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Review

Exploring Adherence to Moderate to High-Intensity Exercises in Patients with Fibromyalgia: The Role of Physiological and Psychological Factors—A Narrative Literature Review

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Abstract: Fibromyalgia (FM) is a chronic condition characterized by widespread chronic pain, muscle tenderness, chronic fatigue, and sleep disturbances. Treatment of FM focuses on the management of symptoms, often using medications, cognitive behavioral therapy, or moderate-to-high-intensity exercises (MHIE). MHIE is highly recommended by the current guidelines from the American College of Sports Medicine and the American Heart Association for people with FM to decrease comorbidities due to sedentary lifestyles. MHIE has also been shown to improve FM symptoms in individuals who can tolerate MHIE. However, individuals with FM present with one of the poorest adherences to MHIE. Most individuals with FM report symptoms worsening at the beginning of an MHIE intervention program. Objectives: This literature review aims to estimate the adherence to MHIE using dropout and compliance rates in individuals with FM who participated in studies that applied MHIE as an intervention and to examine possible reasons for high dropout rates and low compliance with MHIE programs, including psychological and physiological factors. Understanding the scope of potential dropout and compliance rates to MHIE intervention and factors that impact MHIE adherence in people with FM may help researchers and clinicians better design clinical trial studies and develop tailored exercise interventions according to individual patient characteristics. Conclusion: FM is a multi-faceted syndrome that can vary significantly in its presentation from person to person due to the complex duality of psychological and physiological factors. Consequently, clinicians should consider both components when prescribing exercises to FM patients.

Keywords: fibromyalgia; chronic pain; exercise; inflammation

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1. Introduction

Fibromyalgia (FM) is a complex condition with symptoms that overlap with those of other diseases or syndromes [1]. The diagnosis of FM has always been a challenge for clinicians. Up to date, there are no laboratory tests or imaging modalities that can help identify FM. The diagnosis of FM primarily relies on clinical examination. Before 1980, FM was defined by a combination of symptoms such as local, regional, or widespread musculoskeletal pain with or without other symptoms. Most clinicians and researchers refer to FM as "psychogenic rheumatism" [2]. In 1990, the concept of FM was redefined and classified by the American College of Rheumatology (ACR) as a "rheumatic syndrome" of unknown origin, characterized by chronic widespread muscle pain and the presence of multiple tender points that mainly affect women [3]. However, due to the lack of a standard of diagnostic tools capable of measuring pain levels at the tender points, most clinicians could not precisely diagnose FM, and the diagnosis was mostly made at the clinician's discretion. Therefore, there was a need to redefine FM. In 2010, the ACR excluded the tender points as part of the FM diagnosis and included a count of pain location and the clinician's rating of the most discriminative symptoms [4].

FM is one of the leading causes of chronic widespread pain (CWP), which is the main symptom of FM, presented with generalized tender points (hyperalgesia) [5,6]. Other common associated symptoms are chronic fatigue, sleep disturbances, headaches, difficulties with memory and concentration, irritable bowel syndrome, and depression [3]. Some clinicians and researchers still argue that FM is not a distinct clinical condition but part of the spectrum of CWP [7] and deny the validity of the FM diagnosis. They argue that the pain described by the patients might be symptoms of other clinical and/or psychiatric disorders [8].

Clinical guidelines recommend that the treatment of FM should be composed of multidisciplinary approaches [9,10], including pharmacotherapy for the management of pain, depression, and anxiety, cognitive behavioral therapy that helps the patients cope with their symptoms, and moderate-to-high-intensity physical exercise (MHIE) to improve physical fitness and prevent deconditioning. MHIE is highly recommended by the current guidelines from the American College of Sports Medicine and the American Heart Association for people with FM to decrease comorbidities due to sedentary lifestyles. Several studies have reported positive results of MHIE on cardiorespiratory functions, levels of pain, and chronic fatigue [11–16], showing larger effect sizes when compared to pharmacotherapy [17]. However, FM patients present one of the lowest levels of exercise compliance in comparison to patients with other chronic diseases [18]. Future research to develop predictive models for adherence and compliance with MHIE in FM patients may help to address the issue of low adherence and compliance to exercise and ultimately improve outcomes. Other non-pharmacological interventions, such as mind-body interventions and dry needling, have presented promising results for symptom management [19–21]. Recent evidence indicates that a novel manual therapy may effectively improve FM symptoms [22]. However, further studies are needed to confirm its effectiveness.

