

# Fibromyalgia for the Psychiatrist

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## Abstract

*Fibromyalgia (FM) is common in pain clinics and not infrequently encountered in psychiatric practice. It is a poorly understood condition which is ignored in medical school and post graduate psychiatric training. It is a common disorder, poorly understood condition which is the cause of great suffering and disability. FM is associated with a wide range of reproducible pathophysiological findings. Speculation has FM as a form of (1) sleep disorder, (2) CNS sensitization, and (3) dysregulation of the stress response. Treatment can be well managed by psychiatrists and includes (1) education and CBT, (2) antidepressants, (3) analgesics, and (4) a range of other potential treatments including hormones (German J Psychiatry 2001; 4: 1-8).*

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## Introduction

**F**ibromyalgia (FM) is at the severe end of the spectrum of widespread pain. With broad diagnostic criteria, widespread pain was observed in 11.2% of a section of the British population (Croft et al, 1993). Fibromyalgia has been observed in 2% of a section of the North American population (Wolfe et al, 1995; Lawrence et al 1998).

FM (and its forerunner, fibrocystitis) has been a contentious condition. There had been doubt as to whether this was a separate disease entity. However, The American College of Rheumatology adopted diagnostic criteria in 1990 (Wolfe et al, 1990). These include widespread pain (defined as pain in the left and right sides of the body as well as above and below the waist), for at least 3 months. Axial pain (defined as pain in the cervical spine, anterior chest, thoracic spine or low back) must be present. In addition, the patient must report pain in at least 11 of 18 designated sites on digital palpation. While there may be problems with these criteria insofar as they are restrictive, they have allowed standardization of research.

Additional, commonly occurring symptoms/conditions, but which are not diagnostic criteria, include fatigue and non-restorative sleep, irritable (IBS) syndrome, Raynaud syndrome-like symptoms, headache, subjective swelling, paraesthesia, palpitations, significant functional disability, psychological distress (including depression, anxiety) and cognitive com-

plaints (particularly memory problems and inability to concentrate).

The etiology of FM is unknown. Several mechanisms may be involved. A high prevalence in the female relatives of FM patients suggests a genetic vulnerability (Buskila et al, 1997). In the related condition of somatization, genetic factors accounted for 25-50% of the total variance in reports of symptoms, whereas familial and environmental effects accounted for virtually no variance (Kendler et al, 1995). Onset often appears to follow physical or psychological stress. The majority (70%) of patients identify both physical and psychosocial factors (Neerinx et al 2000). Compared to healthy individuals, there is evidence that those with FM have suffered more stressful events in early life and in the previous year (Anderberg et al, 2000a); this does not however, resolve questions of cause and effect.

The prognosis is poor. At 3 year follow-up, only 3% of patients were found to be free of all pain (Felson et al 1986). Current treatment is far from satisfactory.

FM is commonly associated with psychiatric disorders. Macfarlane et al (1999) found that over 25% of those with generalized pain (not precisely FM) had some concomitant mental disorder, most commonly depression. Anderberg et al (1999) found higher figures for FM: 37% suffering depression and 16% suffering anxiety. Depression in FM is independent of the cardinal features of pain severity and hypersensitivity to pressure pain (Okifuji et al, 2000), however, it may contribute to the inability to fully perform the activities of daily life.

FM patients tend to feature high levels of harm avoidance (Anderberg et al, 1999) and a strong tendency to catastrophizing (Hassett et al, 2000). There is evidence that unexplained physical symptoms (which includes FM) is associated with abnormal attachment style (Taylor et al 2000). This suggests that patients with poorer relationships will have poorer social and emotional supports and are more likely to present with such symptoms to the doctor.

## Overlap

There is discussion about FM and symptom overlap with chronic fatigue syndrome (CFS), temporo-mandibular joint disorder (TMD), somatoform disorder and other medically unexplained syndromes.

Some special interest groups want CFS to be accepted as separate condition. The evidence to decide this point is still being accumulated.

