Review

One year in review 2019: fibromyalgia

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ABSTRACT

Fibromyalgia is characterised by chronic pain, fatigue and functional symptoms. Its aetiopathogenesis is still a matter of debate, but various pharmacological and non-pharmacological therapies are currently available for its treatment. We review the literature concerning the most recent findings related to the aetiopathogenesis, diagnosis, clinical aspects and treatment of FM published between January 2018 and January 2019.

Aetiopathogenesis

In the time frame analysed by this review, not so many new aetiopathogenetic hypotheses for fibromyalgia (FM) have been formulated with respect to other years (1). However, the focus of the researchers in this year was on the phenomena related to neuropathies. In 2018, Grayston *et al*. (2) proposed an interesting meta-analysis on the prevalence of small fibre neuropathy in FM. The researcher evaluated 935 scientific articles and underlined the prevalence of small fibre neuropathy (SFN) in 49% of FM patients. This high prevalence of SFN in FM emphasises the importance of identifying standard methods for the description of this neuropathy and understanding the processes leading to the development of SFN, to achieve better therapeutic and diagnostic strategies. Moreover, Caro *et al*. (3) studied for the first time large fibre involvement in FM. In the past few years, several studies have pointed to a link between small fibre neuropathy and FM, but in most of the cases these studies did not evaluate possible alterations in the large fibres.

The researchers included the electromyographic findings of 100 consecutive unselected clinical patients that met the 1990 ACR criteria for FM. After the exclusion of FM subjects with concomitant clinical conditions that could influence the findings of the EMG (for example, family neural degenerative conditions, diabetes mellitus, vitamin B-12 deficiency, etc.) 55 FM subjects remained: 29 subjects with "FM only" and 26 subjects with FM + rheumatoid arthritis ("FM + RA"). All subjects also underwent skin ankle biopsy for the determination of the epidermal nerve fibre (ENFD). Fourteen other subjects, without FM or RA, examined by the same electromyograph, were chosen as an EMG/NCS comparison group. Ninety percent of the "FM only" subjects generated a demyelinating and/or axonal sensory-motor polyneuropathy, and 63% had SFN (ENFD ≤7 fibres/mm), suggesting a mixed fibre neuropathy in most cases. In addition, 61% of The "FM-only" subjects showed suggestive EMG of non-myotomial axonal motor denervation of the lower limbs, most likely a cause of polyneuropathy, and 41% met the criteria for "possible" chronic inflammatory demyelinating polyneuropathy (CIDP). Interestingly, there was little difference in the EMG/NCS findings between the "FM only" and the "FM+RA" groups, while in the comparison group no pathologic finding was shown, with the only exception of carpal tunnel syndrome. The results highlighted by the research group show that the electrodiagnostic characteristics of polyneuropathy, muscle denervation and CIDP are common in FM. These findings are often seen to coincide with SFN and are not significantly affected by the presence of RA. These results, besides helping to understand the aetiopathogenesis of FM, can also be useful for diagnostic purposes.

Diagnosis

The diagnosis of FM is still based on patients' reports and on clinical assessment, mainly because the pathogenesis of FM is still not well understood and

