Review

Unravelling the relationship between anxiety, autonomic nervous system dysfunction and fibromyalgia: a systematic review

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ABSTRACT

Fibromyalgia (FM) is a chronic condition characterised by widespread musculoskeletal pain accompanied by various somatic and psychological debilitating symptoms. Dysfunction of the autonomic nervous system (ANS), as measured by heart rate variability (HRV), including reduced HRV at rest and dysfunctional HRV response patterns, has been consistently reported in patients with FM. Additionally, FM patients commonly exhibit elevated anxiety symptoms and comorbid anxiety disorders. This systematic review aimed to explore the potential relationship between elevated anxiety symptoms and reduced HRV in patients with FM.

Through a comprehensive analysis of the literature, the association between anxiety symptoms and HRV was investigated in FM patients under resting conditions and in response to various interventions. The results suggest that the association between reduced HRV and elevated anxiety symptoms in FM patients at rest is widely supported by most studies. Interventions focused on improving HRV, such as exercise, psychotherapy, and mind-body therapies, also appear to be effective in reducing symptoms of anxiety.

These findings suggest the presence of a possible common underlying mechanism contributing to the high comorbidity of ANS dysregulation and elevated anxiety symptoms in FM. The observed interconnection between anxiety and HRV highlights the need to develop targeted, multimodal interventions aimed at simultaneously reducing anxiety and improving HRV to enhance the overall quality of life for individuals affected by this complex condition. Collectively, this systematic review underscores the importance of recognising and addressing the intricate interplay between psychological and physiological factors in the management of FM.

Introduction

Fibromyalgia (FM) is a chronic syndrome characterised by widespread musculoskeletal pain, persistent fatigue, sleep disturbances, cognitive deficits, anxiety, depression and multiple somatic symptoms including muscle weakness, sleep disturbances and dysautonomia (*e.g.* fatigue, gastrointestinal issues) (1, 2). With a global mean prevalence of 2.7%, FM disproportionately affects females (3). Despite ongoing debates surrounding its aetiopathogenesis, diagnostic criteria, and classification, the pathophysiology remains elusive, lacking objective biomarkers for definitive diagnosis (2, 4). Consequently, the efficacy of treatment strategies is controversial (5).

Among the myriad of symptoms, anxiety has emerged as one of the most prevalent psychological manifestations, contributing significantly to the overall burden on FM patients. The comorbidity of anxiety disorders in FM is well-documented, with prevalence rates ranging from 13% to 63% (6). Notably, the salient connection between FM and anxiety lies in the involvement of the autonomic nervous system (ANS) (7). Concurrently, anxiety disorders are widely associated with excessive activation of the sympathetic nervous system (SNS), which plays a predominant role in the anxiety response (8-11). Anxiety can lead to hypervigilance and somatic tension which in turn may heighten pain awareness, intensifying

its perception and distress (12). Clinically, anxiety symptoms can adversely impact the course of FM, correlating with increased physical symptoms and greater pain intensity, exacerbating the syndrome's severity (13-15).

One accredited hypothesis posits FM as a central pain processing disorder, manifesting as heightened responses to painful stimuli (hyperalgesia) and painful responses to non-painful stimuli (allodynia) (16). Accumulating evidence implicates ANS dysregulation in FM (17, 18). The ANS, comprising SNS and parasympathetic (PNS) branches, regulates most bodily functions (*e.g.* digestion, respiration, cardiac activity) (19). Their interplay results in heart rate variability (HRV), a measure of interbeat interval variations, an index of SNS-PNS balance on heart rate modulation that indicates ANS adaptability in modulating cardiac function in response to environmental or emotional stimuli (20,21). Reduced HRV, reflecting diminished PNS modulation, is associated with compromised cardiac health and increased mortality risk (22).

In FM, ANS imbalance (increased SNS and decreased PNS at rest) have been reported (23, 24). The hyperactive SNS reaches a ceiling effect, limiting adaptability to stressors (25). Most importantly, reduced HRV have been associated with increased pain susceptibility and other common symptoms in FM patients (26). Despite FM being primarily characterised as a chronic pain condition, surprisingly few studies have examined the relationship between anxiety, HRV and pain in FM patients (7, 27-29). Pain assessment was inconsistently reported across these studies, and when present, the criteria and instruments used to evaluate pain varied significantly, hampering meaningful comparisons and conclusions.

ANS dysregulation may be key in understanding the relationship between FM and anxiety, potentially amplifying symptoms of both conditions. However, in patients with FM and comorbid anxiety disorders, HRV may be reduced due to several factors (30).

This framework theoretically explains the multisystemic manifestations of FM, including constant fatigue, morning stiffness, sleep disturbances and gastrointestinal irritability (24, 25). However, previous studies have reported conflicting findings regarding ANS function in FM (25). The underlying mechanisms contributing to this HRV reduction are complex and multifaceted. Chronic stress, inflammation and central nervous system dysregulation, all of which have been implicated in the pathophysiology of FM, can contribute to ANS imbalance (31, 32). Furthermore, the presence of anxiety disorders in FM patients may exacerbate this autonomic dysregulation (33). This vicious cycle of anxiety, ANS dysregulation, and heightened symptomatology can perpetuate and reinforce each other, leading to a further deterioration of overall health and well-being in patients with FM.

