

Fibromyalgia syndrome: Unraveling the mystery

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Abstract

Fibromyalgia (FM) is a common chronic widespread pain disorder. Understanding this disease has increased substantially in recent years with extensive research. Neurochemical imbalances in the central nervous system are associated with central amplification of pain perception characterized by allodynia and hyperalgesia. Despite this increased awareness and understanding, FM remains undiagnosed in an estimated 75% of people with the disorder. Fibromyalgia is a disorder of pain processing. Evidence suggests that both the ascending and descending pain pathways operate abnormally, resulting in central amplification of pain signals, analogous to the “volume control setting” being turned up too high. Patients with FM also exhibit changes in the levels of neurotransmitters that cause augmented central nervous system pain processing; levels of several neurotransmitters that facilitate pain transmission are elevated in the cerebrospinal fluid and brain, and levels of several neurotransmitters known to inhibit pain transmission are decreased. Pharmacological agents that act centrally in ascending and or descending pain processing pathways, such as medications with approved indications for FM, are effective in many patients of FM as well as other conditions involving central pain amplification.

Keywords: Pain signal, Allodynia, Hyperalgesia, Pain Processing, Pain Pathways, Central Amplification of Pain, Neurotransmitters, Central Pain Sensitization, Serotonin, Epinephrine, Substance P, Duloxetine, Milnacipram, Empowerment.

Fibromyalgia is a chronic wide spread neurologic pain condition associated with chronic wide spread pain and tenderness.⁽¹⁾ American College of Rheumatology has put forward the following criteria for this diagnosis-

pain for ≥ 3 months, pain above and below the waist, pain on left and right sides of the body and axial skeleton, pain at ≥ 11 of 18 tender points palpated with 4 kg of digital pressure.

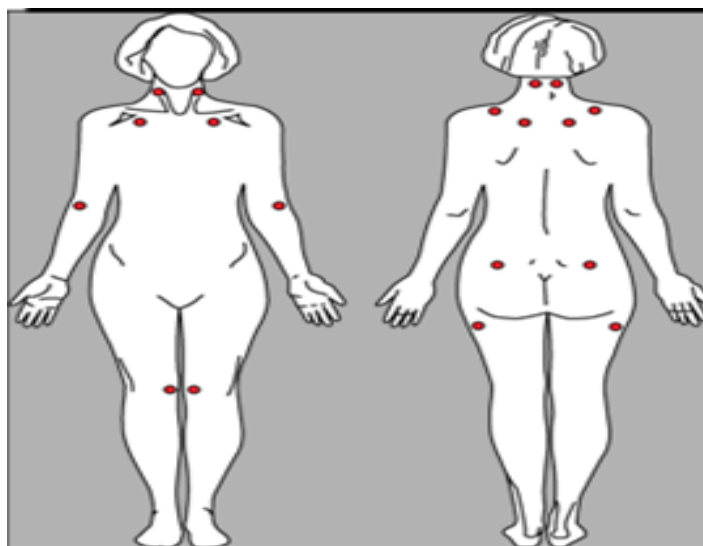


Diagram showing 18 tender points

Overview

Fibromyalgia patients often have heightened sensitivity to pain (hyperalgesia). Additionally know noxious stimulus may result in pain (allodynia). Patients may present with wide range of additional symptoms including tenderness, sleep, fatigue, morning stiffness, cognitive complaints and mood disorder.⁽²⁾

