Review

Fibromyalgia: one year in review 2023

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ABSTRACT

Fibromyalgia (FM) is a chronic syndrome characterised by widespread pain that affects millions of people worldwide. This article discusses various aspects of FM described in scientific papers published in 2022 and indexed in the PubMed database, including the most recent diagnostic acquisitions (especially in relation to the juvenile form of FM), risk factors, co-morbidities and objective measures. Emphasis is placed on the importance of identifying FM early and improving diagnostic methods (e.g. physical measurements, including walking test performance, hand grip force, and autonomic tests). The article also considers hypotheses concerning the pathophysiology of FM, including the role of inflammation, gut dysbiosis, and neuroinflammation, and possible treatment options, including medications such as antioxidants and kinin antagonists, neurostimulation, and mind-body interventions. Although ketamine, vitamin D, and hormone therapy have shown promise in reducing FM symptoms, further research is needed to optimise their use. Neurostimulation techniques, such as transcutaneous electrical nerve stimulation, transcranial direct-current stimulation and transcranial magnetic stimulation, have been investigated in terms of their efficacy in reducing pain and improving the quality of life. Finally, the role of nutrition is discussed as study findings suggest that weight control, modified high-antioxidant diets, and nutritional supplementation can help to alleviate the symptoms of FM.

Diagnosis

Fibromyalgia (FM) is a chronic syndrome characterised by widespread pain that affects a significant number of people worldwide. However, the existing diagnostic criteria still have their limitations and need to be improved (1), not least because there is a moderate implicit bias among clinicians in favour of specific rather than non-specific diseases (2).

FM can be invalidating and hampers the ability to work. One cross-sectional study (3) has shown that its severity is associated with lower productivity and absenteeism. It has also been shown that there is no significant difference in disease severity across five age categories, although patients aged more than 71 years tend to show poorer physical function (4).

Questionnaires are the easiest means of reporting and measuring FM symptoms. Ghavidel-Parsa *et al*. (5) have sought to validate their preliminary nociplastic-based fibromyalgia features (NFF) questionnaire consisting of seven yes or no questions related to the most clinically relevant characteristics of nociplastic pain. A cut-off score of four positive items gave the highest rate of correctly identified FM patients, with a sensitivity of 82% and a specificity of 91%. The performance of the NFF in the clinical setting was good, and it may provide a more pragmatic approach to the timely diagnosis of FM.

Numerous studies have been aimed at identifying risk factors for FM. Álvarez-Nemegyei *et al*. (6) found a positive correlation between fat mass and FM severity measures and a negative correlation between muscle volume and the Symptom Severity Scale. Furthermore, with the aid of new technologies, a model for predicting FM in subjects with a history of chronic pain has been tested on patients with FM or arthritis attending four primary health centres between 2017 and 2020. The model, which included factors such as age at symptom onset, family history, stress, post-traumatic stress disorder (PTSD), chronic pain, co-morbidities,

and pharmacological prescriptionsm had a high adjusted predictive capacity (0.972; 95% CI: 0.955-0.986), and the risk calculator developed on the basis of its results may be useful in identifying subjects at risk of developing FM (7). Another study has highlighted the association between childhood maltreatment and FM: the results suggest that traumatic childhood experiences can lead to psychopathological disorders in adulthood, and mat at least partially explain the development of FM rather than rheumatoid arthritis (8).

A number of studies have focused on the juvenile form of FM (JFM). This is important because the estimated prevalence of chronic widespread pain (CWP) among children and adolescents in primary care is as high as 3.19% (9), but there are currently no diagnostic criteria for JFM and children are obliged to undergo sub-specialty referrals and extensive imaging and testing (10). Dell'Erba *et al*. (11) have compared the psychological characteristics of JFM patients with those of subjects affected by chronic headache or joint pain, and found that both groups had similar characteristics in terms of depression, anxiety, somatisation, alexithymia, school absenteeism, medication use, and reported pain levels. However, the JFM group was characterised by a higher proportion of females, a higher incidence of sleep disturbances, and better cognitive abilities despite some attention and memory deficiencies. This is similar to what is found among adults, in whom similar distress factors seem to lead to more severe FM-related symptoms (12, 13).

