Review

One year in review 2020: fibromyalgia

L. Bazzichi[1], C. Giacomelli[1], A. Consensi[1],
V. Giorgi[2], A. Batticciotto[3], M. Di Franco[4], P. Sarzi-Puttini[2]

[1]Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pisa;
[2]Rheumatology Unit, ASST-Fatebenefratelli L. Sacco University Hospital, Milan;
[3]Rheumatology Unit, Internal Medicine Department, ASST Settelaghi, Ospedale Di Circolo - Fondazione Macchi, Varese;
[4]Rheumatology Unit, Department of Internal Medicine and Medical Specialties, Sapienza University of Rome, Italy.

Laura Bazzichi, MD
Camillo Giacomelli, PhD
Arianna Consensi, MD
Valeria Giorgi, MD
Alberto Batticciotto, MD
Manuela Di Franco, MD
Piercarlo Sarzi-Puttini, MD

Please address correspondence to:
Laura Bazzichi,
Reumatologia, Dipartimento di Medicina Clinica e Sperimentale,
Università di Pisa,
Via Roma 67,
56126 Pisa, Italy.
E-mail: l.bazzichi@gmail.com

Received and accepted on February 14, 2020.

Clin Exp Rheumatol 2020; 38 (Suppl. 123): S3-S8.

Key words: fibromyalgia

Competing interests: none declared.

ABSTRACT

Fibromyalgia (FM) is a frequently encountered syndrome that is characterised by chronic widespread pain, fatigue, sleep disturbances, and many other symptoms that impair the quality of life. Its aetiopathogenesis is still unclear but, although there is no specific therapy, a number of pharmacological and non-pharmacological therapies are available. The aim of this review is to describe the most recent findings concerning the diagnosis, aetiopathogenesis and treatment of FM published between January 2019 and January 2020. They include the new concept of nociplastic pain, some neuroendocrine and metabolic alterations found in FM patients, and investigations concerning not only novel applications of old drugs, but also, and in particular, complementary therapies, such as the hyperbaric oxygen chamber, ozone therapy and mindfulness-based interventions.

Aetiopathogenesis

The aetiopathogenesis of FM is still unclear, and a number of causes and mechanisms have been proposed over the last year. Psychosocial factors may play a role and Casale *et al*. suggested the concept of resilience, which can be broadly defined as a protective factor that makes people less vulnerable to future adverse life events (1), and can be applied to patients with any chronic pain conditions. In FM patients, genotype and, most importantly, environmental factors may play a major role in the development of a more or less resilient personality. One interesting study (2) evaluated the role of domestic violence, as quantified using the Domestic Violence Against Women Scale (DVAWS), and its association with psychiatric disorders in FM patients. DVAWS scores were significantly higher in women with FM than in controls, and the severity of domestic violence was related to the presence of any psychiatric disorder only in the FM patients: almost half of those with high DVAWS score had comorbid mood and anxiety disorders.

It has been hypothesised that immunity plays a pivotal role in the pathogenesis of FM as auto-immunity triggers such as traumas and infections are among the most frequent events preceding its onset. In some cases, FM can be temporally related to vaccinations, silicone breast implants or mineral oil injections as part of an auto-immune/inflammatory syndrome induced by adjuvants, something that is also related to molecular mimicry, and one review (3) suggested that aluminum adjuvants (the second component of human papillomavirus vaccines) may play a role by inducing a neuroinflammatory reaction. A recent study has found a link between autoantibodies and FM as one-third of its FM patients with sicca syndrome and/or xerostomia tested positive for Sjögren's syndrome biomarkers, and the majority of these were also positive for one or more tissue-specific auto-antibodies (4). Another example is the finding of anti-dense fine-speckled 70 antibodies in FM patients, with significantly higher levels being found specifically in patients with arthralgia and sleep disturbances (5). Another aspect under investigation is the gut-brain axis, which connects the gut microbiome with the brain through the enteric nervous system: Clos-Garcia *et al*. found that FM patients have less diverse gut bacteria and altered serum metabolome levels of glutamate and serine, thus suggesting changes in neurotransmitter metabolism (6). One interesting review has hypothesised that thalamic mast cells may contribute to inflammation and pain by releasing neuro-sensitising molecules such as histamine, interleukin(IL)-1β, IL-6, tumour necrosis factor (TNF) and

calcitonin gene-related peptide, which can stimulate thalamic nociceptive neurons directly or indirectly by stimulating diencephalon microglia (7). Finally, FM patients show a Th1 activation, which can be modulated by means of hyperbaric oxygen therapy (HBOT) (8).