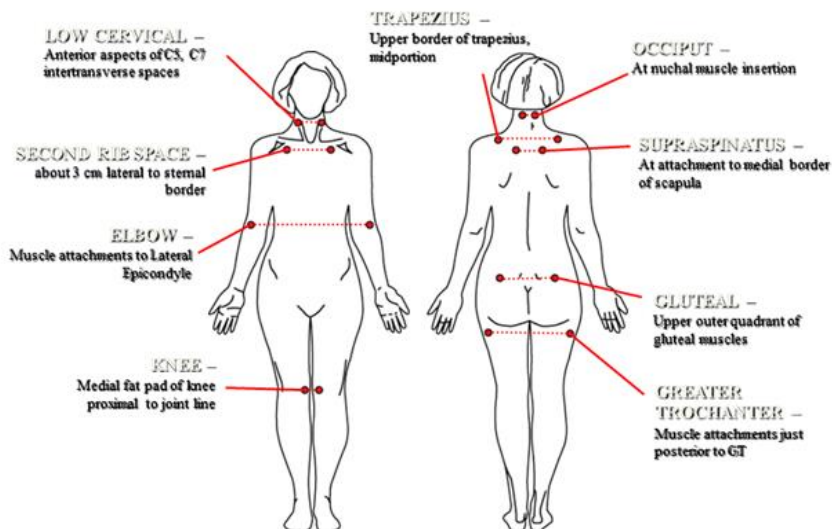
History

Dr. Gowers first described fibrositis in 1904. In 1978 Drs. Smythe and Mold of sky published evidence of fibromyalgia sleep pathology and central pain sensitization. In 1990 Fibromyalgia syndrome was first defined by American College of Rheumatology. In 1994 Dr. Russell found three fold increase of substance p in the CSF in fibromyalgia patients. In 2007 the FDA approved pregabalin, in 2008 Duloxetine and in 2009

Milnacipran all specifically indicated for the treatment of fibromyalgia.

ACR-Recommended manual tender point survey for the diagnosis of fibromyalgia⁽³⁾ presence of 11

tender points on palpation to a maximum of 4 kg pressure (just enough to blench examiner's thumb nail out of 18 such points is made mandatory for the diagnosis).



Risk factors and epidemiology for fibromyalgia:

- a. Genetic factors⁽⁴⁾
 - Relative of fibromyalgia patients are at higher risk of fibromyalgia
 - First degree relatives are significantly more likely to have fibromyalgia
 - Have significantly more tender points
- b. Environmental factors- 50% of cases may have one of the following stressor⁽⁴⁾:-
 - Physical trauma or injury
 - Viral Infections (Lyme disease, hepatitis C)
 - Other stressors (i.e. work, family, life changing events)
- c. Gender⁽⁴⁾
 - Women are diagnosed with fibromyalgia 7 times more than men (3.5% in women and 0.5 % in men)
 - Most common cause of musculoskeletal pain in women aged 20-55 years
- d. Depression – fibromyalgia patients have 50% lifetime hours of depression. Although only 25% meet the criteria of depression at the time of diagnosis.

Normal pain processing pathway

The following flowchart demonstrates the normal pain processing pathway with clarity:-

After the stimulus is sensed by the peripheral nerve i.e. skin impulses form apprehance the polarised the neuron. Then, extra cellular calcium's Ca^{2+} diffuse into neurons causing the release of pain associated neuro transmitters-glutamate and substance P. These neurotransmitters send a signal via the ascending tract in the spinal cord to the brain and this is perceived as

pain. The descending tract in the spinal cord then carries modulating impulses back to the dorsal horn.⁽⁵⁾

Central sensitization: A theory for neurological pain amplification in fibromyalgia is known as central sensitization. Central sensitization is believed to be an underlined cause of the amplified pain perception that results from dysfunction in the CNS.⁽⁶⁾ Hyperalgesia is the amplified response to the painful stimuli whereas allodynia is the result of the pain arising from normal stimuli. The central sensitization theory is supported by the presence of increased levels of glutamate and substance P (pain neurotransmitters).

Central sensitization produces abnormal pain signaling. After nerve injury increased input to the dorsal horn can induce central sensitization resulting into increased pain perception. The diagram is self-explanatory.⁽⁷⁾

Pathophysiology of fibromyalgia: Central sensitization is a leading theory of fibromyalgia. Central sensitization of the CNS explains much of the generalized heightened pain sensitivity of fibromyalgia patients. The CSF levels of substance P are 3 fold higher in fibromyalgia patients, whereas there are decreased levels of Serotonin epinephrine needed for pain modulation through the descending inhibitory pain pathway in the brain and dorsal horn of the spinal cord. Substance P is excitatory neurotransmitter working influencing central sensitization along with prognosis septive amino acid glutamate acting at the alpha-delta and C ascending pain fibers.⁽⁹⁾