In this narrative review, we will first provide an update on the review of the dropout rate and compliance with MHIE in patients with FM in past clinical trials. We will then focus our review on psychological factors or physiological factors that possibly contribute to exacerbating symptoms post-MHIE in patients with FM.

2. Search Strategy for the Dropout Estimation

The search was conducted on the following databases: PubMed, Google Scholar, and Web of Science, using the following keywords: fibromyalgia, moderate-to-high-intensity exercise, aerobic exercise, and randomized controlled trials. The selection of articles was limited to articles published in English within the last 20 years.

3. Adherence and Compliance in People with FM

There have been a number of Randomized Controlled Trials (RCTs) aimed at evaluating the effect of MHIE on people with FM [23–38] within the last 20 years. It is well known that regular, long-term MHIE programs can be beneficial to the well-being and functionality of individuals with FM. However, the issue of low exercise compliance and high dropout rates in the short or long term has been well documented. A comprehensive review of 46 studies investigating the effect of exercises on patients with FM showed that most well-designed RCTs reported low compliance and high dropout rates for MHIE [18]. Patients with FM often report that MHIE programs worsen their symptoms of pain and fatigue [39,40]. More studies are needed to investigate further the connection between individual patient characteristics and dropout from an exercise program.

This review examined the dropout rates of 13 RCTs published since 2002 that applied a type of MHIE to individuals with FM (Table 1). Altogether, the 13 studies recruited a total of 1110 participants with FM, and the dropout rates ranged from 5–34%. The lowest dropout (5%) was from a study where FM participants underwent a swimming program. This finding may be explained by a previous report that aquatic exercises may reduce the pain threshold by reducing the sensitivity of peripheral nerves due to hydrostatic pressure on the skin surface [41]. On the other hand, MHIE outside water generally presents with high dropout rates and low adherence levels.

Table 1. RCT studies on the MHIE effects and dropouts.

Author/Year	Intervention	Key Findings	Dropouts
Richards and Scott 2002 [28]	Aerobic exercise (n = 69) Relaxation and flexibility exercises (n = 67)	Aerobic exercise is effective for the management of FM symptoms. High dropout rates. Reasons include the initial increases in pain and stiffness immediately after exercise and patients believing that exercise worsens the condition.	Aerobic exercise: 12 Relaxation exercise: 12
Rooks et al., 2007 [27]	Aerobic exercise (n = 51) Strength training (n = 51) Educational (n = 50) ST-FSHC (n = 55)	Progressive walking, strength training, and stretching improve functional status and main symptoms in females with FM.	Aerobic training: 16 Strength training: 16 Educational: 23 ST-FSHC: 17
Bircan et al., 2008 [37]	Aerobic exercise (n = 13) Strengthening exercise (n = 13)	Both interventions were similar in improving pain, depression, and quality of life in FM patients.	Aerobic exercise: 2 Strengthening exercise: 2
Sanudo et al., 2010 [26]	Aerobic exercise (n = 22) Combined exercise (n = 21) Usual care (n = 21)	The exercise groups presented better FM symptom improvements when compared to the usual-care group.	Aerobic exercise: 4 Combined exercise: 4 Usual care: 1
Mannerkorpi et al., 2010 [31]	Nordic walking (n = 34) Low-intensive walking (n = 33)	The Nordic walking group presented better improvement in FIQ.	Nordic walking: 5 Low-intensive walking: 4
Sanudo et al., 2011 [25]	Aerobic, strength, and flexibility (n = 18) Routine care: (n = 20)	The combined exercise improved health status, quality of life, and depression.	Combined exercise: 3 Routine care: 1
Kayo et al., 2012 [30]	Walking (n = 30) Strengthening (n = 30) Conventional treatment (n = 30)	Walking and strengthening presented a better improvement in pain than medication or conventional treatment.	Walking: 7 Strengthening: 8 Medication or conventional treatment: 7
Hooten et al., 2012 [32]	Aerobic exercise (n = 36) Strengthening exercise(n = 36)	Aerobics and strengthening presented similar effects on improving pain.	Aerobic: 4 Strengthening: 2
Gavi et al., 2014 [33]	Strengthening exercise (n = 35) Stretching exercise (n = 31)	Both groups presented improvements in pain, functionality, depression, and quality of life.	Strengthening exercise: 5 Stretching exercise: 9
Duruturk et al., 2015 [36]	Balance exercise (n = 12) Aerobic exercise (n = 14)	Both groups presented equal improvements in pain and FIQ functionality.	Balance exercise: 4 Aerobic exercise: 3
Larsson et al., 2015 [29] Ericsson et al., 2016 [35]	Resistance exercise (n = 67) Relaxation exercise (n = 63)	Resistance exercise presented improvements in pain and fatigue.	Resistance exercise: 17 Relaxation exercise: 20
Fernandes 2016 [23]	Swimming (n = 39) Walking (n = 34)	Both groups presented improvements in pain, quality of life, and functional capacity.	Swimming: 2 Walking: 2

