

# Chronic Widespread Pain and the Fibromyalgia Construct

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Fibromyalgia is a clinical construct that has been developed, for the most part, by rheumatologists. It is a direct descendent of "fibrositis", a common misnomer (1) that was first coined in 1904 (2). There are always problems inherent in defining a disorder in purely descriptive terms. Nevertheless the publication of the American College of Rheumatology's 1990 Classification Criteria for fibromyalgia (3) has been coincident with an impressive resurgence of research in this area. This Bulletin attempts to synthesize contemporary research findings.

## Diagnosis

The 1990 American College of Rheumatology's guidelines for making a diagnosis of fibromyalgia are the most widely used criteria in current use (3). They comprise the historical feature is widespread pain of 3 months or more and the physical finding of 11 or more out of 18 specified tender point sites on digital palpation with an approximate force of 4 kg. The 1990 criteria suggested abolishing the distinction between primary and secondary FM. This concept is important as some FM patients get extensive workups to *exclude* another diagnosis. The number of tender points of 11 or more was originally derived from a receiver-operating curve and relates to the number giving the best sensitivity and specificity. In clinical practice, the diagnosis of FM can be entertained when less than 11 tender points are present.

### American College of Rheumatology 1990 Criteria Recommended Tender Point Locations



- (1) insertion of nuchal muscles into occiput;
- (2) upper border of trapezius-mid-portion;
- (3) muscle attachments to upper medial border of scapula;
- (4) anterior aspects of the C5, C7 intertransverse spaces;
- (5) 2<sup>nd</sup> rib space - about 3 cm lateral to the sternal border;
- (6) muscle attachments to lateral epicondyle ;
- (7) upper outer quadrant of gluteal muscles;
- (8) muscle attachments just posterior to greater trochanter;
- (9) medial fat pad of knee proximal to joint line.

A total of eleven or more tender points in conjunction with a history of widespread pain is characteristic of the fibromyalgia syndrome.

## Clinical Features

### **Pain**

The core *symptom* of the FM syndrome is chronic widespread pain (3). The pain is usually perceived as arising from muscle, however many fibromyalgia patients also report joint pain (4). Stiffness, worse in the early morning, along with the perception of articular pain this may reinforce the impression of an arthritic condition. Fibromyalgia pain and stiffness typically have a diurnal variation, with a nadir during the hours of about 11.00 am to 3.00 pm (5). Symptoms also wax and wane in intensity over days and weeks; with flares occurring with increased exertion, systemic infections, soft tissue injuries, lack of sleep, cold exposure, and psychological stressors.

### **Fatigue**

Easy fatigability from physical exertion, mental exertion and psychological stressors are typical of fibromyalgia. The etiology of fatigue in fibromyalgia is multifaceted and is thought to include non-restorative sleep, deconditioning, depression, poor coping mechanisms and secondary endocrine dysfunction involving the hypothalamic pituitary adrenal axis and growth hormone deficiency (6,7,8,7). Patients with the chronic fatigue syndrome (CFS) have many similarities with FM patients (9). Characteristically, patients with CFS have an acute onset of symptoms after an infectious type illness, with subsequent persistence of debilitating fatigue and post-exertional malaise. About 75% of patients meeting the diagnostic criteria of CFS also meet the criteria for diagnosis of FM (10).

### **Disordered sleep**

Fibromyalgia patients invariably report disturbed sleep(11). Even if they report 8 to 10 hours of continuous sleep they wake up feeling tired. Most relate to being light sleepers, being easily aroused by low-level noises or intrusive thoughts. Many exhibit an alpha-delta EEG pattern (12) but this is not an invariable in fibromyalgia and nor is it specific (13,14,15). The experimental induction of alpha-delta sleep in healthy individuals has been reported to induce musculoskeletal aching and/or stiffness as well as increased muscle tenderness (16).

### **Associated disorders**

It is not unusual for fibromyalgia patients to have an array of somatic complaints other than musculoskeletal pain (17,18). It is now thought that these symptoms are in part a result of the abnormal sensory processing – as described elsewhere.

*Restless leg syndrome:* This refers to daytime (usually maximal in the evening) symptoms of (1) unusual sensations in the lower limbs (but can occur in arms or even scalp) that are often described as paresthesia (numbness, tingling, itching, muscle crawling) and (2) a restlessness, in that stretching or walking eases the sensory symptoms. This symptomatology is nearly *always* accompanied by a sleep disorder - now referred to as periodic limb movement disorder (formerly nocturnal myoclonus) (19). Restless leg syndrome has been reported in 31% of fibromyalgia patients compared to 2% of controls (20).

