FIBROMYALGIA

Gregory Kaltsas, MD, FRCP, Professor of Medicine, Department of Pathophysiology, Laikon University Hospital, Athens 115 27, Greece. email: GKaltsas@endo.gr
Konstantinos Tsiveriotis, MD, Consultant in Obstetrics, Gynaecology and Maternal and Fetal Medicine, Greece. email: ktsiver@gmail.com

Updated November 8, 2023

ABSTRACT

Fibromyalgia is a clinical entity characterized by the combination of chronic widespread pain and other non-pain symptoms, including fatigue, poor sleep, and cognitive disturbances, which can exhibit symptom variation not only between different patients, but also in the same patient during the course of the disease. These symptoms are relatively common and non-specific. They can be encountered in other disorders that may overlap with fibromyalgia, often without having clear boundaries, while their nature makes them difficult to be objectively defined and quantified. These issues have led to significant controversy over the definition and the diagnostic criteria of fibromyalgia. It has been suggested that the markers of physical and psychological distress have a continuous distribution in the general population with fibromyalgia patients being at the extreme end of this continuum. Genetic predisposition in combination with environmental factors, are responsible for each individual's position in this this distribution. In recent years more knowledge has been obtained to better understand the environmental factors that seem to be important in triggering fibromyalgia. Most of them act as stressors superimposed onto a deranged stress-response system leading to dys-regulation of the nociceptive system and the appearance of clinical symptoms. The aim of the therapy is to relieve pain and motivate the patients to become more physically active using a multimodal individualized therapeutic strategy that includes education, exercise, cognitive-behavioral approaches and medications. The response to current therapeutic modalities varies significantly, with some patients responding adequately, while others do not seem to experience any long-term benefit.

INTRODUCTION

Fibromyalgia is a clinical entity characterized by the combination of ill-defined symptoms including chronic widespread pain, with concomitant fatigue, sleeping disorders, and cognitive disturbances (1). The severity of these symptoms can vary significantly during the course of the disease. Fibromyalgia has been described as an arbitrarily created syndrome that lies at the extreme end of the spectrum of poly-symptomatic distress (2). The term poly-symptomatic was used to emphasize the variety of multiple different symptoms that can be found in fibromyalgia patients, while the distress can have a physical and/or a psychological component. This exact nature of fibromyalgia makes it difficult to be clearly defined, often overlapping with disorders that are characterized by similar symptoms. It is important to note that fibromyalgia is not an exclusion diagnosis as it can co-exist with other clinical conditions (3).

CLINICAL FEATURES

The main presenting complains of patients with fibromyalgia include chronic widespread pain (also called multisite pain), fatigue, and poor sleep. Usually the pain is initially localized, but eventually it involves many muscle groups. It is characterized as persistent with varying intensity, while it can often be described as a sensation of burning, gnawing soreness, stiffness, or aching. Excessive sensitivity to normally painful stimuli, such as pressure or heat

(hyperalgesia) and painful sensation to normally non-painful stimuli, such as touch (allodynia) are significant features of fibromyalgia. Often patients complain of swollen joints and paresthesias without though the presence of any objective clinical findings during physical examination. Pain is often aggravated by cold and humid weather, poor sleep, physical and mental stress. Additionally the patients may have a variety of less well understood pain symptoms, including abdominal pain, chest wall pain, symptoms suggestive of irritable bowel syndrome, pelvic pain, and bladder symptoms of frequency and urgency suggestive of interstitial cystitis (4–9).

Fatigue is present in almost all patients with fibromyalgia, while many complain of non-refreshing sleep, frequent awakening during the night, and difficulty falling back to sleep. Sleep apnea and nocturnal myoclonus can also be present along with a sensation of light-headedness, dizziness, and faintness. In addition, cognitive difficulties such as short-term memory loss, groping for words and poor vocabulary, are common among patients with fibromyalgia. Mood disturbances, including depression, anxiety and heightened somatic concern, may often also occur. Headaches, either muscular or migraine type, are also commonly present (6,7). Other often co-existing conditions include multiple chemical sensitivity, “allergic” symptoms, ocular dryness, palpitations, dyspnea, vulvodynia, dysmenorrhea, premenstrual syndrome, sexual dysfunction, weight fluctuations, night sweats, dysphagia, restless leg syndrome, temporomandibular joint pain, chronic fatigue syndrome (systemic exertion intolerance disease), Raynaud`s phenomenon, autonomic dysfunction, and dysgeusia (6,8,9). These conditions cannot be used to support the diagnosis of fibromyalgia.

Approximately 40% of fibromyalgia patients have accompanying depression at the time of diagnosis, while 60% of patients have a lifetime history of depression. In addition, an anxiety disorder is present in 30% of the cases at the time of diagnosis while the lifetime prevalence of an anxiety disorder in fibromyalgia patients is approximately 60% (10–14). The levels of depression and anxiety in patients with fibromyalgia seem to be associated with the degree of cognitive impairment, as shown in a meta-analysis of 23 case-control studies (15). Based on the coexistence of depression and anxiety, fibromyalgia patients can be divided into 2 major groups. The first group comprises of patients without coexisting mood disorders, while the second of patients with concomitant depressive mood, often in combination with anxiety. According to the results of a study that intended to subgroup fibromyalgia patients based on: 1) mood status (evaluated by the Center for Epidemiologic Studies Depression Scale for depression and the State-Trait Personality Inventory for symptoms of trait-related anxiety), 2) cognition (by the catastrophizing and control of pain subscales of the Coping Strategies Questionnaire), and 3) hyperalgesia/tenderness (by dolorimetry and random pressure-pain applied at suprathreshold values), it was noted that fibromyalgia patients with depressive mood and anxiety are also ‘catastrophizing’. This term is used to indicate that such patients have a very negative, pessimistic view of what their pain is and what is causing, while they have no sense that they can control their pain. On the contrary fibromyalgia patients who are neither depressed nor anxious and therefore do not catastrophize, have a moderate sense that they can control their pain. These patients can be further divided into 2 subgroups based on the degree of hyperalgesia/tenderness, the first subgroup comprises of patients with high hyperalgesia/tenderness, while the second one of patients with moderate hyperalgesia/tenderness (11). In addition, it has been proposed that depressed fibromyalgia patients can also be divided into 2 subgroups, in the first one depression is a co-morbid condition, while in the second depression is the cause of fibromyalgia (16). All these fibromyalgia subgroups are illustrated in Figure 1.

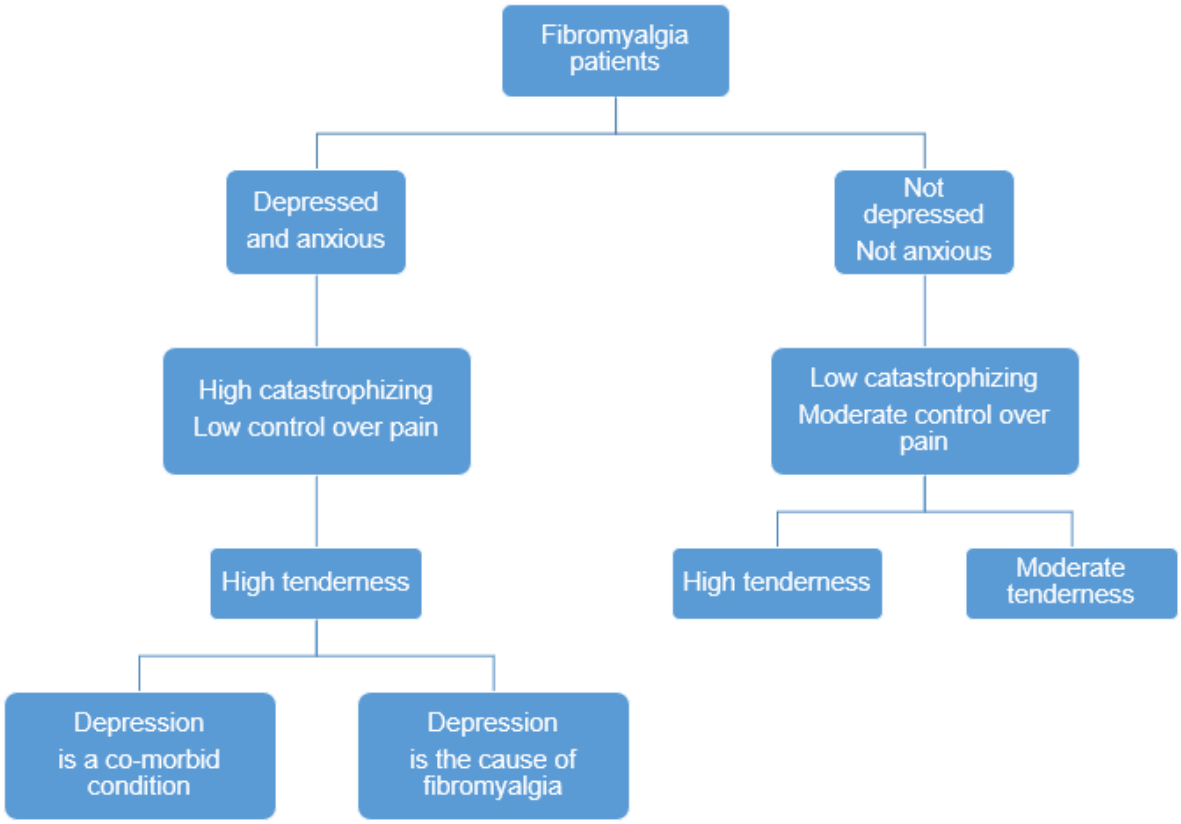

Figure 1. Subgroups of fibromyalgia patients.

In another study fibromyalgia patients were classified as dysfunctional, inter-personally distressed, or adaptive copers, based on their responses to the Multidimensional Pain Inventory. The dysfunctional patients experienced more pain behaviors and overt expressions of pain, distress, and suffering, such as slowed movement, bracing, limping, and grimacing compared to the inter-personally distressed or the adaptive copers (17).

It is of interest that up to 25% of patients correctly diagnosed with a systemic rheumatic disease (e.g. rheumatoid arthritis, systemic lupus erythematosus) will also fulfill the classification criteria for fibromyalgia (18). This is also the case for many patients who experience persistent various forms of pain (including widespread myalgias, arthralgias, and headache), fatigue, neurocognitive dysfunction, and sleep disturbances after an infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) that caused a mild to moderate coronavirus disease 2019 (long COVID) (19,20). The most commonly encountered comorbid conditions in fibromyalgia patients are shown in Table 1.

Table 1. The Most Commonly Encountered Co-Morbid Conditions in Fibromyalgia	
Sleep disorders	Non restorative sleep (alpha-delta sleep anomaly) Sleep apnea Restless leg syndrome Nocturnal myoclonus
Chronic fatigue syndrome (systemic exertion intolerance disease)	
Psychiatric disorders	Anxiety disorders Depression Obsessive compulsive disorder
Headache	Tension type headache Migraine
Irritable bowel syndrome	
Musculofascial pain syndrome	Temporomandibular disorders Interstitial cystitis
Dysmenorrhea	
Premenstrual syndrome	
Non-cardiac chest pain	
Raynaud's phenomenon	
Systemic autoimmune diseases	Rheumatoid arthritis Systematic lupus erythematosus Sjögren's syndrome Ankylosing spondylitis and other seronegative spondylarthritis Polymyalgia rheumatica
Long COVID	

ASSESSMENT

Fibromyalgia is a chronic illness, with a variety of symptoms that can change during the course of the disease and after treatment. Therefore, its core symptoms should be evaluated both in clinical practice and in treatment trials. A working group within OMERACT (Outcome Measures in Rheumatology) reached a consensus regarding the domains that need to be assessed in clinical trials for fibromyalgia, using Delphi exercises within patients and expert clinicians (21). The fibromyalgia core symptom domains include pain intensity, tenderness, fatigue, sleep disturbance, multidimensional function (including health related quality of life and physical function), patient global impression of change, cognitive dysfunction, and depression. However at the present time, there is no consensus on how to evaluate these domains, in order to quantify fibromyalgia disease activity state and/or response (22).

Pain intensity can be assessed using visual analog scales. It has been proposed to use the wording "please rate your pain by circling on the number that best describes your pain on average" and has anchors that vary from "no pain" to "pain as bad as you can imagine" (23).

Tenderness can be measured by evaluating the alteration of the severity of pain at the tender points, using visual or analog scales, but not by the change in their number. The change in the number of tender points is poorly correlated with improvement in fibromyalgia treatment trials. It has been noted that the tender points measure the combination of tenderness and distress an individual has, rendering them inadequate for the evaluation of tenderness *per se* (24).

Fatigue can be evaluated by the Fatigue Severity Scale (FSS), which measures the functional outcomes related to fatigue (25). It has been shown that FSS has the most robust psychometric properties of 19 reviewed fatigue measures, while it had the best ability to act as an outcome measure sensitive to change with treatment, in chronically ill patients (26). Other instruments that have been used to assess fatigue in fibromyalgia patients include the Multidimensional Fatigue Index and the Multidimensional Assessment of Fatigue.