Table 1. *Cont.*

Author/Year	Intervention	Key Findings	Dropouts
Ernberf 2018 [24]	Resistance exercise (n = 67) Relaxation therapy (n = 58)	Plasma levels of proinflammatory cytokines were elevated in FM compared to healthy individuals. The intervention did not show improvement in the cytokine level.	Resistance exercise:18 Relaxation therapy: 15

Only a few studies reported reasons for participant dropout. Richards and Scott [28] enrolled 136 participants with FM who were randomly assigned into two groups (the Exercise group and the Relaxation group) and who underwent a 12-week exercise protocol. During this study, 24 participants dropped out, and only 53% attended over one-third of the exercise sessions. The participants who dropped out of this study and those who had low exercise attendance reported that their pain and stiffness significantly increased immediately after the exercise sessions. Some of them also believed that the exercises worsened their daily FM symptoms. Rooks et al. [27] randomized 207 participants with FM into four groups. Three groups received different types of MHIE, and one group received educational training that encouraged the participants to self-maintain MHIE daily. The authors reported an attrition rate of 31% for each group except for the educational group, which presented an attrition rate of 46%. They listed health problems as one of the causes responsible for most of the dropouts. However, they did not report whether the individuals who dropped out experienced any worsening of their symptoms due to the exercise.

The high dropout rates in trials reviewed here align well with a previous review study [18]. Jones et al. reviewed 46 studies that applied exercise interventions (low to high intensity) to patients with FM. Among the 3035 subjects involved in the reviewed 46 studies, 2888 had a diagnosis of FM, 135 had other chronic diseases, and 12 were healthy control subjects. The attrition rate in studies involving individuals with FM ranged from 0–67%, while it ranged from 0–48% in individuals with other chronic diseases and healthy controls. In addition, it was found that exercise programs with intensity within 50% of the maximum heart rate presented a lower dropout rate than those with higher intensity. Furthermore, programs that used low-intensity exercises such as qigong and tai chi presented the lowest dropout rate.

It is well known by clinicians and researchers in the field that patients with FM typically experience worsening or flaring up of symptoms immediately after MHIE. Over two decades ago, studies showed that FM patients experienced significantly higher exercise-induced pain than healthy individuals [42,43]. However, the underlying mechanisms of the altered response to MHIE experienced by patients with FM remain elusive. Identifying the underlying mechanisms of the exacerbating symptoms post-MHIE is important for developing strategies to increase MHIE adherence. This literature review discusses possible psychological and physiological factors for exacerbating symptoms post-MHIE in patients with FM.

4. Psychological Factors

FM is often associated with many mental disorder comorbidities, such as anxiety, posttraumatic stress disorder, bipolar disorder, and depression [44]. Previous reviews of FM and its concomitant comorbidities suggest that more than half of all FM patients exhibit depressive disorders within their lifetimes [44,45]. Due to the high association between FM and various psychological disorders, this section will seek to elucidate any relationship between FM's psychological comorbidities and low adherence to MHIE.

