Review

Fibromyalgia: one year in review 2024

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ABSTRACT

Fibromyalgia (FM) remains a condition with a pathogenesis that is not completely understood, affecting a significant portion of the global population. This article summarises the main advances in FM during the last year. Even in 2023, research on FM was notably active. From a clinimetric perspective, studies have been conducted to evaluate the possibilities of interchanging the primary indices of disease severity, primarily for studies with substantial case numbers. Regarding FM pathogenesis, ongoing research focuses on small fibre neuropathy: some studies have documented its association with central sensitisation, while others have revealed distinct sensory profiles in patients with FM and small fibre neuropathy compared to those solely with small fibre neuropathy. Dorsal root ganglia seem to play a crucial role in the pathogenesis of FM as they host satellite glial cells, which are targeted by pain-driving immunoglobulin G. These antibodies have been identified in a subset of patients exhibiting high symptom severity. An important study conducted on animal models confirmed the role of neuroinflammation at the level of dorsal root ganglia, in this case mediated by polymorphonuclear neutrophils. Mounting evidence underscores the link between COVID-19 and the persistence of FM symptoms after recovery. In identifying potential biomarkers aiding FM diagnosis, research has also concentrated on studying the expression of specific circulating microRNAs. Recent discoveries have unveiled novel therapeutic strategies for FM, especially focused in non-pharmacological interventions. This includes a focus on non-invasive brain stimulation and exercise programmes, all directed towards relieving symptoms and improving functionality in individuals affected by the condition.

Introduction

Fibromyalgia (FM) remains one of the most contentious medical conditions. There are numerous aspects that require clarification from various perspectives, including diagnostic, pathogenetic, and therapeutic. Research on this condition has been highly active and significant throughout 2023, with approximately 1000 new bibliographic entries on PubMed for this calendar year alone. This article aims to conduct a narrative review of the literature on the main advancements in the field published from January to December 2023.

Diagnosis and clinimetry

To date, the gold standard for diagnosing FM in routine clinical practice remains predominantly the judgment of the clinician. However, there are numerous questionnaires available to assess the symptoms of FM and to determine the severity of the condition. A systematic review of the literature has identified 16 questionnaires proposed for the evaluation of FM, describing their properties primarily in terms of reliability and validity. Although there is a wide variability among the questionnaires, the systematic review concludes that the basic psychometric characteristics are generally good and, in some cases, excellent. This systematic review included widely used clinimetric tools such as the Revised Fibromyalgia Impact Questionnaire (FIQR) and the Fibromyalgia Assessment Status (FAS), but did not consider more modern instruments like the modified version of the FAS (FASmod) and the Polysymptomatic Distress scale (PSD) (1).

Remaining within the realm of clinimetrics, two studies have focused on the main assessment scales, drawing data from the Italian Fibromyalgia Registry. The first study, given the correlation between FIQR, FASmod and

PSD, has determined linear equations for converting the scores of each of these three indices into the others using regression models. For instance, starting with a PSD score, it is possible to determine the corresponding FIQR score (in this case, the equation corresponding to the model y = mx + c is: FIQR = 2.309xPSD + 15.924). This approach, which allows for the conversion of scores between three of the primary instruments, enables the comparison of cases assessed with different clinimetric tools. These types of equations are applicable on large cohorts but lose precision when applied to individual patients (2). The second study mentioned refers to the definition of the Patient Acceptable Symptom State (PASS) for the three already mentioned tools: FIQR, FASmod, and PSD. Based on data from 5914 patients, the study identified a PASS of ≤58 for FIQR, ≤23 for FASmod, and ≤16 for PSD. The PASS is an interpretive cut-off point used to identify those patients who consider their current symptomatic status as acceptable. This allows for an easy interpretation of symptomatic severity based on the instrument used, facilitating a better understanding of the patient's perception of their condition and its management (3).

The application of cut-off points on numerical scales, however, may lead to the loss of some information. The diagnostic approach to a condition like FM should be dimensional, that is, connected to the evaluation of a wide spectrum rather than based on the application of dichotomous criteria. Wolfe and colleagues, using data from a database encompassing over 30,000 patients affected by conditions of rheumatological interest, demonstrated that, in comparing patients without a diagnosis but with a PSD score between 8–11 to those with a diagnosis and a PSD score ranging from 12-18, the scores related to pain, functional limitation, psychological status, and other studied variables are substantially overlapping. The authors advocate for the use of PSD as a tool to evaluate the entire dimension of FM, rather than solely as a categorical variable (4).