FM skin biopsies have shown an increased number of mast cells and increased neuronal production of corticotropin-releasing hormone and substance P, which activate mast cells to release neuro-sensitising pro-inflammatory substances that can exacerbate low-grade inflammation. Given this, IL-37 (an inhibitor of members of the pro-inflammatory IL-1 family) may inhibit inflammation (9). In addition, a recent study found that intra-epidermal nerve fibre density was reduced in two-thirds of its FM patients, and that these patients felt more intense, stabbing pain and paresthesias, leading to greater impairment, a higher disease burden, and more anxiety; furthermore, the length and density of their corneal nerve fibres was reduced (10).

Neuromuscular efficiency seems to be impaired in FM patients. Studies of HBOT have found that a central mechanism related to fibre type recruitment order can be modified in such a way as to allow the generation of the same effort using fewer recruited fibres (11).

The strength of the lower limbs of women with FM is associated with genetic polymorphisms of the serotonin receptor gene HTR2A: the GG genotype or G allele is associated with a greater risk of developing the disease and reduced lower limb muscle strength in comparison with controls. (12)

Analyses of the mechanisms underlying the pathogenesis of FM have increased interest in neuromorphological signatures. One functional magnetic resonance study has found that brain hub topology (including the insulae) is altered in FM patients, and that this correlates pain intensity and neurochemical findings (the glutamate + glutamine relationship) (13). Furthermore, Goldstein *et al*. (14) used magnetoencephalography to investigate the response to pictures depicting pain, and found that FM patients did not show significant differences in alpha activity between their responses to pain and non-pain pictures, thus suggesting an altered interpretation of painful and non-painful situations.

Oxidative stress may play an important role in the aetiology of FM. It has been found that an alteration in thiol/disulphide homeostasis (a decrease in thiol levels and an increase in disulfide levels) significantly correlated with Fibromyalgia Impact Questionnaire (FIQ) scores (15).

Finally, a recent study of neuroendocrine dysregulation has found that hepatic clearance of cortisol is relatively lower in FM patients than in matched controls (16).

Diagnosis

The International Association for the Study of Pain (IASP) developed a pain classification system that is applicable to a wide range of contexts, including pain medicine, primary care, and low-resource environments. Chronic pain is defined as pain that persists or recurs for more than three months (17). In the case of conditions such as FM or non-specific low back pain, it can be conceived as a disease in its own right described as "chronic primary pain", and the existence of such persisting pain, despite adequate treatment and in the absence of any sign of inflammation, has led researchers to look for evidence of central sensitisation.

The fact that FM is associated with chronic pain without any obvious peripheral tissue damage has given rise to the concept of nociplastic pain: *i.e*. pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence of any causative disease or lesion of the somatosensory system (18). This makes FM very difficult to diagnose and requires guidelines that reflect not only the proposed classification criteria, but also the pathogenetic mechanisms.

The frequent misdiagnosis of FM highlights an important classificatory/diagnostic problem. Wolfe *et al*. compared different classification criteria in a large cohort of patients, and found that there is considerable disagreement between an ICD and a criteria-based diagnosis. The criteria of FM are easy to use, but there are still substantial problems due to physician bias, diagnostic validity, and the real significance of a diagnosis itself (19).

The authors of a recent review (20) state that patients should first be screened for chronic widespread pain (CWP: pain in four out of five body regions), and that those with CWP should be further screened for the presence of the major symptoms of FM in accordance with the 2016 criteria of the American College of Rheumatology (ACR).

Stewart *et al*. have proposed a new diagnostic concept that represents a further development of the 2011 ACR criteria and is based on what they call the "ABC indicators" of A) algesia, B) bilateral, axial-symmetric pain distribution, and C) chronic distress (21), which they found were more specific and less sensitive but lead to greater overall diagnostic effectiveness than the original criteria. Other authors have combined the 1990 and 2011 ACR criteria to reintroduce the evaluation of tender points (22), which they suggest can facilitate diagnosis in a realistic manner.

Another important aspect of FM that makes an accurate diagnosis imperative is the co-existence of other pathologies. FM is rarely a stand-alone diagnosis, as most patients meet the criteria for other overlapping chronic pain conditions or mental disorders (20). The prevalence of co-morbid FM among patients with rheumatoid arthritis, axial spondyloarthritis and psoriatic arthritis is considerably higher than in the general population, and its presence seems to affect assessments of the severity of these conditions (particularly patient-reported outcome measures) and may influence treatment responses (23). Fibromyalgia co-morbidities in primary care are similar to those found in specialty care and, except for depression and arthritis, their burden is similar in both sexes (24). It has also been hypothesised that FM may be a risk factor for the development of complex regional pain syndrome after a radius fracture (25).