because of the lack of reliable biomarkers of the disease. The publication of the *2010/2011 American College of Rheumatology (ACR) criteria* for the diagnosis of FM superseded the traditional 1990 ACR classification criteria, according to the identification of the multi-symptomatic nature of FM and the difficulty of the standardisation of the tender points exam, required in 1990 ACR criteria (4). However, subsequent validation studies showed that in spite of the simplification of FM diagnosis through the application of symptom scales, such as the widespread pain index (WPI) and the symptom severity scale (SSS), there was a substantial misclassification mostly of patients with severe regional pain disorders (5). The misdiagnosis occurred principally because the 2010/2011 criteria did not consider the spatial distribution of the painful sites. Therefore, in 2016 a revised set of criteria was published. This revision introduced "generalised pain criteria", defined as the presence of pain in 4 out of the 5 possible painful body regions, which allowed the exclusion of the regional pain syndromes from the diagnosis of FM without losing the diagnostic accuracy of the criteria set (6). Nevertheless, uncertainty and lack of confidence in FM diagnostic criteria use in clinical practice is still reported, especially in primary care settings (7). The Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks (ACTTION) public-private partnership with the U.S. Food and Drug Administration (FDA) and the American Pain Society (APS) in 2013 gathered together an international working group of clinicians and basic scientists. The aim of the working group was to address the problem of the limited reliability and validity of the existing diagnostic criteria for chronic pain disorders in clinical practice. Accordingly, the group initiated the ACTTION-APS Pain Taxonomy (AAPT) initiative, to develop a diagnostic system that would be clinically useful and consistent across chronic pain disorders. The AAPT Taxonomy considers 5 dimensions: dimension 1: core diagnostic criteria; dimension 2: common features; dimension 3: common medical co-morbidities; dimension 4: neurobiological, psychosocial, and functional consequences; and dimension 5: putative neurobiological and psychosocial mechanisms, risk factors, and protective factors (8). Recently Arnold *et al*., in order to address the problem of the limited reliability and validity of the existing diagnostic criteria, published a multidimensional diagnostic framework applied to FM. This is based on the review of the existing diagnostic criteria, it reflects the current understanding of FM and is thought to be useful in a practical clinical setting. Identifying FM mainly as a pain disorder, the core diagnostic criteria (dimension 1) include the presence of multisite pain, defined as the presence of pain in 6 out of 9 possible sites together with moderate to severe fatigue or sleep problems assessed by a health care professional. Those must have been present for at least 3 months. Dimension 2, namely features that may support a diagnosis of FM, is identified in the tenderness to touch (positive tender points exam), the dyscognition (trouble concentrating, forgetfulness, and disorganised or slow thinking), musculoskeletal stiffness and environmental sensitivity (intolerance to bright lights, loud noises, perfumes and cold). A broad spectrum of possible comorbidities (dimension 3) has been identified as frequently associated to FM, which includes several somatic pain disorders, psychiatric conditions, sleep disorders and rheumatic diseases. The outcomes related to the disease, the poor quality of life and the high indirect cost that belong to the burden of FM are described in dimension 4. This last dimension includes the risk factors for the disease, such as familiarity for functional chronic pain disorders and environmental stressors that may trigger the disease, *e.g*. early lifetime adverse events, trauma, medical conditions and psychosocial stressors, together with the current knowledge about the putative pathophysiologic mechanism that may sustain the disease (see Pathogenesis). The AAPT taxonomic approach to FM offers a systematic method to diagnose FM, focusing on limited number of core diagnostic symptoms but at the same time giving the possibility to take into account the many other associated symptoms that may support the diagnosis of FM. This could make the FM identification more practical in clinical settings and at the same time simplify the identification of FM patients for research purposes (9). The multidimensional approach to FM definition offers undoubtedly advantages in terms of current clinical practice and of diagnosis, but considering the heterogeneity of the disease and the possible changes during the time of the disease features, it may be limiting in terms of practical management of the single FM patient. Indeed, a recent retrospective analysis of a large number of patients included in an FM continuum spectrum, identified 4 possible classes of the disease. Class 1 was represented by a mostly regional FM within the contest of the widespread pain while class 2 was characterised by a greater severity of pain, a broader involvement of body regions and several associated symptoms. These two classes represented the most prevalent in the study population, and their clinical phenotype overlaps with the one identified by the diagnostic criteria. Class 3 was characterised by an increase in the level of pain compared to the previous classes, a strict association with sleep disorders and to the possibility of chemical sensitivity. The highest severity of pain and of associated symptoms was present in class 4, which represented the "secondary FM" to other diseases such as multiple sclerosis and lupus, which had a high prevalence in this class. During the follow-up, some patients showed a tendency to progression from the lower to the higher classes in a fairly linear fashion, although the progression was also influenced by the specific comorbidities and the presence of secondary conditions. The results of this study suggest that FM represents a disease continuum in which the centralised pain becomes more centralised as the disease progresses, and that the characterisation of how the patients progress may improve diagnosis and consequent management (10). Considering all the issues in the current clinical diagnosis of FM, in the application of diagnostic criteria and in understanding and possibly predicting the natural history

