

# Pain and fibromyalgia

Jatin D Dedhia DA DNB FRCA

Margaret E Bone DA FRCA FFPMRCA

## Key points

Fibromyalgia is a common chronic pain syndrome characterized by widespread pain, tenderness, and generalized hypersensitivity to painful stimuli.

Pain, fatigue, and sleep disturbance are present in most patients with this condition.

The pathophysiology is not well understood. Central sensitization, abnormalities in descending inhibitory pain pathways, neurotransmitter release, neurohumoral dysfunction, and psychological abnormalities are suggested aetiological mechanisms.

Diagnosis is based on the clinical criteria set out by the American College of Rheumatology, physical examination, and exclusion of other causes for symptoms attributed to fibromyalgia.

The treatment of this syndrome should be individualized and includes pharmacological and other therapies.

Fibromyalgia is a common chronic non-inflammatory pain syndrome characterized by widespread, often disabling pain and tenderness, stiffness, fatigue, and poor sleep. Symptoms of fibromyalgia were first reported in the nineteenth century when it was described as 'neurasthenia' and 'muscular rheumatism'. In 1904, Gower renamed the condition 'fibrositis' and this remained in use until the 1980s. In 1990, The American College of Rheumatology (ACR) established the criteria for a diagnosis of fibromyalgia (discussed later).<sup>1</sup> This represented a significant turning point in our understanding of pathophysiology of fibromyalgia, from muscle inflammation to a central nervous system dysfunction.

## Incidence

The incidence of fibromyalgia in the UK has been reported in various clinical studies as 1–35 per 100 000. It affects 4% of the adult population in Spain, and 2% in the USA and France.<sup>2</sup> There is no difference in gender incidence in childhood, but in adults the ratio of women to men with fibromyalgia varies between 9:1 and 20:1.<sup>3</sup> The condition is mostly diagnosed between the age of 20 and 50 yr. The incidence increases with age, so that, by the age of 80 yr, ~8% of adults meet the diagnostic criteria. About 10–11% of the population has chronic widespread pain at any given time and one-fifth of these people fulfil the ACR criteria. Eighty per cent of these patients also fulfil the criteria for chronic fatigue syndrome, up to 70% have headaches, 75% temporomandibular joint disorders, and 60% irritable bowel symptoms.<sup>4</sup>

## Definition

Fibromyalgia is defined on the basis of criteria laid down by the ACR. The first criterion is a history of spontaneous chronic widespread pain for a continuous period of 3 months. The second criterion requires the patient to elicit tenderness in at least 11 of the 18 defined tender points when palpated digitally (Fig. 1).

## Clinical features

Pain, fatigue, and sleep disturbance are three cardinal features present in most patients.<sup>4</sup> Pain is diffuse, deep, aching, throbbing, and gnawing in nature; it may vary in intensity. Fatigue is most marked in the morning, despite adequate sleep and peaking again by mid-afternoon. Such fatigue is reported to be physically and emotionally draining. Patients describe poor sleeping patterns, with difficulty falling asleep and frequent awakening.

Other clinical symptoms include prolonged morning stiffness, post-exertional pain, skin tenderness, tension and migraine headaches, dizziness, fluid retention, paraesthesias, restless legs, and mood disturbances.

## Co-existing conditions

Fibromyalgia has been reported to co-exist in 25% of patients with rheumatoid arthritis, 30% with systemic lupus erythematosus, and 50% with Sjogren's syndrome.<sup>5</sup> It may be misdiagnosed as chronic fatigue syndrome which shares all the three cardinal features of fibromyalgia, but does not fulfil the ACR criteria.

## Pathophysiology

The pathophysiology is not well understood, but increasing evidence suggests central rather than peripheral neurological mechanisms.

