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Neuropsychiatric Factors Involved in the Development of Fibromyalgia: A Literature Review

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Abstract

Fibromyalgia is a complex neuropsychiatric disorder characterized by widespread musculoskeletal pain, tenderness, and fatigue. Its exact cause remains unknown, but genetic predisposition, physical or emotional trauma, and disturbances in pain processing are believed to play significant roles. The condition redominantly affects women and can occur at any age. Diagnosis is challenging due to the absence of specific tests, but criteria set by the American College of Rheumatology aid in identification. Management involves a combination of pharmacological and non-pharmacological approaches, with analgesics, antidepressants, and anticonvulsants used for pain relief. Non-pharmacological treatments include physical therapy, cognitive-behavioral therapy, and stress-reduction techniques. Neuropsychiatric factors, such as stress, trauma, depression, anxiety, and altered pain processing, play crucial roles in fibromyalgia's development and maintenance.

Understanding the interplay between these psychological factors and physiological mechanisms is vital for improved management. Neurobiological mechanisms involving the central nervous system, nociceptive processing, and neuroinflammation contribute to the persistent pain experienced by individuals with fibromyalgia. Psychosocial factors, including stress, childhood abuse, and coping strategies, also influence the severity of the condition. Assessment and diagnosis of fibromyalgia involves a comprehensive evaluation of pain, fatigue, cognitive symptoms, and other somatic manifestations. Treatment implications focus on symptom management using FDA-approved medications like milnacipran, pregabalin, and duloxetine. Non-pharmacological interventions, such as exercise, cognitive-behavioral therapy, acupuncture, and electrostimulation, also play essential roles in improving patients' quality of life. Future directions in fibromyalgia research include exploring novel therapies, understanding the neurobiological basis, and enhancing the effectiveness of existing treatments.

Introduction

Fibromyalgia is a chronic neuropsychiatric condition characterized by widespread musculoskeletal pain, tenderness, and fatigue. It is considered a complex disorder with no known cause and is often accompanied by various other symptoms such as sleep disturbances, cognitive difficulties, and mood disturbances [1]. The exact etiology remains unclear, but it is believed to involve a combination of genetic predisposition, physical or emotional

trauma, and disturbances in the central nervous system's pain processing [1,2]. Fibromyalgia predominantly affects women, with a female-to-male ratio of approximately 9:1. It typically occurs between 30 and 60. However, it can also affect individuals of any age, including children and older adults. The prevalence varies across populations, but it is estimated to affect around 2-4% of the general population worldwide [3].

The clinical presentation of fibromyalgia is characterized by widespread pain and tenderness in specific tender points. Patients may also experience chronic fatigue, sleep disturbances, headaches, irritable bowel syndrome, and cognitive issues, often called "fibro fog." Diagnosis can be challenging as there are no specific diagnostic tests available. Instead, the American College of Rheumatology has established specific criteria for diagnosing fibromyalgia, including assessing pain and symptoms across various body regions [4]. The management of fibromyalgia is multifaceted and includes both pharmacological and non-pharmacological approaches. Pain relief and symptom management are typically achieved through analgesics, antidepressants, and anticonvulsants [1,5]. Non-pharmacological treatments may involve physical therapy, cognitive-behavioral therapy (CBT), and stress-reduction techniques. Although fibromyalgia is considered a chronic condition, with appropriate management and lifestyle adjustments, many individuals can experience improvement in symptoms and function [3,5]. However, the prognosis can vary widely among patients, with some experiencing long-term symptom relief while others may face challenges in managing their symptoms. This narrative review aims to provide an overview of the neuropsychiatric factors related to fibromyalgia to improve the identification and management of this complex condition. By understanding the underlying physiological and psychological mechanisms involved in fibromyalgia, physicians can better tailor their approaches to treating and supporting patients with this often-debilitating disorder.