Considering the shared ANS dysregulation in FM and anxiety disorders, the primary objective of the present work is to systematically review and synthesise the current evidence to comprehensively examine the relationship between anxiety symptoms and HRV in patients with FM, thereby contributing an up-to-date overview of this topic. It is hypothesised that patients with FM will exhibit a significant increase in anxiety symptoms associated with a significant reduction in resting HRV and dysregulated HRV response, and that interventions aiming at improving ANS balance through HRV would be associated with a reduction in anxiety symptoms in patients with FM.

Materials and methods

Search strategies

A comprehensive systematic review of the international literature was conducted without imposing any time restrictions, utilising the PubMed, ScienceDirect and Scopus databases in November 2024, following PRISMA guidelines (34). The search strategy involved the use of specific terms combined with Boolean operators tailored to each database. The following keywords were searched within the titles and abstracts: 'fibromyalgia', 'heart rate variability' and 'anxiety'. The search yielded 17 results from PubMed, 40 from Scopus, and 6 articles from ScienceDirect, totalling 63 studies.

Eligibility criteria

The list of potential articles generated by the systematic search was screened for eligibility by considering full-text articles. Studies were selected for inclusion if they met the following criteria:

1. the study population comprised patients with fibromyalgia (FM);
2. an anxiety assessment measure and outcome comparison were included;
3. HRV measurement and outcome comparison were reported.

Articles that did not meet all three criteria were excluded. Full-text articles were retrieved for review when they exhibited potential inclusion criteria or when the abstract and title provided insufficient information to make a decision.

Results

Selection of studies

The initial database search identified a total of 63 results in November 2024. After manually removing 19 duplicates and excluding 18 articles (reviews, conference proceedings, and editorials), the remaining 26 articles underwent title and abstract screening. Subsequently, 9 irrelevant studies were excluded due to failure to meet the inclusion criteria. An additional screening process was performed by retrieving the full text of 17 articles. After full-text screening, 4 articles were excluded due to a lack of essential data (*e.g.* insufficient information to draw conclusions about anxiety levels in FM patients), while the remaining 13 articles that met the inclusion criteria were included in the systematic review. A detailed flow chart of the study selection process is presented in Figure 1.

Demographic characteristics of the sample

The selected studies were conducted between 2000 and 2023, including a total sample of 437 patients diagnosed with FM. Of these participants, 397 (91%) were female, 40 (9%) were male. Among the 13 selected studies, 9 studies adopted a sample comprising exclusively female participants (7, 17, 27-29, 35-38), 3 studies included both female and male participants (39-41), and a single study focused on an exclu-

sively male sample (42). The average age of the participants was 55.2 years, ranging from 40 (37) to 78 (38). The selected studies were conducted in Europe (n=5), Israel (n=2), USA (n=2), America (n=3), and India (n=1).

Organisation of the studies

The article selection process allowed for the identification of two distinct groups of articles to further analyse the variables anxiety and HRV and their potential correlation in FM. The first group encompassed observational cross-sectional studies investigating anxiety symptoms and HRV in FM under baseline conditions, where researchers observed and recorded variables of interest without making any modifications or controlled interventions. The second group included studies investigating the effects of an experimental manipulation (*e.g.* intervention providing physical exercise training; pharmacological treatment; electroacupuncture and Cognitive Behavioural Therapy) on anxiety symptoms and HRV in patients with FM. The main characteristics extracted from the studies, including author, title, year, research design, sample characteristics, primary objectives, methods of measuring anxiety and HRV, FM diagnosis criteria and relevant results, are summarised in Table I.

Cross-sectional studies investigating the relationship between anxiety and HRV in patients with FM

In all five cross-sectional studies, the diagnosis of FM was established based on the 1990 American College of Rheumatology (ACR) criteria, which require the presence of chronic widespread pain for more than 3 months and the existence of at least 11 out of 18 possible tender points distributed across various body regions (43). All studies compared FM patients to healthy control groups, except for one study by Mostoufi *et al.* (40), which compared FM patients with patients affected by other forms of benign chronic pain.

Anxiety levels were assessed using various instruments. One study (17) utilised the anxiety subscale of the Symptom Checklist-90 (SCL-90) and the Arthritis Impact Measurement Scale (AIMS). Two studies (39, 42) employed the Hamilton Anxiety Rating Scale (HAM-A), one used also the Beck Anxiety Inventory (BAI). The remaining two studies used the Pain Anxiety Symptoms Scale-Short Form (PASS-20) (40) and the Depression Anxiety Stress Scale (DASS) (41). In all cases, test scores highlighted significantly elevated anxiety levels among FM patients.

HRV was measured, through electrocardiogram (ECG) recordings ranging from 5 to 20 minutes at rest. HRV indexes were extracted from ECG analysis considering time-domain analyses, frequency-domain analyses, or both. Specifically, two studies (17, 42) applied frequency-domain HRV analysis, reporting a significant reduced HRV in FM patients compared to healthy controls, with significantly higher low frequency (LF) and lower high frequency (HF) components. Additionally, a significant correlation was found between anxiety levels and some HRV indexes (*i.e.* LF%, HF%, LF/HF ratio) (17).