In the strictly diagnostic context, no new sets of criteria have been proposed in the last 12 months. However, a position statement from the Italian Society of Neurology Neuropathic Pain Study Group has been published, proposing a flow-chart where the diagnostic cornerstone remains the 2016 criteria of the American College of Rheumatology (ACR). This flow-chart introduces the examination of small somatic and autonomic fibres. For patients with FM, the authors recommend the study of at least two among the following: heart rate variability plus sympathetic skin response and/or laser-evoked responses and/or skin biopsy and/or corneal confocal microscopy. This approach aims to enhance the diagnostic process by integrating neurophysiological and histopathological techniques to assess small fibre function and structure, offering a more comprehensive understanding of the neurobiological aspects of FM (5).

A Mexican study assessed the diagnostic performance of a simple manoeuvre capable of inducing allodynia, such as the measurement of systemic arterial pressure. The allodynia caused by inflating the sphygmomanometer to 170 mmHg demonstrated a sensitivity of 63% and a specificity of 84% (area under the curve 0.751) relative to the 2016 ACR criteria in the diagnosis of FM. The authors conclude that, particularly in the female population (as the test performs poorly in men), assessing pain evoked by the measurement of arterial pressure is a simple and efficient procedure for detecting FM. This finding suggests that routine clinical practices, such as blood pressure measurement, can be utilised as a tool for the initial screening of FM, particularly in settings where more specialised diagnostic tools may not be readily available (6).

Take home messages

- The PASS thresholds for the main clinimetric indices are as follows: ≤58 for the FIQR, ≤23 for the FASmod, and ≤16 for the PSD (3).
- There are conversion equations available that can be applied to large datasets to convert scores between the FIQR, FASmod, and PSD (2).
- The use of the PSD as a strictly dichotomous criterion in the diagnosis of FM should be interpreted with caution due to the significant overlap of pain, functional impairment, and psychological distress in patients with scores around 12 (4).
- Allodynia caused by blood pressure measurement may indicate the presence of FM in the female population (6).

Prognostic implications

The presence of FM appears to confer an increased risk of mortality over time: a systematic review of the literature has revealed that, considering broad temporal intervals (ranging from 16 to 31 years depending on the studies), FM is associated with a 27% increased hazard ratio for all-cause mortality. This conclusion is applicable to all patients except those diagnosed using the ACR 1990 criteria, in which this increase in all-cause mortality was not observed. Although the studies exhibit considerable heterogeneity, in patients with FM, an increased standardised mortality ratio (SMR) is noted for accidents (SMR 1.95), infections (SMR 1.66), and suicide (SMR 3.37), while there is a reduced mortality rate for cancer (SMR 0.82) (7).

In investigating the role of FM in opioid use disorder (OUD), a study in the United States has shown that FM is a predictor of various aspects of pain-related OUD (maintenance, escalation, delay in OUD treatment, and relapse). To investigate these four aspects, the authors proposed the introduction of a new scale (Pain-related OUD Exacerbation Scale [PrOUD ES]), demonstrating that the presence of FM increases the likelihood of a positive response associated with pain-related OUD exacerbation and is therefore a risk factor for this condition (8).

The sequelae of COVID-19, in certain respects, bear a close resemblance to the symptoms of FM across various health domains. A study that examined 707 patients affected by post-COVID-19 syndrome, FM, chronic fatigue syndrome, or combinations of these conditions, revealed that both physical and cognitive functions are

compromised in all three conditions. However, patients diagnosed solely with post-COVID-19 exhibited lower levels of pain and fatigue compared to those with FM and chronic fatigue syndrome. Nonetheless, the presence of overlapping conditions, such as FM in conjunction with post-COVID-19, results in a heightened severity of pain symptoms (9).

Take home messages

- FM is associated with an increased hazard ratio of mortality compared to the general population, especially due to accidents, infections, and suicide, while cancer-related mortality is reduced (7).
- FM is associated with an increased risk of opioid use disorder (8).
- Post-COVID-19 syndrome has a significant overlap with FM symptoms and exacerbates painful symptoms when coexisting with FM (9).