Sleep disturbance in fibromyalgia patients has been evaluated by the Medical Outcome Studies (MOS) sleep scale, the Functional Outcomes of Sleep Questionnaire (FOSQ), and the Jenkins Sleep Scale (JSS). Of these instruments MOS sleep scale lacks validity to assess changes in sleep symptoms in fibromyalgia treatment trials, FOSQ has not been adequately validated in fibromyalgia patients, while JSS has been criticized for possible high-recall bias, since it requires the patients to rate the frequency of their symptoms over a period of a month (23).

Multidimensional function, including health related quality of life and physical function, can be evaluated using the fibromyalgia impact questionnaire (FIQ). This represents a useful tool in assessing functional abilities in daily life and measures patient status, progress and outcomes. FIQ is self-administered and is highly sensitive to changes during the course of the disease. However, its functional items are orientated toward high levels of disability, resulting in a possible floor effect, while its physical function items are addressed to women living in affluent countries, generating gender and ethnic bias. To address these issues the Revised Fibromyalgia Impact Questionnaire (FIQR) was developed, having modified physical function questions and including questions on memory, tenderness, balance and environmental sensitivity, while keeping questions that evaluate overall impact and symptoms (27). Other tools for assessing overall function and quality of life include the Health Assessment Questionnaire, the Symptom Interpretation Questionnaire, the Western Ontario and McMaster Universities Osteoarthritis Index, the Patient Global Impression of Change scale (PGIC), and psychometric scales (28).

Patient global impression of change can be evaluated by the Patient Global Impression of Change scale (PGIC), as recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) (29).

Cognitive dysfunction can be evaluated by the Multiple Ability Self-report Questionnaire (MASQ), which is a self-report questionnaire measuring language, visuoperception, verbal memory and attention (30). However self-assessment is poorly correlated with objective measures of cognitive function and has poor discriminating ability for patients with mild cognitive impairment (31).

Depression can be evaluated using the Hospital Anxiety and Depression Scale (HADS) depression subscale (HADS-D). The use of the original Beck Depression Inventory (BDI) as well as the current BDI-II, should be avoided, since they tend to overestimate the presence of major depressive disorder in fibromyalgia patients by evaluating a number of non-depressive symptoms, which are often encountered in fibromyalgia (23).

DIAGNOSIS

As already mentioned, fibromyalgia is characterized by symptoms that can vary in number and intensity not only between different patients, but also in the same patient during the course of the disease. These symptoms are also common in other disorders that can overlap with fibromyalgia, often without having clear boundaries. Additionally, the nature of the symptoms of fibromyalgia makes them difficult to be objectively defined and measured. All these issues have led to significant controversy over the definition

and diagnosis of fibromyalgia. The clinical entity of fibromyalgia was first described in 1904, under the term “fibrositis”, after focusing on clinical evidence of muscle sensitivity (32). It was not until 1977 that specific criteria for the diagnosis of fibromyalgia were introduced (33). Since then a number of different criteria have been proposed, based on a combination of tender point examination and the presence of symptoms. In 1986 a committee of the American College of Rheumatology (ACR) started a multicenter study, trying to provide a definition of fibromyalgia and establish classification criteria (34). In 2013, the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks (ACTTION) public-private partnership with the US Food and Drug Administration (FDA) and American Pain Society (APS) initiated the ACTTION-APS Pain Taxonomy (AAPT) in an attempt to develop a diagnostic system that would be clinically useful and consistent across chronic pain disorders, including fibromyalgia (35).

In clinical practice either the 2016 revision of the 2010/2011 fibromyalgia diagnostic criteria or the AAPT criteria can be used to help physicians to diagnose fibromyalgia (36). However, these criteria should be viewed as an aid and not as a gold standard for diagnosing fibromyalgia in clinical practice. Good clinical judgment is necessary to interpret the findings of physical examination and to assess psychological factors and associated comorbidities so as to correctly identify the patients with fibromyalgia (37).

Relevant social, personal and family history can be helpful in establishing the diagnosis of fibromyalgia, since there is evidence that the symptoms of fibromyalgia can appear after a physical or emotional trauma, a medical illness, or a surgical operation, while a family history of fibromyalgia, makes the diagnosis of fibromyalgia more likely (38).

1990 ACR Classification Criteria

In 1990 the American College of Rheumatology (ACR) committee established criteria for the classification of fibromyalgia. According to these criteria fibromyalgia is defined as chronic widespread pain involving both sides of the body, above and below the waist, as well as the whole length of the spine, and excessive tenderness in the pressure of 11 of 18 specific muscle-tendon sites (9 pairs of tender points). The locations of the tender points are described in Figure 2 and Table 2. Pressure equivalent of 4 kg/cm is applied to these points using the pulp of the thumb or the first two or three fingers. This can be accurately measured with a dolorimeter or it can be estimated, since 4 kg/cm is the pressure needed to be applied so as to whiten the examiner’s fingernail bed. These criteria specifically state that fibromyalgia is not an exclusionary diagnosis (34).

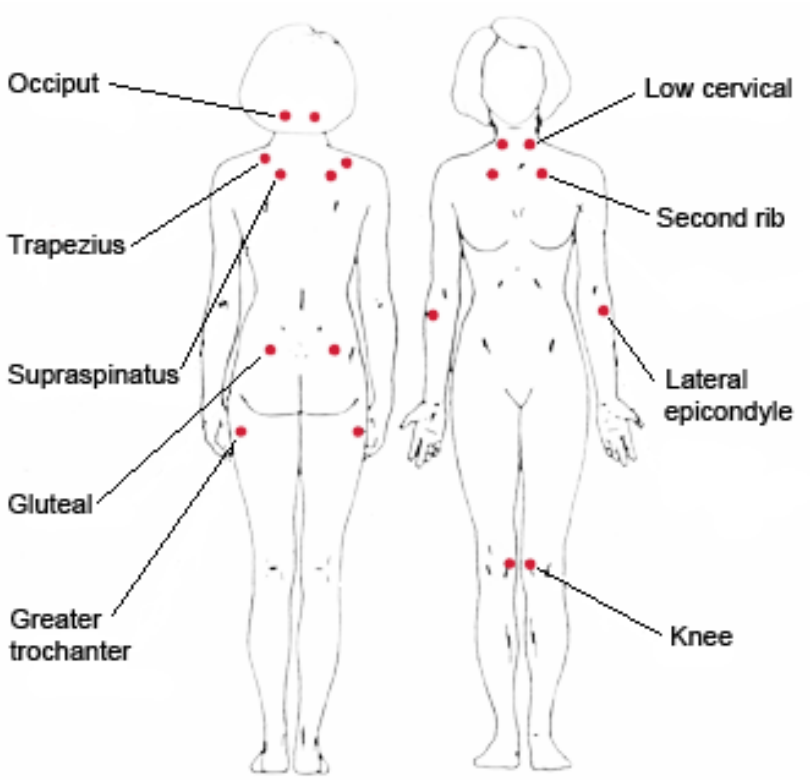

Figure 2. Fibromyalgia tender points.

Table 2. Description of the Location of Fibromyalgia Tender Points	
Occiput:	at the insertions of one or more of the following muscles: trapezius, sternocleidomastoid, splenius capitus, semispinalis capitus
Trapezius:	at the midpoint of the upper border
Supraspinatus:	above the scapular spine near the medial border
Gluteal:	at the upper outer quadrant of the buttocks at the anterior edge of the gluteus maximus
Low cervical:	at the anterior aspect of the interspaces between the transverse processes of C5–C7
Second rib:	just lateral to the second costochondral junctions
Lateral epicondyle:	2 cm distal to the lateral epicondyle
Greater trochanter:	posterior to the greater trochanteric prominence
Knee:	at the medial fat pad proximal to the joint line

The tender points, which are examined in fibromyalgia, are not just areas that the patient feels pain. They are points that fibromyalgia patients are relatively more tender, compared to normal individuals, when pressure is applied on them. But fibromyalgia patients are more tender wherever you apply pressure, not only to some of these 18 specific tender points, including areas previously considered to be “control points” (39). There is evidence that these tender points are areas that everyone is generally

more tender. In contrast, fibromyalgia patients are more tender not only to pressure but to other stimuli such as heat, cold and other sensory stimuli, most probably due to decreased pain threshold. The number of tender points an individual has is highly correlated with distress, as defined by the presence of anxiety, depression, sleep disturbance, fatigue and global severity. Tender points have been described as "a sedimentation rate of distress". Consequently tender points measure the combination of tenderness and distress an individual has (24).

The use of the 1990 ACR classification criteria in clinical practice is surrounded by substantial controversy. Tender points were introduced as an objective physical finding. However, if the physician who performs the physical examination is not experienced enough, tender point counting is impossible to be performed accurately. Most of the physicians examining fibromyalgia patients did not know how to carry out the tender point examination. Consequently, tender point count was not routinely performed, and when performed it was performed inaccurately (40). Another shortcoming of the tender point counting is that it is not as objective as it was initially considered, since the physician can be biased by the patient's interview that precedes the physical examination. These issues lead to a low inter-examiner reliability of the tender point count (41).

Other more sophisticated measures of assessing tenderness, such as applying stimuli randomly, when the individual cannot anticipate what the next stimulus is going to be, are equally abnormal in fibromyalgia patients, but do not correlate with distress (39). These methods require special training and are more time consuming than the trigger point count. Other alternative assessment methods include functional magnetic resonance imaging (fMRI) and nociceptive flexion reflex (NFR) testing, which documents abnormal pain processing in fibromyalgia. Functional MRI demonstrates similar brain activation in regions involved in pain processing in fibromyalgia patients and normal individuals. However fibromyalgia patients have increased pain sensitivity and brain activation during comparable stimulus (42). Nociceptive flexion reflexes are sensory-motor responses elicited by electrical noxious stimuli, which involve activation of spinal and supraspinal neuronal circuits, providing an objective and quantitative assessment of the function of the pain-control system. It has been demonstrated that the NFR threshold in patients with fibromyalgia is significantly decreased compared with that in controls (43). Of these methods fMRI is expensive and complex compared to NFR testing that appears to be more easily accessible and convenient, since standard electromyographic equipment can be used. This test also seems to eliminate subjective bias and dissimulation (44).

The 1990 ACR classification criteria, define fibromyalgia in terms of pain rather than its other features. However, patients with fibromyalgia apart from tenderness and pain, also have a number of other somatic symptoms. Although non-pain symptoms are important, there is no evidence to support the notion that they are more important than hyperalgesia and allodynia, which are key symptoms of fibromyalgia (44). Many clinicians with experience in fibromyalgia did not feel that the 1990 ACR classification criteria were sufficiently reliable for the diagnosis of fibromyalgia in clinical practice and were considering other aspects of the disease in an attempt to reach a more accurate diagnosis (38).

2010 ACR Preliminary Diagnostic Criteria

To address the aforementioned issues the ACR in 2010 proposed the preliminary diagnostic criteria for fibromyalgia (Table 3), that were not meant to replace the 1990 ACR classification criteria, but to represent an alternative simple and easy method of diagnosis in clinical practice (45). These diagnostic criteria do not require a tender point count. Instead, they rely only on symptoms for the diagnosis of fibromyalgia. They introduced the widespread pain index (WPI), which counts the areas that the patient feels pain during one week preceding the examination, and the symptom severity (SS) scale, which describes the severity of fatigue, unrefreshing sleep, cognitive problems, and a number of associated somatic fibromyalgia symptoms. These symptoms need to be assessed and rated by a physician, therefore the 2010 ACR preliminary diagnostic criteria are in-adequate for patient self-diagnosis.

Two more conditions need to be fulfilled so as to diagnose fibromyalgia. The symptoms need to be

present at a similar level for at least 3 months while alternate disorders that would otherwise explain the pain need to be excluded (Table 3). The authors of the 2010 ACR preliminary diagnostic criteria have clarified that the latter condition does not mean that fibromyalgia is an exclusion diagnosis according to these criteria. The diagnosis of fibromyalgia should not be made only when there is not another disease that could explain the pain that would otherwise be attributed to fibromyalgia. It should be noted that rheumatic diseases usually do not cause pain that can be confused with fibromyalgia (3).

Table 3. 2010 ACR Preliminary Diagnostic Criteria

Criteria:

A patient satisfies diagnostic criteria for fibromyalgia if the following 3 conditions are met:

1) Widespread pain index (WPI) ≥7 and symptom severity (SS) scale score ≥5 *or* Widespread pain index (WPI) 3-6 and symptom severity (SS) scale score ≥9.
2) Symptoms have been present at a similar level for at least 3 months.
3) The patient does not have a disorder that would otherwise explain the pain.

