Review

Fibromyalgia: one year in review 2022

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ABSTRACT

Fibromyalgia syndrome (FM) is a chronic widespread pain syndrome characterised by fatigue, sleep disturbances and many idiopathic pain symptoms. The aim of this review is to describe and summarise the most recent findings concerning the diagnosis, aetiopathogenesis and treatment of fibromyalgia syndrome published between January 2021 and January 2022 and appearing on PubMed database. In particular, last year's literature focused on the impact of COVID-19 pandemic on FM patients, on new aetiopathogenetic horizons and the last conclusions about pharmacological and non-pharmacological interventions.

Introduction

Fibromyalgia syndrome (FM) has always given rise to a debate concerning the distinction between disease and illness, and the scientific literature of the past year is not an exception. There were articles about the "measurability" of the disease (1), which is particularly difficult in the case of pain and FM because the lack of objective biomarkers complicates decision making. However, it has been found that empathy is inversely proportional to the difficulty of managing FM patients, once again underlining the importance of the human relationship between patients and their doctors (2).

2021 also saw the publication of many studies on the physical and mental impact of COVID-19 on the lives of the FM patients (3-5), the vast majority of whom not only had to stop their complementary (and sometimes even their pharmacological) treatments (3), and moreover, those who contracted the virus experienced an overall deterioration in the three main FM domains of pain, sleep disturbances, and fatigue (4).

Diagnosis

Not many studies were carried out concerning the diagnosis of FM, as this has been largely agreed on for the last decade. A large-scale study by Salaffi *et al.* (6) did reveal a reliable way of measuring disease severity on the basis of the scores of the revised Fibromyalgia Impact Questionnaire (FIQR: 0–23 = remission, 24–40 = mild disease, 41–63 = moderate disease, 64–82 = severe disease, and >83 = very severe disease), of the modified 2019 Fibromyalgia Assessment Status (FAS 2019 mod: 0–12 = remission, 13–20 = mild disease, 21–28 = moderate disease, 29–33 = severe disease, and >33 = very severe disease), and of the Polysymptomatic Distress Scale (PDS: 0–5 = remission, 6–15 = mild disease, 16–20 = moderate disease, 21–25 = severe disease, and >25 = very severe disease).

There were also attempts to ensure a more accurate clinical diagnosis of FM on the basis of the type and characteristics of pain. Ghavidel-Parsa *et al.* reported a seven-item preliminary Nociplastic-based Fibromyalgia Features (NFF) questionnaire, for which a cut-off value of 4 correctly identified 85% of patients with a specificity of 91% and sensitivity of 82%; it also had 85% concordance rate with expert diagnosis and 77% concordance with the ACR 2016 criteria, thus making it a new and reliable diagnostic aid (7). Bennett *et al.*, whose works have been a cornerstone for FM clinical research, pointed out that confidence in making a diagnosis of FM can be increased by asking about the five symptoms of persistent deep aching affecting most of the body, poor balance, environmental sensitivity, tenderness to touch, and pain after exercise (8), and Habib *et al.* noted that initial FM pain was focal in 90% of their 155 patients (the hands in

25.2%, the back in 19.4%, and both trapezial areas in 11%), and that the initial symptoms were bilateral and symmetrical in 90% (excluding those with back, abdominal, or chest pain) (9).

Patient history

The patient's history is still one of the most important things, particularly adverse childhood experiences and the accumulation of multiple traumas (10). A French study based on machine learning modelling examined the predictive value of 20 social and psychological variables in determining two classes of rheumatic disease: inflammatory and non-inflammatory (FM), and found that childhood mistreatment (odds ratio [OR] 18.92) and an agreeableness personality trait (OR 6.11) were strongly associated with FM, and concluded that the former was relatively more important than demographic, personality traits or psychopathological variables (11). Furthermore, a study by Lawrence-Wolff *et al*. found that the prevalence of FM among active-duty servicemen was similar to that observed in the USA general population, but higher than that usually observed in a predominantly male cohort, and that it was significantly higher among those with concomitant post-traumatic stress disorder (PTSD), and highest of all among those asking for PTSD treatment (12).