Pathogenesis

Immunological mechanisms and neuroinflammation

The pathogenesis of FM is likely one of the most obscure and contentious aspects of the condition, with expert opinions remaining divergent (for example, whether FM is an autoimmune disease or not) (10). Throughout 2023, numerous publications have focused on the pathogenetic aspects of FM.

Caxaria *et al*. have demonstrated a pronociceptive role of neutrophils in FM. By utilising neutrophils from a murine model of widespread chronic pain, as well as neutrophils derived from patients, they employed a back-translational approach to document the infiltration of these neutrophils into the dorsal root ganglia. Neutrophils capable of invading the dorsal root ganglia of naive mice include both exogenous human neutrophils and endogenous murine neutrophils. Beyond the cellular invasion of the dorsal root ganglia demonstrated with immunohistochemical techniques, mechanisms of mechanical and thermal hypersensitivity are established in the recipient mice. The authors conclude that in both mice and humans with widespread chronic pain, neutrophils play a pronociceptive role. However, further studies will be necessary to determine the phenotype of pronociceptive neutrophils and the mediators responsible for the cross-talk between neutrophils and sensory neurons (11).

Since 2021, significant research has focused on the pathogenetic role of anti-satellite glial cell (SGC) IgG antibodies. It has been demonstrated that these anti-SGC IgG antibodies have the ability to bind to the dorsal root ganglia, and that FM can be transferred from humans to mice through these antibodies (12).

Patients with FM carrying these antibodies appear to have a phenotype of disease characterised by increased disease severity. Krock et al. have investigated, in two distinct cohorts of patients with FM, that an increase in the titre of anti-SGC IgG correlates with increased severity of FM. The presence of elevated levels of anti-SGC IgG does not impact other characteristics such as pain pressure threshold, the duration of chronic pain, the duration of FM, and age (13).

Over the past year, a further study has documented the role of these antibodies at the brain level as well. It has been confirmed that patients with high levels of anti-SGC IgG, compared to patients with low levels, exhibit a more severe disease phenotype, both in terms of the Visual Analogue Scale of Pain (VAS-now) and the Fibromyalgia Impact Questionnaire (FIQ); the titre of anti-SGC IgG directly correlates with these two clinimetric parameters. However, the level of anti-SGC IgG does not correlate with pressure-evoked pain. In terms of imaging, researchers have demonstrated that, although no significant differences were observed in the functional MRI analysis of cerebral pain processing in patients with high *versus* low titres of anti-SGC IgG, differences in the presence of certain brain metabolites were noted. Specifically, the titre of anti-SGC IgG negatively correlates with scyllo-inositol levels in the thalamus and the rostral anterior cingulate cortex, and with total choline and macromolecule 12 in the thalamus. Therefore, anti-SGC IgG antibodies are primarily responsible for a clinical phenotype in patients with FM characterised more by spontaneous and unprovoked pain, and with some detectable metabolic repercussions in certain areas of the brain (14).

Positron emission tomography (PET) studies aimed at investigating neuroinflammation in FM have predominantly utilised radioligands capable of binding to the 18 kDa translocator protein (TSPO). TSPO receptors are preferentially expressed in the mitochondria of activated microglia. DPA-714 is a ligand that selectively binds to TSPO. Mueller and colleagues, employing [18F]DPA-714 as the ligand, analysed the distribution volume across 28 brain regions of interest. It was documented that in patients with FM, compared to healthy controls, the distribution volume was significantly higher in specific regions such as the right postcentral gyrus, right occipital grey matter, and the right temporal grey matter, regardless of the genetically determined affinity for TSPO. Patients with high affinity demonstrated additional regions of interest capable of binding [18F] DPA-714 (bilateral praecuneus, the left in addition to the right postcentral gyrus, the bilateral parietal grey matter, the left in addition to the right occipital grey matter, and the bilateral supramarginal gyri). This study provides further evidence supporting the characterisation of FM as a condition marked by neuroinflammation, which can be detected using a novel radiotracer (15).