Ascertainment:

1) WPI

Note the number of areas in which the patient has had pain over the last week. In how many areas has the patient had pain?
(Score will be between 0 and 19)

	-Neck	-Upper arm, left	-Abdomen	-Upper leg, left	
	-Jaw, left	-Upper arm, right	-Upper back	-Upper leg, right	
	-Jaw, right	-Lower arm, left	-Lower back	-Lower leg, left	
	-Shoulder girdle, left	-Lower arm, right	-Hip (buttock, trochanter), left	-Lower leg, right	
	-Shoulder girdle, right	-Chest	-Hip (buttock, trochanter), right		

2) SS scale score

The SS scale score is the sum of the severity of the 3 symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the extent (severity) of somatic symptoms in general.
(The final score is between 0 and 12)

-For the each of the 3 symptoms below, indicate the level of severity over the past week using the following scale:

0 = no problem
1 = slight or mild problems, generally mild or intermittent
2 = moderate, considerable problems, often present and/or at a moderate level
3 = severe: pervasive, continuous, life-disturbing problems
Fatigue (0-3)
Waking unrefreshed (0-3)
Cognitive symptoms (0-3)

-Considering somatic symptoms in general, indicate whether the patient has: muscle pain, irritable bowel syndrome, fatigue/tiredness, thinking or remembering problem, muscle weakness, headache, pain/cramps in the abdomen, numbness/tingling, dizziness, insomnia, depression, constipation, pain in the upper abdomen, nausea, nervousness, chest pain, blurred vision, fever, diarrhea, dry mouth, itching, wheezing, Raynaud's phenomenon, hives/welts, ringing in ears, vomiting, heartburn, oral ulcers, loss of/change in taste, seizures, dry eyes, shortness of breath, loss of appetite, rash, sun sensitivity, hearing difficulties, easy bruising, hair loss, frequent urination, painful urination, and bladder spasms
0 = no symptoms
1 = few symptoms
2 = a moderate number of symptoms
3 = a great deal of symptoms

There is evidence that there is good agreement between the 1990 ACR classification criteria and the 2010 ACR preliminary diagnostic criteria (46–53). However, these criteria are expected not to agree completely, as the former are focused on the presence of tender points while the latter on the presence of symptoms. The 1990 criteria can diagnose fibromyalgia in patients who do not have sufficiently high symptom score according to the 2010 criteria, while the 2010 criteria can diagnose fibromyalgia in patients who do not have sufficient tender points according to the 1990 criteria.

The introduction of the 2010 ACR preliminary diagnostic criteria was surrounded by controversy too. In particular, they have been criticized for being completely symptom focused, ill-defined, and lucking some mechanistic features of fibromyalgia, such as hyperalgesia, central sensitization and dysfunctional pain modulation (54). Additionally, these diagnostic criteria are based on the subjective assessment of the patient's somatic symptoms by the physician, adding ambiguity and influencing repeatability among different physicians (55). A self-reported version of the 2010 ACR preliminary diagnostic criteria was developed in 2011, so as to be used in survey research, and not in clinical practice (56). These criteria are known as the modified 2010 ACR preliminary diagnostic criteria or the 2011 ACR survey criteria. They introduced the fibromyalgia severity (FS) score (originally called fibromyalgianess scale) which is the sum of the self-reported WPI and SS score. This score can be used as an approximate measure of the severity of fibromyalgia. The FS score has also been called polysymptomatic distress (PSD) scale. It has been proposed that the markers of physical and psychological distress have a continuous distribution in the general population with fibromyalgia patients being at the extreme end of this distribution (57). The PSD scale could be useful to define the position of each individual in this continuum, without having to differentiate between patients with fibromyalgia and those without, as this distinction can sometimes be unclear if not arbitrary (58).

2016 Revisions to the 2010/2011 Fibromyalgia Diagnostic Criteria

A limitation of the WPI is the fact that it counts the number of painful areas without considering their distribution in the body. Patients with regional pain disorders can fulfill the 2010 ACR preliminary diagnostic criteria since pain can be located in 3 or more areas in the same region (59). To overcome this issue the 2016 revision of the diagnostic criteria require the pain to be generalized (multisite pain). The areas WPI assesses are divided in 5 regions (Table 4) and the diagnosis of fibromyalgia requires the distribution of pain in 4 out of 5 regions (60). The jaw, the chest and the abdomen area are problematic when they are used to define a region. In this way they are excluded from the definition of generalized pain (61). Since pain needs to be located in at least 4 areas according to the 2016 revision, the previous criterion for diagnosis, WPI of 3-6 and SS scale score ≥9 was changed to WPI of 4-6 and SS scale score ≥9.

The 2010 and 2011 ACR preliminary diagnostic criteria are extremely similar. Their difference is that the 2010 criteria are physician-based and can be used in clinical practice for the diagnosis of fibromyalgia, while the 2011 criteria are self-reported and can be used only in survey research. According to the 2010 criteria the SS scale assesses a wide range of somatic symptoms, which makes them impractical for use in questionnaires. With the 2016 revision the assessment of somatic symptoms that is included in the SS scale is limited to headaches, pain and cramps in the lower abdomen and depression. In this way, there is no longer need for different criteria for clinical practice and for survey research. The same criteria can be used in both settings having 2 different methods of administration.

One prerequisite for diagnosis of fibromyalgia according to the 2010 ACR preliminary diagnostic criteria is the patient not to have a condition that would otherwise explain the pain. The authors of these criteria clarified that this does not mean that the diagnosis of fibromyalgia is an exclusion diagnosis. However, this phrasing was not considered clear enough and caused significant misunderstanding. In this way this criterion was removed in the 2016 revision. The diagnosis of fibromyalgia can be valid even if there is another condition that can cause the pain that is attributed to fibromyalgia. According to this definition fibromyalgia can coexist with other clinically significant conditions that can cause pain.

Table 4. 2016 Revisions to the 2010/2011 Fibromyalgia Diagnostic Criteria

Criteria:

A patient satisfies diagnostic criteria for fibromyalgia if the following 3 conditions are met:

1) Widespread pain index (WPI) ≥7 and symptom severity (SS) scale score ≥5 *or* Widespread pain index (WPI) 4-6 and symptom severity (SS) scale score ≥9.

2) Generalized pain: Pain must be present in at least 4 of 5 regions.
Jaw, chest, and abdominal pain are not included in generalized pain definition.

3) Symptoms have been generally for at least 3 months.

4) A diagnosis of fibromyalgia is valid irrespective of other diagnoses. A diagnosis of fibromyalgia does not exclude the presence of other clinically important illnesses.

Ascertainment:

1) WPI

Note the number of areas in which the patient has had pain over the last week. In how many areas has the patient had pain?

(Score will be between 0 and 19)

	Region 1: Left Upper Region	Region 2: Right Upper Region -Jaw, right *	Region 5: Axial Region -Neck

	-Jaw, left * -Shoulder girdle, left -Upper arm, left -Lower arm, left	-Shoulder girdle, right -Upper arm, right -Lower arm, right	-Upper back -Lower back -Chest * -Abdomen *
	<u>Region 3: Left Lower Region</u> -Hip (buttock, trochanter), left -Upper leg, left -Lower leg, left	<u>Region 4: Right Lower Region</u> -Hip (buttock, trochanter), right -Upper leg, right -Lower leg, right	
	* Not included in generalized pain definition		

2) SS scale score

The SS scale score is the sum of the severity of the 3 symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the sum of the number of 3 symptoms (headaches, pain or cramps in lower abdomen, depression)
(The final score is between 0 and 12)

- For the each of the 3 symptoms below, indicate the level of severity over the past week using the following scale:
0 = no problem
1 = slight or mild problems, generally mild or intermittent
2 = moderate, considerable problems, often present and/or at a moderate level
3 = severe: pervasive, continuous, life-disturbing problems
Fatigue (0-3)
Waking unrefreshed (0-3)
Cognitive symptoms (0-3)

- During the previous 6 months indicate the number of the following symptoms the patient has been bothered by:
  - Headaches (0-1)
  - Pain or cramps in lower abdomen (0-1)
  - Depression (0-1)

The fibromyalgia severity (FS) scale is the sum of the WPI and the SS scale

AAPT Diagnostic Criteria

In an attempt to improve the recognition of fibromyalgia in clinical practice, the AAPT fibromyalgia working group proposed new diagnostic criteria in 2018 (62). These criteria are similar to the ACR criteria as they require the pain to be generalized (multisite), require the presence of non-pain symptoms and require the symptoms to be present for at least 3 months (Table 5). These diagnostic criteria are more simple than the ACR criteria and they can be easily implemented in primary clinical practice, but some of their aspects have been criticized (63). According to

the AAPT criteria the head, the abdomen and the chest are included in the areas that are assessed for the presence of generalized musculoskeletal pain. However, these regions are problematic since pain originating from the teeth, the heart and the bowel can be referred to these areas. Additionally, the AAPT criteria do not have the ability to quantify the severity of fibromyalgia as, apart from the generalized pain, they only assess the presence or absence of the 2 most common non-pain symptoms of fibromyalgia, abolishing all other somatic symptoms. Compared with the 2016 ACR diagnostic criteria, individuals with less symptom severity and fewer pain sites can be classified as fibromyalgia patients, when the AAPT diagnostic criteria are used (64).

Table 5. AAPT Diagnostic Criteria

Criteria:

Multisite pain defined as 6 or more pain sites from a total of 9 possible sites:

- Head
- Left arm
- Right arm
- Chest
- Abdomen
- Upper back and spine
- Lower back and spine, including buttocks
- Left leg
- Right leg

Moderate to severe sleep problems or fatigue

Multisite pain plus fatigue or sleep problems must have been present for at least 3 months

NOTE. The presence of another pain disorder or related symptoms does not rule out a diagnosis of fibromyalgia. However, a clinical assessment is recommended to evaluate for any condition that could fully account for the patient's symptoms or contribute to the severity of the symptoms.

EPIDEMIOLOGY

The prevalence of fibromyalgia depends on the criteria used to define it. Most studies use either the 1990 ACR classification criteria or the modified 2010 ACR preliminary diagnostic criteria (2011 ACR survey criteria) and the prevalence varies between 2-4% (65). Using the 2016 ACR diagnostic criteria the prevalence of fibromyalgia in the general population is 3-4% while with the AAPT diagnostic criteria the prevalence of fibromyalgia is 73% higher, ranging from 5% to 7% (64). In the general population the prevalence increases with age from 2% at the age of 20 to 8% at age of 70. Fibromyalgia appears more often in relatives of patients suffering from fibromyalgia (66), whereas there is a significant difference on the women to men ratio depending on the criteria used to define fibromyalgia. When the 1990 ACR classification criteria are used the women to men ratio is 7:1 while when the 2011 ACR survey criteria are used, that do not use the tender point count, the ratio ranges from 4:1 to 1:1 (58,67–69). Using the 2016 ACR or the AAPT diagnostic criteria there is no statistically significant difference in the prevalence of fibromyalgia between women and men (64).

DIFFERENTIAL DIAGNOSIS

Several conditions can mimic or overlap with fibromyalgia. In order to reach a differential diagnosis, careful history taking should be followed by a thorough physical examination. Careful neurologic and musculoskeletal examination needs to be performed in all fibromyalgia patients in order to exclude the presence of such conditions. Mood and functional impairment should also be evaluated. This can be easily performed using simple self-administered questionnaires. Patients with obvious mood disturbances should have a formal evaluation by a mental health professional. Baseline blood tests should be limited to a complete blood count, erythrocyte sedimentation rate, a comprehensive metabolic panel, and thyroid function tests. These tests are usually normal in fibromyalgia patients. Consequently, the identification of abnormalities in any of these examinations might suggest that a different condition is present. Additional tests are not recommended for a diagnosis, unless they are clinically indicated. The disorders that can mimic and/or overlap with fibromyalgia and the characteristic clinical features which differentiate them from fibromyalgia are described in Table 6. The clinical features of fibromyalgia, chronic fatigue syndrome (systemic exertion intolerance disease), depression, migraine, and irritable bowel syndrome often overlap being so interchangeable that some authors consider that these conditions should be approached as a "spectrum" of associated disorders (10). They are also considered as part of the spectrum of post-traumatic stress disorder (70,71).