Fibromyaglia is significantly associated with depression, although there is still disagreement about a causal relationship. One case-control study (26) has

found that the probability of suffering from some level of depression is greater in women with FM than in healthy controls as they have higher Beck Depression Inventory scores regardless of age.

Pharmacological treatment

An interesting trial evaluating changes in metabolite concentrations and clinical outcomes after three months' treatment with memantine (27) found significant increases in N-acetylaspartate and N-acetylaspartate+N-acetylaspartate glutamate levels in the left hippocampus; an increase in N-acetylaspartate+N-acetylaspartate glutamate in the right hippocampus and the anterior insula; an increased glutamate+glutamine/creatine ratio in the anterior and posterior insula; an increased choline/creatine ratio in the posterior cingulate; and increased creatine levels in the right hippocampus. At the end of the study, it was found that the patients showed improvements in cognitive function assessed using the Cognition Mini-Exam, depression as measured by the Hamilton Depression Scale, and disease severity as measured by the Clinical Global Impression severity scale. However, despite a sound rationale, the benefit of using memantine to treat chronic pain is unclear because, although a systematic review and meta-analysis has shown that memantine may have the potential to decrease pain, it can also increase common adverse effects (28).

A recent small trial of conditioned pain modulation (CPM, an experimental measure of descending pain inhibition) has evaluated the use of tapentadol in FM patients, and found that CPM responses significantly increased during treatment (29).

The possible off-label use of naltrexone has been suggested by Trofimovitch as low-dose naltrexone may also improve mood disorders and enhance the quality of life (30).

A large, open-label study of duloxetine and pregabalin has provided further evidence that duloxetine is more effective than pregabalin in the treatment of pain in patients with FM (31).

A large, retrospective observational study analysed data regarding 407 patients with FM who were prescribed oral ultra-micronised palmitoylethanolamide tablets between 2013 and 2016 (Normast®, Epitech Group SpA, Saccolongo, Italy) regardless of their concomitant pharmacological therapy. The results showed a change in pain over time as assessed using a visual analogue scale (VAS). and an improvement in the quality of life (32).

Oral mirogabalin besylate, hereinafter mirogabalin (Tarlige®, Daiichi Sankyo), has recently been approved as an orally administered gabapentinoid for the treatment of peripheral neuropathic pain (33). The drug was tested in two experimental rat models of FM (the intermittent cold stress model and the Sluka unilateral intramuscular acidic saline injection model), and was found to have analgesic effects in both.

The analgesic effects of inhaled pharmaceutical-grade cannabis have been tested in a small cohort of FM patients using four different cannabis varieties with precisely known tetrahydrocannabinol and cannabidiol content. The trial showed the complex behaviour of inhaled cannabinoids in patients suffering from chronic pain, and revealed small analgesic responses after a single inhalation, especially of THC-rich varieties (34).

A phase I study of NYX-2925, a new chemical entity that acts as a co-agonist of glutamate at N-methyl-D-aspartate receptors, published by Houck *et al*. found that it was safe and well-tolerated in healthy volunteers, and the results support its continued clinical development for the treatment of chronic pain conditions (35).

Complementary treatments

One interesting article has described the findings of a survey concerning the use of complementary and integrative medicine (CIM) in FM patients (36). Three hundred and four (98.1%) of the 310 patients who completed the survey reported using some form of CIM, a percentage that is similar to that found in our 2003 study (98%). The most frequently used CIM therapies in this new cohort were spiritual healing, massage therapy, chiropractic treatments, aromatherapy, exercise for a specific medical problem, melatonin, magnesium, green tea, and fish oil. Given the continued high prevalence of the use of CIM, healthcare professionals should be aware of these various modalities and consider incorporating into a multi-faceted FM treatment regimen.

A randomised controlled trial by Guinot *et al*. evaluated multicomponent therapy and repetitive transcranial magnetic stimulation (rTMS) as pain modulators in FM. Analysis of variance (ANOVA) showed that the reduction in weekly mean daily pain was not significantly different between groups, but two-way ANOVA showed significant improvements in VAS pain, cardiorespiratory fitness, quality of life, depression and catastrophising in week 14 that remained stable until week 40. Cardiac autonomic adaptations and sleep efficiency did not change significantly (37).

