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Review

A comprehensive review of the classification of fibromyalgia, it's possible genetic and environmental causes, and its epidemiology in Pakistan

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Abstract

Fibromyalgia (FM) is a common form of chronic pain that causes pain all over the body. It is thought to affect between 1% and 5% of the world's people. It happens more often in adults, but it can also happen in children. Its exact cause and effect are still not known; however, it is thought to be linked to neuronal over-sensitization, decreased conditioned pain modulation (CPM), cognitive dysfunction, dementia, and problems with how the brain processes information. It is now a somatic symptom disorder (SSD). FM does not run in families, but it seems to happen more often in families where FM has happened before. One of the most common reasons why people get fibromyalgia is an SNP in the serotonin transporter gene, which can also cause emotional stress. The effects of genetic polymorphisms on serotonergic and catecholaminergic processes in the central nervous system seem to make fibromyalgia more likely. It can be averted if it is found and treated quickly. Environmental factors such as post-traumatic stress disorder, poor sleeping routine and lack of physical activities may also contribute to the progression of fibromyalgia. Physical therapy and other treatments that do not involve drugs should be made to fit the person with FM. The Food and Drug Administration (FDA) has given the approval for three treatments. In this review article, we looked again at the possible causes, effects, and treatments for fibromyalgia syndrome.

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Introduction: Fibromyalgia is a predominant pain illness indicated by chronic widespread pain and assumed to affect 1 to 5% of the population [1]. Difficulties in sleeping, fatigue, stiffness, anxiety, as well as cognitive dysfunction, are among the physical and psychological symptoms related to this condition [2]. Its exact pathophysiology is still unknown. However, it is thought to be linked to neuronal over sensitization and diminished conditioned pain modulation (CPM), as well as cognitive dysfunction, memory loss, and impaired information processing. The syndrome causes boosted connectivity across parts of the brain involved in pain processing and alertness, making medicinal treatment arduous. Fibromyalgia often coexists with other chronic disorders and can lead to worse results if left untreated [3]. A study suggest that fibromyalgia may develop spontaneously [4], but it is more likely to be a stereotypical, maladaptive biological reaction to the combined impacts of physical and mental stress in genetically predisposed individuals [5]. It is associated with psychological and physical issues, which might result in diminished outcomes [6]. However, it can also develop following an infection. *B. Walitt et al.* [7] also stated that folks who experience continuous medical issues in general may be more likely to get fibromyalgia.

Fibromyalgia pathophysiology is supported by the advancement of changes in the central nervous system (CNS) [8] that change the preparation of afferent sensory information and can be assembled under the 'Central sensitization' term [9]. Changes in central sensitization are usually caused by long-term physical distress or psychological stress [10]. These changes result in an amplification of the intensity of the stimuli, which are usually painless and are considered painful. Other side effects include sleep cycle abnormalities, such as inability to attain deep, restorative stage IV non-REM sleep, and hypothalamic-pituitary axis instabilities, such as altered serum cortisol levels, weakened 24-hour urinary free cortisol, and diminished cortisol reactions to dynamic testing [11]. The effects of genetic polymorphisms on CNS serotonergic and catecholaminergic processes are still being studied, and they appear to enhance the likelihood of developing fibromyalgia [12]. clinical fibromyalgia is frequently provoked, regardless of any hereditary susceptibility. In a North American internet survey of 2,596 patients with fibromyalgia, 79 percent mentioned plausible triggering events during the outset of their disease [13], whereas 88.7 percent of patients treated in a public hospital fibromyalgia clinic in Australia indicated recognized triggers [14]. In a vulnerable individual, a physical / psychological stressor can trigger a persistent, maladaptive stress response, which then mediates the central alterations [15]. Fibromyalgia may be related to severe disability, but it may be minimized through initial diagnosis and intervention. Fibromyalgia patients usually have other chronic diseases and therefore, managing aggravating factors and performing precise clinical examination may be beneficial. The management strategy must be coordinated, multidisciplinary, and patient focused. Patients need guidance as well as self-management techniques. Physical therapy and other non-drug therapies should be tailored to the particular patient. Drugs can assist in suppressing symptoms, but active rehabilitative measures take precedence in care [16]. The FDA has approved just three drugs for the treatment of FMS: pregabalin (a gabapentinoid that works by blocking calcium channels), duloxetine, as well as milnacipran (both are serotonin-noradrenaline reuptake inhibitors). Still, different types of antidepressants are used to treat chronic pain, including FMS, and there are different levels of proof that they work [17].