Peripheral nerves involved

In recent years, several studies have focused on small fibre neuropathy in the context of FM. Publications on this topic have continued to emerge in 2023. One study conducted a comparative analysis of the sensory phenotypes in patients with concomitant small fibre neuropathy and FM *versus* those diagnosed with isolated small fibre neuropathy. The authors identified markedly distinct sensory characteristics between these two patient groups. In individuals with FM, regardless of the presence of small fibre neuropathy, the normal sensory phenotype and the manifestations of thermal and mechanical hyperalgesia were similarly represented. Conversely, in patients with isolated small fibre neu-

ropathy, the predominant phenotypes were sensory loss and mechanical hyperalgesia. The significant overlap of sensory profiles in patients with FM, both with and without small fibre neuropathy, along with the frequent occurrence of a normal sensory phenotype, underscores the challenges in diagnosing small fibre neuropathy within the context of FM (16).

Another study explored the utility of electrochemical skin conductance (ESC) as a means to assess the integrity of distal autonomic fibres. Reduced ESC values were observed in 20% of the patient cohort. These individuals exhibited pronounced symptoms of pain centralisation. Scores exceeding 60 on the Central Sensitization Inventory (indicative of extreme centralisation) were identified as the primary determinant of ESC abnormalities. Thus, alterations in small nerve fibres are associated with symptoms of centralisation in FM (17).

In addition to studies on small fibre neuropathy, research has been published that identifies ultrasonographic changes in patients with FM, characterised by an increased cross-sectional area (CSA) of certain nerves. By examining the CSA of nerves at 11 predefined anatomical sites, it was found that patients with FM, in comparison to healthy subjects, exhibit a predominantly increased CSA in the sural nerve, the vagus nerve, and the sixth cervical root. However, this increased CSA does not correlate with specific clinimetric data, and therefore does not facilitate the identification of a particular disease subset. The principal hypotheses underpinning these ultrasonographic alterations in CSA could be related to small fibre neuropathy, where damage may lead to altered retrograde axonal flow, or to mechanisms of neuroinflammation (18).

Central sensitisation

Proton magnetic resonance spectroscopy (1H-MRS) enables the visualisation of changes in excitatory and inhibitory neurotransmitters in the brain of patients with FM. A recent study utilised 1H-MRS to assess concentrations of glutamate and γ-aminobutyric acid (GABA) within the anterior insula. During sustained evoked pressure pain, increased levels of excitatory neurotransmitters relative to inhibitors in the anterior insula were found to modulate an enhanced cross-network connectivity between the anterior insula and the default mode network through a reduced occurrence of co-activation patterns that include the attentional networks. Furthermore, sustained evoked pressure pain promotes the presence of a co-activation pattern involving the sensorimotor network (19).

Biomarkers

MicroRNAs (miRNAs) constitute a class of non-coding RNAs capable of regulating gene expression at the post-transcriptional level. Their role is crucial in numerous physiological processes. In recent years, miRNAs have been increasingly utilised for diagnostic purposes as diagnostic biomarkers. A Canadian study has revealed that, compared to healthy controls, the 11 miRNAs (namely, hsa-miR-28-5p, hsa-miR-29a-3p, hsa-miR-127-3p, hsa-miR-140-5p, hsa-miR-150-5p, hsa-miR-181b-5p, hsa-miR-374b-5p, hsa-miR-486-5p, hsa-miR-3620-3p, hsa-miR-4433a-5p, and hsa-miR-6819-3p) previously evaluated in myalgic encephalomyelitis (ME)/CFS are all significantly reduced in patients with FM. Some of these miRNAs have shown stronger correlations with certain symptoms, others with pain. The primary objective of the study was the identification of miRNAs capable of distinguishing ME/CFS from FM. Indeed, three miRNAs (miR-127-3p, miR-140-5p, and miR-374b-5p) appear to be capable of distinguishing between the two conditions, as they are reduced in FM while being overexpressed in ME/CFS (20).

Take home messages

- Neutrophil invasion of the dorsal root ganglia plays a pronociceptive role in the murine model, and through these cells, mechanical and thermal hypersensitivity can be transferred to the recipient mouse (11).
- In addition to having a pathogenetic role, the titre of anti-satellite glial cell IgG correlates with more severe FM and is associated with certain alterations of substances at the brain level (13, 14).
- The presence of small fibre neuropathy in patients with FM does not result in a different sensory profile compared to FM patients without small fibre neuropathy. Furthermore, a reduced electrochemical skin conductance, indicative of damage to the small autonomic fibres, is associated with more severe symptoms of pain centralisation (16, 17).
- Certain microRNAs may have a pathogenetic role in FM and could be supportive in diagnostics (20).