A double-blind trial compared anodal (a)-transcranial direct current stimulation (tDCS) over the dorso-lateral prefrontal cortex with sham treatment in FM patients, and found a significant reduction in pain in the treated group (38). Dailey *et al*. investigated transcutaneous electrical nerve stimulation (TENS) in FM patients, and found that four weeks of active TENS significantly improved movement-evoked pain and other clinical outcomes in comparison with placebo TENS or no TENS (39).

Bosco *et al*. evaluated the clinical and morphological effects of HBOT as a means of relieving interstitial cystitis in FM patients, but did not find any significant changes except for hydrodistension and a slight improvement in the cystoscopic pattern (40).

One interesting study evaluated the effectiveness of ozone-based autohaemotherapy in managing FM in a group of 20 patients. All the patients treated with ozone reported an improvement in sleep and mental alertness, a marked decrease in asthenia and the number of tender points accompanied by a decrease in FIQ scores, and a moderate increase in serotonin levels (41).

Quite a large study of FM patients (42) investigated the effects of neural therapy and exercise, and found significant post-treatment improvements in VAS, FIQ, Short Form (36) Health Survey (SF-36), Beck Depression Scale (BDS) and

Beck Anxiety Inventory (BAI) scores in both groups ($p<0.05$). The combination of neural therapy and exercise may be more effective in terms of pain and depression than exercise alone.

A study of co-enzyme Q10 supplementation with in FM patients treated with pregabalin found that it provided a further benefit in terms of pain relief possibly by improving mitochondrial function, reducing inflammation, and decreasing brain activity (43).

An interesting study of the effects of dietary supplementation with (primarily) an extract of salmon's milt (semen) on symptoms and the blood levels of pro-inflammatory molecules in FM patients found that it led to a reduction in TNF and substance P levels, and a significant improvement in the clinical parameters of functioning, fatigue and pain, as well as overall patient impression (44).

A pragmatic study evaluated the long-term, health-related quality of life (HRQoL) benefits of a comprehensive 8-week group-based, multidisciplinary rehabilitation programme focusing on the coping ability and self-care of FM patients. Baseline findings confirmed the substantially lower physical and mental HRQoL of the patients, as well as high levels of depression, anxiety, and burnout but, by the end of the programme, HRQoL had significantly improved in all domains. This effect on all the sub-scales was maintained after six and 12 months, with the changes after one year being greater in younger patients and those with depressive feelings before the start of the treatment (45).

Cognitive-behavioural therapy-mindfulness-psychotherapy and physical therapies

A randomised, controlled study compared the cost-utility benefits of mindfulness-based stress reduction (MBSR) as an add-on to treatment-as-usual (TAU) with an adjuvant multi-component intervention ("FibroQoL") and TAU alone in FM patients, and found that MBSR significantly reduced costs, especially in terms of indirect costs and primary healthcare services (46).

An interesting study of the impact of attachment-based compassion therapy (ABCT) on the levels of brain-derived neurotrophic factor (BDNF), the inflammatory markers TNF-α, IL-6, IL-10, and C-reactive protein (CRP), analysed whether biomarkers play a mediating/moderating role in improving functional status. The results showed that ABCT significantly improved FIQ scores and decreased the levels of BDNF, CRP, and the pro-inflammatory molecules, with the changes in BDNF mediating FIQ scores. ABCT seems to reduce BDNF levels (a possible mechanism underlying the improvement in functional status) and seems to have anti-inflammatory effects in FM patients (47).

An attention bias modification programme was evaluated in a randomised controlled trial but no significant changes were observed (48).

Park *et al*. published an interesting study about mindfulness and sleep quality in FM patients. Greater mindfulness was associated with better quality sleep and fewer sleep disturbances, as well as less pain interference, anxiety, and depression (49).

One recent small study has evaluated the use of virtual reality as a means of administering guided meditation and biofeedback with the aim of reducing chronic pain. The three most frequent diagnoses among the participants were rheumatoid arthritis, lupus erythematosus, and FM. There was a significant reduction in VAS scores after both biofeedback and guided meditation, but the latter led to a significant reduction in Facial Anxiety Scale scales in comparison with biofeedback (50).

Mindfulness has been evaluated by Cejudo *et al*., who analysed a large cohort of patients and obtained interesting results in terms of a reduction in pain and an improved quality of life improvement (51).

Norouzi *et al*. compared the effects of aerobic exercise training and Zumba dancing on the working memory, motor function and depressive symptoms of female patients with FM, and found a significant improvement in all the evaluated parameters (52).

Fonseca *et al*. compared the effects of aquatic physiotherapy and a health education programme in 46 women with FM. Both interventions led to statistically significant within-group differences in all the outcome measures except a reduction in pain. The findings did not allow any conclusion that either intervention was superior to the other (53).