of the disease, the lack of a reliable biomarker is a main unmet need in FM management. Nonetheless, several new acquisitions in terms of understanding biologic modification of FM patients have been recently reported and some of them have the potential for future clinical application. In recent years, biomarker research on biological fluid has been enriched by the identification of relatively new molecules of interest. For example, peculiar miRNA profiles on blood, saliva (11) and cerebrospinal fluid (12) have shown the ability to diagnose and characterise FM. However, the studied populations were small and a validation on larger cohorts is needed. The application of innovative techniques of proteomic or metabolomic analysis on the same biological fluids offers new potentiality in biomarker identification. Studying a large number of different proteins in the biological fluid gives the possibility to combine more proteins of interest and increase diagnostic accuracy. A proteomic analysis of whole saliva performed on FM patients, compared with healthy controls, patients with migraine and patients with rheumatoid arthritis, showed an increased expression of several proteins like serotransferrin, alpha-enolase, phosphoglycerate-mutase-I and transaldolase. Performing a ROC curve analysis, the combination of apha-enolase, phosphoglycerate-mutase-I and serotransferrin obtained a good discriminative ability (AUC 0.792) (13). Similarly, a proteomic analysis performed on plasma of FM patients identified 33 differently expressed proteins belonging to several patterns like acute-phase reaction, Liver-X Receptor/Retinoid-X Receptor activation, Farnesoid-X Receptor/Retinoid-X Receptor activation, complement and coagulation, suggesting the existence of a plasmatic inflammatory protein signature in FM, which may be related to a neuroinflammatory process. Among the proteins that presented an increased serum level in FM patients, haptoglobin and fibrinogen had the highest FM/control ratio, representing two interesting possible targets of further study on their role as biomarkers (14). As well as proteomics, metabolomics aims to screen a large amount of different metabolites in biologic fluid to identify the variation of the metabolites contents that can represent a fingerprint of a specific condition. An interesting approach recently described involves the metabolomic screening of the low-molecular weight fraction metabolites of human blood collected by finger-stick. Using the intrinsic vibrational pattern of the different molecules after absorbing infrared light, the authors have been able to successfully classify FM patients and discriminate them from patients affected by systemic lupus erythematosus or rheumatoid arthritis, without misclassification. Moreover, the characteristic of the vibrational spectra of FM patients correlated with pain severity measured through the revised fibromyalgia impact questionnaire (FIQR). Apart from being a promising diagnostic tool in FM, this kind of metabolomic analysis may be useful to identify serum metabolites that could be valuable as biomarkers. In fact, the discriminating region of the vibrational spectra was dominated by bands characteristics of pyridine ring, tyrosine residues in proteins and protein backbone, highlighting the importance of aromatic and carboxylic acid molecules as potential biomarkers, including tryptophan and its metabolites (15). The role of tryptophan and its metabolite, serotonin, in FM pathogenesis has been supported by a number of experimental observations and confirmed by the common use in FM treatment of selective serotonin reuptake inhibitors (16). A reduced level of serum serotonin in blood sample of women recently diagnosed with FM compared to controls has been reported. However, there was no relation between the reduction of serum serotonin and clinical manifestation, suggesting a possible use of serotonin levels in FM diagnosis but not in the assessment of the disease severity (17). The investigation of neurologic abnormalities both in the peripheral and central nervous system have been a rich field of research in FM. Several different groups have described the presence of a small fibre neuropathy in a large number of FM patients, represented by a reduction in dermal unmyelinated nerve fibre bundles in skin biopsy, increased cold and warm detection thresholds in quantitative sensory testing and nociceptor hyperexcitability. The study of the small fibre pathology through the skin biopsy represents a promising and easily performable diagnostic test that may allow the identification of FM patients with an underlying neuropathy and thereafter guide the therapeutic choice through drugs that are active on the neuropathic aspects of pain. A technique recently applied to the successful identification of the small fibre pathology in FM, corneal confocal microscopy, is basically an *in vivo* microscopy that may become a useful and non-invasive FM diagnostic test (18). The "central sensitisation" has always been strongly implicated in FM pathophysiology. The neuroimmune activation is one of the potential mechanisms that may be involved in the central nervous system abnormality described in FM. Recently, a combined research group from Sweden and the United States demonstrated for the first time the presence of activated glia, and consequently of active neuroinflammation in the brain of FM patients. Using positron emission tomography (PET) imaging and radioligands that bind to the 18-kDa translocator protein (TSPO), the authors described an increased uptake of the radioligand in FM patients' brain, especially in the brain regions previously implicated in FM pathology. TSPO expression is normally low in healthy brain tissue but is dramatically upregulated in activated glial cells under inflammatory stimuli. Moreover, the radioligand uptake in several brain regions correlated significantly with the subjective fatigue score reported by FM patients. Because it suggests a possible association between neuroinflammation and FM, this work opens to future researches about the role taken by activated microglia in FM with the possible identification of diagnostic biomarkers or therapeutic strategies (19). Unfortunately, to date, none of these diagnostic tests is sufficiently validated to be introduced into clinical practice. Further studies are needed in order to identify the best diagnostic test that can easily help the diagnosis and management of FM patients.

