# One year in review 2017: fibromyalgia

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**ABSTRACT**

*Fibromyalgia (FM) is a complex syndrome characterised by chronic pain, fatigue and functional symptoms. Widespread pain is often its most typical feature, whereas other manifestations may be associated to various extents. 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 relating to the aetiopathogenesis, assessment and treatment of FM published between January 2016 and January 2017.*

**Aetiopathogenesis**

There is still controversy concerning the aetiopathogenesis of fibromyalgia (FM), with genetic predisposition, environmental triggers and neuromodulation all being considered to be involved in the onset and course of the disease.

Jones *et al*. used a genome-wide expression array to profile the peripheral blood cells of 70 FM patients and 70 controls, and found the differential expression of 451 genes, some of which encode kinase molecules, transcriptional regulators and transporter molecules, and are involved in the up-regulation of immuno-inflammatory pathways and the down-regulation of hypersensitivity and allergic responses (1).

An analysis of leukocyte mRNA gene expression in 261 subjects, including 15 patients with FM and 33 with chronic fatigue syndrome (CFS), by Jacob *et al*. considered four clusters (purinergic and immune modulators, those involved in neuronal growth and immune function, mediators of nociception and stress; and those involved in energy and mitochondrial function), and found differences in genetic modulation between the CFS and FM patients depending on the expression of genes related to purinergic and immune modulators and nociception and stress mediators (2), thus highlighting the distinct genetic pathogenesis of the two diseases.

Cordero *et al*. identified a new mitochondrial DNA mutation (m.15804T>C) in the mtCYB gene in peripheral blood cells taken from a FM patient that was maternally inherited and associated with a greater oxidative and auto-inflammatory burden (3). However, the rarity of this mutation and the small sample size means that further studies would be useful to strengthen the association.

The role of the epigenetic modification of DNA was investigated by Burri *et al*., who found a significant association between three 5'-C-phosphate-G-3' islands (CpGs) (including the genes for malate dehydrogenase 2, tetranectin, and heat shock protein beta-6) and the chronic widespread pain (CWP) suffered by twins (4). Although none of these genes has previously been associated with chronic pain, the authors suggested an association between tetranectin and tendon stress that may be mirrored by the lower pain thresholds of the tender points of FM patients following the up-regulated expression of tetranectin.

A recent systematic review by Pyke *et al*. of nine studies involving a total of 482 FM patients (5), revealed a significant association between the risk of suffering from FM and increased brain glutamate levels detected by means of proton magnetic resonance spectroscopy (H-MRS). The highest glutamate concentrations were found in the posterior cingulated gyrus, posterior insula, ventrolateral prefrontal cortex and amygdala. Glutamate has excitatory functions in neuronal cells due to its binding to ligand-gated sodium channels, which induces an intracellular influx of sodium ions that culminates in cell membrane depolarisation. Excess glutamate in the central nervous system (CNS) was significantly associated with a low pain threshold, fatigue, and a poorer quality of life.

As many amino acids may act as neurotransmitters and neuromodulators, Ruggiero *et al*. evaluated the association between free amino acids and the clinical manifestations of FM (6). They found significantly higher serum concentrations of aspartate, cysteine, glutamate, glycine, isoleucine, leucine, methionine, ornithine, phenylalanine, sarcosine, serine, taurine, tyrosine and valine in FM patients than in healthy controls. Moreover, the patients with higher Fibromyalgia Impact Questionnaire (FIQ) scores had the highest levels of alanine, glutamine, isoleucine, leucine, phenylalanine, proline and valine.

Neuron-specific enolase (NSE) is an enzyme expressed by neuronal cells and is usually considered a marker of neuroendocrine differentiation and regeneration. Verim *et al*. investigated the association between serum NSE and the neurocognitive scores of 55 FM patients and 40 healthy controls using the FIQ, Beck's Depression Scale, the mini mental test and the clock drawing test, but failed in finding any significant association (7).

Karras *et al*. reviewed the literature concerning the role of vitamin D in preventing chronic pain and FM (8). In line with the authors of other studies showing a significant association between low vitamin D levels and worse scores on quality of life questionnaires (9), they concluded that FM patients have hypovitaminosis D, and that vitamin D supplementation may improve FM symptoms. However, because of the lack of well-designed trials, the real importance of vitamin D supplementation in FM is still unclear, and it is only recommended in the case of deficiency.