Neuropsychiatric Factors

Fibromyalgia is a complex and multifaceted condition with neuropsychiatric factors playing a crucial role in its development and maintenance. Psychological factors such as stress, trauma, depression, anxiety, and altered pain processing have been extensively studied in their association with fibromyalgia [1]. First, stress exacerbates fibromyalgia symptoms and may even trigger the onset. Chronic stress can lead to dysregulation of the body's stress response system, including the hypothalamic-pituitary-adrenal (HPA) axis, increasing inflammation and heightened pain sensitivity [2,6]. Studies have shown that individuals with fibromyalgia often experience higher levels of perceived stress, which can contribute to the persistence of pain and other symptoms. Secondly, physical and emotional trauma has also been linked to fibromyalgia. Experiencing physical injuries or accidents can initiate the development of fibromyalgia in some individuals.

Moreover, emotional trauma, such as childhood abuse or posttraumatic stress disorder (PTSD), has been associated with an increased risk of developing fibromyalgia. Traumatic experiences can alter the body's stress response and processing systems, contributing to chronic pain and other symptoms of fibromyalgia patients [7]. Depression and anxiety are commonly reported in individuals with fibromyalgia, and there is a bidirectional relationship between these mental health conditions and fibromyalgia symptoms. On the one hand, the chronic pain and fatigue associated with fibromyalgia can lead to depression and anxiety. On the other hand, pre-existing depression and anxiety may increase the risk of developing fibromyalgia or worsen its symptoms [7,8]. The interaction between these psychological factors and pain processing mechanisms in fibromyalgia is complex and can further contribute to the severity of the condition. Moreover, altered pain processing is a crucial feature of fibromyalgia. Research has shown that individuals with fibromyalgia have abnormalities in central pain processing, leading to an amplification of pain signals and a heightened sensitivity to pain stimuli.

This phenomenon, known as central sensitization, is thought to be influenced by both genetic factors and environmental factors, including psychological stress and trauma. Altered pain processing can perpetuate the cycle of pain and contribute to the chronic nature of fibromyalgia [9]. In overview, fibromyalgia is influenced by various neuropsychiatric factors. Stress, trauma, depression, anxiety, and altered pain processing all play significant roles in developing and maintaining fibromyalgia symptoms [1,9]. Understanding the interplay between these psychological factors and the physiological mechanisms involved in fibromyalgia is essential for improving the identification and management of this challenging condition.

Neurobiological Mechanisms

The underlying mechanisms for the continued pain in individuals with fibromyalgia are diverse, and there is a substantial amount of support related to the role of the CNS in nociceptive processing, potential peripheral nervous system changes, and cytokine involvement. The "non-pain" symptoms like fatigue, sleep, and mood disorders, which are extremely common in fibromyalgia, are more likely to be all caused by central rather than peripheral factors. Thus, significant clinical data suggest alterations in the central nervous system (alterations in the hypothalamic pituitary adrenal axis and stress response) [10]. Imaging studies in the early 2000s showed altered central neural processing in nociceptive pathways. A left shift in stimulus-response function in the experimental pain testing suggested that individuals with fibromyalgia have increased gain in brain pain-processing systems, leading to more neuronal activation, especially in the posterior insula and secondary somatosensory cortices [11-14].

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On the other hand, the increased rate of neuropathic findings, such as swelling and dysesthesia, could be explained by the release of inflammatory products such as neuropeptides, cytokines, and glutamate by neuro fiber C-nociceptors, a process called neuroinflammation [15,16]. The peripheral A-beta fibers are essential in a critical clinical feature, allodynia. These afferent fibers interact with receptors neurons in the spinal cord´s dorsal horn and link everyday movements, activities, and postures with fibromyalgia pain [17]. It is worth noting that peripheral nociceptive afferent fibers (C and A-beta fibers) may play a role in central sensitization [18]. Furthermore, individuals with greater muscle involvement, especially in type I fibers and hemoglobin oxygenation, present fatigue in a more significant proportion [16].