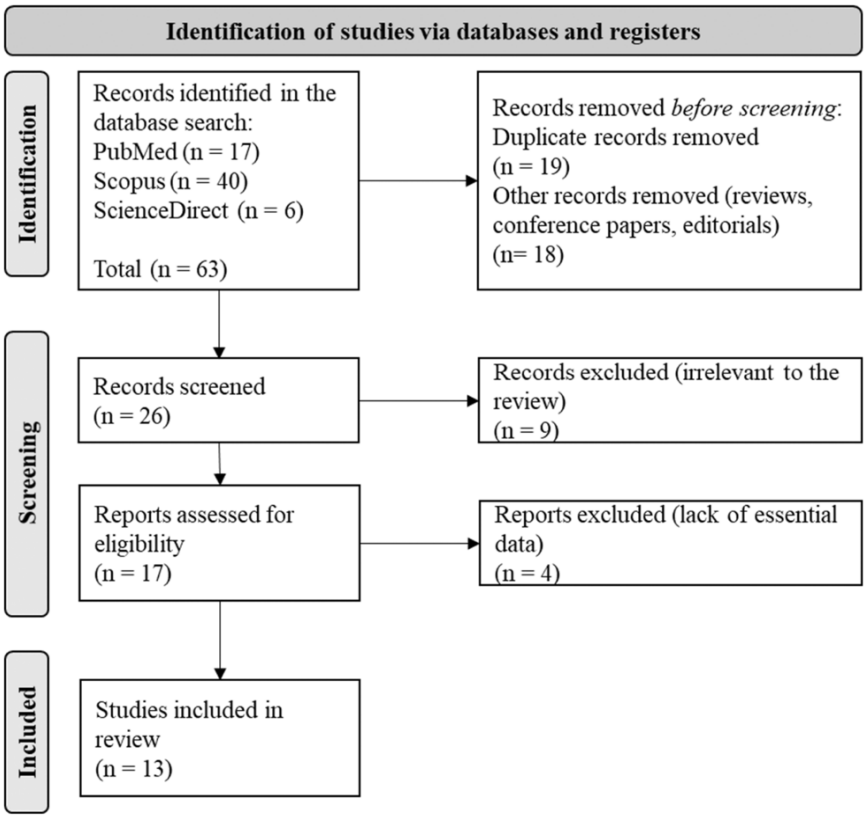

Fig. 1. PRISMA flow diagram illustrating the study selection process.

Two studies (40, 41) employed both time- and frequency-domain analyses. Rost *et al.* (41) detected a reduction in HRV, with significantly lower root mean square of successive differences (RMSSD) and percentage of successive normal sinus RR intervals more than 50 ms (pNN50) in FM patients compared to healthy controls. Mostoufi *et al.* (40) found that increased pain-related anxiety correlated with an increase in the LF band. Finally, Bilgin *et al.* (39) conducted a time-frequency analysis of HRV, highlighting correlations between anxiety test scores (BAI and HAM-A) and specific HF sub-bands (in the range of 0.15 Hz to 0.40 Hz and of 0.15 Hz to 0.29 Hz) with predictive accuracy superior to 90%.

Studies investigating the effects of an experimental manipulation on anxiety and HRV in patients with FM

In all eight studies investigating the effects of an experimental manipulation, the diagnosis of FM was made considering the 1990 ACR criteria, with the exception of the studies by Díaz-Toral

Table I. Cross-sectional studies investigating the relationship between anxiety and HRV in patients with FM.

