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International Physical Medicine & Rehabilitation Journal

Review Article
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Fibromyalgia: recent concepts and treatments

Abstract

Fibromyalgia is a chronic pain syndrome characterized by widespread pain often accompanied by symptoms that compromise quality of life, such as fatigue, sleep disorders, cognitive dysfunction, mood disorders. The pathology affects millions of people around the world and is still often overlooked and misunderstood. Although its pathophysiology is not fully understood, it is believed that Central Sensitization plays a preponderant role in the genesis of the disease. In addition, several studies demonstrate genetic polymorphisms in genes related to pain syndromes, pain thresholds, psychological disorders, and others pathologies frequently associated with Fibromyalgia. Different diagnostics criteria have been proposed to define the disease, however, the 2010 ACR criteria revised in 2016 is considered the most suitable. Functional imaging exams were of great importance in determining the pathophysiological mechanisms and so, the therapeutic options. A variety of randomized controlled studies and systematic reviews demonstrated the therapeutic efficacy of pharmacological and non-pharmacological approach for Fibromyalgia. This article aims to provide a current view of Fibromyalgia concepts, from possible pathophysiological mechanisms to pharmacological and non-pharmacological therapeutics.

Keywords: fibromyalgia, central sensitization, nociplastic pain, serotonin–norepinephrine reuptake inhibitors, gabapentinoid, endocannabinoid system, cannabinoids

Volume 9 Issue 1 - 2024

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Received: December 26, 2023 | **Published:** January 30, 2024

Abbreviations: FM, fibromyalgia; CS, central sensitization; IASP, international association for the study of pain; NoP, nociplastic pain; WPI, widespread pain index; SSS, symptoms severity score; SNRIs, serotonin–norepinephrine reuptake inhibitors; GB, gabapentinoid; ECS, endocannabinoid system; CN, cannabis; CBs, cannabinoids

Introduction

Fibromyalgia (FM) pathogenesis is not fully elucidated but Central sensitization (CS) is the most accepted theory as the main pathophysiological mechanism, generally referred to joint stiffness, chronic pain at multiple tender points, and systemic symptoms including cognitive dysfunction, sleep disturbances, anxiety, fatigue, and mental disorders episodes. CS is defined by The Internacional Association for the Study of Pain (IASP) as an increased responsiveness of nociceptive neurons in the central nervous system to normal or subthreshold afferent input (IASP 2018). CS is referred to a new mechanistic pain descriptor, the Nociplastic Pain (NoP). The term NoP was introduced by IASP as a third pain term to complement the terms nociceptive pain and neuropathic pain. NoP is defined as a pain that arises from altered nociception with sensitization as the major underlying mechanism.[1] Central sensitization is one of the major underlying mechanisms of NoP, but they are not synonyms. NoP is a pain phenotype associated with many features of central sensitization.[2,3] FM patients frequently present other central chronic pain syndromes, such as myofascial pain syndrome, chronic migraine, temporomandibular disorder, irritable bowel syndrome, chemical hypersensitivity syndrome, that have CS as the primary pathophysiological mechanism.[4]

This enhanced response to sensation includes plasticity at a neuronal level, loss of glial cells homeostasis, and other complexes mechanisms.[5] Neuroimaging studies show evidence of changes in brain gray matter in pain processing regions, neurochemical imbalances, and altered resting brain-network connectivity between pronociceptive and antinociceptive brain areas.[6] Some studies show that there is a genetic predisposition in the FM pathophysiology. D'Agnelli et al. (2019), Buskila & Neumann (1997) and Arnold et al. (2013) observed a higher prevalence of this disease if there is a family history of FM than in the general population. These studies showed several genes polymorphisms related to different pain syndromes and altered pain thresholds and indications of single nucleotide polymorphisms related to susceptibility to FM. However, due to the fact that gene polymorphisms do not always account for gene expression, environmental factors are also considered important in the development of chronic pain.[7] These complex concepts regarding the definition of FM and its pathophysiology is undoubtedly extremely important for a better understanding of the disease and a more complete approach, leading to greater therapeutic efficacy and consequently a biopsychosocial reintegration of the patient.

