UNICA

UNIVERSITÀ
DEGLI STUDI
DI CAGLIARI

Ph.D. DEGREE IN

Innovation Sciences and Technologies

Cycle XXXIII

TITLE OF THE Ph.D. THESIS

A randomized controlled trial on the use of biofeedback with wireless technology in the therapy of fibromyalgia

Scientific Disciplinary Sector(s)

MED/50
Regenerative Medicine and Biomedical Applications

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Final exam. Academic Year 2019/2020
Thesis defence: November 2022 Session

CONTENTS

ACKNOWLEDGEMENT

Four years after the last time, I find myself once again taking stock of a path nearing its end. The first evidence that falls before my eyes is how much I have changed over the years. Probably this for the "new me" is and has been the hardest formative path but, in the darkest moments I have always had the opportunity to find, from those who are always there for me, that word able to restart the gear.

Today I want to thank all the people who have supported me over the years.

I thank my advisor Professor Mauro Giovanni Carta for giving me the opportunity to experience myself in this path and for all the precious training that you have the opportunity to learn every time you compare yourself with him. Thank you.

Together with Prof. Carta I would like to thank the staff of the Center for Psychiatry and Psychosomatic Consultation for the work done in recent years.

I thank all the colleagues who collaborated in the study and all the participants who decided to give their contribution to this new project.

In particular, I thank the pain medicine clinic of the San Giovanni di Dio hospital for their collaboration and sharing.

I thank my colleague in studies and life Martina for always having been there at any time and for having been a fundamental driver in my PHD. Even in the moments in which I had already abandoned the possibility of continuing she was also fighting for me. If today I find myself writing the thanks for my PHD thesis I owe a lot to her.

I wish both of us to always be able to achieve what we want and one day to realize our working dream together. Thanks Marti.

I thank my family safe harbor in which to take refuge whenever I need it. Thank you

I thank my partner for always being that shoulder on which you know you can rely. Thanks to your support I am here today.

And finally, last but never the last in my life, I thank my daughter for all that she has been able to teach me in just two years.
I conclude this PHD for you, hoping that what I have done is only a small part of everything you will do.
Thanks Bea.

1. INTRODUCTION

"You can't stand the light, the noises.
Your body lives in relentless pain, freezes.
Tingling everywhere, tremors.
The legs give way, the hands grasp nothing.
A slight strain forces you to bed for days.
But you can't sleep. "
Andrea, 39 years old

Andrea's words describe the condition that many people, for the most part women, have to experience every day due to fibromyalgia.
Fibromyalgia due to its particular characteristics has been defined as a phantom disease and for many years it has not been recognized.
To date, in some contexts, it is not easily recognized and there is no treatment of choice.
Having said all this, the engine that prompted me to work on such an area that is still little known is the possibility of being a small grain of sand that, combined with all the others, can allow those who suffer from it to have a quality of better life and to have tools to fight this battle.

1.1 FIBROMYALGIA

Fibromyalgia (FM) is a chronic disease characterized by persistent and widespread musculoskeletal pain with an indefinite etiology, which often occurs in comorbidity with other functional, organic and psychiatric pathologies [1]. The main clinical manifestation of FM is pain, which is predominantly described by affected individuals as a burning sensation, stiffness, contracture and tension [1]. Pain tends to

vary depending on moment of day, activity levels, weather conditions, sleep cycle and perceived distress [14]. FM is a heterogeneous condition that is often associated to specific diseases such as infections, psychiatric or neurological disorders, diabetes and rheumatic pathologies. FM is more frequent in females, where it causes musculoskeletal pain [3] and significantly affects quality of life, often requiring an unexpected healthcare effort and consistent social costs [51].

The high comorbidity with anxiety and mood disorders and some associated neuro-endocrine changes have led to the hypothesis that FM could be counted among the affective spectrum disorders [12]. In the last decade, however, a series of evidence has been accumulating, coming from neuroimaging studies, which indicate anatomo-functional alterations in brain areas involved in the perception and processing of pain [15].

Two types of FM can be distinguished: "primary", in which laboratory tests are not altered and there is no association with any known disease, and "secondary", in which symptoms emerge during other pathologies also defined as "main diseases" (rheumatic diseases, chronic infections and inflammations, endocrine disorders) [2].

The prevalence of FM in the general population is 2%, with a peak of onset between 45-60 years [2]. The gender prevalence ranges from 0.5% to 5%, occurring more frequently in females (~ 4.2%) than in males (~ 0.2%) [3].

FM patients represent 10-25% of the rheumatology population, 2-6% of the general practitioner population and 8% of patients who need hospitalization [4].

The literature shows that FM has a high cost on the health care system. A research conducted with a cohort of 280 patients shows that the annualized costs of FM per patient are estimated to be around € 2944 for healthcare and € 5731 for lost productivity. The study shows that a greater impact of the disease leads to a high health cost [79]. The same data is demonstrated by several studies which show that

patients with FM have an annual health expenditure higher than patients without FM [80,81].

The literature also shows us that FM patients show greater difficulties in the workplace. The causes of this problem are to be found in physical difficulties and in the need for more rest caused by the typical symptoms of FM [82].

In addition, a study recently, conducted in 2020, with the aim of to observe the behavior of FM symptoms during the course of coronavirus disease 2019 (COVID-19), showed that the typical symptoms of FM were more intense in patients with Covid- 19. The main affected tomorrows are: sleep quality, fatigue / energy, pain, stiffness[83].

1.2 FIBROMYALGIA IN THE HISTORY OF MEDICINE

Throughout the history of medicine, FM has been indicated with various expressions, such as "fibrousness", "muscle-tension pain", "psychogenic rheumatism". In the mid-19th century, German literature began to distinguish joint rheumatism from extra-articular rheumatism, deepening the study of painful muscle syndromes. In 1843, the German doctor Froriep classified the symptoms relevant to today's FM as "diffuse and painful forms of rheumatology" and introduced the expression "muscle calluses" to refer to painful muscle foci perceived by rheumatic patients [16].

Gower (1904), used the term "fibrositis" to indicate low back pain phenomena found in young adults and attributed to inflammation of the fibrous tissue of the muscle mass [16].

During the 1930s, two important definitions were introduced:

- "**fascial pain**", referring to the limited ability to move muscles caused by hypertension of the connective fascia that surrounds and envelops the bones, muscles, nerves, lymphatic vessels and blood

- “**trigger points**", as sites of hyper-irritability, ie muscle segments characterized by groups of fibers showing a continuous state of tension and contracture [16].

  In the post-war period it was realized that the term with which the disease was still defined, "fibrositis", being indicative of the presence of an inflammatory process (suffix "ite"), was not appropriate, as the disease did not show signs of phlogistic origin. Therefore, FM was considered a disease with clinical manifestations mainly of a psychological type until 1976, when the US doctor Hench coined the term "fibromyalgia", specifying that the disease was of a rheumatological nature, not inflammatory [18].

  The current way of characterizing FM through "tender points" dates back to 1978 [17].

  FM was also defined as "Atlas Syndrome", with a mythological reference to the Greek demigod who was forced to bear, as a punishment by Zeus, the entire weight of the celestial vault on his shoulders, since the main symptoms of the syndrome are pain musculoskeletal and exhausting chronic fatigue [17].

  From 1981, following the proposal of Yunus and Masi, the term “fibromyalgia” was unanimously and definitively accepted to identify the pathology [16].

1.3 THE DIAGNOSTIC CRITERIA OF FIBROMYALGIA

The assessment and diagnosis of FM is still subject of dispute . Despite advances in the understanding of the pathologic process, FM remains undiagnosed in as many as 75% of people with the condition [8, 52].

In 1990 the first diagnostic classification for the disease was developed and, starting from 1994, the diagnosis of FM was officially shared by the international scientific community [19].

This diagnosis is clinical, and is commonly made on the basis of the 1990 American College of Rheumatology (ACR) criteria, namely the presence of chronic widespread pain (CWP) for at least 3 months, with pain in at least 11 out of 18 specific points (tenders points).