*Irritable bowel syndrome:* This common syndrome of GI distress that occurs in about 20% of the general population is found in about 60% of fibromyalgia patients (21,22). The symptoms are those of abdominal pain, distension with an altered bowel habit (constipation, diarrhea or an alternating disturbance). Typically the abdominal discomfort is improved by bowel evacuation.

*Irritable bladder syndrome:* This is found in 40-60% of fibromyalgia patients (23). The initial incorrect diagnoses are usually recurrent urinary tract infections, interstitial cystitis or a gynecological condition. Once these possibilities have been ruled out a diagnosis of irritable bladder syndrome (also called female urethral syndrome) should be considered. The typical symptoms are those of suprapubic discomfort with an urgency to void, often accompanied by frequency and dysuria.

*Cognitive dysfunction:* This is a common problem for many fibromyalgia patients (24). It adversely affects the ability to be competitively employed and may cause concern as to an early presentation of a neurodegenerative disease. The cause of cognitive dysfunction is in part related to the distracting effects of chronic pain, mental fatigue and psychological distress (25).

*Cold intolerance:* About 30% of fibromyalgia patients complain of cold intolerance (3,11). Some patients develop a true primary Raynaud's phenomenon, which may lead to misdiagnoses such as SLE or scleroderma(26).

*Multiple sensitivities:* One result of disordered sensory processing is that many sensations are amplified in fibromyalgia patients. Thus patients with fibromyalgia are more likely to receive other diagnoses such as multiple chemical sensitivity (MCS), sick building syndrome and drug intolerance. One report cites a prevalence of 52% of MCS in fibromyalgia (27). Buchwald found a large overlap between fibromyalgia, chronic fatigue syndrome and MCS (28).

*Dizziness:* This is a common complaint of fibromyalgia patients (3). In many cases no obvious cause is found, despite sophisticated testing. Treatable causes related to fibromyalgia include: proprioceptive dysfunction secondary to muscle deconditioning, proprioceptive dysfunction secondary to myofascial trigger points in the sterno-cleido-mastoids and other neck muscles, neurally mediated hypotension and medication side effects.

*Neurally mediated hypotension (NLM):* This syndrome is a lesser variant of "neurocardiogenic syncope". Its prevalence in one report was 60% (29). NLM results from a paradoxical reflex when venous pooling reduces filling of the heart (right ventricle). In predisposed patients, this causes an inappropriately high secretion of catecholamines. This in turn leads to a vigorous contraction of the volume depleted ventricle – leading to an over-stimulation of ventricular mechanoreceptors which signal the midbrain to reduce sympathetic tone and increase vagal tone, with resulting syncope or presyncope. In fibromyalgia patients this may be manifest by severe fatigue after exercise, on prolonged standing or in response to stressful situations.

### ***Initiation and maintenance of fibromyalgia***

Most fibromyalgia patients causally relate an acute injury, repetitive work related pain, athletic injuries or another pain state to the onset of their problems. Others attribute stress, infections and toxins to its onset. Fibromyalgia is commonly found as an accompaniment of rheumatoid arthritis (30), systemic lupus erythematosus (SLE) (31,32,33), low back pain (34), Sjogren's (35,36) and osteoarthritis. One recent study from Israel documented a 22% prevalence of fibromyalgia, one year after automobile accidents causing whiplash; this compares to a 1% prevalence after accidents involving leg fractures (37). However most injured subjects do not develop fibromyalgia, and only 20–35% of patients with rheumatoid arthritis or SLE have a concomitant fibromyalgia syndrome. Buskila has reported a strong familial prevalence of fibromyalgia (38). This suggests that subjects destined to develop fibromyalgia are either genetically predisposed (nature), or have past life events or experiences that favor its later development (nurture). Chronic pain states may also develop during or after some infections (39) (40,41,42). A series of elegant experiments in rats has described a complex neural pathway whereby pro-inflammatory cytokines can cause a hyperalgesic state (43). This pathway involves pro-inflammatory cytokines (IL1, IL-6, and TNF) that activate cytokine binding sites on vagal paraganglia with afferent impulses travelling to the nucleus of the tractus solitarius. Subsequent cross-stimulation of the nucleus raphe magnus activates descending spinal tracts which sensitize second order dorsal horn neurons via an NMDA / substance P / nitric oxide cascade. Thus one can hypothesize that several discrete stimuli may initiate fibromyalgia via a common final pathway that involves the generation of a central pain state through the sensitization of second order spinal neurons.