Biomarkers

There is no lack of attempts to diagnose FM with the aid of biomarkers and biological fluid analyses. In line with the findings concerning the importance of a history of trauma and stress-related changes, Begum *et al*. found that, in comparison with controls, patients with FM and those at risk of developing FM have particularly high salivary cortisol levels, with the most significant risk factors being sleep disorders and stressful experiences, but not the covariates of anxiety or depression (13).

Alves *et al*. published findings showing that mass spectrometry analysis with paper spray ionisation of blood plasma samples, and subsequent supervised and unsupervised multivariate classification of the spectral data, effectively distinguished 10 FM and 10 non-FM patients, and that principal component analysis (PCA) and supervised analysis using a successive projections algorithm with linear discriminant analysis (SPA-LDA) led to 100% accuracy (14). Hsu *et al*. compared urine and serum samples from 30 FM patients and 25 controls and found significant differences in the expression of three urinary and five serum metabolites and eight serum proteins, thus indicating that FM patients show alterations in free radical, lipid and amino acid metabolism networks that lead to the generation of NF-ϰB-dependent cytokines (15). These findings are particularly interesting in the light of a review of peripheral blood cytokine profiles in which a pooled analysis showed that the profile of FM patients includes both pro-inflammatory (TNF-α, IL-6, IL-8) and anti-inflammatory cytokines (IL-10), as well as chemokine (eotaxin) signatures (16).

Neuroinflammation and neurological aspects

It is being increasingly recognised that neuro-inflammation plays a role in FM: Martínez-Lavín *et al*. have postulated that there may be a neuroinflammatory connection between FM and chronic regional pain syndrome (CRPS) that has a common origin in dorsal root ganglia hyperexcitability and small fibre neuropathy (17); Seo *et al*. have used [11C]-(R)-PK11195 positron emission tomography (PET) to show that the brains of FM patients have abnormal neuroinflammation levels in comparison with those of patients with CRPS (18); and Cordón *et al*. have used optical coherence tomography to detect neuro-inflammation and degeneration, and found that FM patients show a reduction in the inner retinal layers of the macular area, and that this degeneration correlates with disease severity and a poorer quality of life (19).

There is also potential for the detection of an EEG pattern. Martín-Brufau *et al*. have found that, in comparison with controls, FM patients have lower values at all frequencies other than the Delta band, that frequency maps reveal greater activity in parietal areas than in other parts of the scalp, and that there is a significant difference in the discriminatory analysis of interconnectivity patterns (20).

J*uvenile FM*

Particular consideration needs to be given to juvenile FM (JFM), which is surging as a distinct clinical entity that requires prompt diagnosis (21). Tesher *et al*. (22) have observed that their juvenile idiopathic arthritis patients who satisfy the criteria for JFM have a greater perception of disease activity than their physicians and are more disabled, thus indicating the importance of diagnosing FM in younger rheumatological patients; all of this was of course already well known in the adult population (23-24). Tesher *et al*. (22) have found that the functional disability inventory (FDI) scores of patients testing positive for JFM are markedly higher than those of patients without JFM (mean score 24.8 *vs*. 6.9), and that their pain catastrophising scores are also significantly higher (~14 points). They also found that the significant tendency for patients to give higher disease activity scores than their physicians was more marked among patients with JFM, whose patient global assessment (ptGA) was a mean 3.7 points higher than that of their physician's global assessment (PGA), and higher than the mean of 0.7 among patients without JFM.

Take home messages

- Salaffi *et al*. revealed a reliable way of measuring disease severity on the basis of the scores of the revised Fibromyalgia Impact Questionnaire (FIQR) (6).
- The Nociplastic-based Fibromyalgia Features (NFF) questionnaire may be a valuable primary screening tool (7).
- Studies underlined high salivary cortisol levels, alterations in metabolites involved in free radical, lipid and amino acid metabolism and in blood cytokine profiles (13-16).
- Neuro-inflammation has been highlighted by OCT and [11C]-(R)-PK11195 PET (18, 19).
- Juvenile idiopathic arthritis patients who satisfy the criteria for JFM have a greater perception of disease activity than their physicians and are more disabled (22).

