tenderness by digital palpation, there was a good intrarater reliability over 26 of 27 paired points, and good interrater reliability at 75% of the points.

The value of a tender point count as a treatment outcome variable (assessment variable) is the last aspect that will be discussed (31-33,29,34). Several authors report different ideas on the importance of the tender point score as an outcome variable in treatment programs in fibromyalgia.

Campbell (31) emphasizes the importance of further study to establish the reliability of tender point scores, in the course of time and as a therapy outcome parameter.

Lautenschlager (32) assessed pain in fibromyalgia patients using different techniques, among them dolorimetric measurements of 56 (!) typical fibromyalgic tender points. A second assessment was made after 4 weeks, during which time patients either got a placebo treatment or treatment with acupuncture. The changes in pain assessments were compared with the aid of Spearman correlation. The dolorimetric findings showed an increase in tenderness threshold after treatment, but from the article it does not become clear what the precise changes in dolorimetric findings at the tender points

were, and if there were differences in the treated and placebo group. However Lautenschlager stated that also dolorimetry makes it possible to assess the value of therapeutic regimens. So this would mean that the authors think that assessment of tender points with dolorimetry will change after beneficial treatment, in other words it can be used as an outcome measure. Scudds (33) found improvements in pain responsiveness, namely a decrease in total myalgic score of the tender points (sum of tenderness measured with a dolorimeter), in a subgroup of fibromyalgia patients treated with amitriptyline. No significant differences were found in pain threshold or pain tolerance measured at control points. Scudds therefor thinks that the use of pressure dolorimeter is an efficient way of evaluating painful symptoms at tender points and that these measures are responsive to change.

The design of a study of Yunus (29) was a double blind placebo controlled trial of the (short term) effects of ibuprofen in primary fibromyalgia syndrome. The total number of tender points was decreased, both after ibuprofen and after placebo. In many other therapy trials the number of tender points or pain scores are used as therapy outcome variables. An example of this is the study of Grassetto and Varotto (34). As therapy was S-adenosyl-L-methionine chosen and one of the evaluations was the score of tender points. This score significantly decreased in the therapy group, and a general well-being score (measured with VAS) significantly improved. In their article the authors state that general wellbeing is related to pain and that reduction of pain improves patient's well-being. In the discussion they even make a stronger point on this relation, where they say that general well-being is strictly related to pain, and an improvement in well-being is an indication of reduction or absence of pain. We certainly can not subscribe this statement. The authors assume there is such a relation, but in our opinion this is as yet not proven. Another critical note can be made in respect of the choice of tender point scores as therapy outcome variables. Are tender points (tenderness, tender point count) really a reliable outcome measure for treatment strategies in fibromyalgia? This strongly depends on what the treatment goals are at the onset of the therapy program. And furthermore it needs to be established that an improvement in tender point score improves the patient's situation. Patients are often unaware of the existence of tender points; they notice them when their physicians are palpating these specific spots. How strong is the correlation between tender points and other characteristics of the syndrome, especially those that bother the patients most, like experiencing wide spread pain, bad sleeping, fatigue and decline in all kinds of activities. Should we not aim at other outcome-variables, like a change in coping mechanisms or a decrease of medical consumption, or increased feeling of well-being? These are questions that need to be answered.

In our study we found no differences in number of tender points in fibromyalgia patients in the course of time. Our data show that tender points are more or less consistent in time. A change in the number of tender points is not proven to be an useful outcome parameter in evaluating therapy programs in fibromyalgia syndrome.

Counting the number of tender points is demanded in classifying a patient with chronic widespread pain as a fibromyalgia patient. As Smythe stated the site specific approach is valuable in diagnostic sense, but more broadly operative mechanisms are needed in future research and therapy studies.

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# Epidemiological and socioeconomic aspects of fibromyalgia

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# Introduction

In this chapter a summary of epidemiological studies in fibromyalgia will be presented. Fibromyalgia is one of the most common chronic disorders seen in rheumatology practices, and patients suffer for years from pain and other symptoms. A few prevalence studies in the general population have been carried out. Fibromyalgia also has been described in children and in elderly people. At the time there is not much knowledge of the natural history and outcome of fibromyalgia, however there have been a few prospective studies on this issue. Being as it is, many patients experience great difficulties in adjusting their lives to a new situation, and fibromyalgia has many implications for a patient and her or his family and social network. To keep up a job becomes difficult, which can result in a financial disadvantage. On the other hand the costs of the health care system and social security system of this patient group must not be underestimated. A last aspect that will be discussed are the encountered medicolegal consequences of fibromyalgia.

# Epidemiological aspects

Exact numbers of patients with fibromyalgia in the total population are unknown. The far majority of papers published on different aspects of fibromyalgia concern patients referred to hospitals or outpatient clinics. The patients seen are therefor a selected group out of a much larger group of persons who will meet the criteria for fibromyalgia. They are very likely the top of the iceberg.
In respect of epidemiological studies a distinction can be made in population based epidemiological studies, in studies where primary care patient populations are concerned, and thirdly the referred population to the specialists in the outpatient clinics or hospitals (secondary and tertiary care). Problems that can be encountered in epidemiological studies, especially when one tries to compare the different outcomes, are the lack of uniformity in diagnosing fibromyalgia (use of different criteria sets) and also the different methods in retailing or contacting the population under study. Some studies are undertaken in a prospective manner, but others try to retrieve patients by earlier filed questionnaires on health problems. And furthermore not all systems of classification of diseases know and acknowledge the diagnosis fibromyalgia. The World Health Organization has incorporated fibromyalgia in the 10$^{th}$ revision of the International Classification of Disease (M79.0).

## Population based studies

During the last years more information has come forward regarding the prevalence of musculoskeletal complaints, and fibromyalgia in particular, in the general population.

Many of the persons recognised in these studies have not sought medical advice for their fibromyalgic complaints. This remains a very interesting phenomena; why do some persons seek medical advice, and others not? The idea that psychological distress in persons with fibromyalgia seen in the clinical setting could be an important factor in health-seeking behaviors is opposed by Wolfe (1). In his study high levels of psychological distress were found in persons with fibromyalgia in the community. Compared with a clinical population of fibromyalgia patients, levels of anxiety and depression were of the same magnitude as in a community population of fibromyalgia persons, as measured with the Arthritis Impact Measurement Scale (AIMS). Wolfe compared also other characteristic features of the syndrome, like symptoms ("pain all over", subjective swelling, paresthesias, stiffness, sleep disturbance, fatigue and irritable bowel syndrome) and dolorimetry scores, but they did not find differences between fibromyalgia in the community and clinic. However differences were found in a number of severity scores, like Global Severity, Health Assessment Questionnaire Disability Index and Visual Analogue Scale of pain. These scores were higher in the clinical fibromyalgia group. They scored also higher on fatigue. Mean age of the community group was higher.

Reports on the prevalence in the general population made at the second world congress on fibromyalgia and myofascial pain syndromes in Copenhagen 1992 (Myopain) speak of a prevalence of approximately 3% in the general population in most countries. Actually this figure is higher than the prevalence of rheumatoid arthritis in the general population.

Jacobsson et al. (2) found in a major Swedish city the prevalence of fibromyalgia, according to the Yunus criteria, of 1.1% in a randomly selected population of 445 persons aged 50 to 70.

A paper was published by Makela et al. (3) on the prevalence of fibromyalgia in the Finnish population. The study design was a cross sectional study of 8000 Finns aged 30 or more who were invited for scree-ning and a main examination for musculoskeletal disorders and other major disorders. The data were collected as part of a mini-Finland health survey, designed to provide information about the populati-on's health, its need for care and rehabilitation, the consequences of disease, and factors affecting

health. The examination was not designed to detect fibromyalgia and therefore

a weak point of this study. There was a systematic recording of pressure tenderness in the wrists, elbows, trapezoid muscles, shoulder joints, knee joint region and achilles tendons, but not all fibromyalgic tender points were examined. The authors used an operational definition of fibromyalgia adapted from Yunus. They found that the prevalence of fibromyalgia was low, 0.75% and related to age (peak prevalence 55-64 years) and female sex (twice as prevalent in women), occupation (no cases among white collar professionals), level of education (strong inverse gradient), and high levels of physical stress at work. No significant associations were found with smoking or mental stress at work. Fibromyalgia did not predict mortality. The sensitivity of the criteria to modification was tested by applying three other, slightly modified criteria sets. The authors found that the prevalence of fibromyalgia was highly dependent on the specific configuration of criteria and disagreement between any two sets of criteria was very high.

In 1992 a study was published by Forseth and Gran (4) in which they described the prevalence of fibromyalgia among women aged 20-49 years in a small town (12216 inhabitants) in southern Norway. All women in the age of 20-49 were invited to participate in an epidemiological study on diseases of the locomotor system. A questionnaire regarding rheumatic complaints was sent out to 2498 women and 81.5% (2038) of the questionnaires returned. Fifty-seven percent of the returned questionnaires were defined as positive responders (pain and/or stiffness lasting for at least three consecutive months). The others were defined as negative responders (870 women) and the ones that did not answer the questionnaires were classified as non responders (463 women). A sample of the positive responders (21% of 1165=242 women) were invited for a clinical examination. About 90% (217) did indeed come for an examination. During this study the ACR criteria for fibromyalgia were used. At the clinical examination it appeared that more than 20% of the 217 women did not have the physical complaints in spite of affirmative responses in the questionnaire. So they scored the total group of positive responders 20% lower (918 instead of 1165). Of the 171 positive responders examined, 40 women (23.4%) satisfied the ACR criteria for the diagnosis of fibromyalgia. It was thus calculated that 215 women (23.4% of 918 positive responders) would be expected to suffer from fibromyalgia. They assumed an equal distribution of fibromyalgia among responders and non responders, and this brought them to an estimation of the prevalence of fibromyalgia of 10.5% in a female population of 20-49 years of age. Of the 40 women they saw in the clinical examination fitting the diagnosis fibromyalgia 34 had consulted a physician because of widespread pain and/or stiffness. Fourteen (41.2%) had received a diagnosis of fibromyalgia. Forseth could not give an estimation of the prevalence of fibromyalgia among all inhabitants of Arendal, because she only saw women between 20 and 49 years old. This makes it difficult to compare these outcomes with those of other prevalence studies.

In a later publication by the same authors, Forseth and Gran (5), they reported on the

occurrence of fibromyalgia-like syndromes in a general female population. Actually this was a second publication on the same study. The purpose of the second study was to study the 129 females that reported pain of the locomotor system of more than three months duration, which could not be appropriately diagnosed, more intensively. Particular emphasis was laid on the presence of clinical signs and symptoms known to occur rather frequently among patients with fibromyalgia. The 129 women were classified into three groups according to whether they lacked either one or both of the main ACR criteria for fibromyalgia. These three groups were compared with the fibromyalgia-diagnosed group and with the group that did not have the complaints longer than three months. There were no significant differences in disease duration between the groups, so the authors concluded that it is not likely that females having a fibromyalgia-like syndrome suffer from any prodromal stage of fibromyalgia. Differences in age distribution among the various groups could not explain the different clinical pictures as well. The study showed that the existence of musculoskeletal pain syndromes is rather frequent in the examined population. The authors conclude that their study has shown a high prevalence of fibromyalgia and fibromyalgia-like syndromes in a general female population, but that whether or not such fibromyalgia-like patients should be treated and informed in a way similar to fibromyalgia patients cannot as yet be answered by their study.

In another publication of Scandinavic origin, Prescott et al. (6), the Danish situation is studied. This study was based on a national health interview survey carried out by the Danish Institute for Clinical Epidemiology in the year 1990/91. Six thousand Danish citizens were randomly selected. A subgroup from this sample, from the eastern part of Denmark aged 18 to 79 years, was asked about widespread muscle pain. Ten percent of this group fulfilled screening criteria (123 persons). Sixty-five persons could be clinically examined (53%). Of these 65 persons 8 met the 1990 ACR criteria for fibromyalgia. These were all women. With these figures they conclude that the prevalence of fibromyalgia in this sample of the Danish population between the age of 18 and 79 was 8/1219, i.e. 0.66%. This is a minimum estimate, because all the dropouts (58 out of 123) were considered as non-fibromyalgia.

Prevalence of fibromyalgia in England is not well examined. However Croft et al. in (7) established the prevalence of chronic widespread pain and associated symptoms in a general population sample in the north of England. The prevalence of chronic widespread pain was 11.2% and this symptom was strongly associated with other somatic complaints and with measures of depression and anxiety. Chronic widespread pain was reported more frequently by women than by men (15.6% against 9.4%), and the prevalence increased with age. In this study there was no clinical examination involved and all information was gathered through postal questionnaires. The criteria of number of tender points therefor was not included.

An epidemiologic study concerning musculoskeletal complaints (not nearer specified to fibromyalgia) and use of health services in a part of Spain was conducted by

Ballina Garcia et al. (8). Seven hundred and two persons over 18 years of age were included in this cross-sectional study, which amounted 75% of the population invited to participate, and were selected from a proportional, polystaged, stratified random sample. A person was considered having musculoskeletal complaints when the symptoms had been present in the spine or in the peripheral joints during the prior year with a minimum duration of one week. The researchers also recorded the visits of the person to health professionals during the last year. A few questionnaires were completed, Health Assessment Questionnaire and AIMS, and also a visual analogue scale scoring the degree of pain. The percentage of persons with symptoms during the last year markedly increased with age, female sex and lower education. The lumbar and cervical spine were the most mentioned localisation of pain. Modulating, worsening factors, were trauma in 6%, related to the profession in 17%, and in 26% climatic factors, like humidity, cold and rain. In the sample of 702 persons 24% were diagnosed as osteoarthritis, 2% as inflammatory disease, soft tissue disease (including fibromyalgia?) in 20% and low back pain in 15%. Rheumatism of unknown origin (fibromyalgia?) was found in 6%. Next the authors evaluated the use of health services. Twenty-two percent of the total sample of 702 persons had needed medical assistance, which was half of the symptomatic group. This means that the other half of the symptomatic group did not seek help by a health professional, probably because their symptoms were not worse enough. A subgroup however said that nothing could be done anyway in relation to their complaints. The authors registered all appointments within the health system and they found that 13% of the symptomatic population was treated by doctors outside the public system. In the symptomatic group 28% were taking antirheumatic drugs. Comparison between different variables showed that people experiencing more pain, in the symptomatic group, used more health services. No significant differences in relation to the degree of depression, anxiety or difficulty in carrying out the activities of daily life were found. In the discussion the authors suggest that their high number of symptomatic cases could be due to the influence of rainy weather that is commonly seen in the part were this study was undertaken. This seems a weak argument and is not based on facts.

Wolfe et al. (1) conducted a prevalence study of fibromyalgia in the general adult population of Wichita, USA. They planned to contact 3500 (by mail and if necessary by telephone) households, in a randomized order. In order to obtain information on pain standard questionnaires were used. The authors categorized the answers in four groups. Group 1 had no pain, group 2 had current pain as well as pain that had lasted no longer than 3 months, group 3 had current non-widespread pain that was present longer than 3 months, and group 4 had widespread pain, longer than 3 months. Group 4 was the potential fibromyalgia group. The ACR classification criteria for fibromyalgia were used. Patients with pain related to cancer, a recent trauma or just plain headache were not included in any of the 4 groups and were further excluded from this study. The authors examined a sample of group 4, as well as a (smaller)

sample of group 1 and 3, matched for age and sex. Tender point count and dolorimetry examination were performed, and the Symptom Check List and the Anxiety and Depression Scales of the Arthritis Impact Measurements Scales were used. The examination was performed without the examinator knowing to what group the person belonged. Their results showed that widespread pain was present in 10.6% of the general population and regional pain in 20.1%. There was no sex-difference across age groups for the persons with regional pain. However the percentage of chronic regional pain increased with age, from 15% in the youngest age group (18-29) to almost 30% in the age group over 80 years. Widespread pain was more present in women, with a maximum in the age group of 50-59 and 60-69, of over 20% compared with approximately 13% for men in these age groups. Pain in the older age group was very often present; by the age of 60 more than 50% of the women had some form of musculoskeletal pain, and almost 40% of the men. A tender point score of at least 11 out of 18 tender points was present in 25.2% of examined women with widespread pain, and 6.8% of men with widespread pain, in total 18.9% of the examined persons with widespread pain. Most persons with fibromyalgia in this community based population study (75%) had seen a physician in last 6 months. The estimated prevalence of fibromyalgia in the general adult population of Wichita is 2%; 3.4% for women and 0.5% for men. Interestingly the prevalence of fibromyalgia was highest in the age group over 50 years in women, and 6 times higher than in men in these alter. Highest prevalence values were seen in women of 60-79 years, >7%. These results are remarkable. The picture of the fibromyalgia patient presenting herself (himself) to the doctor resembles not the older female person. So again we can raise the question; what more is needed than widespread chronic musculoskeletal pain and positive tender points to end up at the doctor's office or clinic? If we were able to find these answers, we might get the possibility to prevent the development of a full blown fibromyalgia syndrome. Results of the above mentioned population based studies are summarized in table 1 .

Table 1
EPIDEMIOLOGIC DATA POPULATION BASED PREVALENCE-STUDIES OF FIBROMYALGIA

| Author | Country | Study population | Criteria | Prevalence |
|---|---|---|---|---|
| Jacobsson (1989) | Sweden (city) | n=445 50-70 yrs | Yunus | 1.1% |
| Makela (1991) | Finnland | n=8000 30 yrs and older | Yunus [1] | 0.75% |
| Forseth (1992) | Norway (small city) | n=2498 women women 20-49 yrs | ACR | 10.5% |
| Prescott (1993) | Denmark | n=6000 18-79 yrs | ACR | 0.66% |

| | | | | |
|---|---|---|---|---|
| Croft (1993) | England | n=?<br>age=?<br>general population | widespread pain | 11.2% |
| Ballina Garcia (1994) | Spain | n=702<br>18 yrs and older | musculoskeletal complaints | - soft tissue disease: 20% (fibromyalgia?)<br>- rheumatism unknown origin: 6% (fibromyalgia?) |
| Wolfe (1995) | USA (city) | n=3500<br>18 yrs and older | ACR | 2%<br>(3.4% ♀♀; 0.5% ♂♂) |

[1] no standard recording of all fibrositic tender points

A Dutch study by van Schaardenburg et al. (9) reported on a community survey on musculoskeletal disorders and disability in persons aged 85 and over. Unfortunately they did not take the diagnosis fibromyalgia in account. However they found that 57% of this population suffered from back or joint pain. Arthritis and osteoarthritis were relatively rare, whereas shoulder disorders were frequently seen, mostly frozen shoulders. There was a high level of disability in this study population. Sixty percent could not walk 500 meters alone and up to 40% needed human assistance in performing daily activities. As the cause of disability other disorders (like neurological disease, impaired vision) were at least as important as musculoskeletal disorders.
There are at the time no known population based studies conducted, concerning the prevalence of fibromyalgia in the Dutch community.

## Primary care population based studies

Prevalence of (symptoms of) fibromyalgia in patients seen in a primary care setting was studied by Hartz (10). The authors wanted to know the frequency of unexplained, chronic, diffuse muscular pain in primary care practice and to evaluate how this pain relates to the criteria for fibromyalgia (modified criteria of Yunus, 11). Six hundred ninety-two patients completed a screening questionnaire (completion rate of 64%) of which 33 (4.6%) had unexplained muscular aching or stiffness in at least three areas for a period lasting longer than three months. The percentage of women was significantly higher. Only 3 patients were already identified by their physician as fibromyalgia patients. Eighteen patients had symptoms sufficiently severe to interfere with their ability to perform their job or household. Different sets of fibromyalgia criteria were used to see how many of these patients met with these different criteria sets. The percentage ranged from 17 (Campbell, 12) to 55 (Yunus, 11). The authors state that their results show that unexplained and diffuse muscular aching is a common problem and that it is at that time rarely diagnosed. The use of criteria sets to define

fibromyalgia excludes many patients with the typical primary symptoms.
In the Dutch primary care classifications of diseases fibromyalgia is not acknowledged as a separate entity, and therefore no figures in relation to the Dutch situation can be presented at this time.

## Clinical or hospital population based studies

Estimates of the incidence are made by a lot of authors. Campbell (12) saw 5.7% of patients in a university general medical clinic who fitted the diagnosis. Yunus in (11) speaks of 20% of new patients in a rheumatic disease clinic who were found to have fibromyalgia. Wolfe and Cathey (13) wrote a brief communication on the prevalence of primary and secondary fibromyalgia. He came to 3.7% of newly seen patients in an outpatient rheumatology clinic that met criteria for primary fibromyalgia. Criteria used in this study were diffuse musculoskeletal aching or pain and 7 or more of 14 tender points. Secondary fibromyalgia was found in 6.7-15.7%. When conditions presuming to be associated with secondary fibromyalgia were excluded primary fibromyalgia was identified in 13.6%. Primary and secondary fibromyalgia together mounted up to 14.6% in a consecutive group of patients of the rheumatic disease clinic. Although the authors speak of prevalence, it reflects probably more an estimation of the incidence.
White et al. (14) conducted a cross sectional random survey of Canadian rheumatologists to determine the perceived proportion of fibromyalgia syndrome among new referrals to the rheumatology practices and they also asked the rheumatologists if this incidence was stable or changing. The participants were not informed about the specific intent of the study. Participants were asked 4 open questions and two closed questions where they were asked to estimate their experiences with each of 13 alphabetically arranged rheumatologic disorders, among them fibromyalgia syndrome. Osteoarthritis (OA) was mentioned the most among the 3 most common disorders seen among new consultations (80.5%), next to rheumatoid arthritis (RA) (51.7%) and fibromyalgia syndrome (48.3%). OA was thought to be the largest percentage of new rheumatology contacts (28.1%), followed by fibromyalgia syndrome (23.4%). RA was presented by 18.4%. A majority of the rheumatologists thought that the prevalence of fibromyalgia syndrome in their practice was increasing over the past 5 years, actually it was the only (of 13 rheumatologic) disorder that the majority saw increasing in prevalence with time.

## Is there a future for epidemiological studies in fibromyalgia

Felson (15) gave an overview of epidemiologic research in general and more specific for fibromyalgia. He recommended several goals for future research in fibromyalgia,

for instance more case studies and prevalence studies are needed to generate causal hypotheses. Also studies are needed that focus on the overlapping syndromes, like chronic fatigue and low back pain, to find out if these syndromes are really different or whether different terms are used to denote the same thing. Case control studies are needed, according to Felson, to test current and new hypotheses, and cohort studies of patients with uncommon disorders thought to be related to fibromyalgia are needed to determine if there is an association between fibromyalgia and these disorders.
Schochat, Croft and Raspe reported on the outcome of a workshop of the standing committee on epidemiology of the European League Against Rheumatism (EULAR) (16). The workshop was organized to discuss the concept, definition and occurrence of fibromyalgia from an epidemiological perspective. The participants agreed that it is very difficult to determine the prevalence of fibromyalgia in the general population and that fibromyalgia is too heterogenous to be one disease. They did not recommend further prevalence studies. Future epidemiological studies should be directed at the distribution of the different features of the syndrome, namely pain, tender points and associated symptoms, and the interrelationships between these different features should be further analyzed.
Fibromyalgia is not a disease, and to study the epidemiology of a complex syndrome where not all the determinants that turns a person with chronic widespread pain and a number of tender points in a patient are as yet known, seems a very difficult task.

## Fibromyalgia in children

The highest number of patients with fibromyalgia are found in adult women. At children's alter the fibromyalgia syndrome is described as well. Calabro (17) described a case history of a female patient where the first symptoms began when she was a girl of 13 years old. We all know many patients who claim that their fibromyalgia began in their teens or twenties. Yunus reported also on the fibromyalgia syndrome in children (11,18). He described a clinical study of 33 children, aged 17 and younger, with fibromyalgia and matched controls. The most frequent age for both presentation and onset lay between 13 and 15 years. Six percent of these children were boys. Frequency of symptoms, like pain and aches, stiffness and fatigue were evaluated, as well as the sites, duration and diurnal variation of symptoms. Furthermore the modulating factors like cold weather and physical overactivity were assessed. A physical and laboratory examination was performed. The results indicated that juvenile fibromyalgia is a similar condition as the adult form of fibromyalgia, although several differences were noted by Yunus when he compared this juvenile group with a group of adult patients. These were items of symptomfrequency and not really of the principal findings in the fibromyalgia syndrome. Yunus found that in his juvenile group, seen by him in ambulatory rheumatology consultation, only 1 patient had the diagnosis fibromyalgia on referral. More than half did not have a diagnosis on

referral, 8 were diagnosed as juvenile rheumatoid arthritis, 4 as arthritis and 1 as a collagen disease. A lot of unwarranted examinations had been pulled through. Yunus remarks that the prevalence of juvenile fibromyalgia can not be exactly estimated. In a period of 18 months they saw roughly the same number of new patients with juvenile rheumatoid arthritis as juvenile fibromyalgia. This could depend strongly on referral patterns. In the Netherlands most children who are suspected to have a rheumatic disorder are referred to the paediatrician. In their study all 33 juveniles and none of the matched normal controls satisfied the criteria earlier published by Yunus. Of course one has to be aware of the circle reasoning, because these juveniles were referred because of musculoskeletal complaints. Malleson (19) described idiopathic musculoskeletal pain syndromes in children, among them fibromyalgia in a retrospective study of 81 children who had presented themselves with localized or diffuse musculoskeletal pain at a paediatric rheumatology clinic. In these 81 children no cause for their complaints could be found. Nearly half of these children had diffuse pain complaints and of these 40 children, 35 fulfilled criteria for fibromyalgia. Criteria used for defining fibromyalgia were those of Yunus (18). Of the 40 children with diffuse musculoskeletal pain 39 were girls. It is remarkable that tender point count could be established in retrospect; this would mean that all children underwent a tender point count examination at the first referral contact. In this study there clearly is a predominance of girls, compared with the study of Buskila et al. (20).
Buskila reported on the assessment of nonarticular tenderness and prevalence of fibromyalgia in 338 schoolchildren. Tender point count (total of 18) was conducted and tenderness thresholds were obtained at some tender points and a few control points. In 6.2% of these 338 schoolchildren the diagnosis fibromyalgia could be made (according to the 1990 criteria). Tenderness thresholds were significantly lower in the girls compared with those of the boys, and the thresholds at tender points were significantly lower than in the control points. Children with fibromyalgia did have significantly lower tenderness thresholds, both at tender and control points, than did the children that did not have fibromyalgia. There was only a very small, but significant, difference in the frequency of fibromyalgia in girls compared with boys (8.8% vs 3.9%). Gedalia, co-author from Buskila, published on joint hypermobility and fibromyalgia, also in the same group of schoolchildren (21). These were all children from a public school in Israel. As we know from the article of Buskila 6.2% of these children had fibromyalgia. Joint hypermobility, according to predefined criteria, was seen in 13% of these children, no significant difference between girls and boys. Both fibromyalgia and joint hypermobility were seen in 17 of the 338 children (5%). Statistical analysis showed that fibromyalgia and joint hypermobility were strongly associated. These studies show that musculoskeletal pain is common, even among children, but that it needs more to become a (fibromyalgia) patient. These children were not referred to their physician because of their suffering from fibromyalgic complaints.

## Fibromyalgia in the elderly

Reports on the occurrence of fibromyalgia in elderly were written by Yunus (22) and Wolfe (23). In the report of Yunus he compared fibromyalgia patients of 60 years and older with younger patients. The fibromyalgia features in the older group were similar with those of the younger group, with the exception of a few modulating (aggravating) factors, which were less common in the elderly group. As in his comparison study in the juvenile group there were no clinical significant differences between the two groups. However in only 17% of this elderly group the diagnosis was earlier on recognised by the referring physician. The same mistreatments as described in his article on the juvenile fibromyalgia syndrome were encountered in the elderly group. Wolfe gave a resume on differential diagnosis and treatment of fibromyalgia in the elderly. In the elderly fibromyalgia is said to be often seen as a concomitant disease, but it is seldom recognised as such. This leads to misdiagnosis and to overtreatment. The finding of tender points is the key in diagnosing fibromyalgia, also in the elderly. These two reports emphasize the role of fibromyalgia in chronic widespread pain in elderly, and that one should be alert of this diagnosis in elderly as well.

## Natural history and outcome

Felson (24) reported on the natural history of fibromyalgia. This was one of the first prospective studies. He followed a group of 39 fibromyalgia patients for three consecutive years by telephone survey. These patients were recruited from an academic, rheumatology referral practice. This selection procedure is biased (referral population), and represents probably a negative selection of the total group of fibromyalgia patients. Sixty percent of these patients had in this period moderate to severe continuing symptoms and took regularly medications because of their fibromyalgic complaints, and the general trend was a continuation of symptoms over time. He found a few indicators of a less severe outcome after the two years of follow up. These were age (younger patients did better), less severe symptoms at the initial survey (this is not surprising), and isolated Raynaud's phenomenon. The symptom remission however was usually transitory.

Another outcome study was performed by Ledingham et al. (25). They reviewed 72 patients with fibromyalgia, from a consultant's general rheumatology clinic, after 4 years following diagnosis. This study was performed in Nottingham, England. Ninety-seven percent had still the typical symptoms of fibromyalgia after these 4 years. Rate of disability, assessed with Health Assessment Questionnaire (HAQ), was significant. Also high levels of anxiety and depression were scored. No patient had developed any inflammatory, metabolic, endocrine or muscle disease. The total group of patients invited to participate in this follow up study consisted of 87 patients: 15

patients were not seen for a follow-up examination. One had died (not fibromyalgia-related, myocardial infarction), 6 patients had moved away and 8 (nearly 10% of the initial group), decided not to come. It is very well possible that this group had no longer complaints and were therefore not motivated to come back, and the patients that did attend the follow-up assessment did indeed still have major problems, for which they hoped a positive turn could come with this visit. In this group the men had fewer tender points than the women. Fifty percent had stopped working because of their complaints. This study shows the chronicity of fibromyalgic complaints.
Buskila et al. (26) reported on an outcome study of the fibromyalgia syndrome in children. Study population was the same as in the author's publication of 1993 (20). After thirty months they invited those children that were diagnosed as fibromyalgia for a second evaluation. The authors were able to see 15 of the original 21 children with fibromyalgia. At the second evaluation 11 out of 15 fulfilled no longer the ACR criteria for fibromyalgia. These results could indicate that the outcome of fibromyalgia in children is much better than in adult fibromyalgia patients. However we have to remember that the population under study by Buskila was not a population seen in a doctors office or hospital setting. These children did not suffer that much of their fibromyalgia symptoms that they presented themselves to a doctor. Most of these children can not been seen as patients in the real sense of the word.
Henriksson (27) reported on the longterm effects of fibromyalgia on everyday life. Patients were recruited from the rheumatology division of a university hospital in Sweden. In this evaluation were only 56 patients included, rather a small sample. These 56 patients were earlier studied in 1984 and then again in 1989. Of the 56 patients there were 53 women and 3 men. The purpose of this follow up study was to summarize the longterm effects of fibromyalgia on everyday life and on changes over time. Henriksson focused primarily on the patients' own perception and evaluation of their symptoms. Objective signs and symptoms were not taken into account in this report. Patients were sent a mail questionnaire and a global health assessment instrument (Swedish form of Sickness Impact Profile). The response rate, the number of patients returning the questionnaire and the SIP, is not mentioned. In the concluding SIP results only the data of 49 female patients were included. Not all questionnaires and SIP's were returned, and also there were missing data. Almost 50% of the patients (of which the data were available) reported an increase of their symptoms in the past 5 years, 35% no change and about 15% reported improvement. Nearly 60% had been in contact with the health care system in the previous year and 11% had contacted alternative medicine. This leaves 30% with no contact at all in the care system concerning their symptoms in the previous year. The authors also found that the fibromyalgia symptoms influenced many aspects of daily life, like work, social activities and relations inside and outside the family. Between individuals however there were marked differences in the consequences for everyday life. Henriksson stated that his data do not suggest an overuse of the health care system

once the diagnosis is established and subsequent information is given, because of his population one third had not been in the health care system and another one third had seen a doctor a few times (mean 1.8 visits) during the previous year. However criteria for overuse of the health care system are not provided, nor are these figures related to other rheumatological disorders. The change in ability to work did not differ greatly from 1984 to 1989. The reason could be that in 1984 the condition was already chronic and that adaptation to diminished capacity already had taken place.
The severity of the fibromyalgia syndrome two years after diagnosis was assessed by Granges et at (28). The study population was recruited from a community rheumatology practice and the patients had been treated in the foregoing two years with minimal interventions. Granges studied 44 patients 2 years after initial diagnosis, along with the following variables; activity score, self-described disability, mood, coping strategies, opinion on medicinal and nonmedicinal treatments, and recent physical activity. The patient group studied had, according to the author, mild fibromyalgia. This statement however is not nearer defined. All patients fulfilled the Smythe criteria for fibromyalgia at the time of diagnosis. Exclusion criteria were psychological or psychiatric support or receiving compensation. All patients were carrying out their usual activities of daily living. Perhaps Granges sees this as a mild fibromyalgia group. Two years later 33 of 44 patients were seen for a clinical examination, the other 11 patients answered a standardized questionnaire about their symptoms. At the follow-up examination the tender point-sites as described in the 1990 criteria were used, among other measurements. These measurements were not performed at time of the diagnosis, so this makes it very hard to compare the initial findings at the time of diagnosis with the standardized clinical examination that took place two years later. The results of the examination after two years showed that 53% of the initial 44 patients fulfilled both the 1990 fibromyalgia criteria and the Smythe criteria. What percentage fulfilled only the Smythe criteria at the follow up examination is not mentioned. This would be interesting because according to these Smythe criteria the patients were diagnosed as fibromyalgia patients two years before. Granges compared different epidemiological and historic data between the group that fulfilled the two sets of fibromyalgia criteria and the group that did not fulfil both criteria sets. The number of tender points was significantly lower in the group that did not fulfil both the diagnostic criteria sets than in the group that did fulfil these criteria. The number of tender points itself is one of the major criteria in the diagnosis! So this is an example of circle reasoning and brings nothing new. Granges concluded that patients with a mild form of fibromyalgia do improve over time and that the management strategy of accurate diagnosis, explanation of the symptoms and of modulating factors, adjustment of medicinal therapy and encouragement to regular physical activity could have been the reason for improvement after years of persisting pain.

## Socioeconomic impact

Bolwijn et al. (29), from the University of Maastricht in the Netherlands, reported on social network characteristics in fibromyalgia, compared with rheumatoid arthritis. To identify the social network they used a structured interview. The networks of the fibromyalgia and rheumatoid arthritis patients were comparable in the small number of intimate friends, the reliance for support on the spouse and the physician, and the relative lack of new social contacts. The fibromyalgia networks were closed networks within a small geographic area and these networks lacked initiative to establish and maintain relations, and according to the authors can barely fulfil the patients' psychosocial needs. A critical note came from the authors themselves in saying that their number of patients was rather small, namely 10 patients in each group. All fibromyalgia patients were married, which does not resemble a true sample of the total of fibromyalgia patients. The RA group was matched with the fibromyalgia group. These preliminary results should be evaluated in a larger, randomized, double blind study, including a healthy control group. Earlier studies about the role of social factors showed that naturally occurring social support is beneficial in terms of recovery, rehabilitation and adaptation to chronic disease.

It is generally accepted that musculoskeletal conditions are among the leading diseases when it concerns social and economic costs to individuals as well as to society. They score high in measures of disabilities, restriction of activity, use of vocational rehabilitation, and medical costs. They score relatively low, compared with other diseases, as a cause of death. The impact of fibromyalgia is not the same in all countries, because there are many differences in social and medical securance and insurance systems, offers for jobs and unemployment rates, and attitude towards work and attitude towards psychosomatic diseases.

Kramer et al. (30) compared four musculoskeletal conditions, among which tendinitis, for social and economic impacts. The other conditions were rheumatoid arthritis, osteoarthritis and lower back pain. Data were obtained from a national, community-based survey. The National Health Interview Survey reports the mean number of physician visits and hospitalizations and the extent of restricted activity for persons in each sample, stratified by demographic characteristics. The results showed that the tendinitis patients did better on almost all outcome variables than the other three diagnoses, and as we know from other publications, for fibromyalgia this is not likely the case. In this study the tendinitis group can not be considered the same as a fibromyalgia group. The authors plead to consider each of the four musculoskeletal conditions separately for health planning purposes, because of the wide variation in impact of disease and utilization of medical services.

A study of the socioeconomic impact of fibromyalgia has been undertaken by Cathey et al. (31). Cathey described the situation in Wichita, Kansas USA, but no mention is made from what fibromyalgia population these patients were recruited. They interviewed 81 fibromyalgia patients, using validated economic and disability

instruments, and they studied utilization of inpatient and outpatient services, drug usages, work loss, and family income. Ninety-five patients were invited, but only 81 agreed to participate. Eighty-one age- and sex-matched community control subjects were surveyed by questionnaire. Their patient group was well educated, 89% had a high school education. This percentage is higher than the mean of all U.S. citizens. Thirty-eight percent were employed, and only 6% were disabled. Forty-four percent described themselves as "homemakers". The remaining 10% were either retired or student. The patients reported high levels of pain, mild disability and moderate impairment of global health. The results suggested that work disability was limited and most patients were able to work full weeks. Compared with control subjects and national averages the utilization of outpatient medical services was increased, but was more or less the same as those from patients with other rheumatic diseases. Medication usage was limited and seemed appropriate, according to the authors. Prior to the diagnosis there were high hospitalization rates, both musculoskeletal and non-musculoskeletal hospitalizations. These rates dropped in the year after the diagnosis was established. No further mention is made of the 14 patients that did not accept the invitation. This group could very well experience more disabilities, but that is hard to tell. The high percentage of high school education makes this patient-group not very representative of all the fibromyalgia patients as well. It seems that establishing the diagnosis puts an end to fruitless doctors' shopping and hospitalizations.