Several studies focused on a condition known as alexithymia, the lack of emotional awareness that commonly presents in patients with FM [46]. A review of studies assessing alexithymia and FM found that alexithymia prevalence is higher in FM patients than in patients with rheumatoid arthritis [47]. This finding suggests that alexithymia prevalence in FM depends not solely on localized pain but is perhaps more associated with psychological factors such as trauma [48]. People with alexithymia have difficulty identifying and describing feelings. This mentality can lead to increased affective pain but not sensory-motor pain [49]. In addition to an increased emotional reaction to pain, the lack of ability to describe feelings in many FM patients is also correlated to a lack of sleep quality, increased depression and anxiety, and fear of pain [50]. The avoidance or inability to process feelings and emotions may lead to increased attention to physical pain [51]. This assertion is supported by a meta-analysis of alexithymia and FM studies where, once anxiety was controlled, the association between alexithymia and pain intensity became non-significant [47]. Unfortunately, the current research only shows an association between alexithymia and FM; however, a causal relationship has not been established [47]. Alexithymia in patients with FM may better explain low adherence to MHIE. However, just like the causal relationship between alexithymia and FM, more research is needed to reveal any direct evidence.

Potentially increased fear of pain or fear-avoidance beliefs are often observed in patients with FM and may contribute to low adherence to MHIE. FM patients may have a reduced emotional modulation of pain that could present as fear [52]. Those findings proposed an extension of the central sensitization theory that has been widely accepted. Furthermore, patients with FM are likely to experience increased perceived exertion at work, which is correlated with fear and anxiety [53]. A few studies have suggested that the fear of pain post-exertion may be an important factor contributing to low adherence to exercise [54,55]. Turk et al. discovered that high-fear groups exhibited greater depressive mood and pain severity, along with lower treadmill performance [56]. Shillam et al. argued that the most distressing symptom in patients with FM is the fear that their symptoms are worsening, and a better understanding of patients' fear of symptom worsening may help guide future implementation of exercise in those individuals [55]. Nevertheless, previous reports suggest that progressive MHIE may decrease fear-avoidance beliefs and improve adherence to exercise [57]. However, direct evidence linking psychological factors and exercise-induced pain in FM patients is lacking in the literature. More research is needed to better understand whether any specific psychological factor(s) may directly contribute to exercise-induced pain in FM patients.

5. Physiological Factors

A better understanding of the physiological pain that these FM patients experience is essential to tailoring exercise programs. Below are the most plausible physiological systems that could be affected in patients with FM, which may explain some of the exacerbated pain symptoms and responses post-MHIE.

5.1. HPA Axis

The Hypothalamic-Pituitary-Adrenal (HPA) axis is one of the key players in the body's regulation and response to stress. The HPA axis is stimulated by physical and psychosocial stress, circadian rhythm, and food consumption. The hypothalamus secretes corticotropin-releasing hormone (CRH) in healthy individuals, leading to the release of cortisol from the adrenal gland. While cortisol is a stress hormone that directly impacts many structures within the body, the HPA axis assists in regulating homeostasis and helps the organism adapt to its changing environment [58].

Research in animal models has shown that experiences greatly influence the HPA axis's ability to adapt to stress and environmental changes in early development. Exposure to low to moderate levels of stress has been shown to improve the HPA axis' ability to manage stress and promote greater resilience in handling stress [59]. On the contrary, early exposure to high levels of stress or consistent stress has been shown to develop a hyperactive HPA axis, resulting in vulnerability to stress.

Research with human participants has shown that stressful events such as childhood abuse result in a hyperactive HPA axis and increased secretion of CRH, leading to heightened neuronal firing. With repeated exposure to high stress levels, CRH receptors in the anterior pituitary gland become down-regulated, resulting in depression and anxiety [60]. Interestingly, there are contradictory findings regarding hyper- and hypofunction of the HPA axis in patients with FM. Most data suggest that these patients have hypo-HPA axis function. However, the conflicting results may be due to differences in the patients studied, differences in testing methods, and differences in the stages of FM [58].

Elevated cortisol levels, commonly seen in patients with fibromyalgia [61], may contribute to fatigue and decreased motivation, making it harder for individuals to adhere to a regular exercise program. Additionally, individuals with fibromyalgia may be more susceptible to post-exercise malaise, which may be related to HPA axis dysregulation [62]. Despite these challenges, exercise interventions have been shown to be effective non-pharmacological interventions for people with FM and may help improve the dysregulated HPA axis over time [63].