## Central sensitization

Central sensitization is common to several pain states and involves spontaneous nerve activity, expanded receptive fields causing larger geographic distribution of pain, and augmented stimulus responses such as temporal summation within the spinal cord. In fibromyalgia, there is an exaggeration of this temporal summation, often referred to as 'wind-up'. The *N*-methyl *D*-aspartate (NMDA) receptor is largely responsible for central sensitization and pharmacological attenuation of this receptor is associated with a reduction in 'wind-up', pain at rest, and hyperalgesia.<sup>6</sup>

Jatin D Dedhia DA DNB FRCA

SpR in Anaesthetics  
University Hospitals of Leicester NHS Trust  
Leicester Royal Infirmary  
Leicester LE5 1WW, UK

Margaret E Bone DA FRCA FFPMRCA

Consultant in Pain Medicine  
University Hospitals of Leicester NHS Trust  
Leicester Royal Infirmary  
Leicester LE5 1WW, UK  
Tel: +44 116 2585253  
Fax: +44 116 2586261  
E-mail: margaret.bone@uhl-tr.nhs.uk  
(for correspondence)

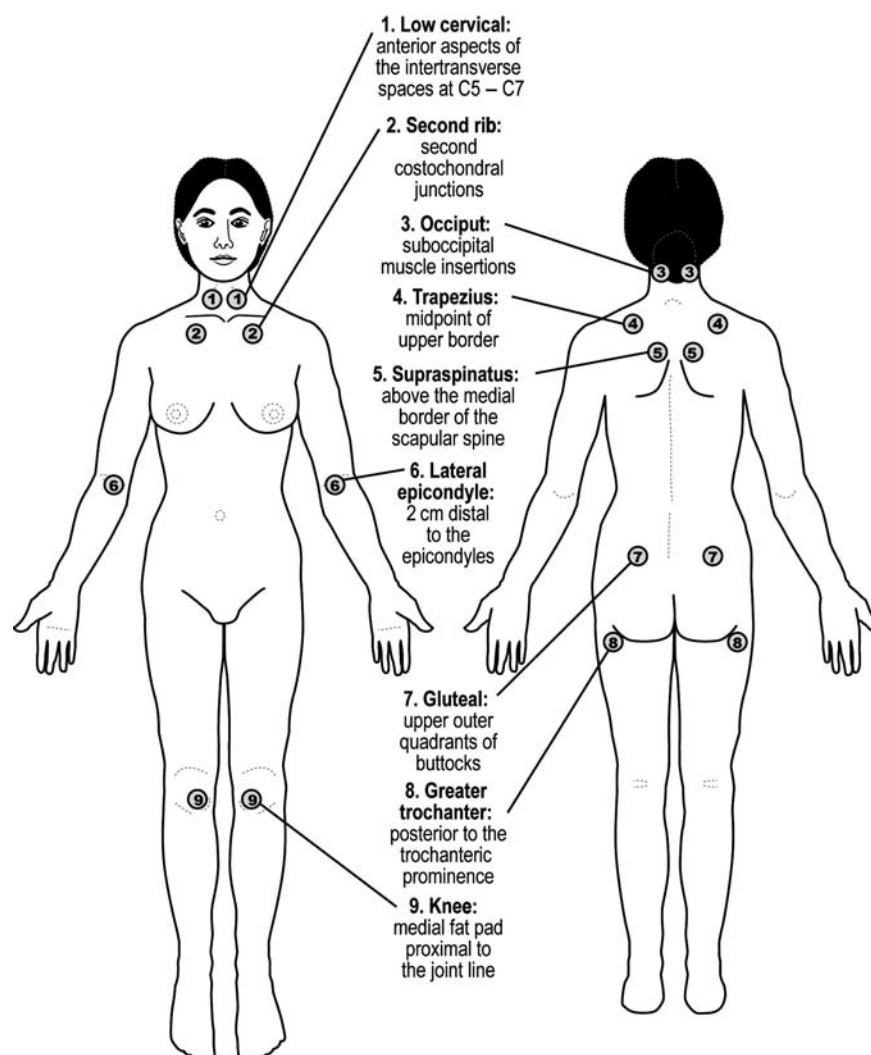
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**Fig 1** Tender points in fibromyalgia.

### Descending inhibitory pain pathway dysfunction

In healthy people, signals originating in the brain down-regulate spinal cord responses to painful stimuli via the descending inhibitory pathway. In fibromyalgia, this modulatory response may be defective. Many neural systems that contribute to the descending inhibitory pathways appear to be dysfunctional resulting in a reduction or absence of modulation to noxious stimuli. In addition, pain facilitating descending pathways may be implicated as a causal factor of the chronic pain in fibromyalgia.