Clauw and Chrousos (1997) point out that CFS has severe chronic fatigue as a necessary diagnostic feature, which must occur in the presence of four of eight symptoms (myalgia, arthralgia, sore throat, tender nodes, cognitive difficulty, headache, post-exertional malaise, sleep disturbance), and that five of these are pain based. FM, however, has pain as the single necessary and sufficient feature (albeit with particular conditions), and is frequently accompanied by fatigue, sleep disorder, fatigue, cognitive difficulties, headache, post-exertional malaise and sleep disturbance.

In a recent study 58% of females and 80% of males with fibromyalgia met the full criteria for CFS (White et al, 2000). Thus, significant overlap between FM and CFS would seem to be beyond question.

Also, FM and CFS have similar comorbid illnesses/conditions, including IBS, interstitial cystitis and generalized pain sensitivity. The lifetime rates of IBS are 77% in FM and 92% in CFS (Aaron et al (2000).

## Pathophysiology

While the etiology of FM remains uncertain, a range of pathophysiological phenomena have been reported. Which (if any) are primary and which are epiphenomena remains to be determined.

Naturally, the early studies focused on the structure of muscle. Fibers were sometimes described as "moth eaten" or in similar terms. However, such changes have not been observed in controlled studies and FM is no longer considered to be a muscular disorder (Sims, 1998).

The pain threshold of peripheral structures and viscera is globally diminished. It has been demonstrated for pressure, heat, cold and electrical stimulation (Dessein et al, 2000). These observations, in the absence of detectable peripheral pathology, have moved attention to the central nervous system.

Somatosensory induced electroencephalographic potentials in FM are significantly different from those of normal individuals and objectify the subjective reports of patients indicating a lower pain threshold. There is a significant amplitude enhancement of cerebral potentials in response to painful CO<sub>2</sub>-laser stimulation (Gibson et al, 1994; Lorenz, 1996).

Transcranial magnetic stimulation (TMS) was applied to the motor cortex of FM patients in various conditions (eg single pulse, paired pulse, relaxed and contracted muscles) (Salerno et al, 2000). Responses were captured from different sites and range of calculations were performed. Motor cortical dysfunction was demonstrated in both excitatory and inhibitory mechanisms. However, similar findings were obtained from rheumatoid arthritis patients and may be a universal feature of chronic pain disorders.

The autonomic system is impaired. The sympathetic system may manifest diminished baseline tone, lability and a reduced responsiveness to stressors. Raj et al (2000) studied the heart rate over 24 hour periods and during tilt table experiments. Qiao et al (1991) studied conductance and blood flow of palmar skin during acoustic stimulation and cold pressor tests. The results of these studies suggests increased activity of cholinergic and decreased activity of adrenergic components of the peripheral sympathetic nervous system.

Non-restorative sleep is reported by 75% of FM patients (Wolfe, 1989). There is a well established alpha wave intrusion during the non-REM sleep stages 3 and 4 (Moldofsky et al, 1975).

Endocrine abnormalities have been detected in hypothalamic-pituitary-adrenal axis (HPA) function, in low levels of growth hormone (GH) and insulin-like growth factor-1 (IGF-1; which is produced in response to GH and has many biological activities), in varying degrees of gonadal hypofunction, and in blunted secretion of thyrotropin and thyroid hormone release in response to thyroid-releasing hormone (TRH) (Clauw and Chousos, 1997).

On examining the HPA axis, the 24 hour levels of free cortisol in urine is low and there is a blunted cortisol response to exogenous CRH and (Crofford et al 1994). Insulin-induced hypoglycemia has been reported to both increase (Griep et al, 1993) and decrease (Alder et al, 1999) adrenocorticotrophic hormone (ACTH) release. Very low levels of IGF-1 occur in one third of FM patients and may be specific to FM (Bennett et al, 1992).

The immune responses are frequently abnormal. Low natural killer cell numbers and function has been reported (Caro et al, 1993). However, the enhanced humoral immune responses which have been demonstrated in CFS do not appear to be a feature of FM.

Alterations in neurotransmitters and receptors are reported. The cerebrospinal fluid (CSF) has a threefold increase in substance P (SP; Vaeroy et al, 1988) and decrease in norepinephrine (NE; Russell et al 1992a). Serum serotonin and tryptophan are decreased and the density of serotonin receptors on circulating platelets is increased (Russell et al 1992b).