Population characteristics

Increasing importance has been attributed to the risk factors for cardiovascular disease (CVD) and the metabolic syndrome when studying the population of FM patients. It has long been known that the average body mass index (BMI) of FM patients is higher than that of healthy controls, and the potential interplay between obesity and FM-related symptoms has been investigated in a review with meta-analysis by D'Onghia *et al*., who have shown that obesity is albeit weakly associated with the severity of pain, tender point counts, stiffness, fatigue, physical functioning/disability, sleep, cognitive dysfunction, and the quality of life, although the correlation with depression and anxiety was inconsistent (25). In line with this, a recent study has found that FM patients have a greater glycaemic response to glucose load after one hour and two hours, a larger glucose area under the curve than healthy controls (26), and higher mean glycated HbA1c levels (27).

Given this prevalence of obesity and glucose intolerance, an Indian study calculated the 10- year and lifetime risk of developing CVD using the atherosclerotic cardiovascular disease (ASCVD) calculator and found that FM patients aged 40-59 years had increased lifetime CVD risk than controls (OR = 1.56), regardless of FM severity or duration (28). It is therefore important to monitor the metabolic syndrome in FM patients, not least because careful weight control is a forerunner of an improvement in pain levels.

The sexuality of FM patients has also started to attract greater interest. Sexual dysfunction is highly prevalent (29) together with depressive symptoms (30), and these characteristics have been well described in a recent meta-analysis (31).

Pain neurophysiology

A great deal of research has been dedicated to the neurological aspects of FM pain, with various studies describing the brain areas involved in its perception (32-34) and their associations with specific metabolites (35). Interestingly, Muller *et al*. found that the pattern of brain activation is not due to functional or structural alterations in the areas involved in acute pain (36), once again underlining that chronic pain is not just "longer-lasting pain" (37).

Small fiber neuropathy (SFN)

SFN is highly prevalent among FM patients, and Boneparth *et al*. have found that this was also true of their albeit small sample of 15 patients with juvenile FM, eight (53%) of whom had an epidermal neurite density of <5th centile as against only one (4%) of 23 healthy controls (38).

Two studies investigated the non-invasive diagnosis of SFN in FM patients. In the first, Di Carlo *et al*. (39) used the Pain Detect Questionnaire (PDQ) and the Douleur Neuropathique 4 questions (DN4) to determine the optimal cut-off point of sural nerve cross-sectional area (CSA) for identifying the features of neuropathic pain that suggest SFN in FM patients and found that a CSA of 3 mm^2 had a sensitivity of 70% and a specificity of 90%; however, a better performance was provided by DN4.

In the second, Ramìrez *et al*. (40) found correlations between corneal denervation and SFN and the symptoms of dysautonomia in female FM patients unaffected by severe anxiety or depression, whereas their profoundly anxious or depressed counterparts showed no clinical-pathological correlations even though their symptoms were more intense, thus confirming that severe psychiatric symptoms play a confounding role.

Take home messages

- FM patients have a higher prevalence of obesity and glucose intolerance, and have increased lifetime cardiovascular disease incidence (25-28).
- Neurophysiologically, the pattern of brain activation is not due to functional or structural alterations in the areas involved in acute pain, thus chronic pain is not just "longer-lasting pain" (36, 37).
- The Pain Detect Questionnaire (PDQ), the Douleur Neuropathique 4 questions (DN4), sural nerve cross-sectional area and corneal denervation can be used to non-invasively diagnose SFN (39, 40).

