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Fibromyalgia position paper

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ABSTRACT

Fibromyalgia syndrome is one of the most common causes of chronic widespread pain, but pain accompanies a wide range of ancillary symptoms. To date, its aetiopathogenesis remains elusive, and diagnosis is exquisitely clinical, due to the lack of biomarkers or specific laboratory alterations in fibromyalgia patients. This position paper has the purpose to summarize the current scientific knowledge and expert opinions about the main controversies regarding fibromyalgia syndrome, namely: (i) fibromyalgia definition and why it is still not recognized in many countries as a distinct clinical entity; (ii) fibromyalgia severity and how to evaluate treatment outcome; (iii) how to treat fibromyalgia and which is a correct approach to fibromyalgia patients.

INTRODUCTION

Fibromyalgia (FM) or fibromyalgia syndrome is characterized by chronic pain, fatigue, sleep disturbances and functional symptoms. Its aetiopathogenesis, diagnostic and classification criteria are still a matter of debate, and, therefore, so are treatment strategies [1]. Even if physicians started to recognize fibromyalgia as a clinical entity decades ago [2], it endures to be a controversial disease, even regarding its nosological classification. The last decade showed a growing interest for FM in the scientific community, not only as a model of pain chronicization, but also of the exemplification of the complex interaction among biopsychosocial factors in the pathogenesis of disease [3]. Moreover, no biomarkers are available to evaluate the severity and the evolution of FM, hence, it is still controversial how to assess the degree of disability of patients [4].

This consensus paper aims at giving a brief commentary of some of the current controversies regarding FM, including: (i) prevalence and diagnostic criteria; (ii) disease severity and treatment outcome evaluation; (iii) appropriate therapeutic approach.

FIBROMYALGIA DEFINITION

FM is one of the most common causes of chronic widespread pain [1]. Even though it appears as a distinct clinical entity in all international chronic pain classifications [5, 6] and it is recognized in many countries at the level of the public health system or at the private insurance level, there are some exceptions, among which Italy or Spain [7–9]. FM is a recognized medical condition, defined by diagnostic criteria, and evaluated through severity scales [10]. However, many patients may have considerable diagnostic delays with a consequent impact on the disease in the long term [11]. Among the most important factors that impair prompt diagnosis is the lack of biomarkers: although some salivary (e.g. cortisol, alpha-amylase) or serum (e.g. cytokines) biomarkers have been proposed for FM diagnosis [12], their validity is still not demonstrated.

Accordingly, the prevalence of FM varies depending on the diagnostic criteria used to define it, oscillating from 2 to 3% of the general population [13, 14]. Diagnostic complexity is increased by its complex polysymptomatology, which can continuously evolve during the course of the disease in each single patient [15]. Therefore, diagnostic and classification criteria are continuously evolving. In the 90s, FM was just officially recognized as a discrete clinical entity: the first diagnostic criteria for FM were originally published in 1990 and considered chronic widespread pain (defined as pain in the left side of the body, pain in the right side of the body, pain above the waist, pain below the waist, and axial skeletal pain [cervical spine or anterior chest or thoracic spine or low back]) for at least 3 months associated with tenderness in ≥ 11 out of 18 tender point sites [16]. However, the tender point examination soon revealed to be impractical and not reliable enough to be used in a clinical setting: in fact, it is extensively examiner-dependent, too variable among