Classification: Fibromyalgia has been classified into various group of disorders depending upon its etiology. For instance, chronic somatoform pain disorder, depression, tiny fiber neuropathy, somatic symptom disorder, and a brain disorder have all been connected to FM.

Fibromyalgia: A Pain Disorder: Given that the etiology of various forms of prolonged pain is unidentified, the latest definition of pain has been created. The eleventh International Classification of Diseases revision committee chose the term primary pain because it was closely related and the committee realized that it was a hugely appropriate term from a non-specific viewpoint [18]. Allodynia and spontaneous pain explain sixteen different dysfunctions in pain modulation. This shows that fibromyalgia could be a painful illness marked by a higher sensitivity to pain and a lower ability to control pain [19].

Fibromyalgia: A Symptom of Depression: Another misconception is that fibromyalgia is an emotional spectrum disorder or an insidious form of depression [20]. Depending on the diagnostic methods and standards applied, the lifetime occurrence of depression in fibromyalgia patients ranges from 40-80 percent [21]. In any event, not all fibromyalgia patients feel continuous, widespread pain, and not all people with depressive disorders do [22]. The overlap of symptoms, for example, shared biological (e.g., genes) and psychological (e.g., childhood experiences) causes, can shed light on the link between FM and depressive disorders [23]. German criteria [24] say that fibromyalgia and (masked) depression are not the same thing.

Fibromyalgia_A Neuropathy of the Small Fibers: The fact that the fibromyalgia is a neurological condition (also known as "small fibre neuropathy") was brought up after it was discovered that some patients had small-nerve-fiber pathology [25]. On the other hand, not all patients who meet the FM criteria will exhibit tiny fibre pathology findings [24]. Additionally, in most chronic pain diseases and other conditions that aren't typically associated to them, like amyotrophic lateral sclerosis and postural tachycardia syndrome, modest indicators of disease have been detected, such as a reduced IENFD (intraepidermal nerve fibre density) [26].

Fibromyalgia is a chronic somatoform pain disorder: Some psychosomatic medical specialists came up with the name "chronic somatoform pain condition" due to the lack of a well-defined aetiology and the connection between fibromyalgia symptoms and psychosocial stress [27]. [28] say that psychosocial stress and emotional conflicts cause or make fibromyalgia symptoms worse in 60–80% of FM patients. The German guideline [24] says that fibromyalgia and persistent somatoform pain disease are not the same thing.

Fibromyalgia is a Disorder of Somatic Symptoms: Fibromyalgia is increasingly being ordered as an SSD (somatic symptom disorder). In the recent Diagnostic and Statistical Manual of Mental Disorders (DSM-5) fifth

edition, the American Psychiatric Association renamed the category of pain disorder to SSD. [29]. when there are persistent, severe somatic symptoms that have lasted for more than six months disruption of daily routine (criteria A and C), as well as disproportionately high or excessive symptom-related emotions, thoughts, and actions, SSD may be diagnosed (criteria B) [30]. FM has been classified as an SSD in recent papers [31].

Fibromyalgia: A Brain Disease: Central sensitization, or FM, is the most developed pathophysiological, increased functional connectivity with pre-receptive brain areas, decreased connection with the antinociceptive area, and associated changes in CNS neurotransmitters and in the size as well as the shape of brain areas. A group of people showed improvement in the cardinal symptoms of component of fibromyalgia when these CNS abnormalities were treated with pharmacological or nonpharmacological therapies that were known to change CNS function. D. J. Clauw [19] discovered a relationship between these outcomes and enhancements in functional, chemical, and structural neuroimaging outcomes, supporting the hypothesis that fibromyalgia is a brain disorder.

Genetic Factors and Fibromyalgia: Although the causes and fundamental pathologies dictating the progress of fibromyalgia disease are unknown [32], The majority of other chronic pain illnesses, including fibromyalgia, have substantial hereditary bases, according to recent study [33]. Several familial studies [34] suggest that genetic susceptibility is likely to play a role, and its transmission is estimated to be polygenic [35]. The most important genes studied are linked to neurotransmitters. The serotonin transporter gene has a single nucleotide polymorphism, with the allele "S" (short) being more common in fibromyalgia and psychological pain patients [36]. The catechol-O-methyltransferase gene [37], the dopamine D4 receptor gene [38], as well as the HLA-region [39] are all believed to be involved in this disease.