Changes in circulating nerve growth factor (NGF) and BDNF levels may affect nociception/pain in FM patients but, although exercise leads to clinical improvements, it has been shown that it does not normalise the levels of BDNF or NGF (54).

Eröksüz *et al*. compared the efficacy of intermittent and consecutive balneological treatment (hydrotherapy and peloidotherapy) in a parallel 1:1, single-blind, pilot study of outpatients with FM. There was no significant difference between the groups, so they seem to have similar effects on the clinical status of patients with FM (55).

Conclusions

In terms of diagnosis, the last year has seen the materialisation of the concept of nociplastic pain, underlined the importance of a physician's diagnosis of FM and of co-morbidity as an aggravating factor, and led to the suggestion of a return to tender point examinations (22).

In terms of pathogenesis, the concept of resilience (1) has been seen as a protective factor with a genetic component; the role of immunity has become even more intriguing, also as a disease triggering factor (vaccines, auto-antibodies) (3); and it has been suggested that alterations in the intestinal-brain axis and microbiota may a play a role (6). Skin and thalamic cells have been seen to play an interesting role, with the release of a neuro-inflammatory substitute on microglia (7), and the correlation between oxidative stress and disease severity has reappeared.

Treatment options have become increasingly rich in terms of ideas and modalities. Memantine seems to improve cognitive status and symptom severity (28); the therapeutic usefulness of naltrexone (30), tapentadol (29), duloxetine (31) and palmitoylethanolamide tables (32) has been confirmed; and mirogabalin, (33), four types of inhaled cannabis (34) and the glutamate co-agonist NYX-2925 have been proposed at various levels of study development (35). Cannabi-

noids may be useful in the management of rheumatic disorders for two broad reasons: their anti-inflammatory and immunomodulatory activity, and their effects on pain and associated symptoms (56, 57).

However, partial efficacy and a reluctance to use drug therapies that seem to have nocebo effects on a very high percentage of FM patients mean that over 98% turn to complementary therapies, of which TENS has proved to be effective (39); systemic ozone treatment reduced fatigue and pain in 20 patients (41); and adjuvant MBSR and ABCT also seem to be useful (48, 49), being linked to a change in BDNF levels and improved quality of sleep. The effectiveness of HBOT is interesting as it improves efficiency and muscle recruitment (40), and affects the response to Th1 modulators. Using virtual reality to administer guided meditation and biofeedback as a means of reducing chronic pain can be as useful as targeted drugs.

Finally, the therapeutic use of the various types of medical cannabis (alone or in combination) and clarification of the biochemical mechanisms underlying treatments such as HBOT or oxygen-ozone plus physical activity suggest that there is a role for personalised and precision medicine in the management of FM.