individuals, and women appear to have more tenderness at digital pressure on tender point sites. Moreover, FM needed to be characterized with a more exhaustive list of symptoms. Hence, the subsequent criteria (the 2010 criteria[17]), changed the definition of FM to that of a polysymptomatic disorder and eliminated tender point exam as a requirement for diagnosis. Additionally, they specified the concept that a diagnosis of FM is not excluded by the presence of comorbid diseases. Anyway, although comprehensive, these criteria were not very feasible in daily clinical practice. They started to be simplified in 2011 [18], shortening the list of associated symptoms, and afterwards in 2016 [19], including nonrefreshing sleep, chronic fatigue, cognitive and mood disturbances and abdominal pain as ancillary symptoms. The latest AAPT diagnostic criteria [20] tried to create a really feasible tool for physicians in order to facilitate FM diagnosis. They divided the criteria in different dimensions. Dimension 1 includes Core diagnostic criteria, which are three: (1) multisite pain defined as 6 or more pain sites from a total of 9 possible sites; (2) Moderate to severe sleep problems OR fatigue; (3) Multisite pain plus fatigue or sleep problems must have been present for at least 3 months. Other dimensions can reinforce diagnostic conviction: common features, epidemiology, psychiatric comorbidities, functional consequences and risk factors can all be taken into account by the physicians and have all to be thoroughly investigated during the history taking. For example, often FM develops in people who have a clinical history of chronic pain conditions. The patient predisposed to FM pain manifests many episodes attributable to chronic pain conditions during his/her life; in fact, FM patients often refer headache, dysmenorrhea, temporomandibular dysfunction, chronic fatigue, interstitial cystitis/irritable urethra syndrome, irritable bowel syndrome and other regional pain syndromes (e.g. cervicgia and low back pain) [21]. What physicians might see as an acute manifestation may simply be another painful region of the body associated, occasionally or permanently, with FM widespread chronic pain [11]. At the moment, ACR diagnostic criteria and international guidelines advise against using only self-administered questionnaires for FM diagnosis; instead, the global anamnestic picture of the patient is much more important to be filtered by the competent health personnel [22–24]. *Table 1* summarizes all criteria sets and their characteristics.

Criteria set	Measures of pain	Tender points	Associated symptoms	Diagnosis/Classification
ACR 1990 Classification criteria	Pain in all four quadrants (both the left and right side of the body, above and below the waist); plus axial skeletal pain (pain in the cervical spine or anterior chest or thoracic spine or lower back)	Yes (≥ 11 out of 18)	None included	Widespread pain and at least 11 tender points for at least 3 months

ACR 2010 Preliminary diagnostic criteria	WPI: a 0-19 count of the body regions reported as painful by the patient over the last week. *	No	SSS: a score of the sum of severity of three symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus various somatic symptoms in general (on a 0-12 scale)	<ul style="list-style-type: none"> - WPI ≥ 7 and SSS ≥ 5; or WPI 3-6 and SSS ≥ 9 - Symptoms present at a similar level for at least 3 months - The patient does not have a disorder that would otherwise explain the pain.
ACR 2011 Modifications of the ACR preliminary diagnostic criteria (Designed for epidemiologic and clinical studies, and not for clinical diagnosis)	WPI: a 0-19 count of the body regions reported as painful by the patient over the last week *	No	SSS: a score of the sum of severity of three symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the sum of the number of the following symptoms occurring during the previous 6 months: headaches, pain or cramps in the lower abdomen and depression. (On a 0-12 scale)	<ul style="list-style-type: none"> - WPI ≥ 7 and SSS ≥ 5; or WPI 3-6 and SSS ≥ 9 - Symptoms present at a similar level for at least 3 months - The patient does not have a disorder that otherwise sufficiently explain the pain
2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria	<p>Generalized Pain defined as pain in at least 4 out of 5 regions (Left upper region Right upper region, Left lower region, Right lower region, Axial region).</p> <p>Pain in the jaw, chest and abdomen are not evaluated as part of the generalized pain definition.</p> <p>Use of WPI: a 0–19 count of the body regions reported as painful by the patient over the past week *</p>	No	SSS: a score of the sum of severity of three symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the sum of the number of the following symptoms occurring during the previous 6 months: headaches, pain or cramps in the lower abdomen and depression.	<ul style="list-style-type: none"> - WPI ≥ 7 and SSS ≥ 5; or WPI 4-6 and SSS ≥ 9 - The presence of generalized pain - Symptoms have been present at a similar level for at least 3 months. - A diagnosis of fibromyalgia is valid irrespective of other diagnoses and does not exclude the presence of other illnesses.
AAPT Core diagnostic criteria for fibromyalgia	MSP: pain in ≥ 6 of 9 sites (consisting of the head, right arm, left arm, chest, abdomen, upper back and spine, lower back and spine (including buttocks), left leg and right leg)	No	Moderate to severe sleep problems or moderate to severe fatigue	<ul style="list-style-type: none"> - MSP ≥ 6 - Moderate to severe sleep problems or fatigue - Symptoms have been present for at least 3 months