The role of the neurological modulation of pain in the pathogenesis of FM has been widely investigated, and pain sensitivity may crucially involve both the CNS and the peripheral nervous system (PNS). Baek *et al*. investigated the contribution of both to the modulation of nociceptive stimuli in 24 FM patients and 24 healthy controls by evaluating the cutaneous silent period (CSP) from the abductor pollicis brevis muscle. The CSP is a protective spinal reflex mediated by the inhibitory A-delta cutaneous afferent circuit that temporarily pauses muscle action potentials after the strong stimulation of the cutaneous nerve during a protracted voluntary muscle contraction. The authors found a significantly longer CSP in FM patients that suggested central dysregulation at the spinal and supraspinal levels rather than peripheral small fibre dysfunction (10).

The course of FM is often accompanied by sleep disorders and a polysomnographic study of 132 FM patients by Roth *et al*. showed that, in comparison with controls, their total sleeping time and the duration of slow-wave sleep were shorter, the latency to persistent sleep was longer, and their waking bouts were shorter and more frequent (11). A study of 54 pre-menopausal female FM patients found that non-restful sleep as evaluated by means of the Pittsburgh Sleep Quality Index (PSQI) significantly affected their sexual function as evaluated by means of the Female Sexual Function Index (12). Palagini *et al*. considered sleep disturbances a key problem connecting pain and cognitive disturbances as a result of the activation of the stress system (13).

Neuroinflammation was addressed in a study by Tsilioni *et al*., who showed corticotropin-releasing hormone (CRH), substance P (SP) and SP-structurally-related haemokinin-1 (HK-1) levels closely correlated with the likelihood of FM (14). CRH and SP may favour the release of interleukin (IL)-1 and tumour necrosis factor-alpha (TNF-α) from mast cells, thus contributing to pain sensitisation. Furthermore, activated monocytes from FM patients release more eotaxin, C-C Motif Chemokine Ligand 22 (CCL22) and C-X-C Motif Chemokine Ligand 1 (CXCL1) than those of healthy subjects (15). Neuroinflammation may also be triggered by the activation of autoinflammatory pathways: Bullòn *et al*. found reduced levels of phosphorylated adenosine monophosphate-activated protein kinase (AMPK) and adenosine triphosphate (ATP), and increased levels of mitochondrial reactive oxygen species (ROS) in blood cells taken from FM patients, as well as high IL-1β and IL-18 levels that were restored after treatment with metformin (16). Mitochondrial superoxide production was significantly increased in FM fibroblasts in comparison with controls, and this may be related to impairment of the AMPK pathway, which plays a protective role against oxidative damage.

Diet is one of the environmental factors that may influence the onset and course of FM. Coeliac disease has been previously associated with the risk of developing FM, but Nisihara *et al*. did not find a significant association between FM and the laboratory or histological markers of coeliac disease in a cohort of 94 FM patients (17). A Puerto Rican study of 144 FM patients found that obese patients were more likely to develop self-reported memory impairments and urinary disturbances than non-overweight patients, and visceral adiposity also correlated with a higher tender point count (18). Another study found that being overweight was associated with increased serum levels of C-reactive protein (CRP), apolipoprotein B and triglycerides in FM patients, although it was also found that CRP and apolipoprotein B levels were higher in normal-weight FM patients than in healthy controls. Moreover, apolipoprotein B, nitric oxide (NO) and CRP levels correlated with FIQ scores (19).

According to Alman *et al*., patients with eating disorders, migraine and pelvic pain were more likely to develop overactive bladder syndrome, which has been associated with FM and CPS (20).

Finally, social distress, feelings of social exclusion and poor social relationships may modulate the threshold of pain sensitivity, as demonstrated by the studies of Canaipa *et al*., who explored the effect on nociception of the psychic stress induced by the Cyberball virtual reality game (21, 22).

**Assessment**

The assessment of FM requires a global evaluation of the patient's neurocognitive, psychological, physical and functional dimensions in order to be able to tailor the most appropriate therapeutic approach.