Psychosocial Factors

The pathophysiological causes of fibromyalgia (FM), a chronic disabling disease, are poorly understood and a topic of extensive research currently. FM is thought to be linked to a malfunction in how the brain processes pain. Patients typically develop increased pain sensitivity, which can also be psychological. The primary dysfunction in FM is in monoaminergic neurotransmission, which results in increased levels of glutamate and substance P and decreased levels of serotonin and norepinephrine at the descending antinociceptive pathways of the spinal cord. Dopamine imbalance and altered endogenous opioid activity in the cerebellum are other reported irregularities [19]. Numerous somatic symptoms, such as broad musculoskeletal discomfort, hyperalgesia, neuropathy, limb immobility, chronic fatigue, and headaches, define the illness. These events collectively appear to explain the pathophysiology of FM [19,20].

According to the diagnostic criteria, the prevalence of fibromyalgia is estimated to range from 0.4 to 9.3% globally [20]. The incidence of FM is more prominent in females than males due to increased anxiety and depression, reaction to pain, and hormonal factors associated with the menstrual cycle. Peripheral pain factors have also been identified as potential FM etiology. These patients display mood disorders, interstitial cystitis, chronic fatigue, cognitive impairment, and sleep abnormalities. Neuroendocrine factors, family history, peripheral abnormalities, oxidative damage, and environmental and behavioral alterations also seem to play a role in the pathophysiology of FM [19]. According to the most recent American College of Rheumatology guidelines, a diagnosis is made when there has been generalized broad pain for at least three months, and no other neurological conditions could account for the underlying symptoms. Fibromyalgia patients frequently struggle with mental health and cognitive functioning, like sleep and memory problems [20].

Research supports the notion that long-term exposure to environmental stressors causes the stress response to become accustomed to the body, which typically interferes with the HPA axis's ability to produce cortisol. Studies are divided on if fibromyalgia is caused by hypo- or hypercortisolism. However, it has been found that various stress-related disorders share similar dysregulation patterns. For instance, patients with functional neurological disorders, chronic fatigue syndrome, and post-traumatic stress disorder have dysregulated cortisol levels. On the other hand, people with depression and chronic pain have been found to have hyperactive HPA axis and elevated basal cortisol levels; higher levels of these hormones were linked to a history of more severe childhood abuse. Similar findings in fibromyalgia patients show a connection between stressful life experiences and long-term modifications in HPA axis functioning. Elevated cortisol levels upon awakening were associated with a history of childhood sexual and physical abuse [20].

It is known that we still do not have a specific cause of fibromyalgia. There is a set of factors that have been associated with worsening symptoms. Fibromyalgia, like many other diseases, can have a negative impact on the patient's social level. Due to all the symptoms the patient can present, they can see the effect of the disease on their social relationships, place of work, family relations, daily life, and mental health [21]. Moreover, patients already diagnosed with fibromyalgia are more susceptible to changes in their mood which can affect their daily life routine due to different causes like increased stress due to health issues already happening in their lives. It has been described that energy labels can be decreased where the patients feel pain, fatigue, and muscle weakness [21]. Here is where family support becomes one of the most critical factors in overcoming the difficulties that fibromyalgia causes in patients' lives. At the same time, it is essential to encourage the patients to continue with their regular lives as far as possible because it has been mentioned that those patients who assist in working have better outcomes than those who are not working due to increased symptoms.

In a study done at the University of Alabama, some coping strategies predict the level of disability that a patient with fibromyalgia will have [22]. Those mechanisms are coping attempts and catastrophizing. There are five coping attempts of five scales where the patient needs to reinterpret pain, ignore pain sensations, divert attention, and cope with self-statement accompanied by increased activity levels. It was found that coping attempts impact a higher physical level and lower rates of getting total disability. Instead, catastrophizing was related to a higher incidence of getting total disability due to the severity of the symptoms. Fibromyalgia treatment will require a significant commitment from the patients. It has been shown that those involved in support groups sharing knowledge about controlling the symptoms will have better control and fewer complications, improving their quality of life [23].