Table 1. Disorders that can Mimic and/or Overlap with Fibromyalgia Along with Characteristic Clinical Features that Differentiate Them from Fibromyalgia

Disorders	Differentiating clinical features
Rheumatoid arthritis, Systematic Lupus Erythematosus, Sjögren's syndrome	Characteristic synovitis and systemic features of connective tissue disease, apart from musculoskeletal pain, fatigue, Raynaud phenomenon, dry eyes and dry mouth, are usually not features of fibromyalgia. Routine serologic tests are not recommended because of low positive predictive value.
Ankylosing spondylitis, other inflammatory back conditions	Generally, there is normal spinal motion in fibromyalgia. Characteristic radiologic features of these disorders are not present in fibromyalgia.
Polymyalgia rheumatica	Tender points are not always present in polymyalgia rheumatica. Stiffness is more prominent than pain in polymyalgia rheumatica. Most patients with polymyalgia rheumatica have increased erythrocyte sedimentation rate, while it is normal in fibromyalgia. Patients with polymyalgia rheumatica respond extremely well to modest doses of corticosteroids, in contrast to fibromyalgia patients.
Inflammatory myositis, metabolic myopathies	Myositis and myopathies can cause muscle weakness and muscle fatigue, but they are not usually associated with diffuse pain. Patients with myositis or myopathies have abnormal muscle enzyme tests and specific histopathologic findings on muscle biopsy, in contrast

	to fibromyalgia patients (muscle biopsy should be limited to cases that there is clinical evidence suggestive of myositis or myopathy).
Statin myopathy	Statin myopathy symptoms are limited to muscle weakness and pain without other symptoms associated with fibromyalgia. Statin myopathy pain is temporally associated with statin therapy. Statin myopathy can be associated with abnormal muscle enzyme tests.
Infection: chronic viral infection (e.g., infectious mononucleosis, HIV, HTLV, HBV, HCV, Lyme disease), long COVID	In fibromyalgia patients there is no objective evidence of inflammation or organ system dysfunction
Hypothyroidism	Although thyroid autoantibodies are common in fibromyalgia patients, thyroid function tests are usually normal.
Hyperparathyroidism	Hypercalcemia is not present in fibromyalgia.
Cushing's syndrome	Cushing's syndrome is associated with muscle weakness rather than pain. The characteristic facial and skin signs of Cushing's syndrome are not present in fibromyalgia.
Adrenal insufficiency	Adrenal insufficiency causes severe exhaustion, while it is not typically associated with chronic widespread pain.
Hypophosphatasia	Most hypophosphatasia patients have low alkaline phosphatase
Neurologic diseases: peripheral neuropathies, cervical radiculopathy, entrapment syndromes (e.g., carpal tunnel syndrome), multiple sclerosis, myasthenia gravis	Multiple sclerosis and myasthenia gravis are associated with post-exercise muscle and generalized fatigue, but not with widespread pain. Thorough neurologic examination can reveal neurologic signs characteristic of specific diseases.
Myofascial pain syndromes (they may include other common regional pain disorders such as tension headaches, occupational overuse syndrome, cumulative trauma disorder, work related musculoskeletal disorder, idiopathic low back and cervical strain disorders, chronic pelvic pain temporomandibular disorder and interstitial cystitis)	In myofascial pain syndromes the pain and the tenderness is confined in one anatomic region
Chronic fatigue syndrome (systemic exertion intolerance disease)	Criteria for the diagnosis of chronic fatigue syndrome:

	According to the modified United States Centers for Disease Control and Prevention chronic fatigue syndrome is diagnosed when two criteria are fulfilled (72): Clinically evaluated, unexplained, persistent or relapsing fatigue that is of new or definite onset; is not the result of ongoing exertion; is not alleviated by rest; and results in substantial reduction in previous levels of occupational, educational, social, or personal activities Four or more of the following symptoms that last six months or longer: Impaired memory or concentration Post-exertional malaise where physical or mental exertions bring on "extreme, prolonged exhaustion and sickness" Unrefreshing sleep Muscle pain Arthralgia in multiple joints Headaches of new kind or greater severity Frequent or recurring sore throat Tender cervical or axillary lymph nodes According to the proposed diagnostic criteria of the United States Institute of Medicine the chronic fatigue syndrome (systemic exertion intolerance disease) is diagnosed when two criteria are fulfilled (73): All of the following symptoms: A substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities that persists for more than 6 months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest Post-exertional malaise* Unrefreshing sleep* Two or more of the following manifestations: Cognitive impairment* Orthostatic intolerance The diagnosis should be questioned if patients do not have these symptoms at least half of the time with moderate, substantial, or severe intensity. Chronic widespread pain is not included in the criteria for diagnosis of chronic fatigue syndrome

Psychiatric disorders: depression, anxiety disorders, posttraumatic stress disorder	In fibromyalgia patients with a concurrent psychiatric disorder, the attribution of symptoms to fibromyalgia or the psychiatric disorder is not always possible.
Sleep disorders: obstructive sleep apnea, restless legs syndrome, periodic limb movement disorders	Detail history can identify the majority of the primary sleep disorders. Chronic widespread pain is uncommon in primary sleep disorders.
Irritable bowel syndrome	According to the 2009 American College of Gastroenterology recommendations for the diagnosis of irritable bowel syndrome, it is defined by abdominal pain or discomfort that occurs in association with altered bowel habits over a period of at least three months (74).
Temporomandibular disorders	Temporomandibular disorders are characterized by recurrent facial/jaw pain and/or limitation in jaw opening occurring in the past six months.
Tension – Migraine headache	Tension – migraine headache is characterized by recurrent headaches (at least five for migraine, at least 10 for tension-type) lasting 30 minutes.
Interstitial cystitis	According to the American Urological Association guidelines interstitial cystitis is defined as an unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than six weeks duration, in the absence of infection or other identifiable causes (75).

HIV: human immunodeficiency virus, HTLV: human T-lymphotropic virus, HBV: hepatitis B virus, HCV: hepatitis C virus, COVID: coronavirus disease

PATHOPHYSIOLOGICAL MECHANISMS

Pain sensitivity in the population occurs over a wide continuum, forming a classic bell-shaped curve, just like any other physiologic variable. Genetic predisposition in combination with environmental factors, determine the place that each individual takes in this continuum. People who are placed in the right end of this curve are very sensitive to pain and they can probably develop pain even without having any inflammation or damage in the peripheral tissues. This pain can be either regional or widespread (39).

In the past fibromyalgia was thought to be a primary muscle disease. However, controlled studies found no evidence of significant pathologic or biochemical muscle abnormalities that can be the cause of chronic widespread pain and tenderness. Most investigators believe that any muscle pathology is secondary to chronic pain and inactivity, rather than primary in nature (76–79). Current research suggests that altered central nervous system (CNS) physiology might underlie the symptoms of fibromyalgia. Abnormal central sensory processing of pain signals seems to play a significant role in the pathogenesis of fibromyalgia. This dysregulation of the nociceptive system can arise from a combination of interactions between neurotransmitters, cytokines, hormones, the autonomic nervous system, behavioral constructs, and external stressors.

Abnormalities in Sensory Processing

Fibromyalgia overlaps with several other similar syndromes including chronic fatigue syndrome (systemic exertion intolerance disease) and myophasial pain syndrome (Table 6). It has been proposed that these disorders should be considered

as members of the central sensitivity syndromes (Table 7). These similar and overlapping syndromes are bound by the common mechanism of central sensitization that involves hyper-excitement of the second-order neurons, especially the wide-dynamic-range neurons (WDR) in the dorsal horns of the spinal cord, by various synaptic and neurotransmitter/neuromodulator activities (6). Central sensitization is clinically and physiologically characterized by hyperalgesia, allodynia, expansion of the receptive field (pain expanding beyond the area of the peripheral nerve supply, after the application of a nociceptive stimulus), prolonged electrophysiological discharge, and an after-stimulus unpleasant quality of the pain (e.g., burning, throbbing, tingling or numbness). Parallel to central sensitization, temporal summation takes place in the second-order neurons. It is characterized by a progressive increase in electrical discharges (and consequently increase in the perceived intensity of pain) in response to repetitive short noxious stimuli. Temporal summation involves the production of second pain, which is described as dull or burning, and leaves an after-stimulus unpleasant sensation (80).

Table 7. Central Sensitivity Syndromes
Fibromyalgia
Chronic fatigue syndrome (systemic exertion intolerance disease)
Irritable bowel syndrome
Tension type headaches
Migraine
Temporomandibular disorder
Myophasial pain syndrome
Restless leg syndrome
Periodic limb movements in sleep
Primary dysmenorrhea
Interstitial cystitis
Posttraumatic stress disorder

N-methyl-D-aspartate (NMDA) receptors are mostly responsible for escalation of hyperexcitability of the second-order nociceptive neurons. The role of the major neurotransmitters of the nociceptive system that participate in signal conduction at the level of the spinal cord is briefly illustrated in Figure 3 (6).

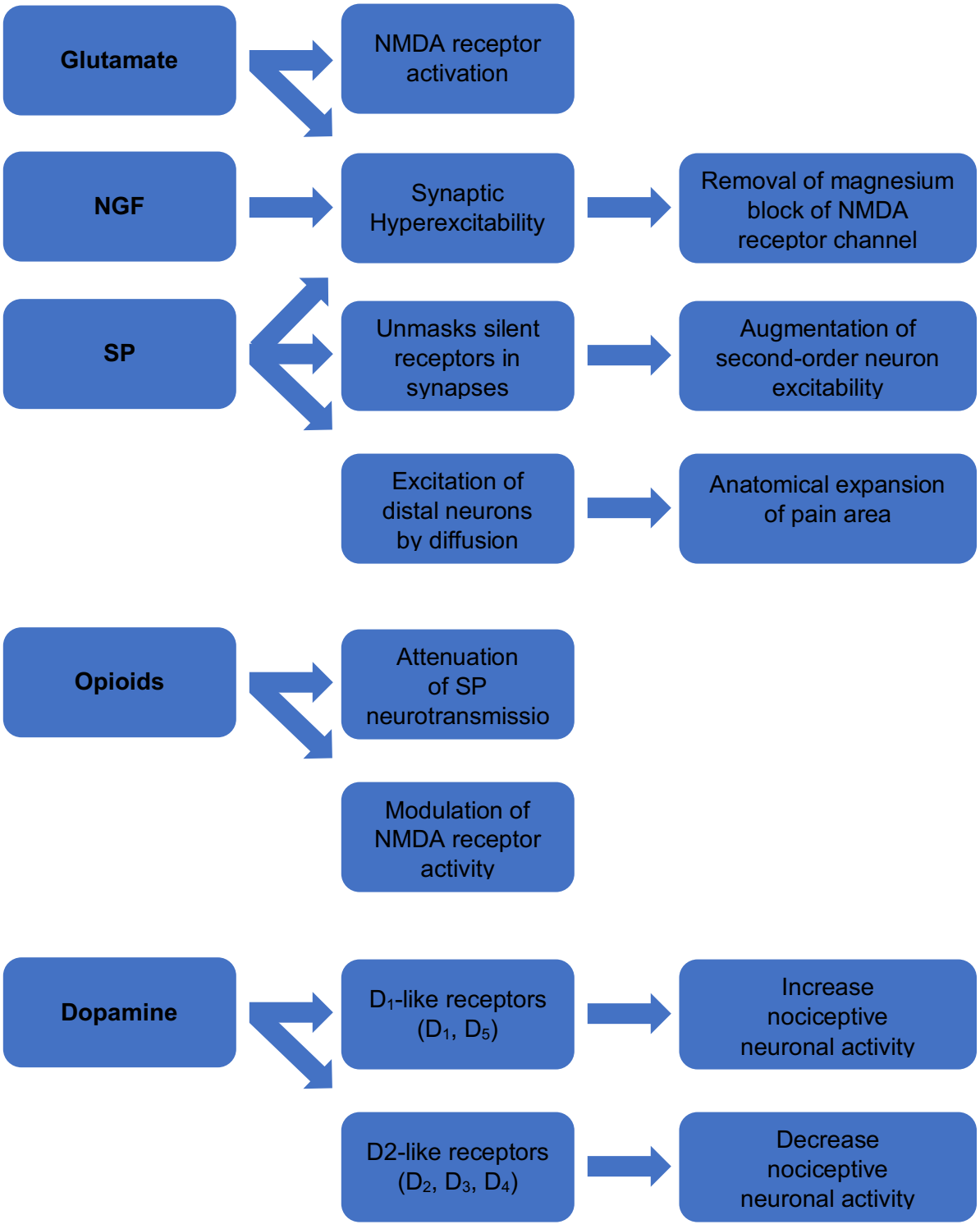

Figure 2. The role of the major neurotransmitters of the nociceptive system that participate in signal conduction at the level of the spinal cord. SP: Substance P, NGF: nerve growth factor, NMDA: N-methyl-D-aspartate, D: dopamine.

The second-order neurons have ascending projections to the thalamus, hypothalamus, the limbic system and the somatosensory cortex. These supraspinal structures are involved in the sensory, evaluative and affective dimensions of pain (e.g., unpleasantness, emotional reaction). Several descending pathways from the cortico-reticular system, locus ceruleus, hypothalamus, brain stem, and local spinal cord interneurons terminate to the dorsal horn cells. These pathways utilize neurotransmitters that include serotonin (5-HT), norepinephrine, γ-amino-butyric acid (GABA), enkephalins and adenosine (6). This descending system, once thought to be predominantly inhibitory, is now known to have a facilitatory potential (81). Evidence suggests that the 5-HT_3 receptor has a facilitatory function, while the 5H-T_{1A} receptor is inhibitory. The ascending and descending pathways should not be considered as dichotomous in function. They are interactive and their functions are bidirectional. Both pathways can either facilitate or inhibit pain, depending on the site of action and the neurotransmitters that are used (6).