5.2. Glial Cells

Glial cells are found in the brain and spinal cord. Their primary functions are maintaining homeostasis and promoting the immune response. At rest, glial cells monitor and scan the environment and become active when they are aware of abnormal environmental changes. Peripheral injury can result in phenotypic changes to nerve and glial cells, resulting in hyperexcitability and a secondary cascade of events leading to persistent pain [64]. Astrocytes are a type of glial cell involved in developing chronic pain and hypersensitivity after injury. Astrocytes use Glutamate Transporter 1 (GLT-1) to remove the neurotransmitter glutamate from the extracellular fluid. Injury to peripheral nerves down-regulates the GLT-1 receptor in the spinal dorsal horn, resulting in increased levels of glutamate in the synaptic cleft. Unbound glutamate binds with the present *N*-methyl-D-aspartate (NMDA) receptors, increasing excitatory signal transmission. In a study using human-induced glial-like cells from 14 patients with FM and 10 healthy individuals, Masahiro et al. [65] reported that the expression of tumor necrosis factor (TNF-α) at mRNA and protein levels significantly increased in ATP-stimulated glial-like cells in FM patients but not in healthy individuals. Furthermore, a moderate correlation was noted between ATP-induced upregulation of TNF-α expression and clinical outcomes of pain, depression, and anxiety. These data suggest that increased activation of glial cells in patients with FM results in a heightened level of excitatory sensory signaling. Human studies showed that MHIE stimulated the production of proinflammatory markers such as TNF-α [66], further stimulating the already overactivated glial cells in patients with FM, resulting in an exacerbated pain response post-MHIE.

5.3. Cytokines

Cytokines are a broad range of proteins that are essential to cell signaling. They bind to receptors and directly affect the behavior of their target cells. There is enormous data on cytokine concentration in patients with FM, yet results are inconsistent among past studies. The cytokines are linked to immune responses, pain, and hyperalgesia [67,68]. Patients with FM experience long-term central sensitization (CS) without any detectable nerve lesions or inflammation present. The CS presents as a pain amplification of neuronal signaling in the central nervous system [69]. This enhanced excitability results in spontaneously receptive fields to neural firing and neural plastic changes in large and small afferent sensory neurons [69,70]. The activation of NMDA receptors in the spinal dorsal horn also enhances dorsal horn sensory nerve responsiveness [71]. These and many other factors combine to create what is termed FM "sickness behaviors", including pain, allodynia, hyperalgesia, fatigue, insomnia, anxiety, and cognitive dysfunction [72].

Generally, proinflammatory cytokines interleukin-1 (IL-1), IL-6, IL-8, and TNF-α are associated with increased sickness behaviors [73]. Elevated IL-1 is associated with numerous FM-like symptoms; elevated IL-6 has been shown to induce cognitive deficiencies and depression, and elevated IL-6 and TNF-α have been shown to trigger pain and sleep disturbances [74,75]. Although contradictory data exists, a large body of evidence concludes that FM patients have elevated levels of proinflammatory cytokines IL-1, IL-6, IL-8, and TNF-α when compared with healthy controls. IL-10 is an anti-inflammatory cytokine released during physical exercise that modulates the effects of proinflammatory cytokines [76]. Studies using the Balke protocol [77] demonstrated that FM patients' IL-10 levels during exhaustive exercise are blunted compared with healthy controls [78,79], and IL-8 levels in both groups showed a dramatic drop during exhaustive exercise. IL-8 is a chemokine that plays an essential role in infiltrating neutrophils and increasing blood flow in the area. This acute effect on IL-8 following high-intensity exercise in FM patients is not yet understood.

A few other studies have investigated the effect of exercises on cytokine expression in patients with FM. Previous studies have reported that FM patients present a higher serum level of IL-8 at baselines when compared to healthy subjects [80,81]. Ortega et al. reported that their 8-month aquatic exercise program had a retention rate of 90% and generated significant decreases in the levels of proinflammatory cytokines IL-1β and IL-6 and an increase in the anti-inflammatory IL-10 level [82].