### Biochemical factors

#### Biogenic amines

The levels of biogenic amines such as 5-hydroxytryptamine (5-HT) and norepinephrine, which modulate pain at the central and peripheral levels, are reduced in patients with fibromyalgia. 5-HT

acts pre-synaptically to inhibit the release of certain neurotransmitters such as substance P and excitatory amino acids, both of which are involved in pain processing. Dysregulation of the 5-HT system, which plays an important role in mood regulation, may lead to depression and anxiety commonly seen with fibromyalgia. Serotonin is known to regulate sleep and pain perception, both of which may be altered in fibromyalgia.<sup>7</sup>

#### Substance P and amino acid neurotransmitters

Levels of substance P and excitatory amino acids such as glutamate and aspartate are increased in fibromyalgia. This is attributed to reduced levels of 5-HT.

#### Neurohumoral dysfunction

In fibromyalgia, the hypothalamic–pituitary–adrenal axis (HPA), the hypothalamic–pituitary–thyroid axis, and the growth hormone

axis are disturbed. Such changes result in high levels of corticotrophin and follicle-stimulating hormone and low levels of cortisol, insulin-like growth factor, free tri-iodothyronine, and growth hormone. HPA axis abnormalities may also be related to depressed autonomic nervous system seen in fibromyalgia.

### Behavioural and psychological factors

Such factors may contribute to the continuing symptoms of fibromyalgia. The most common psychological conditions observed in patients with fibromyalgia include depression (22%), panic disorder (7%), and simple phobia (12%).<sup>6</sup>

### Regional central nervous system blood flow

A reduction of regional cerebral blood flow has been reported in patients with fibromyalgia, including flow to the caudate nucleus and thalamus (both involved in pain and mood regulation). However, it should be noted that such reports involve a small number of patients and warrant further evaluation.

### Abnormal muscle energy metabolism

Several histopathological changes consistent with tissue anoxia and reduced high-energy phosphate levels (e.g. 'moth-eaten' and 'ragged fibres') have been demonstrated at the site of tenderness which may suggest an abnormal muscle energy metabolism.

### Trigger factors for fibromyalgia

In the absence of a defined pathogenesis, attempts have been made to identify possible precipitants of fibromyalgia. It has been found that patients with hepatitis C and HIV have a higher incidence of fibromyalgia. Such viral infections are thought to trigger the condition by activation of cytosine system in the central nervous system via viral neurotropism and subsequent glial activation. Physical trauma may precipitate fibromyalgia. Patients with whip-lash injury and neck injuries are known to be at a higher risk of developing the condition. In addition, stress, anxiety, depression, exertion, emotional trauma, lack of sleep, and weather changes may trigger or exacerbate fibromyalgia.

### Diagnosis

Fibromyalgia is a diagnosis of exclusion; it is made on the basis of history, assessment of symptoms, investigations, and exclusion of other causes of symptoms similar to fibromyalgia.

### History

Patients often present with a history of widespread pain, fatigue, sleep dysfunction, joint pains, anxiety, and depression. Such symptoms overlap with multiple other conditions. The diagnosis of fibromyalgia is therefore based on the diagnostic criteria laid down

by The ACR as noted above. *The spontaneous widespread pain must involve all four limbs and the trunk.*

### Assessment of symptoms

#### Pain

A number of tools can be used to assess pain in clinical setting. The short-form McGill pain questionnaire (SF-MPQ) provides information on the character of pain by using adjectives divided into sensory, affective, evaluative, and additional categories. The Leeds assessment of neuropathic symptoms and signs (LANSS) scale helps to differentiate between neuropathic and nociceptive pain. The brief pain inventory assesses pain intensity, the patient's perception of pain, and the role of pain in interference in day-to-day activities.

#### Fatigue

Fatigue is common in a wide variety of conditions. The Multidimensional Assessment of Fatigue Index is a tool which measures various types of fatigue, including emotional and physical fatigue. This may be helpful in fibromyalgia.

#### Sleep

Quality of sleep can be assessed on a 100 mm linear scale with 'no problem with sleep' at one end and 'sleep is impossible' at the other end.

### Investigations

Currently, there are no routine laboratory tests or imaging procedures which facilitate the diagnosis of fibromyalgia. However, many investigations (e.g. full blood count, ESR, liver function tests, hepatitis C antibody, calcium and thyrotropin levels, neurophysiological studies, and various imaging procedures) are undertaken to exclude other causes of pain which mimic fibromyalgia.