Treatment

Pharmacological therapy

Duloxetine. The optimal daily dose of duloxetine (DLX) in FM is still controversial, and a systematic review investigated efficacy and safety of DLX at different doses. DLX demonstrated to be more effective than placebo in improving symptoms of FM at all doses investigated (30, 30-60, 60, 60-120 and 120 mg/daily). Exploring the different outcomes, the 60 mg/daily cohort obtained the best result in the FIQ, the 30–60 mg/daily group reported the worst outcome in the Brief Pain Inventory interference and severity pain scores, while no differences were found between different groups of treatment in the Clinical Global Impression severity scale. The rate of study discontinuation due to the occurrence of adverse events were lower in the 60–120 group, followed by the other groups; the placebo cohort reported the lowest rate of adverse events. The perfect dose should therefore be adjusted according to each patient (21).

Pregabalin. Pregabalin (PGB) is an antiepileptic drug used for the treatment of pain-related conditions. An experimental research with 85 female participants investigated variations in serum concentrations of proinflammatory cytokines (IL-2, IL-6, IL-12, IL-17, IFN gamma, and TNF alpha) with PGB therapy. It was found that cytokines were higher in patients with FM not using PGB than in healthy subjects ($p<0.001$). Above all, when

comparing patients using and not using PGB, cytokine levels were remarkably lower in the first group ($p<0.001$), suggesting a possible anti-inflammatory role of PGB, which seems to inhibit the release of cytokines (22).

Opioids. Despite opioids (except for tramadol) have not been shown benefits in patients with FM, a significant proportion of FM patients are treated with them. A study made in Columbia identified factors associated with the use of opioids in FM. They saw male sex, concomitant treatment with gabapentinoids and suffering from arterial hypertension, obesity or degenerative disease of vertebral discs were associated with a major probability of opioid use. The most commonly prescribed opioid in this study was hydrocodone, while in previous international studies it was tramadol (23).

Naltrexone. Interest in low-dose naltrexone (LDN), a drug indicated for the treatment of alcohol abuse and opioid dependence, as an off-label treatment option in FM is growing. LDN seems to have paradoxical analgesic and anti-inflammatory effects. A systematic review firstly investigated the use of LDN solely in the management of FM, where the evidence is scarce. It demonstrated the potential efficacy of LDN in treatment of FM and no severe adverse events were reported. However, there is no consensus on interventional parameters (such as specific dose, frequency, duration) and LDN doses varies from different studies, with 4.5 mg once daily as the most common option (24).

Cannabinoids. The role of cannabis in FM patients represents an area of growing interest; a systematic review published in 2023 examined its efficacy and tolerability. It was found a potential role for cannabinoids in reducing pain and improving measures of quality of life (QoL) in FM, but the results were largely varying across studies and further researches are needed to strengthen this low-quality evidence. However, the review reported no severe adverse events associated with this treatment (25). A recent prospective cohort study investigated the potential role of cannabis treatment (20 grams per month for 6 months, administered by smoking, vaporising or ingestion) in a cohort of 30 women suffering from FM; it showed improvements in general QoL, physical and psychological domain after starting cannabinoid treatment (26).

Cyclobenzaprine. A trial evaluated efficacy and safety of a low-dose sublingual formulation of cyclobenzaprine (TNX-102 SL) in a cohort of 503 patients with FM. Cyclobenzaprine, although not approved, represents a possible treatment strategy in FM. Compared with oral formulation, TNX-102 SL has a transmucosal absorption instead of an immediate release, and therefore results in a circadian variation in peak-to-trough drug levels and in a minor exposure to norcyclobenzaprine. At week 14, the study observed a significant greater reduction in daily pain with TNX-102 SL than with placebo, and also improvements in global symptoms and functioning. In general, their bedtime dosing demonstrated to be safe and well tolerated. The most common adverse event reported were orally related (hypoesthesia, paraesthesia or abnormal taste) and only 8.9% patients discontinued TNX-102 SL because of side effects (27).