N.	Ref	Authors	Title	Research design	Sample	Mean age n ± SD	Objective	Methods	Results
1	(17)	Cohen *et al*. (2000)	Autonomic dysfunction in patients with fibromyalgia: application of power spectral analysis of heart rate variability	Observational case-control study	n=44 (F) Patients with FM (n=22) *vs*. healthy controls (=22)	47.0±7.1	Study the association between power spectrum measures of HRV, measures of painfulness, FM symptoms, physical function, psychological well-being, and quality of life	Anxiety: SCL-90; AIMS HRV (frequency domain) from 20' ECG - Holter in supine position at rest; FM: ACR 1990	Patients with FM show higher anxiety levels, lower HRV, higher LF, lower HF power and correlations between LF%, HF%, LF/HF ratio and anxiety symptoms.
2	(42)	Cohen *et al*. (2001)	Abnormal sympathovagal balance in men with fibromyalgia	Observational case-control study	n=38 (M) Patients with FM (n=19) *vs*. healthy controls (n=19)	45.8±7.1	Study the pathogenesis of orthostatic intolerance. Through power spectral analysis of HRV in postural change in men with FM.	Anxiety: HAM-A HRV (frequency domain): ECG recording - Holter in supine position at rest (20') and standing position (20'). FM: ACR 1990	Men with FM had higher anxiety symptoms, lower HRV in all postural phases, higher LF and lower HF power in supine position.
3	(40)	Mostoufi *et al*. (2012)	Health and distress predictors of heart rate variability in fibromyalgia and other forms of chronic pain	Observational case-control study	n=84 F:M=23:3 Patients with FM (n=26) *vs*. patients with benign chronic pain (n=58)	52.0±12	Examine ANS dysfunctions, health and psychological impairment, in patients with FM and with other forms of benign chronic pain.	Anxiety: PASS-20 HRV (time and frequency domain): cardiac pulse sensor for 10' sitting at rest. FM: ACR 1990	No significant differences in HRV indices or anxiety between the two groups.
4	(39)	Bilgin *et al*. (2015)	Investigation of the relationship between anxiety and heart rate variability in fibromyalgia: A new quantitative approach to evaluate anxiety level in fibromyalgia syndrome.	Observational case-control study	n=90 F:M=54:2 Patients with FM (n = 56) vs healthy controls (n = 34)	46.0±11	Study the association between anxiety symptoms and HRV indexes in patients with FM.	Anxiety: BAI; HAM-A HRV (time-frequency analysis): 20' ECG recording in supine position, sitting and while swallowing FM: ACR 1990	Combined analysis of LF and HF power spectrum sub-bands predicted anxiety symptoms with overall accuracy above 90%.
5	(41)	Rost *et al*. (2017)	Generalised hypervigilance in fibromyalgia: normal interoceptive, but reduced self-regulatory capacity	Observational case-control study	n=92 F:M=39:16 Patients with FM (n=47) *vs*. healthy controls (n=45)	45.5	Replicate previous findings on reduced HRV in patients with FM compared to healthy controls and study the predictive value of self-regulatory ability.	Anxiety: DASS HRV (time and frequency domain): Polar watch 5' recording sitting at rest. FM: ACR 1990	Patients with FM showed higher anxiety symptoms and lower HRV (*i.e*., RMSSD and pNN50) than healthy controls.
Studies investigating the effects of an experimental manipulation on anxiety and HRV in patients with FM									
6	(29)	Schmidt *et al*. (2012)	Psychological and physiological correlates of a brief intervention to enhance self-regulation in patients with fibromyalgia	Interventional pilot study: short, focused breathing technique	n=20 (F) Same group pre- and post-treatment	40.8±13.7	Test the effects of a short, focused breathing training to improve HRV on reactivity to a standard laboratory stressor (cold pressor test), anxiety and depressive symptoms, self-efficacy, fatigue, sleep quality, and pain.	Anxiety: STAI HRV (time and frequency domain): 15' ECG recordings. FM: ACR 1990	After the short, focused breathing training patients with FM showed an increase in total HRV power and a reduction in anxiety symptoms.
7	(37)	Kulshreshtha *et al*. (2012)	Effect of low-dose amitriptyline on autonomic functions and peripheral blood flow in fibromyalgia: a pilot study	Interventional pilot study: treatment with amitriptyline	n=21 (F) same group pre and post treatment	40.0	Observe the effects of low-dose amitriptyline (10mg) on ANS function and peripheral blood flow in patients with FM.	Anxiety: STAI HRV (time and frequency domain): 5' ECG supine recording. FM: ACR 1990	From pre- to post-intervention HRV did not change, anxiety and clinical symptoms scores decreased significantly at post-intervention.
8	(36)	Gavi *et al*. (2014)	Strengthening exercises improve symptoms and quality of life but do not change autonomic modulation in fibromyalgia: a randomised clinical trial	Randomised controlled trial (RCT): Reinforcement exercises	n=80 (F) Patients with FM randomised into the strengthening (STRE; start n=40, end n=35) and flexibility (FLEX; start n = 40, end n = 31).	46.0±8.5	Investigate the long-term effects of strengthening exercises on ANS modulation, pain perception, and quality of life in patients with FM.	Anxiety: IDATE-TRATE; IDATE-STATE HRV (time and frequency domain): 10' ECG recordings in supine position. FM: ACR 1990	From pre- to post-intervention HRV did not change in the 2 groups. Patients in the FLEX group showed improvement in anxiety symptoms.
9	(28)	Sañudo *et al*. (2015)	Vagal modulation and symptomatology following a 6-month aerobic exercise program for women with fibromyalgia	Randomised controlled trial (RCT): Aerobic exercise	N=32 (F) Patients with FM randomised into aerobic exercise (AE; start n=16, end n=16) *vs*. control group (start n=16, end n=12) no exercise	58.0±2.0	Examine the effect of a 6-month aerobic exercise program on HRV parameters and symptom severity in women with FM.	Anxiety: VAS scale HRV (time and frequency domain): 10' ECG supine at rest recording. FM: ACR 1990	After AE a significant increase in HRV (HF) and reduction in anxiety symptoms emerged compared to control.