A narrative review by Ahmed *et al*. (14) explored the implications of nerve fibre density for the diagnosis and treatment of JFM, and concluded that an assessment of intra-epidermal nerve fibre density (IENFD) should be made if small fibre neuropathy (SFN) is included in the differential diagnosis as its presentation can be similar to that of JFM but their recommended treatments are different. Distinguishing between the two conditions is important, as the recommended therapies differ. However, there is no evidence to support the use of a skin biopsy to distinguish the two JFM phenotypes (those with SFN and those without), and further studies are needed.

Many of the studies published in 2022 focused on the measurements that could help to identify FM patients. One study found different walking test performance and gait patterns (15), and another (16) found that hand grip strength is significantly associated with physical function indicators such as height, body mass index (BMI), worst pain at rest, pain during activities of daily life, and the Timed Up and Go Test, but not with fear-avoidance behaviours or the pain-related features of FM. Hand grip strength could be a simple means of identifying the risk of falling and poorer physical health in women with FM, but the quest for biomarkers that can aid diagnosis in this population continues.

Two studies (17, 18) have examined the serological characteristics of FM patients. The first found a high prevalence of primary immunodeficiency (PID) revealed low levels of immunoglobulins and mannose-binding lectin, and the results correlated with the patients' clinical history of recurrent infections and reduced density of epidermal nerve fibres. The second used artificial neural networks and matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF MS) to classify and diagnose pathological pain subtypes in preclinical models, and has led to the development of a simple and innovative clinical decision-making support method that allows their highly specific identification and classification.

The association between FM and neuropsychiatric symptoms has led to the investigation of neurotrophins as potential biomarkers. One study (19) has found that the levels of brain-derived neurotrophic factor (BDNF) are significantly lower in FM patients than healthy controls, which suggests that BDNF levels may be a diagnostic biomarker. Another study has found that serum calcitonin gene-related peptide (CGRP) levels are higher in FM patients than in healthy controls but there is no significant difference in the levels of vascular endothelial growth factor (VEGF) (20), which suggests that CGRP may also be a reliable diagnostic parameter. A third study (21) assessed the relationship between serum niacin and dopamine levels in 53 female FM patients and 35 healthy female controls, and found that the levels of both were significantly lower in the patients, and that there was a strong positive correlation between the two (r=0.96, $p<0.001$). Niacin and dopamine levels may therefore be additional diagnostic parameters as their area under the curve (AUC) values were respectively 0.73 ($p<0.001$) and 0.68 ($p=0.004$).

It has also been shown that the AKAP12 and RNF11 genes can be used as diagnostic markers, and that CD8+ T cells may be involved in the occurrence and development of FM: AKAP12 positively and RNF11 negatively correlated with CD8 + T cells (22).

However, although these studies provide newer insights into the investigation of biomarkers, meta-analyses have failed to reveal a systematic correlation. One systematic review and meta-analysis (23) assessing the levels of blood biomarkers in JM patients and healthy controls found that the former had lower levels of interleukin-1 β and higher levels of IL-6, IL-8, tumour necrosis factor-alpha, interferon gamma, C-reactive protein, and BDNF, but the findings did not support the idea that these biomarkers are specific markers of FM. However, they may identify underlying conditions that often co-exist with FM.

As FM is now recognised as a neuroplastic pain condition, there have been various attempts to find a "neurophysiological/neuroimaging signature" of FM patients. It has been found that FM affects brain morphometry (24), and that FM patients may have a unique retinal signature (25). Other imaging studies have shown a trend towards decreasing volumes in the right anterior insular cortex (rAIC) of three subgroups showing an increased number of areas experiencing pain (26), and reduced echogenicity in the midbrain raphe area of patients with FM or depression and physical pain regardless of the presence or severity of the pain, FM or depressive symptoms (27).