MRI data also provides supporting evidence that fibromyalgia involves altered central pain processing.⁽⁸⁾

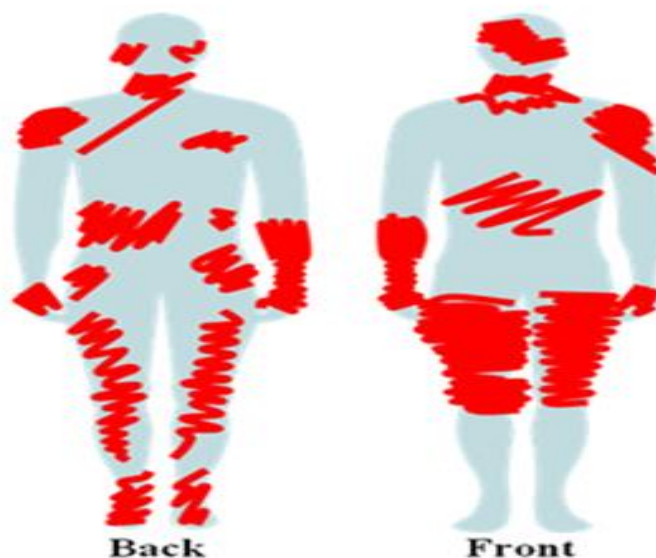
fMRI data supports fibromyalgia as a disorder of central pain amplification-reas activated by high intensity stimuli in control patients were activated by low intensity stimuli in patients with fibromyalgia.⁽¹¹⁾

Wind Up pathophysiology: “Wind up mechanism” have been demonstrated by Drs. Price and Staud resulting into activation of wide range of dorsal horn neuronal pain discharges in the CNS following increasing repetitive nociceptive stimuli. “Wind up” involves recruitment of MMDA pain receptors in the CNS and neural plasticity of nociceptive spinal cord pathways in central sensitization. It has been amply shown that exercise can activate indogenous oppoys and reduce wind up.⁽¹⁰⁾

Proposed etiology of fibromyalgia: HPA axis dysfunction is proposed resulting in low AM cortisol, high ACTH resulting in irritable bowel syndromes, paresthesia’s and numbness of extremities.

Abnormal sympathetic tone and autonomic dysfunction is proposed to produce nocturnal tachycardia and loss of normal circadian rhythm. Neutrally mediated hypotension absorbed by abnormal tilt testing.⁽¹²⁾

Patients with fibromyalgia present with a global pain disorder: While ACR classification criteria focuses on 18 points, patients do not usually speak of tender points. A patient should be allowed to draw a pain sketch coloring all areas of the body where they feel pain. Such diagram shows that the pain of fibromyalgia is widespread.⁽¹³⁾



Adapted from pain drawing provided courtesy of L. Baterman

Differential Diagnosis

1. Polyarticular arthritis
 - Rheumatoid arthritis
 - SLE
 - Polymyalgia rheumatic
2. Endocrine disorders
 - Hypothyroidism
 - Hyperparathydoism (hypercalcemia)
3. Myopathies
 - Polymyositis
 - Rhabdomyolysis
4. Neuropathies
5. Depression
6. Chronic fatigue syndrome
7. Myofascial pain syndrome
8. Anemia

- Rheumatoid arthritis (12%)
- SLE
- Hepatitis C
- Myofascial pain syndrome
- TMJ
- IBS
- Osteoarthritis (7%)
- Depression
- Migraine headaches
- OSA
- Restless legs

Common Symptoms

- Fatigue
- Subjective joint / muscle swelling
- Difficulty sleeping
- Night sweats
- Dyspnea
- Palpitations

Overlapping syndromes and symptoms

Common comorbidities:

- Pelvic pain
- Dysmenorrhea

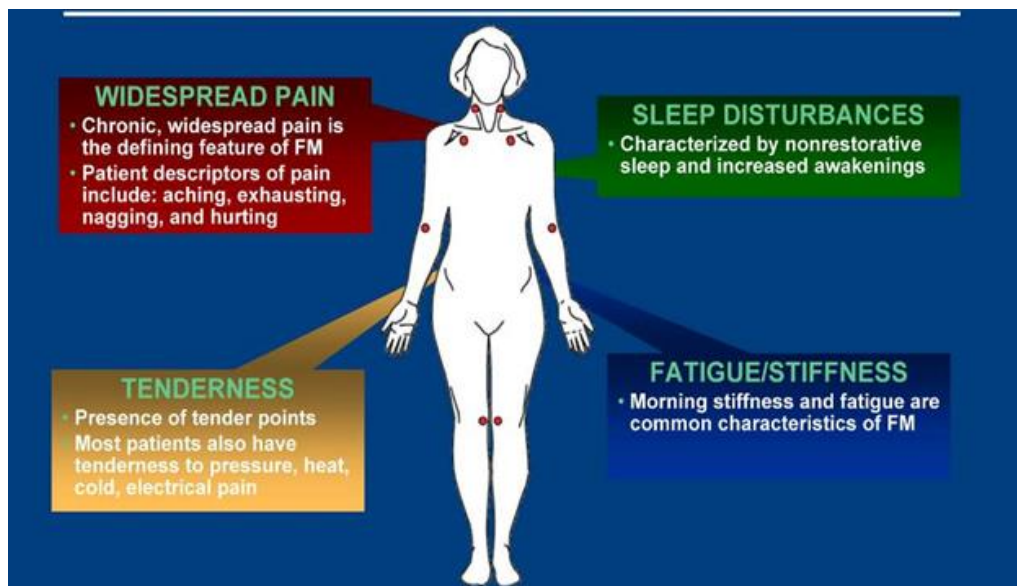
- Non-cardiac chest pain
- Diarrhea / constipation (IBS)

Clinical features of fibromyalgia

The following two diagrams clearly show the clinical presentation of the patient of fibromyalgia:-



<p>Chronic Widespread Pain</p> <ul style="list-style-type: none"> • CORE criteria of FM - Pain is in all 4 quadrants of the body ≥ 3 months • Patient descriptors of pain include: <ul style="list-style-type: none"> - Aching, exhausting, nagging, and hurting
<p>Tenderness</p> <ul style="list-style-type: none"> • Sensitivity to pressure stimuli <ul style="list-style-type: none"> -Hugs, handshakes are painful -Tender point exam given to assess tenderness • Hallmark features of FM <ul style="list-style-type: none"> -Hyperalgesia -Allodynia
<p>Other Symptoms</p> <ul style="list-style-type: none"> • Fatigue • Pain-related conditions / symptoms <ul style="list-style-type: none"> -Chronic headaches / migraines, IBC, IC, TMJ, PMS -Subjective morning stiffness • Neurologic symptoms <ul style="list-style-type: none"> -Non-dermatomal paresthesia's -Subjective numbness, tingling in extremities • Sleep disturbance <ul style="list-style-type: none"> -Non-restorative sleep, RLS



Mood disorders in fibromyalgia

- Fibromyalgia patients tend to have dysthymia and reactive depression, and not major depression.
- Fibromyalgia patients have increased anxiety that correlates with their pain.
- Giving patients some control of their condition through education and pain control, improves

physical function and diminishes mood disorders in many patients.

Fatigue in Fibromyalgia

Fatigue is an important symptom in fibromyalgia being present in 90% of patients. It is often associated with:-

- Non-restorative sleep

- Chronic pain
- Exercise deconditioning
- Ineffective energy conservation
- Ineffective stress coping techniques
- Sedative effects of prescribed medications