Treatment

Due to the heterogeneity of symptoms and the poorly known pathogenesis, the therapy of fibromyalgia (FM) still remains a challenge for physicians. According to the most recent European League Against Rheumatism (EULAR) guidelines, once the diagnosis of FM is made, priority should be given to non-pharmacologic treatment (20). The reason lies in cost-effectiveness, patient's preference, safety and availability. Physical exercise, having the best profile of efficacy and safety, should be prescribed to every patient with a diagnosis of FM. The efficacy of pharmacologic intervention has a weak level of evidence, and, due to potential side effects and low compliance, should be indicated in specific cases (*e.g.* unresponsive pain or sleep disturbances). In the most severe situations, patients could benefit from a multimodal therapeutic approach.

Pharmacological therapies

The therapeutic management of FM includes the use of drugs modulating neurotransmission and acting on the pain, emotional and reward circuits. Recent European guidelines provided a detailed list of recommended therapies according to a review of published meta-analyses and systematic reviews (20). The authors evaluated the efficacy and safety profile of several drugs, including antidepressants, pain modulators, hormones, anticonvulsants and muscle relaxants. For some of them, including amitriptyline, pregabalin and duloxetine, encouraging results on pain have been reported. Other symptoms, such as sleep disturbance, fatigue and disability, may ameliorate at a different rate under amitriptyline, pregabalin or serotoninergic agents. On the contrary, based on the disadvantageous profile of efficacy and safety, the use of other compounds, such as cyclobenzaprine, growth hormone, non-steroideal anti-inflammatory drugs (NSAIDs), steroids, strong opioids and monoamino oxidase inhibitors has been discouraged. Further evidences on the effects of other molecules on FM symptoms emerged from small trials or additional reviews conduced in the last 12 months. The antidepressant drug mirtazapine is a central presynaptic α2 adrenergic antagonist with serotonergic and noradrenergic effects, acting on amygdala, hippocampus, frontostriatal circuits, cortical midline structures and parietal cortex. This drug increases neuronal response to positive emotional and reward boosts, and attenuates the processing of threatening stimuli (21). In addition, mirtazapine contrasts the effects of histamine on H1 receptors and this confers sedative properties that may be exploited in the treatment of sleep disorders. A recent systematic review aimed to evaluate the effects of mirtazapine in FM patients (22). Data from selected articles (three randomised placebo-controlled trials and one open-label trial) reported an improvement in pain, sleep and quality of life, despite different treatment doses and duration. Another systematic review by the Cochrane group on the use of mirtazapine in FM evaluated the efficacy *versus* placebo in pain relief, patient's perception of efficacy, safety and tolerability (23). The analysis of data from 3 low-quality studies on more than 500 FM patients treated for at least 7 weeks revealed modest efficacy of mirtazapine over placebo in pain relief and Patient Global Impression of Change (PGIC), but also reported a higher incidence of adverse events in the mirtazapine arm, including somnolence, increase in serum transaminases and weight gain.

The serotonin and norepinephrine reuptake inhibitor antidepressant milnacepram was tested in a prospective, randomised, controlled double-blind clinical trial in patients with FM (24). The researchers evaluated the effects of milnacipram titrated up to 100 mg/daily in a group of 54 FM patients who were randomised to receive the active compound or placebo. After 1 month of treatment, no significant difference emerged between the two arms according to conditioned pain modulation, global pain, mechanical and thermal thresholds, allodynia, cognition, and tolerance.