Table 1 The evolving classification and diagnostic criteria for fibromyalgia.

AAPT, ACTTION-American Pain Society Pain Taxonomy; MSP, multisite pain; SSS, Symptom Severity Score; WPI, Widespread Pain Index. *Regions assessed by the WPI: left shoulder girdle, right shoulder girdle, left hip (buttock or trochanter), right hip (buttock or trochanter), left jaw, right jaw, upper back, lower back, left upper arm, right upper arm, left upper leg, right upper leg, chest, neck,

abdomen, left lower arm, right lower arm, left lower leg and right lower leg. Table modified from Sarzi-Puttini P, et al. *Nat Rev Rheumatol.* 2020;16:645–660.

Nowadays, epidemiological studies underline a male/female ratio of 1/3 (similarly to the ratio present in other chronic pain diseases), a possible FM onset at any age (even during childhood) and a prevalence that does not depend on ethnicity, and it is therefore similar across different countries. Also, there is not a higher prevalence in industrialized or culturally advanced countries [25, 26]. The picture is complicated by the mutable character of the whole constellation of symptoms, with patients moving between criteria-positive and criteria-negative states [15]. Moreover, confounding factors such as diagnostic delay, duration of symptoms, other comorbidities and social or environmental factors can influence the course of the disease over time [27, 28].

Finally, it is getting clearer that, even though diagnostic criteria are quite accurate in delineating the typical symptomatic profile of fibromyalgia patients, people suffering from FM are actually divided into subpopulations on the basis of their main symptoms, symptom progression and coping strategies [29–31]. In particular, it is important to separate those patients whose main complaint is pain from those patients who have a prominent mood disorder component of their disease (mainly anxiety and depression). The creation of these, still hypothetical, patient subgroups in daily clinical practice would be of extreme utility from a therapeutic perspective.

We still do not have enough data showing how early diagnosis of FM could influence clinical progression, but it is clear that early recognition of the syndrome or prodromal symptoms could prevent the use of pharmacological treatments, preferring instead nonpharmacological approaches such as psychotherapy or physical reconditioning. General practitioners should be educated for the early detection of patients with or even at risk of FM encountered during normal routine clinical activity.

DISEASE SEVERITY AND TREATMENT OUTCOME EVALUATION

FM has a significant impact on society, considering both an individual point of view, due to the generally poor quality of life of FM patients, and a societal point of view, due to the relative direct and indirect costs [32, 33]. FM may also overlap and aggravate other rheumatologic diseases, influencing their course and response to therapy [17]. There is therefore the need of a consensus evaluation of disease severity and treatment outcome. However, the peculiar challenge posed by FM implies that there is the need for a further refinement and validation of existing measures or the development of new composite measures or response criteria that better reflect the multidimensional nature of FM and can also be used in everyday clinical

practice[34]. Simply relying on a single symptom such as pain intensity as a measure of clinical outcome is not appropriate in a syndrome complex and protean in clinical aspects such as FM [35–37].

An attempt to include the patients' perspective was made by the Outcome Measures in Rheumatology (OMERACT) Fibromyalgia Syndrome Workshop [38], which included a set of core symptoms (pain, tenderness, patient global status, fatigue, the health-related quality of life [HRQoL], physical function, disturbed sleep, depression and anxiety, and cognitive dysfunction) in the appropriate outcome domains. The use of patient-reported outcomes (PROs) could allow identifying the most important symptom for each individual patient and guiding a tailored therapy, also allowing the creation of sub-categories of patients that could benefit from distinct and individualized treatments [29, 39].