### Treatment of fibromyalgia

Fibromyalgia does not result in death; however, it causes severe disability and compromises quality of life. Complete resolution of symptoms is rare, but significant improvements can be achieved with adequate treatment. Treatment is aimed at reducing or controlling the symptoms and improving the quality of life. In the past, due to the absence of guidelines for management of fibromyalgia, various treatments were attempted with variable success and these were not individualized. This led to development of a multidisciplinary taskforce consisting of 19 experts on fibromyalgia from 11 European countries—The European League Against Rheumatism (EULAR). The treatment discussed below is based on their recommendations.<sup>8</sup>

**Table 1** Drugs evaluated in treatment of fibromyalgia. Summary of randomized controlled trials and side-effects. —, no benefit; +, beneficial; blank, not tested in trials. TCA, tricyclic antidepressants; NMDA, *N*-methyl *D*-aspartate; AH, antihistaminergic; AC, anticholinergic; SSRI, selective serotonin reuptake inhibitor; DRI, dual reuptake inhibitor; HT, serotonin; NE, norepinephrine; MAOI, monoamine oxidase inhibitor; NRI, norepinephrine reuptake inhibitor; NSAIDs, non-steroidal anti-inflammatory drugs; AED, antiepileptic drugs; BZ, benzodiazepine

Class/drug (dose)	Mechanism of action	Pain	Sleep	Fatigue	Mood	Side-effects
TCA/amitriptyline (5–50 mg)	5HT/NE re-uptake blockade, NMDA blockade, AH/AC	+	+	+	—	Sedation, diplopia, dry mouth, tremors, urinary retention, constipation
SSRI/fluoxetine (20–40 mg)	5-HT reuptake blockade	+/-	+	+/-	+	Nausea, loss of appetite, dry mouth, diarrhoea, dizziness, drowsiness
DRI/duloxetine (30–60 mg)	NE > 5HT reuptake blockade	+	—	+	+	Nausea, loss of appetite, dry mouth, fatigue, vomiting, constipation, tremors
MAOI/pirlindole (75 mg b.d.)	MAO-A inhibitor	+	+	+	+	Dizziness, drowsiness, headache, high arterial pressure, arrhythmias, sweating, muscle twitch
NSAIDs/ibuprofen (200–400 mg q.d.s.)	COX inhibitor	—	—	—	—	Rash, ringing in ears, abdominal pain, diarrhoea, gastritis, headaches
AED/pregabalin, (150–450 mg day <sup>-1</sup> ) gabapentin (300–1800 mg day <sup>-1</sup> )	Ca <sup>2+</sup> channel blocker	+	+	+	+	Dizziness, weight gain, nausea, drowsiness, peripheral oedema, fatigue, headache, confusion
Hypnotics/zopiclone (3.75–15 mg day <sup>-1</sup> )	BZ receptor agonist	—	+	—	—	Dizziness, tremor, muscle spasms, agitation, dyspepsia, paraesthesia, nightmares, dry mouth, diarrhoea
Neuromuscular blocking agents/ cyclobenzaprine (10–20 mg q.d.s.)	5HT <sub>2</sub> antagonist	+	+	+/-		Heartburn, constipation, headache, dizziness, dry mouth
Opioids/tramadol (50–100 mg q.d.s.)	μ-agonist	+				Nausea, constipation, headache, dizziness, dry mouth, vomiting

## General measures

Recommendations for the management of fibromyalgia take into account general considerations including the importance of education. Patients and their families should be instructed to view fibromyalgia as a chronic pain condition which is not crippling. They should be encouraged to take an active and positive self-help approach. Emphasis should be laid on a physician-guided approach to treatment and enrolment into patient support groups. Awareness of fibromyalgia within the UK has been raised by The Fibromyalgia Association and more information can be accessed by visiting the website [www.fibromyalgia-associationuk.org](http://www.fibromyalgia-associationuk.org).

## Oral pharmacological therapy

Different classes of drugs for the treatment of fibromyalgia have been studied extensively and many of them demonstrate promising results in randomized controlled trials.<sup>9</sup> A list of drugs commonly used in managing fibromyalgia is shown in Table 1.