### Prognosis and Impact

Kennedy and Felson reported on follow up of 39 patients, mean age 55, who had experienced fibromyalgia symptoms for 15 years. All of them still had fibromyalgia. Moderate to severe pain or stiffness was present in 55% of patients; significant sleep difficulties were reported in 48%; and notable levels of fatigue were present in 59%. Despite continuing symptoms, 66% of patients reported that FMS symptoms were somewhat improved compared to when first diagnosed. Wolfe et al analyzed 1604 fibromyalgia patients followed for 7 years in academic rheumatology centers (44). Symptoms of pain, fatigue, sleep disturbance, functional status, anxiety, depression, and health status were abnormal at initiation and were the same after 7 years of follow up. Fifty nine percent of the patients rated their health as only fair or poor. There is some evidence that fibromyalgia patients seen in the community, rather than tertiary care centers, have a better prognosis. Granges et al reported a 24% remission rate after 2 years of patients seen in an ambulatory care setting (45). The consequences of pain and fatigability influence motor performance. Henriksson, et al, have noted that every-day activities take longer in fibromyalgia patients, they need more time to get started in the morning and often require extra rest periods during the day (46). They have difficulty with repetitive sustained motor tasks, unless frequent time-outs are taken. Tasks may be well tolerated for short periods of time, but when carried out for prolonged periods become aggravating factors (47). Prolonged muscular activity, especially under stress or in uncomfortable climatic conditions, was reported to aggravate the symptoms of fibromyalgia (47). The adaptations that fibromyalgia patients have to make in order to minimize their pain experience, has a negative impact on both vocational and avocational activities.

### Disability

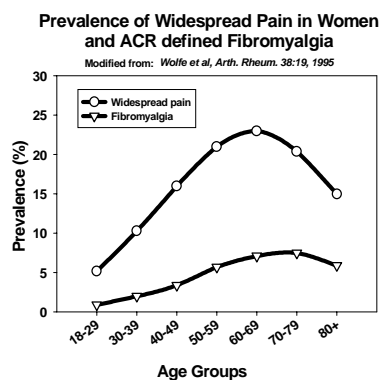
Despite the superficial appearance of normality many fibromyalgia patients have difficulty with remaining competitive in the work force (48). Most FM patients report that chronic pain and fatigue adversely affect the quality of their life and negatively impact their ability to be competitively employed (49,50,51). The extent of reported disability in FM varies greatly from country to country (11,52,53) – probably reflecting differences in political philosophies and socio-economic realities. A survey of fibromyalgia patients seen in 6 US centers reported that 42% were employed and 28% were homemakers. Seventy percent perceived themselves as being disabled. Twenty six percent were receiving at least one form of disability payment (44). Sixteen percent were receiving Social Security benefits (SSD); this compares to 2.2% in the overall US population.

## Pathogenesis

Fibromyalgia articles commonly begin with the admonition that "the cause of fibromyalgia is not known". This assertion is no longer justified. Impressive advances have been made in understanding the neurobiology of chronic pain. As fibromyalgia is now considered part of the spectrum of chronic pain, these advances are relevant to understanding pain in fibromyalgia patients.

### Epidemiology

Non-malignant persistent pain is common. Wolf found that the prevalence of chronic widespread musculoskeletal pain was more common in women and increased progressively from ages 18 to 70 -- with 23 % prevalence in the seventh decade (3). The American College of Rheumatology has defined fibromyalgia in terms of chronic widespread pain involving 3 or more segments of the body plus the finding of at least 11 out of 18 designated tender points (54). When Wolfe's patients were examined, 25.2% of females and 6.8% of men had 11 or more tender points. The overall (M+F) prevalence of fibromyalgia was 2%, with a prevalence of 3.4% in women and 0.5% in men. Croft reported prevalence rates of 11.2% for chronic widespread pain, 43% for regional pain and 44% for no pain (55). When subjects with widespread pain were examined, 21.5% had 11 or more tender points, 63.8% had between 1 and 10 tender points and 14.7% had no tender points (56). Interestingly the tender point count did not correlate with widespread pain, but it did correlate with depression, fatigue, and poor sleep. The results of these 2 studies indicate that a history of chronic widespread pain is more prevalent than the strictly defined diagnosis of fibromyalgia. Thus the concept is emerging that fibromyalgia is towards one end of a continuous spectrum of chronic pain.



### **Central Pain Mechanisms**

There are several lines of evidence to suggest that the pain experience of fibromyalgia patients is in part the result of disordered sensory processing at a central level.

#### *Qualitative differences in pain*

A study using an electronic dolorimeter recorded the subject's assessment of pain intensity on a 0 to 10-cm visual analogue scale (VAS) at varying levels of applied force (57). Distinctly different response curves were obtained for controls and fibromyalgia patients. It was found that in pain free controls exhibited a logarithmic type of increase in pain intensity whereas fibromyalgia subjects showed a linear increase. Similar abnormalities of pain processing in fibromyalgia patients have also been reported for heat and cold (58).