Hawley (32), described a 12-month follow-up study of severity in fibromyalgia, concerning pain, functional disability and psychological status. In their study they send monthly questionnaires for a period of one year to 75 patients with fibromyalgia. As an instrument functional disability index of the Stanford Health Assessment Questionnaire (HAQ) was chosen to measure functional ability. Next to this assessments of pain, sleep disturbance, morning stiffness and psychological distress were made and the authors tried to find interrelationships between all these variables over time. Psychological status was measured using the anxiety and depression subscales of the Arthritis Impact Measurement Scale (AIMS). The other variables were to be scored with numbers, mostly on scales like the VAS scales. A list of anatomic regions was used to check the painful regions. They also tried to determine if severity of fibromyalgia and the symptoms fluctuated or not over time and to find an answer to the question which features are most directly linked to the subjective severity of the syndrome. Analysis of all variables, in different ways were made. The strongest correlations with severity were pain, HAQ functional disability, sleep disturbance and depression. Sleep disturbance and morning stiffness were not found to be explanatory factors for disease severity in regression models. They also found significant variation in variables between patients, but not in each patients' individual scores over the study period. In the discussion they conclude that fibromyalgia symptoms are remarkably stable over time and they could not detect any seasonal effects. The authors did not use a control group, and therefor the effect of answering a

monthly questionnaire can not be analyzed. Maybe the patients remembered what they answered the last time and this could partly explain the stability of symptoms over time. The acknowledgement of the perceived functional disability as a determinant of severity, is very important. Treatment programs should also be aimed at diminishing these disabilities. A difficult task awaits us in developing reliable disability-scales or assessments.

Hawley and Wolfe (33) studied pain, disability and pain/disability relationships in 1522 patients (with 7 different rheumatic disorders). The HAQ was used to assess functional disability. Pain was assessed with visual analogue scores. Two hundred forty-eight fibromyalgia patients were included and they compared the demographic data from these seven disorders with each another. Overall the authors found that individual differences between patients were more striking than the differences between the different rheumatic disorders. Rheumatoid arthritis (RA) group as a whole had the highest disability, least pain, lowest pain/disability ratio and least abnormal scores. Highest pain and psychological distress was noted in fibromyalgia (and 2 of the other disorders). Disability in activities of daily living was equal high in RA and fibromyalgia, and higher than in all the other diagnostic groups. In this study again emphasis is laid on the functional disabilities that are frequently reported by fibromyalgia patients. Most information is gathered by self-reported questionnaires and this makes the observations subjective.

Hidding et al. (34) compared self-report measures and clinical observations of functional disability in fibromyalgia patients, ankylosing spondylitis and rheumatoid arthritis. In the fibromyalgia group there was a marked discordance (statistically significant) between the self-report questionnaires, namely 7 selected items of the AIMS, and the observed functional disability by blinded observers (blinded towards the rheumatological diagnosis and unaware of the study objective) who scored the disability on seeing the patient performing tasks that were videotaped. In the ankylosing spondylitis group there was a very small discordance and in the rheumatoid arthritis group a moderate discordance. Functional disability was rated on a visual analogue scale, by patients on the questionnaires, as well as by the observers on seeing the physical activities on video tape. The authors gave several possible explanations of the discordance between the rated functional disabilities in fibromyalgia patients and observers. An observer can not see the perceived experiences of pain, fatigue which the fibromyalgia patient her/himself does take into account and also the self-assessment of impairment is related to foregoing experiences with repetition of the activities that are performed. The authors also suggested that the observers might be intimidated by the physical deformities of the other two patients groups in contrast with the fibromyalgia group. A striking result from the observed tasks in the three different patients groups is that the observed disability was comparable for all three groups. In the summary the authors say that the effort to do daily activities and the concomitant pain could very well contribute to the discordance

between the self rated level of functional disability and the observations made by objective observers, who are unaware of the patients history and diagnosis. The self-report questionnaires used in characterizing the functional disability in rheumatological conditions should not be used interchangeably between the different conditions. Maybe fibromyalgia patients think they can not perform certain tasks and have lost confidence in their own abilities.

Again Wolfe (1) reported on severity and functional disability in fibromyalgia, this time following a prevalence and characteristics study of fibromyalgia in the general population. They found that overall severity, pain and functional disability were more severe in a clinic population of fibromyalgia patients than in a general (fibromyalgia) population. They found a strong association between fibromyalgia and female sex, and also with failure to complete high school and with reduced household income. Two thirds had taken some form of pain medication and almost 20% had applied for disability benefits. Actually only 7.3% did receive a disability benefit.

Bakker et al. (35) studied the feasibility of utility assessment in patients with fibromyalgia and in patients with ankylosing spondylitis by rating scale and standard gamble. An utility measurement questionnaire (Maastricht Utility Measurement Questionnaire, a Dutch translation and adaptation of the McMaster Utility Measurement Questionnaire) was applied to the participating patients and patients were asked to value their own health state by means of a rating scale (VAS) and standard gamble techniques. The choice for the use of utility measures is explained by the fact that utility measures can be used for comparisons across different patient populations and that patients have to combine positive and negative effect of, for example a carried out intervention, into one value. As an additional advantage is mentioned that these utility measurements provide one overall value with which one can compare patient outcomes of different diseases or results of different health care interventions. Patients' derived utilities provide overall estimates of the impact of disease on the patients' well being. According to the authors the feasibility of applying the questionnaire was generally satisfactory in both patient groups. Both patient groups valued their own health state higher on the standard gamble than on their rating scale. Patients with ankylosing spondylitis scored considerably higher on the rating scale than patients with fibromyalgia concerning their personal health. The use of utility assessment in fibromyalgia should be further studied, but it could be a valuable asset in analyzing patient well being.

ln 1994 Elizabeth Badley and coauthors (36) reported on the socioeconomic risk factors and musculoskeletal disability, as well as on the relative importance of musculoskeletal disorders as a cause of chronic health problems, disability, and health care utilization. These studies were undertaken in Canada. For the study of socioeconomic risk factors on musculoskeletal disability Badley used the data from the Health and Activity Limitation Survey that was conducted in 1986, and this survey was focused on persons with disabilities. It was a cross sectional study design.

Sociodemographic characteristics obtained were sex, age, marital status, number of people in household, income, educational level and labour force status. Disability was independently associated with increasing age, not being married, less years of schooling, lower income and being unemployed. Risk factors associated with musculoskeletal disability are similar to those for other causes of disability. However Badley states that one can not say that there is a causality to any of the associations found. The association between reported disability and low socioeconomic status may reflect factors resulting from disability as well as those predisposing to development of disability. The socioeconomic variables could also be indicators of other, still unknown, factors. She thinks it is possible that people with lower socioeconomic status have an increased risk of disease, but also when disease does occur, have an increased risk of disability. Although this study does not report on fibromyalgia specifically, we can place the fibromyalgia patients in the total group of patients with musculoskeletal disorders, as described in this study.

In another study of Badley et al. (37) the findings of the 1990 Ontario Health Survey (people of 16 years and older) were used to look into the relative importance of musculoskeletal disorders as a cause of chronic health problems, disability and health care utilization. Fibromyalgia as a distinct patient group was again not recognised in this study. Compared with other body system disorders, musculoskeletal disorders were the first cause when it concerned the prevalence of chronic health problems, longterm disabilities, and consultation with a health professional. The musculoskeletal disorders were on the second place when it concerned restricted activity days and use of both prescription and nonprescription drugs. Other body systems recognised were for example the circulatory system, respiratory system, digestive system, metabolic system, and allergies. Musculoskeletal disorders were the most frequently reported type of chronic condition. Arthritis and rheumatism included more than half of the conditions in the musculoskeletal disorder group, fibromyalgia being one of them. The impact of musculoskeletal disorders in the group of 65 years and older was still even greater. In the Dutch population the situation is similar and the last years there has been an increasing interest in the chronic diseases and diseased. The Dutch National Committee on Chronic Diseases has been of course a tremendous important factor in acknowledging the needs and disadvantages of chronic diseased persons. The attention for the chronic diseases should be a never-ending commitment in the political and health organization forces.

Kolar et al. (38) tried to identify factors that are associated with severity of symptoms in patients with chronic unexplained muscular aching. Doing this they recruited subjects with unexplained aching from a primary care practice, and also patients from a rheumatology practice and a few patients from a pain clinic. These patients were not selected on basis of tender points. There was a difference found in patients with mild and moderate symptoms and patients with severe symptoms in regard to the presence of fatigue on awakening (non-restorative sleep), number of tender points, difficulty in

sleeping, and the degree of tenderness in typical fibromyalgic areas as measured with dolorimetry. These results led the authors to the conclusion that muscular aching is of greater severity if other symptoms, mentioned above, are also present. Other variables were also evaluated, like demographic data, presence of symptoms related to somatisation and effects of various modulating factors on the degree of their muscle aching, but these variables were not found to be predictive of the severity of muscle aching. Patients with fibromyalgia have a complex of symptoms and these symptoms are not independent. This means the results put forward in this study are not very surprising.

## Quality Of Life/Fibromyalgia Impact Questionnaire

Burckhardt et al. (39) developed and validated an instrument to assess the current health status of women with fibromyalgia; "Fibromyalgia Impact Questionnaire". This Questionnaire is used as a self-administered instrument, has only 10 items, and measures physical functioning, work status, depression, anxiety, sleep, pain, stiffness, fatigue and well being. In the process of validating the new questionnaire the authors used the AIMS for comparison. Burckhardt found no relation between age and years of having fibromyalgia on one side and functioning on the other side. Also no relation was found between level of education and the individual items of the questionnaire. The authors found their questionnaire to have construct validity, sufficient test-retest reliability and content relevance. Further testing in other fibromyalgia studies is necessary.

In 1993 Burckhardt (40) published on a comparative analysis of fibromyalgia and quality of life. Burckhardt compared the quality of life of fibromyalgia women with the quality of life of other patients group (all women), like RA, osteoarthritis (OA), but also women with lung disease and women with diabetes mellitus, and healthy controls. All patients had been diagnosed using standard criteria for the different diseases. As a study instrument the Quality of Life Scale (QOLS) was used and two other instruments were used to measure health status. One of these was the AIMS, which was given to the RA, OA and fibromyalgia patients in this study. The demographic sheet from the AIMS however was used to obtain general information of all participating women. The questionnaires were mailed to the participating women. The patients were retrieved from specialists practices. Regarding the demographic variables it appeared that the fibromyalgia group and the healthy control group were statistically significant younger than the other groups. The healthy group also had more education. Evaluating the QOLS-scores it became evident that the mean score of the fibromyalgia group was lower than the means of, among others, the RA and OA groups. The fibromyalgia group showed greater dissatisfaction. Mean scores of the AIMS-subscales were compared and there were no differences found between fibromyalgia and OA, and no differences between RA and OA. Compared with the

fibromyalgia group the RA group scored significantly higher on dexterity scale, and the fibromyalgia group scored significantly higher on the depression and on the anxiety scale. Depression and anxiety were highly correlated. The total scores on QOLS of the fibromyalgia group were as low as those with chronic diseases like diabetes mellitus and chronic lung disease. The fibromyalgia group, however, was younger, had higher incomes, higher educational level, and a higher percentage was married. These last three demographic variables has been linked to higher quality of life in randomly selected groups of American adults. Burckhardt states that their findings suggest that far reaching negative feelings and dissatisfactions permeate almost all aspects of life of patients with fibromyalgia, and that dissatisfactions are not entirely explained by physical health status, psychological distress or demographic variables. Burckhardt hypothesized that fibromyalgia patients are more dissatisfied while they have not well adapted to the new situation of their chronic illness. Their disorder is not fully accepted and acknowledged, and this could cause feelings of dissatisfaction.

## Medicolegal aspects

In a retrospective study by Moldofsky et al. (41) the authors report on litigation, sleep, symptoms and disabilities in postaccident pain. This group of patients had features of fibromyalgia syndrome after a nonphysically injurious, but distressing accident. One third of 24 patients in the study had their litigation resolved, compared with two/third who had their medicolegal claims unresolved. In the resolved group the number of men and women was the same, in the unresolved group there were clearly more women. Patients of the first group were older, with a longer duration of their symptoms and more occupation handicap than those of the second group. There were no differences in other demographic data, nature of accident, symptoms, polysomnographic findings and disability. One could not differentiate the outcome of their symptoms by medicolegal claim status. The accident was not enough to alter the patients' physical ability to continue work or return to work the next day. Subsequent medical and psychiatric assessment showed no evidence for physical damage that could be attributed to their symptoms and none of the patients had any physical diagnosis. All patients were rated as having restricted social participating or having impoverished social relationships such that they had difficulty in sustaining relations with friends, neighbours, and colleagues. This study showed that in patients with resolved litigation claims and unresolved claims there was an uniform clinical presentation and altered sleep physiology. In the resolved group the duration of symptoms was longer (12 vs 2 yrs), so maybe the unresolved group will get their settlement in due time. It would be better to see if there are any differences in an unresolved and resolved claim group, with equally long duration of symptoms. On the other hand these results show that symptoms persist, even after the claim has been resolved. Other limitations of this study are the small number of patients, being not a prospective study, and there was a referral bias (renowned centre).

In an earlier presentation of Romano (42) he described that symptoms continued in patients with posttraumatic fibromyalgia following resolution of litigation and the receipt of a monetary award. Finally the author state that these observations suggests that the delay in the award of compensation or treatment is not justified. Moreover they think it is possible that an early settlement of medicolegal claims may improve psychosocial adjustment and facilitate rehabilitation efforts. This, of course, is an interesting statement, but may not be the same in other populations in different countries, where the security and social systems maybe completely different. In many of the Dutch rehabilitation centres patients with unresolved claims, whether it involves insurance claims after accidents, or work disability claims, are withheld from chronic pain treatment programs, until their claims are resolved. Patients in those situations are thought to need their pain and complaints to get their settlement and before that is (re)solved they can not focus on getting well.

Littlejohn (43) reported on the medicolegal aspects of fibromyalgia. In his article however the issue addressed is more the localized "fibrositis" syndrome, with

accentuation of the epidemic of arm and neck pain that occurred in the workplaces of Australia in the eighties, also known as the repetitive strain injury. Malingering was not found to contribute to this epidemic in any important way. The symptoms were attributed to work practices despite the lack of any scientific evidence for this association. It created an enormous amount of disability and this has led to great losses in production and high costs due to activation of medicolegal processes, increased use of health resources and the introduction of many ergonomic changes. He also reminds the readers that fibromyalgia commonly follows minor motor vehicle accidents, which might also be called whiplash. Littlejohn probably refers here to a localized "fibrositis" syndrome and this must not be confused with the fibromyalgia syndrome. Although Moldofsky (see above) also speaks of post-accident fibromyalgia. The term repetitive strain injury was adopted by the National Occupational Health and Safety Commission of Australia and this, unfortunately, gave an official status to the condition. Patients could now also enter the compensation system. According to Littlejohn the outcome of community based generalized fibromyalgia is usually good, when it is correctly recognized and handled in the right way. This idea seems rather optimistically. However a crucial point is, according to Littlejohn, that the patient does not longer believe he/she is injured and that his/her pain is caused by tissue damage. In the discussion on persisting complaints and medicolegal verdicts Littlejohn takes the stand that pain syndromes generally persist while there are outstanding medicolegal considerations. He also thinks that when the final medicolegal proceedings are concluded the fibromyalgic complaints will improve. He does not believe that financial compensation of litigation is the only motivation for patients to follow the medicolegal pathway. It is more that they want to get recognition to establish the reality of their problem through the medicolegal process. There are various factors involved, like the psychological impact of the supposed injury, cultural factors related to illness behavior and interpersonal and family dynamics.

Bennett (44) wrote an editorial with the title "Disabling fibromyalgia: appearance versus reality". He commented on the phenomenon of the so called accident neurosis, which refers to patients with chronic pain after an accident, and who obtained a worthwhile improvement after successful litigation, and he argues there is such a thing as posttraumatic fibromyalgia. He addressed the difficulty of obtaining the impairments and disabilities of the fibromyalgia patient. Here he stated that the functional disability of the fibromyalgia patients is not so much that of a 2 dimensional impairment but a 3-dimensional impairment. There are no impairments in range of motion or strength, but there are problems with activities in time and with the ability to sustain repetitive activity or other forms of a chronic workload (third dimension). An answer as to how to assess the functional disability is not given by Bennett.

Reilly et al. (45) discussed the influence of the law in the epidemiology of soft tissue

rheumatism. This topic became very relevant with the "epidemic" of repetitive strain injury in Australia and the authors themselves experienced something similar with patients after so called whiplash injuries. Many chronic pain patients could be classified as being ill, but with no disease. And furthermore, very true, they state that it is the decision whether or not to be ill that can be influenced by legislation, and not the presence or absence of morbid anatomy. Interesting in future research would be to focus on why a person presents with soft tissue symptoms, rather than focus on who and how.

McCain and coauthors (46) reported on the longterm disability payments and litigation in fibromyalgia syndrome from the Canadian perspective. The determination of disability is considered to be a great problem, because of the perceived subjective nature and the absence of well defined criteria for diagnosis. Together with the uncertainty about the natural history this sums up to create problems in litigation and determination of rehabilitation costs. The article was written by McCain together with a medical director of a major Canadian longterm disability insurance carrier and with a barrister involved in litigation surrounding patients with fibromyalgia. They think it is important that lawyers and third party payers, like insurance companies, should cooperate with physicians to determine the hidden costs (longterm disability payments and compensation arising from litigation) of fibromyalgia so that it is possible to make a fairer estimate of longterm disability. This article puts up three headlines, which if they were reached would result in less costly litigation, predictable outcome and also predictable costs for the third party insurers, fairer treatment of litigants and a more efficient jurisprudence system. These headlines were accurate definitions of the syndrome using standardized diagnostic criteria, assessment procedures which are valid, reliable and responsive to the degree of disability and last, formal rehabilitation programs aimed at returning the individual to longterm employment at reasonable costs. These headlines are at this time not accomplished and the question of the degree of disability needs to be answered separately in each different person, because of the variability in symptoms. To find objective assessment methods to obtain the degree of disability in fibromyalgia is indeed very important. The diagnosis of fibromyalgia should never on its own have the implication of a disability payment. In 1990 classification criteria were published after a multicentre criteria study, but these are not diagnostic criteria. And surely a patient with only 10 tender points should not be withheld from treatment programs for fibromyalgia patients. It has been shown that the presence of tender points, which in itself is a subjective experience identified by the patient at physical examination, can be objectively screened, for instance the consistency of tender points (chapter 7). But there is no relation between number of tender points and disability established.

There certainly are major differences concerning disability payments and litigation in the different countries. In the Netherlands compensation claims for workrelated fibromyalgia are not made, but claims on insurance companies following an accident,

become more common. An example of the last is the whiplash. At this time there are fibromyalgia patients that receive a disability pension, because of the supposed inability to perform work. The assessment of the degree of disability is in this field a major issue as well.

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# Clinical aspects, natural history and medical consumption in fibromyalgia: a description of a patient group

A.A. KNIPPING, A.C.E. DE BLÉCOURT.

# Introduction

When fibromyalgia in the seventies (fibrositis in those years) became known as a syndrome, a series of publications have emerged in which clinical aspects of this syndrome are described. Different criteria sets made a comparison between the patient groups that were described in these studies very difficult. When the ACR 1990 criteria for fibromyalgia (1) were developed, comparison between different patient populations could be made more easily. For a good understanding of fibromyalgia and the relation of this syndrome to other syndromes (e.g. chronic fatigue syndrome, irritable bowel syndrome, myofascial pain syndrome), it is necessary to describe the clinical aspects and its natural history. The latter has been done by Felson and Goldenberg (2). They used interviews and followed 39 patients from an office-based, academic, rheumatology referral practice over a period of 3 years. They concluded that fibromyalgia is a chronic disease, with symptoms that usually persist for at least 3 years after diagnosis. Symptom remissions are rare, and when they occur, are often transitory. Longterm medication use is the rule. Generalization to the total fibromyalgia population is doubtful however. A referral population was studied, which may be a biased sample of those with relatively severe, long-standing symptoms. Hawley et al. assessed 75 fibromyalgia patients at monthly intervals during a 1-year period (3). The symptoms of individual patients and the group as a whole regarding sleep, pain, severity, psychological status, and functional disability were remarkably stable over the 1-year period. The authors noted no global trends toward improvement or worsening, nor seasonal effects.

Pain is the primary characteristic of fibromyalgia. For example, Wolfe et al. (1) found that 97.5% of fibromyalgia patients complained of widespread pain; in comparison, 71.1% of chronic pain controls expressed a similar complaint. Several studies, using visual analogue scales, numerical rating scales and multidimensional approaches to pain, such as the McGill Pain Questionnaire, point out that high levels of pain are perceived by fibromyalgia patients, when compared to other patient groups in which chronic pain is involved (4).

The presence of tender points is another important factor in fibromyalgia, as has been described in chapter 7.

In a description of the clinical features of fibromyalgia Wolfe (5) makes a distinction between core features (present in all patients: generalized pain and widespread tenderness), characteristic features (present in more than 75% of patients: fatigue, non-refreshed or disturbed sleep, morning stiffness), common features (present in more than 25% of patients: irritable bowel syndrome, Raynaud's phenomenon, headache, subjective swelling, paresthesias, psychological abnormality, and functional disability), and coexisting rheumatic conditions, for example arthritis, low back and cervical disorders, tendinitis etcetera, whose symptoms intertwine and overlap with those of fibromyalgia. Generally there are no clinical or laboratory abnormalities in fibromyalgia beyond that what one might expect by chance or when other disorders

are present.
Very little is known about the pattern and amount of medical consumption in fibromyalgia. The wide variety of possible medication types and many different treatment forms make a stock-taking a difficult task.
Henriksson (6) concluded on basis of a study on the longterm effects of fibromyalgia that this syndrome must be regarded as a chronic non-remitting pain syndrome, with considerable social consequences and involvement in all aspects of daily life. Adaptation seems to be dependent of individual characteristics in the patients. Successful adaptation from the viewpoint of the patients does not implicate the same from the viewpoint of the society. A great amount of medical consumption may seem a satisfactory way for the patient, but clinicians feel that medication use should be minimized.
Studies have been made of the socioeconomic impact of fibromyalgia (see also chapter 8), but the great differences in social security systems and medical care facilities between countries make a meaningful comparison between studies that are carried out in different countries very difficult.
A description of clinical features in a Dutch population of fibromyalgia patients has not been made yet. The objective of this chapter is to make a description of the clinical features of a Dutch fibromyalgia population. Also a description is made of the pattern and amount of medical consumption in this group. An inquiry, carried out in 1986 by the Dutch patient's organisation for fibromyalgia shows that more than 60% underwent therapy (varying from physical therapy to non-allopathic forms of treatment) for their fibromyalgia complaints, with only moderate effects. For the Dutch health insurance system the high costs of the various forms of treatment and medical supplies without certainty about the necessity or effectiveness form a problem (7).

# Methods and subjects

In the years 1989 till 1992 clinical aspects of 161 fibromyalgia patients were charted, serving research aims that are described in chapters 14 (n=100) and 15 (n=61). Also 44 extra fibromyalgia patients were screened solely on medical consumption and natural history, making the total amount of patients that were involved in this study 205. All patients were recruited from the rheumatology outpatient clinic of the University Hospital of Groningen (the Netherlands) in a random selection procedure. All patients were diagnosed by their rheumatologist as having fibromyalgia. The patients first received a letter in which the aims of the research program was explained. Approximately 1-2 weeks later they received a telephone call and were asked to participate.
As part of the measurement procedure, a standardized interview was used to obtain data about the description and development of the complaints, the medical

consumption, and also some sociodemographic variables. Also a physical examination was performed by the physiatrist.

- Duration of complaints was measured with an interview question: "For how long have you had these complaints?" If an estimation by the patient proved to be difficult, the first time a doctor was visited because of their fibromyalgia complaints was taken.
- Perceived onset of complaints was measured with the question "How did your complaints start?", an open end question. The answers given by the patients were scored into one of the six possible categories: following an accident, following an operation, following an illness, after or during a period of overexertion, gradually, without preceding or provoking events, or different answers.
- Perceived natural history over the past year was measured with the open end question "Were there changes in your complaints over the last year?" Answers of the patients were scored in one of the 6 categories: better, no changes, more painful localizations, higher pain intensity (more pain), more painful localization and higher pain intensity, or changing/unclear.
- Patients were also asked to give a description of their complaints ("What are your most important complaints") and a description of their pain ("Can you describe your pain"). Some complaints were asked explicitly, such as sleeping problems, headaches, and irritable bowel syndrome.
- Factors influencing the fibromyalgia complaints were measured with two interview questions: "What worsens your complaints?" and "What makes you have less complaints?"
- Physical examination by the physiatrist included standardized musculoskeletal examination, in which presence or absence of posture abnormalities, problems with joint- or spine mobility, paresis, sensibility problems, abnormal reflexes and skin-fold tenderness were evaluated in a dichotomous way.
- Problems with activities of daily life were evaluated with help of an ADL-checklist, which is a part of the Fibromyalgia Impact Questionnaire (8). Patients had to state wether they could or could not perform a certain activity. The activities that could be performed by the patient were summarized, which yields in a score between 0 (not a single activity possible) to 9 (all activities possible).
- Finally, medical consumption was measured in two ways. The types of treatment were evaluated with the question "What treatment do you get for your fibromyalgia complaints?" The answers were grouped into four categories: no treatment, physical therapy, medication, and non-allopathic treatment (e.g. acupuncture, Reiki etc.). Combinations of the latter three categories were also possible.

If the patients used medication, the type of their medications was asked and then scored into one of the three possible categories: non-steroid anti inflammatory drugs (NSAID's), analgesics, and a category containing benzodiazepines and

antidepressants.
Some of the interview questions were expelled in later stages of the research program, for practical reasons. Total number of patients are given with each variable in the results, described below.

# Results

## Sociodemographic data

The group of 205 fibromyalgia patients consisted of 100 persons who took part in the research program in which we evaluated the effect of a combined treatment of psychomotor therapy and marital counselling (see also chapter 14), 61 persons who took part in the research program in which we evaluated the effect of psycho-education on a behavioral therapy basis (see also chapter 15), and 44 persons who were screened solely on a set of retrospective variables.
In table 1 some sociodemographic variables of the research group are summarized.
In a study performed by Leavitt et al. (9) the mean age for a group of 50 hospitalized fibromyalgia patients is 45.1 (SD=12.0), with 88% female and 78% married. In the report of the Multicenter criteria committee (1) several groups of fibromyalgia outpatients are described (n=558). The mean age varies from 48.0 (SD=2.0) to 49.1 (SD=12.8) years. Other studies (10) show that fibromyalgia is much more common in woman (76-95% female), and the

Table 1
SOCIODEMOGRAPHIC VARIABLES

| | | |
|---|---|---|
| Age | mean=44.3 SD=9.4 range 21-66 yrs | |
| % Female | 87.8 | |
| Marital status | 87.3% | married or living with partner |
| | 5.9% | divorced |
| | 1.0% | widowed |
| | 5.4% | single |
| | 0.5% | living with parents |
| Level of education | 26.3% | elementary education (finished or unfinished) |
| | 40.0% | low level secondary school |
| | 25.4% | medium level secondary school |
| | 8.3% | high level secondary school or university |
| Level of occupation | 79.2% | unskilled, housewives or unemployed |
| | 17.4% | skilled |
| | 3.5% | leading position |
| Disability compensation (Dutch: WAO) | 21.5% | full compensation |
| | 8.8% | partial compensation |
| | 10.2% | unknown |
| | 50.7% | no compensation |

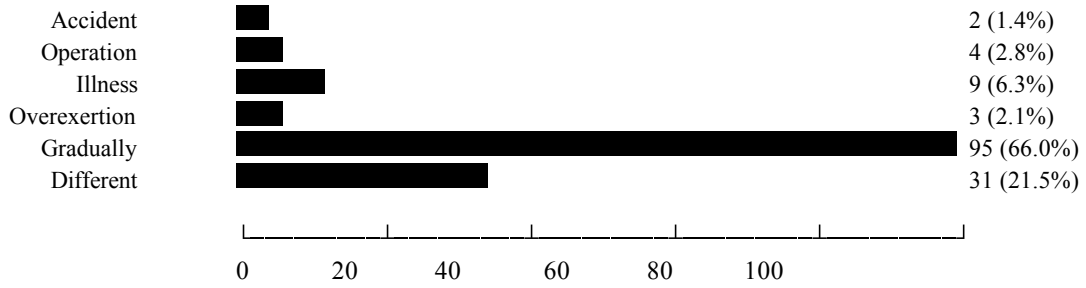
age of onset in clinical series varies from 12 to 45 years. Onset after 60 is rare. In most clinical studies the mean age is between 40 and 55 years. These data are very similar to those of our study.

The sociodemographic data of fibromyalgia patients do not seem to differ much of those of other chronic pain patients, except for the sex ratio. In the study of Reitsma (11) the mean age of a group of 219 chronic pain patients is 48.7 (SD=12.4), with 64.7% female. In his study 74.6% is married or living with a partner and 29.1% receives disability compensation. 61.3% of the chronic pain patients has a low level of education (our study: 26.3 + 40 = 66.3%), 30.1 medium and 8.6 had a high level of education.

# Complaints

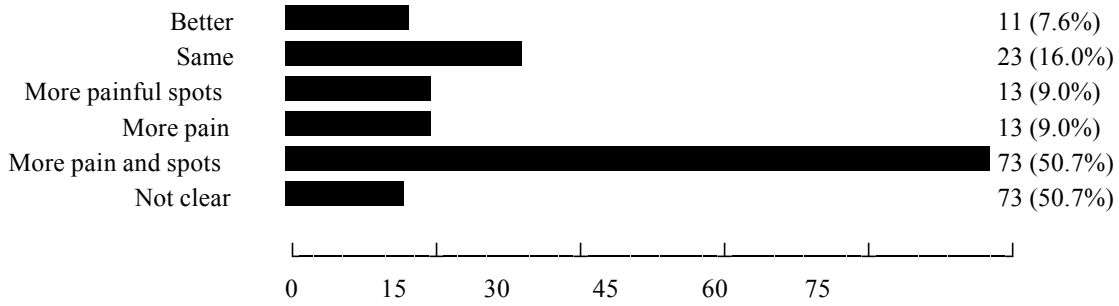
The mean duration of the complaints is 10.1 year (SD=5.8). Some data about the onset of the complaints (as perceived by the patients) is summarized in figure 1 .

Figure 1
PERCEIVED ONSET OF COMPLAINTS (N=144)




The vast majority (66%) of the group did not indicate a preceding or provoking event and stated that their complaints came spontaneously and gradually. Only 12.5% stated a provoking or preceding event.
The natural history of the complaints in the past year is shown in figure 2 .

Figure 2
NATURAL HISTORY OF COMPLAINTS IN PAST YEAR AS PERCEIVED BY THE PATIENTS (N=144).




Few patients (16%) stated that the situation remained the same as referred to their complaints. Only a small group (7.6%) had the feeling that their complaints were gradually diminishing.
The vast majority (almost 70%) of the group complained about a worsening of their complaints in some way.
In the Swedish study of Henriksson (6), mentioned earlier 50% of the patient group (n=56) reported an increase of their symptoms in the past 5 years, 35% reported no change and approximately 15% reported improvement. The Dutch fibromyalgia patients seem to evaluate the natural history of complaints as being a little more negative.
Pain was present in almost all patients; only one person did not mention pain as part of the subjective complaints. Fatigue was mentioned spontaneous by 58.6% and stiffness by 26.4%

of the patient group.
The most frequent spontaneous descriptions of the pain complaint was "nagging" (Dutch: "zeurend") which was mentioned by 47.9% as the most prominent pain description. Another frequently mentioned description was "stabbing" (30.6%) (Dutch: "stekend").
Patients were also asked about the presence of some frequently reported concomitant complaints. Results are presented in table 2 .
Problems with sleeping and a nonrestorative sleep seem to be "normal" in fibromyalgia and headaches and fatigue is reported by almost 60% of the total group.

Table 2
PRESENCE OF SOME CONCOMITANT COMPLAINTS IN FIBROMYALGIA

| | |
|---|---|
| Sleeping problems | 73.6% |
| Unrefreshing sleep | 91.0% |
| Headaches | 59.7% |
| Irritable Bowel Syndrome | 30.3% |
| Raynaud symptoms | 23.2% |

Also questions were asked about factors that could have a possible influence on the complaints. The results can be found in table 3 .

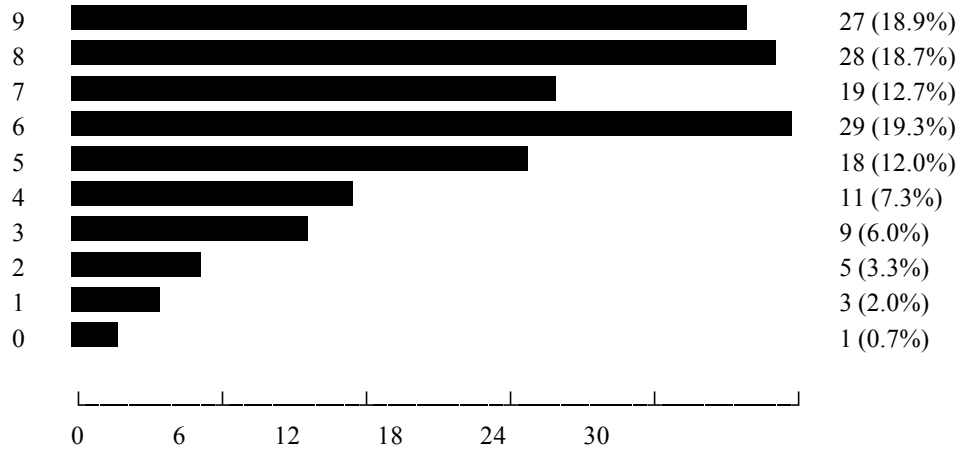
Table 3:
FACTORS INFLUENCING THE FIBROMYALGIA COMPLAINTS AS PERCEIVED BY THE PATIENTS.

| | |
|---|---|
| Worse through humidity | 49.7% |
| Worse through cold | 42.7% |
| Worse through stress | 44.1% |
| Worse through physical exercise | 83.2% |
| Better through warmth | 66.4% |
| Better through resting | 18.2% |
| Better through relaxation | 12.6% |
| Better through seeking distraction | 15.4% |

Fibromyalgia patients can easily tell what worsens their complaints, but apart from warmth (especially hot showers) they perceive their complaints as being fairly uncontrollable.
Physical examination as performed by the physiatrist show that clear musculoskeletal abnormalities are rare. In 2.9% structural posture abnormalities were seen. In 10.2% there were problems with joint- or spine mobility. Paresis did not appear as phenomenon. Only 2% showed clear sensibility problems. Absence of reflexes were found in 1% of the patient group.

Skin-fold tenderness was present in 57% of the total group, in 41.4% in both scapular regions, in 13.4% only on the left side and in 2.5% only right.
Results obtained from the ADL-checklist are represented in figure 3 .
Only 19% of the patients indicate no problems at all with activities of daily life.
Approximately 20% claim to have severe problems in this area (0 to 4 activities possible).
Apparently the patients themselves seem to perceive fibromyalgia as a crippling and debilitating syndrome and they experience several disabilities.

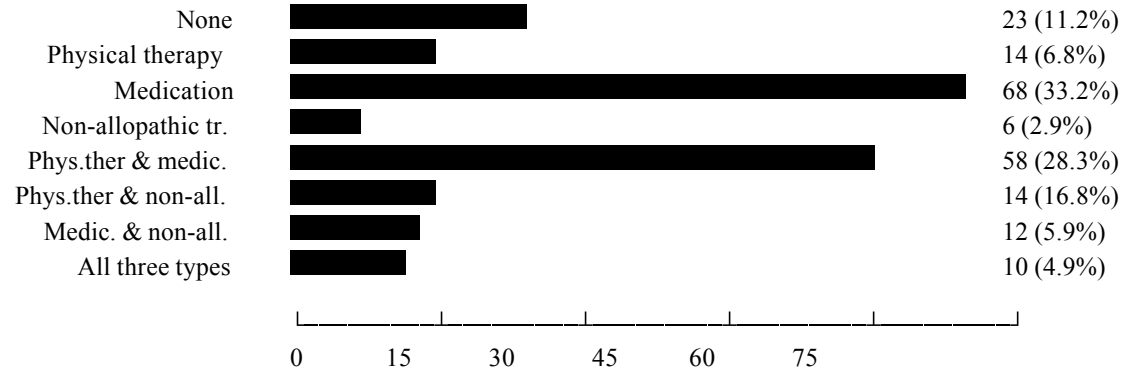
Figure 3
NUMBER OF ADL-ACTIVITIES THAT COULD BE PERFORMED BY FIBROMYALGIA PATIENTS




## Medical consumption

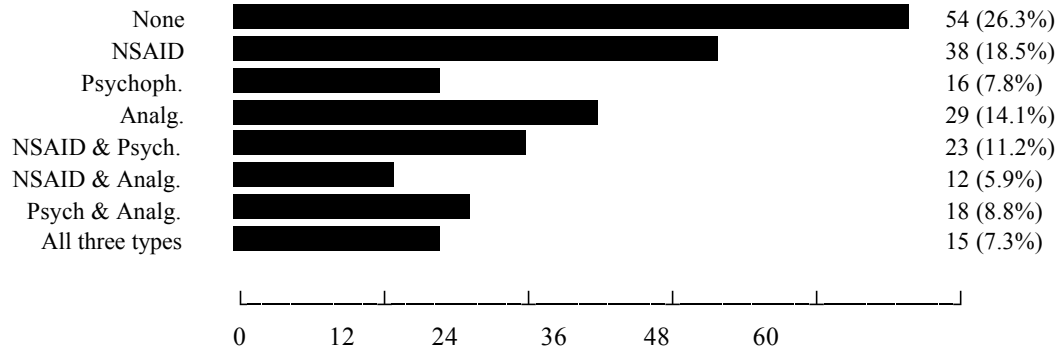
Many types of therapy seem to be tried out by fibromyalgia patients. The main described forms of treatment are 1) physical therapy, 2) medication and 3) non-allopathic treatment. Very often combinations of these types can be found. The results of the group that was examined in this study can be found in figure 4 .