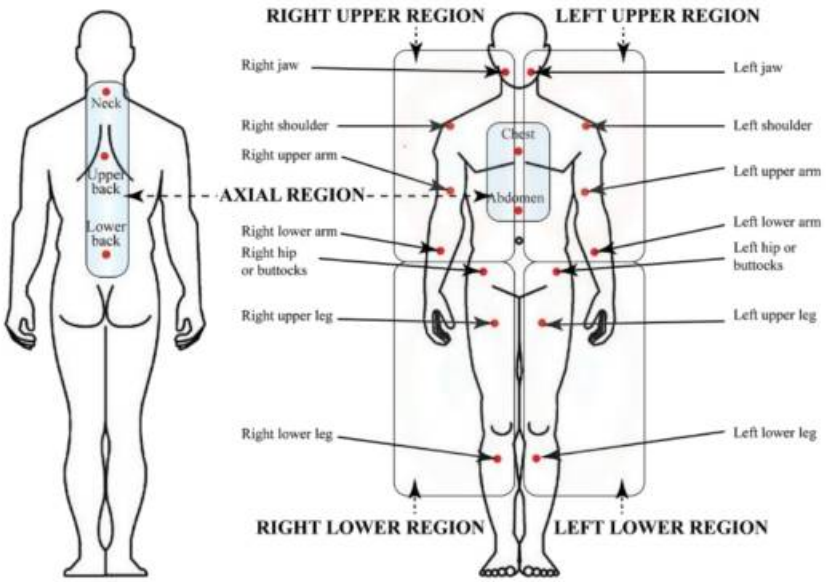

Fig 1: Widespread Pain Index from ACR 1990 criteria for the classification of fibromyalgia and related regions.

In 2010, the ACR revised the diagnostic criteria to facilitate greater agreement on the diagnostic process, also considering other symptoms referable to the common clinical manifestations that characterize FM, such as cognitive deficits, fatigue, memory and sleep problems, limitation in carrying out daily activities. The tenders points test has been replaced by a widespread pain index, the WPI (Widespread Pain Index), and a symptom severity scale, the SS (Symptoms Severity) [6]. A further revision of the criteria was made in 2011, through the creation of a survey questionnaire that allows to facilitate epidemiological and clinical studies on FM [4].

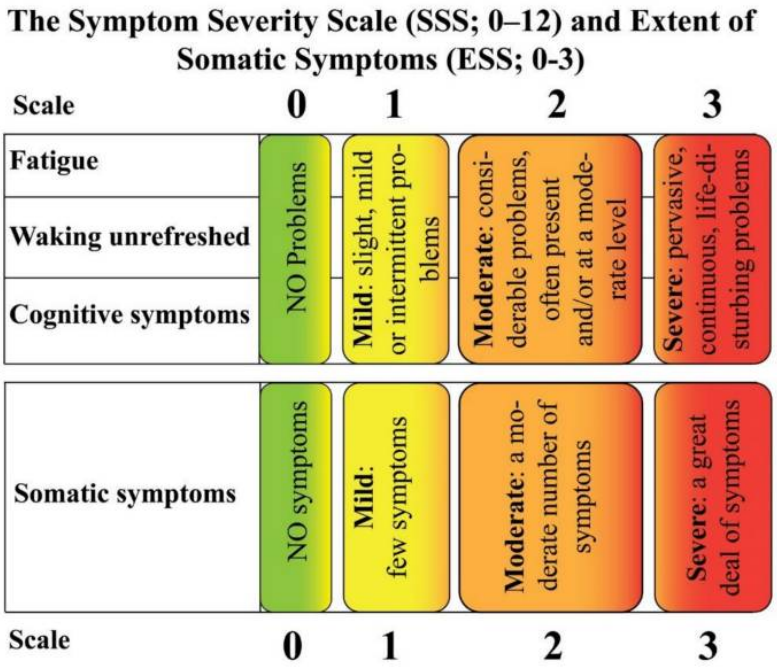

Fig 2: Symptom Severity scale (SSS) and Extent of Somatic Symptoms (ESS)

1.4AETIOPATHOGENETIC FACTORS IN FM

The etiology of FM is unknown. However, the gained evidence over the last 40 years [1] suggests that several factors affect the origin of this disorder.

Different pathogenetic hypotheses have been formulated which refer to:

- psychological alterations;
- sleep disturbances;
- neuroendocrine alterations;
- immunological alterations;
- inheritance;
- genetic and epigenetic processes;
- viral infections;
- muscle changes;
- neurotransmitter modifications;
- alterations of the autonomic nervous system.

In particular, recent studies have shown that FM is associated with a greater sensitivity to pain resulting from a dysregulation, at a central level, of the pain modulation process such that, compared to subjects not affected by this pathology, those with FM have thresholds. of lower pain [7]. It has also been found that cortical activities activated in response to nociceptive stimuli are more intense in subjects with FM [8].

Furthermore, low levels of serotonergic activity (5-hydroxytryptamine) and dysregulation of the dopaminergic system have been found in FM patients. Patients with FM show an increased response of prolactin to the challenge test, suggesting a greater sensitivity of dopaminergic D2 receptors [9].

Numerous studies show that patients with FM exhibit hyperactivity of the sympathetic-adrenergic system (SA), especially of the hypothalamic-pituitary-adrenal axis (HPA) in response to stressful events [13].

Other evidence found muscle abnormalities, especially hypoxia, supporting the hypothesis of a peripheral abnormality [1].

Some studies have also shown reduced levels of adenosine triphosphate and phosphocreatine in FM, suggesting that these metabolic abnormalities could contribute to muscle weakness and fatigue in FM.

Muscle blood flow has been shown to be decreased in people with FM compared to unaffected individuals [20]. The problems inherent in muscular vasoconstriction common in FM and explain, at least in part, the possible comorbidity with Raynaud's syndrome. This evidence suggests that peripheral ischemia may contribute to muscle pain in FM [21].

1.5 THE ROLE OF LIFE EVENTS IN THE PATHOGENESIS OF FIBROMYALGIA

Stressful and possibly traumatic life events can also be associated with the onset of painful symptoms typical of FM, and can also affect the perception of pain, quality of life and the impact of FM [11].

Among the stressful and possibly traumatic events we can list [22]:

• physical fatigue, such as work, daily activities;
• transition periods of life;
• natural disasters, war;
• socio-economic status;
• loss of job, partner, safety;
• psycho-physical damage;
• trauma, disease;
• personality disorders;
• climatic factors (metereopathy).

The role of life events in the onset of psychic pathology is generally admitted by most clinicians even if, from time to time, it is appropriate to establish which ones actually assume the role of "stressor" for each individual . Vulnerability to life events is, in fact, extremely variable from person to person: exposure to life events of the same type, only in some subjects can contribute to determining the onset of a certain pathology, psychiatric or other [22] .

From this perspective, FM could be considered the "painful solution" of multiple life events, perceived as stressors, and of the psycho-neuro-endocrine modifications they induce, with a cumulative effect over the course of one's existence.

1.6 FIBROMIALGIA AND PSYCHIATRIC DISORDERS

Psychiatric disorders are very frequent and disabling diseases. As reported by the ESEMeEd study [23], psychiatric pathologies are an important health problem at European level. Specifically, the survey shows that in a sample of 21,425 people from 6 different European countries, 14% reported mood disorders, 13.6% anxiety disorders, 4.1% dysthymic disorder and 5.2% a previous history of alcohol abuse [23].
Like psychiatric pathologies, chronic pain affects a high percentage of subjects, worsening their quality of life [24].
Several studies support the close correlation between FM and psychiatric disorders, in particular with mood disorders (depression), anxiety disorders and post-traumatic stress disorder (PTSD) [25].
Specifically, research shows that FM patients have a greater lifetime risk of major depression, with comorbid rates ranging between 20% and 80% [26].
The risk of developing anxiety disorders, particularly OCD and PTSD, is approximately five times higher in women with FM than in the general population [27].
Furthermore, comorbidity is more prevalent among women, and in particular among women belonging to ethnic minorities [27].

1.6.1 DEPRESSION

Raphael et al. [28], examining the correlation between FM and major depressive disorder (MDD), they propose two different explanatory hypotheses. The first hypothesis is that FM is a depressive spectrum disorder, the second that depression is a consequence of living with FM. The study involved relatives of a group of FM patients and found that rates of DCS in relatives of FM patients but no personal history of DCS are similar to rates of DCS in relatives of FM patients who suffered from DCS in their lifetime. The authors conclude that FM is a

depressive spectrum disorder, in which FM and MDD are characterized by shared risk factors that depend, in part, on familiarity [28].

1.6.2 POST TRAUMATIC STRESS DISORDER (PTSD)

There is a very relevant link between PTSD and chronic pain syndromes and, more generally, between stress and pain sensitization [29].

Chronic pain is very common in patients with PTSD and the latter is common in patients with chronic pain. The prevalence of PTSD comorbid with FM ranges from 15% to 56% [30].

From a psychobiological point of view, a chronic condition of significant distress or traumatic contributes to causing a sensitization to stress and pain [31].