FM patients often lack a diagnosis because of the wide range of manifestations. The 1990 American College

of Rheumatology (ACR) diagnostic criteria and the modified 2010 ACR preliminary diagnostic criteria for FM may identify patients with different clinical expressions of the disease who therefore require different therapeutic strategies (23). Moreover, a large UK survey of the electronic health records of general practitioners relating to pain consulters showed that three-quarters of these patients did not have a definite diagnosis; furthermore, 50% of these patients did not satisfy the criteria for the Widespread Pain Index (WPI), and only one-third of those who did also satisfied the criteria for recurrent regional pain (24). Recurrent regional pain syndrome is therefore a distinct and often misdiagnosed syndrome in the broad spectrum of chronic pain disorders whose somatic symptoms it shares even though it is characterised by a more favourable course.

In 2016, Wolfe *et al*. revised the 2010-2011 diagnostic criteria for FM by adding the item *generalised pain* (criterion 2), the definition of which is different from the 1990 definition of widespread pain insofar as refers to pain in at least four out of five regions, excluding the jaw, chest and abdomen (25). They also replaced the separate physician and patient criteria with a physician estimate of the burden of somatic symptoms (headache, pain or cramps in the lower abdomen, and depression during the previous six months) that is to be combined with the WPI to obtain the FM symptom scale (FSS) as a full component of the fibromyalgia criteria and a means of estimating symptom severity. The new revised criteria make it possible to distinguish FM from other local painful syndromes while simultaneously including overlapping medical conditions with a good degree of sensitivity and specificity.

FM may in fact overlap many rheumatic and non-rheumatic diseases. Rheumatoid arthritis (RA) patients with overlapping FM have higher disease activity scores than those without FM because of their greater sensitivity to pain, and worse self-reported questionnaire and visual analogical scale VAS) scores (26). A Brazilian study of 256 RA patients (including 32 with FM) who were followed up for 6.2±2.0 years found that the patients with FM had higher baseline 28-joint disease activity scores (DAS28) and Health Assessment Questionnaire (HAQ) scores than non-FM patients, and also used higher doses of tricyclic antidepressants, leflunomide and prednisone, and lower doses of methotrexate (27). However, radiographic assessments were not significantly different between the two groups, and may be a useful means of preventing mistreatment in patients with a lower pain threshold. Furthermore, in the case of overlapping RA and FM, Lee *et al*. proposed measuring the serum concentrations of 12 biomarker proteins (including CRP) and extrapolating the results to a scale of 1–100, but no significant difference was found between 25 RA patients with and 173 without FM (28).

In addition to a medical examination, the assessment of FM also involves the use of self-administered questionnaires concerning patient-reported outcomes in order to explore symptoms, the health-related quality of life, and medical compliance. These include the revised FIQ, which evaluates six domains (pain, tenderness, fatigue, stiffness, multidimensional function, and sleep) and is a standardised means of assessing function and the health-related quality of life. Salaffi *et al*. (29) carried out a national Internet-based survey of 353 Italian FM patients by providing the FIQ and the self-administered Fibromyalgia Activity Score (FAS28) questionnaires (30), which allows the categorisation of patients into three groups on the basis of the severity of their self-reported symptoms, and the collection of some demographic data (sex, weight, education). The use of dedicated portals available on Internet platforms is an innovative means of identifying clusters of FM patients and carrying out epidemiological studies even though the use of Internet browsers varies in the general population on the basis of education and socio-economic status; however, patients may also magnify their symptoms when responding to such questionnaires, and the results may not corresponding to those of an objective evaluation. Estévez-López *et al*. conducted a population-based, cross-sectional study of 405 women with FM and 193 age- and gender-matched controls who were asked to complete the Pain Catastrophising Scale (PCS), the Chronic Pain Self-efficacy Scale, the physical functioning subscales of the Revised FIQ, and the Short Form-36 (SF-36) health survey, but they also measured objective physical function using the Senior Fitness Test battery. The patients with high PCS scores also had the greatest burden of subjective physical symptoms, but there was significant discordance between subjective and objective physical function; in such cases, the authors suggest a careful physical examination in order to complement physical rehabilitation with cognitive management techniques (31). Previous traumatic events, including sexual abuse, are usually more common in younger FM patients (mean age 23.4 yrs), who are also significantly more likely to develop psychiatric disorders such as bipolar syndrome, panic attacks and anxiety, and to make greater use of healthcare resources (medications, psychotherapy) (32). Moreover, the perception and intensity of pain may be modulated in children and adolescents depending on the attitude of their parents or caregivers, being more acute in those with whose parents have a more protective attitude painful symptom-centred responses (33). One epidemiological study of 95,150 Taiwanese patients with incident FM found a mild-to-moderate risk of a suicide event in patients with a primary form of the disease, which may be increased by concomitant comorbidities (34). On the basis of these findings, especially younger FM patients should undergo psychiatric counselling and be assessed by means of a semi-structured interview (*i.e*. the Structured Clinical Interview for the DSM-IV).