Combination therapy. The management of FM patients is complicated by incomplete efficacy and dose-limiting adverse effects of drugs, leading to the hypothesis that benefits can be improved by combining two different agents. A randomised trial investigated efficacy and safety of an alpha-lipoic acid (ALA)–PGB combination. However, this association was not supported by the results of this study (28).
Also, an integration of nutraceuticals to drug therapy may show some benefits. A randomised controlled study evaluated the efficacy of adding palmitoylethanolamide (PEA) and acetyl-L-carnitine (ALC) for 24 weeks in FM patients in stable treatment with PGB (up to 150 mg/daily) and DLX (up to 60 mg/daily). The supplement of PEA+ALC led to the overall reduction of FM-related symptoms, as assessed using WPI scores (at least a 30% reduction, $p=0.048$), FIQR ($p=0.033$) and FAS-mod scores ($p=0.017$). The addition of these two nutraceutics to PGB+DLX treatment was generally well tolerated and none of the patients discontinued the study prematurely (29).

Take home messages

- Duloxetine is a recommended drug in the management of FM, but the dosage is still controversial (21).
- Pregabalin appears to reduce proinflammatory cytokines which seems to be elevated in FM patients (22).
- Low-dose naltrexone is found to be safe and effective, but there is no consensus about interventional parameters (24).
- Cyclobenzaprine represents an area of interest, especially in its sublingual formulation (TNX-102 SL) (27).
- Nutraceuticals and drugs combinations can apport some benefits in treatment strategy (28, 29).

Non-pharmacological therapy

Active therapies. Exercise therapy has been shown to improve symptoms of FM through various mechanisms. A trial found moderate effects of a 16-week physical exercise programme on aerobic exercise in improving the growth hormone response, suggesting the possible role of aerobic exercise in endocrinological modulation (30).
After aerobic exercise, resistance training (RT) is the most common modality of exercise. A systematic review found clinically relevant improvements in pain intensity, functionality and severity of the disease with RT. Anyway, the absence of an immediate benefit is often responsible for the discontinuation of the treatment (31).
Talking about settings, centre-based exercises demonstrated to be superior to home-based exercises (HBE) in terms of effectiveness in alleviating pain, improving depression and enhancing QoL. However, a programme of HBE showed significant pain reduction when compared with no exercise (32).
A trial enrolling 28 women affected by FM compared reformer Pilates exercises (whose equipment consists of springs, rollers, ropes and sliding plat-

forms) with home mat Pilates (performed just with a mat). When compared to the baseline, reformer Pilates exercises seemed to be better than home mat Pilates in improving clinical status (assessed by FIQ) and muscle strength (assessed by Chair Stand Test) while home mat Pilates exercises performed better on the number of painful regions (measured by Pain Location Inventory, PLI), clinical and biopsychosocial status (assessed by Cognitive Exercise Therapy Approach-Biopsychosocial Questionnaire, BETY-BQ) and physical component QoL (estimated by SF-36). No statistical differences between the groups in terms of delta value were found. The physician should therefore take in consideration patient's needs and major symptoms in the choice of the modality of treatment (33).

In addition, in the era of the development of telecommunication technology, also telerehabilitation was studied in terms of efficacy and safety in FM. It was seen it could improve FIQ score, pain intensity, depression level, pain catastrophising, and QoL, but with uncertainties about the safety (34).

In general, muscle stretching exercises are recommended for the treatment of FM as they preserve flexibility and decrease the retraction of myofascial and articular structures. A recent study on 40 adults with FM compared the global posture re-education method with segmental muscle stretching exercises and found no statistically significant differences between them at the end of the treatment (10 weekly sessions). They both reduced pain intensity (assessed by Visual Analogue Scale) and improved QoL, pain threshold and postural control (35).

A meta-analysis showed (with a low certainty of evidence) that exercises interventions in general are effective in improving sleep quality compared to minimal intervention, no intervention or usual care, but especially mind-body exercises or combined exercises performed better results than aerobic ones alone (36).

Among mind-body techniques, traditional Chinese exercises (TCE), including Taichi, Qigong, Badunjin, Wuqinxi, etc., play an important role in managing FM. A recent review concluded that TCE may significantly be effective in reducing pain, relieving depression and improving QoL and sleep quality, even if with different heterogeneity (37).

Low to very low levels of evidence suggested that an aquatic training based on aerobic and stretching exercise may improve FM-associated symptoms, but it was not observed to be superior to land-based programmes (38). However, a systematic review studying effects of aquatic therapy highlighted its importance in improving sleep quality, even if with few studies in support (39).