Neuro-inflammation is also important. Brain up-regulation of the TSPO translocator protein (a biomarker of glial activation) has been reported in FM patients. One study (28) has found that translocator protein high-affinity ligands (HABs) have higher thalamic glutamate concentrations and show a pattern of positive correlations between glutamate and γ-aminobutyric acid in the rostral anterior cingulate cortex that is not observed in mixed/low-affinity ligands (MLABs). It has been demonstrated that a number of pain indicators (temporal summation of pain, conditioned pain modulation, and evoked pain) combined with neuroimaging effectively reveal central sensitisation involvement in FM patients (29), and EEG-based studies have also shown that FM patients show maladaptive affective attention modulation (30) and hyper-connectivity between the left motor cortex and prefrontal cortex (31), which is associated with the severity of the dysfunction of the descending pain modulatory system. The future of FM diagnosis could therefore involve the use of dynamic evoked pain assessments in combination with neuroimaging, although further research is necessary to clarify the underlying mechanisms and optimise diagnostic protocols.

Take home messages

- Various potential diagnostic biomarkers have been studied, including hand grip strength, neurotrophins and serum niacin and dopamine levels, the *AKAP12* and *RNF11* genes, and $CD8^+$ T cells; however, meta-analyses do not reveal a consistent link between biomarkers and a diagnosis of FM (15-22).
- FM affects brain structures and may have a unique retinal pattern. Pain indicators and neuroimaging can effectively study central sensitisation. Future diagnoses may involve dynamic evoked pain assessments with neuroimaging (24, 25, 29).
- Childhood trauma may contribute to the development of FM (8). A predictive model based on factors such as age, family history, and chronic pain can be used to identify subjects at risk of developing FM (7).
- There are no diagnostic criteria for JFM. The psychological characteristics of JFM patients are similar to those of subjects with chronic headache or joint pain. If small fibre neuropathy is a possibility, intra-epidermal nerve fibre density should be assessed (9-11, 14).

Differential diagnosis

FM often accompanies other rheumatic diseases such as connective tissue disorders, ankylosing spondylitis and spondyloarthritis. One systematic review of 11 studies (32) has found that the concomitant diagnosis of FM and hypermobile Ehlers-Danlos syndrome, hypermobility spectrum disorders, and generalised joint hypermobility respectively range from 68% to 88.9%, 8.0% to 64.2%, and the existence of shared symptoms such as joint pain, joint swelling, muscle weakness, and dysautonomia. All chronic overlapping pain conditions (COPCs) such as fibromyalgia, migraine, and back pain frequently co-occur with rheumatic diseases: one study of patients attending rheumatology clinics over a 10-year period found that 36-62% had a COPC diagnosis, with the highest prevalence among patients with Sjögren's syndrome (62%). However, differential diagnosis is not always easy: agreement between the American College of Rheumatology (ACR) 1990 FM tender points and enthesitis scores has been found in patients with axial spondyloarthritis, thus suggesting a significant overlap between the two scores even in patients without concomitant FM, and a need for further evaluation by means of differential diagnosis (33). There are differences between FM-derived and arthritis-derived pain, and these have been investigated in a functional magnetic resonance imaging (fMRI) study comparing disease-relevant cerebral pain processing in patients with FM or rheumatoid arthritis (RA) (34). The study found distinct differences in pain modulation between the two groups, with the FM patients showing increased brain activation in certain regions. Furthermore, and only within the FM group, anxiety scores positively correlated with the pain-related brain activation, thus highlighting the complex interaction between the affective and sensory dimensions of FM patients. Accordingly, another study has found that the descriptors of central sensitivity-related pain differ from those of disease activity-related pain (35).