Aetiopathogenesis

Life traumas

One thing that needs to be borne in mind is that trauma plays a major role in the life of FM patients as an acknowledged aetiopathogenetic factor that has been robustly demonstrated; and this should concomitate with the developing autoimmune hypothesis. A history of childhood abuse and neglect substantially contributes to physical disease in adulthood, although this has been more widely studied in the context of mental illnesses (41). A meta-analysis of 19 studies by Kaleycheva *et al*. (42) has confirmed significant associations between adult FM and exposure to stressors such as physical abuse, total abuse, sexual abuse, medical trauma, other lifetime stressors, and emotional abuse. Life traumas are probably related to personality tendencies, as reference is often made to a "fibromyalgic personality" (43) or a form of hyporeactivity to stress (44) that is mirrored by altered vagal activity, in line with Porges' polyvagal theory of the aetiopathogenesis of trauma (45). This has been investigated in more detail by Green *et al*. in a study of male and female rats exposed to the early-life stress of neonatal limited bedding (NLB), who were found to have a significantly lower mechanical nociceptive threshold in skeletal muscle than adult controls previously exposed to neonatal standard bedding. As the controls that had received exogenous corticosterone via the milk of their mothers on post-natal days 2-9 had a similarly decreased mechanical nociceptive threshold, the authors supposed that persistent glucocorticoid receptor (GR) signalling contributed to muscle hyperalgesia in NLB rats, and found that the nociceptor expression of GR was markedly reduced by the spinal intrathecal administration of an oligodeoxynucleotide (ODN) anti-sense to GR mRNA in adult male NLB rats, but not in the females (46).

Immunity

The high prevalence of FM among rheumatological patients indicates a link between FM and autoimmune disorders. In their nationwide Taiwanese study, Gau *et al*. (47) found that FM

patients were at higher risk of developing Sjögren's syndrome, with an adjusted hazard ratio of 2.00 overall, and 3.07 in those aged 20–49 years.

The increasingly recognised role of autoimmunity has been highlighted by Dotan and Shoenfeld description of the way in which COVID-19 infection helped identify the possibly autoimmune pathogenesis of FM-ME/CFS (myalgic encephalomyelitis/chronic fatigue syndrome) (48).

A differentially methylated regions (DMRs) test (49) has revealed greater methylation of GCSAML in women with FM than in their unaffected sisters. This epigenetically regulated gene encodes a signalling molecule that is thought to be associated with the proliferation and differentiation of mature B lymphocytes, thus supporting possible existence of immune system dysregulation in FM patients. Furthermore, an elegant study by Merriwether *et al*. (50) has shown that women with FM have higher levels of the spontaneous and lipopolysaccharide-evoked secretion of IL-5 and other selected cytokines by circulating monocytes than pain-free women. Furthermore, in the women with FM, the greater secretion of IL-5 significantly correlated with pain and other clinically relevant somatic and psychological symptoms, and greater levels of pain and pain-related symptoms correlated with a smaller proportion of intermediate (CD14++/CD16+) monocytes and a larger proportion of non-classical (CD14+/CD16++) monocytes.

However, the most important recent study of autoimmunity was published by Goebel *et al*. (51), who found that mice treated with IgG taken from FM patients were more sensitive to noxious cold and mechanical stimulation, and that the nociceptive fibres in preparations of skin nerves from the treated mice were more responsive to the same stimulation. The findings were the same regardless of sex. Furthermore, the locomotor activity and paw grip strength of the treated mice was reduced, and there was a significant reduction in intra-epidermal nerve fibre density (IENFD) after two weeks of FM IgG treatment. On the contrary, the transfusion of IgG-depleted serum from FM patients or IgG from healthy controls had none of these effects. One of the main findings of the study was that patient IgG did not directly activate naïve sensory neurons: they labelled satellite glial cells and neurons *in vivo* and *in vitro*, myelinated fibre tracts, and a few macrophages and endothelial cells in the dorsal root ganglia (DRG), but none of the cells in the spinal cord (neither neuronal nuclei nor cytoplasm). Furthermore, FM IgG also bound to human DRG. These findings indicate that FM IgG induces painful sensory hypersensitivity by sensitising peripheral nociceptive afferents and suggest the possible efficacy of treatments capable of reducing IgG titres in FM patients.