Environmental factors and fibromyalgia: Several environmental factors are there that upsurge the odds of FM indirectly. These include stress and mood disorders like anxiety and depression, etc. People having Post-Traumatic Stress Disorder (PTSD) as a result of a terrible event like an accident, war, or rape tend to be depressed, and thus they feel even more pain, which escalates the degree of pain in FM [40]. Children who have been abused emotionally and physically during childhood are believed to develop FM more easily as their brains tackle pain and stress differently because of abuse. Fibromyalgia is far more common in people who suffer from persistent pain caused by peripheral pain generators. As a result, those who suffer from inflammatory joint conditions such as rheumatoid arthritis or ankylosing spondyloarthritis should avoid smoking [41] and joint hyperlaxity [42] are more likely to have fibromyalgia symptoms.

Furthermore, poor eating and sleeping habits also provoke fibromyalgia. Moreover, FM may also be caused by an injury or trauma [40]. Obesity is caused by a poor lifestyle, and studies show that obesity triggers fibromyalgia. People with fibromyalgia syndrome are more likely to be overweight [43]. Overweight or obese women were 60-70 percent more chances to develop fibromyalgia than normal-weight women [44]. In a community-based, longitudinal study of Norwegian women, sleeplessness symptoms nearly quadrupled the chance of new-onset fibromyalgia, although high levels of physical activity protected against it. Fibromyalgia is known to be caused by certain viral and bacterial infections as well as vaccination [45]. People often talk about infections like Epstein-Barr virus or parvovirus infections, brucellosis, and Lyme disease. However, any persistent feverish illness, especially if it comes with a long period of bed rest [45], could also be a cause.

Different diagnostic criteria for FM: The publishing of at least five different sets of classification and diagnostic criteria for fibromyalgia during the past 30 years or more is the outcome of continuing research. In the early criterion sets, fibromyalgia was initially classified as a chronic widespread pain (CWP) condition with a range of symptoms.[46]. The 1990 ACR classification criteria [47] only used CWP is described as pain and tenderness on the left and right sides of the body, above and below the waist, as well as axial skeletal pain, such as neck or back pain, chest pain, and low back pain (defined as pain when palpating 11 out of 18 tender point sites).

However, the 1990 ACR criteria were impracticable to employ in a clinical context because they required a tender point assessment (which has intrinsic intra-individual and inter-individual variability and is examiner dependent).The 2010 and 2011 ACR criteria [48] altered the definition of fibromyalgia to a condition with several symptoms and did away with the need for a tender point test as part of the diagnosis process. While the criteria did resume focusing on the accompanying symptoms, perhaps too little attention was paid to persistent pain as the primary symptom. The 2016 updates to the 2010/2011 ACR diagnostic criteria placed a strong emphasis on the concept of "generalised pain." This idea is also at the heart of the 2018 [49]ACTTION-APS Pain Taxonomy diagnostic criteria.

Fibromyalgia Research in Pakistan: Various studies have been performed to measure the occurrence and severity of Fibromyalgia in Pakistani population and it was noted that about 33.33% (n = 250) of hospital visiting patients had FMS, of which 76% (190) were females [50]. The existence of diabetes, anxiety and rheumatoid arthritis were discovered to be notably associated with FMS. About 13.66% patients (n = 161) with Chronic Kidney Disease (CKD) stage III and IV were found to have fibromyalgia syndrome [51]. A research conducted in Allama Iqbal Hospital, Lahore discovered that patients with vitamin D deficiencies had strong associations with FMS [52]. Women are affected by rheumatoid arthritis (RA) roughly 1–5 times more frequently than men. It is an extremely common autoimmune inflammatory joint illness. Women are affected by rheumatoid arthritis (RA) roughly 1–5 times more frequently than men. It is an extremely common autoimmune inflammatory joint illness [53,54]. According to a research at Indus Hospital, Karachi, about 26% (n = 120) patients with RA also had FMS [55].Depression is one of the most common causes of FMS and about 69% patients of FM were diagnosed with severe depression [56].