Two recent studies (36, 37) have investigated the differentiation of FM from other chronic pain disorders or myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), which is also very co-morbid. The first evaluated 158 pain patients attending two primary care clinics, and found that five symptoms best distinguished FM from other chronic pain disorders: persistent deep aching over the body, poor balance, environmental sensitivity, tenderness to touch, and pain after exercise. The second was a meta-analysis of 21 publications aimed at defining the clinical overlap between FM and ME, which found that there was a 47.3% overlap between the two conditions using the old 1990 FM diagnostic criteria and concluded that the concordance would probably be even higher using the most recent 2016 criteria. These findings underline the need for very careful evaluation and the use of multiple diagnostic methods in order to diagnose FM accurately.

Take home messages

FM often co-exists with other rheumatic diseases, and its differential diagnosis can be difficult as the shared symptoms include joint pain, swelling, muscle weakness, and dysautonomia. There is also a significant overlap with ME/CFS. However, there are some neurophysiological differences as highlighted by the fMRI study investigating pain (32, 33, 35, 37).

Aetiopathogenesis

The possible etiopathogenesis of FM was relatively under-studied in 2023. The gut microbiome appears to be a promising feature as it apparently shows unique differences that cannot be explained by dietary intake alone (38). Minerbi *et al*. (39) have found that FM patients show alterations in the relative abundance of certain bile acid-metabolising bacteria that can lead to changes in circulating bile acids. These alterations are associated

with symptom severity (including pain intensity and fatigue), and may provide insights into the development of molecular diagnostic aids, which is particularly interesting given the similarities between irritable bowel syndrome (IBS) and FM. One review (40) of the pathogenic processes of both syndromes found that they have in common the involvement of mast cells, the immune system, hormones, neurotransmitters, and the microbiota. An association with altered immunity has been proposed by a group suggesting that oral exposure to flavouring substances and hygiene products may sensitise FM patients and possibly elicit symptoms of systemic contact allergy (41), and the importance of inflammation related to co-morbidities is underlined by the presence of specific COMT DNA methylation, which may be an independent factor contributing to both CFS and FM (42).

However, another group investigating whether FM-related pain parameters assessed by quantitative sensory testing (QST) and psychological disturbances are accompanied by alterations in faecal microbiome has concluded that the gut microbiome plays only a limited role in the pathophysiology of FM (43).

Two studies have investigated cellular and synaptic alterations in chronic pain conditions (44, 45). The first found that, in mice whose nociceptors were being primed to a state of chronic pain, the local infusion of pregabalin or the chemogenetic inactivation of somatostatin-expressing CeA neurons during the priming phase prevented the pain from becoming chronic. CeA-SST neurons show increased excitatory synaptic drive and enhanced neuronal excitability in states of chronic pain but either their chemogenetic inactivation or pharmacological suppression of the nociceptive afferents from the brainstem alleviated the pain and anxio-depressive symptoms. The second study examined the cerebral cortex of patients with pain-sensitised knee osteoarthritis or FM, and found that changes in local connectivity were involved in both conditions, but the osteoarthritis patients had weaker connectivity in the insula, and the FM patients had weaker connectivity in the sensorimotor cortex. These findings suggest that pain sensitisation in the two groups may be due to different neurophysiological mechanisms.

Finally, Hernandez *et al*. have published preliminary data suggesting an association between central pain sensitisation and autonomic nervous system deficiency due to small fibre neuropathy, which is certainly an interesting research hypothesis to work on in the future (46).

Similarities with post-COVID syndrome

A close relationship between post-COVID syndrome and FM has been highlighted by the autonomic dysfunctions present in both conditions (47). One recent study suggests that some FM patients have an impaired autonomic cardiovascular response to orthostatic and clinostatic challenges that reduces autonomic flexibility and adaptability to situational demands, and that the magnitude of the autonomic adjustments to postural changes is inversely associated with the severity of chronic pain (48).