Genetics

It is known that chronic pain is moderately inheritable, and many studies have tried to discover which genes are involved. However, we shall consider just a few of these in order to summarise the main findings. Although the review by Janssen *et al*. identified a total of 30 FM-related genes (52), individual studies usually concentrate on fewer associations. For example, the study of Gerra *et al*. used family-based and SNP combination analyses but did not find any evidence of genes associated with FM *per se*, although SNP rs6454674 (*CNR1*, the cannabinoid receptor 1 gene) was found to be a potential marker of FM-related depression (53).

Rheman *et al*. published the findings of the largest genome-wide association study of chronic widespread pain. The study involved 249843 participants, and identified three significant loci involving *RNF123, ATP2C1* and *COMT*. However, the association with *RNF123* was replicated; the association with *ATP2C1* was only suggestive; and the association with *COMT* was not replicated in 43080 subjects belonging to independent cohorts. *RNF123*, which is more expressed in skeletal muscle than in other tissues, encodes E3 ubiquitin-protein ligase and plays a role in innate immunity, protein metabolism and cell cycle progression; *ATP2C1* encodes the ATP-powered magnesium-dependent calcium pump protein hSPCA1 that mediates the Golgi uptake of cytosolic Ca(2+) and Mg(2+) (54).

Others

Katz *et al*. have found that FM patients have highly abnormal intra-muscular pressure (which could be a consequence of all of the above): mean muscle pressure in the FM patients was 33.48 ± 5.90 mmHg (only two of the 108 patients had a pressure of <23 mmHg, whereas that of the control patients with rheumatic disease was 12.23 ± 3.75 mmHg (range 3–22 mmHg). Both dolorimetry and digital palpation revealed that the FM patients also had more tender points than the controls (55).

Finally, Levine *et al*. used mass spectrometry to reveal significant differences in the concentration of 2-arachidnoylglycerol (2-AG) and anandamide (two endocannabinoids) in different brain areas between male and female rats: the concentration of 2-AG was lower in the females' peryaqueductal gray (PAG) than in the males' PAG, whereas there was no difference in PAG 2-AG concentrations between the females in different stages of the oestrous cycle. Immunohistochemistry followed by proteomics confirmed the prevalence of 2-AG-endocannabinoid system enzymes in the female PAG (56).

Take home messages

- Studies confirmed significant associations between adult FM and exposure to stressors such as physical/sexual/emotional abuse, medical trauma; it could be related to glucocorticoid signalling alterations (42, 46).
- An animal study found that mice treated with IgG taken from FM patients were more sensitive to noxious cold and mechanical stimulation, and that the nociceptive fibres in preparations of skin nerves from the treated mice were more responsive to the same stimulation (51).
- Although the review by Janssen et al. identified a total of 30 FM-related genes (52), individual studies usually concentrate on fewer associations (52-54).

Treatment

One of the most important treatments

for FM is the use of antidepressants, the validity of which was confirmed by a 6-month naturalistic study by Carmassi *et al*. (57). However, clinicians should be careful not to use it indiscriminately, especially in the case of juvenile patients, as Hengartner *et al*. found that duloxetine leads to a statistically significant higher incidence of severe treatment-emergent psychiatric adverse events than placebo in JFM patients (58). Furthermore, although they are not recommended in the guidelines, recent studies have shown that many FM patients are still treated with opioids (59).

Pharmacological clinical trials

The results of two trials worth mentioning were published in 2021. The first, which did not primarily focus on FM, investigated the long-term pain-modulating properties of ketamine after one year of follow-up in 256 patients who underwent at least one monthly administration in 30 French pain clinics in which ketamine is frequently prescribed. The study's primary endpoint was pain intensity before and after each of the 12 administrations as measured using a 0–10 numerical pain rating scale, which significantly decreased from a mean of 6.8±1.8 at baseline (n=240) to 5.7±1.8 after 12 months (n=93). The effect size of the main endpoint was 0.61, but the FM patients had the worst outcomes (60).

The second trial involved low-dose naltrexone, which is not only a promising treatment for FM, but also for patients "intoxicated" by unjustified opioid treatment. Jackson *et al*. investigated the role of naltrexone in patients with opioid-induced hyperalgesia and patients with FM and found that pain tolerance improved in both groups in a statistically significant manner and that there was a large effect size (61), thus confirming the importance of opioid system modulation.