N.	Ref	Authors	Title	Research design	Sample	Mean age n ± SD	Objective	Methods	Results
Studies investigating the effects of an experimental manipulation on anxiety and HRV in patients with FM									
10	(35)	Díaz-Toral *et al*. (2017)	Impact of electroacupuncture treatment on quality of life and heart rate variability in fibromyalgia patients	Interventional study: Electroacupuncture	n=20 (F) Same group pre- and post-treatment	47.0±10.8	Compare health-related quality of life and ANS function in patients with FM, before and after 10 sessions of electroacupuncture treatment.	Anxiety: FIQ; SF-36 HRV (frequency domain): 5' ECG supine at rest recording. FM: ACR 2010	After electroacupuncture significant increases in LF, LF/HF, decreases in HF; improvement of anxiety
11	(27)	Prados *et al*. (2022)	Effect of cognitive-behavioural therapy on nocturnal autonomic activity in patients with fibromyalgia: a preliminary study.	Randomised controlled trial (RCT): Cognitive-behavioural therapy	n=25 (F) Patients in CBT-P group (n=12) *vs*. CBT-C group (n=13).	50.0±7.9	Investigating the effect of CBT on ANS functions in FM.	Anxiety: HADS HRV (frequency domain): polysomnography (PSG). FM: ACR 1990	At post-intervention HRV increased during sleep stages N2 and N3 and were related to better sleep quality but not to anxiety.
12	(7)	Zetterman *et al*. (2023)	Heart rate variability responses to cognitive stress in fibromyalgia are characterised by inadequate autonomous system stress responses: a clinical trial	Non-randomised clinical trial: Cognitive stress	n=82 (F) Patients with FM (n=51) *vs*. healthy controls (n=31)	45.0±12.7	Examining HRV responses to cognitive stress in FM patients.	Anxiety: FIQ; STAI HRV (time domain): 3' extraction of ECG signals from sEMG recording. FM: ACR 1990	Patients with FM have lower HRV and higher anxiety symptoms than healthy controls.
13	(38)	Moreira *et al*. (2023)	Effect of systemic and auricular acupuncture in fibromyalgia: a randomised clinical trial, pilot study	Randomised clinical trial, pilot study: electroacupuncture	n=18 (F) Patients with FM randomised into Experimental group (n=9) *vs*. control group (CG, n=9)	58.0 ± 9.89 57.0 ± 9.28	Evaluating the effects of electroacupuncture for pain intensity, HRV and quality of live in FM.	Anxiety: FIQ HRV (time and frequency domain): Polar watch 5' recording FM: ACR 2010	After electroacupuncture, improvement in anxiety and no changes in HRV.

et al. (35) and Moreira *et al*. (38) which employed the 2010 ACR criteria (44). These criteria use a widespread pain index (WPI) that indicates body areas with pain in the last week and a symptom severity scale (SSS) that indicates the sum of the severity of three symptoms (fatigue, unrefreshing sleep, cognitive symptoms) plus the severity of somatic symptoms in general.

Several measures were used to assess anxiety levels. The most commonly used instrument was the State-Trait Anxiety Inventory (STAI), employed in 4 out of the 8 studies (7, 29, 36, 37). Gavi *et al*. (36) adopted a version of the STAI validated in Brazilian and Portuguese-speaking individuals, the Idate Trait-State Inventory (IDATE). Other used instruments include the "mental health" subscale of the Short Form 36 Health Survey (SF-36) questionnaire (35), the psychological state subscale of the Fibromyalgia Impact Questionnaire (FIQ) (7,35,38), the Visual Analogue Scale (VAS) (28) and the Hospital Anxiety and Depression Scale (HADS) (27).

HRV was obtained by analysing ECG recordings (duration range from 3 to 15 minutes), except in Prados *et al*. (27) which used ECG data from polysomnographic recordings with recording time dependent on the participants' sleep duration. Zetterman *et al*. (7) extracted ECG recordings from surface electromyographic recordings (sEMG). All studies included both time- and frequency-domain HRV analyses.

The interventions varied across studies. Two studies investigated the effectiveness of physical exercise in patients with FM. Gavi *et al*. (36) compared a strengthening exercise program to a flexibility exercise program, with participants completing 45-minute sessions twice a week for 16 weeks. An improvement in anxiety was observed only in the flexibility training group, while no significant change in HRV emerged. The study by Sañudo *et al*. (28) investigated the effect of a 6-month aerobic exercise program that consisted of 45-minute sessions, twice a week. Patients were randomly assigned to either the aerobic exercise group or the control group without exercise. After the intervention, there was a significant improvement in anxiety levels and a significant change in HRV with an increase in the LF band and a decrease in the LF/HF ratio.

The study by Kulshreshtha *et al*. (37) evaluated the effectiveness of a pharmacological treatment, specifically the use of low-dose amitriptyline (10mg) in patients with FM. After treatment lasting three months, patients showed a significant reduction in anxiety scores, but no significant differences in HRV parameters emerged.

Two studies investigated non-pharmacological treatments involving electroacupuncture (35, 38). In the study by Dìaz-Toral *et al*. (35), electroacupuncture was administered twice a week for 10 weeks, evaluating the same group of patients at pre- and post-treatment. Results showed a significant increase in LF and LF/HF ratio, alongside a decrease in HF parameters, as well as a significant decrease in anxiety levels was found. The study by Moreira *et al*. (38) assessed the effects of systemic electroacupuncture, combined with auricular acupuncture. Participants in the experimental group underwent six systemic and auricular electroacupuncture sessions, lasting 20 minutes each, administered twice weekly over six consecutive weeks. This intervention led to a significant reduction in anxiety levels, though no changes were observed in HRV parameters.

The study by Prados *et al*. (27) investigated the effects of psychotherapeutic therapy, specifically cognitive-behavioural therapy (CBT), on nighttime autonomic activity in patients with FM.