There is evidence of decreased regional cerebral blood flow in women with fibromyalgia. Comparing FM with healthy women Montz et al (1995) found those with FM demonstrated significantly lower regional cerebral blood flow (rCBF) of the cortex and thalamic and caudate nuclei. While this was a small study and replication is awaited, it points toward central changes in FM.

## Speculation

As mentioned, which (if any) of the pathophysiological findings listed above are primary and which are epiphenomena remains to be determined. Nor is it always clear in which direction the biological events are occurring. Nevertheless, attempts have been made to organize the existing information.

## FM as a sleep disorder

The hypothesis that FM is the result of sleep disorder is suggested by the frequent clinical finding of disturbed and non-restorative sleep, and fatigue. It is supported by the findings of alpha wave intrusion during the non-REM sleep stages 3 and 4 (Moldofsky et al, 1975) and the observation that disrupting the non-REM sleep of normal subjects leads to muscular aching and generalized tender points (Moldofsky and Scarisbrick, 1976). However, temazepam, melatonin and other hypnotics have been found to improve the sleep disorder without concomitant improvement in pain or fatigue.

Sleep has not been extensively studied in FM and it remains unclear whether sleep disorder is a cause or consequence of the condition. However, important pieces of the puzzle include, 1) low ILGF-1 levels may be related to sleep pathology, as GH secretion occurs during stage 4 sleep (Clauw and Chrousos, 1997), and 2) serotonin modulates stage 4 sleep (Moldofsky, 1982).

## FM as a consequence of CNS sensitization

The pain threshold of a range of modalities is lower in FM than in normal controls. This has been objectified using evoked potentials. This leads, as no abnormality with muscle has been detected, to speculation regarding altered CNS sen-

sory information processing. The term sensitization is used in such circumstances and is defined as an increased excitability of spinal and supraspinal neural circuits.

Sensitization develops consequent to ongoing nociceptive input. Various forms have been identified. One involves wide dynamic range (WDR) neurons, these are second order dorsal horn neurons which respond to either non-nociceptive or nociceptive input. When WDR neurons become sensitized, consequent to ongoing nociceptive input, they respond to all input, including non-nociceptive, as though it is nociceptive. Thus, light touch or movement may cause pain (Gracely et al, 1993).

Once central sensitization has occurred, this mechanism could sustain painful muscles. It is possible that associated painful organ specific syndromes such as IBS have a similar basis. As to the initiating event, FM is often consequent to insults such as rheumatoid and osteoarthritis and physical trauma (it may also have roots in psychological trauma).

As noted, in FM, the CSF SP may be three times normal. This is important as SP is believed to be a major factor in the process of central sensitization (Watkins et al, 1994).

## FM as dysregulation of the stress response

This model posits that FM is a consequence of dysregulation of the human stress response, which is mediated predominantly by the endocrine and sympathetic systems. It has been argued that while the stress response was adaptive during human evolution, it is generally maladaptive for man in the 20<sup>th</sup> century, who rarely faces threats to survival (Meaney et al, 1993).

Mention has been made of reported impairments of the autonomic and endocrine systems in FM. A large number of reviews support the stress response dysregulation hypothesis (Clauw and Chrousos, 1997; Dessein et al, 2000; Heim et al, 2000; Neek et al, 2000; Neek and Croford 2000, Torpy, et al 2000)

Corticotropin-releasing hormone (CRH) is a principal modulator in the stress response. The CRH neurons, which are mainly localized in the paraventricular nucleus of the hypothalamus, are widely distributed throughout the CNS. It has a profound effect on the function of the endocrine system. CRH also mediates arousal and stress-induced analgesia via beta-endorphin and excitatory amino acids secreting neurons which project from the hypothalamus to the brain stem and spinal cord. It has input to the sympathetic system which exerts antinociception via the spinal descending inhibitory pathways with the release noradrenalin, serotonin and neuropeptide Y at the dorsal horn.