Figure 4
COMMON TYPES OF TREATMENT IN FIBROMYALGIA (N=205)




As can be derived from figure 3 , medication is the most frequently applied type of treatment in fibromyalgia. All together 72.3% of the patients receive medication. Physical therapy is a less frequently used type of treatment (46.8%). Combination of medication and physical therapy is applied in almost one third (28.3%) of the patient group.
Medication was divided into three categories: 1) the non-steroid anti inflammatory drugs (NSAID's), 2) analgesics and 3) psychopharmacons (tranquillizers, antidepressants and hypnotics).
Results are presented in figure 5 .

Figure 5
MEDICATION USE IN FIBROMYALGIA PATIENTS (N=205)




Almost three quarter (73.7%) of the patient group use medication that fit into these three categories. NSAID's are the most frequently prescribed medication (37.0%). Analgesics and psychopharmacons are prescribed in respectively 27.3% and 27.8%.
More than a quarter of the total group (25.9%) use a combination of two medication types and 7.3% even three types.

# Discussion

One of the most striking findings found in research on clinical and epidemiological aspects is the high percentage of female patients in fibromyalgia. In spite of extensive research and discussion a good explanation for this still has to be found. Hormonal and sociocultural aspects, or perhaps a combination of these two are likely to be important as explanatory factors. Also in our study the percentage of female patients is high, comparable to the findings in other studies (9).

The fibromyalgia patient group described in this chapter has a duration of complaints of 10.1±5.7 years, which seems to be long. The duration of symptoms in the study of Felson and Goldenberg, mentioned earlier (2) was 4.3±4.7 years. In a study performed by Campbell et al. (12) the mean duration was 7.6 years. Their patient group consisted of 22 patients selected from a general medical outpatient population. Twelve patients (54.5%) identified events which they felt precipitated their fibromyalgia; these included injury (36.4%), illness (13.6%) and emotional stress (4.5%). There seems to be a difference with the Dutch patient group, described in this chapter, in which 66% of the patient state that the fibromyalgia complaints emerged gradually, without a precipitating event. In a controlled study on 113 fibromyalgia patients from an ambulatory clinic, Yunus et al. report a duration complaints of 6.9±7.9 years (13).

Diagnosing fibromyalgia is time-consuming, since the possibility of other diseases (e.g. rheumatoid arthritis) have to be excluded. This may play a role in the strong feelings of uncertainty that are expressed by these patients, even after the diagnosis has been given. The fact that the complaints are worsening over time, as perceived by the patients themselves, is rarely supported by an objective worsening in the view of the doctor, which also contributes to the feelings of uncertainty.

In spite of the fairly neutral outcome of physical examination the patients themselves perceive fibromyalgia as a crippling and debilitating syndrome, which keeps them of a normal pattern of daily activities and work.

Medical consumption seems to be high in fibromyalgia. A typical phenomenon is that many patients state that the beneficial effect of most forms of treatment is insignificant, without a changing of their pattern of medical consumption.

A more detailed analysis of medical consumption is not possible, using only interview questions. Further research on this issue could be based on a registration of the family doctor, in a longitudinal research design. Retrospectively the registration of health-insurance companies can be used also for this purpose.

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Chapter 10

# Psychological aspects of the fibromyalgia syndrome

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# Introduction

Fibromyalgia is a form of nonarticular rheumatism characterized by chronic and diffuse musculoskeletal pain accompanied by exaggerated tenderness at specified anatomical sites. These sites are termed tenderpoints. X-rays and laboratory blood tests show no abnormalities in fibromyalgia patients.
In spite of extensive research in the field of fibromyalgia, its relation to the accompanying psychological problems is still unclear. It has been suggested that fibromyalgia is a psychogenic disorder (1) or a somatic component of an affective disorder (2). In many research reports a relation between fibromyalgia and psychological distress is proven but there is little certain about the direction of the relation between these matters. In this section the literature on the psychological aspects will be reviewed. Because chronic widespread pain is the most prominent feature in fibromyalgia, the relations between psychological aspects and pain are evaluated. Finally, an attempt will be made to determine whether the psychological aspects can be seen either as cause or consequence of the fibromyalgia complaints based on the presented studies.

# Fibromyalgia and depression

Payne et al. (3) found no differences between fibromyalgia patients (n=30) and rheumatoid arthritis (RA) patients (n=30) on the Depression scale of the Minnesota Multiphasic Personality Inventory (MMPI). The mean score of both groups were not in the pathological range. Both patient groups in this study consisted of hospitalized patients, which makes generalization to the total population of patient groups difficult.
Ahles et al. (4) also did not find a significant difference between fibromyalgia patients (n=45) en RA patients (n=30) on the Depression scale of the MMPI. Both groups differed significantly ($p<0.01$) from a group of normal controls (having no illness). The mean scores of the RA and fibromyalgia group were also in this research report not in the pathological range.
Fibromyalgia patients (n=46) did not have higher score on the depression scale of the MMPI than RA patients (n=76) according to Wolfe et al. (5). A group of patients who were diagnosed as having fibromyalgia as well as RA (n=32) described themselves as being more depressed than both other groups. Wolfe et al. (6) also used the Arthritis Impact Measurement scales (AIMS). In this inventory the fibromyalgia patients had significant higher scores than both other groups on the depression scale.
Hudson et al. (7) used the NIMH Diagnostic Interview Schedule (DIS), which generates diagnoses by DSM-III criteria. Current major depression was present in 26% of the fibromyalgia patients (n=31) and in none of the RA patients (n=14). Seventy-one percent of the fibromyalgia patients had current or past diagnoses of major depression versus 14% in the RA group. The fibromyalgia patients also had

significantly higher scores on the Hamilton Rating Scale for Depression. An extension of this study by Goldenberg (8) showed similar results.
In 1985 Clark et al. (9) performed a study in which fibromyalgia patients (n=22) were compared with patients without fibromyalgia (n=22). Both groups were selected from a general medical outpatient population. Both groups were given 3 standardized psychological questionnaires: the Beck Depression Inventory (BDI), the Spielberger State and Trait Anxiety Inventory (STAI) and the SCL-90. No differences were found between the two groups on the depression scale of the SCL-90 and the BDI.
Kirmayer et al. (10) compared a group of 20 fibromyalgia patients with 23 RA patients with a structured psychiatric diagnostic instrument (DIS: Diagnostic Interview Schedule), a depression scale (CES-D) and a modified version of the somatization scale of the SCL-90. Their results did not support the contention that fibromyalgia is a form of somatized depression because there were no significant differences on variables related to depression. Fibromyalgia patients reported significantly more somatic symptoms, however, indicating a process of somatization.
Ahles et al. (11) compared the responses of a group fibromyalgia patients (n=45) with a group of RA patients (n=29) and a group of healthy non-pain controls (n=31) on the Zung Self-Rating Depression scale and found no difference between the fibromyalgia and the RA group. Their hypothesis that the presentation of chronic pain in absence of a known organic pathology is a variant of "depressive disease" was not supported by these results. In both groups approximately 30% appeared to experience depressive symptomatology.
From the studies described above it has become clear that fibromyalgia and RA patients show more depressive features than normal healthy controls which is not surprising. Having chronic pain complaints will have a negative effect on mood and it is almost certain that depression subscales of questionnaires contain items that relate directly or indirectly to physical complaints (e.g. becoming inactive, losing interest in sexual activity, spending time in bed) as well to depression.
Another remark has to be made referring to the definition of the concept "depression". If questionnaires are used to evaluate the presence of depression, it is conceptualized as a continuous spectrum, not as a psychiatric diagnose. For the latter one needs to have made an evaluation with help of diagnostic criteria such as DSM III. Results of studies using different techniques can not be compared directly for this reason. Depressive symptoms are well accepted to accompany most chronic medical conditions, and 12-36% of medical outpatients have depressive symptoms (12).

# Fibromyalgia and stress and anxiety

In the study of Ahles et al. (4) a comparison was made between 45 ambulatory fibromyalgia patients, 30 RA patients and 32 normal controls on the Life Events Inventory (LEI). Fibromyalgia patients scored significantly higher on this inventory

than both other groups, indicating that they experienced more stressful life events. Within the group of fibromyalgia patients the group of "psychological disturbed" patients (31%), based on MMPI scores, had the highest scores on the LEI. Ahles suggests further investigation based upon DSM III criteria, to determine if psychiatric diagnosis can be found in subgroups of fibromyalgia patients. Furthermore, it should be noted that the association of psychological factors in a medical condition is not unique to fibromyalgia.

Hell et al. (13) found in a comparison between fibromyalgia outpatients (n=48) and outpatients with RA (n=25) that fibromyalgia patients showed significantly more stress and problem situations in their actual life and before outbreak of their rheumatic problems than RA patients, using a standardized psychiatric interview. Both studies described above seem to suggest that there may be a relation between life stress and anxiety in fibromyalgia.

Wolfe et al. (5) discovered that fibromyalgia (n=46) patients had higher scores on the Anxiety scale of the AIMS than RA patients (n=76). In contradiction with the results of Hell (13) and Ahles (4) in this study there were no differences between the fibromyalgia patients and the RA patients in tests of life stresses using the Family Inventory of Life Events.

Hudson et al. (7) discovered more anxiety disorders in the current or past (in 55% of the patient group), based on DSM-III criteria in fibromyalgia patients (n=31) than in RA patients (n=14; no anxiety disorders) using the DIS.

In the study of Clark (9), mentioned above, no differences were found between fibromyalgia patients (n=22) and a control group of patients having other complaints than fibromyalgia (n=22) on the anxiety and phobic anxiety scales of the SCL-90, and the anxiety-state and anxiety-trait of the STAI. These findings contrast with those of other studies. However the control group in this study was heterogenous with respect to medical diagnosis. In this group 60% also complained of musculoskeletal pain, which makes it very difficult to conclude what the meaning is of these findings. Perhaps many of the patients in this group had complaints that share a common basis or are closely related. Another explanation for the fact that no differences were found between the two groups, is the way the patients were selected. The fibromyalgia patients were selected of a group of 596 patients attending a general medicine and medical subspeciality clinics and these patients were not seeking help for their musculoskeletal complaints. Most other studies use outpatients from rheumatology departments.

Uveges also used the SCL-90 in a study in which 25 ambulatory fibromyalgia were compared with 22 subjects with RA (14). Their analysis show significant differences on 6 of the 12 subscales, indicating more psychological distress in the fibromyalgia group than in the RA group.

Fibromyalgia patients had also higher scores on the two subscales of the Hassles Scale: number of hassles and severity of hassles, indicating that the fibromyalgia

subjects experience more life stress than the RA subjects. The number of hassles appeared to be a significant covariate for each of the SCL-90 subscales, except Somatization. This is an interesting finding which makes further stress-related research in the field of fibromyalgia necessary.
Another study in which the relation between psychological stress and fibromyalgia is examined is that of Dailey et al (15). In this study participated three groups of volunteers, all outpatients: 28 patients with fibromyalgia, 20 patients with RA, and 28 pain-free normal controls. The Life Experience Survey (LES), the Hassles scale, and the Daily Uplifts Scale were used to assess levels of stress. The AIMS was used to assess the extent of functional impairment in the two patient groups. Their results demonstrate a relationship between daily hassles and fibromyalgia. Patients with fibromyalgia reported more hassles than either patients with RA or controls but did not report more major life events. Further analysis revealed relationships between stress scores and subscales of the AIMS, with the Hassles Scale being closely related to disease impact.

# Fibromyalgia and other psychosocial aspects

Payne et al. (3) discovered that fibromyalgia patients produced higher scores on the neurotic scales hypochondriasis and hysteria and the psychotic scales paranoia and schizophrenia of the MMPI than RA patients. The scores of the fibromyalgia patients on the both neurotic scales were in the pathological range. The design of this study may have led to some selection bias because the subjects were hospitalized patients. It can be hypothesized that patients with milder complaints (i.e. ambulatory patients) also show less psychological problems (16).
Ahles (4) used ambulatory patients and found higher scores of fibromyalgia patients on the both neurotic scales (hypochondriasis and hysteria) and also on the psychasthenia and the schizophrenia scales of the MMPI. The group means of the fibromyalgia group were not in the pathological range. Ahles also stated that the group of fibromyalgia patients could be divided into three subgroups: group 1 (normal), group 2 (typical chronic pain) and group 3 (psychological disturbance). Each group consisted of approximately one third of the studied group of fibromyalgia patients.
Wolfe et al. (5) found higher scores on several scales of the MMPI for fibromyalgia patients when compared with RA patients. Patients with fibromyalgia (n=46) and patients with RA as well as fibromyalgia (n=32) had higher scores on the "neurotic scales" when compared with RA patients (n=76), and fibromyalgia patients had mean scores in the pathologic range on psychopathic deviancy, psychasthenia and paranoia scales.
The use of the MMPI to study psychological aspects in patients with somatic complaints was criticized by Smythe (17). Many of the items in the MMPI are pain-related and the scales are not independent. Formal definitions of syndromes as

fibromyalgia, with widespread chronic pain, often accompanied by fatigue can lead tot bias towards neurotic scores. In other words: there may be a relation between the experienced severity of complaints and the MMPI scores. Ahles et al. (18) reanalysed their data of the 1984 study and concluded on basis of contemporary norms that the number of "psychologically disturbed" fibromyalgia patients was appreciably reduced. In a study performed by Hell et al. (13) fibromyalgia patients (n=48) reported more negative childhood experiences than RA patients (n=25) such as early separation from their parents (25% versus 8%) in a standardized psychiatric interview. Fibromyalgia patients described themselves as more inhibited in aggressions, more uncommunicative, less prevailing and emotionally more unstable than RA patients on the Freiburg Personality Inventory. Leichner-Hennig (19) found no difference on the mean scores on the Freiburger Personality Inventory between fibromyalgia patients (n=20) an RA patients (n=20), nor on a questionnaire for psychosocial relations (Giessen Test) and a questionnaire on pain experience.
Martinez et al. (20) compared 44 women with fibromyalgia with 41 women with RA on quality of life aspects with the help of several questionnaires. They concluded that fibromyalgia has a negative impact on quality of life, similar to RA. Clinical, functional, and economic problems related to the fibromyalgia complaints were observed, such as: global health status, physical disability, helplessness, sleep quality, and professional life. The alterations observed appeared to remain relatively stable over time.
Coping is they way a person deals with conflicts and stressful events. If there is a relation between stress and impact of the disease in fibromyalgia (15), it is interesting to find out how fibromyalgia patients cope. Spanjer (21) compared 35 fibromyalgia patients who were seen by a medical health-insurance officer (GMD-verzekeringsgeneeskundige) with 32 patients with other complaints than fibromyalgia. Fibromylagia patients had higher scores on the subscale "Comforting cognitions" than the control group. Spanjer suspects that patients with complaints without a clear anatomic substrate (such as fibromyalgia) use this style of coping with an expectancy or hope of treatment in the future. Having a syndrome that is known in medical practice is perhaps also less threatening than having to deal with the possibility of a psychogenic source of the complaints.

# Psychological factors related to pain

Pain is the most prominent complaint in fibromyalgia. As will be demonstrated in chapter 11 many psychological aspects in fibromyalgia can be seen as aspects of having chronic pain complaints. For this reason it is useful to look at research in the field of chronic pain.

## Perception of pain

To perceive an unpleasant sensoric sensation as pain some criteria have to be fulfilled (22). If the pain sensation develops rather gradual than it will be recognized as such if the organism is not to busy with important activities. Pain can therefore remain unnoticed for a long time if the person has to deal with important and difficult conditions of life. This can be part of the explanation why it is often very difficult to establish the starting point of the complaints in fibromyalgia. Another aspect which makes it difficult to perceive a unpleasant stimulus as pain is the so called figure-ground transition. Pain must be recognized as such before an appropriate reaction can be carried out. If the recognition stays out, the pain remains hidden in a vague, unpleasant bodily sensation (hidden pain).

## Pain and attention

The amount of attention that is given to a pain sensation can influence the perceived intensity of the pain itself. Athletes can sometimes continue their contest without noticing pain in spite of a serious injury. Only after the contest the pain and the injury are discovered (23).
For an organism it is important to direct its attention to a noxious event accompanied by an acute pain. In this way the amount of tissue damage can be assessed and necessary action can be undertaken (22).
If pain becomes chronic than a sustained attention on the pain is no longer beneficial. The reason for attention to the painful spot is no longer necessary because there is no longer a threat for tissue damage. But vigilance can grow into a perceptual habit and can develop into hypervigilance. Unpleasant bodily sensations are monitored continuously. Hypochondria can eventually be the result. Of cause these processes are controlled by other psychological mechanisms such as reinforcement, cognitions and also personality.
When the focus of the attention is directed towards other aspects of life, the pain is experienced as less annoying. Manipulating the attention in combination with strong suggestions is probably the reason why hypnosis can establish an analgetic effect (24).

## Pain and anxiety

Anxiety can be a consequence of pain, almost certainly if there is serious tissue damage or if the cause of the pain is unknown. Anxiety does also influence the amount of perceived pain. The higher the level of anxiety the higher the pain that is experienced. Anxiety and pain are in a reciprocal relationship (25).
Anxiety is mainly related with the acute phase of pain in which there is much uncertainty about the amount of tissue damage or the cause of the pain. In chronic pain anxiety plays a less important role. Apparently the uncertainty and the bewildering of the pain sensation diminish over time, unless a threatening diagnosis (e.g. cancer) is made (22).

## Pain and depression

As with anxiety it is also unclear with depression whether it is cause or consequence of the pain complaints. Depression is mainly related to the chronic phase of pain. This can be the result of the belief that control over the pain is impossible and negative cognitions about the future in relation with the pain complaints (26).
Pain complaints are perceived as meaningless by chronic pain patients, certainly if the pain complaint cannot be treated because of the unknown cause. The pain is often perceived as an undeserved punishment, even more if the pain complaints are

perceived as an impregnable obstacle towards a normal life. If there is a lack or shortage of adequate coping skills these patients may fall into a pattern of lethargy. This reaction can be seen as a form of "learned helplessness" (27).
The depression can also be out of the focus of attention and be pushed to the background through the pain complaints. If this is the case then the pain complaints serve a function: keeping the depression out of consciousness. Treating the pain complaints may bring forward the depression which may worsen the overall situation for these patients. If these processes take place than the interaction between the pain and the depression is described as a "masked depression" (26).

## Pain, early childhood experiences and learning processes

Responding adequately on noxious events does not seem to be innate. Dogs who are separated and raised in special dog-kennels where scratches and broozes are avoided were later not able to react adequately on noxious events. Reflexes remained intact, but these dogs did not show the normal emotional agitation that normally accompanies painful events (24).
With young children the anxiety that is related to a pain stimulus probably plays a more important role than the pain itself. A relative small medical operation (e.g. an injection) may bring about a vehement emotional reaction. If a child grows up it can make use of earlier acquired experiences and it is also capable of controlling emotions more adequately. Also the upgrowing child learns to recognize essential signals for dysfunctions and it also learns to communicate about it, which gives the child more control over the situation (28).
Experiencing pain can also be the consequence of a learning process. A somatic substrate for the pain is not a necessary condition. Fordyce (29) gives as an example the salivation that occurs when people are talking about delicious food. The salivation takes place without the presence of the food. People have learned to salivate when talking or thinking about food, just like the dogs of Pavlov who learned to salivate on the sound of a bell. Something similar can happen with pain complaints. If a person experiences pain after working in the garden, only seeing the garden or thinking about working in the garden can bring forward the pain. The garden itself has become a conditioned stimulus for pain. This process is known as classical conditioning.
Having pain, and even more, showing pain behavior does also have consequences. Persons can be relieved of difficult or unpleasant duties when they show pain behavior. It can also be followed by care and attention. According to the theory of operant conditioning the pain behavior will be performed more frequently. The consequences of this behavior (avoiding unpleasant duties or being looked after and receiving attention) can act as reinforcers for the pain behavior itself. A somatic substrate for the pain complaints is not necessary.

## Pain and cognitions

The appraisal of a noxious event is an important factor in how the person responds. If an unpleasant bodily sensation is thought to be a forerunner of a serious disease than the reaction of the patient will differ dramatically of the reaction of someone who thinks he has to deal with a harmless event (22).

The context in which pain complaints take place are important for the cognitions that arise. Beecher discovered that only 30% of serious injured soldiers wanted morphine for their pain and that approximately 80% of civilians with similar injuries asked for morphine. The wounded soldiers were more relieved because of the fact that they had survived and that they could leave the battlefield. For the civilians it was different. Their injury was mainly perceived as a depressing and ominous event which had only negative consequences (24).

Cognitions about pain are formed as the consequence of continuous learning processes. Several inadequate or incorrect cognitions can be the result, which on its turn can be the base for emotional disturbances and inadequate pain behavior (30).

The amount of perceived control over the pain complaint is an important factor in the forming of cognitions and coping behavior. In experimental situations subjects appear to complain less if they believe to have control over the painful stimulus than subjects who are told that they cannot control the painful stimulus. It appeared that is not important if the persons actually has control. Only believing that one has control is sufficient to diminish pain complaints (31).

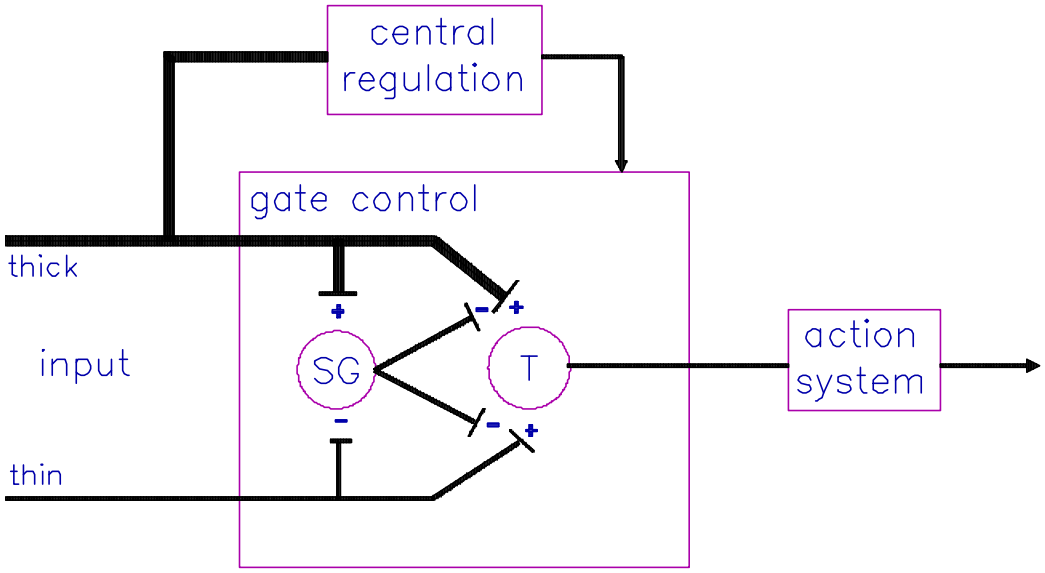
## Pain and social modelling

The perception of pain and also the amount and type of pain behavior are influenced by the context in which the pain takes place. Persons who expect to experience pain will tend to observe others in a similar condition. If the observed other persons reacts stoical, the observer will express less pain than if the person observes an over-sensitive role model. Observing an over-sensitive role model had a diminishing effect on pain threshold and pain tolerance (32).
Social modelling can give an explanation for the fact that pain complaints are more common in persons who live in families in which other persons also have pain complaints. This is even more the case if there are also emotional problems within the family system (28).
The way in which in a family is reacted on pain complaints is important for the further development of the pain complaint and the pain behavior. especially in families in which the pain patient is relieved from unpleasant duties and in which the patient receives attention and loving tender care, there is a high risk of reinforcing the pain behavior by means of operant conditioning (33).

## The gate-control theory of Melzack and Wall

Pain cannot be described in terms of neurophysiological processes only. Pain is not simply a function of the amount of damaged body tissue, but it is strongly modulated by processes such as attention, anxiety and other psychobiological processes. Based on these insights Melzack and Wall developed their gate-control theory of pain (34). Roughly described, the theory states that pain information that is transferred through the nervous system can be modulated. This modulation takes place in a specialized gate-control-mechanism situated in the dorsal areas of the spinal cord. A schematic reproduction of this model is presented in figure 1 .
If the gate is "open" the pain information can be transferred to the cortex: we are aware of the pain, but if the gate is closed the information is blocked and it cannot reach the cortex: we are unaware of the pain. The opening and closing of the gate is regulated by two different type of nerve fibers. Thick myelated nerve fibers excitate cells in the substantia gelatinosa, which in its turn inhibit the activity of the transmission cell: the gate is closing. Thinly
myelated fibers (a-δ fibers and c-fibers) inhibit the activity of the cells in the substantia gelatinosa. The inhibition of the transmission cell is diminished: the gate opens. Descending fibers from higher cortical and subcortical regions can facilitate or inhibit the information transmission via
the gate.

Figure 1
GATE-CONTROL THEORY OF MELZACK AND WALL




According to Melzack and Dennis (23) there are three dimensions that influence pain perception:

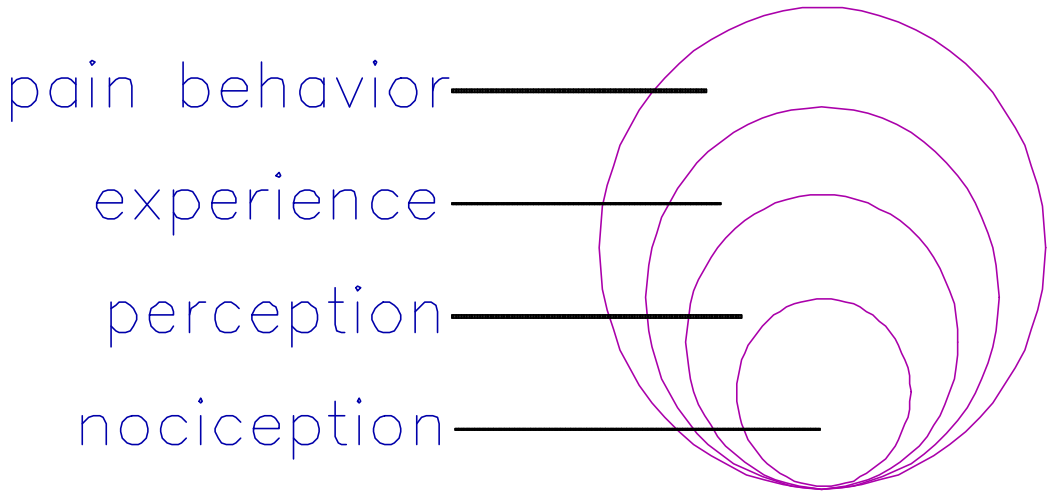
1. the sensoric-discriminative dimension
2. the motivational-affective dimension
3. the cognitive-evaluative dimension.

The gate-control model of pain is in accordance with many clinical findings about pain and also with physiological research. But some criticism is in its place because of a shortage of empiric foundation of the model. The question how and why some pain becomes chronic can not be answered with the help of this model alone.

## The multidimensional pain model of Loeser

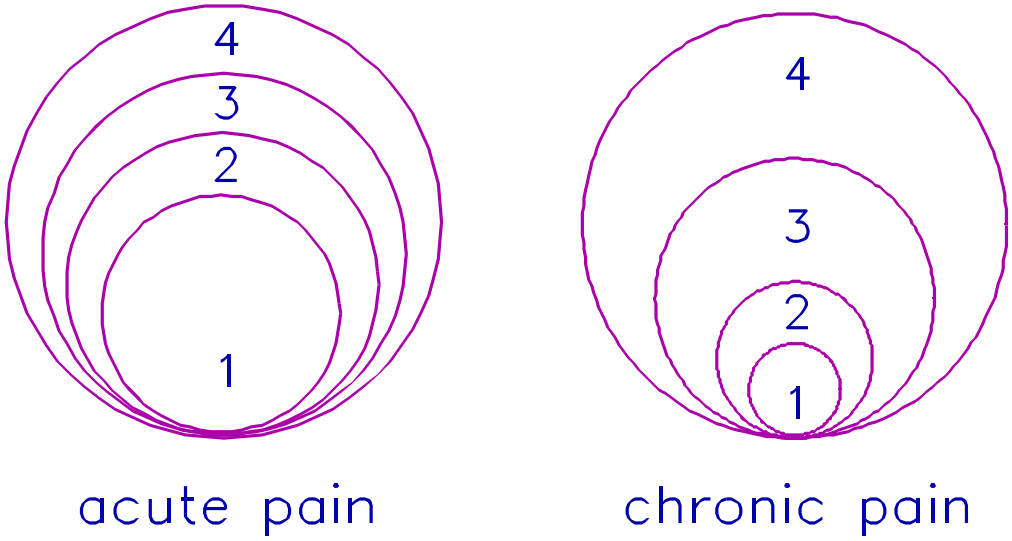
A model that combines neurophysiological and psychological aspects of pain in a completely different way is the pain model of Loeser (35) It is depicted in figure 2 .
The neurophysiological processes that underlie the pain stimulus is called nociception: neurotransmission, stimulation of the pain receptors. It has a direct relation with the amount of tissue damage.

Figure 2
THE MULTIDIMENSIONAL PAIN MODEL OF LOESER




The nociception gives rise to pain perception: The stimulus is recognized as pain. The perception of pain is influenced by a variety of psychosocial and cultural factors and expresses itself in pain experience, which incorporates the emotional response on the pain. This pain experience will differ from person to person, depending on prior experience en personality.
Pain behavior is the way the persons expresses his pain to the outside world. Pain behavior is any type of behavior that can be observed by others and that is related to the pain. Not only for example limping or groaning is pain behavior according to Loeser, but also absenteeism (work) or visiting a doctor.
With help of this model some important differences between acute and chronic pain can be made clear in an easy way (see figure 3 ).
In the case of acute pain the processes that are most prominent are nociception and pain perception. Pain experience and pain behavior are of less importance in this phase. As pain becomes chronic (and especially if there is no demonstrable tissue damage) than the pain is more under control of pain experience and pain behavior. Emotional factors develop over time, of which anxiety, depression and hostility seem to be the most important ones. The role of pain behavior is also increasing over time. Significant others are going to respond in a predictable way, which in its turn attributes to several forms of operant conditioning.
The pain model of Loeser can serve as a starting point for many types of research in the field of pain and it has proved its value in this respect. But one has to bear in mind that this model is purely descriptive en it does not give an explanation for the reason why many aspects of pain change over time. Also cognitive aspects remain unclear in this model (36).

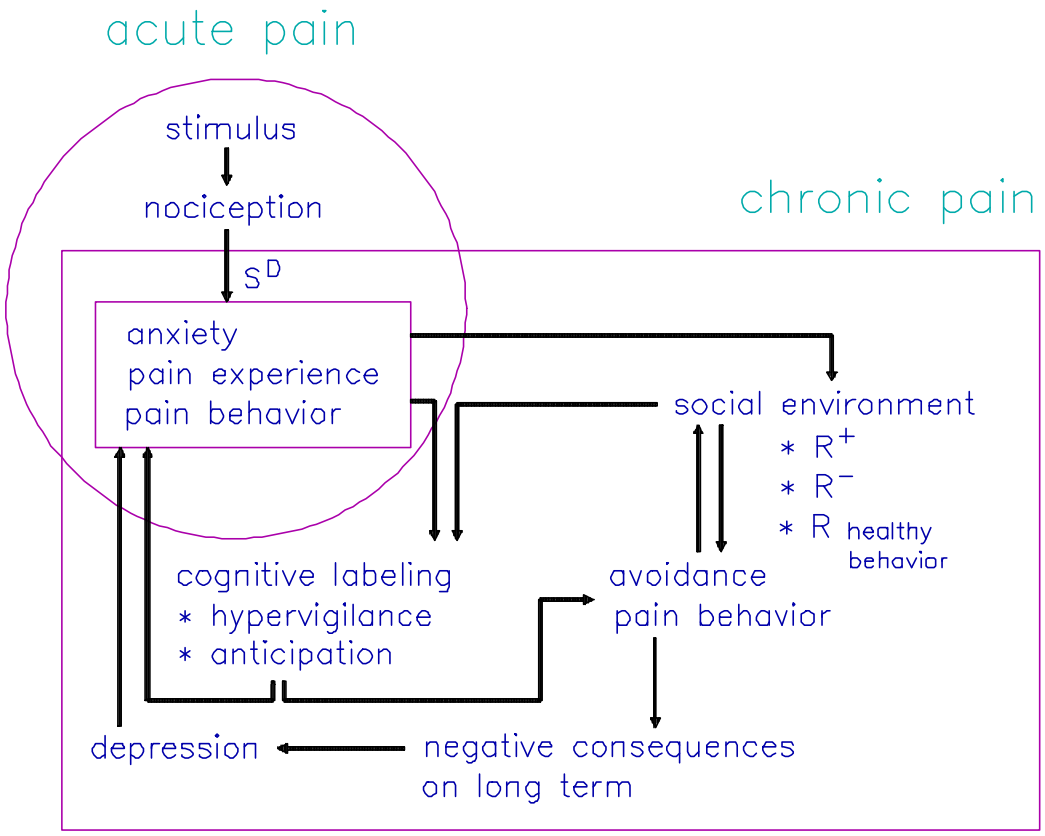
Figure 3
ACUTE VERSUS CHRONIC PAIN ACCORDING TO LOESER. 1=NOCICEPTION; 2=PAIN PERCEPTION; 3=PAIN EXPERIENCE; 4=PAIN BEHAVIOR




## A cognitive behavioral oriented model of pain

When pain becomes chronic behavioral factors play an important role, by means of classical and operant conditioning. Also cognitions about pain and pain-related factors play their role in the process of chronisation. There is in fact a reciprocal relation between cognitions and behavior that is explained in a very clear way in the model that is drawn up by Vlaeyen (37). It is depicted in figure 4 .
The factors that play an important role in the chronic phase are in the circle of this model while the chronisation process is surrounded by the rectangle.
For example, if pain is labelled as a symptom of a serious illness, this will also affect behavioral factors (illness behavior) and emotions (anxiety, depression). In the reverse, when healthy behavior is not reinforced, this may have as a consequence that the patient thinks that there must be something seriously wrong (cognition), which in its turn may inflict a fixation on the
somatic aspects of the pain (behavior). These reciprocal relationships between cognitive behavioral and emotional factors make clear why chronic pain can be so persistent. The chronic pain patient is tangled in vicious circles of reciprocal influencing factors. In this way there is a constant risk that the patient will become dead-locked in a depressive pattern of behavior and emotions.

Figure 4
A COGNITIVE-BEHAVIORAL MODEL OF PAIN (VLAEYEN)




# Psychological problems: cause or consequence?

There seems to be little doubt that the fibromyalgia complaints in patients are accompanied by psychological problems. For the early notion that fibromyalgia is a manifestation of a psychiatric disorder seems to be little evidence, however. Although depressive symptoms in fibromyalgia are reported, these aspects reflect usually elevated scores on subscales of questionnaires, but not the fulfilling of necessary diagnostic criteria. The majority of fibromyalgia patients did not meet the criteria for psychiatric diagnosis in the research reports mentioned earlier.

Hudson (7) stated that the affective symptoms in fibromyalgia might be either secondary to the pain or disability caused by the disorder or be symptoms of a primary psychobiologic abnormality that causes both the affective and rheumatic symptoms. For the latter hypothesis seems to be some evidence in their data, since major affective disorder was significantly more common in the relatives of fibromyalgia patients and major depressed patients than in the relatives of RA patients. Also in 64% of the fibromyalgia patients who experienced major depression the depression occurred at least 1 year before the development of the fibromyalgia complaints. Goldenberg (35) argues that also other syndromes, such as Chronic Fatigue Syndrome and the Irritable Bowel Syndrome share common basic traits with depression and

fibromyalgia.

Hawley et al. (39) studied the relation between disease severity and psychological status in 75 fibromyalgia patients during a one-year period, using the functional disability index of the Stanford Health Assessment Questionnaire (HAQ), visual analogue scales and the Arthritis Impact Measurement Scale (AIMS). Their results suggest that fibromyalgia symptoms are remarkably stable over time and that there are clear individual differences in disease severity. Pain, psychological status and functional disability were independent explanatory factors for disease severity in their regression analysis.

As has been demonstrated above, there is a clear relationship between pain and psychological factors such as anxiety and depression. Psychological distress can be the consequence of having pain complaints for a prolonged period of time, but these aspects can also have a negative effect on the pain itself by means of changing behavior or changing cognitions. Inadequate pain behavior, for example, can be reinforced unintentionally, which will make this type of behavior more and more prominent in the patient.

In their review article Boissevain and McCain (40) conclude that it is clear that psychopathology is associated with fibromyalgia, but that the direction of this association is unclear. Therefore fibromyalgia may be the result of an underlying affective disturbance as Hudson (7) argues, but it is equally clear that all chronic pain has a significant psychological component, which also will be demonstrated in the next chapter.

Another possible explanatory factor is stress. Several studies mentioned above suggest that stress (or perhaps even more inadequate stress coping) may be an important etiologic or at least modulating factor in fibromyalgia.

The possible role of stress in fibromyalgia is very interesting, because of the possible explanations it can offer for the biochemical abnormalities in fibromyalgia. Further research in this field is necessary. Only longitudinal studies can give the definite answer to the question if stress is indeed an important etiologic factor, since the pain experience itself can also act as a stressor.

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# Psychological aspects of fibromyalgia compared with chronic and non-chronic pain

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Revised version of:
D.J. Birnie, A.A. Knipping, M.H. van Rijswijk, A.C.E. de Blécourt, J.N. de Voogd.
Psychological aspects of fibromyalgia compared with chronic and nonchronic pain.
J Rheumatol 1991;18:1845-1848.

# Introduction

In spite of extensive research on fibromyalgia prompted by increasing interest in this syndrome, many aspects remain poorly understood. At the clinical level much research has been done to describe the clinical features of the syndrome (1). As a result of these studies, making a correct diagnosis is no longer a great problem. Many, but not all studies showed evidence for psychological abnormality in patients with fibromyalgia (2-10).

Most of the aspects that are found are elevated scores on subscales of questionnaires. Anxiety and depression are the most prominent aspects that are reported (see also chapter 10). Anxiety and depression are also common features in other chronic pain conditions.