A review analysing data concerning clinical symptoms and pathogenic mechanisms in subjects with CFS, FM, silicone breast implants (SBIs), COVID and post-COVID syndrome, postural orthostatic tachycardia syndrome (POTS), and some autoimmune diseases found an imbalance in autoantibodies against G protein-coupled receptors (GPCRs) in those with autoimmune diseases, post-COVID syndrome, and SBIs. This has allowed the recognition of a new entity called autoimmune autonomic nervous system imbalance, which is frequently accompanied by symptoms characteristic for dysautonomia, such as severe fatigue, dizziness, fogginess, memory loss, dry mouth and eyes, hearing dysfunction, and tachycardia, symptoms that are very common among FM patients (49).

Take home messages

- The gut microbiome shows unique differences in subjects with FM, which may provide insights for the future development of molecular diagnostic aids. FM and IBS share common mechanisms involving mast cells, hormones, neurotransmitters, and the microbiota (38, 40, 41).
- FM patients have impaired autonomic cardiovascular responses to postural challenges that reduce autonomic flexibility and adaptability to situational demands. Pain is associated with cognitive dysfunction (47, 48).
- An imbalance in autoantibodies against GPCRs is present in patients with autoimmune autonomic nervous system imbalance, which frequently accompanied by dysautonomic symptoms that are frequently observed in FM patients (49).

Treatment

Multi-disciplinary and multi-modal treatment is currently the gold standard for the treatment of FM, but it is important to tailor it to each patient's main symptoms. One meta-analysis has concluded that exercise, psychological treatment, multidisciplinary modalities, balneotherapy, and massage improve symptoms, but different types of exercise are effective in improving pain, depression, fatigue, and sleep: mind-body and strengthening exercises improve fatigue (ES -0.77 to -1.00), whereas aerobic and strengthening exercises improve sleep (ES -0.74 to -1.33); furthermore, psychological treatments improve symptoms but not fatigue (50).

Exercise is a well-known first-line treatment. One systematic review of 11 studies has shown that aerobic exercise (walking or cycling at sub-maximal intensity with incremental increases for 40-60 minutes) increases pressure pain thresholds or decreases pain ratings in patients with musculoskeletal pain (51). Comparisons of the efficacy of different exercise protocols indicate that exercise programmes lasting 13-24 weeks should be used to reduce pain, with each session lasting for between 30 and 60 minutes at gradually increasing intensity (52). Exercise sessions may be more effective if they are accompanied by education programmes (53, 54). Tomas-Carus *et al*. have published the findings of a randomised controlled trial showing that respirato-

ry muscle training improves the health-related quality of life of FM patients (55).

Cognitive-behavioural therapy (CBT) and mindfulness are the most widely studied psychological interventions for managing pain. The changes in different brain regions observed after CBT include grey matter volume, activation/deactivation, and intrinsic connectivity. CBT mainly involves cognitive and emotional regulation, with the dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), right ventrolateral prefrontal cortex (VLPFC), posterior cingulate cortex (PCC), and amygdala being the key regions. After CBT, the brain shows stronger top-down pain control, cognitive reassessment, and altered perception of stimulus signals (56). CBT also seems to be effective in treating insomnia (CBT-i), leading to significant improvements in sleep quality, pain, anxiety, and depression in comparison with other non-pharmacological treatments. However, according to one meta-analysis of very few studies with low-quality evidence, the effect sizes are only small to moderate, and so more research is needed to confirm the findings (57).

Mindfulness was found to have a significant indirect effect on physical impact, anxiety/depression and emotional distress in a study of 51 FM patients (58).