Recent research into the mechanisms underlying FM has shown the significant involvement of both the CNS and PNS. Neuroimaging may reveal interesting findings in the neuronal circuits that are activated in FM patients depending on the different clinical phenotypes. Truni *et al*. assessed the functional status of the periaqueductal grey

(PAG) of 20 FM subjects by means of functional magnetic resonance imaging (fMRI), and found a significant increase in PAG connectivity with the insula, anterior cingulate cortex, and anterior prefrontal cortex that was also significantly associated with pain severity, disease duration, and a depressive personality trait (35). Similarly, other authors (36) found altered cerebral (f)MRI signals in 37 FM patients in comparison with 35 controls following the administration of pressure pain or non-painful stimuli, with particular brain patterns distinguishing FM patients from those with other chronic pain conditions with a sensitivity of 92% and a specificity of 94%. Pomares *et al*. used T1-weighted MRI to study 26 pre-menopausal FM patients and 25 controls, and found a reduction in grey matter water content in the posterior cingulate cortex, precuneus, anterior cingulate cortex (ACC), bilateral insula, right medial prefrontal cortex (MPFC), left precentral gyrus, and left middle temporal gyrus (MTG) of the FM patients, as well as increased grey matter volume in the angular gyrus, cuneus, and right postcentral gyrus that was also associated with increased GABAA receptor concentrations as measured by means of [18F] flumazenil Positron emission tomography (PET) (37). The latter finding was also associated with worse current pain level scores, the anxiety subscale of the Hospital Anxiety and Depression Scale, and the PCS, which possibly mirrored neuro-inflammatory damage (neuronal edema) and an attempt at neuronal regeneration in more symptomatic patients. Montoro *et al*. used functional transcranial Doppler sonography to analyse the temporal dynamics of cerebral blood flow (CBF) during painful stimulation in 24 FM patients and 20 controls, and found a significant anticipatory increase in CBF before stimulation in the anterior cerebral arteries of the FM patients, which may be related to cognitive, emotional and behavioural factors (38).

Cranial and peripheral nerves may also be involved in FM patients. Optical coherence tomography (OCT) may detect anatomical changes in the retinal nerve fibre layer (a decrease in the minimum thickness of the inner plexiform layer and atrophy), which may be the expression of axonal damage as it is also present in a very early phase of the disease (39, 40). Corneal nerve fibre density and morphology may mirror the small nerve fibre pathology recently associated with FM disorders: using cornea confocal microscopy, Oudejans *et al*. demonstrated that more than half of 39 FM patients examined had small fibre pathology in the cornea; moreover, when assessed for central sensitisation, four phenotypes could be distinguished, which may underlie different pathogenic pathways: normal cornea morphology with or without signs of central sensitisation, and abnormal cornea morphology with or without signs of central sensitisation (41).

Functional pulmonary tests may indirectly reflect autonomic nerve dysfunction, and may be helpful for monitoring FM patients. Rizzi *et al*. detected a lower rate of diffusing capacity for carbon monoxide (DLCO), transfer factor per unit alveolar volume (Kco), tissue conductance (DM) and vital capacity (VC) in 45 FM patients than in 45 healthy controls (42), and these parameters also significantly correlated with composite autonomic symptom scale 31 (COMPASS-31) and pain VAS scores.