We could therefore hypothesize this evolution process: a subject genetically predisposed to poor psychological resilience undergoes an affective development disturbed by experiences of abuse or by anaffective and negligent parental attitudes. In relation to this, an inadequate capacity for emotional regulation and processing of experiences may develop. Subsequent stressful and / or traumatic events could, therefore, not be sufficiently elaborated and integrated into the current experience, triggering paralyzing affective and cognitive "spirals" that would often take the form of a real PTSD. At this point, progressive psychological, neuroendocrine, neuroimmunological and neurobiological modifications would create a stable modification of the stress response systems and those involved in the perception, transmission and processing of pain. This psychobiological condition would eventually lead to a central sensitization disorder, with the contribution of precipitating factors such as infections, prolonged physical fatigue, psychosocial stress [29].

1.6.3 ANXIETY DISORDERS

Chronic pain is often associated with comorbidities such as anxiety and depression, resulting in a health-related low quality of life. However, the mechanisms underlying this association are not currently clear [53].
Anxiety disorders are present in 27% - 60% of FM patients [32].
Chronic pain is often associated with anxiety disorders. [33].
Several studies state that anxiety is strongly correlated with the perception of pain [54]
The intensity of the anxious state is also related to the perception of pain, a fundamental component of FM [55].

1.7 THE TREATMENT OF FIBROMIALGIA

Although knowledge of FM has deepened over the years, to date, there is no treatment of choice.
The complexity of FM symptoms requires a multidisciplinary treatment in which drug therapy is accompanied by patient education, cognitive-behavioral therapy and rehabilitation [34].
However, there are guidelines that suggest the approach to be adopt. The guidelines are designed to guide healthcare professionals and patients in choosing treatment options.
However, the debate on which is the first choice of treatment for FM remains open.
The first guidelines were formulated in 2005 by the American Pain Society (APS). The subsequent ones were formulated in 2007 by the European League Against Rheumatism (EULAR) and in 2008 by the Association of Scientific Medical Societies in Germany (AWMF). The EULAR guideline assigned the highest level of recommendation to a range of drug treatments, while the APS and AWMF guidelines assigned the highest level of recommendations to primarily non-drug treatments that included aerobic exercise, cognitive behavioral therapy.

and multicomponent treatment, identifying amitriptyline as the only strongly recommended pharmacological agent [35].

From a multidisciplinary perspective, ongoing FM rehabilitation is of significant utility [36].

The approach to managing FM has evolved over the last few years, as evidenced by the recent update of the EULAR guidelines [37].

Specifically, the EULAR guidelines, developed by 18 specialists from 12 European countries, provide evidence-based recommendations for the care of patients with FM. These new recommendations represent the first update of the Eular guidelines for the management of FM in more than a decade, and include evidence to support pharmacological, non-pharmacological, complementary and alternative therapies, specifically: Mind-Body Therapies (TMC), and cognitive-behavioral therapies [38].

This document allows Eular to "move from recommendations predominantly based on expert opinion to recommendations firmly based on scientific evidence drawn from high-quality reviews and meta-analyzes" [56].

The authors stressed the effectiveness of patient education and non-pharmacological intervention (eg: physical exercise) as part of the initial therapy. In addition, the recommendations stress the need for an individualized approach, which may include pharmacological, psychological and / or rehabilitative interventions, based on the individual patient. The authors, however, warn that the "effect size for various treatments is relatively modest" and further research is needed to achieve optimal treatment strategies and improve patient outcomes [39].

In evaluating the data, the working group took into account factors such as the number of trials, the number of patients, the results evaluated and adverse events. He then based the recommendations on a 4-point scale ("strong for / weak for / weak against / strong against"), with the strength of the recommendation based on "the balance between desirable and undesirable effects (considering the values and

preferences), confidence in the magnitude of the effects and the use of resources "[56].

Overall, the data in the literature indicate that integrated therapies in FM, which therefore include non-pharmacological interventions, are more effective than exclusively pharmacological ones and have effects that last longer over time [57].

1.7.1 PHARMACOLOGICAL TREATMENTS

The choice of drug therapies in the treatment of the patient with FM should be guided by the patient's clinical characteristics, the profile of secondary and collateral effects, and the response. FM patients taking specific drug therapies need to be re-examined frequently, and the dose needs to be adjusted according to the patient's response. If the therapy has not shown any positive effects or if the patient has developed important side effects, treatment should be stopped [40].

Tricyclic antidepressants are the first drugs evaluated in the treatment of fibromyalgia. Amitriptyline (AMT) is the drug most used and known to inhibit both the reuptake of serotonin and norepinephrine, and has long been used for the management of neuropathic pain and FM [41].

Serotonin reuptake inhibitor (SSRI) drugs are also effective in the treatment of FM [42].

Serotonin and norepinephrine reuptake inhibitors (SNRIs) [43] and anticonvulsants [44] are also effective. However, it is not recommended to use anti-inflammatory and analgesic drugs. [45].

1.7.2 NON-PHARMACOLOGICAL TREATMENTS

Major non-drug treatments include a multidimensional approach that includes cognitive-behavioral therapy and patient education [46].

Further interventions of proven efficacy are physical exercise, both aerobic (cardiorespiratory training) [47] and muscle strengthening [48], which, combined with patient education, favors the improvement of general well-being, fatigue and sleep disorders. Furthermore, exercises

that promote muscle elasticity are more effective than muscle relaxation techniques [49]. Finally, water aerobic exercises (aqua-gym), as well as being well accepted by the patient, are associated with an improvement in the quality of life and a reduction in pain even in the long term [50].

1.8 BIOFEEDBACK

FM can cause severe limitations in carrying out daily activities. Therefore, the assessment of QoL in these people is of great scientific interest. There is evidence that QoL is profoundly affected by FM, more significantly than other chronic diseases [58].

One of the tools used in the treatment of FM, in order to favor the reduction of typical symptoms and improve perceived QoL, is biofeedback.

Biofeedback is a tool that allows the person to learn the self-regulation of some physiological processes through the visual or sound restitution (feedback) of the detected parameters, with the aim of improving health and its performance [59, 60].

Biofeedback tools measure muscle activity, skin temperature, electrodermal activity (sweat gland activity), respiration, heart rate, heart rate variability, blood pressure, brain electrical activity, and blood flow blood and provide, quickly and accurately, the subject with feedback of the chosen activity, teaching him to take a more active role in maintaining personal health and the health of the mind and body.

Biofeedback is based on the psychophysiological approach.

The "psychophysiological principle" (Green, et al., 1970) proposes a two-way relationship between physiological and psychological functioning: "every change in the physiological state is accompanied by an appropriate change in the mental emotional state, conscious or unconscious, and on the contrary, every change of mental emotional state, conscious or non-conscious, is accompanied by an adequate change in the physiological state ».

The bio-detection is carried out using various transducers (electrodes, thermistors, or other methods as appropriate) applied to the subject, which detect the bioelectric activity of the monitored function and, after processing by a central amplification and integration unit, they return it in real time in the form of a signal, more often light or sound signal , that the subject can clearly perceive.

The feedback signal varies from moment to moment, depending on the variation of the activity being monitored. For example an increase in local muscle tension in the forehead is translated into an increase in the tone or intensity of an acoustic signal, while a decrease in muscle tension is translated into a reduction in the tone or intensity of the signal itself. In practice, the sound varies perceptibly with even the slightest variation in the state of tension or relaxation.

Since the level of subjective tension is accompanied, in most cases, by a concomitant increase in muscle tension, in the course of subsequent biofeedback sessions the subject can learn to hear the level of his anxiety in the form of sound, to discriminate the physiological modifications of his state of muscular tension, to develop awareness of these variations, and progressively to control them voluntarily. The basic principle of feedback is, in theory, applicable to any detectable bioelectrical signal.

As learning progresses, changes can be maintained over time without the need to use additional biofeedback tools.

Biofeedback according to the ranking of the National Institute of Health - USA is part of the mind-body medicine (mind-body medicine) and it is an intervention:

- Which allows the person to have an active role;
- It is not invasive;
- Stimulates the body's natural responses;
- Teaches to use internal resources in achieving one's goals.

Research shows that biofeedback, alone and / or in combination with other behavioral therapies, is effective for treating a variety of medical and psychological disorders, ranging from headaches to hypertension, temporomandibular disorders, and 'attention.

HRV seems to be the most effective parameter in fibromyalgia. A study by Hesset et al. notes an improvement in depressive and painful symptoms, as well as improvements in sleep.

The evidence-based practice in biofeedback has assigned the treatment of BF for fibromyalgia to level 2 efficacy, possibly effective.