Summary: Fibromyalgia is a common chronic pain illness that affects about 2% to 5% of the general population. It is neither an autoimmune disorder nor an inflammation-based illness, but it involves the nervous system as

suggested by the research. The pathophysiological mechanism behind FM is not fully appreciated. FM is not transferred from parents to offspring directly. However, it does appear to congregate within families. The probability of coming across FM is much higher in the vicinity of families of people with FM than in families in which there is no prior case of FM. Also, DNA studies of FM patients and those who have chronic pain syndrome in their family have revealed that the myth of FM can be resolved with the help of several genes that play a vital role in CNS pain response, depression, and anxiety. This gives a hint as to why certain antidepressants help mitigate FM pain. Clear answers to the question of the nature of fibromyalgia require scientific techniques that consider the wide range of factors that may predispose persons to develop the condition and sustain the symptoms. The Research Domain Criteria (RDoC) initiative at the National Institute of Mental Health (NIMH) [57] is an example of a method that targets complicated and polygenic psychological illnesses. This ambitious project aims to create a framework for the classification of mental disorders for research purposes by fusing discoveries from genetics, neurology, and behavioural science. The complex and interconnected physiology of fibromyalgia may be better understood by future studies that use the same method.

Conclusion: Fibromyalgia is a complex medical subject. The criteria used to define FM have changed significantly over the past few decades. While neurologists, psychiatrists, and pain experts may dispute that the symptoms connected to FM belong to their respective fields, FMS is typically thought of as a rheumatic disorder characterized by chronic generalized pain, disrupted sleep, and cognitive impairment. Sedentary lifestyle and obesity are two possible fibromyalgia risk factors that can be changed. Other risk factors are more difficult to alter, such as inheritance, low socioeconomic status, and physical and sexual abuse during childhood and adolescence. Despite these advancements, no one mechanism has been identified to account for the entire spectrum of fibromyalgia symptoms.

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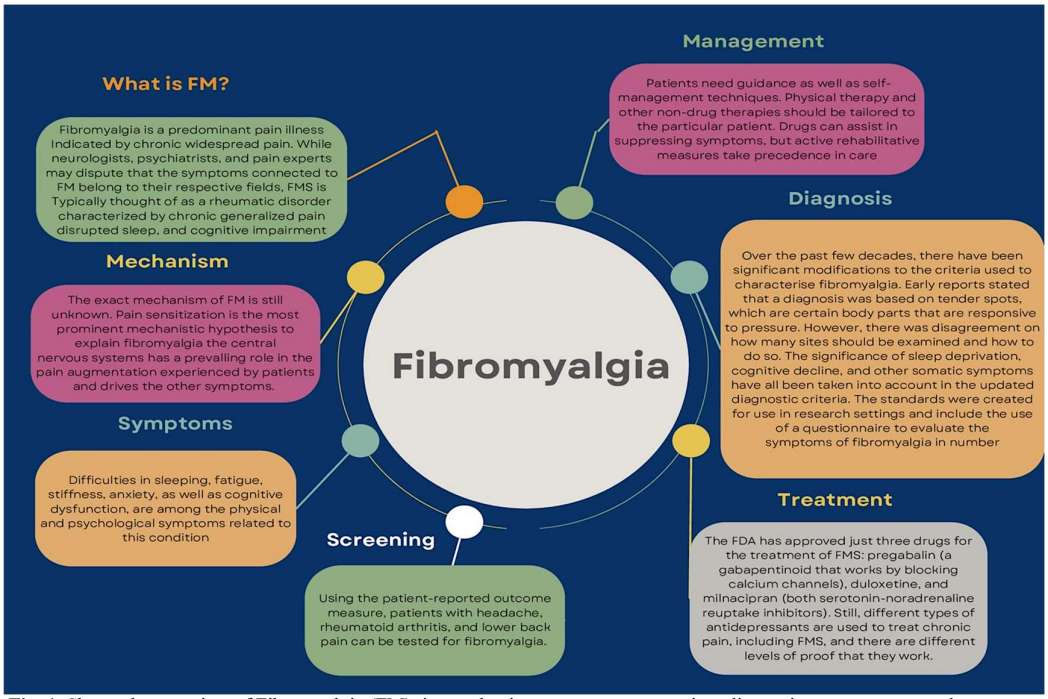

Fig. 1. Shows the overview of Fibromyalgia (FM): its mechanism, symptoms, screening, diagnosis, management, and treatment.