Therefore we hypothesize that most of the psychological features of fibromyalgia patients can be considered to be aspects of chronic pain, that is, pain existing for a period longer than 6 months and which lacks an apparent somatic explanation. If so, then this has implications for possible forms of treatment for fibromyalgia. As has been proven useful in (multidisciplinary) treatment programs for chronic pain patients, fibromyalgia patients have to learn coping with their complaints and problems related to their complaints, such as professional status. In this treatment programs the attention of the patients is shifted from things that are no longer possible to activities that the patients still can perform, thus increasing the activity, and possibly also the level of self esteem.

According to an advisory committee of the Dutch Ministry of Health (11) patients with chronic pain share several characteristics. These are derived from the International Association for the Study of Pain (12).

1. At onset of the chronic pain syndrome the patient with chronic pain cannot be distinguished from other patients with pain.
2. The pain is present for a period of at least 6 months.
3. There is no clear causal relationship between the pain and somatic pathology.
4. The chronic pain patient has a history many contacts with medical and paramedical specialists, often in addition to a fair number of contacts with non-allophatic healers. The chronic pain patient has undergone a variety of diagnostic procedures, therapies (sometimes even surgery) without lasting beneficial effect, and appears to be a regular visitor of the general practitioner for relatively harmless physical complaints.
5. There is an important, partly iatrogenic reinforced fixation on the pattern of complaining.
6. The pain complaints are incrementally accompanied by disturbed psychosocial functioning and by some related features:
   - medication abuse
   - diminished physical functioning and ability of performance paired to the pain and/or the fear of damaging the body due to physical activity (inadequate signal

function)
- dependency on passive forms of physiotherapy
- increased helplessness and hopelessness, highly resistant to therapy
- emotional conflicts with persons in the direct social environment
- withdrawal from psychosocial activities
- lasting negative emotional and affective changes
- receiving or attempting to receive money from a social security fund.

Many of these characteristics seem to describe the psychological problems of fibromyalgia patients as well as those of other chronic pain patients. Therefore our hypothesis is that fibromyalgia patients share many psychological and other aspects as stated above with other chronic pain patients.

# Materials and methods

Three groups of patients with pain:
1. a non-chronic pain group (n=34),
2. a chronic pain group (n=99),
3. and a fibromyalgia group (n=36)

were compared, using a standard interview technique and three self-administered standardized psychologic tests (Dutch versions, translated and adapted from already existing questionnaires):
- the Symptom CheckList (SCL-90R)(13),
- the Illness Behaviour Questionnaire (IBQ)(14),
- and the Chronic Illness Problem Inventory (CIPI)(14).

The subjects of chronic pain group and the fibromyalgia group were outpatients of the Department of Rehabilitation of the University Hospital of Groningen (the Netherlands) in the period january 1986 - may 1987. The patients in the non-chronic pain group were selected in a period of 6 weeks in february-march 1987. Patients visited the department because of musculoskeletal pain, and they were mainly referred by family practitioners, neurologists or surgeons.
The inclusion and exclusion criteria of the three groups are represented in table 1 . Among patients in the non-chronic group, 38% had pain complaints in the lower extremities, and 32% in the neck-shoulder region. The pain complaints in this group were mainly caused by distortion, rupture or fracture. In the chronic group 39% had low back pain, 48% had pain complaints in the lower extremities, and 35% in the neck-shoulder region which could not be explained by underlying somatic pathology in the vision of the physiatrist. In this group the physiatrist discovered no dysfunctions in strength, mobility, coordination, sensibility, tonus, balance, condition, or posture. In the fibromyalgia group 94% had pain complaints in the lower extremities, 81% in the

neck-shoulder region and 75% in the lower back region.

Table 1
INCLUSION AND EXCLUSION CRITERIA FOR THE NON CHRONIC PAIN, CHRONIC PAIN AND FIBROMYALGIA GROUP

| | non chronic | chronic | fibromyalgia |
|---|---|---|---|
| inclusion criteria | * musculoskeletal pain | * musculoskeletal pain | * fibromyalgia according to criteria of Yunus (15) |
| | * duration < 6 months | * duration ≥ 6 months | |
| | * clear relation between pain and somatic pathology | * no (clear) relation between pain and somatic pathology | |
| exclusion criteria | * fibromyalgia diagnosis | * fibromyalgia diagnosis | |

The variables that characterize chronic pain as described in the report of the Dutch advisory committee are shown in table 2 .
Duration of complaints was determined on the interview question: "How long have you had these complaints?". If the patient could not give a clear, reliable answer, the first time that he visited a doctor with the complaints was taken as the measuring point.
The groups were compared with each other using the Oneway analysis of variance, where a parametric test was allowed (16). Multiple comparisons were made with the modified least-significant difference test. Applying the Bonferroni procedure (17) (with type-I error for each comparison set to 0.05) significance was set to 0.005.
For the analysis of nominal variables a chi-square test was used to determine statistical dependency between groups and variables.

Table 2
CONCEPTS THAT CHARACTERIZE CHRONIC PAIN

| Concept: | Mode of measurement: |
|---|---|
| Duration of the pain complaint: | Duration (in months) according to the interview data. |
| Progress of the complaints since onset: | Answer on interview question. (better, no change, worse) |
| Number of other physical complaints: | Answer on interview question: the subjects were asked to check off a list. |
| Medication use: | Answer on interview question. (yes or no) |
| Number of painful localizations: | Subjects had to mark the spots in a drawing of a human body. Considered as a localization were: a) head and neck b) upper back c) low back d) gluteal/genital region e) chest f) abdomen g) arms h) legs. |
| Extent of somatization: | Somatization-scale SCL-90R |
| Fixation on complaining: | Preoccupation-scale IBQ |
| Diminished physical functioning: | Body Deterioration-scale CIPI |
| Emotional conflicts with others: | Hostility-scale SCL-90R |
| Negative emotional and affective changes: | Anxiety- and Depression-scale SCL-90R |

# Results

The mean age and standard deviation in the three groups were: 43.7±17.1 in the non-chronic pain group, 36.0±11.3 in the chronic pain group and 39.0±10.4 in the fibromyalgia group. There was a difference between the three groups on age (Oneway $F=5.11$ $p=0.0070$). The least significance procedure reveals that the mean age in non-chronic group is significant ($p<0.05$) higher than in the chronic pain group. The percentages female subjects were 56 in the non-chronic pain group, 74 in the chronic pain group and 64 in the fibromyalgia group.
No significant differences ($p<0.05$) between the three groups were found for sex, using the chi-square-test.
We found no satisfactory explanation for the relatively low percentage of female subjects in the fibromyalgia group when compared with other researcher reports (1).
The comparison of the three groups involved in this study is displayed in table 3 . To keep the focus on the variables related to our hypothesis, other subscales of the questionnaires were not included in this table (e.g. the sensitivity-scale SCL-90R).

Table 3
COMPARISON OF MEAN SCORES IN THE THREE GROUPS.
* = SIGNIFICANT DIFFERENCE BETWEEN CHRONIC AND NON CHRONIC GROUP
@ = SIGNIFICANT DIFFERENCE BETWEEN CHRONIC AND FIBROMYALGIA GROUP
# = SIGNIFICANT DIFFERENCE BETWEEN NON CHRONIC AND FIBROMYALGIA GROUP
NS = NO DIFFERENCES BETWEEN GROUPS (ONEWAY, $P<0.005$)

| variable | chronic group (mean ± SD) | non-chronic group (mean ± SD) | fibromyalgia (mean ± SD) | sign. diff. |
|---|---|---|---|---|
| Duration (months) | 53.9±58.8 | 3.3±2.7 | 82.0±60.0 | * # @ |
| N other complaints | 5.0±4.0 | 1.8±2.3 | 6.5±3.3 | * # @ |
| N painful localizations | 2.3±1.4 | 1.4±0.6 | 4.8±1.8 | * # @ |
| Somatization SCL-90R | 23.1±8.0 | 17.8±4.8 | 28.2±5.7 | * # @ |
| Preoccupation IBQ | 1.8±1.4 | 1.0±1.5 | 1.6±1.1 | NS |
| Body Deterioration CIPI | 7.3±3.7 | 5.6±2.5 | 8.5±4.4 | * # |
| Hostility SC-90R | 8.0±3.0 | 6.9±1.1 | 7.7±2.7 | NS |
| Anxiety SCL-90R | 15.7±7.0 | 13.2±3.3 | 16.0±4.7 | NS |
| Depression SCL-90R | 25.3±10.5 | 21.0 ±5.4 | 26.1±9.7 | NS |

As expected, the chronic group had higher scores on most of the variables when compared to the non-chronic group. Difference in the variable "duration" was caused by the selection criteria of the groups.
When compared to the non-chronic group, the chronic group has more "other complaints", not directly related to the complaint for which they visited the physician, more painful localizations and they show more somatization. Differences on the variables preoccupation IBQ, body deterioration CIPI, hostility, anxiety, and depression SCL-90R did not reach significance. Almost the same pattern of differences occurs when fibromyalgia patients are compared with non-chronic pain patients. Fibromyalgia patients report also more body deterioration than non-chronic pain patients.
Fibromyalgia patients report more painful localizations than chronic pain patients and have a higher score on the somatization scale. Other variables show no differences between these two groups.
On the variable "progress of complaints" 44% of the non-chronic group stated that they were getting better, 29% reported no change and 27% a worsening of their complaints. In the chronic group only 3% reported that they were getting better, 17% reported no change and 80% a worsening of their complaints. In the fibromyalgia group no subject stated that he or she was getting better, 6% reported no change and 94% reported that the complaints were getting worse (chi-square = 61.6, $p<0.00001$).
In the non-chronic group 18% used medication, in the chronic group 46%, and in the

fibromyalgia group 50% used medication (chi-square = 9.3, $p<0.009$).

# Discussion

We started our research in 1986, using the criteria for fibromyalgia diagnosis from Yunus et al. (15) In the meantime, in 1990, the American College of Rheumatology adopted new criteria for the classification of fibromyalgia (18): widespread pain in combination with 11 or more of the 18 specific tender point sites. In their report the authors also provide the sensitivity, specificity and accuracy of previous criteria sets in their study population. It appeared that the criteria described by Yunus et al. performed fairly well in their study sample, with a sensitivity of 83.6% and a specificity of 76.6%. Therefore we don not expect very much problems with the generalizability of our data.

The hypothesis that fibromyalgia patients are very similar to other chronic pain patients when compared on psychological variables is supported by the results above. The fibromyalgia group shows many characteristics of chronic pain and even more painful localizations and a higher extent of somatization. The fact that fibromyalgia patients report more painful localizations is not very surprising, because one of the clinical characteristics of fibromyalgia is having "pain all over". The fact that fibromyalgia patients have higher scores on the somatization scale of the SCL-90R seems to be related to this aspect of fibromyalgia, since this scale contains items such as: headaches, low back pain, painful muscles, etc. When the items that are related to the physical complaints of fibromyalgia patients are removed, there is no longer a significant difference between the two groups (chronic group: m=8.9 SD=3.8, fibromyalgia group: m=10.0 SD=2.7; t-value=-1.79, $p<0.078$).

An important aspect is the duration of the pain complaint. All but one of the fibromyalgia patients had pain complaints for over one year. Many researchers in the field of chronic pain state that having pain complaints for a period between 2 and 6 months can be sufficient to develop chronic pain (19,20).

The finding that our fibromyalgia group is characterized by a long duration of the pain complaint is probably not exceptional. The recognition and acknowledgement of the diagnosis "fibromyalgia" is complex and time-consuming.

Considering fibromyalgia patients as chronic pain patients has important implications for treatment. A strictly somatic approach of the complaints in treating chronic pain patients may lead to a strong fixation on the somatic aspects of these complaints (21-23).

A multidisciplinary approach seems to be the best way to deal with complexity of the patient's situation in the treatment of chronic pain (24,25). Further research must point out if this is also a good option in the treatment of fibromyalgia.

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# Comparison between rheumatoid arthritis, chronic low back pain and fibromyalgia

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# Introduction

Fibromyalgia syndrome and rheumatoid arthritis are, together with arthrosis, among the commonest diagnoses made in a rheumatological practice. The medical history and initial presentation of patients with fibromyalgia compared with patients with rheumatoid arthritis makes it sometimes difficult to discriminate between the two. The finding of swollen joints and other objective physical signs during physical examination, as well as laboratory and radiological parameters are good discriminators. Striking, however, remains the amount and intensity of subjective complaints of patients with fibromyalgia syndrome, and disabilities and handicaps following from these complaints.

Several authors compared different features of the fibromyalgia patient with the patient with rheumatoid arthritis.

Leavitt (1) compared different pain properties in patients with fibromyalgia and rheumatoid arthritis. In both groups participated 50 patients, and interestingly, the pain intensities in both groups measured with visual analogue scales were not different. In the fibromyalgia group the pain was more diffuse localized and description of the pain involved more (sensory, affective, evaluative and mixed) words. As a pain questionnaire an adaptation of the McGill Pain Questionnaire was used. The pain words were put in random order. Pain intensity was measured with a linear scale from 0 (no pain) to 100 (severest pain). Patients were asked to give their average pain a number on this scale. A third instrument used was a pain location sheet, divided in 25 body sites. Patients were asked to mark all the sites in which pain was currently being felt.

Analyzing the pain questionnaire the authors found that there was a high degree of similarity in pain description in the two patients groups. In the fibromyalgia group more words were used in describing the pain. The word radiating discriminated best between the two patients groups. Evaluating the pain sites showed that there were differences in the sites marked by fibromyalgia and RA patients. Best discrimination between the two groups were the lower back, thigh, abdomen, shin, hips and head in the fibromyalgia group, and wrist, foot and fingers in the RA group. Fibromyalgia pain is less localized and is spatially diffuse. Leavitt makes the connection between radiating and the spatial diffusion of the pain.

Scudds (2) compared age and sex matched patient groups of fibromyalgia and rheumatoid arthritis and normal controls regarding personality variables and responsiveness to experimentally induced pain. Pain thresholds and tolerance were determined for three stressors, namely electrical stimulation, constant pressure and dolorimeter, with gradually increasing pressure. The fibromyalgia group had lower pain threshold and tolerance with the dolorimeter than the normal group. There were no statistical significant differences between the fibromyalgia group and RA group concerning pain threshold and tolerance. A visual analogue scale was also used. Significant difference was found between the fibromyalgia group and the normal

controls, but with the RA group as well. No statistically significant differences in VAS scores were found between the RA group and the control group. Evaluating the personality variables measured by the Basic Personality Inventory for the scale hypochondriasis a significant difference was found between each of the groups, where the fibromyalgia group showed the highest score. For depression, anxiety and social introversion there was found a significant difference between the normal and fibromyalgia group, where the fibromyalgia group had the higher scores. An a priori expectation was that significant differences would be found between the groups on three pain measures (pain threshold, tolerance and VAS) and on the personality measures of hypochondriasis, depression and anxiety. This expectation came through. Confirmatory stepwise discriminant analysis of these data revealed that the greatest weight is given to the VAS score and hypochondriasis scores.

Burckhardt (3) compared the quality of life of fibromyalgia women with the quality of life of other patients group (all women), like rheumatoid arthritis, osteoarthritis (OA), but also lung diseased women and women with diabetes mellitus, and healthy controls. All patients had been diagnosed using standard criteria for the different diseases. As a study instrument the Quality of Life Scale (QOLS) was used and two other instruments were used to measure health status. One of these was the AIMS, which was given to the RA, OA and fibromyalgia patients in this study. The demographic sheet from the AIMS however was used to obtain general information of all participating women. The questionnaires were mailed to the participating women. The patients were retrieved from specialists practices. Concerning the demographic variables it came out that the fibromyalgia group and the healthy control group were statistically significant younger than the other groups. The healthy group also had more education. Evaluating the QOLS-scores it became clear that the fibromyalgia group mean score was lower than the means of, among others, the RA and OA groups. Fibromyalgia group showed greater dissatisfaction. Mean scores of the AIMS-subscales were compared and there were no differences in between fibromyalgia and OA, and no differences between RA and OA. Between RA and fibromyalgia the RA group scored significantly higher on dexterity scale, and the fibromyalgia group scored significantly higher on the depression and on the anxiety scale. Depression and anxiety were highly correlated.

The total scores on QOLS of the fibromyalgia group were as low as those with chronic diseases like diabetes mellitus and chronic lung disease. Regarding the QOLS scores the fibromyalgia group closely resembled those of patients that were severely impacted by their disease. The fibromyalgia group, however, was younger, had higher incomes, higher educational level, and a higher percentage was married. These last three demographic variables has been linked to higher quality of life in randomly selected groups of American adults. Burckhardt states that their findings suggest that far reaching negative feelings and dissatisfactions permeate almost all aspects of life of patients with fibromyalgia, and that dissatisfaction is not entirely explained by

physical health status, psychological distress or demographic variables. Another suggestion Burckhardt makes is that patients with fibromyalgia are more dissatisfied while they have not well adapted to the new situation of their chronic illness. Still, she sees another factor in the dissatisfaction of the fibromyalgia patients, namely the absence of a sanctioned reference group.

Viitanen (4), among others, compared the pain intensity in patients with fibromyalgia and rheumatoid arthritis. Pain was measured using a visual analogue scale. The study group consisted 20 female fibromyalgia patients and 20 female RA patients. VAS scores in the fibromyalgia group were constantly twice as high as in the RA group. All 40 patients followed a three week inpatient rehabilitation course. The rehabilitation program was based mainly on physiotherapeutical methods, but their was a distinct difference in approach in both groups. The fibromyalgia group had also an individually adjusted cardiovascular fitness training, whereas the RA patients got individually physiotherapy of affected joints. During the three week rehabilitation course no changes in medication were made in either group. In the RA group the effect of the course on pain intensity was significantly higher than in the fibromyalgia group. At the end of the course the pain intensity in the RA group decreased significantly. Although patients with fibromyalgia were more depressed than the RA group, a positive correlation between pain intensity and depression was only found in RA patients. So the authors state that depression in fibromyalgia patients does not explain the high pain intensity in these same patients.

Mengshoel and Forre (5) described several aspects of pain and fatigue in different rheumatic disorders, like fibromyalgia, rheumatoid arthritis and ankylosing spondylitis. In this study a high pain intensity was measured with the visual analogue scale and the McGill Pain Questionnaire in the fibromyalgia group, compared to the other patients groups. In the fibromyalgia group there was a high frequency of gastrointestinal problems and high intensity of fatigue. All patients were unhospitalized (in the study of Leavitt the patients were hospitalized), the mean age of the patient groups differed (in Leavitt's study the mean age was the same in the fibromyalgia and RA group), and Mengshoel fibromyalgia group consisted of only women. In the statistical analysis there was a correction made for the group differences with respect to age and duration of symptoms. The pain questionnaire was administered in a different manner. The visual analogue scale was probably not used in a very different way. However comparing the results of Leavitt and Mengshoel is dangerous because of the different group samples. Study results of these two investigators were actually contradictory.

Mengshoel recorded general fatigue and amount of sleep problems by visual analogue scales, which both were highest in the fibromyalgia group. Pain coping was measured using the Vanderbilt Pain Management Inventory. No statistically differences between the groups were found. However in the fibromyalgia group the item "seeking health professionals" was chosen significantly more than in the other two patients groups. If

this also means higher costs is not elucidated. Another interesting founding is that "weather-sickness" was reported frequently in all three groups.
Perry et al. (6) looked in on different pain measures in chronic pain syndromes with and without explicable organic cause. For this they used VAS scores and scores from subscales of the McGill Pain Questionnaire in patients with fibromyalgia (fibrositis) and inflammatory arthritis and these scores were correlated with each other.
Ahles et al. (7) used ambulatory patients and found higher scores of fibromyalgia patients on the both neurotic scales (hypochondriasis and hysteria) and also on the psychasthenia and the schizophrenia scales of the MMPI. The group means of the fibromyalgia group were not in the pathological range. Ahles et al. also stated that the group of fibromyalgia patients could be divided into three subgroups: group 1 (normal), group 2 (typical chronic pain) and group 3 (psychological disturbance). Each group consisted of approximately one third of the studied group of fibromyalgia patients.
Also in other studies psychological aspects in fibromyalgia patients were compared with those RA patients (8-10). In chapter 10 these studies are described in more detail. Multiple, but not all studies show evidence for psychological problems in patients with fibromyalgia.
Although there seems to be very little doubt that patients with fibromyalgia have more psychological distress than RA patients it is not clear what can be concluded from these findings. It is certainly not clear that the psychological problems precede the somatic complaints in fibromyalgia. Only studies with longitudinal designs may give the answer to this question. With the use of RA patients as a reference group the factors pain and somatic complaints are controlled but there is also an important difference between these groups. In RA the somatic pathology is known, although much of the etiology is still unknown. Fibromyalgia patients have complaints without a known somatic substrate, which may be of importance when we look at psychological factors. If you do not know what you are dealing with as a patient, experiencing physical complaints with prolonged and uncontrollable pain, than this may have a strong negative effect on some psychological aspects, such as depression and anxiety. In the study described below the fibromyalgia patients are not only compared with RA patients as in many other studies but also other patients with pain complaints without a known somatic pathology are included in this study

# Methods and subjects

Hundred fibromyalgia patients who had visited the rheumatology ward of the University Hospital in Groningen were selected in an at random procedure. These patients participated in a research project in which the effects of a combined treatment of psychomotor therapy and marital counselling was evaluated (see also chapter 14). All patients underwent a medical screening as part of the research project and they

also were interviewed and they had to fill out psychological questionnaires. These data were used as a pre-treatment evaluation before the start of the treatment programm in which 50 of these patients participated as an experimental group and the other 50 as non-treatment controls. This pre-treatment evaluation was extended with some extra interview questions and personality checklists for another purpose which is the issue here in this chapter. Also 25 patients with rheumatoid arthritis were selected in an at random procedure (matched on age and sex with the fibromyalgia group) from the total population of outpatients of the rheumatology ward of the University Hospital in Groningen. These patients were included in the study of rheumatoid arthritis was their primary diagnosis and if they were able and willing to undergo the medical examination, interview and the filling out of the questionnaires. The third group that participated was a group of 22 patients with chronic low back pain, randomly (also matched on age and sex) selected from the total population of outpatients of the rehabilitation ward of the University Hospital of Groningen.
What is of special interest in this study is the way the severity of the somatic complaints are perceived by the patients. Visual analogue scales and tender point counts are used for this purpose. The amount of psychological distress is another important aspect, mentioned as a problem in fibromyalgia. The SCL-90 (12), described in more detail below is used for this purpose. Furthermore some personality aspects are included in this study to determine if neurotic traits and perfectionistic traits are possibly involved in the etiology of fibromyalgia. These perfectionistic traits are mentioned in several textbooks concerning rheumatic diseases (11). For this reason the Achievement Motivation Test (Dutch: Prestatie Motivatie Test) is used in this study (13). Neurotic traits are suggested as being a problem in fibromyalgia patients by authors using the MMPI as a comparative instrument. However MMPI-subscales contain items that are influenced by somatic (non psychogenic) problems which makes these findings less meaningful. The Amsterdamse Biografische Vragenlijst (14) has two subscales in which neurotic lability is measured, one with and one without somatic factors. In this way the problem that arose in the MMPI is ruled out here. In chapter 10 is concluded that the role of stress and coping may also play an important role in fibromyalgia. The Utrechtse Copinglijst (15), also used in the study of Spanjer (11) is used in this study to compare the three groups on this aspect. Finally, it can be expected that the complaints influence interpersonal relationships, such as the marital one. These aspects are measured with the Maudsley Marital Questionnaire (16).
The variables that were used to compare the three groups are described below:

- Visual analog scales: patients had to score their pain (PAIN), the quality of their sleep (SLEEP) and a global estimate of their complaints by the patient (PAGLAS) and by the physiatrist (PHGLAS). 0 is having no pain or complaints; 100 is the worse possible option.
- Number of tenderpoints: number of positive tenderpoints of the 14 examined sites

(NTENDER). A tenderpoint was scored positive if the patient experienced pain expressed in any way on palpation.

- Symptom Checklist 90R (SCL-90): this questionnaire is a translated (in Dutch) and adapted version of the original checklist as developed by Derogatis et al. It can serve as an instrument to evaluate the amount of psychological distress.
  Subscales: Anxiety (ANX), Agoraphobia (AGO), Depression (DEP), Somatization (SOM), Sensitivity (interpersonal) (SEN), Inadequacy (IN), Hostility (HOS) and Sleep disturbances (SLE).
- Amsterdamse Biografische Vragenlijst (ABV): this questionnaire is developed to measure personality aspects and in particular neurotic lability, which is supposed to be a relatively stable aspect within personality. The SCL-90 is supposed to measure the psychological state the person is in, while the ABV measures mor trait-like aspects. The subscales that are used in our study are: Neurotic Lability (N-scale), Neurotic Lability manifested in somatic complaint (NS-scale), Extraversion (E-scale), Testability (T-scale; self critical versus self defensive way of presenting yourself), and Social Desirability (SD-scale).
- Maudsley Marital Questionnaire (MMQ): This questionnaire was used to evaluate the quality of the relationship. Only married patients or the ones who lived together with a partner had to fill out this questionnaire.
  Subscales: Relation satisfaction (interpersonal aspects) (RS), Sexual satisfaction (SS), and General life satisfaction (housework and social aspects) (GLS).
- Achievement Motivation Test (AMT): (In dutch: Prestatie Motivatie Test) This questionnaire measures the amount of motivation one has to excel (in self-opinion and in opinion of others) and also fear of failure. These aspects are supposed to be stable over time, thus being more trait-like aspects.
  Subscales: Achievement Motivation, Negative Fear of Failure (performance thought to be influenced in a negative way by tension), and Positive fair of Failure (performance thought to be influenced in a positive way by tension).
- Utrechtse Coping Lijst (UCL): This questionnaire was used to evaluate aspects of coping in the three groups. This checklist is developed measure more trait-like aspects of coping.
  Subscales: Active approach (Act), Palliative reaction (Pal), Avoidance (Avo), Seeking social support (Soc), Depressive reaction (Dep), Expression of emotions (Exp), Comforting cognitions (Com).

Chi-square tests and Oneway analyses of variance were performed to evaluate differences between the three groups. Differences with $p<0.05$ were regarded as significant.

# Results

As stated earlier sex and age were not different in the three groups because of

matching on these variables.
Other sociodemographic variables were compared using chi-square tests. Sometimes it was necessary to combine two or more values to fulfil Cochran's criteria: not more than 20% of cells with an expected frequency of less than 5 and none of the expected frequencies should be less than 1.
There is no difference in marital status between the groups. The vast majority (approximately 90%) is living together with a partner whether or not married.
There is a statistical dependency between group and level of education (chi-square = 17.9, $p<0.00131$). In the fibromyalgia group are less persons with a high level of education than in the two other groups. Only 8% in the fibromyalgia group had followed a high level of secondary school or university against 28% in the RA group and 36% in the chronic pain group.
This difference does not express itself in statistical differences in level of occupation between the three groups.
There is also no statistical difference on the variable "disability compensation" (Dutch: WAO). In our research population 18% of the fibromyalgia group received full compensation against 32% in the RA group and 27% in the chronic pain group. This is surprising if we look at the percentage of patients who have received compensation in the form of auxiliary devices or house adaptations (Dutch: GMD-voorzieningen). In the RA group 64% received compensation in this way against only 6% in the fibromyalgia group and 5% in the chronic pain group (chi-square=52.9 $p<0.000005$).
In the fibromyalgia group the mean tenderpoint score is 9.1 (SD=3.2). In the RA group and the chronic pain group the mean tenderpoint scores are 2.7 (SD=3.4) and 3.5 (SD=3.0) respectively. Oneway analysis shows a significant difference between the fibromyalgia group and both other groups ($p<0.05$).
In figure 1 the results of the VAS-scales are shown.
Oneway analysis of variance yields the following results: The fibromyalgia patients have higher patients global assessments than both other groups. The physician scored the fibromyalgia patients as having more health problems than the chronic pain group. Fibromyalgia patients have also higher pain scores than RA patients and more sleeping problems than the chronic pain patients ($p<0.05$).
The three groups were also compared with each other using several psychological questionnaires. The results between the three groups on the SCL-90 are shown in figure 2 .

Figure 1
MEAN SCORES ON GLOBAL ASSESSMENTS OF PATIENT (PAGLAS) AND PHYSICIAN (PHGLAS), PAIN AND SLEEP, MEASURED WITH VISUAL ANALOGUE SCALES

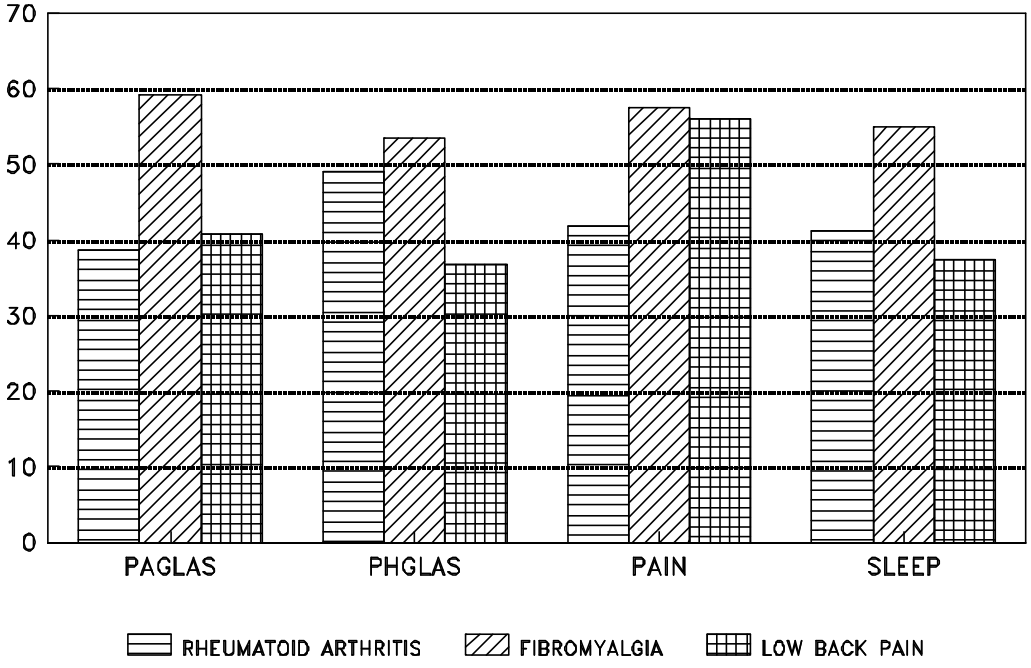
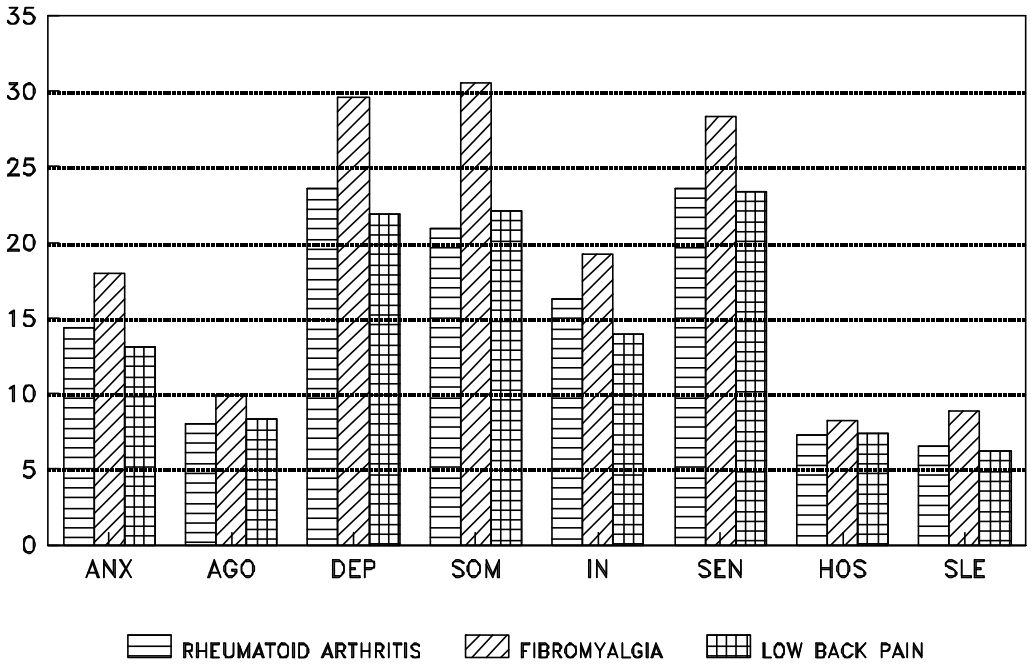



Figure 2
MEAN SCORES OF THE THREE GROUPS ON THE SCL-90



It is clear that fibromyalgia patients have more psychosocial problems as measured with the SCL-90 than the two other groups. Oneway analysis indicates significant differences ($p<0.05$) between the fibromyalgia group and the two other groups on the Anxiety scale, the Depression scale, the
Somatization scale, the Inadequacy scale, the Sensitivity scale and the Sleep Disturbances scale. There was also a difference between the fibromyalgia group and the RA group on the Agoraphobia subscale. There are no differences between the three groups on the Hostility subscale. The analysis showed no differences between the chronic pain group and the RA group.

Figure 3
MEAN SCORES OF THE THREE GROUPS ON THE AMSTERDAMS BIOGRAFISCHE VRAGENLIJST (ABV)

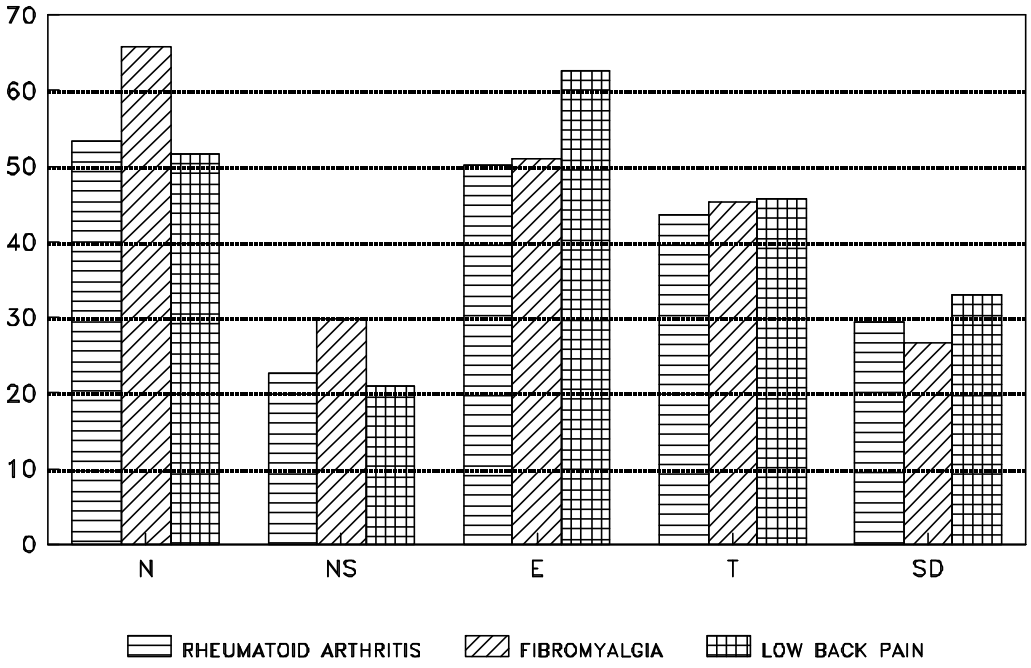
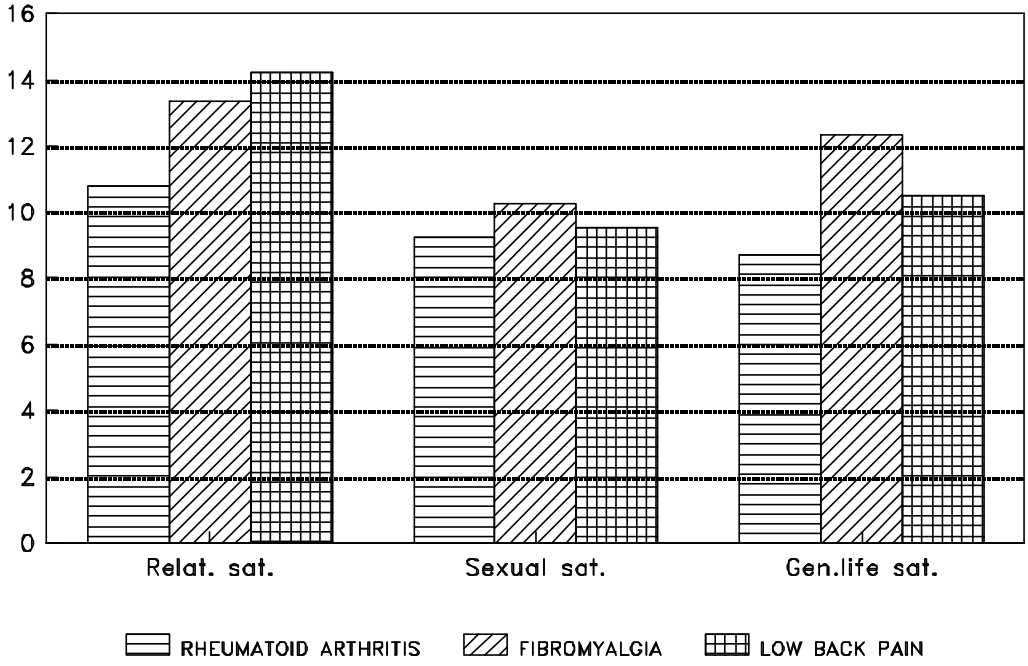



Figure 3 shows that the fibromyalgia group has higher scores on both the neurotic subscales (N and NS) than both other groups. Chronic pain patients present themselves as being more extravert than both other groups and they show more social desirability than the fibromyalgia group (Oneway, $p<0.05$). There are no significant differences on the Testability-subscale.