Pharmacological treatment

Three meta-analyses have investigated the efficacy of various drugs, and found that duloxetine (DLX) and pregabalin (PGB) led to the greatest improvement in symptoms and the lowest rate of adverse events leading to study discontinuation (59). In comparison with placebo, DLX 120 mg was associated with a greater improvement in pain and depression, whereas amitriptyline (AMT) was associated with greater efficacy in improving sleep, fatigue, and the overall quality of life, but its acceptability was similar to that of placebo (60); DLX 20 mg and 30 mg were not superior to placebo. The calculation of SUCRA indicated that PGB 450 mg was the best performing option for R30%, and AMT 25 mg for R50%; PGB 150 mg was the worst performing drug in both cases (61). It is also important to remember that PGB has a thinning effect on the retinal nerve fibre layer and should therefore not be used to treat FM patients with retinal nerve fibre layer damage, such as those with diabetic retinopathy or glaucoma (62).

Finally, a meta-analysis has shown that vitamin D supplementation is more effective than placebo in reducing Fibromyalgia Impact Questionnaire scores (but not visual analogue scale scores) (63).

Neurostimulation

Transcranial direct current stimulation (tDCS) has been investigated as a potential treatment for FM, but the data are contradictory. Two randomised, double-blind trials have studied its effectiveness in reducing various FM symptoms. One of these found that home-based anodal tDCS on the left dorsolateral prefrontal cortex was associated with a moderate effect size in reducing pain catastrophising and pain-related disability, and improving depressive symptoms, sleep quality, and pain tolerance; it also found a correlation between its effect on pain catastrophising and the delta-value of serum BDNF (64). However, another trial aiming to establish the optimal area for tDCS also found evidence of a placebo effect, thus challenging its effectiveness as a treatment for FM (65). Furthermore, tDCS applied together with exercise does not seem to provide any additional benefit (66, 67).

A lot of research has focused on the therapeutic effects of different types of transcranial magnetic stimulation (TMS) in FMS patients. It is thought that TMS acts on FM symptoms via neuroplastic changes and functional alterations in brain areas whose structural changes potentially occur over a more extended treatment period. One study found that the reduction in FM-related symptoms following transcranial magnetic stimulation of the motor cortex (M1-rTMS) occurred only with real treatment and correlated with changes in resting-state functional connectivity in the brain areas associated with pain processing and modulation (68). Various meta-analyses have assessed the efficacy of rTMS, with consistent results. The meta-analysis of Toh *et al*. found that rTMS was more effective than sham stimulation in improving the quality of life, but not in reducing depression or anxiety: a subgroup analysis showed that primary motor cortex stimulation was more effective than sham stimulation in improving pain, but neither dorsolateral prefrontal cortex nor primary motor cortex stimulation was more effective than sham stimulation in improving depression or anxiety (69). Two other meta-analyses by Choo *et al*. and Zhu *et al*. (70, 71) considered the effects of rTMS delivered to different locations (left primary motor cortex vs left dorsolateral prefrontal cortex) and follow-up time points (immediately, 1-4 weeks, and 5-12 weeks after rTMS sessions), and the use of 10 Hz rTMS. Both studies found that rTMS was effective in reducing pain and improving the quality of life of FM patients, but not in reducing depression. The first found that high-frequency rTMS on the left primary motor cortex had a significant pain-reducing effect immediately and 1-4 weeks after the completion of the rTMS sessions, and that the patients' quality of life improved after 5-12 weeks. However, high-frequency rTMS on the left dorsolateral prefrontal cortex did not reduce FM-related pain. Overall, these meta-analyses suggest that rTMS is a promising treatment option for FM, but further research is needed to determine the optimal stimulation locations and follow-up time points.

Other treatments

A randomised, double-blind and placebo-controlled study found that the addition of ozone therapy to autohemotherapy improved the quality of sleep and the subscale scores of feel good and fatigue in 200 FM patients treated with 3-4 runs of ozone therapy, and Tirelli *et al*. found that, in comparison with controls, ozonated autohemotherapy significantly improved pain and quality of life in 100 FM patients (72, 73).