The dysregulation of the nociceptive system, either at the level of the dorsal horns of the spinal cord, or at the level of the ascending and descending pathways, can lead to its hyper-excitability. In other words, it can lead to central sensitization. Several factors may amplify and sustain central sensitization through interactive and synergistic actions. These factors are summarized in Table 8 (80). Central sensitization can become self-sustained, even when the event that triggered it no longer exists, due to long-term CNS plasticity.

Table 2. Factors that may Amplify and Sustain Central Sensitization

Genetics
Sympathetic over-activity
Endocrine dysfunctions
Viral infection
Peripheral nociception generators (e.g., arthritis)
Poor sleep
Environmental stimuli (e.g., weather, noise, chemicals)
Psychological distress (e.g., adverse childhood experience)

Neuroimaging studies provide moderate evidence for structural changes in the brain of patients with fibromyalgia. Gray matter volume appears to be reduced in areas related with pain processing, such as the cingulate, the insular, and the prefrontal cortices (82). Functional MRI studies reveal alterations in the functional connectivity of brain areas responsible for pain processing and provide support of functional dysregulation of the ascending and descending pain pathways in fibromyalgia patients (82–85). Additionally, alterations in neuronal activity between the ventral and the dorsal spinal cord have been demonstrated in fibromyalgia patients (86).

Although nearly all of the research on sensory processing in fibromyalgia has focused on the processing of pain, there are some data suggesting a more generalized disturbance in sensory processing. There is evidence that fibromyalgia patients have a hypersensitivity to unpleasant stimuli of other sensory systems. For example, many patients experience reduced tolerance to loud noises, bright lights, odors, drugs, and chemicals (87,88).

Neurotransmitters

The levels of Substance P (SP) in the cerebrospinal fluid (CSF) in patients with fibromyalgia are significantly increased compared to normal individuals, whereas CSF levels of serotonin metabolites are decreased, as are metabolites of dopamine and norepinephrine (89).

The first direct evidence that fibromyalgia patients may have abnormal dopamine response to pain originated

from positron emission tomography (PET) competitive binding studies using the D_2/D_3 receptor antagonist [^{11}C] raclopride. It was shown that dopamine is released in response to tonic toxic noxious muscle stimulation, but not after non-painful muscle stimulation in healthy human subjects. In contrast the dopamine response in fibromyalgia patients did not differ between painful and non-painful muscle stimulation (87). There are indications that disturbances of the opioidergic system occur in fibromyalgia patients, as there is an up-regulation of opioid receptors in the periphery, with a reduction of the brain opioid receptors (90,91). This implies an increased baseline endogenous opioidergic activity. Opioids can activate glial cells, via a non-stereoselective activation of toll-like receptor 4 (TLR4). Glial cells in turn can mediate pain by releasing neuroexcitatory, pro-inflammatory products (92).

In a study where fibromyalgia patients were evaluated for cortical excitability and intracortical modulation using transcranial magnetic stimulation of the motor cortex, it was shown that there were deficits in intracortical modulation of GABAergic and glutamatergic mechanisms (93). Diminished inhibitory neurotransmission resulting from lower concentrations of GABA within the right anterior insula of patients with fibromyalgia was documented using proton magnetic resonance spectroscopy (94). Evidence for enhanced glutaminergic neurotransmission in fibromyalgia patients is derived from studies that used magnetic resonance spectroscopy. It was shown that fibromyalgia patients have significantly higher levels of glutamine within the posterior insula and in the right amygdala (95,96). The levels of brain-derived neurotrophic factor, which is involved in neuronal survival and synaptic plasticity of the central and peripheral nervous system, have been found to be increased both in the brain and in the plasma of fibromyalgia patients (97).

Cytokines

Although fibromyalgia is not considered an inflammatory disorder, the interaction of immunological mechanisms with pain physiology, has led to the identification of alterations in the levels of various cytokines (98). However, it is not clear whether cytokine changes are the cause of pain in these patients, or just its consequence.

The serum levels of interleukin 1 receptor antibody (IL-1Ra), IL-6, and IL-8, and the plasma levels of IL-8 are higher in fibromyalgia patients, compared to controls (99). Inflammatory cytokines such as IL-1β, IL-6 and tumor necrosis factor alpha (TNFα) have been detected in skin biopsies taken from fibromyalgia patients, possibly indicating an element of neurogenic inflammation (100). Lower levels of the anti-inflammatory cytokines IL-4 and IL-10 have been reported in fibromyalgia patients compared to healthy controls (101,102). However, the interpretation of cytokine levels is not always easy. Most cytokines are expressed in low levels and a sensitive bioassay is needed for their detection. Consequently, a negative result can merely be the ramification of a not sensitive enough method. Additionally, cytokine levels can be vigorously influenced by a number of factors, including circadian rhythmicity, physical activity, and co-morbid conditions, including depression.

Inflammatory cytokines like IL-1β, IL-6 and TNFα can elicit pain, induce hyperalgesia and they are associated with neuropathic pain (103), although they do not appear to be involved in “normal” pain. Although serum cytokines do pass the blood brain barrier the release of pro-inflammatory cytokines by immune cells in the body leads, in turn, to release of pro-inflammatory cytokines by glial cells within the brain and spinal cord (104).Inflammatory cytokines like IL-1β, IL-6 and TNFα can also cause activation of the hypothalamic-pituitary-adrenal (HPA) axis alone, or in synergy with each other. There is evidence to suggest that IL-6, which is the main endocrine cytokine, plays the most significant role in the immune stimulation of the axis, especially in chronic inflammatory stress (105). IL-6 can stimulate the hypothalamic secretion of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), leading to the increase of serum adrenocorticotropic hormone (ACTH) and cortisol levels (106).

Hypothalamic-Pituitary-Adrenal Axis

There is substantial data supporting an abnormal function of the HPA axis in fibromyalgia. However, the results from studies on the HPA axis function in

fibromyalgia patients are relatively heterogeneous and partially contradictory (107). The 24-hour urinary free cortisol (UFC) has been found to be reduced or normal (108). Findings regarding alterations in diurnal variation of cortisol secretion are also inconsistent. Although normal diurnal patterns of ACTH and cortisol have been reported, there is data demonstrating flattened cortisol diurnal rhythm with normal morning peak and higher evening cortisol, levels (109). It has been demonstrated that there is a significant decrease in the rate of decline from acrophase (peak) to nadir for diurnal cortisol levels in fibromyalgia patients, compared to controls, while there is no change in the ACTH to cortisol ratio (108). This implies a decreased ability of the HPA axis to return to baseline after a physiologic stimulation by meals, several other activities or even pain (108). Decreased morning cortisol release and reduced frequency of cortisol pulses over 24 hours have also been reported. There is evidence to suggest that the reduced cortisol release in fibromyalgia patients is associated with depressive symptoms and experiences of childhood trauma (109).

In line with studies suggesting reduced adrenal output in fibromyalgia patients, reduced cortisol secretion has been reported in response to pharmacological challenge with synthetic $ACTH_{1-24}$ and insulin tolerance test (109). Patients with fibromyalgia exhibit increased ACTH, but normal cortisol response to CRH stimulation, compared to controls. This finding suggests a sensitization of the pituitary in combination with a degree of adrenal insufficiency (109). Arginine vasopressin (AVP), an ACTH secretagogue, has been found to be more increased in response to the postural challenge test in fibromyalgia patients, compared to controls (110). Alterations in the feedback regulation of HPA axis have also been reported in fibromyalgia patients, using the overnight dexamethasone suppression test (DST). Increased rates of non-suppression following the standard (1 mg) DST have been reported in fibromyalgia patients, compared to controls, but this finding was difficult to be interpreted as it was associated with depression. Interestingly, other studies have revealed lower rates of non-suppression in fibromyalgia patients (111).

There are indications that there is a dissociation between total and free cortisol levels in fibromyalgia patients, with normal salivary and plasma free cortisol despite diminished total cortisol levels. One possible explanation of this finding is a reduced concentration of the glucocorticoid binding globulin (CBG). Reduced levels of CBG have been reported in fibromyalgia patients compared to controls. It is of particular interest that chronic social stress might result in reduced CBG levels, whereas IL-6 and IL-1β that can also inhibit the production of CBG may contribute further (109). Apart from HPA axis abnormalities in fibromyalgia patients, abnormal levels of growth hormone have also been found in some, but not all reports (112). On the other hand the levels of sex hormones have not been clearly shown to differ between female fibromyalgia patients and controls (113).

Autonomic Nervous System

Sympathetic hyperactivity, often associated with sympathetic hypo-activity in response to stressors, or parasympathetic underactivity has been described in fibromyalgia. Attenuated sympathetic and parasympathetic activity was demonstrated in a study where fibromyalgia patients and healthy controls were assessed for 24 hours in a controlled hospital setting, including relaxation, a test with prolonged mental stress and sleep. The urinary catecholamine levels were found to be lower in fibromyalgia patients compared to controls. Patients with fibromyalgia had significantly lower adrenaline levels during the night and the second day of the study, and significantly lower dopamine levels during the first day, the night, and the second day. Furthermore, heart rate during relaxation and sleep was significantly higher in patients than in controls (114). In another study, plasma catecholamines, ACTH, and cortisol levels were reduced in 16 fibromyalgia patients compared to 16 healthy controls while performing static knee extension until exhaustion (115). Nocturnal heart rate variability indices have been shown to be significantly different in fibromyalgia women compared to healthy individuals, indicating a sympathetic predominance (116). In addition, orthostatic hypotension and increased pain in response to tilt table test have been described along with increased resting supine heart rate and decreased heart rate variability (117,118). IL-6 administration causes exaggerated norepinephrine responses and increases in heart rate, as well as

delayed ACTH release, suggesting an incapacitated stress-regulating system (119). In-vitro testing of beta adrenergic receptor mediated cyclic AMP generation has revealed decreased responsiveness to beta-adrenergic stimulation (120).

Overall, it has been suggested that sympathetic dysfunction can not only cause diffuse pain, but also contribute to other symptoms like sleep disturbances, due to sustained nocturnal sympathetic activity, and fatigue, due to deranged sympathetic response to stress (6).

Psychological, Cognitive, and Behavioral Factors

Pain apart from a sensory-discriminative dimension, which includes the location and the intensity of pain, has a very significant psychological component. This includes the affective dimension of pain, the emotional valance of pain in other words, as well as attention and cognitive aspects, which are based on CNS mechanisms. Emotion and selective attention can enhance pain perception, with the involvement of the descending pathways that have a facilitatory effect on the spinal cord dorsal horn neurons (80). Catastrophizing has been shown to be related to decreased pain threshold and tolerance to heat stimuli in fibromyalgia patients. However there is a subgroup of fibromyalgia patients that is very tender, despite the fact that they do not catastrophize and they have a moderate control over their pain (11). A fMRI study has shown that although depression is associated with the magnitude of neuronal activation in brain regions that process the affective-motivational dimension of pain, neither the extent of depression nor the presence of comorbid major depression modulated the sensory-discriminative aspects of pain processing in fibromyalgia patients (121). Catastrophizing, has been associated with increased activity in brain areas related to anticipation, attention and the emotional aspects of pain, as shown by fMRI in response to pressure stimuli. This study also revealed an association between catastrophizing and increased activity in the secondary somatosensory cortex, indicating that the way patients think about their pain might actually influence its sensory processing (80).

Genetic Predisposition

It is currently well established that familial aggregation is a characteristic of fibromyalgia. First degree relatives of fibromyalgia patients are 8.5 times more likely to have fibromyalgia than relatives of patients with rheumatoid arthritis (12). As with other complex and multifactorial syndromes, the occurrence of familial aggregation in the case of fibromyalgia does not necessarily imply a genetic basis. Shared environmental factors and learned patterns of behavior that may evolve within families are equally valid targets of investigation.

Genome-wide association studies have shown significant differences in allele frequencies between fibromyalgia patients and controls. However many of the results are inconsistent, without being replicated. Additionally the small sample size of these studies limits the genetic variants that can be identified only to those with large effects (122–126). The coexistence of other comorbidities in fibromyalgia patients further obscures these results. In a large scale genome-wide association study of 26,749 individuals the overall estimated heritability of fibromyalgia was 14%. There was a significant difference between age groups, with the heritability in individuals less than 50 years of age to be 23.5%, while in those over 60 years of age it was only 7.5% (126).

Although no specific candidate gene has been identified, the following genes have been associated with fibromyalgia:

SEROTONIN TRANSPORTER (5-HTT) GENE

An increased frequency of the S/S genotype of the 5-HTT gene has been found in fibromyalgia patients compared to controls (127,128). However this putative association may be limited to patients with concomitant affective disorders, since it was not confirmed in fibromyalgia patients without depression or anxiety (129).