## Treatment

Current evidence suggests that small doses of tricyclic antidepressants, cardiovascular exercise, cognitive behavioural therapy, and patient education are effective in FM; however, their efficacy is often unsatisfactory and there is an urgent need for new clinical interventions. The treatment of FM requires a multidimensional approach that involves physical, pharmacological and cognitive measures; however, one important problem is poor compliance, which is usually due to an inadequate clinical response and the difficulty of correctly characterising FM patients clinically.

According to the latest European League Against Rheumatism (EULAR) guidelines (43), once a diagnosis of FM has been confirmed, information, education and physical exercise should represent the first steps in a multi-model panel but, if a patient is suffering from sever pain, cognitive symptoms or sleep disorders, a pharmacological or a psychological approach may be preferred. Patients with chronic pain due to other medical conditions should be promptly identified and referred to other specialists. Other international guidelines (the American Pain Society, 2005; the Association of the Scientific Medical Societies in Germany, 2012; the Canadian Pain Society, 2013) mainly focus on combined aerobic exercise, cognitive-behavioural therapy, and the use of amitriptyline as multicomponent treatment (44). As can be seen, there is still no consensus among the international guidelines, probably because of the methodological heterogeneity of research studies and the broad symptomatic spectrum of FM patients.

### *Pharmacological therapies*

Various drugs for the management of FM have been proposed over the last year. Antidepressants (including amitriptyline and selective serotonin reuptake inhibitors [SSRIs]) proved to be helpful in treating mood disorders in several trials, but were ineffective in counteracting pain or sleep dysfunction, and SSRIs were also associated with increased suicidal tendencies (45). The use of anti-psychotic drugs was reviewed by Walitt *et al*., who pointed out the low quality evidence concerning the efficacy of short (4-12 weeks) treatment with quetiapine in reducing pain, sleeping problems, depression and anxiety in FM patients with major depression (46). Mirtazapine, which promotes the release of noradrenaline and serotonin by blocking α2-adrenergic autoreceptors and heteroreceptors, was tested in a Japanese phase IIa, parallel-group, randomised, double-blind, placebo-controlled trial involving 430 FM patients without concomitant depression (47). In comparison with placebo, there was a significant reduction in the mean Numeric Rating Scale for Pain (NRS pain) core from the sixth week onward and an improvement in the quality of life, with minimal side effects (somnolence, weight gain and increased appetite).

Pregabalin, which binds to the α2δ subunit of voltage-gated calcium chan-

nels in the CNS, has proved to be successful in controlling pain and improving the quality of sleep and the global quality of life, although it is less effective in patients with concomitant depression. However, its association with concomitant antidepressant therapies is well tolerated and indicated in the case of concomitant depressive symptoms (48). Mirogabalin, which is currently being tested in phase II trials, is a promising drug that has fewer side effects and is more effective at a lower dose than pregabalin.

The neuronal pathogenesis of FM provides a rationale for the use of muscle relaxants (cyclobenzaprine), dopaminergic agonists (pramipexole), memantine, neurotropin and opioid blockers (naltrexone), although experience is still limited. A recent review found little evidence that pure opioids are effective but, when used in combination with drugs that act on norepinephrine-related pain modulatory pathways such as tramadol, they can be clinically useful in some patients (49). Schaefer *et al*. carried out a two-year longitudinal study of 76 FM patients prevalently treated with opioids, and found a significant mean change over time in symptoms, including pain and disordered sleep (50). The use of cannabinoids may be considered in patients suffering from chronic pain and poor quality sleep who do not respond to opioid or non-opioid interventions, although available data are still controversial (51, 52).

A German pivotal trial compared the efficacy of 15 weeks' treatment with gamma-hydroxybutyrate with that of placebo in a group of 25 female FM patients, without finding any significant improvement in pain intensity, depressive mood, physical impairment, or the quality of sleep (53).

The usefulness of local therapies such as transdermal testosterone, capsaicin and oxytocin needs to be validated in wider randomised controlled trials (45).

The use of vitamin D was tested in a spontaneous trial by Yilmaz *et al*., who gave 50,000 IU/week of oral vitamin D3 for three months to 58 patients affected by widespread chronic pain (52% with FM). The treatment significantly reduced pain and asthenia VAS scores, sleep disturbances, tender point counts, and Beck Depression Inventory scores, and led to a concomitant increase in the quality of life as assessed by means of SF-36 (54).