Diagnosis

There have been continuous efforts to improve the diagnostic accuracy of FM over the past few decades. Despite the appearance of newer criteria for FM diagnosis, the 2016 ACR criteria demonstrate the best performance.[8] The American College of Rheumatology (ACR), concluded that for research and clinical practice purposes FM can be diagnosed following a series of clinical criteria. Their first publication was in 1990, but this one was replaced for the ACR criteria published in 2010/2011.[9] In 2016, based on a new revision, the ACR developed a new criterion based on Widespread Pain Index (WPI) and Symptoms Severity Score (SSS). This new criterion combines a physician and questionnaire criteria. The changes from the anterior ones allow this criterion to function as a diagnostic criteria, while still being useful for classification. Patient will be diagnosed with FM if he meets the following[10]:

I. WPI is 7 and SSS is 5, or WPI is between 3 to 6, and SSS is 9.

II. Chronic Pain is present for at least 3 months.

III. And not demonstrate any other disorder that could explain the pain.

Treatment

Due to the complexity of FM physiopathology, it is important a multidisciplinary approach to FM treatment. Both pharmacological and non-pharmacological interventions are necessary. Recent updates

in FM management offer additional options to alleviate symptoms and improve the quality of life for individuals with fibromyalgia. The FM patients' education is the first and a decisive approach for a better understanding of their illness and satisfactory adherence to treatment. Patients should be reassured that FM is a real and a complex disease not already completely understood but where a dysfunction in the brain perception of pain must be the main mechanism responsible for the disease. They must be made aware of the importance of an anti-inflammatory diet, good sleep hygiene, exercise, as well as adequate physical and medication therapy.[11] Treatment should combine non pharmacological and pharmacological treatments aiming the pain relief and the body and emotional rehabilitation.[12] Physicians should inform patients that FM is a chronic illness with no cure but, that and an individualized therapeutic approach, both non-pharmacological and pharmacological, can help the individual to regain control of his life and achieve significant improvement. With this objective, patients must be monitored regularly, both to feel more welcomed and to report doubts and possible adverse effects that may arise during treatment and make the necessary changes in the therapeutic approach.

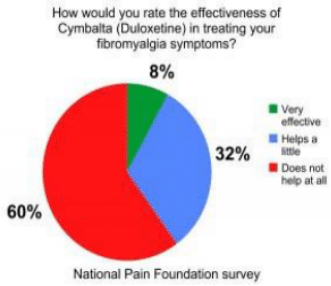
Non-pharmacological management

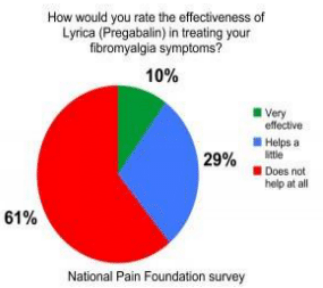
Non-pharmacological treatment aims to address the mental aspect of the disease with the development of self-management skills and identify the patients' difficulties and problems to help them better deal with these situations. In relation to the physical part, techniques to strengthen the body and reduce the pain are vital. The non pharmacological approach includes: Acupuncture, Physical Measures: Myofascial Release, Physiotherapy, Massage, Global Postural Re-education, Local Heat, Cognitive Behavioral Therapy, Meditation, Yoga, Physical activity, Stretches.[12]