The results on the Maudsley Marital Questionnaire are presented in figure 4 .

Figure 4
MEAN SCORES OF THE THREE GROUPS ON THE MAUDSLY MARITAL QUESTIONNAIRE (MMQ)




Oneway analysis shows here that there are no significant differences between the three groups on the Relation Satisfaction subscale and the Sexual Satisfaction subscale.
Fibromyalgia report more problems in the General Life Satisfaction subscale than RA patients (Oneway, $p<0.05$).
In figure 5 the results of the comparison between the three groups on the Achievement Motivation Test are shown.
There are no significant (Oneway; $p<0.05$) differences between the three groups on the subscales of this questionnaire.
Figure 6 contains the mean scores on the UCL subscales. Oneway analysis of variance shows that fibromyalgia patients have higher scores on the palliative, avoiding, and depressive subscales. Also the fibromyalgia patients use more comforting cognitions as a way of coping than low back pain patients. RA patients and low back pain patients do not differ on copingstyles when measured with the UCL.

Figure 5
MEAN SCORES OF THE THREE GROUPS ON THE ACHIEVEMENT MOTIVATION TEST (PMT)

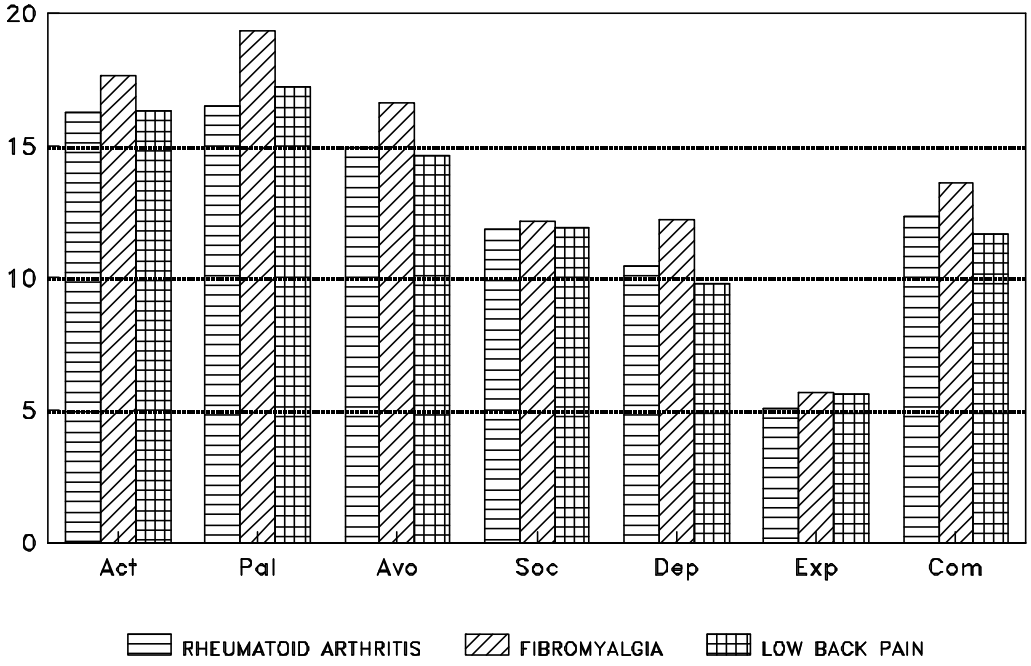
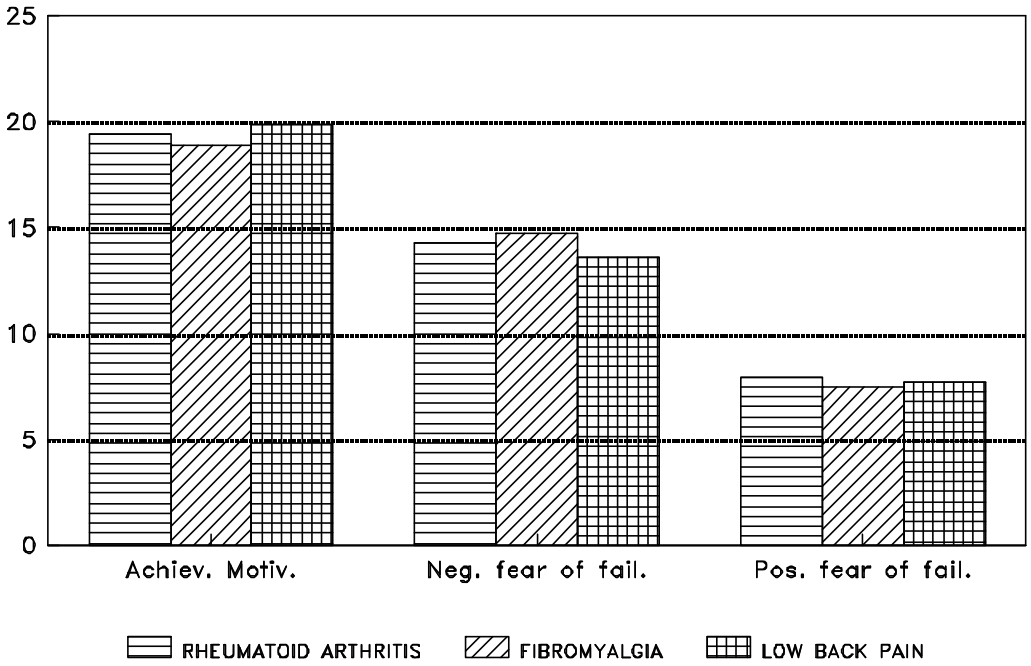



Figure 6
MEAN SCORES ON SUBSCALES OF THE UTRECHTSE COPINGLIJST (UCL)



# Discussion

In our study the fibromyalgia patients indicated more pain problems than both other groups, which differs from the study of Leavitt et al. (1), in which fibromyalgia patients and RA patients did not differ on the experienced amount pain as evaluated by a VAS. In their study the fibromyalgia group had a score of 60.8 on a scale of 100. In our study the fibromyalgia patients scored 57.8 on a scale of 100, which is almost equal to the pain score we measured. The RA patients in the Leavitt study however had a VAS score of 58.7 while in our study they had a VAS score of (only) 39.5. Leavitt used hospitalized patients as subjects in his study, which may be the explanation for the differences in pain scores in RA patients. Apparently the difference between the fibromyalgia patient groups is small, when looked at pain severity.

Our results show that psychological problems are much more present in the fibromyalgia group than in both other groups.

When compared with the norm group of 577 normal healthy controls (women) of the SCL-90 (12), almost 60% of the women in our fibromyalgia group would have total scores that are categorized as "high" or "very high". Almost 20% would have an "average" or higher score when compared with a norm group of 1074 women of psychiatric outpatients' departments

The fact that fibromyalgia patients have high scores on the NS scale of the ABV is not very surprising, since fibromyalgia is often accompanied by various somatic complaints such as fatigue, sleeping problems, etc. These aspects can also play an etiological role in fibromyalgia. But is also clear that many fibromyalgia patients show much "neurotic lability" as measured by the N-scale of the ABV, in which somatic aspects are excluded. When compared with the norm group of the ABV (14) 47% of the women in our fibromyalgia group have scores that are in the $8^{th}$ decile or higher and 27% even in the $10^{th}$ decile. Neurotic lability can be conceived as a relatively stable personality aspect which makes it more likely for a person to develop psychiatric, psychosomatic, or psychological complaints or which may lead to social maladjustment and feelings of distress and insufficiency (14).

There are no significant differences between the three groups on the Achievement Motivation Test, but when the groups are compared with the norm group of the test (13) 42.2 % of the fibromyalgia group has high scores (decile 8 or higher) on the Achievement Motivation scale and 60% has high scores on the Negative Fear of Failure scale. A combination of these two aspect can be regarded as perfectionistic, which is the case for many fibromyalgia patients, but also for many RA patients and chronic pain patients. The coping styles that are the most prominent ones in fibromyalgia patients: palliative reactions, avoiding activities that may worsen the complaints, becoming inactive, in a rather depressive way, and trying to reassure yourself, would be appropriate if complaints are expected to disappear soon. But when the complaints have become chronic, these coping styles may lead to a further

deterioration of the condition these patients find themselves in. Physical deconditioning, medical shopping (seeking relief of symptoms) and becoming increasingly depressed may be the result, and this is in fact probably much of what we see in fibromyalgia patients and what is measured in questionnaires. In summary: there is evidence for predispositional psychological factors in fibromyalgia syndrome (high scores on neurotic lability and inadequate coping styles). From the data presented here it cannot be proven however that there is not a reversed effect: fibromyalgia complaints leading to neurotic lability and certain coping styles. Longitudinal studies must eventually provide us the definite answer.

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# Treatment of Fibromyalgia

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# Management of the Fibromyalgia Syndrome

Diagnosing fibromyalgia is one thing; treating it is a completely different issue. Until now there has not been one adequate therapy or strategy, and therefore it is better to speak of managing of the fibromyalgia syndrome. The number of studies involving evaluation of treatment regimens are by far outnumbered by the articles considering other aspects of the syndrome. Buckelew (1) summarized the rehabilitation approach of the fibromyalgia syndrome. She made a strong plea for long-term effective intervention programs which would require a multidisciplinary rehabilitation team approach. Felson in 1989 (2) put forward important suggestions regarding treatment regimens and evaluation of these regimens. Clinical trials, randomized, controlled or uncontrolled, try to give an answer to the question whether a certain treatment is effective and secondly if this treatment is well tolerated. Future clinical trials in fibromyalgia should also answer the question why do treatments work. An example to underline this is "are the patients who improve in amitriptyline trials those whose sleep study improve?" Maybe these investigations can reveal why these therapies work and how this relates to the pathogenesis of this syndrome. Another strong recommendation is that widely used criteria for clinical improvement are needed. In treatment trials subgroups of patients can be identified which improve and therapies can be compared. Furthermore the long term efficacy and tolerability of therapies should be studied. In 1991 Simms, together with Felson and Goldenberg (3), reported on the development of preliminary criteria for response to treatment in fibromyalgia. They analyzed the outcome measures of an earlier published study (randomized controlled trial of amitriptyline and naproxen) using stepwise logistic regression analysis. They stated that clinically important improvement was until then not uniformly defined. They identified clinical assessment variables that predicted whether patients received either effective treatment or placebo. These variables were physician global assessment, patient sleep assessment and tender point score. A limitation of their study, pointed out by the authors, is that they did not include psychological outcome measures and functional assessments.
Goldenberg (4) provided an overview of treatment approaches in fibromyalgia. He formulated important methodological issues that should be met in clinical trials concerning the fibromyalgia syndrome. The study design should be with a random assignment, with comparable intervention and control groups, with an adequate number of patients, including drop-outs, patients should meet the ACR criteria, and patient and observer should be blinded. Furthermore there should be standardized measures of disease activity, like symptoms such as pain, sleep and mood, a psychological evaluation, tender point scores and an evaluation of function.

In this chapter several treatment-regimens and therapies described in the literature, will be discussed. Unfortunately not all study-designs fulfil the criteria mentioned

above. Different therapies aim at different outcomes and use different outcome variables. To bring some order in the review of these articles, the studies are divided in those that are targeted on 1) pain relief, 2) on improvement of sleep and fatiguability and 3) those that are aimed to bring about a change in behavior and/or mood symptoms.
An overlap in these three treatment targets is present in many studies.

# Studies targeted on pain relief

## Drugtrials

Pain is the major symptom in fibromyalgia. Morning stiffness is also often mentioned by fibromyalgia patients. Logically one tried the efficacy of the anti-inflammatory drugs, often useful in the classical rheumatic diseases. Non-steroidal anti-inflammatory drugs (NSAID)are commonly used, and have been anecdotally described to be beneficial in the fibromyalgia syndrome.
As we now know fibromyalgia is not an inflammatory condition, but NSAID's might work through their analgesic effects (5). These effects are thought to be mediated through peripheral mechanisms, including a diminution in the sensitivity of peripheral nerve receptors due to decreased peripheral prostaglandin synthesis.
Yunus' study (5) was well designed, and he described the results of a short term (6 weeks) double blind, placebo controlled trial of ibuprofen in fibromyalgia syndrome. Study variables were a tender point examination and self-assessed symptoms regarding pain, fatigue, sleep, depression, anxiety and stress. No significant differences were found between the ibuprofen and placebo group, and tender points significantly improved over time in both groups. Improvement in fibromyalgia features might have occurred as a result of physician or study interactions. Yunus concluded that his results showed that NSAID have no beneficial effects in fibromyalgia, and that the pain in fibromyalgia is probably central in origin. Although the study length was short, it is not very likely that a positive effect would be reached after a longer study duration.
A double blind comparison of ibuprofen, placebo and ibuprofen with meptazinol was performed by Le Gallez et al. (6) in patients with soft tissue rheumatism. Musculoskeletal rheumatism was defined as a periarticular condition or non-specific seronegative musculoskeletal condition requiring treatment with a non-steroidal anti-inflammatory agent. Meptazinol is a centrally-acting analgesic with opiate antagonistic properties, and experimently it has been shown that the co-administration of ibuprofen with meptazinol potentiated and prolonged the analgesic effect of meptazinol in both inflamed and non-inflamed animal models. Study design was a randomized, double blind three-way crossover study of placebo, ibuprofen and ibuprofen plus meptazinol. Study length was again short, 7 weeks. Outcome variables

were pain parameters using visual analogue or verbal rating scales. Patients' overall impression and final preference showed both active treatments to be better than placebo and demonstrated a slight preference for the combination. Although in this study no mention is made of fibromyalgia, it probably is the same group of patients we know as fibromyalgia patients. These results are contradictory with those of Yunus (see above).

Russell et al. in 1991 (7) studied the effect of ibuprofen as well, in combination with alprazolam in patients with fibromyalgia. It was a randomized, double-blind, double-dummy, placebo-controlled pilot study. Alprazolam is a triazolobenzodiazepine and is used in the treatment of anxiety and/of depression with anxiety. Outcome measures were tender point examination, patient and physician assessment using Visual Analog Scales (VAS) scores, and Health Assessment Questionnaire (HAQ) was used as a measured of functional status. Furthermore a few psychometric test were used. The authors found no significant relationship between clinical measures of physical discomfort and psychological measures. This observation should be evidence against the notion that the pain in fibromyalgia has a psychological etiology. Clinical improvement in patient rating of disease severity and in the severity of tenderness upon palpation was most apparent in the subgroup of patients who were receiving both ibuprofen and alprazolam. Study length was short, 8 weeks, and the placebo effect was substantial. Analyses of variance did not reveal a significant difference in the mean change in outcome variables between the double-placebo and the other treatment groups. These results also indicate that the effect of NSAID's in fibromyalgia is very limited.

Ibuprofen was studied in combination with cyclobenzaprine in fibromyalgia (8) in an open randomized study. Cyclobenzaprine is a muscle relaxant. The authors thought there might be a synergistic effect between the two drugs in fibromyalgia patients, therefor they compared ibuprofen with cyclobenzaprine and cyclobenzaprine alone. Outcome-scores were number of tender points, muscle tightness, sleep difficulty, pain intensity and duration of morning stiffness. In both treatment groups the outcome scores had improved to the same extent and no significant differences were observed. Morning stiffness however was significantly more reduced in the patients taking the combination medication. Study length was very short, 10 days. As we know from other studies the placebo-effect could be significant, and therefore the results of this study should be reevaluated in a controlled study.

Goldenberg et al. (9) performed a randomized, double-blind, placebo-controlled trial of amitriptyline and naproxen in patients with fibromyalgia. At the time of the study both naproxen and amitriptyline were described to be effective in fibromyalgia, but these reports were mainly anecdotal and uncontrolled. In this (short, 6 weeks) study of Goldenberg amitriptyline was associated with significant improvement in all outcome parameters, including patient and physician global assessments, patient pain, sleep difficulties, fatigue on awakening, and tender point score. Patients on naproxen

showed no significant effect on any outcome parameter. Patients taking the combined naproxen-amitriptyline regimen experienced minor, but not significant, improvement in pain when compared with patients who took amitriptyline alone. Amitriptyline could have a positive effect on pain by a central analgesic effect by blocking the removal of serotonin from synaptic clefts, or by the effect of amitriptyline on endogenous opioids, like endorphins or enkephalins.
In retrospect the outcomes of the different studies mentioned above question the relevance of NSAID's in fibromyalgia. But why are these medications prescribed so often by the physicians of these patients? Is it that the doctor has to do something to satisfy the patient, and is a possible positive effect only based on the placebo-effect of the (NSAID) medication?

In the last studies mentioned above NSAID's are compared with drugs acting on the central nervous system, like the tricyclic agents
Bennett et al. (10) studied the efficacy of cyclobenzaprine, as compared with placebo in a double-blind, controlled trial of fibromyalgia patients. Cyclobenzaprine is a tricyclic agent with a chemical structure similar to that of amitriptyline, but its antidepressant effects are said to be minimal. It is used as a muscle relaxant for acute musculoskeletal disorders. Its muscle relaxant properties emanate from its ability to modulate muscle tension at a supraspinal level by reducing motoneurone efferent activity. What the authors expected to change with the therapy does not become quite clear. Patients taking cyclobenzaprine experienced a significant decrease in the severity of pain and a significant increase in the quality of sleep. There was a trend toward improvement in the symptoms of fatigue, but morning stiffness was not alleviated. These improvements in symptoms were associated with a significant reduction in the total number of tender points and in muscle tightness. Study length was 3 months. A critical note can be made on the blinded state of this study; over 50% of the cyclobenzaprine group experienced a dry mouth and/or drowsiness. So it is very well possible that these patient knew they were taking the active drug and not the placebo. The physicians also had this knowledge, because they recorded the adverse reactions.
Cyclobenzaprine was also studied by Quimby et al. (11) in a randomized, double blind, placebo controlled trial. Regarding the literature the authors postulate three hypotheses about the nature of fibromyalgia, which could explain the mode of action of these tricyclics drugs. Tricyclics may relieve fibromyalgia symptoms by prolonging non-Rapid Eye Movement (nREM) sleep (sleep disorder hypothesis), the central nervous system (CNS) pain regulation abnormality hypothesis indicates that it is the effect of tricyclics on serotonin metabolism which is important, the third (peripheral) hypothesis, the muscle spasm and local hypoxia hypothesis, suggests that cyclobenzaprine could alleviate fibromyalgia symptoms by breaking the pain-spasm-pain cycle and allowing muscles to function more normally. Cyclobenzaprine has been found to

act in the brain stem as a muscle relaxant reducing tonic motor activity. Outcome measures included daily pain diaries and patient ratings, improvement in musculoskeletal stiffness and aching, muscle pain, fatigue, poor sleep and overall improvement. Physicians also rated overall improvement. Study length was 6 weeks. The outcome measures indicated that cyclobenzaprine is effective in alleviating the symptoms of fibromyalgia in a subgroup of patients. However most patients with fibromyalgia in this study had a more accurate awareness of drug effects on their own bodies than had been expected, rendering the double blind procedure ineffective, as was recognized by the authors. In both studies (10,11) the improvement could be explained by a placebo-effect.

In 1991 a study was published by Jaeschke et al. (12), in which the results of 23 N-of-1 randomized controlled trials were reviewed concerning the clinical usefulness of amitriptyline in fibromyalgia. In this study 23 double blind, randomized, multiple crossover trials of amitriptyline were conducted in fibromyalgia patients. The participating patients had shown an improvement in a open trial of amitriptyline. The authors state that the use of amitriptyline, which has serotonergic and anticholinergic properties, is based on the hypothesis that the low pain threshold and distorted sleep pattern found in fibromyalgia may be related to the low brain serotonin. Because not all patients with fibromyalgia benefit from the use of amitriptyline, the authors tried to find a way to determine its benefit for a particular patient, for which they used the N-of-1 randomized controlled trials. After several trials it became clear to the authors that the drug benefit, if present, was evident after a short period of treatment (2 weeks). Outcome variables were tender point count and a symptom questionnaire score. The doses that were used differed, and analyzing the doses of amitriptyline used in the trials which confirmed the efficacy of the treatment, it became evident that amitriptyline can be effective in doses that might have been considered homeopathic (5 mg).

Carette and co-authors (13) reported on a 9-week double-blind trial comparing amitriptyline with placebo. The choice of amitriptyline was explained because of the serotonergic and anticholinergic activities and because in low doses it has predominantly hypnotic properties, causing REM suppression and prolongation of stage 3 and 4 nREM sleep. The patients who received amitriptyline improved significantly in their morning stiffness and pain analog scores, whereas no changes were noted in these parameters in the placebo group. Total myalgic score did not improve significantly in either group. When compared with the placebo group, the amitriptyline group improved significantly with respect to sleep pattern and patient and physician global assessments. Side-effects, however, were mentioned in 70% of the amitriptyline group.

Improvements in pain responsiveness (at local tender points and generalized sensitivity to pain at non-tender points) and assessment of well being in patients with fibromyalgia was reported by Scudds et al. (14) after treatment with amitriptyline in a

randomized, placebo controlled, double blind crossover study. This study lasted for 10 weeks. The authors tried to replicate the results of Carette et al. (13). No statement is made on number of patients that experienced side effects of the drug.

In 1994 Carette (15) and coworkers compared amitriptyline, cyclobenzaprine and placebo in a randomized, double blind, placebo-controlled clinical trial. Next to the comparison of the relative efficacy and tolerability of the different drugs and placebo they tried to identify predictors of response to cyclobenzaprine and amitriptyline. The results showed a short term efficacy (after 1 month) of amitriptyline and of cyclobenzaprine in a small percentage of the patients. Evaluation after 6 months (long term efficacy) showed no significant differences in the three groups. The placebo response after 6 months was higher than expected. The authors were not able to determine predictors of response to cyclobenzaprine or amitriptyline. Using dolorimetry scores as an outcome measure showed no significant changes in myalgic scores over baseline values at any of the monthly other assessments. At this point they question the usefulness of these scores as an outcome measure in trials of patients with fibromyalgia. They also suggest that the tricyclic agents might be slightly more effective in improving sleep than in reducing pain.

Vaeroy et al. (16) performed a placebo controlled, double blind trial with carisoprodol, paracetamol and caffeine (Somadril comp®). Active treatment gave statistically significant improvement after treatment for pain, for sleep quality and for the general feeling of sickness. However, also in the placebo group improvement was found for the pain and sleep quality. A methodological error in this study is the wide use of other drugs in the placebo group, which makes it impossible to compare these two groups. Another critical remark is the choice of a combination of three different drugs, where the efficacy of either one alone is as yet not established. Carisoprodol is chemically related to mephenesin and meprobamate, and it is not only a muscle relaxant but also an analgesic. Furthermore it is said that carisoprodol has a depressant action on the reticular formation, but does not produce behavioral changes, in contrast to the effects of barbiturates and other hypnotics. It is suggested that the analgesic action of carisoprodol affects the central nervous centres concerned with pain perception. The consumption of paracetamol is relatively high among patients with fibromyalgia, but the efficacy of paracetamol containing drugs in these patients still remains an open question. Caffeine is believed to potentiate the effects of prostaglandin synthesis inhibitors and also to inhibit histamine release from mastcells. Based on the hypothesis that fibromyalgia might have both a peripheral and a central pain component, and on the fact that sleep disturbances may be involved in the pathogenesis of the syndrome, they designed this study as a parallel double-blind trial testing the combination of drugs mentioned earlier, versus placebo. However, because of this insufficient study design, no conclusions can be drawn.

An anecdotal report on lithium carbonate augmentation therapy in fibromyalgia is written by Tyber (17). The author stated that lithium may augment the antidepressant

effect of tricyclic antidepressants (TCA) in treating depressions in psychiatry, and that the combination of amitriptyline and lithium has been effective in treating the painful shoulder hand syndrome, so the clinical features common to fibromyalgia suggest that lithium is a useful adjunct therapy to TCA therapy for fibromyalgia. This theory should be tested in a randomized, placebo-controlled, double blind study.

Clark et al. (18) presented the results of a double blind crossover trial of prednisone versus placebo in the treatment of fibromyalgia. Their choice for a corticosteroid drug is explained by the possibility that fibromyalgia may represent the prodromal phase of one of the classical connective tissue diseases like RA or SLE. Each patient was randomly assigned to either prednisone 15 mg/day or placebo for 14 days of therapy and then therapy was switched for a further 14 days. Study length was 4 weeks. The assessments made included analogue scores for pain, sleep disturbance, morning stiffness and fatiguability, and dolorimetry readings of pain tolerance over 14 representative tender points. Overall there was no improvement while taking prednisone, in fact most measured variables showed a trend towards deterioration with this therapy.

A number of studies are performed with S-adenosylmethionine (SAM) (19-23). One of the first of these studies was by Tavoni (19). This was a report on a double blind, placebo-controlled, crossover study in 25 fibromyalgia patients with intramuscular administration of SAM. Seventeen patients completed the study; 6 withdrew for unexplained reasons and 2 developed an abscess at the site of the intramuscular injection.The choice for SAM is explained by the known anti-depressant properties of this drug. SAM is a methyl donor in many important methylation reactions in the brain. Study length was 8 weeks. Outcome variables were number of painful areas and tender points, assessment of depressive state (Hamilton Depression Rating Scale). The authors do not take clearly take a stand at what they wanted to achieve with SAM treatment. Their results showed that the number of tender points and tender areas decreased and that the score of the Hamilton Depression Rating Scale improved with SAM treatment, where these variables did not significantly change after placebo treatment. Furthermore the authors describe a good correlation between number of tender points and depressive state (assessed with Hamilton Depression Rating Scale). These results are promising, but only a small number of patients participated in this study and study length was relatively short.

Oral SAM as treatment in 44 fibromyalgia patients was studied in a double blind clinical evaluation by Jacobsen et al. (20). Five patients dropped out because of side-effects (4 during active treatment, 1 during placebo treatment). According to the authors this drug has, next to anti-depressant effects, also anti-inflammatory and analgesic effects. Study length was 6 weeks, which is very short. Improvements were seen for clinical disease activity (VAS for subjective quantification of pain at rest, pain at movement, quality of sleep and overall well-being), pain experienced during the last week, fatigue, morning stiffness and mood evaluated by Face Scale. The

tender point score, isokinetic muscle strength, mood evaluated by Beck Depression Inventory and side effects did not differ between the treated and control group. These results are different from those of Tavoni et al., where a significant improvement was seen in the depressive state. These studies did not use the same assessments of depression, and therefor a reliable comparison can not be made.
SAM was also studied by Di Benedetto (21). He compared SAM with transcutaneous electrical nerve stimulation (TENS). Both groups consisted of 15 patients. It was a 6-week controlled trial. No mention is made of drop-outs in this study. In the TENS-group were five sessions a week in which four tender points were treated. Clinical evaluations included manual and instrumental assessment of tender points, assessment of anxiety and depression using psychological rating scales (Hamilton and Zung), evaluation of subjective parameters using visual analogue scales of pain, sleep, fatigue and well-being, and laboratory tests. In conclusion SAM significantly decreased the total number of tender points, unlike TENS, had a significant beneficial effect on the subjective symptoms of pain and fatigue and significantly reduced the scores on the psychological rating scales (anxiety and depression). In the TENS group there was only at the end of the treatment significantly reduced scores on an used anxiety scale (Hamilton Anxiety Scale). The authors ascribe this effect of TENS to the placebo-effect (increased attention given to the patients). This study was not performed in blinded manner, which is very difficult to do in TENS-treatment regimens.
SAM was subject of further study by another Italian group (22). They studied the effect of an intramuscular injection of SAM in Sjögren's syndrome and fibromyalgia. Study population consisted of 10 patients with Sjögren's syndrome, 10 patients with fibromyalgia and 10 patients with both syndromes (no dropouts). Clinical and psychologic evaluations took place at baseline and after 4 weeks. The group with only the fibromyalgia symptoms had the best results. After treatment they had a lower number of tender points and painful areas, and decreased scores on the depression scales used. In the group with both of the syndromes, the number of tender points and number of painful areas were reduced as well. In the Sjögren group there was no improvement in symptoms. The number of patients in each group was small and this study was not placebo-controlled; the improvements could be based on the placebo-effect. The investigator was not blinded to the diagnosis of the patients.
Again another study was published from Italy (23). They treated a group of 47 fibromyalgia patients with SAM for 6 weeks (intramuscular and orally) and found significantly decreased tenderness at painful sites and significantly improved general well being compared with the baseline, and reduction of scores on several psychological inventories (scales). In their patient group no adverse side effects were reported. Furthermore they noted that SAM is known as an antidepressive agent, with no anticholinergic activity. This in contrast with tricyclics drugs, where anticholinergic side effects are often a limitation in usefulness. This study was performed without a control group and had no blinded design. Therefor the findings of this particular study

are not very reliable and conclusions can not be drawn.
In a study Bengtsson (24) showed that a complete sympathetic blockade by a stellate ganglion blockade with a local anaesthetic markedly reduced the number of tender points and also produced a marked decrease in resting pain. An intravenous regional sympathetic blockade with guanethidine reduced the number of tender points in the neck, shoulder and arm, but had no effect on resting pain. The authors hypothesized that the sympathetic blockade brings about an improvement in microcirculation followed by reduction in pain and tender points, which would imply that sympathetic activity may play a role in the pathogenesis of fibromyalgia. The authors tried to perform this study in a controlled and a double-blind fashion, which is very difficult to achieve with this kind of treatment, and that could not be accomplished. Only 8 patients had the real blockade (stellate ganglion and regional sympathetic), which is a small number. Because pain and tender points are widespread existent in most patients with fibromyalgia this treatment modality can not be used in daily practice. A year later Bengtsson et al. (25) published on epidural opioid blockade, at rest and during exercise in 9 fibromyalgia patients. The authors hypothesized that the pain is nociceptive and due to muscular changes. Although this study was not primarily conducted to examine treatment of fibromyalgia, they found that resting pain and tender points diminished significantly after the opioid injection. A local anaesthetic epidural blockade (with lignocaine) abolished pain at rest and tender points. These findings were, according to the authors, evidence for the peripheral (nociceptive) or spinal origin of the pain in fibromyalgia. No pain relief would have pointed to more central, supraspinal causes. This, again, was an uncontrolled and unblinded study.
In 1994 a study on the effect of an antidiencephalon immune serum on pain and sleep in patients with fibromyalgia was published (26). This study comprised a double-blind, randomized, therapeutical trial of 36 female ambulatory fibromyalgia patients, and lasted 8 weeks. Patients received either the immune serum, or amitriptyline or a placebo. Three assessments were made, at the start of the treatment, at 4 weeks and at the end, at 8 weeks. Study variables were clinical parameters, like a tender point count, subjective pain scores and associated symptoms (sleep disturbance, fatigue, finger swelling etc), and sleep EEG polygraphic data. Also mood ratings and VAS scores on sleep quality, morning restfulness and fatigue were obtained. The immune serum is said to belong to the group of heterologous polyspecific polyclonal antibodies and these are shown to improve some psychosomatic disorders. They are supposed to act as functional immunomodulators at the level of the organ or tissue. Drop-out ratio in this study was over 35%, and a large placebo response was seen. This meant that in the three groups just 6 or 7 patients were left for further analysis. For future studies they suggest to include also a non-treated group with minimal health care contacts to eliminate the placebo response as best as possible. A global subjective improvement was seen in the immune serum group, and also most prominent changes in stage-4 sleep and fatigue scores. No improvement in pain scores was observed in this group.

The placebo response in this study was substantial.
Next we will describe two studies that used homeopathic treatment. Fisher et al. (27) stated that the homeopathic medicine Rhus toxicodendron 6c (a 10-14 dilution of poison oak leaves in ethanol) was effective for a selected subgroup of patients with fibromyalgia. The authors don not tell how to select possible positive responders. The trial was double blind, placebo controlled, and of crossover design and included 30 patients. Study length was 2 months. Assessments comprised the number of tender points, VAS of pain and sleep, and overall assessment. Comparison was made between values at the end of active and placebo treatment periods. The authors described that the patients did better in all variables when they took active treatment rather than placebo. No side-effects are reported and we have to assume that the patients could not tell if they got active treatment or placebo.
Jacobs et al. (28) performed a double blind, placebo-controlled modified cross over examination with injections with rheumajecta and vasolastine in 30 patients with fibromyalgia. Rheumajecta and vasolastine are complementary, homeopathic substances which are used occasionally in the Netherlands in all kinds of rheumatic conditions, but its usefulness has not been established. The effect of rheumajecta and vasolastine was compared with that of a placebo over two periods of three months. Assessments made included tender point examination, use of analgetics and NSAID's, subscales "pain" and "health" of a Dutch, validated version of the Arthritis Impact Measurement Scale (AIMS), and furthermore an extended version of the (translated) Campbell Questionnaire, number of drop-outs in relation to lack of result between the placebo and homeopathic treatment, and patient assessment. The authors did not find significant differences in effectiveness between rheumajecta and vasolastine and the placebo treatment. There were no serious side effects seen in the patients who used the rheumajecta and the vasolastine. This means there is no rationale for the use of these substances in fibromyalgia; the choice for a placebo is cheaper and just as effective.
In 1995 Russell et al. (29) reported on the effects of Super Malic® on different pain scores in 24 fibromyalgia patients in a randomized, double blind, placebo controlled, crossover pilot study. This study lasted 10 weeks. Super Malic® is a proprietary tablet containing malic acid and magnesium. Malic acid is a naturally occurring, nontoxic, organic dicarboxylic acid. The choice for these two substances is explained by the role these two substances play in the processes of generating ATP. Russell suggests there is a muscle energy metabolism problem, but as we know from other studies (see chapter 2) that is questionable. However, no treatment effect was seen in this blinded, placebo controlled study. In an open label trial with higher doses and longer duration the authors did find improvements in pain scores, but this should be replicated in a blinded, placebo controlled study as well.

## Non-drugtrials

It is rather stunning that there are so little controlled studies published, or perhaps even undertaken, on the effects of physiotherapy (physical therapy), one of the most used therapy-forms in fibromyalgia. Mostly this form of physiotherapy is a passive one, like massage, all kinds of warmth-applications and electrotherapy. An Austrian group of researchers (30) compared two non-medicinal treatment methods, hydrogalvanic baths on the one hand (12 patients) and progressive Jacobson relaxation training on the other hand (13 patients), with regard to the effect on various psychological pain parameters. Both therapies lasted 5 weeks. The authors wanted to assess the subjective pain experience in two different ways: from a psychophysical and a behavior-oriented point of view. Prior to the start of the therapies different pain scales regarding different aspects, accompanying symptoms, correlation with sleep and of pain behavior were filled in by the patients. At the end of the therapies this procedure was repeated. With factor analysis they found three different factors; pain behavior, consequences of pain and coping behavior. Comparing the two groups, both at the beginning and at the end of the two treatment methods, no significant differences were found. Both groups did better after the treatment. A very weak point of this (pilot) study is that they did not use a control group with no interventions, and that the positive effect could be explained by the attention the patients got during the study period (placebo-effect).

# Studies targeted on sleep symptoms

Goldenberg et al. (9) in his randomized controlled trial of amitriptyline and naproxen in the treatment of patients with fibromyalgia, see above, found a significant improvement in the amitriptyline group in all outcome parameters, including patient and physician global assessments, patient pain, sleep difficulties, fatigue on awakening, and tender point score. Goldenberg hypothesized that the effect of amitriptyline in fibromyalgia patients could be related to the effect on the sleep disturbances, but their results showed that there were more positive effects in outcome variables than sleep alone (see above).

Wysenbeek (31) presented his results of a therapeutic trial of imipramine in 20 fibromyalgia patients. Imipramine is a tricyclic drug and it is said that these psychotropic drugs are known to facilitate nREM deep sleep pattern and thus were suggested beneficial for treatment of fibromyalgia. Of 20 patients only 2 patients responded favourably. This study was not carried out in a randomized, placebo-controlled, double-blind way. Study length varied from 1 week up to more than 3 months (1 patient). What outcome parameters were used is not clear. This study shows a lack of response of fibromyalgia patients to tricyclic therapy, e.g. imipramine. The study design, however, makes definite conclusions impossible.

The effects of cyclobenzaprine on sleep physiology and symptoms in patients with

fibromyalgia were studied by Reynolds et al. (32), in a randomized, double blind placebo controlled crossover study. Study population was small, only 12 patients, and the study lasted 12 weeks. Only 9 patients completed the study. They found that patients receiving cyclobenzaprine showed a decrease in evening fatigue and an increase in total sleep time. Pain, including tender point count and dolorimetry, mood ratings, and α-nREM sleep anomaly were unchanged by cyclobenzaprine. With the exception of a decrease in evening fatigue, the authors were not able to demonstrate an effect of cyclobenzaprine on symptoms in a small number of patients with fibromyalgia. Similarly, with the exception of an increase in total sleep time, they were unable to document any specific effect of cyclobenzaprine on sleep physiology. Because of the small number of patients no definite conclusions can be drawn from this study.

Chlormezanone, an effective muscle relaxant and probably acting via reduction of the τ-efferent discharge to motor fibres of muscle spindles was studied by Pattrick et al. (33). Chlormezanone should also have some benzodiazepine-like effects on sleep physiology, but without reduction in phase IV sleep. The authors conducted a double blind placebo controlled study, which lasted for 6 weeks in 42 fibromyalgia patients. Outcome measures included sleep quality, inactivity and morning stiffness, morning alertness, tender point score, mood change and global opinion of patient and observer. In conclusion the authors could not find a beneficial therapeutic effect after use of chlormezanone. The authors suggest that the lack of results of a peripherally acting relaxant, in this case chlormezanone, supports the importance of more central abnormalities in fibromyalgia. Chlormezanone had no apparent clinical effect on sleep in the fibromyalgia patients that participated in the study.