D_4 RECEPTOR GENE

Polymorphisms affecting the number of repeats in the third cytoplasmic loop of the dopamine D_4 receptor

gene have been shown to be significantly decreased in frequency in fibromyalgia patients (130).

CATECHOL-O-METHYL TRANSFERASE (COMT) GENE

The homozygous low activity (met/met) and the heterozygous low activity (val/met) COMT genotypes occur more often in fibromyalgia patients than in controls, whereas the homozygous high activity (val/val) genotype is less frequent (131). However in a meta-analysis COMT gene val(158)met polymorphism was not associated with an increased risk for fibromyalgia (132). The met/met genotype has been associated with greater fibromyalgia illness severity across the domains of pain, fatigue, sleep disturbance, and psychological distress, while fibromyalgia patients with the met/met polymorphism experienced a greater decline in exhibiting a positive attitude on days when pain was elevated than did patients with the val/met or val/val genotype (133).

OPIOID RECEPTOR μ 1 GENE (OPRM1)

The 118G allele frequency has been described to be significantly lower in patients with fibromyalgia than in the control group (134).

ADRENERGIC RECEPTOR GENES

The presence fibromyalgia and its symptom severity is associated with various adrenergic receptor gene polymorphisms (135).

Other genes associated with the regulation of nociceptive and analgesic neuronal pathways
Specific variants of trace amine-associated receptor 1 (TAAR1) gene, regulator of G-protein signaling 4 (RGS4) gene, cannabinoid receptor 1 (CNR1) gene, and glutamate receptor, ionotrophic, AMPA 4 (GRIA4) gene, have been associated with fibromyalgia (123).

External Stressors

Almost all diseases are caused by a combination of genetic predisposition and the effect of environmental factors. We are now beginning to better understand the environmental factors that seem to be important in triggering fibromyalgia. Most of them act as “stressors” that when superimposed onto a deranged stress-response system can lead to the dysregulation of the nociceptive system.

PERIPHERAL PAIN SYNDROME

Pain due to damage or inflammation of peripheral tissues may trigger fibromyalgia. Additionally, small fiber neuropathy can be associated with fibromyalgia (136–138). Chronic localized – regional pain can lead to central sensitization and pain dis-inhibition, causing pain hypersensitivity and widespread pain. Systematic autoimmune diseases can be associated with fibromyalgia too. Approximately 20-25% of patients with rheumatoid arthritis, systemic lupus erythematosus and ankylosing spondylitis, have co-morbid fibromyalgia (18). In such cases, it is important to realize that many symptoms may be attributed to fibromyalgia rather than the underlying disorder. This recognition has significant clinical implications.

INFECTIONS

Various infections have been linked to the development of fibromyalgia and chronic fatigue syndrome (systemic exertion intolerance disease). Epstein-Barr virus, parvovirus, Lyme disease, Q fever, HIV and hepatitis C virus (HCV), have been suggested as triggers of fibromyalgia or chronic fatigue syndrome (systemic exertion intolerance disease), but more robust evidence is needed. The role of vaccination in precipitating fibromyalgia and related syndromes is still not clear (139,140).

PHYSICAL TRAUMA

Various forms of physical trauma have been considered as culprits of triggering the pathogenesis of fibromyalgia. Many patients report the initiation or the exacerbation of their symptoms after a traumatic event such as whiplash injury, while increased rates of fibromyalgia have been demonstrated among patients undergoing cervical trauma during motor vehicle accidents (141,142).

PSYCHOLOGICAL DISTRESS

It has been considered that psychological factors that give rise to chronic stress may initiate the chain of events that leads to fibromyalgia. The chronic stress can be a result of the accumulation of daily stress events. Emotional stress, catastrophic events such as war, job loss, marital discord and excess family responsibilities such as caring for sick elders, have been implicated as triggers of fibromyalgia (143). However the data that supports the notion that psychological stress and distress directly causes fibromyalgia is rather weak (39).

MANAGEMENT

The treatment of fibromyalgia is challenging because of our limited understanding of its pathogenesis and the poor response of patients to conventional pain treatments. The aim of the therapy is to relieve pain and increase function using a multimodal individualized therapeutic strategy which, in most cases, includes pharmacologic and non-pharmacologic interventions. Current clinical-based evidence supports the use of a multimodal program that includes education, exercise, cognitive-behavioral approaches and medications. The treatment should be individualized based on the symptoms, the comorbidities and the preferences of the patient, who should be encouraged to participate in the decision-making process of selecting the optimal therapies (144,145). Coexisting disorders are common in fibromyalgia patients. Their identification and effective treatment can have beneficial effects on fibromyalgia symptoms. It is also important to assure that adequate adherence to both pharmacological and non-pharmacological treatment is maintained, so as to achieve the optimal benefit from these treatments.

Non-Pharmacological Management

PATIENT EDUCATION

The first step should be the education of the patient. The patients with fibromyalgia need to understand their illness before any treatment modality is used (146). Providing a diagnosis, “labeling” the patient with fibromyalgia, may have beneficial effects. It has been shown that fewer symptoms and an improvement in health status is noted after the patients are informed of their diagnosis (147,148). The physician should clarify that fibromyalgia is a real illness and the symptoms the patient experiences are not imaginary. The role of neurotransmitters and neuromodulators in pain perception, fatigue, abnormal sleep and mood disturbances should be discussed, so as the patient to understand the rationale of the pharmacologic therapy, especially when antidepressant drugs are used. The significance of good sleep hygiene should be reviewed and poor sleep habits should be addressed. Fibromyalgia patients who are overweight or obese should be informed for the adverse effect of increase body mass index to fibromyalgia symptoms and quality of life (149). For these patients weight reduction should be encouraged. The patient also needs to acknowledge that fibromyalgia is a chronic relapsing condition without though being life-threatening nor deforming.

EXERCISE

Another potent non-pharmacological treatment for fibromyalgia is exercise. It has been reported that an exercise program incorporating aerobic, strengthening, and flexibility elements can lead to greater benefits than a relaxation program. Exercise in fibromyalgia patients should have two major components: strengthening to increase soft-tissue length and joint mobility, and aerobic conditioning to increase fitness and function, reduce fibromyalgia symptoms and improve quality of life (144,150–153). Exercise should be of low impact and of sufficient intensity so as to be able to change aerobic capacity (28). Successful interventions include fast walking, biking, swimming, water aerobics, tai chi, and yoga. Land and aquatic training appears to be equally beneficial (154). An improvement in the severity of fibromyalgia symptoms has also been achieved with web-based exercise programs (155). A gradual incremental increase in physical activity should be encouraged as it is common for fibromyalgia patients to initially perceive an aggravation of their pain and fatigue at the beginning of a training program. It has been suggested that in the presence of exercise-induced pain, the intensity and duration of exercise should be reduced, while its frequency should be maintained, so as to avoid any further decrease in exercise tolerance (144). The type and intensity of the

exercise program should be individualized and should be based upon patient preference and the presence of any other cardiovascular, pulmonary, or musculoskeletal comorbidities.

COGNITIVE-BEHAVIORAL APPROACHES

One of the goals of the management should be to help patients understand the effect of thoughts, beliefs and expectations on their symptoms. This can help them to abolish the perception of helplessness and the catastrophizing thoughts that can adversely influence their condition. Patients with greater self-efficacy are more likely to have a good response to treatment programs and experience better outcomes. The beneficial effect of cognitive-behavioral therapies in fibromyalgia patients with anxiety and depression disorders is limited to a reduction of negative mood, while the rest of the patients also demonstrate a reduction of pain and fatigue. Psychologically based interventions, have been proven to be useful when they are compared to no treatment or treatment other than aerobic exercise (156). In a 2021 systematic review and meta-analysis there was high quality evidence that cognitive-behavioral therapy can significantly reduce the pain intensity in fibromyalgia patients for 3 months (157). Preliminary data from functional MRI studies suggest that cognitive-behavioral therapies have the ability to restore the alterations in the functional connectivity of brain areas responsible for pain processing observed in fibromyalgia patients (158,159).

COMPLEMENTARY AND ALTERNATIVE APPROACHES

Acupuncture

Acupuncture is the insertion of needles in the human body. There are different styles of acupuncture depending on the location and the depth the needles are inserted. The inserted needles can be stimulated by heat, electrical current (electro-acupuncture), mechanical pressure (acupressure), or laser (laser acupuncture). The most common type of acupuncture involves skin penetration without stimulation (manual acupuncture). Sham or fake acupuncture is a research tool to control the effects of real acupuncture. It can involve skin contact with the needles without actual penetration or needle insertion in areas other than the ones usually targeted.

In a high quality meta-analysis it was demonstrated that the effects of manual acupuncture on pain, sleep quality and global well-being did not differ significantly from the effects of sham acupuncture. On the contrary electro-acupuncture significantly reduced pain, fatigue, and stiffness, while it improved sleep quality and global well-being when compared to sham acupuncture. Additionally, electro-acupuncture significantly improved pain, stiffness, and global well-being when compared to non-acupuncture. The beneficial effects of acupuncture could be observed at 1 month after treatment, but they were not maintained at 6-7 months (160).

Other

The effectiveness of meditative movement therapies (qigong, yoga, tai chi) on sleep and fatigue improvement and of hydrotherapy on pain reduction has been supported by some studies (161,162). A number of other modalities has also been utilized for the treatment of fibromyalgia including biofeedback, chiropractic therapy, massage therapy, hypnotherapy, guided imagery, electrothermal therapy, phototherapeutic therapy, music therapy, journaling / storytelling, static magnet therapy, transcutaneous electrical nerve stimulation, and transcranial direct current stimulation. However there are no well-designed studies to advocate their general use (145).

Pharmacologic Treatment

A wide range of drugs has been used in the treatment of fibromyalgia including antidepressants, sedatives, muscle relaxants and antiepileptic drugs. The choice of medication is influenced by patient preference; prominence of particular symptoms, including fatigue, insomnia, and depression; potential adverse effects; patient tolerance of individual medications; cost and regulatory limitations on prescription choice (163,164). Nonsteroidal anti-inflammatory drugs and opioids, although often prescribed for fibromyalgia, are not an effective form of treatment (39,165). However analgesics and anti-inflammatory medications can be

useful in case of coexisting conditions that cause regional pain, like arthritis, which can aggravate or trigger the fibromyalgia symptoms. Regarding opioids, with the exception of tramadol, apart from not being effective for the treatment of fibromyalgia symptoms, their long-term use also curries a dose-dependent risk for serious adverse effects, including overdose, abuse, fractures, myocardial infarction and sexual dysfunction (166). Additionally opioids in fibromyalgia patients can reduce the effectiveness of psychological therapy (167), while their long-term use can cause sleep disturbances (168).

Patients should be informed that for most pharmacologic therapies several weeks may be needed until they experience a benefit. Initially a single drug should be administered. However, in the case of non-responsiveness combination therapy should be considered. Since therapeutic responses are rarely durable, physicians should not be surprised when the initial efficacy of a medication is abolished. Successful treatment of fibromyalgia may require regular reassessment and possible rotation or combination of medications (169). Adequate dose prescription and patient adherence are significant for the effectiveness and tolerability of pharmacologic treatment (170). The doses of the most commonly used medications with strong and moderate evidence of effectiveness are shown in Table 9.

ANTIDEPRESSANTS

Tricyclic Antidepressants (TCAs)

TCAs are often used as initial treatment for fibromyalgia. Their analgesic effect is independent of their antidepressant action and is thought to be mediated by inhibition of norepinephrine (rather than serotonin) reuptake at spinal dorsal horn synapses, with secondary activity at the sodium channels. The most widely studied drugs of this group are *amitriptyline* and *cyclobenzaprine*. They should be administered at lower doses than those required for the treatment of depression, a few hours before bedtime, and their dose should be escalated very slowly. A clinically important improvement is observed in 25-45% of patients treated with TCAs compared to 20% in those taking placebo (171–175). However their use is limited by the fact that they are ineffective or intolerable in 60-70% of patients (144), while their efficacy may decrease over time (171,176).

Amitriptyline is more efficient compared to the serotonin-norepinephrine reuptake inhibitors duloxetine and milnacipran in reducing pain, sleep disturbance, and fatigue, without differences in acceptability, as it was shown in a systematic review and meta-analysis (177). In a 2022 network meta-analysis comparing amitriptyline, duloxetine and pregabalin it was shown that treatment with amitriptyline 25 mg was superior to duloxetine and pregabalin for the reduction of pain intensity for at least 50% (178). The combination of 20 mg of fluoxetine in the morning with 25 mg of amitriptyline at bedtime has been shown to be more effective than either medication alone (179). Side effects of amitriptyline include dry mouth, constipation, fluid retention, weight gain, difficulty in concentrating and possibly cardiotoxicity.