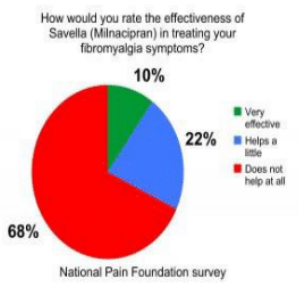
Pharmacological management

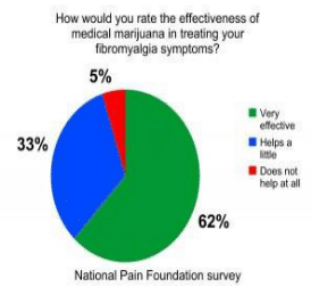
Pharmacological therapy must be individualized, following the principle of "Go low, go slow". Drugs should be started with low doses and increased slowly too. Some patients can't tolerate or can't respond to the drug. There is a predisposition to side effects due to the chemical hypersensitivity syndrome as comorbidity.[13] According to some studies, pharmacological therapy leads to 25% to 40% of pain reduction and 40% to 60% of the patients referee meaningful relief. Based on these data it is preferable the multimodal therapy with a combination of different drugs with different mechanisms of action that may be more tolerable and effective than monotherapy. At the moment, many drugs are used for FM symptoms management. Randomized controlled trials have shown a wide range of different medications for FM treatment, including antidepressants, opioids, nonsteroidal anti-inflammatory drugs, sedatives, muscle relaxants, and antiepileptic drugs. The USA Food and Drugs Administration (FDA) has approved only three drugs for FM therapy: duloxetine and milnacipran, antidepressants selective serotonine and norepinephrine reuptake inhibitors (SNRIs) and the anticonvulsant gabapentinoid pregabalin, based on the pathophysiological mechanisms.[14] Pregabalin acts in the subunit α2-δ of calcium channel decreasing neuronal hyperexcitability. The SNRIs produce central analgesia by acting on descending inhibitory nerve pathways.[8,15] Sumpton and Moulin found that the tricyclic antidepressant amitriptyline is effective in reducing FM-associated pain by ≥30%.[16]Amitriptyline also allowed improvement in fatigue, sleep, and quality of life.[17] More recently several publications demonstrate the effectiveness of cannabis in chronic pain and research reveals its effectiveness in the different symptoms present in fibromyalgia. There is a rising global trend of cannabis use in FM and evidences support cannabis use among FM patients.[18] Due to the complex action of the endocannabinoid system (ECS) in pain modulation, it is hypothesized that deficiency of endocannabinoids activity is among the underlying pathophysiology of FM.[19] Different studies show that cannabinoids reduce the sensitization of nociceptive sensory pathways in chronic pain states.[20] The endocannabinoid system is also involved in the modulation of other physiological functions, such as inflammation, endocrine function, cognition, memory, nausea, anti-nociception, and vomiting.[21]

Another article suggests that the action of cannabinoids in reducing stress and modulating cognitive and emotional functions is of great value for the patient's holistic recovery.[22]A longitudinal six-month study conducted on 367 FM patients taking medical cannabis, showed a significant decrease in the average intensity of pain, sleep disturbances, and symptoms associated with depression.[23] An online survey of over 1,300 FM patients conducted by the National Pain Foundation and National Pain Report published on May 30, 2022 showed surprising results[24]:









More than sixty percent of the patients considered medical cannabis more effective at treating symptoms of fibromyalgia than the others three drugs approved by the Food and Drug Administration to treat the disorder. 33% said it helped a little and 5% said it did not help.

Novel therapies to be considered for FM[25]

Non-pharmacological

I. CBT: can be effective in reducing pain, improving the quality of life, and decreasing depression and anxiety.

II. Mind-body therapies, such as yoga and tai chi, can be effective in reducing pain and improving physical function.

III. Provide patients education about fibromyalgia and its management to improve patient outcomes.

IV. Use a multi-modal approach to fibromyalgia treatment that combines different treatments for optimal outcomes.

V. Tailor treatment plans to individual patient needs for optimal outcomes [83-85]. Involve patients in the treatment decision-making process to improve treatment outcomes.

VI. Early intervention and regular monitoring of symptoms and treatment outcomes are important for optimal outcomes

Pharmacological

I. Mirogabalin, Lacosamide: anticonvulsants

II. Cannabinoids

III. Sodium oxybate: central nervous system depressant However, further long term studies with these emerging drugs are needed to prove their safety and effectiveness as a treatment for FM.

Conclusion

FM is a NoP due to an abnormal central processing that significantly impairs the quality of life and where pain is the disease itself. In spite of continuous efforts to improve the accuracy of FM diagnosis, the 2016 ACR criteria remain the most accurate. Despite many advances in FM therapy, thanks to neuroimaging and genetic studies, still there is considerable space for improvement in the treatment of FM. At present, the most effective strategy is to combine various treatment modalities to reduce symptoms and promote better functioning. Because FM is a heterogeneous disorder in terms of symptoms and severity, treatment plans should be individualized based on each patient's characteristics. So, treatment must be based on the pathophysiology, individualized and multidisciplinary. A holistic body–mind–soul therapy can provide a better and appropriate response. Despite FDA-approved three medications: Duloxetine, Milnacipran and Pregabalin like medicines whose efficacy has the greatest evidence in the literature for FM treatment, the limitation of efficacy on pain relief shows the necessity of new therapeutic options. Medical Cannabis has been used as an important therapeutic option in chronic pain treatment and, in particular, in the treatment of FM. Although there is a predominant use of cannabis-based medicines for NoP conditions, there is a necessity of solid evidences based on high-quality randomized studies. Besides this, more studies are needed to better elucidate the pathophysiology of the disease and new targets options.

Acknowledgments

None.

Conflicts of interest

Authors declare no conflicts of interests.