Last year also saw the continuation of studies concerning the role of cannabis in the treatment of FM. A recent survey of FM patients found that 632 (72.0%) said that they had changed to using cannabinoid products instead of non-steroidal anti-inflammatory drugs (NSAIDs) (59.0%), opioids (53.3%), gabapentanoids (35.0%), or benzodiazepines (23.1%) (62). Although there are still only a few formally conducted trials of cannabis, its use is supported by the results of spontaneous, naturalistic studies in outpatient clinics and patient surveys (63-65).

Non-pharmacological clinical trials

Di Carlo *et al*. have investigated the benefits of a fixed acupuncture formula in 16 different body areas of 96 patients, and found a statistically significant improvement in 12 areas, particularly the abdomen and forearms, whereas the worst results were obtained registered for the neck, chest, left buttock, and right thigh. The treatment also significantly improved fatigue and the quality of sleep (66).

It is well known that education has a positive effect on FM patients, and a study by Ceballos-Laita *et al*. has confirmed the importance of pain neurophysiology education (67). Furthermore, a 12-week study by Serrat *et al*. tested the effects of adding pain neuroscience education to multi-component treatment (exercise, cognitive behavioural therapy, and mindfulness in addition to usual treatment) and found that the multi-component treatment led to significant improvements in pain, kinesiophobia, physical function and functional impairment with a large effect size, as well as moderate improvements in fatigue, anxiety and depression with a medium effect size; the number of patients needed to treat was two, and the non-responders had higher baseline depression scores (68).

Neurophysiology clinical trials

Most of the 2021 trials involved repetitive transcranial magnetic stimulation (rTMS) or direct current stimulation (DCS). In a trial conducted by Argaman *et al*., 27 female FM patients received real and dummy series of 10 Hz M1-rTMS over two weeks separated by a washout period (69). Only the real series led to the expected reduction in FM-related symptoms, which correlated with changes in resting-state functional connectivity (rsFC) in the brain areas associated with pain processing and pain modulation.

Interestingly, Guinot *et al*. found that the addition of rTMS to a multi-component treatment regimen (MT) consisting of aerobic training, pool-based exercises, and relaxation had no additional effect on pain as the reduction in the weekly mean number of pain episodes reported daily (n=39) was not significantly different between the two groups. Two-way analysis of variance (ANOVA) of pain visual analogue scale, cardiorespiratory fitness, quality of life, depression, and catastrophising scores all improved significantly after 14 weeks and remained stable until week 40 (70).

A Spanish study of 170 female patients divided into three groups: the first group underwent an 8-week programme of low-intensity physical exercise (PE) (two 60-minute sessions/week), the second received high-frequency TMS during five 20-minute sessions/week for two weeks, and the third was a control group. At the end of the treatments, the TMS group showed significant improvements in all of the study variables other than for satisfaction; the PE group showed improvements in the average pressure pain threshold, perceived overall impact of FM and total scores, speed and power, endurance and functional capacity, anxiety, depression, and stress; and there was no improvement in any of the variables in the control group. The authors concluded that TMS and PE have similarly beneficial effects on physical status, whereas TMS has more beneficial effects on emotional status than PE (71).

A review of the efficacy of rTMS (72) in 18 studies involving a total of 643 participants found that it significantly reduced the impact of FM as assessed using the Fibromyalgia Impact Questionnaire that was greater in older patients and persisted for at least two weeks after the final treatment session. The same was true of the reductions in pain, depression and anxiety, with the effects on pain and depression being still significant for as long as six weeks after the last session. There was no serious adverse event in any of the reviewed studies.

Caumo *et al*. (73) have found that home-based anodal(a)-tDCS (twenty 20-min-

ute sessions at 2 mA bi-frontally, with the anodal electrode on the left dorsolateral prefrontal cortex (l-DLPFC) reduced total Pain Catastrophising Scale (PCS) scores by 51.38% compared with 26.96% after sham tDCS, and total Profile of Chronic Pain: Screen (PCP:S) total by 31.43% compared with 19.15% in a sample of 48 patients. It also improved depressive symptoms and the quality of sleep, and increased heat pain tolerance (HPTo).