Assessment and Diagnosis

According to The American College of Rheumatology, the diagnostic criteria for fibromyalgia focus on assessing pain as

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well as fatigue, muscle weakness, cognitive symptoms such as challenges remembering things/memory disturbances, ability to concentrate, staying focused, depression, anxiety, insomnia, and many more somatic symptoms and additionally quantify their severity [3,24]. Based on the number of tender points the individual is experiencing, for the Fibromyalgia diagnosis to be met, there needs to be a painful response evoked and a complaint of generalized pain and overall symptoms for a minimum of 3 months. Furthermore, other fibromyalgia manifestations aside from pain must be experienced by the individual and explored by the rheumatologist for a comprehensive and complete diagnostic Fibromyalgia assessment and diagnosis [3,24].

This form, written by the ACR, is subdivided into two parts. Part one's focal point is pain; using a Widespread Pain Index (WPI), the patient identifies which areas of the 19 mentioned by the questionnaire did they feel pain. Followed by Part Two, which focuses more on overall symptoms and their severity. Foremost, the individual is asked to measure the intensity from 0 (No problem) up to 3 (severe, life-disturbing problems) of three common symptoms: fatigue, waking up unrefreshed and cognitive symptoms. This is followed by a second scale which refers to other symptoms experienced by these patients; the physician doing the assessment quantifies the number of somatic symptoms mentioned by the patient and matches the most appropriate score starting from 0 (No symptoms) to 3 (plenty of symptoms).

This scale consists of 40 symptoms (Muscle pain, Irritable bowel syndrome, fatigue/tiredness, thinking or memory problems, muscle weakness, headache, pain/cramps in abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud's, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, and bladder spasms). Lastly, the 2 scores, the one from Part One (WPI score) and Part Two (Symptoms severity scales added) are analyzed; if the WPI score is 7 or above and the Symptoms severity scales' score is 5 or above, then the patient meets the Fibromyalgia diagnostic criteria. The second and other option that meets the Fibromyalgia criteria is the WPI score range from 3-6, the Symptoms severity scales score of 9 or above, the patient experiencing symptoms for a minimum of three months, and no other medical explanation for their pain [3,24].

Another instrument commonly used to evaluate fibromyalgia and the overall impact it has evoked on an individual's life is known as the Fibromyalgia Impact Questionnaire (FIQ) [25,26]. FIQ measures and evaluates symptoms, function, and the overall impact this condition has had on the patient. The revised FIQ (FIQR) tool is the most updated and current version, but physicians and healthcare professionals use both. The FIQR questionnaire is subdivided into the three domains mentioned previously, and using a scale from 0-10, the individual chooses which number best describes their current status based on the question being asked.

The first domain asks questions regarding their day-to-day function, including the difficulty of brushing or combing their hair, continuously walking for 20 minutes, climbing a flight of stairs, and having the ability to sit in a chair for 45 minutes. The second domain examines the overall effect on the individual's life, such as their weekly goals, the effect the symptoms have had on their life, and how overwhelmed the patient felt. Lastly, the third domain's focal point is rating the level of intensity of the most prevalent symptoms within this condition in the past week. These symptoms include pain, energy, stiffness, sleep, depression, memory disturbances, anxiety, tender points, balance and hearing, vision, smell, and cold sensitivities [26].

The total sum of all the scores is calculated by dividing Domain One by three; Domain Two remains unchanged, and Domain Three is divided by 2; then, add the three final numbers together, which will be the total score [26]. The final total FIQR scores have notably and significantly remained similar to the preceding FIQ scores. Ultimately, the diagnosis of fibromyalgia can be obtained once all other medical explanations are excluded. These require a thorough inspection of the individual's medical history, blood tests, urinalysis, autoantibody tests(to rule out any autoimmune diseases or comorbid conditions), physical examination focused on musculoskeletal and neurological tests, and referral to the appropriate specialists [27].

Treatment Implications

Fibromyalgia (FM) is difficult to treat due to its chronic nature and inadequate comprehension of its etiology and pathophysiology [28,29]. The current treatments aim to improve symptoms and quality of life. Even though numerous treatments are available, they provide inadequate relief for many FM patients [28]. There is no gold standard treatment for fibromyalgia syndrome (FMS). The current therapies generally address symptoms, with few studies attempting to address the underlying cause. For effective long-term treatment of FMS, a multidisciplinary team approach encompassing pharmaceutical interventions, lifestyle changes, and other complementary techniques is required, and the treatment must be individualized [29,30]. Despite the individualization of therapy, many FM patients seldom achieve complete remission; pharmacological agents reduce pain by 25% to 40%, just 40% to 60% of patients experience substantial alleviation, and only 25% of these patients find sustained symptom relief [29,31].