The results showed that while no improvements in anxiety levels emerged, CBT effectively improved HRV, with an increase in HF during light and deep non-REM sleep (*i.e.* stages N2 and N3). Two studies focused on the relationship between anxiety and HRV in patients with FM when inducing some kind of stress. The study by Schmidt *et al.* (29) investigated the effectiveness of a short, focused breathing technique on pain severity, fatigue, pain self-efficacy, and autonomic stress response induced through a cold pressor test. Patients underwent two assessments including autonomic response (measured through HRV) to the cold pressor test before and after the intervention. For the intervention patients were instructed to practice slow paced breathing at 6 breaths per minute for three 10-minute sessions daily for two weeks. At the end of the intervention, there was an improvement in their stress response, as indicated by an increase in the total power of HRV and a significant reduction in anxiety levels, associated with improvements in pain severity, fatigue, pain self-efficacy and pain tolerance. Zetterman *et al.* (7) took a unique approach, focusing on stress induction rather than evaluating the effects of an intervention. Specifically, it aimed to explore patterns of ANS response (heart rate and HRV) to cognitive stress (arithmetic calculation) in patients with FM compared to healthy controls. The results showed that compared to controls patients with FM reacted to repeated cognitive stress with an altered pattern of ANS response characterised by an attenuated rise in heart rate. Moreover, the authors were able to characterize patients with FM based on their level of HRV reactivity, dividing them in three groups: patients with normal levels of resting HRV and HRV reactivity to stress, patients with moderately reduced levels of HRV and impaired HRV reactivity, and patients showing the lowest resting HRV and most impaired HRV response to cognitive stress. Intriguingly, the three groups were characterised by different levels of anxiety, such as those with a normal HRV reactivity showed low levels of anxiety, while those with the most impaired HRV reactivity had the highest anxiety as well as depressive scores. Ultimately, of the eight studies focusing on the effects of an experimental manipulation on anxiety and HRV in patients with FM, most of the studies found an increase in both HRV (27-29, 35) and a reduction in anxiety symptoms (28, 29, 35-37). Also, Schmidt *et al.* (29) and Sañudo *et al.* (28) reported a significant inverse correlation between HRV increase and the reduction in anxiety levels from pre- to post-intervention.

Discussion

The primary aim of this systematic review was to investigate the potential relationship between anxiety symptoms and altered autonomic activity, as measured through HRV parameters, in patients with FM. This endeavour was motivated by the high prevalence of anxiety as a prominent symptom in this syndrome (45, 46), and the shared involvement of somatic symptoms supported by ANS dysregulation as a potential common pathophysiological mechanism in both FM and anxiety disorders (13). This systematic review represents the first attempt to synthesise the current evidence regarding the relationship between anxiety and HRV in FM patients, an area that remains largely unexplored in the scientific literature. It is crucial to emphasise that only one study specifically and directly addressed the association between anxiety symptoms and HRV indexes as the primary focus of the research (39). Other studies included in the present review addressed these variables within broader and more diversified research questions. This distinction underscores the centrality of Bilgin *et al.* (39) study and its findings in contributing to the understanding of the relationship between anxiety symptoms and HRV in FM. The study identified specific HRV bands that predicted with an accuracy above 90% the presence of clinically relevant anxiety levels.

To ensure a uniform analysis, the assessment of baseline values was extended to the studies investigating the effects of an experimental manipulation, to equate the studies under the same conditions. One study found a significant correlation between HRV parameters and anxiety levels (17). One study reported a significant relationship between pain-related anxiety and LF of HRV in patients with FM (40). The LF component of HRV is thought to reflect a complex interplay between sympathetic and parasympathetic influences, as well as baroreceptor activity (47). This finding suggests that anxiety related to pain perception and experience may play a role in modulating ANS function in FM patients. The increase in LF of HRV in response to heightened pain-related anxiety could be indicative of an adaptive response aimed at mobilising physiological resources to cope with perceived threats or stressors (30). Alternatively, it could also reflect a maladaptive state of chronic sympathetic overactivation and reduced parasympathetic tone, which has been implicated in the pathophysiology of FM and other chronic pain conditions (31). Further research is needed to elucidate the mechanisms underlying this relationship.

Taken together, these studies contribute to demonstrate an association between reduced resting HRV and elevated anxiety symptoms. It must be noted that studies included in the present review show different methodological approaches, in example the questionnaires used to assess anxiety symptoms widely varied. Nonetheless, results were consistent, confirming that anxiety is a highly prevalent and relevant symptom among patients with FM. These findings underscore the importance of considering anxiety as an integral part of FM management, as it can have a significant impact on the quality of life of these patients.

Regarding HRV, the results consistently revealed a significant reduction in most indexes (*i.e.* lower HF power, lower RMSSD, and pNN50) in patients with FM. These data corroborate the findings of previous studies suggesting a reduction in HRV and an ANS imbalance in patients with FM. This decreased parasympathetic activity, increased sympathetic activity, or both, contributes to the overall autonomic imbalance observed in FM patients. The reduced vagal tone and heightened sympathetic

outflow may stem from various factors, including central nervous system dysregulation, chronic stress, and inflammatory processes, all of which have been implicated in the pathophysiology of FM. The observed interconnection between reduced HRV, elevated anxiety symptoms, and FM may be attributed to shared underlying neurobiological mechanisms. Accumulating evidence suggests that both anxiety disorders and FM involve dysregulation of the central nervous system's pain processing pathways, leading to amplified perception and interpretation of bodily sensations as noxious or threatening (62, 63). This central sensitisation process is thought to be mediated by aberrant neurotransmitter systems, including dysregulation of serotonin, norepinephrine, and dopamine signalling, which can contribute to both chronic pain and anxiety symptoms (52). Additionally, neuroinflammatory processes and autonomic imbalance, characterised by increased sympathetic and decreased parasympathetic activity, have been implicated in the pathophysiology of both conditions (32, 53).