Mind-body interventions such as yoga and tai chi have gained increasing recognition as effective complementary treatments in FM patients. A system-

atic review and meta-analysis of randomised controlled trials found that tai chi was effective in reducing pain and improving overall well-being (74), and a separate randomised controlled trial (75) found that a 12-week yoga programme was effective in reducing pain and improving the quality of life.

Multiple studies have demonstrated the benefits of high-antioxidant, high-fibre foods such as fruits and vegetables, low-processed foods, high-quality proteins, and healthy fats in FM patients. Although there is no specific dietary therapy, studies suggest that weight control, modified high-antioxidant diets, and nutritional supplementation can help alleviate FM symptoms (76). Furthermore, an 8-week study of the consumption of ancient Khorasan wheat showed that it improved intestinal microbiota composition and that this positively correlated an improvement in FM symptoms: for example, there were positive correlations between Actinobacteria and the scores of the Tiredness Symptoms Scale ($p<0.001$) and Functional Outcome of Sleep Questionnaire ($p<0.05$), and between Verrucomicrobiae and the scores of the Widespread Pain Index (WPI) + Symptom Severity scale (SS) ($p<0.05$) and the WPI ($p<0.05$), thus suggesting that gut microbiota modulation can improve FM symptoms (77).

Preclinical studies

A preclinical study aimed at evaluating the efficacy of etanercept and infliximab (10 mg/kg) in the management of pain sensitisation induced by reserpine in rats has found that infliximab greatly reduced thermal hyperalgesia and mechanical allodynia. In molecular terms, it reduced the activation of microglia and astrocytes and the expression of the purinergic P2X7 receptor that is ubiquitously expressed on glia and neurons; downstream of the P2X7 receptor, it also reduced the p38-MAPK overexpression induced by reserpine (78).

Another study has found that broad-spectrum cannabis oil is an effective alternative means of reversing the reserpine-induced FM model. *Cannabis sativa* has analgesic, anti-inflammatory, neuroprotective, and immunomodulatory activity, and the study evaluated the analgesic effect of broad-spectrum cannabis oil with a low THC concentration on mechanical hyperalgesia, thermal allodynia, locomotor activity, and depression- and anxiety-related behaviour after reserpine administration. Repeated cannabis oil administration markedly mitigated mechanical and thermal sensitivity, and reduced the depression-like behaviour induced by reserpine (79).

Take home messages

- Duloxetine and pregabalin are the most effective drugs for managing FM as they lead to the greatest improvement in symptoms and the lowest rate of adverse events requiring study discontinuation. Amitriptyline is more effective in improving sleep, fatigue, and the overall quality of life. However, pregabalin should not be used in FM patients with retinal nerve fibre layer damage (59-62).
- Transcranial magnetic stimulation (TMS) is a promising means of treating FM that has led to consistent results in meta-analyses. High-frequency rTMS over the left primary motor cortex (but not over the left dorsolateral prefrontal cortex) has a significant pain-reducing effect (68-71).
- Transcranial direct current stimulation (tDCS) may be effective in reducing the FM symptoms of pain catastrophising, disability-related pain, depressive symptoms, sleep quality, and pain tolerance, but the study data are not consistent (64-67).
- A modified high-antioxidant diet, weight control, and nutritional supplementation can help to alleviate FM symptoms. An 8-week study of the consumption of ancient Khorasan wheat improved intestinal microbiota composition, and this positively correlated with an improvement in FM symptoms (71, 72).

Conclusions

This article based on studies published in 2022 provides a wealth of information concerning the diagnosis of FM and the demographic, genetic and environmental risk factors associated with it. The most significant advances have been made in the diagnosis of juvenile FM. Many of the studies focused on the co-morbidities frequently associated with FM, such as irritable bowel syndrome, chronic fatigue syndrome, and other rheumatological conditions, and researchers have made considerable progress in investigating potential treatments for FM. These advances provide promising avenues for further research and, with the right combination of medications, neurostimulation, nutrition, and mind-body interventions, it may be possible to improve the quality of life of FM patients significantly.

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