Level 2 has been assigned because some studies have had negative results and there are conflicting views in the literature and it is equated to other mind-body therapies [61].

1.8.1 BIOFEEDBACK IN HISTROY

Biofeedback to this day still has a controversial history.

Biofeedback developed in the United States in the late 1960s, when some researchers (Miller, Kamiya, Sterman, Brener, Snyder, Noble et al.) demonstrated that it is possible to control certain parameters in both animals and humans, such as heart rate, electroencephalographic rhythms, cutaneous vasoconstriction and electrodermal response. Subsequently, starting from the 1970s, it also spread to Europe and Italy.

Both the public and academic worlds recognize Joe Kamiya as the father of biofeedback. In 1966, while monitoring subjects' EEGs in his sleep lab at the University of Chicago, he performed a novel experiment by ringing a bell whenever an alpha burst occurred. He discovered that some subjects could discriminate when they produced alpha activity. His 1968 publication of ''Conscious Control of Brain Waves'' in Psychology Today summarized research that showed that subjects could learn to discriminate when alpha was present or absent and that they could use feedback to shift the dominant alpha frequency about 1 Hz. Almost half of his subjects experienced a pleasant alpha state, which they characterized as an ''alert calmness.'' Kamiya's article made biofeedback accessible to the public and made it exciting because it suggested that individuals can learn to control their own consciousness [79].

Fundamental to the development of biofeedback were the first studies conducted by Neal Miller, who first encouraged students to train mice to achieve autonomous control through instrumental learning.

Miller and his research team conducted a groundbreaking study that showed that trained rats can operatively learn to control their

autonomic functions. Their 1968 publication, "Instrumental Learning of Vasomotor Responses by Rats: Learning to Answer Differentially in Two Ears," in the influential journal Science challenged the dogma that autonomic processes cannot be voluntarily controlled (DiCara and Miller, 1968) [80].

1.8.2 HEART RATE VARIABILITY (HRV) AND BIOFEEDBACK

Dwelling on heart rate variability (HRV), we can say that it is the spontaneous change of heart rate and is correlated with the influences of the sympathetic and parasympathetic nervous system on the heart rate. HRV interacts with breathing and blood pressure regulation.

The detection of HRV with the use of biofeedback involves monitoring the single heart rate or heart rate for multiple breaths. Heart rate can be detected by plethysmographic sensors placed on the finger or earlobe or by ECG monitors. Most commonly, the trace reflecting the cyclic changes in heart rate is displayed on a video screen. What is taken into consideration is not the average heart rate, but the variability of the heart rate.

The user observes the trace (or a derived graphic display) and uses it as feedback to regulate breathing and / or emotional state. Heart rate variability is maximized at a particular "resonant rate" (respiratory rate per minute), and this rate, usually about six times per minute, can be determined for each individual by observation and experimentation.

The time to obtain an improvement through HRV during the use of biofeedback varies on average from 4 to 10 sessions. While, learning time varies, by subject, as with any biofeedback procedure. Generalization in the everyday environment, away from biofeedback monitoring, takes longer than achieving success in the context of biofeedback. Practicing with HRV biofeedback provides a model for real-life self-regulation; the goal is to develop awareness of one's breathing and one's emotional state, both of which interact and

influence the autonomous balance. This balance, in turn, has been found useful for several disorders involving chronic maladjustment of the autonomic nervous system.

In FM, there are several areas in which research has shown benefits with the use of biofeedback, especially quality of sleep, self-efficacy, pain threshold and emotional adaptation [61].

In particular, a study conducted with the use of HRV biofeedback, in which the sample learned breathing at the resonant frequency, showed decreases in depression and pain and improvement in functioning [62].

2 MATERIALS AND METHODOS

2.1 STUDY DESIGN

The study is a 10-weeks Randomized Controlled Trial (RCT). Participants (N=36) were assigned by randomization to either an active interventional protocol based on HRV-BF plus usual care (N=16) or to a control intervention (N=16), which followed the usual care.

2.2 AIMS

The main objective of the study is to verify the feasibility of a HVR biofeedback training protocol in FM patients; the study also aims to produce a preliminary measure of any improvement induced with the technique in relation to:

- quality of life;
- sleep quality;
- perception of pain;
- depressive symptoms;
- anxious symptoms.

These measures will be useful, in the future, in estimating the expected improvement in case-control studies.

Overall, the research aims to help study the efficacy of biofeedback training treatment in FM patients, with the use of HRV detection.

2.3 SAMPLE AND INCLUSION AND EXCLUSION CRITERIA

The sample consists of 36 patients, being treated at the pain therapy and palliative medicine outpatient clinic of the "San Giovanni di Dio" Hospital, Cagliari, Italy.

- **Inclusion Criteria**: women aged >18 years with a diagnosis of fibromyalgia meeting the diagnostic criteria of the American

College of Rheumatology (ACR) Revised (Häuser et al 2016), verified by a medical researcher.

- **Exclusion Criteria**: Patients with mild / severe cognitive impairment. Men were not included in the study given their extreme rarity (approximately 1/50) in those with fibromyalgia that usually access the clinical center. Psychiatric comorbidities were not exclusion criteria.

2.4 TOOLS, PHASES AND DATA COLLECTION

In the first phase of the study, participants were subjected to a clinical interview, based on the guidelines of the DSM 5, aimed at obtaining a diagnostic evaluation.

The standardized tools used in the research are:

- 12-item short form survey (SF-12)
- Patient Health Questionnaire-9 (PHQ-9)
- Visual Analogue Scale (VAS)
- Fibromyalgia impact Questionnaire (FIQ)
- Sleep scale from the medical outcomes study (MOS)
- Emotional and Body Pain Perception Questionnaire (BEEP)
- Sense of coherence - Life Orientation Questionnaire (SOC).

All instruments and questionnaires used in the study have been reported in Italian and are used regularly in clinical practice.

2.4.1 12-ITEM SHORT FORM SURVEY (SF-12)

Quality of life was assessed with the Short Form Health Survey (SF-12) -appendix 1- [63]. The questionnaire starts from the SF-36 questionnaire, and allows to describe the state of health through two synthetic indices calculated starting from the twelve questions addressed to the respondent. The SF-12 includes the following dimensions:

physical activity, physical health limitations in certain tasks or activities, emotional state, physical pain, self-assessment of general health, vitality, social activity and mental health. Higher SF-12 scores correspond to better health and QoL.

2.4.2 PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

The Patient Health Questionnaire-9 (PHQ-9)- appendix 2- is a short self-administered tool used for screening, diagnosing, monitoring, and measuring the severity of depression. The PHQ-9 is composed of 9 items that correspond to the symptoms of major depression according to the DSM-IV. The score has a range between 0 and 27. Scores between 0 and 9 indicate the presence of subthreshold depression. The score of 10 is indicated as the point at which the sensitivity and specificity of the instrument are recognized as optimal for highlighting depressions of clinical relevance [65]. The severity level of depression is broken down by PHQ-9 scores [65]:

- 5-9 = Minimal depressive symptoms / Sub-threshold depression
- 10-14 = Minor depression / Mild major depression
- 15-19 = Moderate major depression
- ≥ 20 = severe major depression [66].

2.4.3 VISUAL ANALOGUE SCALE (VAS)

The Visual Analogue Scale (VAS)- appendix 3- is a scale that measures the subjective perception of pain. It consists of a 10cm line with two ends representing "no pain" and "worst pain imaginable". Patients will be asked to rate perceived pain by placing a mark on the line corresponding to their current pain level. The distance along the line from the "no pain" marker is
then measured with a ruler that gives a pain score out of 10 [67].

2.4.4 FIBROMYALGIA IMPACT QUESTIONNAIRE (FIQ)

The Fibromyalgia Impact Questionnaire (FIQ) -appendix 4- : self-administered questionnaire, consisting of 20 questions,
divided into three parts. The first contains 11 items relating to the ability in the last week to carry out activities of daily life, with a variable score between 0 (always) and 3 (never). In the second and third, the number of days in the last week in which the patient felt well and in which he was unable to carry out his work (including housework) due to FM symptoms is requested. Questions 4 to 10 relate to the extent of FM interference with one's work, the intensity of pain and asthenia, the quality of night's rest, the intensity of stiffness and the presence of anxiety or depression; responses range from 0 (no disturbance) to 10 (very important disturbance), marked on a horizontal linear scale. The maximum score of the FIQ, corresponding to the highest degree of disability, is 100 [68, 69].