Over the years, FDA has approved a few medications for the treatment of fibromyalgia, and some of these medications have shown breakthroughs in these patients. Some of the drugs approved by the FDA for FM include serotonin-norepinephrine reuptake inhibitors (SNRI) (milnacipran, duloxetine, and venlafaxine) and gabapentinoid (pregabalin). There are numerous

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other pharmacological and nonpharmacological FM treatments, some of which are still under investigation [32]. Milnacipram (savella), an SNRI, is approved by FDA as a first-line treatment for FM for pain reduction and improvement in FM syndrome and physical activity [31-34]. Milnacipram is not approved for patients younger than 18 years. Although milnacipran's mechanism of action is similar to that of antidepressants, it is not utilized to treat depression or other mental illnesses [35]. It can worsen the risk of suicide and depression. It can lead to a life-threatening condition known as serotonin syndrome if taken with monamine oxidase inhibitors, linezolid, or methylene blue [31-34]. Milnacipram is effective in managing pain and fatigue in FM patients, with the therapeutic benefit of enhancing pain alleviation by 30% or more but not over 50% [32].

This medication class blocks the reuptake of serotonin and noradrenaline, two essential neurotransmitters in the brain. Additionally, a meta-analysis of duloxetine and milnacipran found that they reduced pain significantly and improved patients' perceptions of pain relief [31-34]. Tricyclic antidepressants (TCAs) such as amitriptyline and mirtazapine have been used to treat FMS [30,32,34]. However, amitriptyline is the preferred TCA for the management of FM. It has been shown to reduce general discomfort, increase sleep, and improve overall quality of life in FM patients [32]. The gabapentinoid, pregabalin, has been approved by FDA for chronic pain management in FM patients. Gabapentin, even though not approved for FM pain, has been used off-label for the treatment of FM patients. Pregabalin is an analog of gamma-aminobutyric acid and an alpha2delta (α2δ) calcium channel ligand in the central nervous system (CNS) [31-34]. A meta-analysis of randomized controlled trials evaluating the effects of gabapentin and pregabalin on FM patients revealed substantial evidence that the gabapentinoids effectively reduced pain, improved sleep quality, enhanced overall health, and enhanced quality of life [31-33]. Other pharmacological agents for treating fibromyalgia include naltrexone, terguride, certain opioids, vitamins, and antioxidants.

Naltrexone, an antagonist of opioid receptors and an inhibitor of the descending pain pathway, has demonstrated beneficial effects on FM-related pain and depression. Naltrexone also has an anti-inflammatory effect by inhibiting the activation of microglia cells and, consequently, reducing neuroinflammatory processes. Tramadol, an opioid and SNRI, and other weak opioids and analgesics such as acetaminophen have been used to manage fibromyalgia pain [33,35]. Papaver somniferum, a medicinal plant, and a natural opioid, is widely used for FM pain [33]. Tramadol may be helpful in the management of FM, but studies have shown that the use of opioids in the management of FM is not effective, and its use has been discouraged [34]. But it can be used in most extreme cases of FM and for a short term. One study found that using opioids in conjunction with caffeine decreased symptom severity and pain in FM patients, and the same result was not observed in non-opioid users, showing that caffeine can be used as adjuvant therapy in FM treatment [31,35]. Terguride, a dopamine receptor antagonist (DRA), has shown modest benefit in FM patients with spinal stenosis; nevertheless, DRAs are not FDA-approved and are ineffective in FM patients without spinal stenosis [32,36].