#### *Deficient pain modulation in response to repeated thermal stimuli*

Down-regulation of pain threshold can be demonstrated in normal individuals by subjecting them to repeated skin stimulation. This effect, known as diffuse noxious inhibitory control (DNIC), was investigated in female fibromyalgia patients and compared to age-matched healthy women (59). Tonic thermal stimuli at painful and non-painful intensities were used to induce pain inhibition. Concurrent tonic thermal stimuli, at both painful and non-painful levels, significantly increased the electrical pain threshold in the healthy subjects but not in the fibromyalgia patients.

#### *Hyper-responsive somatosensory induced potentials*

Gibson et al reported an increased late nociceptive (CO<sub>2</sub>-laser stimulation of skin) evoked somatosensory response in 10 FM patients compared to 10 matched controls (60). Lorenz et al (61) have recently reported increased amplitude of the N170 and P390 brain somatosensory potentials in fibromyalgia compared to controls evoked by laser stimulation of the skin. Furthermore they observed a response in both hemispheres – in controls the somatosensory potential was strictly localized to one side of the brain. These 2 studies provide direct objective evidence of altered processing of nociceptive stimuli in fibromyalgia patients.

#### *Secondary hyperalgesia on electrocutaneous stimulation*

Secondary hyperalgesia refers to pain elicited from uninjured tissues (62). Arroyo and Cohen, while attempting to treat fibromyalgia patients with electrical nerve stimulation, noted that the pain was made worse and often caused dysthetic sensations (63). Compared to controls fibromyalgia patients had a reduced pain tolerance and 2 unexpected phenomena: (i) a spread of dyesthesia (mainly tingling and burning) that was felt both distally and proximally to the stimulator, and (ii) a persistence of dyesthesia around the stimulated locus that lasted for 12 to 20 minutes after the stimulation was terminated. Therefore electrical stimulation of the skin in fibromyalgia patients resulted in several features that are characteristic of secondary hyperalgesia.

#### *Abnormalities on SPECT imaging*

Functional CNS changes can be demonstrated by several different imaging techniques. It is interesting that chronic pain states have been associated with reduced thalamic blood flow, whereas acute pain increases thalamic blood flow. The reason for this difference is postulated to be a disinhibition of the medial thalamus which results in activation of a limbic network. Mountz et al reported that fibromyalgia patients had a decreased thalamic and caudate blood flow compared to healthy controls on SPECT (single-photon-emission-computed tomography) imaging (64). A similar finding has been reported in-patients with unilateral chronic neuropathic pain, using O-15 positron emission tomography (65). Thus functional imaging studies are supportive of an altered processing of sensory input in fibromyalgia patients.

#### *Elevated levels of substance P in the CSF*

Substance P lowers the threshold of synaptic excitability, permitting the unmasking of normally silent interspinal synapses and the sensitization of second order spinal neurons (66). An increased production of neurotransmitters within the spinal cord may be detected as increased levels in cerebrospinal fluid (CSF) (67). Animal models of hyperalgesia and hypoalgesia, have implicated substance P as a major etiological factor in central sensitization. There are 2 definitive studies that have shown a 3 fold increase of substance P in the CSF of fibromyalgia patients compared to controls (68,69)

#### *Beneficial response to an NMDA receptor antagonist*

There is persuasive evidence that glutamine reacting with NMDA (N-Methyl-D-Aspartic acid) receptors plays a central role in the generation of non-nociceptive pain. Two studies from Sweden reported that intravenous ketamine (an NMDA receptor antagonist) attenuates pain and increases pain threshold, as well as improving muscle endurance in FM patients (70,71). In some patients a single intravenous infusion over a course of 10 minutes (0.3 mg/kg) resulted in a significant reduction in pain that persisted for up to 7 days. This therapeutic pain

analysis supports the notion that activation of NMDA receptors is relevant to disordered sensory processing in fibromyalgia patients.