5.4. Neurotransmitters

Neurotransmitters are directly involved in the ascending and descending pain pathways. They can trigger the cascade of events sending sensory inputs from the periphery to the brain and can also trigger pain modulation signals from the brain to the periphery. Peripheral afferent neurons carry sensory input into the dorsal horn of the spinal cord, through which sensory input rises to reach the appropriate area of the brain. Descending signals of pain inhibition are sent from the periaqueductal gray area to the rostral ventromedial medulla and dorsolateral pontine structure in the spinal dorsal column [83]. The sensory afferent neuron's primary excitatory neurotransmitter released into the spinal dorsal horn is glutamate, which binds to NMDA and AMPA receptors to release substance P and neurokinins A and B [83].

Nearly all patients with FM suffer from sleep disturbances, resulting in light, restless, and unrefreshing sleep [84]. Serotonin is a neurotransmitter highly involved with pain perception and sleeping patterns [83]. For example, serotonin deficiency results in hyperalgesia and sleep disturbances [85,86] and elevated serum levels of substance P [87], which can also lead to neuron hypersensitivity as well as sleep disturbances. Changes in serotonin levels can impact mood, emotions, anxiety, fear, eating, sleep, sexual desires, and the feeling of pleasure [88]. Noradrenaline is another neurotransmitter that helps to regulate attentive and cognitive functioning [89]. A dysfunctional level of either serotonin or noradrenaline will likely impact both the ascending and descending pain pathways, resulting in motor, psychological, and pain symptoms [90].

6. Discussion and Conclusions

In this narrative literature review, we summarized the findings of past studies that examined the contribution of psychological and physiological factors to the exacerbation of symptoms post-MHIE in FM. The interplay between psychological and physiological factors in FM patients' symptoms and adherence to MHIE programs requires integrated interventions. Clinical practice should prioritize individualized exercise prescriptions, considering baseline age, physical fitness, pain, and stress levels. Behavioral interventions, such as graded exposure and goal setting, may mitigate exercise avoidance behaviors based on fear of symptom exacerbation. Healthcare providers should acknowledge FMs' complexity and consider psychological and physiological factors when prescribing MHIE. Holistic and patient-tailored approaches may significantly enhance the quality of life for FM patients, promoting better adherence to MHIE programs and symptom management.

There have been an increased number of investigations into the etiology of FM that report the psychological and/or physiological factors potentially involved in the FM symptom manifestation. The potential factors covered in this review, both psychological and physiological, may be directly related to symptom exacerbation post-MHIE, consequently impacting the capability of patients with FM to adhere to MHIE programs. In addition, individual patient characteristics should be taken into consideration when prescribing MHIE to patients with FM. The ability to deal with stress, pain, barriers to exercise, and disability were noted as the factors correlated with exercise maintenance in women with FM post-treatment [91]. The same group of researchers later examined adherence to an individualized 12-week home exercise program and had some interesting findings [92]. Participants with higher baseline physical fitness, older age, and higher baseline stress showed lower long-term adherence to the exercise program compared to other participants. A higher level of lower body pain at baseline was correlated with lower adherence to stretching exercise, and a higher level of upper body pain at baseline was correlated with reduced adherence to aerobic exercise. Lastly, it is important to note that the lockdown due to COVID-19 may not only affect the health status of people with FM [93]; however, it may also significantly affect the adherence to exercise interventions among FM patients. Lockdowns, social distancing, and health concerns disrupted their exercise routines, potentially worsening their symptoms.

Based on currently available research, we cannot solely blame either psychological or physiological factors for poor adherence to exercise programs in FM patients. FM is a multifaceted syndrome that can vary significantly in its symptom presentation from person to person due to complex physiological and psychological factors. We believe it is possible that physiological factors such as cortisol release can induce post-exercise pain in FM patients, which may increase the fear of symptom worsening and subsequently result in avoidance of exercise and low adherence to MHIE. Both physiological and psychological factors can combine to profoundly affect adherence to MHIE programs. Clinicians should consider all factors when prescribing exercises to FM patients. Future studies need to investigate the effect of interventions that take into account both psychological and physiological factors of FM and the underlying mechanisms involved in FM symptom exacerbation post-MHIE.

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