Antioxidants from extra virgin olive oil containing natural polyphenols have shown some benefit in managing FM [33]. Additionally, antioxidants from CoQ10, vitamins A, C, D, and E, have improved FMS symptoms in some patients [33,37]. Due to the effects of selenium on GABAergic neurons, parvalbumin- (PV-) interneurons, selenium replete in FM patients can alleviate clinical symptoms and enhance the quality of life [33,38,39]. Cannabinoids and cannabis are an emergent treatment option for FMS. Studies have demonstrated that these agents have minimal adverse effects, can alleviate the debilitating symptoms of FMS, and can be used when all other therapy options have been explored [32,40]. Furthermore, some FMS patients respond to the glutamate receptor antagonist N-Methyl-D-aspartate; nevertheless, these medicines are not well tolerated and rarely utilized [34]. Few studies have indicated some benefits to combination medication for pain reduction in FM patients compared to monotherapy. Amitriptyline with fluoxetine, amitriptyline and melatonin, and duloxetine and pregabalin are examples of such combinations [41].

Additionally, nonpharmacological therapies, such as physical therapy, acupuncture, and electrostimulation, have attracted substantial attention recently as alternate therapeutic options with minimal or no harmful effects for FM patients [30,32,33,42]. There is moderate to strong evidence that physical therapies such as aquatic therapy, stretching, resistance, and aerobic exercises enhance the quality of life in FM patients [30,32,33,42]. Electroacupuncture and transcutaneous electric nerve stimulation (TENS) are two forms of electrostimulations studied for FM [28,31]. TENS was ineffective in the treatment of FM. Nonetheless, there is moderate evidence that electroacupuncture improves pain relief in FM patients but does not affect their quality of life or fatigue [28,30]. Regardless of the patient's treatment plan, education, patient support, physical therapy, nutrition, and exercise must be incorporated to enhance the quality of life [32].

Other therapies evaluated for FM treatment include cognitive behavioral therapies such as mindfulness-based stress reduction. Mindfulness-based stress reduction (MBSR) was associated with sustained improvements in pain, anxiety, depression, and coping skills during a 3-year observational follow-up [43]. A systematic review and meta-analysis of acceptance- and mindfulness-based interventions for patients with chronic pain states revealed positive long-term effects on pain, depression, anxiety, and overall health-related quality of life [44,45]. Comparing female patients with FM to controls, the same studies demonstrated modest to moderately uncertain effects on pain, depression, anxiety, sleep quality, health-related quality of life, and mindfulness [44,45].

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Future Directions

Fibromyalgia affects the nervous system as well as our musculoskeletal structure. Among the psychological symptoms, it is very common for the patient to have memory problems, depression, anxiety, or sleep disorders. All patients with chronic pain, whether from fibromyalgia or not, are more likely to develop psychiatric disorders, particularly depression and anxiety [46]. Fibromyalgia patients should be systematically assessed for psychiatric comorbidity by a skilled clinician [47]. A multidisciplinary therapeutic approach would favor the patients' quality of life and disease course [48]. The approach of those patients is based on the combination of pharmacologic and alternative therapy, including thermal, light, electro-stimulatory, and body exercise treatments that could improve the quality of life and reduce pain and other symptoms related to fibromyalgia. However, patients' ability to participate in alternative therapies is sometimes impeded by the level of pain fatigue, poor sleep, and cognitive dysfunction. These patients may need to be managed with medications before initiating nonpharmacologic therapies [49]. Pregabalin, duloxetine, and milnacipran are the only FDA-approved medications for managing fibromyalgia. Additional pharmacologic treatment should focus on symptoms of fatigue, insomnia (sleep quality), blues (depression and anxiety), and rigidity (stiffness).

Non-pharmacologic interventions are an essential part of treatment; without them, only limited improvement is possible. Effective interventions include exercise, cognitive behavioral therapy, and multidisciplinary approaches combining exercise, physical therapy, and education. Some physical therapy techniques, such as massage, myofascial release, ultrasound, or transcutaneous electrical stimulation (TENS) unit use, may provide temporary benefits [50]. Cognitive-Behavioral therapy has demonstrated positive effects on patients' ability to cope with the pain associated with fibromyalgia [51]. Aerobic exercise treatment benefits patients with fibromyalgia, resulting in improvements in the patient's well-being, physical functioning, and tenderness. Aerobic exercise has also been recommended as a treatment for depression. The energy expenditure needed to influence depression was 17.5 kcal/kg per week or approximately 30 minutes of moderately intensive physical activity, 3 to 5 days per week [49]. A physical therapy referral for stretching and strengthening exercises or pool therapy may help the patient get started. Slow, steady exercise increases are recommended and best tolerated [50].