2.4.5 SLEEP SCALE FROM THE MEDICAL OUTCOMES STUDY (MOS)

The Medical Outcomes Study sleep (MOS) -appendix 5- is a self-administered self-assessment questionnaire consisting of 12 items and is aimed at evaluating certain fundamental parameters in sleep disorders such as falling asleep, sleep continuity, sleep duration, somnolence and disturbances. breathing during sleep. The evaluated period is the last month.
The total score on the scale ranges from 0 to 100. Higher scores indicate more disturbed sleep [70].

2.4.6 BODILY AND EMOTIONAL PERCEPTION OF PAIN (BEEP)

The BEEP -appendix 6- is an instrument made up of 23 items with Likert scale with six-step interval (from 0 to 5), organized into three subscales that can be defined according to the following denomination: "Emotional reaction" induced by pain (including 15 items), "Limitation" caused by pain in daily life (comprising 4 items), and "Interference" of pain on mood, interpersonal relationships, sleep and pleasure to live (4 items).

2.4.7 SENSE OF COHERENCE (SOC)

The sense of coherence- appendix 7-, is a self-administered questionnaire consisting of 13 items that provides a total score and a score for each dimension: "understandability" (C), which refers to the ability to perceive life events as coherent, structured and clear; "Manageability" (Ma), which refers to the ability to perceive that available resources meet the needs of life; and "Significance" (Me), which refers to the feeling that life, emotionally, makes sense. The total score ranges from 13 to 91, with higher scores indicating a higher SOC [71].

2.5 MEASURED VARIABLES

Sample variables:

- Gender;
- Age;
- Province of origin;
- Profession;
- Marital status;
- Educational qualification;

● Duration of painful symptoms;

● Duration of taking office at the pain therapy clinic of the San Giovanni di Dio Hospital;

● Psychiatric pathologies;

● Family history of psychiatric pathologies;

● Organic pathologies;

● Drugs taken.

2.6 INCLUSION AND EXCLUSION CRITERIA

All patients diagnosed with fibromyalgia belonging to the pain therapy clinic of the San Giovanni di Dio hospital over the age of 18 were included. Patients with cognitive difficulties and / or diagnosed mental retardation and male patients were also not included in the study. Male patients were excluded because access by male patients diagnosed with fibromyalgia is infrequent in the pain therapy clinic and it was decided to avoid bias, such as in the situation where identified a very low percentage compared to the rest of the sample under examination.

Psychiatric comorbidities do not have an exclusion criterion.

2.7PHASES OF THE PROJECT

The first phase of the study consists of the selection of the sample through the collection of personal and anamnestic data, which were collected in collaboration with the pain therapy and palliative medicine clinic of the San Giovanni di Dio hospital, through a specific format. paper. Each paper personal data sheet allows you to identify each patient with a code.

Patients eligible for participation were those who met all the inclusion criteria. At the end of the sample selection, each participant was evaluated through a clinical interview, aimed at making a diagnosis according to the DSM-V criteria, and a battery of standardized tests to be carried out in digital format with specific anonymous modules, such

as SF-12, PHQ-9, Visual Analogue Scale (VAS), Fibromyalgia impact questionnaire (FIQ), Sleep scale from the medical outcomes study (MOS), Body and emotional pain perception questionnaire (BEEP), Sense of Coherence - Life orientation questionnaire (SOC), aimed at assessing the subjective perception of the pathology. Specifically, fundamental aspects in FM were considered, such as the perception of the quality of life, the subjective perception of pain, the quality of sleep, the emotional impact of pain, mood and the presence or absence of depressive and anxious symptoms.

Each participant in the first evaluation phase was asked to fill in a personal data sheet and informed consent in paper format.

At the end of the evaluation phase, the selected sample was subjected to a total of 10 sessions of Biofeedback Training, once a week. Each session lasted 45 minutes. The overall duration of treatment was 10 weeks. At the end of the treatment all the participants were re-evaluated using the standardized, validated scales described above.

The measurements were carried out at T0 (time of taking charge), T1 (end of the proposed biofeedback treatment), T2 (three months from the end of the treatment), T3 (six months from the end of the treatment).

All data were treated in total anonymity. The collection of personal data took place with the use of a paper card which gave, in addition to the collection of data relevant for the research, the ability to assign each participant a unique identification code that will replace the name and surname of the subject. The latter was used only to record the patient's profile in the Biofeedback instrumentation in order not to disperse the data recorded by the session history of the individual participant.

The evaluation phase was carried out through standardized and validated questionnaires in digital format. Each questionnaire was totally anonymous and there were no references to names, personal details and / or numbers.

The personal data sheets and informed consents were managed by different investigators than those who managed the evaluation questionnaires.

The participants were blind about which condition (HRV-BR and usual

care, or usual care alone) will be used as control. The medical and psychological examiners were blind to whether the participants were assigned to the active intervention or the control condition. The trainers involved in the administration of the active intervention or the control condition were blind about the psychological status of the participants.

2.8 ETHICAL ASPECTS

The researcher was responsible for keeping the data obtained and informing the participants about the results of the analyzes, thus allowing their approval.

Each participant has consented, through a specific form, to the administration of the treatment in question

The Study Manager has ensured that all personnel involved in the study are qualified and adequately trained in the study procedures.

The Head of the study made sure that all the data reported faithfully correspond to the subject's profile and to all the information specifically requested by the protocol.

The data were processed in accordance with regulation (EU) 2016/679 of the European parliament and of the council of 27 April 2016 (General Data Protection Regulation) on the processing of personal data.

Also, the study was carried out according with the 1995 Declaration of Helsinki and subsequent revisions (World Medical Association, 2013).

The institutional review board on ethics of the "Azienda Mista Ospedaliero Universitaria di Cagliari" has approved the study protocol (Prot. N. NP/2019/3385, approved on 27/06/2019).

2.9 STATISTICAL ANALYSIS

Analyses were carried out with the Statistical Package for Social Sciences (SPSS) version 20. All tests were two-tailed (alpha set at $p<0.05$). The statistical analysis was carried out for continuous data with one-way analysis of variance (ANOVA). A multivariate analysis of variance (MANOVA) was used to test the effect of the two

independent time variables on the score of the scale for the pain outcome (VAS) and the scales for the secondary variables (as dependent variable). Secondary analyzes were carried out by introducing a specific cut-off for each scale, based on the international literature, which distinguished the probands in functionality / dysfunctionality with relation to the specific indicators.

The sample size of a hypothetical effect of HRV-BF on main and secondary outcomes for $\alpha<0.05$ and $\beta=0.20$ and a bidirectional hypothesis, was calculated from the differences in each outcome between active and control according to the Altmam method applied to RCT (Campbell et al 1995) as revised by Carley (Carley et al. 2005). The study is of a preliminary nature, and compare the effects of HRV-BF as add-on to the usual care versus the effects of the treatment as usual as it is applied to the population of people diagnosed with FM. The results of this study will be used to estimate the sample size needed for future studies, integrating them with the findings of a recent meta-analyzes that have established the effect size of the placebo in fibromyalgia on the same main and secondary outcomes of this study (Chen et al 2017).

3. RESULTS

The general characteristics of the sample are summarized in Table 1. The Table also shows the characteristics of the sample at the beginning of the trial (age, duration of disease and VAS score, main outcome) and compares these characteristics between those who finished the trial (N = 21) and those who abandoned the trial (N = 15).

Patients who finished the trial were older at the enrollment (50.2±4.9 vs 45.3±6.5; F[1;34]=6.577; p=0.015) and tended to a worse score on the pain scale (14.5±4.1 vs 11.8±4.5; F[1;34]=3.423;p= 0.073); they did not differ from those who dropped regarding the length of the illness (7.8±3.6 vs 6.6±3.1; F[1;34]=1.162; p= 1.162). The reasons for the withdrawal were recurrence of fibromyalgia symptoms for 13 patients (86.7%), while 2 patients did not indicate the causes of the withdrawal. A comparison with historical records did not reveal a significant increase in days with active disease during the trial in 14 patients out 15 (93%).

In the three parameters that were considered (age, length of illness and severity) we found no differences at the beginning of the trial between the 11 women (61.1%) that completed the trial in the active group and the 10 women (55.5%) that completed the trial in the control group: age 50.6±4.7 in the active group vs 49.8±5.1 in the control group (F[1;19]=0.136; p=0.717); length of illness: 8.1±3.7 in the active group vs 7.6±3.5 in the control group (F[1;19]=0.05; p=0.774); score at VAS scale: 14.1±4.6 in the active group and 14.9±3.6 in the control group (details in Table 2).