References

1. CASALE R, SARZI-PUTTINI P, BOTTO R *et al*.: Fibromyalgia and the concept of resilience *Clin Exp Rheumatol* 2019; 37 (Suppl. 116): S105-13.
2. GÜNDÜZ N, ERZINCAN E, POLAT A: The relationship of intimate partner violence with psychiatric disorders and severity of pain among female patients with fibromyalgia. *Arch Rheumatol* 2019; 34: 245-52.
3. RYABKOVA VA, CHURILOV LP, SHOENFELD Y: Neuroimmunology: what role for autoimmunity, neuroinflammation, and small fiber neuropathy in fibromyalgia, chronic fatigue syndrome, and adverse events after human papillomavirus vaccination? *Int J Mol Sci* 2019; 20.
4. APPLBAUM E, LICHTBROUN A: Novel Sjögren's autoantibodies found in fibromyalgia patients with sicca and/or xerostomia. *Autoimmun Rev* 2019; 18: 199-202.
5. JEONG J, KIM DH, PARK G, PARK S, KIM H-S: Clinical significance of anti-dense fine speckled 70 antibody in patients with fibromyalgia. *Korean J Intern Med* 2019; 34: 426-33.
6. CLOS-GARCIA M, ANDRÉS-MARIN N, FERNÁNDEZ-EULATE G *et al*.: Gut microbiome and serum metabolome analyses identify molecular biomarkers and altered glutamate metabolism in fibromyalgia. *EBioMedicine* 2019; 46: 499-511.
7. THEOHARIDES TC, TSILIONI I, BAWAZEER M: Mast cells, neuroinflammation and pain in fibromyalgia syndrome. *Front Cell Neurosci* 2019; 13: 353.
8. GUGGINO G, SCHINOCCA C, LO PIZZO M *et al*.: T helper 1 response is correlated with widespread pain, fatigue, sleeping disorders and the quality of life in patients with fibromyalgia and is modulated by hyperbaric oxygen therapy. *Clin Exp Rheumatol* 2019; 37 (Suppl. 116): S81-9.
9. CONTI P, GALLENGA CE, CARAFFA A, RONCONI G, KRITAS SK: Impact of mast cells in fibromyalgia and low-grade chronic inflammation: Can IL-37 play a role? *Dermatol Ther* 2020; 33: e13191.
10. EVDOKIMOV D, FRANK J, KLITSCH A et al.: Reduction of skin innervation is associated with a severe fibromyalgia phenotype. *Ann Neurol* 2019; 86: 504-16.
11. CASALE R, BOCCIA G, SYMEONIDOU Z *et al*.: Neuromuscular efficiency in fibromyalgia is improved by hyperbaric oxygen therapy: looking inside muscles by means of surface electromyography. *Clin Exp Rheumatol* 2019; 37 (Suppl. 116): S75-80.
12. DE LIMA LO, ZICARELLI CAM, MATSUMURA AS *et al*.: Lower limb muscle strength and serotonin receptor gene polymorphism as factors associated in women with fibromyalgia. *Adv Rheumatol* 2019; 59: 59.
13. KAPLAN CM, SCHREPF A, VATANSEVER D *et al*.: Functional and neurochemical disruptions of brain hub topology in chronic pain. Pain 2019; 160: 973-83.
14. GOLDSTEIN A, ZEEV-WOLF M, HERZ N, ABLIN JN: Brain responses to other people's pain in fibromyalgia: a magnetoencephalography study. *Clin Exp Rheumatol* 2019; 37 (Suppl. 116): S70-74.
15. TUZCU A, BAYKARA RA, ALIŞIK M *et al*.: Alteration of thiol-disulfide homeostasis in fibromyalgia syndrome. *Acta Medica* 2019; 62: 12-8.
16. PEDNEKAR DD, AMIN MR, AZGOMI HF, ASCHBACHER K, CROFFORD LJ, FAGHIH RT: A system theoretic investigation of cortisol dysregulation in fibromyalgia patients with chronic fatigue. *Conf Proc IEEE Eng Med Biol Soc* 2019; 2019: 6896-901.
17. TREEDE RD, RIEF W, BARKE A *et al*.: Chronic pain as a symptom or a disease: The IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). *Pain* 2019; 160: 19-27.
18. TROUVIN AP, PERROT S: New concepts of pain. *Best Pract Res Clin Rheumatol* 2019; 33: 101415.