*Non-pharmacological therapies*

Another important point of view regarding FM therapy is represented by the proposal of non-pharmacological therapies. The most recent international guidelines have proposed the use of physical exercise, and physical and cognitive behavioural therapy (CBT), alone or in combination with pharmacological treatments. Salvat *et al*. showed the superiority of 12 weeks' multidisciplinary treatment over conventional pharmacological therapy in terms of the FIQ, charts developed by the Dartmouth Primary Care Cooperative Research Network and the World Organization of National Colleges, Academies, and Academic Associations of General Practitioners/Family Physicians (COOP/WONCA) and the distance walked in six minutes in 81 *vs* 74 FM patients (55).

The combination of CBT and imagery/hypnosis was reviewed in a meta-analysis by Zech *et al*. (56). Hypnosis, which is characterised by enhanced suggestion and a low response to peripheral stimuli, has long been used to control chronic pain, whereas imagery is a psychic process characterised by imagining an internal reality in the absence of external stimuli; together, these techniques may induce changes in subjective experiences, perceptions, sensations, emotions and behaviours. The authors found low-quality evidence that the combined therapy led to a clinically relevant benefit in terms pain relief, psychological distress and sleeping problems, and was considered generally acceptable at the end of treatment.

There is growing interest in using psychotherapy to treat neurocognitive disorders in FM patients. In an attempt to accelerate and spread access to psychotherapeutic interventions, a Canadian group of researchers used an Internet-delivered programme entitled *Pain Course* on 30 FM patients who were compared with a group of FM controls on a waiting list (57). The 8-week course consisted of on-line lessons combined with homework assignments, and led to significant improvements in scores concerning depression, pain and the fear of pain that were maintained during the 4-week follow-up.

Transcranial direct current stimulation (tDCS), a non-invasive cranial stimulation technique that can modulate cortical excitability, has attracted widespread attention as it is safe and easy to perform. Anodal tDCS over the primary motor cortex led to significant improvements in pain and general fibromyalgia-related function, although the pressure pain threshold was not affected (58). De Ridder *et al*. used occipital nerve tDCS in 19 FM patients and 19 controls, and found significant improvements in NRS pain scores, the FIQ, and PCS scores, which were also associated with neurophysiological changes detected by means of electroencephalography (59). In particular, the authors described reduced activity over the dorsal anterior cingulate cortex, which presides over the connection between nociception and somatosensory stimuli, thus underlining the potential use of this technique in FM patients with a high somatic symptom burden.

A phase II, sham-controlled, randomised clinical trial involving 45 FM subjects found that the combination of tDCS with aerobic physical exercise had more beneficial effects than single treatments alone on pain, anxiety and mood (60).

Acupuncture is a useful alternative for the treatment of FM (61). Individualised acupuncture led to good pain threshold results after 10 weeks of treatment in a Spanish multicentre, double-blind, randomised and controlled trial involving 164 FM patients (62). Electroacupuncture was tested in 32 mice injected with acid saline (FM murine models), and led to an interesting reduction in N-methyl-D-aspartate receptor (NMDAR) pathway activation (the NMDAR subunits, calmodulin-dependent protein kinase II, and cyclic AMP response element binding protein), which plays a crucial role in pain signalling (63).

The use of music has recently been considered for relieving chronic painful conditions because listening to music

activates the opioid system and thus induces relaxation, emotional feelings and distraction. Alparslan *et al*. investigated the effect of music therapy in 21 FM patients compared with 16 FM controls, and found a significant reduction in the 14-day pain VAS scores in the music therapy group (64). A single-blind, randomised and controlled pilot trial involving 35 FM patients found that the combination of music and aerobic exercise was more effective in improving depression, quality of life, general discomfort and balance than aerobic exercise alone (65).

## Conclusions

Over the last year, there have been no substantial changes in the management of fibromyalgia. It seems well established that genetics plays a role in the development of the disease, as do environmental and neuro-psychic factors. FM patients should be globally evaluated in order to detect their prevalent phenotype early and be able to tailor the most appropriate therapy.

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