Zopiclone, a nonbenzodiazepine hypnotic, was studied in the treatment of sleep abnormalities in 45 fibromyalgia patients by Drewes et al. (34). The study design was double blind, placebo controlled and lasted 12 weeks. Four patients dropped out of the study. Reduced δ-sleep and α-contamination in nREM 2-4 have been found in fibromyalgia patients. As δ-sleep is thought to be essential for physiological restoration it has been proposed that various symptoms in fibromyalgia could be considered part of a non-restorative sleep disorder. Zopiclone has been found to induce sleep structure comparable to normal sleep and to increase δ-sleep in some patients, contrary to traditional benzodiazepines which normally reduce δ-sleep. In this study a significant improvement of tiredness during the day and subjective sleep complaints was observed, but no effects on pain or stiffness were recorded. The sleep structure remained unchanged during treatment. There was no increase or reduction of the δ-sleep during zoplicone treatment, and there was no significant change in the α-intrusion in the deeper sleep stages during treatment. This seems contradictory; the sleep structure did not change but the subjective symptoms of tiredness and sleep complaints showed an improvement. This is not further explained by the authors.

In another study the effect of zoplicone was evaluated as well (35). This concerned an

eight week double-blind randomized trial with zoplicone and a placebo in 49 fibromyalgia patients. Sixteen patients dropped out of the study. Parameters used were widespread tenderness and pain, visual analogue scales and pain drawings. Additional outcome measures used were a subjective global sleep score, duration and severity of morning stiffness and subjective improvement (scored by patient and examiner). In the zoplicone group there was an improvement in subjective sleep quality (like in the study of Drewes), but in the placebo group there was similar improvement. Patient-assessment in the zopliclone group was scored higher than in the placebo group. The examiner scored 50% of the patients in both groups, treatment with zoplicone and placebo, higher at 8 weeks. Widespread tenderness, visual analogue scales and pain drawings were not scored differently in the treatment and placebo group. These results show a very limited (positive) effect of zoplicone over placebo treatment.
5-Hydroxy-L-tryptophan was studied in an open study in 50 fibromyalgia patients (36). Thirty percent reported side effects. The study lasted three months. All the clinical variables studied, i.e. number of tender points, anxiety, pain intensity, quality of sleep and fatigue showed a significant improvement compared with the baseline results. Nearly 50% of the patients had a good or fair clinical improvement in the overall evaluation of the patient condition as assessed by the patient and investigator. These results could be due to the placebo-effect, because it was an uncontrolled, non-blinded study. However in an earlier study Caruso et al. found in a double blind study that 5-hydroxy-L-tryptophan was more effective than placebo in the treatment of fibromyalgia. The choice of tryptophan was explained by the supposed insufficient concentration of circulating tryptophan in fibromyalgia, which in turn fails to provide adequate serotonin for the maintenance of slow-wave sleep.
An anecdotal remark in regard to treatment of fibromyalgia came from Geller in a case report treated with fluoxetine hydrochloride (37). The theoretical background of the possible working mechanism is that this drug is known to block re-uptake of serotonin in the brain, and therefor could influence the sleep problems and pain experience in fibromyalgia patients. It took 5 years before a double-blind placebo controlled trial of fluoxetine in fibromyalgia appeared (38). Study length was 6 weeks. Forty-two fibromyalgia patients participated in this study, but only 25 completed the trial. The goals were to improve the clinical status (assessed with tender point count, dolorimetry scores and several VAS scores) in fibromyalgia and to see if an alteration in depressive symptomatology would appear (Beck Depression Scales, AIMS Anxiety and Depression). The authors found no differences between the groups after treatment, and concluded that fluoxetine does not improve signs and symptoms in fibromyalgia. Drop-out ratio was fairly high. The study group was not very depressed at baseline, and this makes it hard to evaluate if fluoxetine could play a role in the treatment of depressed fibromyalgia patients. Fluoxetine is known to be effective in the treatment of depressive patients, in general.

# Non Pharmacologic treatment programs, aimed at improvement in pain, sleep and mood

Moldofsky (39) suggested exercise in the form of cardiovascular fitness training as a possible treatment-modality in the fibromyalgia syndrome. This observation was prompted by the great difficulty he had in inducing fibrositic tender points in a marathon runner who, as it happened, was participating in his sleep studies. Tender points could not be induced in this normal subject after experimental induction of α-intrusion during his usual slow-wave stage IV or δ-rhythm sleep. In other normal subjects, florid tender points and a nonrestorative sleep pattern developed. From this observation Moldofsky hypothesized that cardiovascular fitness training might be favourable in patients with the fibromyalgia syndrome. Because formal proof of this hypothesis was lacking McCain et al. (40,41) studied the effect of physical fitness training in the fibromyalgia syndrome. He said that exercise could lead to alterations in opioid and non-opioid as well as neural and hormonal intrinsic pain regulatory systems. Strenuous exercise leads to predictable increases in serum levels of β-endorphin-like immunoreactivity, ACTH, prolactin, and growth hormone. Such alterations are associated with decreased pain sensitivity, commonly known as "post-run hypalgesia". An additional mechanism why exercise may be beneficially is that exercise improves mental status. According to McCain there are several studies that confirmed this statement. Ratings of self esteem and Beck Depression Inventory scores were significantly improved after cardiovascular fitness training compared with the ratings of the placebo and no-treatment control groups. Exercise may also benefit fibromyalgia patients because of its effects on slow-wave sleep. It appears that exercise results in a delay and decrease of REM sleep, an increase in stage II sleep, and a weak decrease in slow-wave sleep latency. An important remark McCain makes after these theoretical explanations is that strenuous exercise at sustained levels not only induces physiologic changes but may also be responsible for the development of a stress response. McCain suggested stress could play an very important role in the induction or perpetuation of the fibromyalgia syndrome. How this could be studied is not further elucidated. A definition of stress is not given either. In McCain's study 42 patients with fibromyalgia were randomly assigned to enter either a cardiovascular fitness training program or a program consisting only of flexibility exercises. There was not a no-treatment group included. Patients met in supervised groups three times weekly for a 20-week observation period. Thirty-eight patients completed the study. The cardiovascular fitness group underwent gradual heart rate-elevated training using a bicycle ergometer. Patients undergoing flexibility training had no statistically significant net reduction in their peak work capacity (at 170 beats per minute). Patients in the fitness group had statistically significant improvements in total myalgic scores at five selected tender points and patient's and physician's global assessment scores. Psychologic profiles as measured by Symptom Checklist-90R improved

in both groups. The author concluded that cardiovascular fitness training in fibromyalgia patients improves subjective and objective measurements of pain, but only moderately. As noted before, a no-treatment group should have been involved as well.

Mengshoel et al. (42) reported also on the effects of 20 weeks of physical fitness training in 18 female patients with fibromyalgia. There were two training sessions a week. There was a control group as well (17 patients), who were asked not to change their level of physical activity. Patients were assigned at random to the training or control group, with age as a randomization block factor. In order to improve endurance capacity in their fibromyalgia patients Mengshoel developed a modified low impact aerobic dance program. In this study they wanted to evaluate the effects of twenty weeks of endurance training on the variables of pain, fatigue, physical fitness and pain coping. Assessments were at the start of the program and at the end of the program, after 20 weeks. In the training group the intensity was kept at a heart rate level of 120-150 beats per minute. To prevent muscular fatigue frequent changes in the activation of different muscle groups were undertaken. Aerobic fitness, dynamic endurance work of the upper extremities, static endurance work of the upper extremities and dynamic endurance work of the lower extremities were measured following standard procedures. To assess the subjective symptoms pain and fatigue visual analogue scores were used. The Vanderbilt Pain Management Inventory was used to assess pain coping. The study was completed by 11 patients in the training group and 14 in the control group. After twenty weeks of exercise all the patients in the exercise group felt that exercising had increased their feelings of general well-being. Improved dynamic endurance work performance for the upper extremity was found in the training group, not in the control group. No statistical significant changes or differences in general pain, pain coping and fatigue were seen after 20 weeks. The authors conclude that fibromyalgia patients may undergo low-intensity dynamic endurance training without experiencing exacerbation of their general pain and fatigue symptoms. If this program is of benefit for the patients seems questionable, because the results are modest. The increased feeling of well-being could be related to the attention the patients received by just being in the training program.

Burckhardt et al. (43) tried to overcome this pitfall in a randomized controlled clinical trial of education and physical training in 99 female fibromyalgia patients. These 99 patients were assigned to three different groups, one group received a standardized 6-week selfmanagement education program, a second group got besides this education program a 6h physical training program and the third group served as a control group. The training program was designed to assist the patients to exercise independently (at home). Eighty-six completed the study. The control group however got treatment after three months. This means that follow-up of the control group was limited. The follow up of the experimental groups was 6 months. Assessments were made at pretest, at three months (6 weeks after finishing the experimental program), and after 6 months.

As outcome measures were used self-report questionnaires (Fibromyalgia Impact Questionnaire, Fibromyalgia Attitudes Index, Quality of Life Scale-Satisfaction, Self Efficacy Scale), physical fitness test, tender point count, and a myalgic score. The Beck Depression Inventory was also administered. The experimental programs had a significantly positive impact on quality of life and self-efficacy. There were however no significant differences between the two treated groups on any of the outcome variables. There were no changes in tender points scores or any of the physical fitness variables at any testing point. The authors suggest several reasons that may have influenced their outcomes. The length of time of the experimental programs was short, namely 6 weeks, especially in relation to behavioral changes. Furthermore the authors think that some participating women had no motivation to become better, or show a better symptom management, because of the financial benefits of being sick-listed. A hypothesis brought up by the authors why there was no significant difference between the two experimental groups is that the measurements of these two different group were made in other seasons, which may have had an influence on outcome. The most simple interpretation of the results is not mentioned; the treatment programs are just not effective in this study population. The positive changes measured could be due to the placebo-effect. A trial with a group of patients who are offered social contacts with other patients compared with a group with no further contact or other interventions should be set up to evaluate the role of these social contacts on feelings of well-being, pain experience and sleep problems.

A controlled trial of hypnotherapyin the treatment of fibromyalgia was published by Haanen et al. (44). Forty fibromyalgia patients were randomly divided over a hypnotherapy group and a group which physical therapy. They did not use a control group. The physical therapy consisted of massage and training in muscle relaxation. Because of established usefulness of hypnotherapy in certain diseases where psychological factors are thought to contribute to the pathogenesis (like chronic asthma, irritable bowel syndrome, peptic ulcer disease) the authors hypothesized that hypnotherapy could play a role in the management of fibromyalgia. Therapy lasted 3 month, and the last evaluation took place at 24 weeks, which makes a study length of 6 months. The exact number of drop-outs is not given. The patients in the hypnotherapy group showed a significantly better outcome with respect to their pain experience, fatigue on awakening, sleep pattern and global assessment at 12 and 24 (follow-up) weeks. There was no improvement in the total myalgic score measured by a dolorimeter. This means the subjective parameters improved, but the (relatively) objective parameter, myalgic score, did not change significantly. Feelings of somatic and psychic discomfort as measured by the Hopkins Symptom Checklist, showed a decrease in the hypnotherapy group, but they remained abnormally strong in many cases. At the baseline these feelings were already very strong. In this trial hypnotherapy was more successful than physical therapy in improving complaints in fibromyalgia patients. However the group with physical therapy could be regarded as

a control group, because all patients already had had some form of (unsuccessful) physical therapy in the past. The hypnotherapy was really new and the impact of this therapy could be based on the placebo-effect.

Cognitive behavioral treatment (CBT) in fibromyalgia patients was studied by Bradley (45) and Nielson et al. (46). Bradley (45) described CBT-procedures in general and presented experimental designs that could be used in randomized controlled clinical trials of CBT in patients with fibromyalgia. Bradley stated that several investigators have attempted to use cognitive-behavioral interventions to alleviate pain and disability among patients with rheumatic diseases, because they assume that patients perceptions and evaluations of their life events influence their emotional and behavioral reactions to those events. Fibromyalgia patients are confronted with chronic complaints that can not be fully explained or are fully understood, and can not be cured. Therefor they develop the belief that the pain, disability and other complaints are uncontrollable. These feelings lead to increased negative affect, pain and sleep disturbances, as well as reduced attempts to engage in activities of daily live and to develop effective coping behaviors. Cognitive-behavioral interventions are designed to teach patients skills necessary to control their pain and other forms of impairments and disabilities and to believe that they can successfully employ these skills.

In the study of Nielson (46) the treatment was conducted in an inpatient program and included 30 fibromyalgia patients. Number of drop-outs was 5. The program lasted 3 weeks and included medical, psychological, social work, physiotherapy, occupational therapy and nursing staff. All team members were skilled in the nature of the CBT approach. The authors defined target and nontarget variables and the hypothesis was that only target variables, specifically addressed by the CBT program, would change and that no changes would be expected in nontarget variables for which no treatment had been purposely devised. Assessments were made 5 months for study entry, i.e. start of the program, at the start of the program and at the end of the program. Target variables were pain severity, perceived interference with life, sense of control over pain, emotional distress and pain behavior and variables distillated from several used psychometric instruments. Nontarget variables were perceived support by others, response by significant others to pain, marital adjustment and activity level. There were no significant changes, not in the target and not in the nontarget items, at the 2 pretreatment assessments. Comparison of the pretest and posttest scores indicated that the target variables changed in the expected direction, and these changes were significant. The nontarget variables did not change significantly. The authors themselves made some restrictions as to the generalization of the result of their study. One thing was of course the short observation period and no follow up assessment. The program consisted, next to CBT, also of some other interventions, like cardiovascular fitness training, flexibility exercises and use of tricyclic antidepressants. This makes it hard to establish if the improvements can be accounted

for by the CBT alone, or any of the other interventions or the combination of them. The authors stressed the effect of the multidisciplinary nature of their interventions, which they thought relied heavily on cognitive-behavioral strategies. Three years later the outcomes of a longterm follow up of this same study were published (47). The followup assessment was conducted after a mean of 30 months after discharge in 22 (of 25) patients. Compared with the pretreatment psychometric variables, longterm improvement was found in three of 10 target variables (worry, observed pain behavior, control over pain), the other 7 variables changed in the direction of improvement. The posttreatment assessment, directly after the 3-week treatment period, showed a significant improvement in all 10 target variables, see above. The results of the follow-up assessment made the authors conclude that CBT could play a role in the longterm treatment of fibromyalgia syndrome. However they did not take into account any cointerventions that might have taken place in the follow-up period. To achieve a change in behavior in 3 weeks time seems unlikely, the more since this behavior would have been present for many years before.

Cognitive-behavioral intervention in juvenile primary fibromyalgia syndrome was studied by Walco et al. (48) in a pilot study. They treated (just) seven girls (8-18 years old) with fibromyalgia using cognitive-behavioral techniques aimed at reducing pain and facilitating sleep, as well as strategies aimed at increasing mastery over the pain and improving mood. In the treatment techniques muscle relaxation and guided imagery were used. Before treatment the average pain intensity was measured with a VAS. The intervention consisted of 4 to 9 sessions, dependent of the result. In which time span this was executed is not mentioned. The girls who completed the treatment (5 girls) reported that the pain was absent or negligible at the end of the program. Based on an interview it was concluded that the girls returned to premorbid levels of functioning. A contact by telephone was made after several months and from these interviews the authors concluded that the results were still very good. Of course these results can not lead to any definite conclusions; a randomized, controlled and blinded study should be performed.

Deluze et al. (49) published the results of a controlled trial of electroacupuncture in 70 fibromyalgia patients. It was a randomized study with blinded patients and evaluating physician. The duration of the study was three weeks. Fifty-five patients completed the study. Acupuncture is said to raise pain threshold in for instance painful nerve stimulation. Mode of action in acupuncture may be a neurohormonal mechanism, by activating some endogenous pain control mechanisms. Patients were randomized to electroacupuncture or a sham procedure. Outcome measures used in this study were pain threshold, number of analgesic tablets used, regional pain score, pain recorded on visual analogue scale, sleep quality, morning stiffness, and patient's and evaluating physician's appreciation. Seven of these eight outcome measures showed a significant improvement in the treatment group and none were improved in the sham treatment group. The authors state that with the sham treatment they used

the patients could not distinguish this from a real electroacupuncture treatment. Study duration was very short and long-term efficacy of this treatment form should be established.

EMG-biofeedback trainingin 15 patients with fibromyalgia was studied by Ferraccioli et al. (50). Because several psychosomatic syndromes have been successfully treated with biofeedback the authors saw reason to undertake this particular study. First a number of patients entered an open study and after that a controlled trial was conducted (with other patients). Fifteen sessions were given, twice weekly. Treatment period was 8 weeks. The electrodes were placed on the forehead. The intention was to learn the patients to relax, using auditory feedback of ongoing muscular tension. The authors found in more than half of the participating patients a longstanding clinical benefit. Clinical assessments were, among others, number of tender points, morning stiffness and VAS scores. A follow up of twelve months was conducted, with assessments every 3 months. Patients continued the relaxation training at home. The authors can not explain the possible working mechanisms of EMG-biofeedback training in fibromyalgia. A decrease of plasma ACTH and β-endorphins may occur during EMG-biofeedback training, and this may bring about an antistress effect. In the controlled trial a sham EMG-biofeedback training was difficult to carry out. What these patients did at home, following the 15 sessions, is not clear. In the controlled study only 12 patients participated, which is a very small number (6 in each group).

A pilot study on the effects of a multidisciplinary program, consisting of cognitive and exercise aspects, showed after ten weeks a reduction in general pain intensity and all (16 female) patients had made adjustments to their everyday life (51). The purpose of the program was to learn fibromyalgia patients how to solve their problems related to activities of daily life, and thereby reduce stress. Assessments were made by using a questionnaire related to the adjustments of daily life they carried out after the 10 week program. These adjustment are divided (by the authors?) in practising relaxation techniques, dietary changes, changes in goal setting and coping with activities, increased physical activity level and ergonomical improvements. It remains vague if the assessments were just based on subjective reports or on objective data. No control group was included and this makes it difficult to draw definite conclusions on the efficacy of this program. Furthermore at six months follow-up the score values had returned to baseline values, with the exception for the sensory pain score. The rationale behind the possible benefit of dietary changes in fibromyalgia is not explained.

# Concluding remarks

There is no golden standard in the treatment approach of fibromyalgia patients. Treatment strategies aimed only at one of the symptoms of the fibromyalgia syndrome

seem not to be appropriate. The fibromyalgia syndrome has to be considered as a chronic pain syndrome, with many implications for social and emotional functioning, and therefore these aspects have to be taken into account as well. To achieve this a multidisciplinary approach is necessary. The choice for relevant outcome variables is a very difficult one and many different variables are used. this makes it even harder to compare the different studies. Many trials were not able to show that the occurrence of a positive change after an intervention was not merely due to a placebo-effect. To keep up a blinded design was also difficult in most studies. Another problem encountered in evaluating therapytrials is that if the difference in outcome between two groups is statistically significant, is it clinically significant as well? And, if the difference is not statistically significant, was the trial big enough to show a clinically important difference if it had occurred? With a small number of patients a type II error is large and the power of the study (sensitivity) very low. Follow-up assessments and study length were mostly short and number of patients were small. Longterm follow up studies to establish the longterm effects of treatment protocols are very needed.

Therapy trials with NSAID's showed no convincing positive results. No studies are known on the effect of paracetamol in fibromyalgia, but it is frequently prescribed. The same is true for physical therapy. No controlled studies are published on the effect of physiotherapy in fibromyalgia. Whether endless passive modalities of physical therapy (including massage) have to be continued, despite lack of improvement, remain very doubtful. Continuing the therapy could make the patient dependent of the therapist (therapy), without having any actual profit of the therapy. There seems to be a modest place for tricyclic drugs (amitriptyline) in alleviating symptoms in a subgroup of fibromyalgia patients, especially related to sleep complaints.
At this time there is no substantial proof that fitness programs alleviate the symptoms of the fibromyalgia patients.

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Chapter 14

# Treatment of fibromyalgia syndrome with psychomotor therapy and marital counselling

A.A. KNIPPING, A.C.E. DE BLÉCOURT.

# Introduction

Patients with chronic pain complaints experience their pain as uncontrollable. Their pain will have a negative effect on their feelings of well-being and self-confidence. The pain itself can be the cause of negative emotions e.g. irritability and feeling tense, but the belief that the pain is uncontrollable will cause a negative affect e.g. feeling depressed and powerless. In progress of time these emotional aspects are believed to play an increasing role in the complaints of chronic pain patients. Many chronic pain patients seem to have problems with coping with these aspects, which results in so called pain behavior such as medical shopping, taking pain medication while others are watching etcetera.
From the viewpoint of behavior therapists, pain behavior is seen as behavior that is learned under certain conditions. Experiments have proven that many types of behavior are under control of reinforcement (1). Getting attention and care of others, avoidance of duties or obligations can work as reinforcers for pain behavior, regardless of the accompanying negative affects.
If pain behavior can be learned than this is probably also the case for healthy behavior if there is sufficient reinforcement.
This was one of the basic idea's behind our treatment program for fibromyalgia.

# Materials and methods

## Subjects

Hundred fibromyalgia patients who had visited the rheumatology ward of the University Hospital in Groningen were selected in an at random procedure.
Sex and age matched couples were made and divided into two groups: a treatment group (n=50) and a non treatment control group (n=50). All fibromyalgia patients were diagnosed as such by their rheumatologist. Exclusion criteria: having other prominent rheumatological, psychiatrical complaints or diseases which could interfere with research goals or treatment program (e.g. serious cardiac problems). Also patients who were attempting to receive money from a social security fund or entangled in a medicolegal procedure were excluded. Fifty patients participated as non-treatment controls after being matched on sex and age.

## Objectives

The treatment goals were: Learning the patient to cope with the impairments and disabilities of fibromyalgia (pain, fatigue, stiffness and disabilities) on a personal level and in relations towards others in the first place their spouses and also significant others (family/friends). Prior and throughout the therapy-program the patients were, explicitly, told that pain reduction was not a specific goal of the program.

## Treatment program

Psycho-motor therapy, as defined in our research project, is a behavioral therapy oriented approach which refers to body-experience and awareness. It consists of relaxation techniques, visualisation techniques, stimulation of social activities and aims to break through the process of preoccupation with pain and other physical complaints. The fibromyalgia patients were offered 10 group sessions of one hour and a half each over a period of 9 months. The groups consisted of 8 to 9 patients.
The first part of the treatment was to break through the preoccupation with the physical complaints. By way of relaxation techniques the attention of the patients was focused on their body. In this part of the treatment the patients were also stimulated to balance their activities. Being more aware of their physical state and being able to relax the patients should be able to dose their activity level in a more adequate way. Some patients chose not to; they only relaxed when the complaints were at a level that completely forced them to do nothing.
The second part of the treatment was to change the avoidance behavior. Most patients avoided certain activities, for instance social activities out of fear of having to experience a lot of pain or other complaints during or after such activities. This could deprive them of meeting others and receiving social reinforcement. The patients were feeling helpless and powerless by this and these feelings contributed to their depression. By way of structured homework assignments the patients were stimulated to engage certain activities that were pleasing to them. They were instructed to reward themselves directly after the effort, as a method of reinforcement of healthy behavior.
The third and last part of the treatment was learn to cope with the disabilities of the syndrome in relation towards others. By way of sociodrama exercises and homework-assignments the patients trained their assertiveness and social skills. The therapy was ended with an evaluation session.

The group therapy was combined with 10 one hour sessions marital coun-selling for the patients and their spouses. These counselling sessions were based on directive therapeutic techniques. The focus was on improving the communication between the patient and their spouse and/or their direct environment (significant others).
The marital counselling was partly a back-up of the psycho motor treatment and partly

to improve the partner relationship with relation to coping with the syndrome. Sometimes a sidestep was necessary because some, already existing, unsolved problems came up.

## Design

Each patient underwent psychological and medical screening, prior to, after and 6 months after therapy (T0, T1 and T2). The patients had to fill out a number of questionnaires and were interviewed in a standard way. The medi-cal screening consisted of a short medical history and a global screening of musculoskeletal aspects (muscle tone, stretch reflexes etcetera) and an examination of tenderpoints using the method of Smythe (1).

## Instruments and hypotheses

The variables that were used to evaluate the effect of the treatment program are described below:

- Medication use:three groups of medication were scored: analgetic, NSAIDS and a group that consisted tranquillizers, hypnotics and antidepressant drugs. The total number of groups (range 0-3) of medication was used for further analysis. Learning to cope with the impairments, one of the objectives in the treatment program also means learning when medication is necessary. A decrease of the mean number of medication groups is expected in the experimental group.
- Visual analogue scalespatients had to score their pain, the quality of their sleep, and a global estimate of their complaints (Paglas). 0 is having no pain or complaints; 10 is the worse possible option. Since the treatment program was not meant to deal with the physical problems, no changes were expected in these variables.
  Number of tenderpointsnumber of positive tenderpoints of the 14 examined sites (Ntender). A tenderpoint was scored positive if the patient experienced pain expressed in any way on palpation.
- Symptom Checklist 90R (SCL-90)this questionnaire is a translated (in Dutch) and adapted version of the original checklist as developed by Derogatis et al. (3). It can serve as an instrument to evaluate the amount of psychological distress. This is expected to decrease in the experimental group.
  Subscales: Anxiety (Anx), Agoraphobia (Ago), Depression (Dep), Somatization (Som), Sensitivity (interpersonal) (Sen), Inadequacy (In), Hostility (Hos) and Sleep disturbances (Sle).
- Utrechtse Coping Lijst (UCL)(4) This questionnaire was used to evaluate changes in coping behavior for both groups. This checklist appears to be a method to evaluate more trait-like aspects of coping, but it can also serve as an instrument to

gain data about changeable aspects of coping. The patients were given the instruction to fill out this questionnaire with the question in mind "how do you react nowadays (appr. last month) on your fibromyalgia complaints?". In chapter 12 has been demonstrated that many fibromyalgia patients have inadequate coping styles. The treatment program aimed on a changing from passive to active ways of coping, which can be measured with the UCL.
Subscales: Active approach (Act), Palliative reaction (Pal), Avoidance (Avo), Seeking social support (Soc), Depressive reaction (Dep), Expression of emotions (Exp), Comforting cognitions (Com).

- Maudsley Marital Questionnaire (MMQ): This questionnaire was used to evaluate the quality of the relationship (5). Only married patients or the ones who lived together with a partner had to fill out this questionnaire. Having physical complaints and especially pain for a prolonged time may have a negative influence on the interpersonal relationship, especially with the spouse. Learning how to communicate about the pain and the related problems was one of the objectives in this treatment program. Therefore a reduction of marital problems was expected.
  Subscales: Relation satisfaction (interpersonal aspects), Sexual satisfaction, and General life satisfaction (housework and social aspects).

# Results

The mean age in the total group (n=100) was 41.9 years (range 22-59 years), mean duration of complaints 102.7 months (range 23.1-230.5 months). The percentage of female participants was 90.

17 (34%) of the 50 patients dropped out before the end of the program for several reasons, 7 relating to the program (not useful, to difficult etcetera) 10 not relating directly to the program (to much pain, distance between house and hospital to far, getting a job etcetera).
Directly after treatment the patients were asked to fill-out an openquestioned treatment evaluation form. Seventy percent reported to be satisfied with regard to self-confidence and methods to enhance relaxation. Two third of the patients reported to have been improved in dealing with the disabilities. Some patients (24%) asked for a more structured approach.

Multivariate analysis of variance (MANOVA) with repeated measurement designs were used to compare the experimental and control group on the three assessments (T0, T1, and T2). Post hoc univariate tests were used if the multivariate tests proved significant differences ($p<0.05$).

The means and standard deviations of the two groups on T0, T1 and T2 on medication

use, number of positive tenderpoints and the visual analogue scales are given in table 1. A summary of of the MANOVA (repeated measurement) is displayed in table 2 .

Table 1
MEANS AND STANDARD DEVIATION FOR MEDICATION USE, NUMBER OF TENDERPOINTS AND VISUAL ANALOGUE SCALES (PAGLAS: PATIENT GLOBAL ASSESSMENT) AT PRETREATMENT (T0), POSTTREATMENT (T1) AND FOLLOW UP (T2)

| | Treatment group | | | Control group | | |
|---|---|---|---|---|---|---|
| | T0 | T1 | T2 | T0 | T1 | T2 |
| Medic | 1.1±0.9 | 1.1±0.9 | 1.1±0.9 | 1.2±0.8 | 1.2±0.9 | 1.2±0.9 |
| Ntender | 8.9±3.0 | 9.0±3.0 | 8.4±3.2 | 9.8±3.2 | 9.2±2.7 | 9.5 ± 2.6 |
| Paglas | 63.1±20.4 | 57.1±26.6 | 54.3±25.2 | 60.1±27.6 | 58.2±28.0 | 62.2±27.1 |
| Pain | 58.3±21.9 | 62.6±18.7 | 63.5±24.7 | 58.8±25.2 | 65.8±23.3 | 70.2±23.6 |
| Sleep | 49.6±31.8 | 49.2±34.9 | 51.4±38.0 | 57.5±31.5 | 59.4±30.5 | 54.8±33.7 |

MANOVA showed that there was a significant effect for assessment. Univariate F tests showed that the pain increased over time for both groups ($F(2,140) = 3.6$). Although it seems that the patients global assessment in the experimental group is decreasing (the lower the score is, the better the patient estimates his/her overall somatic condition), this effect does not reach to significance.
Tender point score, quality of sleep and medication use remains the same for both groups over time.

Table 2
RESULTS OF MANOVA (REPEATED MEAURES) FOR GROUP (G), ASSESSMENT (A), AND GROUP X ASSESSMENT INTERACTION (G X A) ON SOMATIC VARIABLES

| | Hotelling's $T^2$ | Approx. F | Hypot. df | p< |
|---|---|---|---|---|
| G | 0.026 | 0.44 | 4 | 0.777 |
| A | 0.707 | 5.57 | 8 | 0.001 |
| G x A | 0.066 | 0.52 | 8 | 0.834 |

The results on the SCL-90 are shown in table 3 and 4.

Table 3
MEANS AND STANDARD DEVIATIONS FOR SCL-90 SUBSCALES AT PRETREATMENT (T0), POSTTREATMENT (T1) AND FOLLOW UP (T2)

| | Treatment group | | | Control group | | |
|---|---|---|---|---|---|---|
| | T0 | T1 | T2 | T0 | T1 | T2 |
| Anx | 19.1±6.1 | 17.7±6.5 | 16.9±6.5 | 17.6±6.3 | 16.4±5.3 | 16.0±8.3 |
| Ago | 9.0±2.5 | 9.3±3.5 | 9.6±4.1 | 10.3±4.7 | 9.3±4.5 | 10.4±11.5 |
| Dep | 32.1±10.4 | 28.4±10.8 | 26.8±7.8 | 28.9±10.2 | 27.4±8.5 | 25.8±8.6 |
| Som | 31.6±7.2 | 29.9±7.3 | 28.8±7.0 | 32.1±8.0 | 29.3±7.0 | 28.8±6.4 |
| In | 21.1±6.1 | 19.7±6.0 | 19.1±6.1 | 18.6±4.2 | 18.3±4.7 | 18.1±8.0 |
| Sen | 29.7±9.8 | 28.8±9.0 | 27.1±8.2 | 27.4±8.7 | 27.1±7.7 | 24.7±7.6 |
| Hos | 8.0±2.3 | 8.2±2.2 | 7.2±1.4 | 8.3±2.1 | 7.7±2.0 | 8.1±5.3 |
| Sle | 7.8±3.4 | 7.9±3.7 | 7.9±3.8 | 9.1±3.6 | 8.5±3.5 | . 67.6±3.5 |

Table 4
RESULTS OF MANOVA (REPEATED MEAURES) FOR GROUP (G), ASSESSMENT (A), AND GROUP X ASSESSMENT INTERACTION (G X A) ON THE SCL-90

| | Hotelling's $T^2$ | Approx. F | Hypot. df | p< |
|---|---|---|---|---|
| G | 0.214 | 1.66 | 8 | 0.127 |
| A | 0.858 | 2.89 | 16 | 0.002 |
| G x A | 0.512 | 1.73 | 16 | 0.069 |

Multivariate testing shows no significant differences between groups. However, also here there is an effect for assessment. Patients of either groups have decreasing scores over time on the Anxiety ($F(2,138)=4.5$), Depression ($F(2,138)=14.7$), Somatization ($F(2,138)=10.0$), and Sensitivity ($F(2,138)=6.1$) subscales. The Group x Assessment interaction (treatment effect) is not significant, but part of the Assessment main effect seems to be explained by changes in the experimental group. None of the univariate F-

tests for the Group x Assessment interaction are significant, however.

In table 5 and 6 the results on the UCL are shown.

Table 5
MEANS AND STANDARD DEVIATIONS FOR UCL SUBSCALES AT PRETREATMENT (T0), POSTTREATMENT (T1) AND FOLLOW UP (T2)

| | Treatment group | | | Control group | | |
|---|---|---|---|---|---|---|
| | T0 | T1 | T2 | T0 | T1 | T2 |
| Act | 17.5±3.5 | 17.7±3.0 | 17.5±3.5 | 18.2±2.9 | 17.3±3.8 | 17.0±3.5 |
| Pal | 19.1±3.0 | 18.5±3.5 | 18.3±3.5 | 20.0±3.8 | 18.9±3.5 | 18.8±4.1 |
| Avo | 16.1±3.5 | 15.0±2.6 | 15.5±3.5 | 16.9±3.3 | 15.3±2.9 | 15.0±3.5 |
| Soc | 12.0±3.6 | 12.6±4.3 | 12.3±4.0 | 12.4±3.1 | 11.9±3.5 | 12.2±3.5 |
| Dep | 12.8±3.3 | 11.6±3.2 | 11.1±3.1 | 11.9±2.7 | 11.3±2.6 | 10.8±2.7 |
| Exp | 5.6±1.4 | 5.7±1.5 | 5.5±1.8 | 5.9±1.1 | 5.5±1.4 | 5.4±2.2 |
| Com | 13.2±2.6 | 13.0±2.9 | 12.8±2.8 | 13.7±2.6 | 13.0±3.0 | 13.0±3.0 |

Table 6
RESULTS OF MANOVA (REPEATED MEAURES) FOR GROUP (G), ASSESSMENT (A), AND GROUP X ASSESSMENT INTERACTION (G X A) ON THE UCL

| | Hotelling's $T^2$ | Approx. F | Hypot. df | p< |
|---|---|---|---|---|
| G | 0.036 | 0.29 | 7 | 0.956 |
| A | 0.772 | 2.70 | 14 | 0.005 |
| G x A | 0.263 | 0.92 | 14 | 0.543 |

MANOVA concerning the data on the UCL shows no overall group effect, and also here no treatment effect (Group x Assessment) was found.
For both groups multivariate analysis showed a significant change for Assessment. Univariate analyses showed that the scores on Palliative reactions (F(2,124)=2.3), Avoidance reactions (F(2,124)=8.3), and Depressive reactions (F(2,124)=10.0) are decreasing over time.
Data on the MMQ can be found in table 7 and 8.
Multivariate analysis showed there were no main effects for Group or Assessment or Group x Assessment (treatment) interaction effects.

Table 7
MEANS AND STANDARD DEVIATIONS FOR MMQ SUBSCALES AT PRETREATMENT (T0), POSTTREATMENT (T1) AND FOLLOW UP (T2)

| | Treatment group | | | Control group | | |
|---|---|---|---|---|---|---|
| | T0 | T1 | T2 | T0 | T1 | T2 |
| Rel.sat. | 14.4±12.2 | 16.5±13.0 | 16.1±11.4 | 12.9±10.4 | 14.2±12.0 | 12.4±11.8 |
| Sex.sat. | 11.7±9.4 | 12.6±9.7 | 11.8±9.7 | 10.0±7.4 | 11.5±7.7 | 9.7±7.2 |
| Gen.l.sat. | 13.0±5.0 | 11.7±4.3 | 12.3±4.7 | 11.8±5.4 | 12.2±6.4 | 12.2±5.0 |

Table 8
RESULTS OF MANOVA (REPEATED MEAURES) FOR GROUP (G), ASSESSMENT (A), AND GROUP X ASSESSMENT INTERACTION (G X A) ON THE MMQ

| | Hotelling's $T^2$ | Approx. F | Hypot. df | p< |
|---|---|---|---|---|
| G | 0.015 | 0.28 | 3 | 0.842 |
| A | 0.152 | 1.30 | 6 | 0.275 |
| G x A | 0.076 | 0.65 | 6 | 0.694 |

# Discussion

On T0 the two groups did not differ significantly from each other. Apparently there is no difference in the perception of the complaints (either somatic or psychological) between the treatment group and the control group prior to treatment, which makes a further comparison between the two groups possible.

One of our objectives for this treatment program was to change the pattern of coping styles into more adequate types of coping. We expected the amount of psychological distress to decrease because patients would have the perception of having more control over their complaints, or at least would be aware that shifting attention from what you cannot do to what actually can be achieved, despite the (pain) complaints, would be more satisfactory.
The results show that indeed coping styles were changing towards a more adequate pattern and that scores on anxiety, depression, somatic complaints and interpersonal sensitivity were dropping, even despite an increase in perceived pain intensity, but this was also true for the control group.
Inviting these patients to participate in a research study and giving serious attention to their problems, examine them thoroughly on somatic as well as psychological aspects, is probably the most important reason for these changes. Many patients expressed their relief for being taken seriously at last, and were hoping for the development of treatment programs that would improve their situation, or even better, would cure them.

The results described above led to the conclusion that this program of psychomotor

therapy combined with marital counselling was not sufficient to enhance significant and durable changes in fibromyalgia patients. The fairly positive evaluation could be the result of social desirability or may be an attempt by the patient to prevent herself/himself of facing cognitive dissonance. People tend to minimize the extend of cognitive dissonance by readjusting their thoughts about the things they are doing or the things they have done (external justification) (6). The patients had to spend time and effort in the treatment program and they probably do not want their time and effort having spent for nothing. This makes it more likely that they will evaluate the treatment in a rather positive manner when asked directly.

The high percentage of drop outs (34%) was another problem in this study. This problem was partially caused by the selection procedure. Participants were approached directly (first by letter, followed by a telephone call) and asked if they were willing to participate. This may have resulted in the participation of subjects who were not very motivated to follow through the whole treatment program. High drop out rate has a negative effect on the power of the statistical analysis, and this may have been another reason why significant treatment effects were not found.

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# Treatment of fibromyalgia with psycho education based on behavior therapy

A.A. KNIPPING, A.C.E. DE BLÉCOURT.