Table 2 shows the comparison at the beginnings and at the end of the trial of the means (±standard deviation) scores in active and control groups on the main outcome measure (VAS scale for pain). The score at the VAS scale tends to improve in both groups but while in the group treated with HRV-BF the difference between the end and the beginning of the trial is statistically significant according to the predefined threshold (F[1;20]=4.414; p=0.049, one way-ANOVA), in the control group it doesn't (F[1;18]=0.309; p=0.585).

The multivariate analysis that considers the two independent variables (time and group) confirms that the improvement in the active group is greater than in the control group ($F[1;19]=4.457$; $p=0.047$).

Using the Altman method, the sample size that would have had to be selected to verify the results for alpha = 0.05 and Beta = 0.20 would be of 50 subjects. If you want to plan a study against placebo, the result must be corrected considering the placebo. The main effect of placebo on pain in fibromyalgia measured by VAS is equal to an effect size=0.52 (95% confidence interval [CI]: 0.48 to 0.57) i.e. about a moderate effect or 20% of the total improvement in the control group against the trials with control groups in waiting list (Chen et al 2017). In our case, if the expected effect on the control group had increased by this measure, with this sample size (N = 21) there would have been an increase of a VAS score in the control group of 14.2 instead of 14.0. Introducing this correction, the sample size for a placebo-controlled trial would be 60.

Table 3 shows how in the three measured secondary items, in coherence with the main outcome, a slightly more marked improvement was observed in the treatment group: perception of the pain (BEEP, 16.3% improvement in active group vs 14.2% in control group), impact of fibromyalgia in daily life (FIQ, 9.5% in active group vs 6.9% in the control group), sleep disturbances (MOS, 11.2% vs 3.4%). However, in none of the three dimensions does the difference by time and group reach statistical significance.

To verify the hypothesis that the difference that emerged is real (at $\alpha<0.05$, and Beta=0.20, bi-directional hypothesis), based on the Altman calculation, the size of a study sample should be: 160 individuals (BEEP), 440 (FIQ), and 140 (MOS). The effect of placebo is detectable in literature on two of the three dimensions mentioned, i.e. improvement in the FIQ (Effect Size = 0.47; 95%CI: 0.43 to 0.49) (Chen et al. 2017) and improvement in the sleep pattern (many of the studies analyzed they adopted the MOS scale) (Effect Size = 0.41; 0.32 to 0.49) (Chen et al. 2017). The BEEP scale is new as a construct and therefore we have no estimates of the placebo effect on this measure

but, since it is a pain measure, we made the change based on the placebo effect measured on pain (Effect Size = 0.52; 0.48 to 0.57) (Chen et al. 2017). Taking these corrections into account, the sample sizes required for a placebo study become respectively: 180 (BEEP); 480 (FIQ); 148 (MOS).

Table 1. Comparison at the beginnings of the trial between characteristics of the patients who ended the trial and patients who didn't

	T0	**Age**	**Mean year duration of illness**	**Mean Score at Pain VAS**
Total of patients at the beginning of the trial	*n=36*	48.18±5.58	*7.32*±3.42	*13.39*±4.29
Patients who completed the trial	*n=21*	50.20±4.90	*7.84*±3.65	14.52±4.14
Patients who dropped out the trial	N=15 (8 Cr; 7 Act)	45.32±6.53	6.59±3.09	11.83±4.52
Difference between people at the end and dropping out		**F=6.577 df 1, 34, 35 p=0.015**	F= **1.162 df=1,34,45 p= 1.162**	F= **3.423 df=1,34,45 p= 0.073**

Table 2. Comparison at the beginnings and at the end of the trial on the scores at VAS scale in active and control groups (main outcome)

	To*	T1°	CHANGES OVER TIME Within groups	BETWEEN GROUP DIFFERENCES OVER TIME	Sample size needed for $\alpha<0.05$ Beta=0.20
VAS -Control Group	14.91±3.63 (N=10)	13.99±4.15 (N=10)	F=**0.278** **df 1,18,19** P=**0.604**	F= **4.457** **df 1,19,20** P=**0.047**	**50**
VAS-Active Group	14.12±4.61 (N=11)	10.42±3.60 (N=11)	F=**4.414, df 1,20,21** P=**0.049**		

Table 3. Comparison at the beginnings of the trial on the scores at BEEP, FIQ, and sleep MOS in active and control groups (secondary outcomes)

	To*	T1°	CHANGES OVER TIME Within groups	BETWEEN GROUP DIFFERENCES OVER TIME	Sample size needed For α<0.05 B=0.20
BEEP-Control Group	89.05±19.68 (N=10)	76.35±23.56 (N=10)	F=**1.712** **df 1,18,19** P=207	F=**0.180** **df 1,19,20** P=0.676	**160**
BEEP- Active *Group*	85.89±27.15 (N=11)	71.91±24.32 (N=11)	F=**1.618** **df 1,20,21** P=**0.218**		
FIQ- Control Group	**74.44±9.14** (N=10)	**69.26±16.02** (N=10)	F=**0.746** **df 1,18,19** P=0.399	**0.910** **df 1,19,20** P=0.352	**440**
FIQ- Active Group	**69,96±16.88** (N=11)	**63.33±11.67** (N=11)	F=**0.009** **df 1,20,21** P=**0.925**		
Sleep MOS- Control Group	36.03±6.00 (N=10)	34.80±7.79 (N=10)	F=**0.156** **df 1,20,21** p=0.697	F=**1.521** **df 1,19,20** P=0.233	**140**
Sleep MOS- Active Group	35.11±5.53 (N=11)	31.18±5.58 (N=11)	F=**2.753** **df 1,20,21** P=0.113		

4. DISCUSSION

This study was carried out on a small sample and its main aims were to determine whether, considering the initial hypothesis, an effectiveness of HRV-BF in the treatment of pain in fibromyalgia could be assumed, and to see if it is actually useful to continue this kind of research. Our goal was also to be able to conduct an estimate of the sample size necessary to verify the hypothesis of the efficacy of HVR-BF in contrasting pain (main outcome) and other symptomatic components of fibromyalgia (secondary outcome).

Our preliminary study confirmed the possible usefulness of HVR-BF in the therapy of pain in fibromyalgia. With regard to this main outcome, our study, albeit with limited power, showed that in the experimental group (which took HVR-BF as an add-on to usual care) the patients experienced a statistically significant decrease in pain compared to the control group (who only took the usual care). Even taking into account a role for the placebo effect, the hypothesis can be tested more robustly with samples of a size that can be afforded in a study of moderate complexity (N = 60). As far as the secondary outcomes were concerned, in all these measures there was a trend for a more marked improvement in the active treatment group compared to the control, but the observed improvement did not reach the predefined statistical threshold. Therefore, large samples would be required to check whether the observed improvement indicates an actual improvement of the same size. It should be considered that the present study was a 10-week trial and that more complex symptomatic components of FM, and the impact of the improvement on the quality of everyday life probably require longer times to fully manifest.

The estimate of the sample needed for future studies concerned the final sample. Our study unfortunately incurred in a considerable loss of patients in the trial (15 patients out of 36 = 41.6%, balanced between experimental and control group). If the role of dropout is taken into account, the possible sample to be used for the study of the effects of HRV-BF on pain in fibromyalgia should be no less than 85 patients. It

is interesting to note that, although most patients indicated the recurrence of the symptoms as the cause of the withdrawal from the trial, the severity of the disorder was no different between those who finished and those who withdrew. Therefore, it cannot be excluded that (unmeasured) motivational factors could have influenced the engagement in the trial.

In planning future studies, it will therefore be useful to consider these elements:

1) It is necessary to strongly motivate patients, as suggested by the present trial. It is also necessary to explain in detail the rationale of the study. Since the present study was exploratory and patients with FM often experiment with remedies that were not always scientifically proven, it has been ethically correct to explain the absence of evidence of efficacy and this may have reduced for some patients the motivation to engage in the trial.

2) In this trial, we had adopted a scheme that provided for the withdrawal of the patient of the trial after the absence of two sessions. Although methods of intention-to-treat analysis can partly overcome the problem of excessive withdrawal, however, our rigid scheme may not be easy to maintain in fibromyalgia and ways of recovering sessions should be considered in case of recurrence of symptoms.

The results of this study confirm the evidence emerging in open label studies on HVR-BF [72, 73] and can be justified on the basis of strong interpretative assumptions. Robust evidence has shown that people suffering from FM have HRV dysregulation [74]; currently it is not known if this aspect is a primary element of the disorder or is secondary to painful and / or anxious depressive symptoms, which are related to HRV dysregulation [75, 76, 77]. It is known that the central sensitization of people with fibromyalgia induces short circuits that trigger exaggerated alarm mechanisms in the presence of any nociceptive threat [78]. It is intuitive, but also experimentally demonstrable, that HRV also responds to mechanisms of greater dysregulation triggered by alarm [77]. Obviously, acting on the HRV control deals with the control of the hyper alarm short circuits.