The most widely used self-administered questionnaires include the Fibromyalgia Impact Questionnaire (FIQ) [40] and its revised version (FIQR) [41, 42], the Fibromyalgia Assessment Status (FAS)[34], the modified Fibromyalgia Assessment Status (FAS 2019 mod) [43], the Fibromyalgia Survey Criteria (FSC) [44] and the Patient Health Questionnaire 15 (PHQ15) [45]. These composite tests are capable of quantitatively measuring multiple aspects of the disease, including a patient's everyday functioning, although there is a risk of missing the effect of FM on a single dimension [46]. Recently, we establish optimal cut-off values for the scores of the FIQR, the FAS 2019mod, and the Polysymptomatic Distress Scale (PDS) in order to distinguish five levels of FM disease severity [47]. The overall median FIQR, FAS 2019 mod and PDS scores (25th–75th percentiles) were respectively 61.16 (41.16–77.00), 27.00 (19.00–32.00) and 19.0 (13.00–24.00). Reconciliation of the mean 75th and 25th percentiles of adjacent categories defined the severity states for FIQR: 0–23 for remission, 24–40 for mild disease, 41–63 for moderate disease, 64–82 for severe disease and >83 for very severe disease; FAS 2019 mod: 0–12 for remission, 13–20 for mild disease, 21–28 for moderate disease, 29–33 for severe disease and >33 for very severe disease; PDS: 0–5 for remission, 6–15 for mild disease, 16–20 for moderate disease, 21–25 for severe disease and >25 for very severe disease[47] (*Table 2*).

Clinimetric test	Scores	Severity scores
FIQR	0-100	>83: very severe 64-82: severe 41-63: moderate 24-40: mild 0-23: remission
FAS 2019 mod	0-39	>33: very severe 29-33: severe 21-28: moderate

		13-20: mild 0-12: remission
PDS	0-31	>25: very severe 21–25: severe disease 16–20: moderate disease 6–15: mild disease 0–5: remission

Table 2 Multi-dimensional, disease-specific measures of fibromyalgia and cut-offs for disease severity [47].

The appropriate application of clinimetric measures to signs and symptoms gives a modern perspective, as the benefits and risks of therapeutic options can be evaluated not only on the basis of a clinician's observations and opinions, but also (and above all) on the basis of the personal preferences and wishes of individual patients. This is particularly important in the case of a disease such as FM, which has no objective signs or biomarkers and can only be diagnosed and followed up on the basis of the symptoms reported by the patients themselves. An individualized target that can be applied in daily practice is the improvement of everyday function, rather than the improvement of specific symptoms. Similarly, focusing on short-term goals that are tangible may be more significant than a calculated number derived from questionnaires. Defining a realistic goal, such as 30% improvement in symptoms, and focusing specifically on improving daily functions, in a shared decision setting, could be a reasonable and applicable goal in clinical practice.

FIBROMYALGIA MULTIMODAL THERAPY

The need of an individualized, tailored-to-the-patient treatment is never stressed enough [48]. Individual differences among patients not only with FM, but with chronic pain in general, should be considered in the planning, development, and prioritization of interventions to improve pain care and to prevent worsening of symptoms [49]. From this perspective, it is difficult to interpret randomized controlled trials, which take a random sample in an FM population and measure treatment effectiveness on average.

The publication of the recent EULAR recommendations for the treatment of FM [50] allows us to get important hints for our clinical practice. The therapeutic approach remains multimodal and multidisciplinary, in which non-pharmacological and pharmacological treatments play a synergistic role in patient management [51]. In general, there are essentially three pillars of FM treatment: 1) patient education and fitness; 2) pharmacological treatment; 3) psychotherapy.