Thus, the biological consequences of low CRH state are the opposite of that seen in acute stress and are similar to those noted in fibromyalgia and fatigue states: hypoarousal or fatigue and diffusely increased peripheral and visceral nociception

(generalized pain). Also, along with the dysregulation of the autonomic system may come dysregulation of smooth muscle and cardiovascular function which underpin at least some of the organ specific syndromes (IBS, palpitations, Raynaud) which occur in this spectrum of disorders.

Various stressors can initiate the stress response. It is purported that continuous stress can cause the hypofunction and blunting of this response. The pain of FM is a stressor and may become involved in a pathological self-sustaining cycle. It is proposed that CRH hyperactivity leads, eventually, to alteration of the set points of the various hormonal axes. Thus, the observed hormonal deviations in FM may represent a CNS adjustment to chronic pain and stress.

Much attention in FM research has focused on the effect of CRH on the HPA axis. However, CRH also stimulates somatostatin secretion at the hypothalamic level, which in turn modulates GH secretion. (GH and IGF-1 levels have been reported as low in FM.) Daily GH injections given to a subgroup of FM patients with low serum IGF-1 levels produced a good response in 68% of subjects (Bennett et al, 1992). Thus, dysregulation of the stress response may also influence GH levels. As mentioned, serum serotonin has been reported as low. Serotonin can stimulate HPA axis activity. It is therefore possible that FM reflects a disorder of serotonin concentration or function. Alternatively, SP, which has been found elevated in CSF in FM, may have a role in inhibiting CRH secretion.

## Speculation - Summary

FM may prove to be a range of disorders with separate pathophysiologies. All of the above speculations have at least some underpinning which has been replicated. How to integrate this material is currently uncertain, but the final answer needs to address the following.

The evidence supporting FM as a primary sleep disorder is not strong, but symptomatic fatigue and sleep problems and the non-REM sleep abnormalities require explanation. The observed low IGF-1 levels may be related to sleep pathology, as GH secretion occurs during non-REM sleep.

The evidence supporting a reduced pain threshold and a CNS sensitization is strong. This may be the result of various stressors. SP is elevated in CSF and this may play a role in the sensitization process.

The evidence supporting dysregulation of the stress response system is moderately strong. There is evidence for some changes in endocrine and sympathetic systems function, but there is little to indicate whether this is cause or consequence. Dysregulation could logically follow sustained stress and could explain the generalized pain, reduced arousal and some organ specific syndromes.

The dysregulation of the stress response mechanisms is compatible with sensitization of the nervous system, and these two

may be different faces of the same process. Abnormal GH level is a component of both the stress response dysregulation and the sleep disturbance and may serve to integrate these hypotheses.

Serotonin in serum and SP in CSF may both be abnormal in FM. Both of these agents can influence the endocrine system function and play a role in CNS sensitization. Thus, a neurotransmitter hypothesis may warrant consideration in the future.

## Treatment

The response to treatment is poor. Most patients have used over the counter analgesics and a range of alternative treatments such as vitamins and prayer. Many have also used acupuncture (which is now being incorporated into mainstream medicine) with some benefit (Berman et al, 1999).

In this setting of relative therapeutic impotence, it is especially important to attend to any concomitant psychiatric disorders. These can be anticipated in at least one quarter of FM patients and respond to standard treatments.

## Exercise, Education and CBT

Exercise, education and CBT have the advantage of being relatively free of side-effects and involving the patients in the treatment process. There is some evidence of efficacy, but less of prolonged benefit. Many treatment programs include combinations of relaxation, meditation, cognitive restructuring, aerobic exercise and stretching, activity pacing and patient and family education. It is difficult for the clinician to determine which of the elements are responsible for any improvement.

Exercise programs have produced significant reductions in pain and tender point count (Martin et al, 1996). Sleep and level of fatigue are unaffected. Long-term benefits, however, have not been demonstrated. In spite of the initial improvement, patients have ceased to exercise (Wigers et al, 1996).