# Introduction

In chapter 14 an evaluation has been made of management of the fibromyalgia syndrome with help of a combined treatment with psychomotor therapy and marital counselling.
In the treatment program evaluation by the participants it appeared that many of these patients found that the approach was not sufficiently structured. This seemed to be mainly caused by the indirect way the psychomotor therapy works, in spite of the fact that more behavior therapy-oriented techniques were incorporated. This led to the belief that the treatment program should be more direct. The conclusions that were made in chapter 11 indicate that a treatment approach similar to that of other chronic pain syndromes may be useful.
Treatment programs that are based on learning principles (behavior therapy) have proven to be useful in the management of chronic pain syndromes (1).
More recently cognitive-behavioral treatment approaches were developed, in which not only the behavior itself is changed but also the thoughts and beliefs that accompany this behavior. These programs do not aim on pain reduction but on the learning and application of adequate coping skills (2).
Several investigators have attempted to use cognitive-behavioral interventions to alleviate pain and disability among patients with rheumatic diseases (3).
Persons with rheumatic syndromes such as fibromyalgia are confronted with complaints of which the cause is not known, the course is chronic and for which no cure is available. Fibromyalgia patients often believe that their pain, disability and other consequences of their symptoms are uncontrollable. This belief leads to increased negative affect, pain and sleep disturbance as well as to reduced attempts to engage in activities of daily living and to reduced attempts to develop effective coping behavior. Cognitive-behavioral interventions may provide these patients with skills necessary to control their pain and other forms of disability and to believe that they can successfully employ these skills.

# Materials and Methods

## Subjects

Sixty outpatients of the Department of Rheumatology of the University Hospital of Groningen, diagnosed as having fibromyalgia by their rheumatologist, were randomly selected and invited to participate in the research program.
Two groups of 30 patients were created, stratified on age and gender, but otherwise in an at random procedure. One group served as a treatment group, the other as a non-treatment control group.
Both groups were screened on medical and psychological aspects before the start of

the treatment program (T0), directly after the end of the program (T1) and six months after the treatment program as a follow up (T2).

## Objectives

The treatment goals were:

1. Establish adequate coping skills, based on realistic beliefs and thoughts.
2. Shifting the "locus of control" of the patients from external into an internal one.
3. Thus, diminishing the negative emotional aspects and feelings of helplessness regarding the pain and the other fibromyalgia complaints.

## Treatment program

The treatment program was based on cognitive-behavioral therapy principles, such as the Rational Emotive Therapy (4) and the stress-inoculation therapy (5). Self management techniques were demonstrated and practised in order to improve the coping abilities of the patients. Cognitive aspects of pain were discussed and evaluated. In adapting these aspects into our treatment program, we identified two goals: 1) to teach patients about the influence of their thoughts on their emotions and behavior, and 2) to present a simple formula that patients may use to identify and alter those irrational thoughts that have often resulted in unpleasant emotions and poor problem solving. Furthermore information was given about medical and psychological aspects of fibromyalgia.

The form of the treatment program was based on ideas of psycho-education rather than actual therapy.

The experimental group (n=30) was divided into three groups of 10 participants. These groups received the psycho-education in 15 sessions. Three phases could be distinguished: First the education phase, in which general information about fibromyalgia was given and explanation about relation between stress and pain and cognitions and stress. Second the training phase, in which skills and techniques were demonstrated and practised, e.g. relaxation techniques and stress-inoculation.

The third phase was the application phase, in which the patients were encouraged to apply their skills in daily situations. In the second and third phase homework assignments were given. All treatment sessions were conducted by a psychologist.

## Design

Each patient underwent psychological and medical screening, prior to, after and 6 months after therapy (T0, T1 and T2). The patients had to fill out a number of questionnaires and were interviewed in a standard way. The medical screening

consisted of a short medical history and a global screening of musculoskeletal aspects (muscle tone, stretch reflexes etc.) and an examination of tenderpoints using the ACR-1990 tenderpoint score (6).

## Instruments and hypotheses

The following instruments were used to evaluate the effect of the treatment program:

- The Symptom Checklist 90 (SCL-90; Dutch version) (7). This questionnaire measures the extent of psychoneuroticism and is divided into eight subscales: Anxiety (Anx), Agoraphobia (Ago), Depression (Dep), Somatization (Som), Inadequacy (In), (interpersonal) Sensitivity (Sen), Hostility (Hos) and Sleep (Sle). The SCL-90 is a suitable, widely used and reliable instrument for measuring distress in a recent period. The reliability of the subscales is between 0.88 and 0.97. If the treatment program were to be successful then a decrease of psychological distress would be expected for the treatment group.
- The Pain Cognition List (PCL; in Dutch: Pijn Cognitie Lijst (8). This questionnaire measures the beliefs and thoughts the patients have about their pain. It has five subscales: Negative Selfefficacy (NS), Catastrophizing (CA), Positive Expectancy (PE), Acquiescence (AC) and Reliance on health care (RE).
  The reliability of the subscales is between 0.61 and 0.88.
  Negative selfefficacy and catastrophizing are cognitions that are thought to contribute to be irrealistic and undesirable when having chronic pain complaints. Because the treatment program aims a reduction of these cognitions, a decrease of scores on these variables are expected for the treatment group. The subscale Positive Expectancy contains items that may be related to intern locus of control and being able tot cope successfully with pain complaint. The scores on this subscales are expected to increase in the treatment group.
- The Pain Control Questionnaire (PCQ; in Dutch: Pijn BeheersingsVragenlijst (9). In this questionnaires the patients have to estimate their extend of control over several pain aspects on visual analogue scales. With this questionnaire a distinction can be made between internal versus external "locus of control" regarding pain aspects. It has two subscales: Internal pain control and External pain control. Locus of control is related to illness behavior. Persons who have an internal locus of control are less frequent visitors of doctors, use less medication etc (10). A shifting from external to internal locus of control is expected for the treatment group, because of the increasing controllability that is supposed to be the result of the treatment program.
- Visual Analog Scales for: pain, quality of sleep, and patients global assessment (PAGLAS).
- Medication use The medication the patients used were divided into three categories, firstly the NSAID's, secondly the analgetic medication and a third group

consisting of antidepressant drugs, neuroleptics and hypnotics. The number of categories of medication was used for further analysis, thus ranging from 0 to 3 (MEDIC) A decrease in medication use was expected in the treatment group as result of an increase in internal locus of control.

- Number of positive tenderpoints Eighteen tenderpoints according to the 1990 ARA criteria for fibromyalgia were examined manually. A tenderpoints was scored from 0-4 according to the ACR-1990 criteria (6). A tenderpoint was scored as positive when it had a score of 2 or higher (NTENDER).
- Problems with the activities of daily living were scored with an ADL checklist, which is part of the FIQ (11) Patients had to state wether they could or could not perform a certain activity. The activities that could be performed by the patient were summarized, which yields in a score between 0 (not a single activity possible) to 9 (all activities possible) (ADL).
  An increase in ADL-activities is expected for the treatment group, as a result of the cognitive-behavioral treatment.

# Results

The mean age was 45.3 years (range 26-26 years), mean duration of the complaints 11.1 years (range 0.4-25.6). Eighty-five percent of the total group were female.
Ten (30%) of the 30 patients in the treatment group dropped out before the end of the program; 5 of them mentioned a worsening of their complaints (not related to the treatment program) as a reason to stop, 2 subjects judged the treatment program as not useful for them, 1 subject stopped because of moving to another town, as a result of getting a job elsewhere, and 2 subjects stopped for unknown reasons.
Multivariate analysis of variance (MANOVA) with repeated measurement designs were used to compare the experimental and control group on the three assessments (T0, T1, and T2). Post hoc univariate tests were used if the multivariate tests proved significant differences ($p<0.05$).
The means and standard deviations of the two groups on T0, T1 and T2 on medication use, number of positive tenderpoints, ADL-checklist and the visual analogue scales are given in table 1 . Results of the MANOVA with repeated measures are summarized in table 2 .

Table 1
MEANS AND STANDARD DEVIATIONS FOR VISUAL ANALOGUE SCALES (PATIENTS' GLOBAL ASSESSMENT, PAIN AND SLEEP), MEDICATION USE, NUMBER OF TENDERPOINTS AND ADL-ACTIVITIES THAT WERE POSSIBLE OUT OF 9 AT PRETREATMENT (T0), POSTTREATMENT (T1) AND FOLLOW UP (T2)

| | Treatment group | | | Control group | | |
|---|---|---|---|---|---|---|
| | T0 | T1 | T2 | T0 | T1 | T2 |

| | | | | | | |
|---|---|---|---|---|---|---|
| PAGLAS | 62.2±29.3 | 45.8±30.5 | 49.2±34.4 | 42.3±31.7 | 56.3±25.1 | 56.7±22.6 |
| Pain | 50.0±24.2 | 65.6±23.7 | 60.7±29.2 | 54.0±29.2 | 66.2±19.2 | 69.5±20.5 |
| Sleep | 52.6±35.5 | 43.8±36.1 | 46.8±37.5 | 56.8±30.5 | 50.9±32.1 | 48.0±36.1 |
| MEDIC | 1.6±0.8 | 1.4±0.7 | 1.6±0.6 | 1.5±0.9 | 1.1±0.7 | 1.3±0.6 |
| Ntender | 12.8±4.0 | 10.4±4.3 | 11.0±5.0 | 10.5±3.0 | 8.5±4.1 | 8.8±3.7 |
| ADL | 6.3±2.4 | 7.0±2.0 | 6.1±2.8 | 6.9±1.5 | 6.8±1.6 | 7.0±1.6 |

Multivariate analysis showed that there was not a group effect, nor a group x assessment effect (treatment effect). There was, however an effect of assessment. Univariate analyses show that the number of tenderpoints decreases over time in both groups ($F(2,58)= 10.8$). An increase in pain intensity (VAS) did not reach to significance.

Table 2
RESULTS OF MANOVA (REPEATED MEAURES) FOR GROUP (G), ASSESSMENT (A), AND GROUP X ASSESSMENT INTERACTION (G X A) ON SOMATIC VARIABLES

| | Hotelling's $T^2$ | Approx. F | Hypot. df | p< |
|---|---|---|---|---|
| G | 0.284 | 1.14 | 6 | 0.371 |
| A | 3.213 | 4.82 | 12 | 0.001 |
| G x A | 0.568 | 0.85 | 12 | 0.604 |

Means and standard deviations on the SCL-90 are presented in table 3 and the MANOVA results can be found in table 4 .

Table 3
MEANS AND STANDARD DEVIATIONS FOR SCL-90 SUBSCALES AT PRETREATMENT (T0), POSTTREATMENT (T1) AND FOLLOW UP (T2)

| | Treatment group | | | Control group | | |
|---|---|---|---|---|---|---|
| | T0 | T1 | T2 | T0 | T1 | T2 |
| Anx | 20.1±8.0 | 18.0±7.1 | 16.8±6.6 | 16.7±6.0 | 16.0±6.1 | 16.3±7.1 |
| Ago | 11.8±6.4 | 11.3±6.8 | 10.8±6.5 | 8.5±2.4 | 8.8±2.7 | 11.8±16.4 |
| Dep | 30.9±10.2 | 28.9±10.3 | 26.4±9.7 | 28.9±9.4 | 25.3±8.4 | 29.2±15.6 |
| Som | 33.0±9.3 | 30.0±9.4 | 29.7±8.2 | 30.6±8.5 | 30.0±8.8 | 32.4±14.6 |
| In | 20.7±5.7 | 19.9±5.9 | 20.9±10.1 | 20.8±5.3 | 20.2±5.6 | 22.0±6.6 |
| Sen | 31.8±12.8 | 30.3±11.9 | 27.1±10.9 | 27.8±7.9 | 26.3±6.8 | 29.9±14.1 |
| Hos | 8.7±4.3 | 8.2±3.9 | 7.9±2.7 | 8.3±2.1 | 7.7±2.2 | 11.1±11.8 |
| Sle | 7.4±3.4 | 7.4±3.4 | 7.9±3.4 | 9.1±3.7 | 9.1±3.7 | 9.6±5.8 |

Table 4
RESULTS OF MANOVA (REPEATED MEAURES) FOR GROUP (G), ASSESSMENT (A), AND GROUP X ASSESSMENT INTERACTION (G X A) ON THE SCL-90

| | Hotelling's $T^2$ | Approx. F | Hypot. df | p< |
|---|---|---|---|---|
| G | 0.474 | 1.72 | 8 | 0.136 |
| A | 0.513 | 0.67 | 16 | 0.788 |
| G x A | 1.000 | 1.31 | 16 | 0.276 |

Multivariate analysis did not show an overall group effect, nor a treatment effect (group x assessment), although there seems to be a decrease in anxiety, depression, somatization and sensitivity for the treatment group if looked at the means. Also there was not a main effect for assessment.
Results on the Pain Cognition List for both groups can be found in table 5 and 6.

Table 5
MEANS AND STANDARD DEVIATIONS FOR PCL SUBSCALES AT PRETREATMENT (T0), POSTTREATMENT (T1) AND FOLLOW UP (T2)

| | Treatment group | | | Control group | | |
|---|---|---|---|---|---|---|
| | T0 | T1 | T2 | T0 | T1 | T2 |
| NS | 44.1±10.0 | 41.8±9.7 | 39.2±9.7 | 42.6±8.6 | 42.2±11.5 | 41.4±9.2 |
| CA | 42.7±11.4 | 40.3±11.9 | 40.4±11.9 | 44.3±9.3 | 42.8±9.6 | 43.5±9.5 |
| PE | 24.7±4.5 | 24.3±3.8 | 24.3±4.8 | 25.4±2.4 | 24.6±3.5 | 24.7±3.2 |
| AC | 10.9±3.5 | 11.9±3.4 | 12.0±3.7 | 11.8±2.8 | 10.8±2.2 | 11.8±3.5 |
| RE | 17.6±3.0 | 16.3±2.1 | 16.9±1.7 | 18.3±2.6 | 16.5±2.2 | 18.1±3.1 |

Table 6
RESULTS OF MANOVA (REPEATED MEAURES) FOR GROUP (G), ASSESSMENT (A), AND GROUP X ASSESSMENT INTERACTION (G X A) ON THE PCL

| | Hotelling's $T^2$ | Approx. F | Hypot. df | p< |
|---|---|---|---|---|
| G | 0.054 | 0.35 | 5 | 0.881 |
| A | 0.801 | 2.16 | 10 | 0.054 |
| G x A | 0.606 | 1.63 | 10 | 0.150 |

No effects on the factors group or group x assessment (treatment effect) were found in MANOVA tests. Also here there was an (almost) significant effect on assessment. Univariate tests showed an effect for Negative Selfefficacy ($F(2,72)=5.1$) and Reliance on health care ($F(2,72)=5.7$. As expected there is a decrease in mean score on negative Selfefficacy in the treatment group, but apparently also, although less clear, in the control group.
Mean scores and standard deviations on the PCQ can be found in table 7 . MANOVA results are presented in table 8 .

Table 7
MEANS AND STANDARD DEVIATIONS FOR PCQ SUBSCALES AT PRETREATMENT (T0), POSTTREATMENT (T1) AND FOLLOW UP (T2)

| | Treatment group | | | Control group | | |
|---|---|---|---|---|---|---|
| | T0 | T1 | T2 | T0 | T1 | T2 |
| Int. l.o.c. | 28.2±12.4 | 26.6±11.5 | 29.6±10.6 | 32.2±11.1 | 32.1±10.4 | 30.1±11.2 |
| Ext. l.o.c. | 15.8±8.5 | 16.1±10.7 | 14.3±8.2 | 13.5±7.3 | 15.7±8.2 | 16.8±9.7 |

Table 8
RESULTS OF MANOVA (REPEATED MEAURES) FOR GROUP (G), ASSESSMENT (A), AND GROUP X ASSESSMENT INTERACTION (G X A) ON THE PCQ

| | Hotelling's $T^2$ | Approx. F | Hypot. df | p< |
|---|---|---|---|---|
| G | 0.044 | 0.77 | 2 | 0.470 |
| A | 0.047 | 0.39 | 4 | 0.812 |
| G x A | 0.198 | 1.63 | 4 | 0.189 |

MANOVA revealed no significant effects on group, treatment (group x assessment) or assessment.

# Discussion

The main problem in this study was the high dropout rate (30%), which seems to be the result of the selection procedure. The same remarks as made in chapter 14 are also of importance here. In further research it is worthwhile to select only motivated participants e.g. by using newspaper advertisements to recruit subjects.
There seem to be changes in the treatment group in the expected direction: decrease of psychological distress (several SCL-90-subscales), decrease in negative self efficacy and decrease in catastrophizing, but these changes are not large enough to result in significant test results. The overall power of the tests, however is influenced in a negative way by the high drop out percentage (30%).
This indicates that there may be a positive effect of treatment, but a replication with a larger (more motivated group) should give the definite answer.
Nielson et al. (12) performed a study in which a cognitive-behavioral treatment was attempted to decrease pain severity, perceived interference with life and emotional distress in fibromyalgia patients, whereas an increase was expected in sense of control over pain. Twentyfive participants, all fibromyalgia patients from a rheumatic diseases outpatient department and fulfilling the ACR-1990 criteria for fibromyalgia took part in the program. Nielson did not use a control group, but used patients as their own waiting list controls (one pretest 5 months before start of the treatment program,

and one just before the start), and also used "target" variables (expected to change with treatment) and "nontarget" variables (not expected to change) to assess potential demand characteristics. Nielson hypothesized that if participants were dissimilating in order to please those conducting the study, higher scores would be obtained on all outcome measurements. If, on the other hand, changes reflected true treatment responses, improvements should only occur for the target variables. Comparison on both pretest assessments showed no significant differences on all variables. Comparison of the pretreatment and posttreatment indicated that the target variables, but not the nontarget variables changed in the expected direction. A follow up assessment (13) indicated that the short term improvement that had been observed improvement was maintained over a period of 30 months after discharge of the program. Although chapter 14 indicates the importance of a control group, it seems that cognitive-behavioral treatment may have a role in the longterm treatment of fibromyalgia. The data from our study support this hypothesis, but are not strong enough to prove this point on their own.

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# Fibromyalgia: towards an unifying model

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# Introduction

Fibromyalgia has been examined from different viewpoints by different type of researchers. It has been perceived as a non-disease (1), a psychiatric disease (2), a variant of depressive disease (3), the result of a sleep disturbance (4), a primary somatic phenomenon (5), a result of inappropriate stress coping (6) and so on. Many research reports seem to shed light on part of the problem without illuminating the whole. In the previous chapters is illustrated that fibromyalgia is a complex phenomenon which cannot be explained or dealt with in a simple manner.

The presence of tender points seems to be the most important feature in fibromyalgia. On the basis of tender points these patients can easily be distinguished from other patient groups, which has been demonstrated in chapter 7.

But it is also clear that the fibromyalgia syndrome contains more than just widespread pain and the presence of tender points, or else the visions on fibromyalgia as stated above would not have emerged.

The etiology and pathogenesis of fibromyalgia are presently not known. The consensus document on fibromyalgia: the Copenhagen declaration (7) states that psychological factors play a role but not an etiological one. Fibromyalgia patients often suffer from depression and other psychological problems, but this is thought to be the consequence of the fibromyalgia complaints. Whether this is true or not can only be determined by means of longitudinal studies. Another aspect that is not addressed in this declaration is the reciprocal relation between psychological factors, such as anxiety, depression and coping styles, and pain. In this way the emotional distress can become part of the problem.

Chapter 2 of this dissertation shows the increasing evidence for centrally induced pain problems in fibromyalgia, in which neurohormonal dysfunctions are present. So far studies have failed to show clear global defects of muscle metabolism in fibromyalgia, making a peripheral mechanism unlikely.

But then again: neurohormonal dysfunctions do not stand on itself. At this level psychological factors play their part, either as a consequence (e.g. feeling depressed as a result of a shortage of serotonin in the brain) or as a possible cause (e.g. noradrenergic arousal as a result of fright).

For a good understanding of the fibromyalgia complaints one has to bear in mind that somatic and psychological factors are entangled and can not be seen apart from each other.

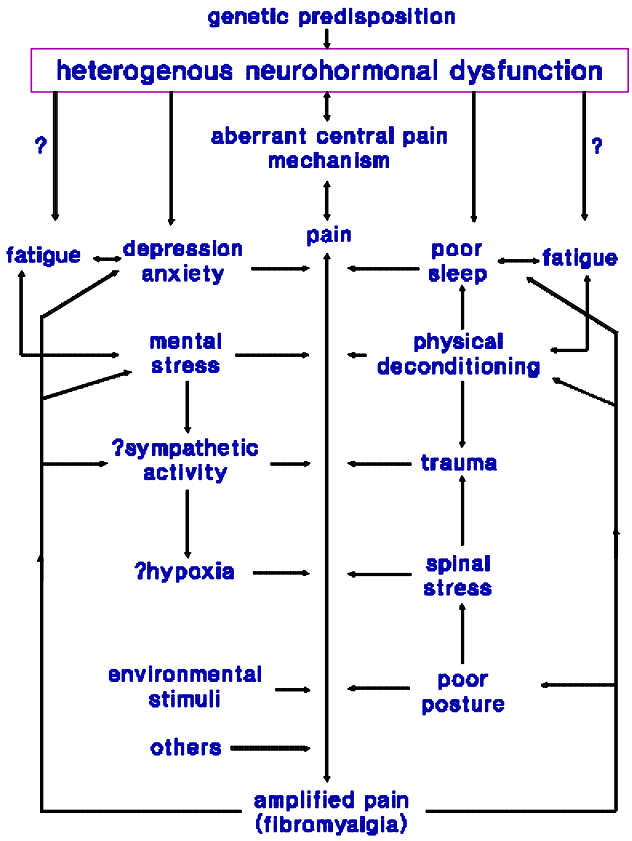
# Fibromyalgia models

## Central versus peripheral explanations

An evaluation of studies in the field of fibromyalgia was made by Yunus (8). He postulates that the main problem in fibromyalgia is a complex network of

neurohormonal dysfunctions leading to aberrant central pain mechanisms, which alone could cause fibromyalgia in many patients; in others interactions of other factors, including peripheral ones ( e.g. trauma, mechanical stress) and those secondary to the pain itself (e.g. physical deconditioning), may amplify the pain in a vicious cycle. The model that gives insight in these mechanisms is depicted in figure 1 .

Figure 1
PROPOSED CENTRAL AND PERIPHERAL MECHANISMS INTERACTING IN FIBROMYALGIA WITH AMPLIFICATION OF PAIN: THE PRIMARY DEFECT IS "IN THE BOX", I.E., HETEROGENOUS NEUROHORMONAL DYSFUNCTION




An important role in the heterogenous neurohormonal dysfunction in this model is thought to be attributed to the neurotransmitter serotonin. Animal studies suggest that serotonin inhibits pain and mediates sleep. A problem with this assumption is that data are not suggestive of serotonin deficiency in all fibromyalgia patients (9-10). Amitriptyline however, which has proven to decrease pain as well as tender points (11-12) works at the neurohormonal level. These findings support this model. Not every relation between the mentioned factors is clear in this model and the model contains several question marks. Yunus states that "future studies should further explore the box and also include early stage cases seen at primary care levels to prevent several biases" (8).

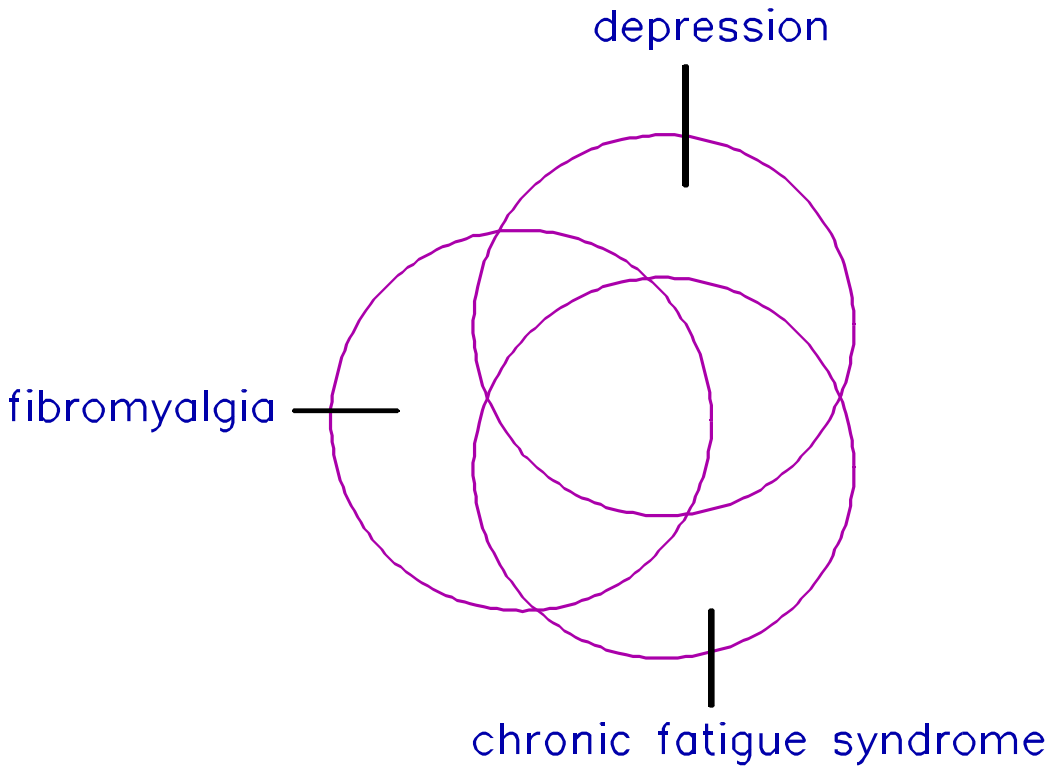
## Fibromyalgia and related syndromes

Although fibromyalgia is no longer regarded as being a purely psychiatric problem, it is often related to psychological problems. Depression and anxiety are the most frequently mentioned problem in this respect. In a study of Hudson et al. (13) current major depression was present in 26% of the fibromyalgia patients (n=31) according to DSM-III criteria, and in none of the RA patients (n=14). Seventy-one percent of the fibromyalgia patients had current or past diagnoses of major depression versus 14% in the RA group. The fibromyalgia patients also had significantly higher scores on the Hamilton Rating Scale for Depression. An extension of this study (14) showed similar results. It seems that there is a relation between fibromyalgia complaints and depression, although not all the fibromyalgia patients can be diagnosed as having a depression. Depressive symptoms should be distinguished from the diagnosis of major depression in patients with fibromyalgia as has been argued in chapter 10. Hudson and Pope (15) assume that fibromyalgia and depression share a common basic trait. There are also other syndromes that share many characteristics with fibromyalgia, e.g. chronic fatigue syndrome (CFS). Fatigue, for example, is often mentioned as one of the main problems by fibromyalgia patients and pain is not uncommon in CFS. Associations between related syndromes can be depicted with the help of Venn diagrams (see figure 2 ) (16).

### An integrated model for fibromyalgia

Preceding chapters and what has been described above make it clear that the fibromyalgia syndrome is a complex phenomenon that cannot be understood in terms of a single cause and effect relation. Fibromyalgia is more than muscle pain or tender points alone and regarding fibromyalgia as (the result of) a psychological problem does not give the ultimate insight either. Approaching the fibromyalgia problem in this way leads to the pitfall of

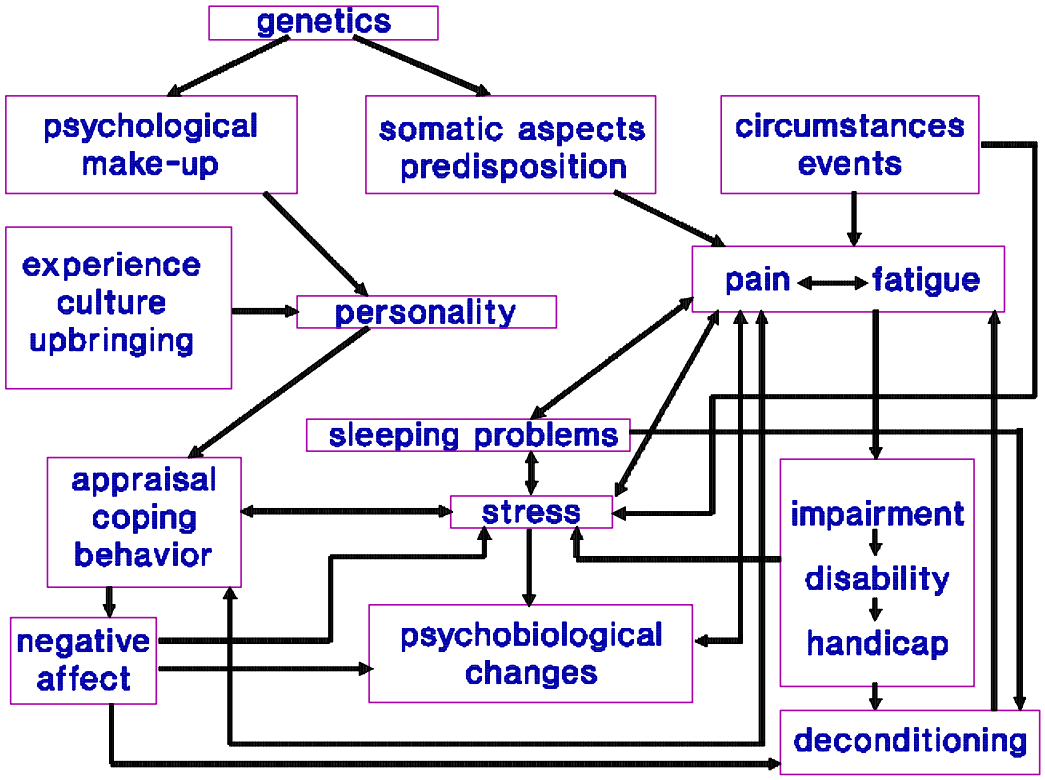
Figure 2
FIBROMYALGIA AND RELATED SYNDROMES




cartesian dualism or to an analogy of the famous story in which blind visitors all give very dissimilar descriptions of an elephant after researching the animal. For a better understanding of fibromyalgia it has to be considered as a multi-caused syndrome, in which somatic, psychological and (social)-environmental aspects have to be taken into consideration. Efforts in this respect have been made by only a few authors, of which Yunus is mentioned above. Bennet (17) hypothesizes a proneness to muscle micro-trauma which can lead to fibromyalgia complaints under influence of a defective repair mechanism, such as defective growth hormone production. In its turn this defective repair mechanism is caused by α-δ sleep anomalies and deconditioning. Deconditioning further enhances proneness to muscle micro-trauma, which causes pain intensified by eccentric contractions. Pain leads to sleeping problems and inactivity, which, in its turn leads to deconditioning etc. Inactivity, fatigue and sleeping problems are also interrelated, which makes up a vicious cycle of influencing factors. The role of psychological aspects remains underexposed in this model.

The model that is presented in figure 3 is an attempt to illustrate the complex interrelations between the factors that are thought to play a role in the development and continuation of the fibromyalgia complaints. The findings described in the previous chapters are included in this model, in which somatic and psychological factors are interrelated.

Figure 3
A PROPOSED FIBROMYALGIA MODEL




A somatic predisposition (e.g., proneness to muscle micro-trauma, or a low pain threshold) in combination with certain circumstances or eliciting events (injury, illness, operation, period of physical strain) can have pain and fatigue as a consequence. Pain and fatigue may act as a stressor and it may also have a negative effect on the quality of the sleep. Stress and sleeping problems also have a negative effect on the amount of pain and fatigue. Cognitions about pain and stress are also important factors. If a patient experiences the pain as a threatening phenomenon (e.g, a serious illness), the reactions of such a patient will differ from those who regard pain as a signal for an excess of physical or psychological strain. Thus, the way a person copes with pain, stress and sleeping problems is dependent of attributions and other cognitions about pain and stress (appraisal). Illness behavior or adapting, "healthy" behavior are the results. These cognitive and behavioral aspects are influenced by the personality of the patient, which is formed by a combination of genetic aspects (psychological make-up) and environmental factors (e.g., childhood experience, culture and upbringing). If pain and stress are present over a longer period of time, as a result of inadequate coping and reinforced pain behavior, other problems may arise. If phasic stress passes into tonic stress, psychobiological (neuro-hormonal) changes take place, which may have a negative effect on the pain and fatigue. If the patient experiences his situation as uncontrollable, a depressive mood (negative affect) will

emerge, which influences the amount of stress and it may also lead to psychobiological changes. Depressed patients become inactive which has a negative effect on the physical condition of the patient. Deconditioning increases fatigue and it makes the patient less able to cope in an active way (increasing of pain experience). In terms of rehabilitation models (18), the patient may become increasingly handicapped as result of the sequence impairment → disability → handicap. In this respect an impairment is defined as every possible deviation in anatomical, physiological or psychological function (e.g., strength, mobility of joints, coordination of movement, pain). An impairment is not restricted to somatic factors, but it also contains psychological aspects. If impairments cannot be dealt with by means of direct treatment, disability is the result. This is defined as being less able or unable to perform normal skills and actions (problems with activity of daily living, driving a bicycle, walking for more than 500 meters, being unable to work etc.). The term handicap concerns the disadvantageous position of the patient as a result of the disabilities. This has to be seen in the light of the role the patient plays with regard to age, social-cultural background, gender etc.
This process can form a source of stress and may have as a result a deconditioned patient. In this model the predominantly psychological aspects are depicted on the left hand side of the model and the somatic aspects more on the right. Stress, pain and fatigue are the central aspects of this model. They influence each other and are influenced by several other aspects that are of importance in the understanding of fibromyalgia. This model illustrates that fibromyalgic complaints cannot be relieved by diminishing the pain alone (analgesics) or treating one of the other aspects. All aspects of the syndrome have to be taken into consideration for a successful management. Patient education and increasing the patients' control over the complaints are important features in this respect, thus making the patient more responsible for his own situation.

# Recommendation for further research

In spite of extensive research in this field an adequate treatment for fibromyalgia has not been developed yet. Given the fact that fibromyalgia is a complex syndrome that is influenced by many factors this is not very surprising. Treatment, therefore, should not be based on a single cause and relation model, but the complexity and multicausal aspects must be taken into consideration. Further research has to shed light onto those aspects that are suitable for a treatment approach. Fibromyalgia syndrome should be seen as a phenomenon with chronic aspects, which makes it clear that learning to cope is more important than cure. Attempts to cure fibromyalgia have not been very successful so far. The attentional focus of the researchers should be aimed at maintaining the "quality of life" aspects of these patients and maintaining a full-fledged role for the patients in the society, thus minimizing their handicap. For a

better understanding of the syndrome the psychobiological aspects and their relation to (tonic) stress must become clear. These aspects could be important mediating factors in fibromyalgia and related syndromes, such as chronic fatigue syndrome. Our studies (chapter 14 and 15) and other clinical therapy trial have been aimed at effects for the total group that was treated. But it is conceivable that only a certain number of patients respond partially to any single therapeutic intervention. Future research should try to identify subgroups which respond more effectively to a particular intervention or combination of therapies.
In clinical practice and also in research situations patients who have only recently developed their complaints are rarely seen. Most patients (66% in our patient group; see chapter 9) state that their complaints have developed gradually over time. Their is very little knowledge about the early stage of fibromyalgia. Therefore controlled risk factor studies as well as longitudinal course of illness research on fibromyalgia patients starting in the earliest stage of the complaints is essential in order to determine factors that may contribute to onset and prognosis versus those which result from the pain and dysfunction of this chronic condition. Only then an attempt can be made to develop treatment programs to prevent a process of chronization.

# Recommendations for management of fibromyalgia in clinical practice

The remark that "fibromyalgia is not life-threatening and that swimming in warm water is good for you" is not enough to improve the situation of a fibromyalgia patient.
The foremost important action that has to made before any type of treatment is given, is giving the patient accurate information about what fibromyalgia is. An increased understanding is likely to decrease anxiety and to lead to better treatment compliance. If a patient is misinformed, there is a great risk that incorrect cognitions about their complaints are formed, which yields inadequate coping strategies and the risk of depression.
Another important factor is the risk that the patient becomes increasingly deconditioned, as a result of a decreased activity level, caused by pain, fatigue and depression. The activity level of the patient should be increased gradually, by means of concrete directives. If there is already a progressive deconditioning, a moderate fitness program can be useful which must be aimed at increasing the activity level of the patient. Only active forms of physical therapy serve this purpose. Passive forms (e.g., UKG, massage) can make the fibromyalgia patient believe the problems can be dealt with in a passive way. The emphasis of any treatment given to fibromyalgia patients should be based on the premiss that the patient is responsible for his or her situation, thus increasing the motivation for an intern locus of control.

Drug treatment (painkillers, anti-depressive drugs, sleeping-tablets) should be regarded as a possible support for other types of treatment, not as a treatment in itself, because of the possible side effects when used for a prolonged time. Drug treatment can be effective however when it is important to break through the vicious cycle of interrelating factors concerning pain, poor sleep and depression, making the patient more motivated for other types of treatment. Multidisciplinary treatments which employ a combination of approaches using modalities such as patient education, aerobic conditioning, behavioral therapy and cognitive restructuring seem to be the best option if such a treatment form is available.
We feel that the patient should be given the diagnosis fibromyalgia, if appropriate, because this probably decreases the feelings of uncertainty and anxiety in the patient, but immediately after that the patient should be educated in what the consequences are of this diagnosis (e.g. not automatically a justification for disability coverage) and that regaining control is very important for improvement of the situation. The emphasis should be on breaking through the vicious cycles these patients find themselves in, not on relieving the symptoms, because this will make the patient believe that only the doctor has control, which will make the patient passive and feeling helpless.

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# Summary

In this dissertation various aspects of the fibromyalgia syndrome are discussed. Fibromyalgia (syndrome) is a common disorder seen in rheumatology practices, and has been known under a variety of names during the years. The introduction to the syndrome and a historical review of fibromyalgia are described in chapter 1. Criteria for the fibromyalgia syndrome have evolved during the years from a wide spectrum of different symptoms to just two criteria:

1. the existence of chronic widespread pain and
2. a number of positive tender points on palpation (11 out of 18).