Electrophysical agents. A review on the effectiveness of electrophysical agents in FM found low to moderate quality evidence that microcurrent, low-level laser therapy, repetitive transcranial magnetic stimulation (TMS) and bath therapy are effective for improving at least one outcome in FM. The selection of the best electrophysical agent should be guided by a particular outcome of interest; for example, transcutaneous electrical nerve stimulation (TENS) and microcurrent best improved pain symptoms, TMS improved patient functional status and microcurrent and TMS both significantly improved mood (40).

Among non-invasive brain stimulation (NIBS) techniques, TMS, transcranial direct current stimulation (tDCS) and electroconvulsive therapy (ECT) are playing a revolutionary role in managing pain, fatigue, and sleep disorders (41). More in detail, a review revealed that the application of tDCS to the motor cortex (M1) best alleviates pain in patient with FM, while stimulations over the dorsolateral prefrontal cortex (DLPFC) reports uncertain analgesic effects. In addition, both TMS and tDCS showed improvements in pressure pain threshold, catastrophising and QoL when applied to the M1, and in fatigue when the DLPFC were the target. The effects on anxiety and depression were unclear (42).

On the contrary, a review recently published found electrical neuromodulation is significantly effective in improving depression in FM patients. In detail, anode tDCS electrode positions adjacent to DLPFC (and not to M1) revealed a significant effect on mood; TMS showed non-significant effect on depression and anxiety. In addition, age seemed to have a significant influence on the tDCS effects on depression, with older subjects showing lower levels of improvement (43). In addition, another review assessing the effectiveness of 10-Hz repetitive TMS in FM suggested that DLPFC appears to be more effective for analgesia at high frequencies and for mood disturbances at low frequencies (44). Regarding tDCS protocols, anodal stimulation is generally applied in sessions of 20 minutes, at an intensity of 1.5-2 mA, with a minimum of 5 sessions. The most effective strategy to achieve pain relief of active tDCS seems to be the application at an intensity of 2mA to the left M1 (45).

The combination of tDCS with other strategy of treatment is another field of interest. A trial evaluating the association LDN+tDCS showed a significant improvement in pain intensity after treatment, but a significant reduction of VAS was also seen in LDN+tDCS Sham and placebo+tDCS groups. All active interventions performed benefits over depressive symptoms. However, the LDN+tDCS group obtained also reduced pain frequency and intensity, effect of pain on activities and emotions (46).

About the mechanisms involved, a recent trial investigated on 12 patients with FM how M1-tDCS repeated for five consecutive days modulates brain's flexibility and efficiency (indicated by regional temporal variability of blood-oxygenation-level-dependent [BOLD] signals) and its association with pain improvement. In particular, variation of fMRI signals in the left rostral anterior cingulate cortex, ventromedial prefrontal cortex and posterior insula were linked pain changes (47).

These mechanisms differ from the ones implicated in other techniques (such as hypnotic analgesia) (48).

Even if with few studies exploring them, lesser-known technologies like Transcranial Alternating Current Stimulation, reduced Impedance Non-Invasive Cortical Electrostimulation, Transcranial Focused Ultrasound and Transcranial Random Noise Stimula-

tion represent emerging options in the treatment of FM (40). A meta-analysis determined the efficacy of TENS on pain in individuals with FM and its dose-dependent effects. It showed that TENS could reduce pain in individuals with FM when applied at high or mixed frequencies, at high intensity, and for an appropriate number of sessions (at least 10); the electrode position of TENS was irrelevant (49).

Acupuncture, a Traditional Chinese Medicine technique that involves the insertion of thin needles into specific points of the body, is often used in FM patients. According to a review focused on the mechanisms of acupuncture for FM, this technique seemed to improve FM related symptoms by regulating the afferent pain and descending inhibitory pain pathways and by modulating peripheral inflammation and the autonomic nervous system (50). As it is important to identify clinical predictors of unfavourable response to acupuncture in cost-effective terms, a study found predictive variables of treatment failure in FM (defined as a reduction of the FIQR less than 30%) were tender point count and pain magnification (assessed with the Pain Catastrophising Scale) at the end of the eight weeks of treatment while concomitant treatment with DLX was associated with failure at three months after acupuncture cycle completion (51).