Educating patients regarding disease and treatment, and initiating a fitness program (exercise regimen and proper nutrition) are the first steps to be taken, also starting a productive patient-physician relationship

allowing shared decision making. Pharmacologic therapy should be based on individual needs, and non-pharmacologic or “alternative” measures can be initiated based on cost, availability and patient’s preferences. Patients can be encouraged to continue non-pharmacologic measures, following his/her individual needs, as long as they do not cause harm. Education, cognitive behavioral therapy, and exercise have strong evidence for efficacy in FM, especially for function improvement[50, 52].

It is important that patients with FM understand their illness before the prescription of any medications [1, 53]. There are some key elements that have to be included [54, 55]:

1. Reassuring the patient that FM is a real disease and legitimating his/her suffering is crucial. Also, it has to be cleared that FM, although an invalidating condition, is not progressive and not due to damage to peripheral tissues.
2. In parallel, it should be stated that the patient him/herself has a predominant role in disease management. Patients should be able to learn their own, particular techniques and approaches to maximize quality of life. This is the concept of “self-management” and should be applied for any chronic condition [3, 56]. When the patient becomes persuaded that he/she can actually handle his/her own symptoms, here it comes the concept of “self-efficacy”.
3. Stress and mood disturbances play an important role, and patients should be encouraged to learn relaxation techniques as well as to take part in formal stress reduction programs, up to proper psychiatric consultation.
4. Good sleep hygiene is an essential part of FM management. Therefore, recognizing and treating sleep disorders, which may contribute to FM symptoms, is important [57].

Improved fitness can be regarded as a goal, but despite of the level of fitness, persons with FM need to regularly exercise, due to its positive effects on several levels, including its beneficial effect on sleep [58]. The most effective method of raising the pain threshold is physical activity, and indeed, the only “strong” EULAR recommendation for FM is in favour of exercise [50]; very recently published long-term studies further confirm its efficacy [59, 60]. The objectives of physical exercise in this type of patient include first of all the interruption of the vicious cycle of pain-inactivity-pain, reducing physical deconditioning, and the amelioration of mood and pain. The exercise regimen should be individualized based on symptoms, pain tolerance and psychological factors [61]. Exercise should begin below the threshold with respect to the patient's physical capabilities and gradually increase to a moderate level; the patient should be educated about the possible increase in pain and fatigue in the short term, but be reassured that these will return to baseline or improve after a few weeks. Muscle stretching/light training and the gradual increase in cardiovascular (aerobic) fitness have to be recommended to patients [62]. Low-impact aerobic activity, such as walking, cycling, swimming or exercising in water are generally the best way to start an exercise program. Regular training, for example every other day, is equally important. The recommended optimal

cardiovascular fitness training consists of a minimum of 20 minutes of aerobic exercise three times a week. It is important to gently stretch muscles and move joints through adequate joint mobilization daily and before and after aerobic exercises. It is useful to consult a rehabilitation therapist who helps establish a specific exercise program to improve posture, flexibility and physical fitness [63].

The drugs that have proved most effective in treating FM are centrally acting medications, particularly antidepressants and anticonvulsants [1], which act on FM pain in a mechanism-oriented fashion (in particular, increasing the presence of pain-inhibitory neurotransmitters or decreasing systemic hyperexcitability). Opioids are burdened by severe side effects and are not really effective for FM pain, therefore their use should be avoided. Tramadol is the only analgesic drug that may be effective in reducing FM pain [50], since it acts as an opioid agonist but also as an inhibitor of noradrenaline and serotonin reuptake. Antidepressants [64] include mainly duloxetine and milnacipran, both Food and Drug Administration (FDA)-approved for FM, since they had good results in terms of efficacy and tolerability in patients with FM; a recent systematic review found 17% of side effects related to duloxetine in FM patients [65]. Data about antidepressant treatment for FM patients with comorbid depressive disorder were confirmed by a recent real-world analysis [66]. Among the anticonvulsants [67], recent meta-analyses underlined that pregabalin is, in fact, effective and safe for FM [68–70], and it is so far the only FDA-approved anticonvulsant for FM. In Europe, there are currently no drugs approved by the European Medicines Agency (EMA). Cannabinoids have also been recently proposed as a promising phytotherapeutic family for FM therapy, although its medical use has not been thoroughly studied [71–74]. The attention of the medical community on cannabis-based medication was drawn on the basis of patient surveys giving positive results, which highlighted the need for additional rigorous studies to better understand cannabis potential for FM management [75–77]. Recently, a small (17 women), double-blind, randomized, placebo-controlled clinical trial was conducted for eight weeks to determine the benefit of a THC-rich cannabis oil [78]. The authors concluded that phytocannabinoids can be a low-cost and well-tolerated therapy to reduce symptoms and increase the quality of life of patients with fibromyalgia. Future studies are still needed to assess long-term benefits, and studies with different varieties of cannabinoid.