Transcutaneous electrical nerve stimulation (TENS), a nonpharmacological treatment, is the delivery of pulsed electrical currents across the intact surface of the skin to stimulate peripheral nerves, principally for pain relief. TENS aims to stimulate low-threshold cutaneous afferents to inhibit onward transmission of nociceptive information in the spinal cord and brainstem and relieve pain [52]. Tai Chi is a traditional Chinese exercise that integrates body and mind. It includes breathing control, slow movements, mental relaxation, and meditation. Originating in martial arts, the principle of Tai Chi is the appropriate distribution of internal energy, termed "qi," throughout the body. With the harmony of "qi" flowing smoothly and powerfully within the body, people can cultivate physical and mental health. Advances in neural technology have also revealed the effects of Tai Chi on anatomical morphologies and neurological activities in the brain [53].

Finally, it has been found that pharmacological agents such as d-cycloserine—a partial NMDA (N-Methyl-D-Aspartate) receptor antagonist-can be effective in enhancing the extinction of aversive memories [54]. NYX-2925 ((2S,3R)-3-hydroxy-2-((R)-5-isobutyryl-1-oxo-2,5-diazaspirooctan-2-yl) butanamide) is a new NMDA receptor modulator which was shown to affect NMDA receptor synaptic plasticity. This finding led to the hypothesis that it would be effective in NMDA receptor-associated CNS disorders. NYX-2925 induces efficient analgesia in rat models of neuropathic pain. NYX-2925 was shown to be safe, well tolerated, and to cross the blood-brain barrier. These promising findings support further clinical development of the drug as an agent for treating chronic pain conditions, such as diabetic neuropathy and fibromyalgia [55]. Another promising agent is cannabinoids, which can effectively modulate extinction and might be further investigated in extinction training [56]. Since pain generally increases excitability, substances that decrease excitation (e.g., gabapentin or pregabalin) would also seem suited to serve as enhancers of extinction. To counteract the context specificity of extinction training, as many environments and behaviors as possible should be included. For the prevention of relapses, training with episodes of stress and pain is essential. In addition, cognitive and emotional aspects of pain need to be targeted [57].

Conclusion

This narrative review has provided a comprehensive overview of the neuropsychiatric factors associated with fibromyalgia, shedding light on the intricate interplay between psychological and physiological mechanisms in this complex condition. Stress, trauma, depression, anxiety, and altered pain processing have all emerged as significant contributors to the onset and perpetuation of fibromyalgia symptoms. The bidirectional relationship between psychological distress and fibromyalgia further highlights the importance of addressing mental health aspects in managing this condition. The evidence presented underscores the need for a holistic approach to fibromyalgia, considering the physical symptoms and the emotional and psychological well-being of patients. Healthcare providers should be vigilant in screening for and addressing potential psychological comorbidities, as they can significantly impact the overall quality of life and treatment outcomes for individuals with fibromyalgia.

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However, it is evident that the current understanding of the neuropsychiatric factors in fibromyalgia still needs to be improved, and more in-depth research is required. Further, more extensive prospective studies are essential to unravel the intricate complexities of fibromyalgia and its underlying mechanisms. A better comprehension of these factors can aid in developing targeted and personalized treatment strategies, potentially leading to improved outcomes and enhanced quality of life for patients. As the burden of fibromyalgia continues to affect a substantial portion of the population, continued efforts to explore the psychological and neurobiological aspects of the condition are warranted. By advancing our knowledge in this area, healthcare professionals can make significant strides in enhancing the identification, management, and overall care of individuals with fibromyalgia, ultimately striving towards a more effective and patient-centered approach to tackle this challenging and enigmatic disorder.

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