Cyclobenzaprine has a similar tricyclic structure and presumed mode of action with amitriptyline in fibromyalgia, but is thought to have minimal antidepressant effect (163). A meta-analysis of five placebo-controlled trials has revealed improvement of the global functioning, with a similar effect size as this reported for amitriptyline. The group that received cyclobenzaprine had a significant decrease in pain for 4 weeks, compared to those treated with placebo, but the decrease in pain was not significantly different after 8 and 12 weeks. Sleep was improved at all time points in both cyclobenzaprine and placebo groups, while no effect was noted on fatigue (171–173). It has been demonstrated that the use of very low-dose cyclobenzaprine (1 to 4 mg at bedtime) can improve the symptoms of fibromyalgia, including pain, fatigue, and depression, compared to symptoms at baseline and to placebo. Significantly more patients who received the very low-dose of cyclobenzaprine experienced improved restorative sleep, based upon analysis of cyclic alternating pattern of sleep by electroencephalography. The increase in nights with improved sleep by this measure correlated with improvements in fatigue and depression (180).

Desipramine has fewer anticholinergic and sedative effects than other TCAs, which can make it a possible

alternative, although its efficacy is not well studied in fibromyalgia.

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

SNRIs are similar to TCAs in their ability to inhibit the reuptake of both serotonin and norepinephrine, but they differ from TCAs in being devoid of significant activity at other receptor systems, resulting in diminished side effects and increased tolerance. *Venlafaxine, duloxetine* and *milnacipran* have been shown to be effective in diminishing fibromyalgia symptoms (147,181,182). These drugs can be used in fibromyalgia patients who do not respond to a trial of low-dose TCAs or who have intolerable side effects. They can also be administered as an alternative to amitriptyline for initial therapy especially for patients with significant fatigue or depression. Of these medications *duloxetine* and *milnacipran* are better studied and they are preferred to be administered to patients with fibromyalgia. There are more limited data regarding the efficacy of *venlafaxine* for fibromyalgia, while withdrawal symptoms if a dose is missed occur more often, because of the short half-life of this medication (183). A meta-analysis has shown that fibromyalgia patients treated with *duloxetine* at 60mg daily are more likely to have more than 50% reduction in pain, compared to patients taking placebo (184). However, *duloxetine* at 30mg daily does not significantly reduce pain (185). The efficacy of *duloxetine* can be maintained at 3 and 6 months of treatment (186). In a 2018 systematic review and meta-analysis it was shown that *duloxetine* and *milnacipran* were not superior to placebo in the frequency of pain relief of at least 50%, but there was a benefit in reducing the pain at least by 30% and in the patient's global impression to be much or very much improved. Additionally, there was not a significant difference in the reduction of fatigue, in the reduction of sleep problems, nor in the improvement of health-related quality of life (187). Another meta-analysis has shown that *duloxetine*, *pregabalin* and *milnacipran* were superior to placebo for pain relief, while *duloxetine* and *pregabalin* were superior to *milnacipran*. These drugs also differed in their effects on sleep disturbances, depression and fatigue (188). A fMRI study in fibromyalgia patients treated with *milnacipran* and placebo demonstrated that pain reduction with *milnacipran* treatment was associated with decreased functional connectivity between the insular cortex and the rostral part of the anterior cingulate cortex as well as the periaqueductal gray, while these changes were not demonstrated with the placebo (189). Regarding their side effects, headaches and nausea are more common with *duloxetine* and *milnacipran* treatment, while diarrhea is more common with *duloxetine* treatment. Other side effects related to SNRIs include dry mouth, constipation, somnolence, dizziness and insomnia (188).

Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors block the catabolism of serotonin, increasing its levels in the brain. It has been indicated that pirlindole and moclobemide have a significant beneficial effect on pain, without a significant effect on sleep nor fatigue. Their use for the treatment of fibromyalgia patients is limited (190).

ANTICONVULSANTS

Antiepileptic medications useful for the treatment of fibromyalgia patients include *pregabalin* and *gabapentin*. Both of these medications are structurally related to GABA and they bind with high affinity to the alpha2-delta subunit site of cellular voltage-dependent calcium channels. Although their exact mechanism of action is unknown their therapeutic effects can be mediated by blocking the release of various neurotransmitters. They can be used in cases where other medications initially administered to the fibromyalgia patients become intolerable or ineffective, or as the initial treatment for patients with significant sleep disturbance in addition to pain.

Pregabalin has been reported to be efficient against pain, sleep disturbances and fatigue in fibromyalgia. In a recent meta-analysis a reduction of at least 50% in pain intensity was found in 22-24% of patients taking pregabalin 300-600 mg per day, approximately 9% higher compared to the placebo group. A reduction in pain intensity of at least 30% was found in 39-43% of patients on pregabalin 300-600 mg per day, compared to 28% of patients taking placebo (191). In addition to pain, pregabalin at doses 300-600 mg per day can improve sleep and patient function, as it is

demonstrated in a 2018 review of clinical trials, meta-analyses, combination studies and post-hoc analyses (192). The improvement in pain and sleep can be apparent as early as 1-2 days after the onset of treatment (193). In a 2022 network meta-analysis it was shown that treatment with pregabalin 450 mg per day was superior to duloxetine 30 mg for the reduction of pain intensity of at least 30% (178). A randomized placebo-controlled neuroimaging study demonstrated that the reduction in pain intensity from pregabalin was associated with a reduction in connectivity between the posterior insula and the default mode network (DMN) and that pregabalin but not placebo can reduce the response of the DMN to experimental pain (194). It is of interest that baseline patterns of brain connectivity have been used in a machine-learning model to successfully distinguish fibromyalgia patients who have a favourable response to pain intensity after the treatment with milnacipran from those who achieve a reduction of pain intensity after the treatment with pregabalin (195). Common side effects of pregabalin include somnolence, dizziness, weight gain and peripheral oedema. Discontinuation due to side effects is approximately 10% higher in patients treated with pregabalin compared to placebo, while discontinuation due to inefficiency of treatment is 6% lower (191). The intensity of adverse effects and the frequency of discontinuation of the treatment due to adverse effects is dose dependent. It is important for pregabalin to be titrated to the maximally tolerated therapeutic dose for each patient (192).

Gabapentin has been shown to be efficient in treating fibromyalgia associated pain, while it was well tolerated (196). Side effects include dizziness, sedation, lightheadedness, and weight gain. Its efficacy and tolerability is not well studied in fibromyalgia patients, however it can be considered as an acceptable alternative in case pregabalin cannot be administered due to its cost or due to regulatory limitations (197).

SEDATIVE HYPNOTIC AGENTS

Zopiclone and *zolpidem* have been used in fibromyalgia. It has been suggested that they can improve the sleep and perhaps fatigue, without any significant effects on pain (144).

Sodium oxibate, a precursor of GABA with powerful sedative properties has been shown to improve pain, fatigue and sleep architecture in fibromyalgia (198). However, in view of safety concerns the European Medicines Agency and the US Food and Drug Administration have not approved it for use in fibromyalgia patients.

TRAMADOL

Tramadol has multiple analgesic effects, since it inhibits norepinephrine and serotonin reuptake, and its major metabolite binds weakly to opioid μ receptors (144). The use of tramadol (with or without acetaminophen) is both effective and well tolerated for the management of pain in fibromyalgia (199,200). There are some concerns regarding the long-term potential of abuse of tramadol, although the risk is less than that of more potent narcotic analgesics that have also been used in fibromyalgia.

Table 3. The Doses of the Most Commonly used Medications with Strong and Moderate Evidence of Effectiveness in Fibromyalgia	
Drugs	**Doses**
Tricyclic antidepressants	
Amitriptyline	Start 5-10 mg at bedtime, increase up to 25-50 mg
Cyclobenzaprine	Start 10 mg at bedtime, increase up to 30-40mg, decrease to 5mg if 10mg too sedating
Serotonin-norepinephrine reuptake inhibitors	
Duloxetine	Start 10-15mg twice daily, gradually increased to 30 mg twice daily
Milnacipran	Start 12.5mg in the morning, gradually increase to 50mg twice daily
Venlafaxine	167 mg per day
Anticonvulsants	
Gabapentin	Start 100mg at bedtime, increase to 1200-2400 mg per day
Pregabalin	Start 25-50mg at bedtime, increase to 300-450 mg/day
Other	
Tramadol	37.5 mg four times daily

CONCLUSION

Fibromyalgia is a common disease that is often underdiagnosed. Genetic predisposition, in combination with exposure to external stressors may lead to dysregulation of the nociceptive system and to the appearance of clinical symptoms. Fibromyalgia patients do not form a homogenous group with some patients responding adequately to current therapeutic modalities, and some others not experiencing any long-term benefit. Patients treated by primary care physicians in the community have a much better prognosis, compared to patients treated in tertiary referral centers. Certain psychological factors, such as an increased sense of control over pain, a belief that one is not disabled, that pain is not a sign of damage, and behaviors like seeking help from others, decreased guarding during examination, exercising more and having pacing activities are associated with better prognosis. Conversely, catastrophizing is associated with increased awareness of pain and with worsening symptoms.

REFERENCES

1. Bennett RM. Clinical manifestations and diagnosis of fibromyalgia. Rheum. Dis. Clin. North Am. 2009;35(2):215–232.
2. Wessely S, Hotopf M. Is fibromyalgia a distinct clinical entity? Historical and epidemiological evidence. Baillieres Best Pract Res Clin Rheumatol 1999;13(3):427–436.
3. Wolfe F. Editorial: the status of fibromyalgia criteria. Arthritis & Rheumatology (Hoboken, N.J.) 2015;67(2):330–333.
4. Weir PT, Harlan GA, Nkoy FL, Jones SS, Hegmann KT, Gren LH, Lyon JL. The incidence of fibromyalgia and its associated comorbidities: a population-based retrospective cohort study based on International Classification of Diseases, 9th Revision codes. J Clin Rheumatol 2006;12(3):124–128.
5. Mease P, Arnold LM, Bennett R, Boonen A, Buskila D, Carville S, Chappell A, Choy E, Clauw D, Dadabhoy D, Gendreau M, Goldenberg D, Littlejohn G, Martin S, Perera P, Russell IJ, Simon L, Spaeth M, Williams D, Crofford L. Fibromyalgia syndrome. J Rheumatol 2007;34(6):1415–1425.
6. Yunus MB. Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. Semin. Arthritis Rheum. 2007;36(6):339–356.
7. Marcus DA, Bernstein C, Rudy TE. Fibromyalgia and headache: an epidemiological study supporting migraine