Tricyclic antidepressants (TCAs) (e.g. amitriptyline, nortriptyline, and imipramine) have multiple actions including inhibition of the re-uptake of 5-HT (serotonin) and norepinephrine, thereby suppressing the polysynaptic neuronal discharge and reducing the pain in fibromyalgia. Amitriptyline is the first drug of choice in clinical practice and may be prescribed in a low dose of 5–10 mg at night. TCAs are also considered to improve muscle stiffness, tenderness, fatigue, and sleep quality. More selective serotonin/norepinephrine re-uptake inhibitors (e.g. duloxetine) have been shown to reduce pain, fatigue, and improve sleep. Selective serotonin re-uptake inhibitors (e.g. fluoxetine) may improve mood and possibly

fatigue, but appear to have little impact on pain and other symptoms of fibromyalgia.

Anti-epileptic drugs (e.g. gabapentin and pregabalin) have been found to reduce the pain and have been used with variable success (Table 1).

Many opioids have been used in patients with fibromyalgia. However, their use is limited because of potential side-effects and addiction. Weak opioids such as tramadol have been recommended in the treatment of fibromyalgia. Tramadol is a μ-opioid receptor agonist which also inhibits the re-uptake of 5-HT and norepinephrine. Strong opioids are not recommended.

Non-steroidal anti-inflammatory agents and acetaminophen have been used for their analgesic properties, but there is limited evidence to show their effectiveness in fibromyalgia.

Neuromuscular blocking agents (e.g. cyclobenzaprine) have been used on a short-term basis to treat flare ups, based on their ability to reduce brainstem noradrenergic function and motor neurone efferent activity. Hypnotics (e.g. zopiclone) have been used to improve sleep and reduce fatigue.

The NMDA receptors are known to be involved in the maintenance of chronic pain. Blockage of these receptors may alleviate some of the pain in fibromyalgia. However, side-effects of these agents frequently limit their use in clinical practice. 5-HT<sub>3</sub> receptor antagonists (e.g. tropisetron) have been used to treat fibromyalgia. The exact mechanism of action is not known, but it is believed that they reduce the release of substance P.

Monoamine oxidase inhibitors (MAOIs) block the catabolism of 5-HT resulting in increased concentrations in the brain. MAOIs such as moclobemide were clinically unsuccessful, but the newer MAOI pirlindole is known to have significant beneficial effects on sleep, mood, and pain in these patients.

## Trigger point injections

Local injections of trigger points with local anaesthetics, with or without depot corticosteroid, may be used intermittently to provide short-term pain relief in some patients.

## I.V. lidocaine

Our current understanding suggests that there is disordered sensory processing at the peripheral and central levels in patients with fibromyalgia. Interference with this pain process at the central level can be achieved by inhibiting the pain pathway with systemic local anaesthetic agents through their inhibition of voltage-gated sodium channels. Lidocaine has been used i.v., in various administration regimes in the doses of 3–5 mg kg<sup>-1</sup> as single one off infusion over 1–2 h which can be repeated every 3–6 months or as 5 mg kg<sup>-1</sup> minus 100 mg on day 1 and increased by 50 mg day<sup>-1</sup> up to 6 days to a maximum dose of 550 mg to be given over 6 h daily for 6 days. The latter regime has been shown to reduce pain score, mean daily duration of pain, and verbal assessment of pain.<sup>10</sup>

## Non-pharmacological measures

### Exercise

Patients with fibromyalgia are often aerobically unfit due to prolonged periods of inactivity restricted by pain. Unaccustomed exercises can increase the pain and cause delayed onset muscle soreness. Despite this, it has been shown that individualized exercise programmes, including strength and flexibility training, reduce pain in fibromyalgia. It has been suggested that exercise increases the body's production of endogenous opioids. Exercise improves oxygenation and circulation to muscles, improves mood, reduces disability, and helps restore a normal sleep pattern. Patients should be encouraged to perform exercises at least 2–3 times per week.

### Cognitive behavioural therapy

It is known that patients with fibromyalgia exhibit increased levels of stress on a daily basis when compared with normal individuals.

Psychological and behavioural therapies are recommended to improve psychological and social factors. These positively influence perception and maintenance of chronic pain in these patients.

## Complementary therapies

Complementary therapies such as acupuncture, transcutaneous electrical nerve stimulation (TENS), hypnotherapy, EMG-biofeedback, osteopathic manipulation, low-power laser therapy, aromatherapy, hot water baths, and sulphur baths have all shown some beneficial effects in relieving some of the symptoms of fibromyalgia.

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Please see multiple choice questions 20–23