Results obtained with pharmacological treatment alone, however, are often unsatisfactory, and drug treatment should be part of a multidisciplinary therapeutic approach, which also includes non-pharmacological strategies [79]. They may be considered at least adjunctive, if not the core, treatment for many patients [50], and the magnitude of the treatment response for these therapies often exceeds that for pharmaceuticals, as a 2014 meta-analysis underlined [79]. The types of non-pharmacological treatments used by FM patients are innumerable, but strong, systematic scientific evidence is seldomly available. Balneotherapy [80], meditative movement disciplines (e.g. Tai Chi [81, 82]) and acupuncture [83] are among the ones that have the strongest scientific support, and may be of help for FM patients. Recently, much of

the attention has been drawn on mindfulness interventions. Two recent systematic reviews highlighted the usefulness of mindfulness-based therapies for chronic pain [84, 85], mainly in short-term [85].

THE CORRECT APPROACH TO FIBROMYALGIA PATIENTS

FM patients' management can be challenging for physicians. FM patients are usually perceived as more difficult than arthritis patients, so that a high proportion of physicians are reluctant to accept them because they feel emotional/psychological difficulties meeting and coping with these patients [86]. Additionally, there may be a significant reluctance to diagnose FM by some physicians [87], because of uncertainty about diagnosis, especially in the lack of specific biomarkers or pathognomonic signs, hesitancy in "labelling" a patient with a "stigmatizing" syndrome, and so on. On the other hand, FM patients are frequently reluctant to ask for medical help. They often undergo many tests and are visited by many specialists while they are looking for an answer on the cause of their illness [11]. Sometimes they are told that, as their imaging and laboratory tests are normal, they do not have a real disease, and this increases isolation, guilt and anger. Hence, the importance of patient education and knowledge of the disease for FM therapeutic strategy [53]: ~~FM~~ patients must know that FM is a real cause of chronic pain and fatigue and must be treated like any other chronic condition. Often, the mere fact of knowing that FM is not a progressive and debilitating disease allows patients to develop a positive attitude towards their illness. Indeed, the more the patient is informed, the more she or he tries to adapt to the disease itself, the better the prognosis of FM. Support and self-help groups, publications, websites are a source of information for many patients, and often knowing that you are not alone can be a source of support [88].

Some patients may have severe symptoms so that they are unable to perform a normal job and live a satisfying relationship. These patients require greater attention and a multidisciplinary approach involving the rehabilitation and occupational therapist, the rheumatologist and the psychologist. Many patients with FM improve and are able to live with their disease satisfactorily. However, a better understanding of the causes of FM and the factors that can aggravate it, prevent it, or make it chronic, as well as a better drug therapy, still lack: hence, continuous education of both healthcare staff and patients can lead to a better and more appropriate management of available resources, and at the same time to lower expenses sustained by patients and the national healthcare system. Therapeutic recommendations and guidelines can be found in the scientific literature and can help healthcare professionals to better treat FM patients, with an individualized, patient-centered non-pharmacological approach and a more specific pharmacological approach.

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