Management of fibromyalgia

Non-pharmacologic management

Patient education

- Patients generally have fewer symptoms if they are told their diagnosis.
- Group session (6-17 sessions), lectures, written materials seem to improve quality – of-life, pain, sleep, energy levels, improvements lasted 3-12 months.
- 1.5 day educational session improved energy, stiffness, pain severity and depression.
- Aerobic exercise
- 2002 Cochrane review found that aerobic exercise is an effective treatment for fibromyalgia patients had improved pain thresholds, decreased pain and improved aerobic exercise capacity.
- Strengthening exercises appear to provide some improvement.
- Both aerobic exercise and strengthening exercises appear to be more effective than stretching.
- Patients should be counseled to start slowly. They will often feel worse if they embark on a strenuous exercise regimen quickly.
- Swimming and water sports appear to be well-tolerated.
- Low impact aerobic exercise
- Balance and strength training
- Conservation of energy
- Biofeedback
- Cognitive behavioral therapy
- Nutrition
- Accupuncture

Pharmacologic management

- Antidepressants
- Analgesics
- Anticonvulsants
- Sleep medicines
- Muscle relaxants

Pharmacological interventions

FDA approved medications

- Pregabalin (Lyrica) alpha 2 delta ligand – blocks substance P and glutamate
- Duloxetine (Cymbalta) SNRI-0.2:1 serotonin: norepinephrine
- Milnacipram (Savella) SNRI-1:3 serotonin: norepinephrine
- All three drugs achieved about 30% reduction of pain / improved function in 50% of patients and 50% reduction in pain / improved function in 30%

of patients, Treatments with demonstrated efficacy (Non-FDA approved)

- Cyclic medications
- Cybenzaprine (Flexenil)
- Tricyclic antidepressants antitryptline and notriptyline
- Alpha-2 delta ligands
- Gabapentin (Neurotin)
- Sleep medicine
- Sodium oxybate (Xyron)

Sleep medications: Zolpidem has been shown to be effective in preserving normal sleep architecture in fibromyalgia. It reduces fibromyalgia fatigue, but not fibromyalgia pain.

Sodium Oxybate 4.5 and 6 gm 30% achieved > 50% reduction in pain and 40% achieved >30% reduction in pain. Similar improvements in FIQ and PGIC.

Medications

SSRIs: Variable results with fluoxetine, but it appears to improve pain when providers are allowed to escalate the dose to up to 80 mg/day. No improvement found with a fixed dose of fluoxetine (20 mg / day). Pain appears to improve regardless of improvement in mood.

Tricyclic antidepressants: Amitriptyline 25-50 mg qhs effective in multiple RCTs. Cyclobenzaprine (Flexural) 10-40 mg qhs also effective in multiple RCTs. Patients should be allowed to determine the maximum effective dose. Side effects limit use and dose escalation.

Other medications: Pregabalin was found to decrease severity of pain in one RCT. Combination of carisoprodol (Soma), Tylenol, and caffeine improved sleep and pain threshold more than placebo. Tramadol 75 mg q 6 hours appears to improve pain. The effect may be greater with acetaminophen 650 mg q 6 hours.

Medications with “strong” or “moderate” evidence for efficacy- Amitriptyline, Cyclobenzaprine, Tramadol, Fluoxetine, Venlafaxine, Duloxetine, Pregabalin.

Ineffective medications: Corticosteroids, Opioids, NSAIDs, Benzodiazepines, Guaifenesin, Levothyroxine, Cacitonin, Melatonin, Magnesium.

Conclusion

Fibromyalgia is one of the most common chronic widespread neurologic pain conditions associated with hyperalgesia and allodynia. Central sensitization is a leading theory to explain fibromyalgia, demonstrated by excessive release of the pain neurotransmitters glutamate and substance P. Fibromyalgia is commonly seen with other chronic pain-related conditions. ACR criteria for the diagnosis of fibromyalgia are sensitive and specific.

- History of CWP \geq 3 months
- Pain in 4 quadrants and axial skeleton
- \geq 11 of 18 tender points

Check CBC, ESR, TSH, CK depending on symptoms.

Diagnosis is a key to successful management of fibromyalgia. Patient education, aerobic exercise, CBT and TCAs are most effective treatments.

Fibromyalgia patients do not have a progressive disease and do better with comprehensive care-what to expect, what accommodations are needed, conservation of energy, exercises and stretches, medicines and treatments.

Fibromyalgia patients can improve their physical ability to function and quality of life with empowerment through medical supervision.

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