19. WOLFE F, SCHMUKLER J, JAMAL S *et al*.: Diagnosis of fibromyalgia: disagreement between fibromyalgia criteria and clinician-based fibromyalgia diagnosis in a university clinic. *Arthritis Care Res* 2019; 71: 343-51.
20. HÄUSER W, SARZI-PUTTINI P, FITZCHARLES M-A: Fibromyalgia syndrome: under-, over- and misdiagnosis. *Clin Exp Rheumatol* 2019; 37 (Suppl. 119): S90-7.
21. STEWART JA, MAILLER-BURCH S, MÜLLER D *et al*.: Rethinking the criteria for fibromyalgia in 2019: the ABC indicators. J. *Pain Res* 2019; 12: 2115-24.
22. GHAVIDEL-PARSA B, BIDARI A, HAJIABBASI A, SHENAVAR I, GHALEHBAGHI B, SANAEI O: Fibromyalgia diagnostic model derived from combination of American College of Rheumatology 1990 and 2011 criteria. *Korean J Pain* 2019; 32: 120-28.
23. ZHAO SS, DUFFIELD SJ, GOODSON NJ: The prevalence and impact of comorbid fibromyalgia in inflammatory arthritis. *Best Pract Res Clin Rheumatol* 2019; 33: 101423.
24. WAN B, GEBAUER S, SALAS J, JACOBS CK, BREEDEN M, SCHERRER JF: Gender-stratified prevalence of psychiatric and pain diagnoses in a primary care patient sample with fibromyalgia. *Pain Med* 2019; 20: 2129-33.
25. LIPMAN MD, HESS DE, WERNER BC, DEAL DN: Fibromyalgia as a predictor of complex regional pain syndrome after distal radius fracture. *Hand* (NY) 2019; 14: 516-22.
26. PALOMO-LÓPEZ P, BECERRO-DE-BENGOA-VALLEJO R, ELENA-LOSA-IGLESIAS M *et al*.: Relationship of depression scores and ranges in women who suffer from fibromyalgia by age distribution: a case-control study. *Worldviews Evid Based Nurs* 2019; 16: 211-20.
27. FAYED N, OLIVÁN B, LOPEZ DEL HOYO Y *et al*.: Changes in metabolites in the brain of patients with fibromyalgia after treatment with an NMDA receptor antagonist. *Neuroradiol J* 2019; 32: 408-19.
28. KURIAN R, RAZA K, SHANTHANNA H: A systematic review and meta-analysis of memantine for the prevention or treatment of chronic pain. *Eur J Pain* 2019; 23: 1234-50.
29. VAN DE DONK T, VAN VELZEN M, DAHAN A, NIESTERS M: Cornea nerve fibre state determines analgesic response to tapentadol in fibromyalgia patients without effective endogenous pain modulation. *Eur J Pain* 2019; 23: 1586-95.
30. TROFIMOVITCH D, BAUMRUCKER SJ: Pharmacology update: Low-dose naltrexone as a possible nonopioid modality for some chronic, nonmalignant pain syndromes. *Am J Hosp Palliat Care* 2019; 36: 907-12.
31. BIDARI A, MOAZEN-ZADEH E, GHAVIDEL-PARSA B, RAHMANI S, HOSSEINI S, HASSANKHANI A: Comparing duloxetine and pregabalin for treatment of pain and depression in women with fibromyalgia: an open-label randomized clinical trial. *Daru* 2019; 27: 149-58.
32. SCHWEIGER V, MARTINI A, BELLAMOLI P *et al*.: Ultramicronized Palmitoylethanolamide (um-PEA) as add-on treatment in fibromyalgia syndrome (FMS): retrospective observational study on 407 patients. *CNS Neurol Disord Drug Targets* 2019; 18: 326-33.
33. SAEKI K, YASUDA SI, KATO M *et al*.: Analgesic effects of mirogabalin, a novel ligand for α2δ subunit of voltage-gated calcium channels, in experimental animal models of fibromyalgia. *Naunyn Schmiedebergs Arch Pharmacol* 2019; 392: 723-8.
34. VAN DE DONK T, NIESTERS M, KOWAL MA, OLOFSEN E, DAHAN A, VAN VELZEN M: An experimental randomized study on the analgesic effects of pharmaceutical-grade cannabis in chronic pain patients with fibro-