Therefore, it acts on the mechanisms that accentuate sensitivity to pain but also, since offering knowledge to the patient on what is happening, generate awareness of the potential of some ability to intervene. This is a critical point because it interfere with a mechanisms that strongly cause aggravation: the powerless and impossibility to contrast against the arising of pain, which generate the fear to being at the mercy of the disorder, typical of the severe fibromyalgia.

5. CONCLUSION

In conclusion, we can highlight how important it is to continue the research activity for such a complex and, to date, still little known pathology. FM is a pathology that weighs heavily on the QoL of the people who suffer from it and, unfortunately, there is currently no treatment of choice.

Our study, although conducted on a small sample, allowed to highlight important aspects for the treatment of FM.

The results show us that through the use of biofeedback it is possible to work on the typical symptoms of the disease.

We were able to observe a significant decrease in the painful component and the remaining areas, although not significantly, showed improvements.

Therefore it is considered necessary to maintain high scientific interest in such a highly disabling pathology.

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8. APPENDIX -1

STRUMENTO PER LA VALUTAZIONE DELLO STATO DI SALUTE SF-12

Versione italiana a cura dell'Istituto Superiore di Sanità – Roma

La preghiamo di rispondere alle seguenti domande relative al suo stato di salute. Le informazioni che ci darà rimarranno strettamente confidenziali e non saranno comunicate a nessuno senza il suo permesso. Ci serviranno per capire meglio come si sente e fino a che punto è in grado di svolgere le sue normali attività.

1. **Come giudica nel suo complesso la sua salute?**

5 - eccellente
4 - molto buona
3 – buona
2 – passabile
1 – cattiva

Le seguenti domande riguardano le attività che potrebbe fare in un giorno qualsiasi. In che misura le sue condizioni di salute le rendono difficile, la limitano nel fare le seguenti attività:

2. **attività che richiedono discreti sforzi fisici (come spostare un tavolo, manovrare un'aspirapolvere, fare un giro in bicicletta…)**

1 – mi limitano molto
2 – mi limitano un po'
3 – non mi limitano per niente

3. **salire alcune rampe di scale**

1 – mi limitano molto
2 – mi limitano un po'
3 – non mi limitano per niente

Nelle ultime 4 settimane, a causa di malattie fisiche, ha avuto i seguenti problemi al lavoro, o nelle altre attività di tutti i giorni?

4. **ha reso meno o fatto meno bene di quello che avrebbe voluto?** SI NO

5. **ha dovuto rinunciare a fare alcune cose sul lavoro o nelle altre attività?** SI NO

Nelle ultime 4 settimane, a causa di problemi psicologici, ad esempio perché si sentiva depresso o ansioso, o perché gli altri non le credevano o volevano fargli del male:

6. ha reso meno di quello che avrebbe voluto? NO SI

7. Non ha fatto le cose con la stessa cura e attenzione che avrebbe voluto? SI NO

8. nelle ultime 4 settimane, il dolore fisico le ha reso difficile il lavoro o le altre attività, in casa e fuori?

5 – per niente
4 – un po'
3 – abbastanza
2 – molto
1 – moltissimo

Le seguenti domande riguardano il suo stato d'animo nelle ultime 4 settimane. Per quanto tempo nelle ultime 4 settimane si è sentito:

9. calmo e sereno?

6 – sempre
5- la maggior parte del tempo
4 – più o meno metà del tempo
3 – qualche volta
2 – raramente
1 – mai

10. pieno di energia?

6 – sempre
5- la maggior parte del tempo
4 – più o meno metà del tempo
3 – qualche volta
2 – raramente
1 – mai

11. scoraggiato e triste?

1 – sempre
2 - la maggior parte del tempo
3 – più o meno metà del tempo
4 – qualche volta
5 – raramente
6 – mai

12. Nelle ultime 4 settimane, per qunto tempo la sua salute fisica o le sue condizioni psicologiche le hanno causato problemi nella vita sociale (ad esempio nei suoi rapporti con parenti e amici?

1 – sempre
2 – la maggior parte del tempo
3 – qualche volta
4 – raramente
5 – mai

APPENDIX-2

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

QUESTIONARIO SULLA SALUTE DEL/DELLA PAZIENTE-9 72883
(Italian version of the PHQ-9)

THIS SECTION FOR USE BY STUDY PERSONNEL ONLY.

Were data collected? **No** ☐ *(provide reason in comments)*

If **Yes**, data collected on visit date ☐ **or** specify date: _____
DD-Mon-YYYY

Comments:

Only the patient (subject) should enter information onto this questionnaire.

Nelle ultime 2 settimane, con quale frequenza le ha dato fastidio ciascuno dei seguenti problemi?	**Mai**	**Alcuni giorni**	**Per più della metà del tempo**	**Quasi ogni giorno**
1. Scarso interesse o piacere nel fare le cose	0	1	2	3
2. Sentirsi giù, triste o disperato/a	0	1	2	3
3. Problemi ad addormentarsi o a dormire tutta la notte senza svegliarsi, o a dormire troppo	0	1	2	3
4. Sentirsi stanco/a o avere poca energia	0	1	2	3
5. Scarso appetito o mangiare troppo	0	1	2	3
6. Avere una scarsa opinione di sé, o sentirsi un fallimento o aver deluso se stesso/a o i propri familiari	0	1	2	3
7. Difficoltà a concentrarsi su qualcosa, per esempio leggere il giornale o guardare la televisione	0	1	2	3
8. Muoversi o parlare così lentamente da poter essere notato/a da altre persone. O, al contrario, essere così irrequieto/a da muoversi molto più del solito	0	1	2	3
9. Pensare che sarebbe meglio morire o farsi del male in un modo o nell'altro	0	1	2	3

SCORING FOR USE BY STUDY PERSONNEL ONLY

_0_ + _____ + _____ + _____

=**Total Score:** _____

Se ha fatto una crocetta su uno qualsiasi di questi problemi, quanto questi problemi le hanno reso difficile fare il suo lavoro, occuparsi delle sue cose a casa o avere buoni rapporti con gli altri?

Per niente difficile	**Abbastanza difficile**	**Molto difficile**	**Estremamente difficile**
☐	☐	☐	☐

 EPIS05.PHQSP

Confermo l'esattezza di queste informazioni.	Iniziali del/della paziente o del soggetto:	Data:

APPENDIX-3

VAS SCALE

VALUTAZIONE DEL DOLORE DA PARTE DEL PAZIENTE

NESSUN DOLORE POSSIBILE _____ MASSIMO DOLORE

APPENDIX-4

FIBROMYALGIA IMPACT QUESTIONNARIE

FIQ

ISTRUZIONI: nelle domande dal numero 1 al numero 11 del questionario che segue, verranno poste delle domande riguardo alle attività che si è stati in grado di svolgere nell'ultima settimana.
Rispondere a ciascuna domanda, mettendo una crocetta nella casella corrispondente (solo una risposta per ciascuna domanda).
Se normalmente non si svolge l'attività cui la domandasi riferisce, barrare le casella 4.

NEL CORSO DELL'ULTIMA SETTIMANA E' STATO IN GRADO DI	SEMPRE 0	QUASI SEMPRE 1	QUALCHE VOLTA 2	MAI 3	ATTIVITA' NON SVOLTA ATTUALMENTE
1) ANDARE A FARE LA SPESA	0	1	2	3	4
2) FARE IL BUCATO (LAVATRICE)	0	1	2	3	4
3) PREPARARE I PASTI	0	1	2	3	4
4) LAVARE I PIATTI	0	1	2	3	4
5) PASSARE L'ASPIRAPOLVERE	0	1	2	3	4
6) RIFARE I LETTI	0	1	2	3	4
7) CAMMINARE PER QUALCHE ISOLATO	0	1	2	3	4
8) ANDARE A FAR VISITA A PARENTI O AMICI	0	1	2	3	4
9) FARE LAVORI DI GIARDINAGGIO – ORTO	0	1	2	3	4
10) GUIDARE L'AUTO	0	1	2	3	4
11) SALIRE LE SCALE	0	1	2	3	4

12) QUANTI GIORNI SU 7 DELL'ULTIMA SETTIMANA SI E' SENTITA BENE?