Courses of cognitive behaviour therapy which aim to reduce the use of unhelpful behaviors such as excessive rest and over monitoring of bodily symptoms, and unhelpful attributions, to increase confidence in the ability to manage symptoms, and which teach relaxation techniques, have produced promising results (Goldenberg et al, 1992). Unfortunately, long term benefits have not been proven (Richards and Cleare, 2000).

Goossens et al (1996) compared the outcome of three treatment streams, 1) educational, 2) education plus cognitive therapy, and 3) waiting list. Both treatment groups provided benefits. However, there was no significant difference in outcomes between the treatment groups. The addition of a cognitive

component to the educational intervention led to significantly higher health care costs, but no additional clinical benefit.

## Antidepressants

In a relatively bare armory, the tricyclic antidepressants, while only partially effective, are widely used. Arnold et al (2000) performed a meta-analysis of nine randomised controlled trials and found significant clinical response in 25-37% of patients. The largest improvements were in sleep quality, with other improvements in pain, stiffness, tenderness and fatigue. None of the studies which were examined used the dose ranges which are used in the treatment of depression, rather, the range was from 25mg of amitriptyline to 75 mg of clomipramine per day.

O'Mally et al (1999) conducted a meta-analysis of 94 placebo-controlled studies of antidepressants for unexplained symptoms and syndromes, 50 of which dealt with fibromyalgia. A majority (69%) demonstrated benefit for at least one outcome measure, and there was substantial benefit from medication. The absolute percentage difference in improvement between the antidepressant and placebo arms was 32%, yielding the number needed to treat of three to improve one person's symptoms.

While the tricyclic antidepressants are useful, the selective serotonin reuptake inhibitors (SSRIs) have been disappointing in treating the broad range of symptoms of fibromyalgia (O'Mally et al, 1999; Arnold et al 2000). However, there is some evidence that they may be of value in the treatment of concurrent depression (Anderberg et al, 2000b).

## Analgesics

Non-steroidal anti-inflammatory drugs (NSAID) have been disappointing. Ibuprofen was found to be no better, and naproxen only marginally better, than placebo (Richards and Cleare, 2000).

Bennett (1999) makes the statement "Currently opiates are the most effective medications for managing most chronic pain states". However, opioids have not been extensively evaluated in fibromyalgia and receive little support in reviews (Millea and Hollowly, 2000).

Tramadol is an analgesic with weak opioid and monoaminergic actions. It has minimal respiratory depression, dependence and tolerance and is more appropriate for long-term regular treatment than other forms of analgesia (Richards and Cleare, 2000). Leventhal (1999) suggested "that tramadol may be useful for treatment of fibromyalgia pain". This was followed by a group of letters which cautioned that this statement was premature and that side effects limited usefulness. Biasi et al (1998) conducted a double-blind placebo-controlled trial using

injectable preparations and found greater pain relief, but without reduction in the number of tender points. Further studies are needed, but a clinical trial of the oral form of this drug in difficult cases can be justified.

## Local Anaesthetic Injection and Dry Needling

Injection of tender points with local anaesthetic is used in the effort to provide pain relief. Lignocaine has also been combined with triamcinolone. Piercing tender point with a needle but injecting nothing (dry needling) may also be of benefit, suggesting that the release of met-enkephalin may be an important factor (Figuerola et al 1998). These procedures require further examination, but are unlikely to cause damage.

## Hormones

Oral corticosteroids have not been useful.

Bennett et al (1992) found that in the subgroup of patients with low IGF-1, daily injections of GH produced a good global response in 68% of patients. This was not without side effects, one third of patients developed carpal tunnel syndrome. This is an expensive compound and more work needs to be done before regular use could be considered.

## Other Treatments

Ondansetron, a selective 5HT<sub>3</sub> receptor antagonist has shown promise in a double-blind cross over trial (Hrycaj et al, 1996). This is another expensive compound which may find a place in the treatment of FM in the future.

Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist anaesthetic, given intravenously in sub-anaesthetic doses, has attenuated pain, increased pain threshold and improved muscle endurance in controlled trials (Sorensen et al, 1997). This agent has been associated with hallucinations and further work is required.

There are many other drugs which have been found to have benefits in small studies and are awaiting replication.

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