Another strategy often applied as a neuro-modulatory treatment in central nervous system-related conditions is Hyperbaric Oxygen Therapy (HBOT). A review showed that HBOT in FM patients could have a positive effect in improving pain, tender points, fatigue, global functioning and sleep disturbance in FM, with rare, reversible and not serious side effects (52). Moreover, a study conducted on FM patient after brain injury suggested that the beneficial effects of HBOT might be addressed to central neuroplasticity effects, especially in frontal and parietal cortex as suggested by SPECT analysis (53).

Other therapies. Music seems to bring some benefits in FM patients; a trial enrolling 24 patients with FM revealed that music therapy, independently from the type, could improve mental well-being, even without alleviating pain symptoms. In addition, the beneficial effects of Melomics-Health group were maintained at follow-up (54).

Massage therapy is one of the oldest methods to alleviate pain, reduce muscle spasms and improve QoL. A trial explored the effectiveness of spinal manipulation in addition to pharmacological treatment in managing FM patients. The spinal manipulation best improved pain scores at three months after the starting of the treatment when compared to sham manipulation or no treatment (but not at the first month) (55).

In recent years, the relationship between nutrition and gut microbiome, as well as inflammation and oxidative stress has been a source of interest. About how diets can improve pain in FM patients, a literature review suggested that plant-based, anti-inflammatory, gluten-free, and elimination/restrictive diets are all associated with statistically significant beneficial effects. However, further studies should be conducted to recommend any of specific diets, even if plant-based ones seemed to better alleviate pain than elimination/restrictive diets (56).

It has recently been observed that gut microbiota-brain axis can influence mental processes; consequently, prebiotics and probiotics may potentially bring some benefits in the management of FM. A trial enrolling 53 participants confirmed the role of probiotic supplementation in improving psychological status (assessed by the Beck Depression Index and Beck Anxiety Index), sleep quality (assessed by Pittsburgh Sleep Quality Index [PSQI] scores) and pain (assessed by VAS), while prebiotic supplementation only significantly decreased PSQI scores and VAS (57).

New horizons in the FM management worth to be mentioned. New prospective include virtual reality (which seemed to increase cold pain threshold and pain tolerance), specific filters for green-lights (whose efficacy on opioid use, pain, and anxiety was a matter of study), photobiomodulation (which was demonstrated superior to placebo in decreasing degree-of-pain rating and the number of tender points), water-filtered infrared-A whole-body hyperthermia (who obtained a significant and persistent pain reduction in a recent trial) or morning bright or sham light treatment (that achieved significant but similar levels of improvement in pain, functioning, depressive symptoms, and sleep disturbance) (58-62).

Take home messages

- Active therapies (such as resistance training, aerobic exercises, Pilates, muscle stretching exercises, mind-body techniques or aquatic training) demonstrated to be safe and effective in the management of FM. Settings and modalities of treatment should be modulated on patient's needs and major symptoms (31-39).
- Among electrophysical agents, evidences about the effectiveness of TMS and tDCS (applicated adjacent to DLPFC or to M1) are growing; their mechanisms of action are worth further investigation (40-47).
- Acupuncture seems to improve pain and other symptoms in FM patients. Nevertheless, an elevated tender point count, pain magnification and concomitant treatment with DLX may predict treatment failure (50, 51).
- HBOT with its neuroplasticity effects is another possible strategy of treatment which revealed to be safe and effective for FM managing (52, 53).
- Diet changes can bring some benefits in FM patients, as well as probiotic (or prebiotic) supplementation. The relationship between nutrition and gut microbiome is a field of interest, but it is now difficult to recommend any of specific diets (56, 57).
- New prospectives, based on single clinical trials, include virtual reality, photobiomodulation specific filters for green-lights, water-filtered infrared-A whole-body hyperthermia or morning bright or sham light treatment (58-62).
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Conclusions

In 2023, a substantial number of articles were produced concerning FM. This narrative literature review has included original works and literature reviews that were deemed most relevant. Significant advancements have been

introduced regarding the pathogenesis, with an increasingly focused attention on the immunological aspects of the disease, while also considering other aspects such as central sensitisation and the small fibre pathology. Interesting developments also concern the potential therapeutic use of non-pharmacological strategies.

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