However, the results of a larger trial carried out by Samartin-Vega *et al*. involving 130 patients have challenges the effectiveness of tDCS as a treatment for FM. The aim of the trial was to establish the optimal area (using M1, the dorsolateral prefrontal cortex, the operculo-insular cortex, and a sham procedure) to deliver 2 mA anodal tDCS over the left hemisphere in fifteen 20-minute sessions. Linear mixed-model ANOVA showed significant treatment effects in terms of clinical pain, experimental pain, fatigue, and cognitive and sleep disorders regardless of the group, although the three active tDCS groups showed a significantly greater improvement in anxiety and depression scores than the sham group (74).

An interesting trial compared two groups of 15 patients each who underwent three sessions of high-frequency (10 Hz) rTMS or 20 minutes of 2 mA a-tDCS over the left DLPFC during the course of one week (75). At the end of the study, a reduction in the baseline pain VAS score of at least 30% was achieved by 66.6% of the patients in the rTMS group and 26.6% of those in the tDCS group (p=0.028).

Wearable transcutaneous electrical nerve stimulation (TENS) is a promising treatment that can be more feasible than brain stimulation. A controlled trial randomised FM patients to an active (n=62) or sham (n=57) wearable TENS device for three months and, at the end of this period, found no between-group difference in the patient global impression of change (PGIC) score in the ITT population. However, among the 60 subjects who were more sensitive to pain, the between-group in PIGC scores was in favour of the active treatment group, which also showed significant improvements in the total FIQR score, the pain item of the FIQR, the Brief Pain Inventory (BPI)-Interference, and the Perceived Deficits Questionnaire (PDQ) (76).

Reviews

Most of the reviews of FM treatments published in 2021 considered non-pharmacological treatments. A review of nine randomised and controlled trials by Da Silva *et al*. found clinically and statistically significant reductions in pain when each exercise was performed in 1–2 or 3–5 sets of respectively 4–12 or 5–20 repetitions twice a week for 8–12 weeks at intensities of 40–80%, with one repetition at maximum or perceived maximum exertion (77). Another review of 167 randomised controlled trials involving a total of 11,012 patients assessing 22 non-pharmacological treatments by Kundakci *et al*. found that exercise, balneotherapy, massage, psychological treatments, and multidisciplinary interventions improved FIQ scores, and sub-group analyses of all forms of exercise except flexibility exercise, showed improvements in pain and depression, mind-body and strengthening exercises improved fatigue, and aerobic and strengthening exercises improved sleep. Psychological treatments such as cognitive-behavioural therapy and mindfulness improved FIQ scores, pain, sleep and depression, but not fatigue. These findings suggest that non-pharmacological interventions should be individualised on the basis of the predominant symptom (78), as it has been shown that cognitive-behavioural therapy is most beneficial in the case of insomnia (79).

A very comprehensive review of 224 trials by Mascarenhas *et al*. investigated the best associations of treatments for FM patients and found high-quality evidence favouring cognitive-behavioural therapy to improve pain in the short term, and favouring central nervous system depressants and antidepressants in the medium term. High-quality evidence also favoured the use of antidepressants to improve the quality of life in the short term, and central nervous system depressants and antidepressants in the medium-term. However, the associations did not exceed the minimum clinically important change (two points on an 11-point pain scale, and 14 points on a 101-point quality of life scale), and there was a lack of data concerning long-term outcomes (80).

Finally, two reviews concerned the use and effectiveness of emerging treatments with levo-acetylcarnitine (81) and intravenous lidocaine (82).

Take-home messages

- A clinical trial investigating the long-term (1-year) pain-modulating properties of ketamine found the smallest effect size in FM patients (60) .
- Low-dose naltrexone may be useful for FM patients, also in those who are "intoxicated" by inappropriate opioid treatments (61).
- Many studies investigating the role of rTMS and tDCS found that they may significantly reduce the impact of FM, although data are not always consistent (69-76).

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