There have been many different ideas on the possible pathophysiology of this chronic pain syndrome, but no definite answer has been found.

Chapter 2 summarizes the different studies that are performed in the search for a, primarily, somatic origin of the syndrome. Through the years one can see that the ideas on pathophysiology of the fibromyalgia syndrome have changed. In the beginning most studies looked for a disease, e.g. dysfunction of the end organ, the muscle. This evolved to more complex mechanisms of immunologic problems, neuromuscular disturbances, microcirculatory changes, sleep cycle disturbances, chronic (virus) infections and finally neuro-immuno-endocrinologic abnormalities. The results of the different studies makes it highly unlikely that there are specific and consistent abnormalities in the muscle tissue in fibromyalgia, and neither is their substantial evidence for abnormalities in energy metabolism. The studies on immunologic factors bring contradictory results, but overall there is no proof that there are immunologic abnormalities in fibromyalgia or that fibromyalgia is (or will develop into) a (auto-immune) connective tissue disorder. Evidence for neuromuscular abnormalities is not found. There is no abnormal muscle tension present in fibromyalgia. An abnormal reaction to cold vasospasm is observed, although there was no relation between these vasospasm and the subjective experiences of Raynaud-like phenomena.

In the sleep-studies an alpha EEG sleep anomaly in patients with fibromyalgia is frequently found. But if fibromyalgia is caused by sleep anomalies, or that fibromyalgia and sleep anomalies are both the result of another, still unknown factor, remains an open question.

Analyzing the different reports and studies on a possible virus or other invader in the etiology of fibromyalgia, the conclusion is that this theory can not be held upright.

The studies on neuro-immuno-endocrinologic aspects show different outcomes, although abnormal reactions in the hypothalamic-pituitary-adrenal axis are frequently found. The relation between cortisol and stress in the fibromyalgia syndrome should be further analyzed. Evidence for disturbances in serotonin level and metabolism is found as well, and this also needs further study to establish a possible link with depression (and again stress).

The last part of chapter 2 describes different aspect of aerobic capacity and muscle performance in fibromyalgia. The conclusion is that the basic physiological function

of the muscles is normal during exercise, but patients do not bring their maximal effort in the different test situations. Fibromyalgia patients are physically unfit, but this is due to a deconditioning effect.

In chapter 3 different coexisting and modulating factors are discussed. Irritable bowel syndrome is often described as a coexisting factor in fibromyalgia, and so are Raynaud's and Sjögren's syndrome. Patients with fibromyalgia often have a wide variety in symptoms of these different syndromes. The same can be said of the related, or overlapping, syndromes, like the chronic fatigue syndrome and the myofascial pain syndrome. We do not think that these syndromes are separate entities, but it is more like a continuum of different symptoms, with in each patient emphasis on one of more of these symptoms which will define the patient to one of the syndromes.

In chapter 4 a study is described of 31P Magnetic Resonance-Spectroscopy (31P MRS) at the site of tender points in the trapezius muscle of patients with fibromyalgia. 31P MRS provides the opportunity to study high energy phosphate metabolism in muscle tissue. We did not find a significant decrease in the high energy phosphate metabolites in the trapezius muscle of fibromyalgia patients, compared to healthy controls. The results of our study do not support the theory that a state of hypoxia causes the muscle complaints in fibromyalgia, providing an organic origin for the syndrome.

Chapter 5 describes the results of two physiological (hormonal) stress test, and the relation between the results of these stress test to two psychological tests. This study was conducted as a pilot study and no control group was included. 20 patients were tested with a TRH/LHRH test, and also a CRF/GRF test. The psychological tests were the PBV and STAI. Evaluating the different hormonal test results, there are many abnormal values, but not all in the same direction. We found no correlation between hormonal stress scores and psychological test scores in our study. Patient number in our study was limited and there was a wide variation in the abnormal hormonal stress scores, so this makes it very unlikely to find a correlation.

Chapter 6 reports on a study on the relationship between weather conditions and fibromyalgic complaints. Patients with fibromyalgia often state that weather conditions modulate their complaints. We related the subjective symptoms of pain, stiffness, sleep and mood in fibromyalgia patients (reported in weekly diaries), to objective meteorological data (from the Dutch Meteorological Institute at Airport Eelde). Correlation analyses showed no relation between the subjective complaints and meteorological factors. The subjective symptoms pain, stiffness and fatigue, however, showed a strong intercorrelation. One explanation for the discrepancy between the patients' belief on one side and objective findings in this study on the other side, could be found in the attribution theories. Patients with pain feel less helpless if they can relate their pain to some external condition, i.e., the weather, thus justifying it.

Chapter 7 describes different aspects of tender points in fibromyalgia, like mode of examination and identification of positive tender points, the concept of tender points especially in relation to fibromyalgia and compared with other diagnoses, furthermore

the aspect of reliability of tender points in fibromyalgia and last aspect is the value of a tender point count as a treatment outcome variable. The tender points play a crucial role in determining if a patient with wide spread chronic pain will be classified as a fibromyalgia patient. A change in number of tender points is not generally accepted as an useful outcome parameter in evaluating therapy programs in fibromyalgia. A relation between number of positive tender points and severity of the syndrome is not established.

The results of a study are presented, in which the total number and specific localizations of the tender points in individual fibromyalgia patients were consistent in time. In our study we found no differences in number of tender points in fibromyalgia patients in the course of 18 months, and the score of each individual tender point pro patient was consistent as well. Patients with a high number of tender points also have a high number of positive control points. This would mean that in fibromyalgia there is a generalized lowered pain threshold, and also women have a lowered pain threshold compared to men.

Chapter 8 summarizes the results of several epidemiological studies. There are a few population based studies, with prevalence numbers of 0.66% up to 11.2%. This last number reflects all persons with wide spread pain in a general population in England. The latest prevalence study mentions a prevalence of 2% in a general population of 18 years and older. It is very difficult to determine the prevalence in the general population and part of this problem is that fibromyalgia is too heterogenous to be one disease or illness. There are no reliable data on the prevalence in primary care populations. The prevalence in clinical or hospital populations depends strongly on referral patterns, but most studies mention a prevalence of 5-20%. Although fibromyalgia is thought to be most frequently seen in women between 30-50 years, the syndrome also is diagnosed in children and elderly people.

In this chapter an attempt is made to evaluate the severity and socio-economic impact of the fibromyalgia syndrome. Musculoskeletal conditions are among the leading diseases when it concerns social and economic costs to individual and society as well. They score high in measures of disabilities, restriction of activity, use of vocational rehabilitation, and medical costs. They score relatively low, compared with other diseases, as a cause of death. The impact of the fibromyalgia syndrome is not the same in all countries, because there are many differences in social and medical securance and insurance systems, offers for jobs, unemployment rates, attitude to work and attitude to (psychosomatic) diseases.

In chapter 9 some clinical aspects and the natural history of the fibromyalgia patient group in our studies (n=144) are highlighted. A description is made of several aspects of the medical consumption and literature on these aspects is reviewed. There is a high percentage of female patients in fibromyalgia, a phenomenon for which there is no good explanation. In our population 90% of the patients is female, which is comparable to the findings of other researchers. The perceived severity of the complaints make that fibromyalgia patients feel that they are handicapped and the vast majority of patients (70%) in our study population state that their complaints are

worsening over time. Fibromyalgia complaints emerge gradually and spontaneously in most patients (66% in our patient group).

Chapter 10contains a review of literature on psychological aspects in fibromyalgia. The relation between fibromyalgia and anxiety and depression is highlighted. There is no compelling evidence for psychological abnormality in fibromyalgia as an etiological factor. Depressive symptoms and anxiety are present, but are most likely an accompanying factor in a chronic medical condition. Furthermore the relation between pain, the most prominent complaint in fibromyalgia, and psychological aspects are studied in more detail. "Learned helplessness", inadequate behavioral responses, reinforcement of pain behavior, social modelling and cognitive aspects are modulating factors in pain experience and pain behavior. There is a reciprocal relationship between stress and pain at one hand and psychological factors at the other. Whether these psychological factors can be considered as etiologic is still open to discussion.

In chapter 11psychological aspects of fibromyalgia are compared with those of chronic and nonchronic pain. Three groups, a chronic pain group (n=99), a nonchronic pain group (n=34) and a fibromyalgia group (n=36) are compared, using a standardized interview and psychological questionnaires (SCL-90, IBQ and CIPI). It appeared that the chronic pain group and the nonchronic pain group can be easily distinguished from each other on basis of criteria of an advisory committee (Gezondheidsraad) of the Dutch Ministry of Health. The scores of the fibromyalgia group and the chronic pain group were very similar. This leads to the conclusion that many psychological aspects in fibromyalgia can be considered as aspects of having chronic pain complaints.

Chapter 12contains a report of a study in which a group fibromyalgia patients (n=100) is compared with a group patients with rheumatoid arthritis (n=25) and a group patients with chronic low back pain (n=22), using visual analogue scales for pain intensity, quality of sleep and a global estimate of overall complaint. Furthermore the groups were compared on tender point scores and scores on several psychological questionnaires: SCL-90R, Amsterdamse Biografische vragenlijst (ABV), Maudsley Marital Questionnaire (MMQ), Utrechtse Coping Lijst (UCL) and Prestatie Motivatie Test (PMT; Achievement Motivation Test). Results show that fibromyalgia patients perceive their problems as more severe than both other groups and that the amount of psychological distress is larger. Fibromyalgia patients also have higher scores on neurotic lability, as measured by the ABV, which may be an indication for a psychological predisposing factor. Fibromyalgia patients differ in their coping styles of both other groups. Fibromyalgia patients have higher scores on the Palliative, Avoidance an Depressive reaction subscale of the UCL. This seems to reflect inadequate coping behavior.

Chapter 13summarizes the different treatment strategies described in the literature. A major issue in evaluating treatment programs is the choice of reliable outcome measures. This point is not yet resolved and this makes a comparing of the different studies very difficult. NSAID's have no more effect on symptoms in fibromyalgia as

placebo. There is a modest positive effect of tricyclic drugs (amitriptyline) in a subgroup of fibromyalgia patients, especially in regard of sleep disturbances. There have been no controlled studies in regard to physical therapy, however a great deal of fibromyalgia patients follow a kind of physical therapy. The same can be said of allopathic treatment regimens. No substantial proof have emerged that fitness programs alleviate the symptoms of the fibromyalgia patients. In general, study length (and follow-up) was short in most studies, and another observation is that there is a considerable placebo-effect in a number of treatment programs, which makes the outcomes not very reliable.

The fibromyalgia syndrome has to be considered as a chronic pain syndrome, with many implications for social and emotional functioning, and these aspects have to be taken into account as well. This can only work in a multidisciplinary setting with a multidisciplinary approach. Patients have to be an active participant in their own rehabilitation program.

In chapter 14a study is presented in which the effect of treatment of fibromyalgia syndrome with psychomotor therapy, based on behavioral therapeutic principles, and marital counselling is evaluated. Fifty fibromyalgia patients participated in the treatment group and fifty patients participated as nontreatment controls. Treatment goals was to help the patient learning to cope with the disabilities resulting from their fibromyalgia complaints, by means of behavioral therapeutic techniques, relaxation exercises, assertiveness exercises and learning to differentiate between complaints of the syndrome and other bodily and emotional sensations. Pretreatment, posttreatment and follow up assessments were made, based on experience of complaints (VAS-scales), SCL-90, UCL and MMQ. The drop out rate was high (34%), probably related to the way participants were selected. Multivariate analysis of variance showed that there were changes over time for both groups (increase of pain, but decrease of psychological distress and decrease of inadequate forms of coping). An effect for treatment was not found.

In chapter 15the effect of a cognitive-behavioral treatment program is evaluated. Thirty patients were selected in an at random procedure and were asked to participate in the treatment program. Thirty patients served as non treatment controls. Treatment goals were:

1. establish adequate coping skills, based on realistic beliefs and thoughts.
2. Shifting the 'locus of control' of the patients from external into an internal one.
3. Thus, diminishing the negative emotional aspects and feelings of helplessness regarding the pain and the other fibromyalgia complaints.

Assessment took place prior to treatment, after treatment and 6 months after the ending of the treatment program. Outcome variables that were used: SCL-90R, Pijn Cognitie Lijst (PCL), PijnBeheersings Vragenlijst (PBV), visual analogue scales for pain, sleep and global estimates of complaints, tender point score, and an ADL-checklist. As in the study described in chapter 14, the drop out rate is high (33%). No treatment effects were found using multivariate analysis of variance. As a result of the high drop out rate the power of the statistical testing has decreased. Replication with

larger groups, and perhaps other recruitment procedures are necessary.
In chapter 16an attempt is made to bring together the various aspects of fibromyalgia into one model which is explanatory for the most important interrelated factors. Stress, pain and fatigue are the central aspects of this model. They are influenced by several psychological and psychobiological aspects. Many patients with fibromyalgia complaints seem to be trapped in vicious cycles of reciprocal factors. Much is unknown about early stages of fibromyalgia. Further research, based on longitudinal designs, is necessary. Treatment of fibromyalgia should aim primarily on 'care' aspects, not on cure. It is important that patients with fibromyalgia recover the experience of control over their complaints. Treatment programs should therefore aim on breaking through the vicious cycles in which the patients are trapped, thus giving back the patients responsibility for their own well-being.

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| Voorlopige Promotiedatum: | 1 november 1995 |
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| Titel proefschrift: | FIBROMYALGIA: towards an integration of somatic and psychological aspects |


Samenvatting

In dit proefschrift worden diverse aspecten van het fibromyalgie syndroom belicht. In hoofdstuk 1 wordt een algemene introductie gegeven van het fibromyalgie syndroom. In feite is het fibromyalgie syndroom een chronisch pijnsyndroom met enkele specifieke kenmerken. De pijnklachten zijn gelokaliseerd in het houdings- en bewegingsapparaat en de klachten kunnen doen denken aan een reumatische aandoening. Met name vrouwen presenteren zich met deze klachten in het medische circuit. Door de jaren heen zijn er verschillende criteria gepubliceerd aan de hand waarvan de diagnose fibromyalgie gesteld kon worden. In eerste instantie waren ook bijkomende klachten zoals moeheid onderdeel van deze criteria, maar ook de aanwezigheid van modulerende factoren, zoals de invloed van weersfactoren op de klachten. De criteria werden steeds bondiger en uiteindelijk zijn er nog slechts 2 criteria overgebleven: wijd verspreide pijn in het houdings- en bewegingsapparaat die langer dan 3 maanden aanwezig moet zijn, tezamen met positieve drukpunten in tenminste 11 van 18 onderzochte lokalisaties (1990 American College of Rheumatology Criteria). In hoofdstuk 1 wordt ook beschreven hoe er door de jaren heen over dit klachtenpatroon gedacht is, waarbij de oorzaak in eerste instantie gezocht werd direct in de spier. De gedachte was dat er een ontstekingsachtig substraat aanwezig zou zijn, maar geleidelijk aan veranderden de ideeën omtrent de pathogenese naar meer complexe mechanismen. Door de jaren heen zijn er dan ook vele namen aan dit syndroom gegeven, zoals fibrositis, myofibrositis, weke delen reuma, en uiteindelijk fibromyalgie.
Er zijn ook kritische kanttekeningen geplaatst bij het concept van fibromyalgie.
In hoofdstuk2 wordt de literatuur, die verschenen is over mogelijke somatische factoren bij het ontstaan van fibromyalgie, samengevat. In de loop der tijd is geleidelijk aan een verschuiving opgetreden van het zoeken naar een perifere oorzaak naar een meer centraal gelegen pathogenetisch mechanisme. In eerste instantie ging de aandacht uit naar mogelijke afwijkingen in spierbiopten, vervolgens werd ook de spierstofwisseling in de spieren onderzocht. Uit in vitro studies kwamen aanwijzingen naar voren dat er sprake zou zijn van verlaagde concentraties van hoog-energetische fosfaten, maar in vivo studies konden dit bij herhaling niet bevestigen. In de spierbiopten werden geen specifieke, consistente afwijkingen gevonden. Er werd ook uitgebreid gezocht naar immunologische afwijkingen, maar een duidelijk afwijkend immunologisch patroon is niet gevonden. Dit maakt het ook onwaarschijnlijk dat fibromyalgie een voorbode is van een immunologische (auto-immuun) aandoening. Verder zijn er ook geen concrete aanwijzingen gevonden dat er sprake is van een verhoogde spierspanning in de pijnlijke spieren van de fibromyalgiepatiënt. Wel werd er in een bepaald percentage van de fibromyalgiepatiënten een abnormaal, door koude geïnduceerd, vasospasme gevonden. Een relatie met het syndroom van

Raynaud blijft echter discutabel. Veel onderzoek is ook gedaan naar de relatie tussen bepaalde slaapstoornissen en fibromyalgie. Een alpha EEG slaap anomalie is door meerdere auteurs gevonden en beschreven in fibromyalgie, maar een causaal verband kon niet worden aangetoond. Verder zijn er geen aanwijzingen gevonden dat een infectieus agens een rol speelt bij het ontstaan van fibromyalgie. Zoals aangegeven is de zoektocht zich steeds meer gaan bezighouden met meer centrale mechanismen, die ook een rol kunnen spelen in de pijnmodulatie, zoals neuro-immuno-endocrinologische factoren (hormonen). Er zijn aanwijzingen dat er stoornissen zijn in de hypothalamus-hypofyse-bijnier-as, hoewel niet alle publikaties tot dezelfde conclusies komen. Een relatie tussen afwijkingen in serotonine metabolisme en depressie en pijn (en stress?) is interessant en zou verder uitgewerkt moeten worden.

Bij het testen van de aerobe capaciteit en verrichtingen van skeletspieren komen geen afwijkingen in basale fysiologische processen aan het licht. Wat wel opvalt is dat fibromyalgiepatiënten niet hun maximale kunnen laten zien in verschillende spiertesten. Waarschijnlijk weerhoudt de angst voor het ontstaan of verergeren van de pijn patiënten ervan om de maximale inzet te leveren. In het algemeen hebben fibromyalgiepatiënten wel een matige conditie (uithoudingsvermogen), maar dit is te verklaren door te weinig lichaamsbeweging.

In hoofdstuk 3 wordt de relatie met bijkomende factoren, zoals irritable bowel syndroom en Sjögren's syndroom, beschreven. Verder is gesuggereerd dat vrouwen die vroeger mishandeld zijn een grotere kans lopen fibromyalgie te ontwikkelen in hun latere leven. Dit is echter een bewering die nog wel verder getoetst dient te worden. In dit hoofdstuk wordt verder aandacht besteed aan de overeenkomsten tussen het fibromyalgiesyndroom, chronisch vermoeidheidssyndroom en het myofasciale pijnsyndroom. Dit zijn geen separate entiteiten; er is een duidelijke overlap tussen de verschillende syndromen. De klachten behoren alle tot hetzelfde spectrum, maar bij de ene patiënt staat de moeheid op de voorgrond en bij de ander de pijn (al dan niet gegeneraliseerd).

In hoofdstuk 4worden de resultaten van eigen onderzoek gepresenteerd. Er werd met behulp van 31P magnetische resonantie spectroscopie ter hoogte van de tender points in de trapezius musculatuur gekeken naar de spierstofwisseling. Dit werd zowel bij fibromyalgiepatiënten als gezonde proefpersonen gedaan. Uit de resultaten bleek dat er, vergeleken met de controlegroep, geen verlaagde waarden van de hoog-energetische fosfaten in de fibromyalgiegroep aanwezig waren. Deze bevindingen pleiten tegen de theorie dat hypoxie de oorzaak zou zijn voor de klachten bij fibromyalgie.

In hoofdstuk 5wordt eveneens verslag gedaan van eigen onderzoek. Getracht is te onderzoeken of er een relatie bestaat tussen de resultaten van 2 hormonale stress testen (TRH/LHRH- en CRF/GRF-test) en scores van psychologische vragenlijsten (PBV en STAI). Het betrof hier slechts een pilot studie, zonder controle groep. De uitkomsten lieten een zeer gevarieerd beeld zien wat betreft de hormonale stress testen, met diverse afwijkende waarden. Een relatie met de vragenlijsten werd niet gevonden.

Hoofdstuk 6 beschrijft de resultaten van eigen onderzoek naar de relatie tussen weersfactoren en klachten bij fibromyalgiepatiënten. Veel fibromyalgiepatiënten geven aan dat koud, nat weer hun klachten doet toenemen. In onze groep gaf ook 80% een positief antwoord op de vraag of er weersinvloeden op hun klachten aanwezig waren. De scores van wekelijks ingevulde dagboeken t.a.v. pijn, stijfheid, moeheid en stemming, werden vergeleken met diverse meteorologische variabelen verzameld door het KNMI (peilstation Eelde), zoals neerslag, temperatuur, wind-snelheid, vochtigheid, luchtdruk etc. De patiënten waren niet op de hoogte van het feit dat deze

vergelijking plaats zou vinden; de dagboekscores waren primair door ons verzameld om het verloop van de klachten tijdens een behandelperiode te inventariseren.
Uit de analyse van de weersgegevens en de dagboekscores kwam naar voren dat er geen verband tussen beide aanwezig was; oftewel de weersfactoren hadden geen invloed op de klachten. Wel was er een sterke onderlinge samenhang tussen de verschillende subjectieve klachten van de patiënten (pijn, stijfheid en moeheid). Een verklaring voor deze discrepantie tussen het geloof van de patiënten enerzijds dat er weersinvloeden op hun klachten zijn en de objectieve gegevens over deze relatie, zoals in ons onderzoek gevonden, anderzijds zou verklaard kunnen worden door de attributietheorie. Mensen met pijn voelen zich minder hulpeloos als ze de pijn aan een externe factor toe kunnen schrijven, in dit geval het weer.
In hoofdstuk 7wordt de betekenis en de rol van de tender points in fibromyalgie nader belicht. Het lijkt er op dat er bij fibromyalgie sprake is van een gegeneraliseerde verlaagde pijndrempel, dus niet alléén ter plaatse van de tender points, maar wel vooral. Vrouwen hebben een lagere pijndrempel dan mannen. Het aantal positieve tender points is belangrijk in het classificeren van een patiënt met chronische (wijd verspreide) pijn, als een fibromyalgiepatiënt. De score van tender points wordt ook vaak gebruikt bij de evaluatie van bepaalde behandelingen. Het is echter zeer de vraag of dit een geschikte uitkomst-maat is. Een relatie tussen het aantal tender points en de mate van ernst van het syndroom is evenmin vastgesteld. In eigen onderzoek werd gekeken naar de consistentie van tender points in de tijd. In de loop van 18 maanden werd 3 maal een tender point-onderzoek uitgevoerd, waarbij de onderzoeker de score van het vorige onderzoek niet in kon zien. Wel wist de onderzoeker dat de betreffende patiënt fibromyalgie had. Uit de analyse bleek dat het gemiddelde aantal tender points per patiënt constant bleef en dat ook de lokalisaties van de tender points bij elke individuele patiënt grotendeels gelijk bleven. Tender points zijn dus een goed herkenbaar fenomeen in deze patiëntengroep.
In hoofdstuk 8is getracht een overzicht te geven van epidemiologische onderzoeksbevindingen, zoals die in de literatuur staan beschreven. Een vergelijking tussen de verschillende studies is erg moeilijk, aangezien de studie-opzet telkens anders was. De prevalentie in de bevolking, zoals weergegeven in deze studies, schommelt tussen de 0.66% en 11.2%. In klinische populaties hangt de prevalentie sterk af van verwijzingspatronen. In deze populaties worden prevalenties tussen 5% en 20% opgegeven. Interessant is de bevinding dat in de normale bevolking veel mensen aan de beide criteria van fibromyalgie voldoen, maar dat slechts een klein deel van deze groep zich daadwerkelijk als patiënt in het gezondheidscircuit meldt. Wat maakt de één wel en de ander niet tot patiënt?
De gevolgen van het fibromyalgiesyndroom op het dagelijks leven zijn aanzienlijk. De financiële consequenties zijn eveneens niet onaanzienlijk, niet alleen voor de patiënt, maar ook voor de maatschappij (medische kosten, kosten van arbeidsongeschiktheid etc). Het is moeilijk de situaties in de verschillende landen te vergelijken; er zijn andere gezondheids- en sociaal/-economische voorzieningen. Ook de werkgelegenheid, of beter gezegd de afwezigheid hiervan, speelt een belangrijke rol.
In hoofdstuk 9 worden een aantal klinische aspecten, medische consumptie en het beloop van de klachten beschreven van de totale populatie aan onderzochte fibromyalgie patiënten in dit proefschrift (n=144). Deze gegevens worden vervolgens vergeleken met die van andere onderzoekers. Het percentage vrouwen in de fibromyalgie populatie is hoog, een gegeven dat nog altijd niet een bevredigende verklaring heeft gekregen. Het percentage vrouwen in onze on-

derzoeksgroep bedraagt 90, wat vergelijkbaar is met bevindingen van andere onderzoekers. Fibromyalgie patiënten ervaren hun klachten als invaliderend en een duidelijke meerderheid van de patiënten (70%) geeft aan dat de klachten ook nog eens erger worden in de loop der tijd. De fibromyalgie klachten ontstaan doorgaans geleidelijk, zonder duidelijke oorzaak of aanleiding (bij 66% van de onderzochte patiënten).

Hoofdstuk 10 geeft een overzicht van de literatuur over psychologische aspecten van fibromyalgie. In het bijzonder worden de relaties tussen fibromyalgie enerzijds en angst en depressiviteit anderzijds toegelicht. Er zijn geen duidelijke bewijzen voor psychopathologie als etiologische factor bij fibromyalgie. Depressieve en angst symptomen worden weliswaar vaak vermeld als onderzoeksresultaten, maar deze moeten waarschijnlijk worden opgevat als factoren die samenhangen met, danwel het gevolg zijn van een chronische (somatische) klachten. Ook wordt de relatie tussen pijn (een van de meest prominente kenmerken bij van fibromyalgie) en een aantal psychologische aspecten verder uitgediept aan de hand van de bestaande literatuur. "Aangeleerde hulpeloosheid" (learned helplessness), inadequaat (pijn)gedrag, reinforcement van pijngedrag, rolvoorbeelden (social modelling) en ook cognitieve aspecten zijn modulerende factoren in pijnbeleving en pijngedrag. Er is sprake van een wederzijdse beïnvloeding van pijn enerzijds en deze psychologische factoren anderzijds. Of psychologische factoren een rol spelen bij de etiologie van fibromyalgie is niet duidelijk.

In hoofdstuk 11 worden psychologische aspecten van fibromyalgie vergeleken met die van chronische en niet chronische pijn. Drie groepen, een groep patiënten met chronische pijn (n=99), een groep patiënten met niet chronische pijn (n=34) en een groep fibromyalgie patiënten (n=36) worden vergeleken met gebruikmaking van een standaard interview en psychologische vragenlijsten (SCL-90, IBQ en CIPI). Zowel de groep chronische pijnpatiënten als de groep fibromyalgie patiënten verschilt duidelijk van de groep niet chronische pijnpatiënten, op basis van de variabelen die zijn afgeleid van de criteria voor chronische pijn door de Nationale Gezondheidsraad. De fibromyalgie groep en de chronische pijn groep zitten qua scores op deze variabelen dichter bij elkaar. Op basis hiervan kan worden geconcludeerd dat een aantal psychologische aspecten bij fibromyalgie kunnen worden teruggevoerd op factoren die passen bij het hebben van chronische pijnklachten.

Hoofdstuk 12 geeft de resultaten weer van een vergelijking tussen een groep fibromyalgie patiënten (n=100), een groep reumatoïde artritis (RA) patiënten (n=25) en een groep patiënten met chronische lage rugklachten (n=22). Hierbij werd gebruik gemaakt van VAS-schalen voor de mate van pijn, kwaliteit van de slaap, en een inschatting van de revalidatiearts en patiënt over diens algehele gezondheidstoestand. De groepen werden tevens met elkaar vergeleken op basis van de tenderpoint score en een aantal vragenlijsten: de SCL-90, de Amsterdamse Biografische Vragenlijst (ABV), de Maudsley Marital Questionnaire (MMQ), de Utrechtse Coping Lijst (UCL) en de Prestatie Motivatie Test (PMT). De resultaten maken duidelijk dat fibromyalgie patiënten hun klachten als ernstiger (grotere impact) ervaren dan beide andere groepen en dat psychische onlustgevoelens in de fibromyalgie groep groter zijn. Fibromyalgie patiënten scoren ook hoger op de N-schaal (neurotische labiliteit) van de ABV, wat mogelijke een aanwijzing is voor een predispositie op basis van een psychogene factor. Fibromyalgie patiënten verschillen ook van beide andere groepen in de manier waarop zij met klachten en problemen omgaan, blijkens de verschillen in de UCL-scores. Zij hebben hogere scores op de schalen Palliatieven, Vermijding en Depressief reactiepatroon, wat duidt op inadequate vormen van coping.

In hoofdstuk 13wordt een literatuur overzicht van diverse therapie-trials gegeven. Het blijkt heel moeilijk goede uitkomst variabelen te kiezen. Veel studies betreffen slechts een klein aantal patiënten, en de follow-up was meestal erg kort. Een ander probleem is het grote placebo-effect dat in veel studies naar voren kwam. Een dubbel-blind onderzoek is moeilijk op te zetten.
Uit de diverse studies komt naar voren dat NSAID's niet beter werken dan placebo's. Gecontroleerde onderzoeken naar het effect van paracetamol zijn niet verschenen, hoewel dit regelmatig voorgeschreven wordt. Van tricyclische antidepressiva, met name amitriptyline, wordt in een subgroep wel een positief resultaat beschreven, in die patiënten die een slaapstoornis hebben. Effect-studies naar fysiotherapeutische behandelingen zijn nauwelijks verschenen, hoewel dit ook zeer regelmatig wordt voorgeschreven. Fitness training werd onderzocht, en hoewel de conditie van de patiënten wel vooruit ging was er toch geen duidelijke afname van de klachten. Cognitieve gedragstherapie lijkt op theoretische gronden een goede mogelijkheid te bieden, maar zal nog in goed opgezet onderzoek bewezen dienen te worden.
Het fibromyalgie syndroom kan beschouwd worden als een chronisch pijnsyndroom, met gevolgen voor het sociaal-emotioneel functioneren van de betreffende patiënten. Deze factoren moeten ook in het behandelprogramma betrokken worden. Dit houdt in dat de behandeling in een multidisciplinair team dient plaats te vinden. Een actieve participatie van de patiënt bij zijn of haar behandeling is van wezenlijk belang.
In hoofdstuk 14 worden de resultaten weergegeven van een therapie-trial op basis van een gecombineerde aanpak vanuit de psychomotorische therapie (gebaseerd op gedragstherapeutische principes) en echtpaargesprekken bij Medisch Maatschappelijk Werk. Vijftig fibromyalgie patiënten namen deel in de behandelingsgroep en vijftig fibromyalgie patiënten fungeerden als controle-groep. Behandelingsdoelstellingen waren: de patiënt leren omgaan met de beperkingen die voortvloeien uit het fibromyalgie-klachtenpatroon met behulp van gedragstherapeutische technieken, ontspanningsoefeningen, assertiviteitstraining en het leren onderscheiden van pijn van andere lichaamssensaties en emotionele belevingen. Voor- en nametingen en een follow up meting werd verricht bij beide groepen met gebruikmaking van: subjectieve klachten ervaring door patiënt (VAS-schalen), de SCL-90, de Utrechtse Coping Lijst (UCL) en de Maudsley Marital Questionnaire (MMQ). Het aantal uitvallers in de experimentele groep was groot (34%), wat mogelijk een gevolg was van de selectie-methode. Multivariate variantie analyses maakten duidelijk dat er veranderingen waren over de drie meetpunten voor beide groepen: een toename van de pijn, maar afname van psychische onlustgevoelens en een afname van inadequate vormen van coping. Een behandelingseffect kon niet worden aangetoond.
In hoofdstuk 15 worden de resultaten beschreven van een onderzoek naar de effecten van een begeleiding van fibromyalgie patiënten op basis van een cognitief- gedragstherapeutische aanpak, waarbij de nadruk lag op psycho-educatie. Dertig, at random geselecteerde, fibromyalgie patiënten werden benaderd met de vraag of zij wilden deelnemen in het onderzoeks-programma. Dertig andere fibromyalgie patiënten, eveneens at random geselecteerd, maar gematcht op geslacht en leeftijd met de experimentele groep, fungeerden als controle groep. Behandelingsdoelen waren: 1) het aanleren van adequate coping vaardigheden, gebaseerd op realistische gedachten en doelen, 2) verschuiven van de 'locus of control' bij de patiënt van extern naar intern, 3) waardoor de negatieve emotionele aspecten en het gevoel van machteloosheid ten opzichte van de pijn en andere klachten zouden moeten afnemen. Voor en na behandeling, alsmede in een follow up, werden metingen verricht waarbij gebruik is gemaakt van: de SCL-90,

de Pijn Cognitie Lijst (PCL), de PijnBeheersings Vragenlijst (PBV), VAS-schalen voor pijn, slaap en een algehele beoordeling door de patiënt van diens gezondheidstoestand, de tender point score en een ADL-lijst. Evenals bij het onderzoek dat in hoofdstuk 14 werd beschreven is hier het aantal uitvallers in de experimentele groep hoog (33%). Met behulp van multivariate variantie analyse kon geen behandelingseffect worden vastgesteld. Het grote aantal uitvallers heeft de power van de statistische toetsing verkleind, wat pleit voor een replicatie met een grotere groep en met een andere selectie-methode.

In hoofdstuk 16 wordt een poging gedaan om eerdere bevindingen te integreren in een model waarmee het ontstaan en voortduren van fibromyalgie kan worden verklaard. Stress, pijn en vermoeidheid vormen de centrale aspecten van dit model. Deze aspecten worden weer beïnvloed door verschillende psychologische en psychobiologische aspecten. Veel fibromyalgie patiënten lijken 'vast' te zitten in vicieuze cirkels van elkaar wederzijds beïnvloedende factoren, zoals weergegeven in het model. Er is nog te weinig bekend over de periode waarin de fibromyalgie klachten ontstaan, kennis die alleen kan worden verkregen door prospectief, longitudinaal onderzoek. De behandeling van fibromyalgie zal met name gericht moeten zijn op 'care' aspecten, niet op 'cure'. Daarbij is het van groot belang dat fibromyalgie patiënten ervaren dat ze zelf controle kunnen krijgen over het klachtenpatroon. Behandeling dient daarom gericht te zijn op het doorbreken van de vicieuze cirkels waarin de patiënt zich bevindt, waardoor er ruimte ontstaat voor de patiënt om zich wederom zelf verantwoordelijk te voelen voor het lichamelijke en psychische welbevinden.

Stellingen

behorend bij het proefschrift

# Fibromyalgia:
## towards an integration of somatic and psychological aspects

van

A.A. Knipping

Groningen, 1 november 1995.

1. Het grootste gevaar bij fibromyalgie is dat het een "way of life" wordt voor de patiënt.

2. Fibromyalgie dient primair als een ernstig chronisch pijnsyndroom te worden opgevat.

3. Een monodisciplinaire behandeling van fibromyalgie is, gegeven de complexiteit van het syndroom, tot mislukken gedoemd.

4. Het ontkennen van fibromyalgie als syndroom door sommige medici kan vanuit de psychologische optiek als een vorm van afweer worden beschouwd.

5. Een psycholoog met inadequate coping-strategieën is niet per definitie een slechte hulpverlener, er zijn immers ook geen wegwijzer-borden die zelf naar Amsterdam gaan.

6. De constatering dat er psychologische factoren meespelen in het ontstaan of voortduren van een klacht wordt door veel patiënten als een beschuldiging ervaren.

7. De activiteiten van psychologen werkzaam in ziekenhuizen in het kader van patiëntenzorg vallen eerder onder de somatische dan de geestelijke gezondheidszorg.

8. In correspondentie dient te term "er zijn geen objectiveerbare klachten" gelezen te worden als: "ik weet ook niet wat er aan de hand is".

9. Bij de behandeling van patiënten met chronische pijnklachten heeft een interdisciplinaire aanpak een meerwaarde boven de multidisciplinaire benadering.

10. Voor elk type patiënt dient het verhogen van de zelfredzaamheid een wezenlijk bestanddeel uit te maken van de behandelingsstrategie.

11. Bij patiënten met objectiveerbare somatische klachten blijven de psychologische aspecten vaak onderbelicht.

12. Het tempo waarin veroudering plaatsvindt van computers en software leidt tot neurotisch uitstelgedrag bij de aankoop ervan.

13. De recentelijke uitholling van het militaire apparaat wordt al eeuwen voorspeld door de term "leger".

Stellingen

behorend bij het proefschrift

# Fibromyalgia:
## towards an integration of somatic and psychological aspects

van

A.C.E. de Blécourt

Groningen, 1 november 1995.

1. Fibromyalgie is geen ziekte, maar een syndroom.

2. In de pijnlijke spieren bij fibromyalgiepatiënten zijn geen evidente afwijkingen gevonden.

3. Er is geen direct verband tussen weersfactoren en fibromyalgieklachten.

4. Het effect van NSAID's in de behandeling van de symptomen van fibromyalgie lijkt te berusten op een placebo-effect.

5. Vrouwen zijn (druk)gevoeliger dan mannen.

6. Kinderen met chronische (benigne) pijnklachten in het houdings- en bewegingsapparaat kunnen succesvol binnen een (tijdelijke) klinische kinderrevalidatiesetting behandeld worden.

7. In de begeleiding en scholing van motorisch gehandicapte kinderen is de samenwerking tussen professionals binnen de kinderevalidatie en mytylschool essentieel.

8. Het vak revalidatie verandert van LIVRE-lee in RAP-tempo in een vak van registratie.

9. Herkenning en erkenning van fibromyalgie zonder dat een passend begeleidingstraject wordt aangeboden kan resulteren in reinforcement van pijngedrag.

10. De grens tussen normaal en abnormaal is een kwestie van smaak.

11. Een groot mens is hij, die zijn kinderhart nimmer verliest. (Meng-Tse)