The diminished HRV observed in these patients reflects an impaired capacity of the ANS to maintain homeostatic control and adapt to environmental demands, potentially exacerbating the multitude of symptoms associated with FM, including pain, fatigue, and cognitive dysfunction (48, 49).

One HRV index has been suggested to be a marker to be used in clinical setting to identify persons at risk for a range of cardiovascular diseases. Diminished RMSSD has been associated with an increased risk of developing various cardiovascular complications, including hypertension, obesity, metabolic dysregulation and adverse cardiovascular events (50). Importantly, findings from this systematic review showed a reduction in RMSSD values below the established cut-off of 25 milliseconds in a significant proportion of FM patients. Specifically, among the six studies reporting data on RMSSD (28, 29, 35-37, 41), four showed mean values below the cut-off of 25 milliseconds (28, 29, 37, 41). Routine HRV assessment in FM patients could help identify autonomic dysregulation through reduced RMSSD values, enabling risk-based patient stratification.

The cumulative results of the studies included in this systematic review provide substantial evidence supporting the hypothesis that anxiety and HRV, a well-established marker of ANS function, are interconnected in patients with FM.

These evidence suggests that HRV could serve as an objective peripheral psychophysiological indicator in assessing patients with FM complementing anxiety symptoms reports (39). Incorporating physiological measures, such as HRV, alongside traditional psychological assessments could potentially enhance the accuracy and objectivity in evaluating anxiety disorders in FM patients. By integrating subjective self-report measures and objective physiological indices, clinicians and researchers may achieve a more comprehensive and precise understanding of anxiety symptomatology in patients with FM. This multi-modal approach could circumvent potential biases associated with relying solely on self-report measures and provide additional insights into the underlying autonomic dysregulation that characterises both FM and anxiety disorders. Ultimately, the contribution of physiological measurements like HRV indexes could facilitate more precise diagnosis, monitoring of treatment response, and tailoring of interventions for managing anxiety in the context of FM and related conditions characterised by ANS dysfunction.

This finding reinforces the importance of adopting a comprehensive approach to understanding and managing anxiety in FM patients, as it highlights the crucial role played by the ANS in this complex relationship. Future research efforts could explore this complex interaction in greater detail by developing specific interventions aimed at modulating ANS activity in FM patients, including pharmacological agents targeting the ANS, mind-body therapies, or even novel neuromodulation techniques.

Among mind-body therapies, mindfulness-based interventions, such as mindfulness-based stress reduction, have been associated with increased HRV and reduced sympathetic activity in FM patients (54, 55). In this context, a promising approach could be represented by biofeedback training, a non-invasive technique that allows to learn to actively control physiological processes usually outside voluntary conscious control (56). Biofeedback of HRV (HRV-BF) has proven useful in a wide range of disorders accompanied by ANS dysregulation (57). Also, a meta-analysis highlighted the effectiveness of HRV-BF in reducing perceived stress and anxiety symptoms (58). A literature review has indicated potential benefits of HRV-BF in pain reduction, improving ANS balance, reducing depressive symptoms and negative mood and increasing mental health in patients with FM (59). While these findings are promising, further research is needed to establish the optimal protocols, dosing, and long-term efficacy of HRV-BF in FM patients. Nonetheless, the growing body of evidence supporting the potential benefits of HRV-BF in disorders characterised by ANS dysregulation underscores the importance of exploring and integrating such intervention into comprehensive treatment plans for patients with FM.

As for studies investigating the effects of an experimental manipulation on anxiety and HRV in patients with FM, less consistent results emerged. These studies focused on a wide range of treatments and interventions, including physical exercise, psychotherapeutic therapies, pharmacological and non-pharmacological treatments, breathing techniques, and stress induction situations. Two studies reported that increases in HRV following an intervention (*i.e.* slow and focused breathing technique and aerobic exercise) were associated with reductions in anxiety symptoms (28, 29). These results suggest that targeting both psychological and autonomic dysfunction through appropriate treatments may have far-reaching benefits on the overall quality of life for patients with FM.

Electroacupuncture was associated with a reduction in anxiety symptoms, an increase in LF and LF/HF ratio accompanied by a reduction in the HF component after treatment (35). The authors interpreted these results as a

reflection of an increase in sympathetic tone. However, this interpretation is controversial, as the notion of LF power and the LF/HF ratio representing solely sympathetic activity on the heart has been repeatedly questioned in the literature. Numerous studies consistently reported that LF power, with or without respiratory adjustment, reflects baroreflex modulation and advocate that the HRV power spectrum, including its LF component, is mainly determined by the parasympathetic system (47, 60, 61). In light of these considerations, the increase in HRV indices reported by Díaz-Toral *et al*. (35), associated with a reduction in anxiety symptoms, aligns with the literature supporting the association between improvements in ANS balance and reductions in anxiety symptoms following interventions in patients with FM. Nonetheless, further research is mandatory to fully elucidate the underlying mechanisms and autonomic changes associated with the effects of electroacupuncture in this population.