0	1	2	3	4	5	6	7

13) QUANTI GIORNI SU 7 DELL'ULTIMA SETTIMANA NON E' ANDATA A LAVORO O NON HA POTUTO FARE LAVORI DOMESTICI A CAUSA DELLA FIBROMIALGIA?

0	1	2	3	4	5	6	7

Risponda alle seguenti domande apponendo un segno sulla riga sottostante
(estrema sinistra = nessun problema estrema destra = massima difficoltà)

14) SUL POSTO DI LAVORO O A CASA DURANTE I LAVORI DOMESTICI, QUANTA DIFFICOLTA' HA AVVERTITO A CAUSA DEL DOLORE O DEGLI ALTRI SINTOMI DELLA FIBROMIALGIA?

---

15) QUANTO E' STATO FORTE IL SUO DOLORE?

---

16) QUANTO SI E' SENTITA STANCA?

---

17) COME SI E' SENTITA AL RISVEGLIO?

---

18) QUANTO SI E' SENTITA RIGIDA?

---

19) QUANTO SI E' SENTITA ANSIOSA O NERVOSA?

---

20) QUANTO SI E' SENTITA DEPRESSA O TRISTE?

APPENDIX-5

SLEEP SCALE FROM THE MEDICAL OUTCOMES STUDY (MOS)

QUESTIONARIO

	0-15 minuti	16-30 minuti	31-45 minuti	46-60 minuti	Più di 60 minuti
1. Pensando alle ultime 4 settimane quanto tempo ha impiegato ad addormentarsi? (indichi una risposta)	1	2	3	4	5
2. Pensando alle ultime 4 settimane, in media, quante ore ha dormito? Scriva il numero di ore per notte:					
Con che frequenza nelle ultime 4 settimane Lei… (indichi una risposta per ognuna delle affermazioni)					
	Mai	Per poco tempo	Per un bel po' di tempo	Per la maggior parte del tempo	Per tutto il tempo
3. Sentiva che il suo sonno era agitato (si muoveva, parlava, ecc.)?	1	2	3	4	5
4. Dormiva sufficientemente tanto da sentirsi riposato al mattino?	1	2	3	4	5
5. Si svegliava perché Le mancava il respiro o perché aveva mal di testa?	1	2	3	4	5
6. Si sentiva stanco o assonnato durante il giorno?	1	2	3	4	5
7. Aveva problemi ad addormentarsi?	1	2	3	4	5
8. Si svegliava durante la notte e aveva difficoltà ad addormentarsi?	1	2	3	4	5
9. Aveva problemi a stare sveglio durante il giorno?	1	2	3	4	5
10. Russava mentre dormiva?	1	2	3	4	5
11. Faceva sonnellini (5 min o più lunghi) durante il giorno?	1	2	3	4	5
12. Riusciva a dormire per il tempo necessario ai suoi bisogni?	1	2	3	4	5

APPENDIX-6

BODILY AND EMOTIONAL PERCEPTION OF PAIN (BEEP)

Su una scala da 0 a 5 indichi con quale intensità ha provato i seguenti stati d'animo nel più recente momento di maggiore dolore:

1. Irritabilità 0 1 2 3 4 5
(perdo la pazienza per un nonnulla)

2. Sentimento di impotenza 0 1 2 3 4 5

3. Depressione 0 1 2 3 4 5
(profonda tristezza con perdita di interesse)

4. Senso di ingiustizia (perché io?) 0 1 2 3 4 5

5. Pessimismo (visione negativa del futuro) 0 1 2 3 4 5

6. Ansia 0 1 2 3 4 5

7. Senso di colpa 0 1 2 3 4 5
(ad esempio: mi sento un peso per la mia famiglia)

8. Frustrazione 0 1 2 3 4 5
(non posso farci niente e mi fa rabbia)

9. Sfiducia nelle mie capacità 0 1 2 3 4 5

10. Paura di non guarire 0 1 2 3 4 5

11. Confusione (mi sento meno lucido) 0 1 2 3 4 5

12. Non riconosco me stesso 0 1 2 3 4 5

13. Mi sento invecchiato 0 1 2 3 4 5

14. Mi sento menomato 0 1 2 3 4 5

15. Non mi sento indipendente 0 1 2 3 4 5

Su una scala 0 a 5 con quale gravità, nel corso delle ultime due settimane, la sindrome dolorosa ha limitato:

16. La sua prestazione lavorativa 0 1 2 3 4 5

17. La sua capacità di movimento 0 1 2 3 4 5

18. Il suo ruolo sociale 0 1 2 3 4 5

19. La sua attività sportiva 0 1 2 3 4 5

interferito con:

20. L'umore 0 1 2 3 4 5

(tonalità affettivo-emotiva interna,

ad esempio: più spesso triste, più spesso allegro)

21. Le relazioni interpersonali 0 1 2 3 4 5

22. Il sonno 0 1 2 3 4 5

23. Il piacere di vivere 0 1 2 3 4 5

Indichi il numero che meglio descrive l'intensità del suo dolore:

24. In media nelle ultime 24 ore

0 1 2 3 4 5 6 7 8 9 10

25. In questo momento

0 1 2 3 4 5 6 7 8 9 10

APPENDIX-7

Sense of Coherence Scale (SOC)

Dipartimento di Sanità Pubblica – Università degli studi di Cagliari (Italy)

Sense of Coherence – Questionario di Orientamento alla vita

Forma breve- 13 domande

Fonte: Antonovsky, Aaron Unraveling the Mystery of Health. How People Manage Stress and StayWell. San Francisco 1987.

C = comprensibilità Ma = gestibilità Me = significato

1. Ha la sensazione che non le importi realmente ciò che accade intorno a lei? (Me)

1	2	3	4	5	6	7
Molto raramente o mai						Molto spesso

2. Le è capitato in passato di essere sorpreso dal comportamento di persone che pensava di conoscere bene? (C)

1	2	3	4	5	6	7
Mai successo						Sempre successo

3. Le è capitato che le persone su cui contava la abbiano delusa? (Ma)

1	2	3	4	5	6	7
Mai successo						Sempre successo

4. Fino a questo momento la sua vita ha avuto: (Me)

1	2	3	4	5	6	7
Obiettivi e scopi per niente chiari						Obiettivi e scopi molto chiari

5. Ha mai la sensazione di essere trattato ingiustamente? (Ma)

1	2	3	4	5	6	7
Molto spesso						Molto raramente o mai

6. Ha mai la sensazione di trovarsi in una situazione poco familiare e non sapere cosa fare? (C)

1	2	3	4	5	6	7
Molto spesso						Molto raramente o mai

7. Fare le cose di ogni giorno è: (Me)

1	2	3	4	5	6	7
Fonte di profondo piacere e soddisfazione						Fonte di dolore e di noia

8. Ha sensazioni ed idée molto confuse? (C)

1	2	3	4	5	6	7
Molto spesso						Molto raramente o mai

APPENDIX-8

PERSONAL DATA FORM

Scheda n° ____

Cognome _____ Nome_____

Luogo di nascita _____ Data di nascita ____/____/_____

1) Età _____
2) Genere

F	M

3) Provincia di origine

CA	NU	OR	SS	SU

4) Livello di scolarizzazione

	SCUOLA ELEMENTARE
	LICENZA MEDIA
	LICENZA MEDIA-SUPERIORE
	LAUREA
	ALTRO: _____

5) Stato occupazionale

	OCCUPATO/A
	DISOCCUPATO/A
	CASALINGO/A
	PENSIONATO/A
	STUDENTE/SSA
	ALTRO: _____

6) Stato civile

	NON CONIUGATO/NON CONVIVENTE
	CONIUGATO/CONVIVENTE
	VEDOVO NON CONVIVENTE
	VEDOVO CON NUOVO PARTNER

7) Figli

	SI	QUANTI? _____
	NO	

ANAMNESI INDIVIDUALE/FAMILIARE

1) Da quanto tempo accusa la sintomatologia dolorosa?
   Anni_____

2) Da quanto tempo è in carico presso l'ambulatorio di terapia del dolore e medicina palliativa dell'ospedale Civile San Giovanni di Dio?

   _____

3) Ha mai sofferto o soffre di disturbi psichiatrici (depressione, ansia, attacchi di panico, ecc)?

SI	NO

   Se si, quale/i?

   _____

4) Ci sono stati nella sua famiglia (genitori, fratelli, figli, zii, nonni) casi di diagnosi di disturbi psichiatrici?

SI	NO

   Se si, chi e quale/i?

   _____

5) Soffre di altre patologie croniche non psichiatriche?

SI	NO

Se si, quali? _____

6) Assume farmaci?

SI	NO

Se si, quali? _____