#### *Experimentally induced central hyperexcitability*

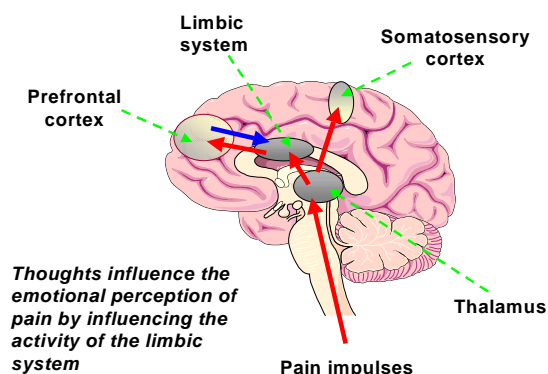
Sorensen et al injected hypertonic saline (2 ml of 5.7% saline over 8 mins.) into the asymptomatic anterior tibial muscle of fibromyalgia patients and healthy controls (72). Compared to controls fibromyalgia patients experienced a longer duration of pain and a larger area of referral. The same subjects were also compared as to pressure pain threshold over the anterior tibial muscle, and pain threshold to both single and repetitive electrical stimulation of the overlying skin and electrical intramuscular stimulation. Pressure pain and the intramuscular summation pain threshold was significantly lower in fibromyalgia patients. These results further support a state of disordered sensory processing in fibromyalgia.

#### *Psychological considerations*

As in many chronic conditions there is an increased prevalence of psychological diagnoses in fibromyalgia patients (73); however the converse is not true. For instance, fibromyalgia is not common in patients with major depression; even depressed individuals who complain of pain did not have multiple tender points in one study (74). Psychological distress in fibromyalgia may in part determine who becomes a patient (75).

The psychiatric diagnoses that are often considered in the differential diagnosis of fibromyalgia are the somatoform disorders, especially *somatization disorder and pain disorder* - as defined DSM-IV (76).

From a management aspect it is seldom useful to characterize fibromyalgia as being solely a psychological problem or solely as an organic problem. Considering the preponderance of studies pointing to a dysfunction of sensory processing in fibromyalgia, one would expect these patients to have an amplification of bodily sensations resulting in a wide range of somatic symptoms. A diagnosis of a somatoform disorder will become a non-psychiatric diagnosis once the symptomatology is adequately explained by disordered physiology(77). There is now good evidence that links pain to "emotional neuro-circuits". Different cortical and sub-cortical structures are involved in different aspects of the pain experience. For instance removal of the



somatosensory cortex does not abolish chronic pain, but excision or lesions of the anterior cingulate cortex reduces the unpleasantness of pain (78). The anterior cingulate cortex is involved in the integration of affect, cognition and motor response aspects of pain (79) and exhibits increased activity on PET studies of pain patients (80). Other structures involved in cortical pain processing include the prefrontal cortex (activation of avoidance strategies, diversion of attention and motor inhibition), the amygdala (emotional significance and activation of hypervigilance) and the locus ceruleus (activation of the "fight or flight" response) (81). All these structures are linked to the medial thalamus, whereas the lateral thalamus is linked to the somatosensory cortex (pain localization). A recent experiment convincingly showed how the prevailing mental attitude of an individual can influence the unpleasantness of a standardized pain stimulus and how this correlated to blood flow changes in the anterior cingulate gyrus (82). Thus prefrontal cortical activity (i.e. positive or negative thoughts) can influence the perception of pain. Is this the neural basis of somatization and cognitive-behavioral therapy?

## **Management**

The current treatment modalities for fibromyalgia seldom lead to long term relief. Basically the current management philosophy is to help the patient constructively adapt to an existence plagued by pain, fatigue and other symptoms. The resistance of fibromyalgia symptoms to contemporary treatments was recently highlighted (83). In a follow up of 530 fibromyalgia patients followed in 6 US tertiary referral centers over 7 years, there was no significant improvement in pain, functional disability, fatigue, sleep disturbance, or psychological status. Half the patients were dissatisfied with their health, and 59% rated their health as fair or poor. Fibromyalgia patients used an average of 2.7 fibromyalgia-related drugs in every 6-month period. The mean yearly per-patient cost in 1996 dollars was \$2,274.

Despite this gloomy picture there is some evidence that fibromyalgia patients can be helped, but not cured, by a multi-disciplinary approach that emphasizes education, cognitive behavioral therapy, therapeutic treatment of pain, participation in a stretching and aerobic exercise program, prompt treatment of psychological problems and attention to associated syndromes(84,85,86,87,88). The fibromyalgia treatment group at Oregon Health Sciences

University has employed a multi-disciplinary treatment using a team of interested health professionals (nurse practitioners, clinical psychologists, exercise physiologists, mental health care workers, and social workers) (89). In this way groups of 10-30 patients can be seen in designated sessions several times a month. Patients are usually appreciative of meeting others who share similar problems and the dynamics of group therapy is often a powerful aid to cognitive-behavioral modifications. Such groups can be encouraged to develop a sense of camaraderie in solving mutual problems. This form of therapy has proved beneficial in one 6 month program, with continuing improvement out to 2 years after leaving the program (90). Turk's group has recently published similar encouraging results (91).

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