The off-label use of gabapentin, a γ-aminobutyric acid (GABA)-mimetic drug, has given rise to noteworthy interest in the last few years, due to prescription in a wide set of chronic pain diseases, including FM, although the real effects on symptom relief are inconclusive (25). However, in an 8-week prospective, single centre feasibility study, the combined treatment with gabapentin 900 mg/daily plus osteopathic manipulative medicine resulted in improved Wong-Baker FACES Pain Rating Scale scores, although the Fibromyalgia Impact Questionnaire (FIQ) score and the number of tender points did not change significantly from baseline (26).

A novel drug, acting as a N-methyl-d-aspartate (NMDA) receptor modulator and known as NYX-2925, is currently investigated in FM patients in a phase 2 clinical trial (NCT03249103, www.clinicaltrials.gov). The rationale for the use of this agent lies in the role played in neuronal plasticity as well as in the control of learning and memory processes, and in the promising results observed in analgesia in preclinical studies (27).

Mexiletine is an anti-arrhythmic drug that blocks in a non-selective way the voltage-gated sodium channels. The drug has also modulatory effects on chronic nociception and muscle stiffness. The retention rate and side effects of mexiletine in neuropathic pain and FM patients was evaluated in a retrospective cohort study (28). Mexiletine was prescribed at daily dosage of 150 up to 450 mg to 21 FM patients. About 30% of patients discontinued the treatment at 6 and 12 months, mainly because of gastrointestinal, neurologic and cardiac events. Although not reported in this study, the risk of serious side effects, such as QT abnormalities and torsades de pointes, limits the widespread use of this treatment in FM patients.

The use of cannabinoids for the management of FM has been diffuse in recent years and some studies evidenced that it could add some benefits in the control of accessorial symptoms, including chronic low-back pain (29). Cannabinoids derive from the plant *Cannabis sativa L.* and exert their effects by interacting with the cannabinoid type 1 receptor (CB1-R) expressed by neuronal cells and cannabinoid type 2 receptor

(CB2-R) present on cells from the immune system. Cannabis contains various amounts of psychoactive components, including the Δ9- tetrahydrocannabinol (THC), which modulates nociception, cognition and motor function by binding CB1-R, and cannabidiol (CBD) which acts as a CB2-R antagonist and a 5-hydroxytryptamine (5-HT) receptor agonist, modulating mood and cognition. Due to the different pharmacodynamics of THC and CBD, a recent randomised placebo-controlled 4-way crossover trial aimed to evaluate the efficacy of 3 inhaled cannabinoids, having a different chemical composition, *versus* placebo for the treatment of FM (30). These drugs (Bedrocan®, Bediol® and Bedrolite®) differ, in fact, for the CBD/THC ratio. Testing 20 FM patients, the authors evidenced a small analgesic effect after a single inhalation of each compound; interestingly, CBD and THC shared synergistic pharmacokinetics, whereas contrasted according to pharmacodynamics and analgesic effects when co-administrated. Bediol®, which has the highest content of CBD, had the most impactful effect on mechanic-induced pain.

Other data from a meta-analysis conducted on patients treated with cannabinoids for non-oncologic chronic pain, including subjects suffering from FM-related pain, evidenced no superiority of cannabinoids over placebo in terms of physical or emotional functioning, whereas low-quality evidence on the improvement of sleep and PGIC was reported (31).

The use of opioids in FM has shown delusive results (32), although tramadol seems to moderately reduce pain (20). Naltrexone, an opioid antagonist, has achieved promising results in FM-related pain due to the increase in the endorphinergic tone related to the transient blockade of opioid receptors in the central nervous system; and some pilot studies evidenced a good profile of efficacy and safety of this drug in the FM setting (33).

Due to the great variability in clinical expression, FM often requires combined therapeutic strategies, including both pharmacologic and non-pharmacologic approaches. A recent Cochrane systematic review evaluated the efficacy (intended as a 30% or 50% improvement of pain from baseline and PGIC amelioration) and safety of drug combination *versus* mono-therapy or placebo in published randomised controlled trials on FM patients (34). The authors selected 16 studies enrolling 1,474 patients. The most frequent combinations of drugs included the association of NSAIDs with benzodiazepine, amitriptyline with fluoxetine, tramadol with paracetamol, and monoamine oxidase inhibitor with 5-hydroxytryptophan. The combination of drugs seemed to give a greater advantage on pain than a single treatment alone, with only mild side effects reported. However, the results were biased by the heterogeneity of the study designs and variability in sample sizes.