myalgia. *Pain* 2019; 160: 860-9.
35. HOUCK DR, SINDELAR L, SANABRIA CR *et al*.: NYX-2925, A Novel N-methyl-D-aspartate receptor modulator: a first-in-human, randomized, double-blind study of safety and pharmacokinetics in adults. *Clin Transl Sci* 2019; 12: 164-71.
36. MOHABBAT AB, MAHAPATRA S, JENKINS SM, BAUER BA, VINCENT A, WAHNER-ROEDLER DL: Use of complementary and integrative therapies by fibromyalgia patients: a 14-year follow-up study. *Mayo Clin Proc Innov Qual Outcomes* 2019; 3: 418-28.
37. GUINOT M, MAINDET C, HODAJ H *et al*.: Effects of repetitive transcranial magnetic stimulation and multicomponent therapy in patients with fibromyalgia: a randomized controlled trial. *Arthritis Care Res* (Hoboken) 2019 Nov 30 [Epub ahead of print].
38. BRIETZKE AP, ZORTEA M, CARVALHO F *et al*.: Large treatment effect with extended home-based transcranial direct current stimulation over dorsolateral prefrontal cortex in fibromyalgia: a proof of concept sham-randomized clinical study. *J Pain* 2019 Jul 26 [Epub ahead of print].
39. DAILEY DL, VANCE CG, RAKEL BA *et al*.: A randomized controlled trial of TENS for movement-evoked pain in women with fibromyalgia. *Arthritis Rheumatol* 2019 Nov 18 [Epub ahead of print].
40. BOSCO G, OSTARDO E, RIZZATO A *et al*.: Clinical and morphological effects of hyperbaric oxygen therapy in patients with interstitial cystitis associated with fibromyalgia. *BMC Urol* 2019; 19: 108.
41. MORENO-FERNÁNDEZ A, MACÍAS-GARCÍA L, VALVERDE-MORENO R *et al*.: Autohemotherapy with ozone as a possible effective treatment for Fibromyalgia. *Acta Reumatol Port* 2019 Sep 29 [Epub ahead of print].
42. ALTINBILEK T, TERZI R, BAŞARAN A, TOLU S, KÜÇÜKSARAÇ S: Evaluation of the effects of neural therapy in patients diagnosed with fibromyalgia. *Turk J Phys Med Rehabil* 2019; 65: 1-8.
43. SAWADDIRUK P, APAIJAI N, PAIBOONWORACHAT S *et al*.: Coenzyme Q10 supplementation alleviates pain in pregabalin-treated fibromyalgia patients via reducing brain activity and mitochondrial dysfunction. *Free Radic Res* 2019; 53: 901-9.
44. TSILIONI I, PIPIS H, FREITAG MSC, IZQUIERDO MDC, FREITAG K, THEOHARIDES TC: Effects of an extract of salmon milt on symptoms and serum TNF and substance P in patients with fibromyalgia syndrome. *Clin Ther* 2019; 41: 1564-74.e2.
45. JACOBS H, BOCKAERT M, BONTE J *et al*.: The impact of a group-based multidisciplinary rehabilitation program on the quality of life in patients with fibromyalgia: results from the QUALIFIBRO study. *J Clin Rheumatol* 2019 Jun 19 [Epub ahead of print].
46. PÉREZ-ARANDA A, D'AMICO F, FELIU-SOLER A *et al*.: Cost-utility of mindfulness-based stress reduction for fibromyalgia versus a multicomponent intervention and usual care: a 12-month randomized controlled trial (EUDAIMON Study). *J Clin Med* 2019; 8: E1068.
47. MONTERO-MARIN J, ANDRÉS-RODRÍGUEZ L, TOPS M *et al*.: Effects of attachment-based compassion therapy (ABCT) on brain-derived neurotrophic factor and low-grade inflammation among fibromyalgia patients: A randomized controlled trial. *Sci Rep* 2019; 9: 15639.
48. CARLETON RN, ASMUNDSON GJG, KOROL SL *et al*.: Evaluating the efficacy of an attention modification program for patients with fibromyalgia: a randomized controlled trial. *Pain* 2020: 161: 584-94.
49. PARK M, ZHANG Y, PRICE LL, BANNURU RR, WANG C: Mindfulness is associated with sleep quality among patients with fibromyalgia. *Int J Rheum Dis* 2019 Nov 27 [Epub ahead of print].
50. VENUTURUPALLI RS, CHU T, VICARI M, KUMAR A, FORTUNE N, SPIELBERG B: Virtual reality-based biofeedback and guided meditation in rheumatology: a pilot study. *ACR Open Rheumatol* 2019; 1: 667-75.
51. CEJUDO J, GARCÍA-CASTILLO FJ, LUNA P, RODRIGO-RUIZ D, FELTRERO R, MORENO-GÓMEZ A: Using a mindfulness-based intervention to promote subjective well-being, trait emotional intelligence, mental health, and resilience in women with fibromyalgia. *Front Psychol* 2019; 10: 2541.
52. NOROUZI E, HOSSEINI F, VAEZMOSAVI M, GERBER M, PÜHSE U, BRAND S: Zumba dancing and aerobic exercise can improve working memory, motor function, and depressive symptoms in female patients with Fibromyalgia. *Eur J Sport Sci* 2019: 1-11.
53. FONSECA ACS, FARIA PC, ALCÂNTARA MA *et al*.: Effects of aquatic physiotherapy or health education program in women with fibromyalgia: a randomized clinical trial. *Physiother Theory Pract* 2019 Jul 15:1-13. doi: 10.1080/09593985.2019.163922. [Epub ahead of print].
54. JABLOCHKOVA A, BÄCKRYD E, KOSEK E *et al*.: Unaltered low nerve growth factor and high brain-derived neurotrophic factor levels in plasma from patients with fibromyalgia after a 15-week progressive resistance exercise. *J Rehabil Med* 2019; 51: 779-87.
55. ERÖKSÜZ R, EROL FORESTIER FB, KARAASLAN F *et al*.: Comparison of intermittent and consecutive balneological outpatient treatment (hydrotherapy and peloidotherapy) in fibromyalgia syndrome: a randomized, single-blind, pilot study. *Int J Biometeorol* 2020; 64: 513-20.
56. SARZI-PUTTINI P, ABLIN J, TRABELSI A, FITZCHARLES MA, MAROTTO D, HÄUSER W: Cannabinoids in the treatment of rheumatic diseases: Pros and cons. *Autoimmun Rev* 2019; 18: 102409.
57. SARZI-PUTTINI P, BATTICCIOTTO A, ATZENI F *et al*.: Medical cannabis and cannabinoids in rheumatology: where are we now? *Expert Rev Clin Immunol* 2019; 15: 1019-32.