One study specifically focused on measuring the impact of induced cognitive stress in patients with FM, showing that reduced resting HRV as well as impaired HRV response to cognitive stress were associated with significantly higher anxiety symptoms (7). This finding suggests that the autonomic dysregulation observed in FM patients may be exacerbated under conditions of heightened stress, leading to a further imbalance in the ANS and a concomitant increase in anxiety symptoms. While this study did not directly evaluate the effectiveness of a therapeutic intervention, its findings have important implications for the development of future treatment strategies. By understanding the intricate interplay between anxiety, stress and autonomic dysregulation in FM, researchers can design interventions that specifically target these interconnected factors, potentially leading to more effective symptom management and improved quality of life for FM patients.

Some of the included studies yielded results that are inconsistent with the initially formulated hypotheses. In three studies, assessing the effect of low-dose amitriptyline (37), electroacupuncture (38) and strength training (36), results showed a reduction in anxiety symptoms, but no variation in HRV indexes emerged. In line with these results, a recent meta-analyses confirmed that exercise training is effective in improving anxiety symptoms among patients with FM (62). Conversely, one study investigated the effects of CBT in patients with FM reporting an improvement in the HF of HRV during sleep, and no significant improvement in anxiety symptoms (27).

Drawing definitive conclusions about the relationship between anxiety and HRV in patients with FM after experimental manipulation was challenging due to several methodological issues. The diversity of interventions, ranging from physical exercise programs to pharmacological treatments, psychotherapeutic approaches, and non-pharmacological therapies like electroacupuncture, complicated direct comparisons and generalisations. Each intervention may exert its effects through distinct mechanisms, potentially influencing anxiety and HRV differently, thereby complicating the interpretation of findings. Many studies, including pilot investigations, had limited sample sizes, potentially affecting statistical power, increasing the risk of type II errors (failing to detect a significant effect when one exists) and limiting generalisability. Some studies, particularly pilots, lacked control groups, making it difficult to attribute changes solely to the interventions. Furthermore, the predominance of female participants limited the applicability of the findings to male FM patients.

Consequently, further research on each specific intervention is warranted to gain a more comprehensive understanding of their impact on the symptomatology of patients with FM, including anxiety and ANS imbalance. Larger, well-controlled studies with adequate sample sizes and appropriate control groups are needed to replicate and validate the findings, as well as to explore potential moderating factors, such as age, sex, disease severity and comorbidities, that may influence the effectiveness of these interventions.

Despite these methodological limitations, it is noteworthy that out of the 13 studies analysed in this systematic review, 8 confirmed the presence of a correlation between anxiety symptoms and HRV in patients with FM, lending support to the initial hypothesis. However, the lack of consensus among all the included studies highlights the need for further research to elucidate the complex interplay between anxiety symptoms, autonomic dysregulation, and FM, and to develop more effective and targeted interventions for this debilitating condition.

This systematic review is subject to limitations that should be acknowledged. First, the included studies show heterogeneity in terms of the measures employed for assessing anxiety and HRV, as well as the diverse treatments and interventions adopted. This variability in methodological approaches and experimental designs may have contributed to part of the inconsistencies observed in the findings. Second, the inherent limitations of the individual studies, such as small sample sizes, a predominance of female participants, the absence of control groups in some cases, and a lack of follow-up assessments, may have affected the overall quality and generalisability of the results. Third, the primary focus was on examining the relationship between anxiety symptoms and HRV, in line with the specific objectives of the review. Consequently, the magnitude of pain, a crucial aspect in FM, was not included as a variable in the analysis. This decision was made because pain assessment data were not consistently retrievable from the cited studies, and the criteria and instruments used to evaluate pain varied widely across studies, making meaningful comparisons difficult. However, it is widely recognised that pain is a central feature of FM and could potentially be involved in the complex interplay between anxiety symptoms and ANS dysregulation. Therefore, future research endeavours should aim to explore in detail how these factors interact and influence one another in the context of FM.

By incorporating comprehensive assessments of pain, anxiety symptoms, and ANS dysregulation, researchers may gain a more holistic understand-

ing of the intricate relationships among these variables and their collective impact on the symptomatology and overall well-being of patients with FM.

Conclusion

In conclusion, the reviewed studies provide substantial evidence supporting a negative association between anxiety symptoms, HRV, and FM.

This relationship suggests potential applications in FM diagnosis, with anxiety levels and HRV parameters serving as auxiliary indicators to complement existing clinical assessments and criteria.

However, establishing a causal relationship between anxiety symptoms, ANS dysregulation and FM remains challenging. Longitudinal studies are needed to evaluate the temporal development and interplay of these factors in individuals at risk for or in the early stages of FM.

The reduced HRV observed in fibromyalgia patients with comorbid anxiety may reflect autonomic dysregulation, potentially perpetuating a cycle of heightened pain perception, somatic hypervigilance, and exacerbated anxiety. Understanding these shared neurobiological underpinnings could lead to targeted, multimodal interventions addressing psychological, physiological, and neurological aspects of FM and comorbid anxiety disorders.

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