Non-pharmacological therapies

The non-pharmacological management of FM has been focused on in many studies and seems to have a stronger impact on clinical manifestations, symptoms and quality of life than the pharmacologic treatment. Novel psychological support therapy showing promising results in FM includes virtual reality, Basic Body Awareness Therapy (BBAT), Cognitive-Behaviour Therapy (CBT) and Group Music and Imagery (GrpMI) intervention. Virtual reality modulates pain perception by influencing attention, concentration and emotions. Therefore, acting through a mechanism that does not directly involve the nociceptive pathway, virtual reality may represent a valid additional tool to pharmacologic prescription in chronic pain conditions, like FM (35). BBAT is a movement awareness training programme that teaches patients how to correctly move in space and time, increasing awareness of body coordination. In a randomised study, 20 FM patients assigned to BBAT and followed-up for 24 weeks showed a significant reduction in pain and anxiety scale scores compared to 21 controls (36). CBT focuses on coping strategies, emotional control and cognitive psychology and has shown successful results in counteracting mood disorders and disability of FM patients (37). When applied to the symptom insomnia, an 8-week CBT has shown to rescue grey matter atrophy observed through magnetic resonance imaging (MRI) in FM patients (38). Several studies have demonstrated, in fact, that long-lasting insomnia may reduce the volume of the hippocampus, amygdala, anterior cingulate cortex, insula, medial frontal cortex, parahippocampus, pre-frontal cortex, and thalamus. When added to relaxation, GrpMI intervention similarly showed beneficial effects on mood and pain sensitisation in 56 FM women enrolled in a 12-week randomised trial (39).

Due to the chronicity of the disease, one of the main concerns in treating FM patients is the poor compliance to a long-lasting treatment. Psychological support given by means of an Internet platform proved to be an efficacious remedy for FM symptoms, including pain, fatigue and mood disorders. A randomised controlled trial on 140 FM patients assigned or not to Internet-delivered exposure showed significant advantages on FM symptoms and a high retention rate (94% of patients in therapy at 12-months) (40). In addition, this strategy showed greater cost-effectiveness than no treatment, concerning both direct and indirect costs in those patients achieving positive results (41). Results on the efficacy of Internet-delivered therapy from 6 randomised controlled trials on 493 FM patients were reviewed by a recent meta-analysis (42). The authors demonstrated a significant reduction in mood disturbances and disability at 6 months, despite no benefit in terms of ≥50% pain relief was observed comparing Internet-derived psychological therapy to waiting list. Another systematic review on Internet-delivered cognitive behaviour therapy in patients with chronic diseases, including FM, showed the greatest effect in anxiety and depression symptom modulation (43). In the near future, the implementation of mobile applications delivering self-administered cognitive behavioural treatment may further enhance the adherence of patients to non-pharmacologic therapeutic programmes (44).

Physical exercise is a cornerstone in

the non-pharmacologic management of FM, however, specific interventions and programmes are poorly defined (45). A number of studies reported a significant benefit of the Chinese discipline Tai Chi over aerobic exercise in terms of mood and sleep disturbance, disability and quality of life (46, 47). However, physical activity does not seem to influence pain sensitivity, the management of which should require the addition of a pharmacologic intervention or other non-pharmacologic approaches (48).