References

1. Kosek E, Cohen M, Baron R, et al. Do we need a third mechanistic descriptor for chronic pain states? *Pain.* 2016;157(7):1382–1386.
2. Nijs J, Malfliet A, Nishigami T. Nociplastic pain and central sensitization in patients with chronic pain conditions: a terminology update for clinicians. *Braz J Phys Ther*. 2023;27(3):100518.
3. International Association for the Study of Pain (IASP). *IASP Terminology*. 2019.
4. Mezhov V, Guymer E, Littlejohn G. Central sensitivity and fibromyalgia. *Intern Med J*. 2021;51(12):1990–1998.
5. Deitos A, Soldatelli MD, Dussán-Sarria JA, et al. Novel Insights of Effects of Pregabalin on Neural Mechanisms of Intracortical Disinhibition in Physiopathology of Fibromyalgia: An Explanatory, Randomized, DoubleBlind Crossover Study. *Front Hum Neurosci*. 2018;12:406.
6. Harte SE, Harris RE, Clauw DJ. The neurobiology of central sensitization. *J Appl Behav Res*. 2018;23:e12137.
7. Janssen LP, Medeiros LF, Souza A, et al. Fibromyalgia: A review of related polymorphisms and clinical relevance. *An Acad Bras Cienc*. 2021;93(Suppl 4):e20210618.
8. Kang J, Choi S, Park D, et al. Disentangling diagnosis and management of fibromyalgia. *J Rheum Dis*. 2022;29(1):4–13.
9. Wolfe F, Clauw DJ, Fitzcharles MA, et al. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR preliminar diagnostic criteria for fibromyalgia. *J Rheumatol*. 2011;38(6):1113–1122.
10. Wolfe F, Clauw DJ, Fitzcharles MA, et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. *Semin Arthritis Rheum*. 2016;46(3):319–329.
11. Bhargava J, Hurley JA. Fibromyalgia. *In: StatPearls [Internet]*. 2023.
12. Cohen-Biton L, Buskila D, Nissanholtz-Gannot R. Review of fibromyalgia (FM) syndrome treatments. *Int J Environ Res Public Health*. 2022;19(19):12106.
13. Fukuda K, Nisebaum R, Stewart G. The relationship between multiple chemical hypersensitivity and fibromyalgia scand. *J.Rheumatol*. 1999;26:364–367.
14. Maffei ME. Fibromyalgia: recent advances in diagnosis, classification, pharmacotherapy and alternative remedies. *Int J Mol Sci*. 2020;21(21):7877.
15. Oliveira Jr JO, Almeida MB. The current treatment of fibromyalgia. *Br J Pain*. 2018;1(3):255–262.
16. Sumpton JE, Moulin DE. Fibromyalgia. *Handb Clin Neurol.* 2014;119:513–527.
17. Konuk N, Ortancil O, Bostanci B, et al. A Comparison of Reboxetine and Amitryptilline in the Treatment of Fibromyalgia Syndrome with Co-Morbid Depressive Symptoms: An Open-Label Preliminary Study. *Klin. Psikofarmakol Bülteni-Bull Clin. Psychopharmacol.* 2010;20:29–37.
18. Berger AA, Keefe J, Winnick A, et al. Cannabis and Cannabidiol (CBD) for the Treatment of Fibromyalgia. *Best Pract Res Clin Anaesthesiol.* 2020;34(3):617–631.
19. Russo EB. Clinical Endocannabinoid Deficiency Reconsidered: Current Research Supports the Theory in Migraine, Fibromyalgia, Irritable Bowel, and Other Treatment-Resistant Syndromes. *Cannabis and Cannabinoid Research*. 2016;1(1):154–165.
20. Maldonado Rafael, Banos Josep E, Cabañero David. The endocannabinoid system and neuropathic pain. *PAIN*. 2016;157(Suppl 1):S23–S32.
21. Khurshid H, Qureshi IA, Jahan N, et al. A Systematic Review of Fibromyalgia and Recent Advancements in Treatment: Is Medicinal Cannabis a New Hope? *Cureus*. 2021;13(8):e17332.
22. Walitt B, Klose P, Fitzcharles MA, et al. Cannabinoids for fibromyalgia. *Cochrane Database Syst Rev.* 2016;7(7):CD011694.
23. Sagy I, Schleider LBL, Abu Shakra M, et al. Safety and Efficacy of Medical Cannabis in Fibromyalgia. *J Clin Med.* 2019;8(6):807.
24. *Marijuana Rated Most Effective for Treating Fibromyalgia*. NPStaff. 2022.
25. Ram Pothuri R, Madhan J, Naveen J, et al. Beyond the Pain: A Systematic Narrative Review of the Latest Advancements in Fibromyalgia Treatment. *Cureus*. 2023;15(10):e48032.