Both hot and cold temperature can modulate nociception by acting on opioid endogenous pain inhibitory system and specific alternation of rhythm in temperature (SART) stress can impair the control of nociceptive stimuli in rats (49). Some studies on the effects of both cold and hot temperature exposure have been carried out in FM patients. Cryotherapy is widely used in sport medicine due to the anti-inflammatory, anti-oedema and analgesic properties. In a study involving 60 FM participants randomly assigned to whole body cryotherapy or rest, the researchers showed reduced FIQ, visual analogic scale (VAS) for pain and Combined Index of Severity of Fibromyalgia (ICAF) scores in treated patients (50). However, side effects were recorded, some of which, including palpitations, muscle stiffness, tremor, sleep disturbance and headache, could have represented a disease flare. Since the pharmacologic background of the examined cohort is not detailed, it may be hypothesised that the combination of cryotherapy plus tranquilliser or muscle-relaxant agents would have improved the final result and avoided some of the reported side effects. Another randomised trial involving 24 FM patients, part of whom were assigned to a whole body cryotherapy group for a total of 10 sessions over a period of 8 days, reported better scores in the Medical Outcome Study Short Form-36 questionnaire, evidencing an improvement in the quality of life (51). On the other hand, due to muscle relaxation, the application of heat has given beneficial effects in FM patients. In a study involving 7 FM patients daily undergoing 40°C mud-bathing for a month, a benefit has been registered in pain sensitisation together with an amelioration of serum biochemical parameters such as triglycerides and C-reactive protein (52). The mechanical, chemical and thermal properties of balneotherapy seem, in fact, to alleviate pain by means of several mechanisms. In particular, an increase has been observed in pain threshold mediated by the activation of the descending inhibitory pain system and gamma-fibres and augmented levels of beta-endorphin, growth hormone and adrenocorticotropic hormone in FM patients undergoing balneotherapy (53). In a randomised controlled 6-month trial, 100 patients with FM were assigned to highly mineralised sulphate water or tap water. VAS pain and FIQ significantly ameliorated in patients assigned to the first arm of treatment at day 15th and benefits were maintained over the follow-up period (54). The application of muscle exercise (*e.g.* using the Tai Chi technique) in a warm water context, namely the aquatic Ai-Chi programme, can represent a further tool to control pain and ameliorate quality of life, as shown by the results of an experimental pilot study on 20 FM subjects (55).

The use of transcutaneous and percutaneous electrical nerve stimulation, laser therapy and pulsed electro-magnetic fields has also been experimented in FM subjects. A 12-week randomised controlled trial on 108 FM women aiming to investigate the analgesic effects of the use of a Bio-Electro-Magnetic-Energy-Regulation (BEMER) device did not find any significant difference compared to women assigned to a sham device (56). Electro-magnetic fields seem to act by increasing microcirculation and restoring the function of the immune cells, however the exact role in FM is uncertain. Similarly, the use of low-level laser therapy added to functional exercise failed to demonstrate superiority to exercise alone in pain, muscle performance, mood disorders and quality of life in a double-blind randomised clinical trial on 22 FM women (57).

On the contrary, the application of 12 sessions of laser therapy on facial muscle tender points, in a randomised clinical trial, showed a significant improvement of pain from baseline in FM-related facial muscle tenderness, achieving similar results to the local injection of lidocaine 2%, which, however, represents an invasive tool of pain control (58). The use of weak magnetic field (2 Tesla) to induce neuro-modulation in the left dorsolateral prefrontal cortex, a brain area crucial for pain sensitisation, has been tested in a 4-week randomised double blind placebo-controlled trial on 26 participants with a diagnosis of FM, showing a significant improvement in the symptom fatigue (59). The results from a comparative study on 120 FM patients evidenced the superiority of repetitive transcranial magnetic stimulation over regenerative injection therapy, such as prolotherapy, in Beck Depression Inventory (BDI) scores and cortical functions, whereas pain was less controlled (60). The technique is not invasive and is well tolerated with site discomfort and headache reported as the most common side effects. In addition, the recent production of portable devices for home use could significantly ameliorate compliance to this kind of therapy (61).

Finally, some studies have reported that dietary changes may have a positive repercussion on muscular pain. FM subjects often have a deficit in selenium, magnesium, zinc, vitamins B and D and proteins, and may benefit from the intake of carnitine, anti-oxidants, lactose-free and low-histamine food and aromatic amino acids (62). These nutrients can reduce systemic and neuronal inflammation and restore muscle strength. In addition, aromatic amino acids, like tryptophan, may normalise the level of neurotransmitters associated to sleep and mood control. The addition of vitamin D 50,000 IU weekly to trazodone 25 mg a day showed a significant improvement in quality of life and pain perception in a cohort of vitamin D-deficient FM patients followed up for 8 weeks (63). According to another recent study, the combination of a lacto-vegetarian diet with exercise seems to represent a more powerful means of pain control and muscle strengthening (64).

To conclude, given the wide range of non-pharmacologic therapies available and showing promising results in FM, physicians should be able to tailor the treatment to the most prevalent FM manifestations (pain, sleep disturbances, mood disorders, somatic symptoms). Moreover, in the near future, the possibility to deliver psychological or physical therapy directly at home by means of a portable device or internet-based platforms could significantly increase the adherence to treatment and reduce direct and indirect costs.

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