as part of the fibromyalgia syndrome. Clin. Rheumatol. 2005;24(6):595–601.
8. Rhodus NL, Fricton J, Carlson P, Messner R. Oral symptoms associated with fibromyalgia syndrome. J Rheumatol 2003;30(8):1841–1845.
9. Aydin G, Başar MM, Keleş I, Ergün G, Orkun S, Batislam E. Relationship between sexual dysfunction and psychiatric status in premenopausal women with fibromyalgia. Urology 2006;67(1):156–161.
10. Aaron LA, Burke MM, Buchwald D. Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder. Arch. Intern. Med. 2000;160(2):221–227.
11. Giesecke T, Williams DA, Harris RE, Cupps TR, Tian X, Tian TX, Gracely RH, Clauw DJ. Subgrouping of fibromyalgia patients on the basis of pressure-pain thresholds and psychological factors. Arthritis & Rheumatism 2003;48(10):2916–2922.
12. Arnold LM, Hudson JI, Hess EV, Ware AE, Fritz DA, Auchenbach MB, Starck LO, Keck PE Jr. Family study of fibromyalgia. Arthritis Rheum. 2004;50(3):944–952.
13. Løge-Hagen JS, Sæle A, Juhl C, Bech P, Stenager E, Mellentin AI. Prevalence of depressive disorder among patients with fibromyalgia: Systematic review and meta-analysis. J Affect Disord 2019;245:1098–1105.
14. Kleykamp BA, Ferguson MC, McNicol E, Bixho I, Arnold LM, Edwards RR, Fillingim R, Grol-Prokopczyk H, Turk DC, Dworkin RH. The Prevalence of Psychiatric and Chronic Pain Comorbidities in Fibromyalgia: an ACTTION systematic review. Semin Arthritis Rheum 2021;51(1):166–174.
15. Wu Y-L, Huang C-J, Fang S-C, Ko L-H, Tsai P-S. Cognitive Impairment in Fibromyalgia: A Meta-Analysis of Case-Control Studies. Psychosom Med 2018;80(5):432–438.
16. Müller W, Schneider EM, Stratz T. The classification of fibromyalgia syndrome. Rheumatol. Int. 2007;27(11):1005–1010.
17. Thieme K, Spies C, Sinha P, Turk DC, Flor H. Predictors of pain behaviors in fibromyalgia syndrome. Arthritis Rheum. 2005;53(3):343–350.
18. Goldenberg DL. Fibromyalgia syndrome a decade later: What have we learned? Arch Intern Med 1999;159(8):777–785.
19. Ursini F, Ciaffi J, Mancarella L, Lisi L, Brusi V, Cavallari C, D'Onghia M, Mari A, Borlandelli E, Faranda Cordella J, La Regina M, Viola P, Ruscitti P, Miceli M, De Giorgio R, Baldini N, Borghi C, Gasbarrini A, Iagnocco A, Giacomelli R, Faldini C, Landini MP, Meliconi R. Fibromyalgia: a new facet of the post-COVID-19 syndrome spectrum? Results from a web-based survey. RMD Open 2021;7(3):e001735.
20. Clauw DJ, Calabrese L. Rheumatology and Long COVID: lessons from the study of fibromyalgia. Ann Rheum Dis 2023:ard-2023-224250.
21. Mease P, Arnold LM, Choy EH, Clauw DJ, Crofford LJ, Glass JM, Martin SA, Morea J, Simon L, Strand CV, Williams DA. Fibromyalgia syndrome module at OMERACT 9: domain construct. J. Rheumatol. 2009;36(10):2318–2329.
22. Mease P, Clauw D, Christensen R, Crofford L, Gendreau M, Martin S, Simon L, Strand V, Williams D, Arnold L. Toward Development of a Fibromyalgia Responder Index and Disease Activity Score: OMERACT Module Update. J Rheumatol 2011;38(7):1487–1495.
23. Boomershine CS. A Comprehensive Evaluation of Standardized Assessment Tools in the Diagnosis of Fibromyalgia and in the Assessment of Fibromyalgia Severity. Pain Research and Treatment 2012;2012:1–11.
24. Endresen GKM. Fibromyalgia: a rheumatologic diagnosis? Rheumatol Int 2007;27(11):999–1004.
25. Taylor RR, Jason LA, Torres A. Fatigue rating scales: an empirical comparison. Psychol Med 2000;30(4):849–856.
26. Whitehead L. The measurement of fatigue in chronic illness: a systematic review of unidimensional and multidimensional fatigue measures. J Pain Symptom Manage 2009;37(1):107–128.
27. Bennett RM, Friend R, Jones KD, Ward R, Han BK, Ross RL. The Revised Fibromyalgia Impact Questionnaire (FIQR): validation and psychometric properties. Arthritis Res. Ther. 2009;11(4):R120.
28. Chakrabarty S, Zoorob R. Fibromyalgia. Am Fam Physician 2007;76(2):247–254.
29. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, Haythornthwaite JA, Jensen MP, Kerns RD, Ader DN, Brandenburg N, Burke LB, Cella D, Chandler J, Cowan P, Dimitrova R, Dionne R, Hertz S, Jadad AR, Katz NP, Kehlet H, Kramer LD, Manning DC, McCormick C, McDermott MP, McQuay HJ, Patel S, Porter L, Quessy S, Rappaport BA, Rauschkolb C, Revicki DA, Rothman M, Schmader KE, Stacey BR, Stauffer JW, von Stein T, White RE, Witter J, Zavisic S. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008;9(2):105–121.
30. Seidenberg M, Haltiner A, Taylor MA, Hermann BB, Wyler A. Development and validation of a Multiple Ability Self-Report Questionnaire. J Clin Exp Neuropsychol 1994;16(1):93–104.
31. Farias ST, Mungas D, Jagust W. Degree of discrepancy between self and other-reported everyday functioning by cognitive status: dementia, mild cognitive impairment, and healthy elders. Int J Geriatr Psychiatry 2005;20(9):827–834.

32. Gowers WR. A Lecture on Lumbago: Its Lessons and Analogues: Delivered at the National Hospital for the Paralysed and Epileptic. Br Med J 1904;1(2246):117–121.
33. Smythe HA, Moldofsky H. Two contributions to understanding of the “fibrositis” syndrome. Bull Rheum Dis 1977;28(1):928–931.
34. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum. 1990;33(2):160–172.
35. Fillingim RB, Bruehl S, Dworkin RH, Dworkin SF, Loeser JD, Turk DC, Widerstrom-Noga E, Arnold L, Bennett R, Edwards RR, Freeman R, Gewandter J, Hertz S, Hochberg M, Krane E, Mantyh PW, Markman J, Neogi T, Ohrbach R, Paice JA, Porreca F, Rappaport BA, Smith SM, Smith TJ, Sullivan MD, Verne GN, Wasan AD, Wesselmann U. The ACTTION-American Pain Society Pain Taxonomy (AAPT): an evidence-based and multidimensional approach to classifying chronic pain conditions. J Pain 2014;15(3):241–249.
36. Clauw D. Time to Stop the Fibromyalgia Criteria Wars and Refocus on Identifying and Treating Individuals With This Type of Pain Earlier in Their Illness. Arthritis Care Res (Hoboken) 2021;73(5):613–616.
37. Goldenberg DL. Diagnosing Fibromyalgia as a Disease, an Illness, a State, or a Trait? Arthritis Care Res (Hoboken) 2019;71(3):334–336.
38. Perrot S, Dickenson AH, Bennett RM. Fibromyalgia: harmonizing science with clinical practice considerations. Pain Pract 2008;8(3):177–189.
39. Clauw DJ. Fibromyalgia: update on mechanisms and management. J Clin Rheumatol 2007;13(2):102–109.
40. Fitzcharles M-A, Boulos P. Inaccuracy in the diagnosis of fibromyalgia syndrome: analysis of referrals. Rheumatology (Oxford) 2003;42(2):263–267.
41. Wolfe F, Walitt BT, Häuser W. What is fibromyalgia, how is it diagnosed, and what does it really mean? Arthritis Care Res (Hoboken) 2014;66(7):969–971.
42. Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum. 2002;46(5):1333–1343.
43. Desmeules JA, Cedraschi C, Rapiti E, Baumgartner E, Finckh A, Cohen P, Dayer P, Vischer TL. Neurophysiologic evidence for a central sensitization in patients with fibromyalgia. Arthritis Rheum. 2003;48(5):1420–1429.
44. Harth M, Nielson WR. The fibromyalgia tender points: use them or lose them? A brief review of the controversy. J. Rheumatol. 2007;34(5):914–922.
45. Wolfe F, Clauw DJ, Fitzcharles M-A, Goldenberg DL, Katz RS, Mease P, Russell AS, Russell IJ, Winfield JB, Yunus MB. The American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia and Measurement of Symptom Severity. Arthritis Care & Research 2010;62(5):600–610.
46. Kim SM, Lee SH, Kim HR. Applying the ACR Preliminary Diagnostic Criteria in the Diagnosis and Assessment of Fibromyalgia. Korean J Pain 2012;25(3):173–182.
47. Ferrari R, Russell AS. A questionnaire using the modified 2010 American College of Rheumatology criteria for fibromyalgia: specificity and sensitivity in clinical practice. J. Rheumatol. 2013;40(9):1590–1595.
48. Marcus DA, Bernstein C, Albrecht KL. Brief, self-report fibromyalgia screener evaluated in a sample of chronic pain patients. Pain Med 2013;14(5):730–735.
49. Usui C, Hatta K, Aratani S, Yagishita N, Nishioka K, Kanazawa T, Itoh K, Yamano Y, Nakamura H, Nakajima T, Nishioka K. The Japanese version of the modified ACR preliminary diagnostic criteria for fibromyalgia and the fibromyalgia symptom scale: reliability and validity. Mod Rheumatol 2013;23(5):846–850.
50. Bennett RM, Friend R, Marcus D, Bernstein C, Han BK, Yachoui R, Deodhar A, Kaell A, Bonafede P, Chino A, Jones KD. Criteria for the diagnosis of fibromyalgia: validation of the modified 2010 preliminary American College of Rheumatology criteria and the development of alternative criteria. Arthritis Care Res (Hoboken) 2014;66(9):1364–1373.
51. Segura-Jiménez V, Aparicio VA, Álvarez-Gallardo IC, Soriano-Maldonado A, Estévez-López F, Delgado-Fernández M, Carbonell-Baeza A. Validation of the modified 2010 American College of Rheumatology diagnostic criteria for fibromyalgia in a Spanish population. Rheumatology (Oxford) 2014;53(10):1803–1811.
52. Carrillo-de-la-Peña MT, Triñanes Y, González-Villar A, Romero-Yuste S, Gómez-Perretta C, Arias M, Wolfe F. Convergence between the 1990 and 2010 ACR diagnostic criteria and validation of the Spanish version of the Fibromyalgia Survey Questionnaire (FSQ). Rheumatol. Int. 2015;35(1):141–151.
53. Jones GT, Atzeni F, Beasley M, Flüß E, Sarzi-Puttini P, Macfarlane GJ. The prevalence of fibromyalgia in the general population: a comparison of the American College of Rheumatology 1990, 2010, and modified 2010 classification criteria. Arthritis & Rheumatology (Hoboken, N.J.) 2015;67(2):568–575.
54. Staud R, Price DD, Robinson ME. The provisional diagnostic criteria for fibromyalgia: One step forward, two steps back: Comment on the article by Wolfe et al. Arthritis Care & Research 2010;62(11):1675–1676.

55. Toda K. Preliminary diagnostic criteria for fibromyalgia should be partially revised: Comment on the article by Wolfe et al. Arthritis Care & Research 2011;63(2):308–309.
56. Wolfe F, Clauw DJ, Fitzcharles M-A, Goldenberg DL, Häuser W, Katz RS, Mease P, Russell AS, Russell IJ, Winfield JB. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. J. Rheumatol. 2011;38(6):1113–1122.
57. Häuser W, Schmutzer G, Brähler E, Glaesmer H. A cluster within the continuum of biopsychosocial distress can be labeled "fibromyalgia syndrome"--evidence from a representative German population survey. J. Rheumatol. 2009;36(12):2806–2812.
58. Wolfe F, Brähler E, Hinz A, Häuser W. Fibromyalgia prevalence, somatic symptom reporting, and the dimensionality of polysymptomatic distress: results from a survey of the general population. Arthritis Care Res (Hoboken) 2013;65(5):777–785.
59. Egloff N, von Känel R, Müller V, Egle UT, Kokinogenis G, Lederbogen S, Durrer B, Stauber S. Implications of proposed fibromyalgia criteria across other functional pain syndromes. Scand. J. Rheumatol. 2015;44(5):416–424.
60. Wolfe F, Egloff N, Häuser W. Widespread Pain and Low Widespread Pain Index Scores among Fibromyalgia-positive Cases Assessed with the 2010/2011 Fibromyalgia Criteria. J. Rheumatol. 2016;43(9):1743–1748.
61. Wolfe F, Clauw DJ, Fitzcharles M-A, Goldenberg DL, Häuser W, Katz RL, Mease PJ, Russell AS, Russell IJ, Walitt B. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Semin. Arthritis Rheum. 2016;46(3):319–329.
62. Arnold LM, Bennett RM, Crofford LJ, Dean LE, Clauw DJ, Goldenberg DL, Fitzcharles M-A, Paiva ES, Staud R, Sarzi-Puttini P, Buskila D, Macfarlane GJ. AAPT Diagnostic Criteria for Fibromyalgia. J Pain 2019;20(6):611–628.
63. Wolfe F. Letter to the editor, "Fibromyalgia Criteria." J Pain 2019;20(6):739–740.
64. Häuser W, Brähler E, Ablin J, Wolfe F. Modified 2016 American College of Rheumatology Fibromyalgia Criteria, the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks-American Pain Society Pain Taxonomy, and the Prevalence of Fibromyalgia. Arthritis Care Res (Hoboken) 2021;73(5):617–625.
65. Queiroz LP. Worldwide epidemiology of fibromyalgia. Curr Pain Headache Rep 2013;17(8):356.
66. Neumann L, Buskila D. Epidemiology of fibromyalgia. Curr Pain Headache Rep 2003;7(5):362–368.
67. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum. 1995;38(1):19–28.
68. Vincent A, Lahr BD, Wolfe F, Clauw DJ, Whipple MO, Oh TH, Barton DL, St Sauver J. Prevalence of fibromyalgia: a population-based study in Olmsted County, Minnesota, utilizing the Rochester Epidemiology Project. Arthritis Care Res (Hoboken) 2013;65(5):786–792.
69. Nakamura I, Nishioka K, Usui C, Osada K, Ichibayashi H, Ishida M, Turk DC, Matsumoto Y, Nishioka K. An epidemiologic internet survey of fibromyalgia and chronic pain in Japan. Arthritis Care Res (Hoboken) 2014;66(7):1093–1101.
70. Amital D, Fostick L, Polliack ML, Segev S, Zohar J, Rubinow A, Amital H. Posttraumatic stress disorder, tenderness, and fibromyalgia syndrome: are they different entities? J Psychosom Res 2006;61(5):663–669.
71. Cohen H, Jotkowitz A, Buskila D, Pelles-Avraham S, Kaplan Z, Neumann L, Sperber AD. Post-traumatic stress disorder and other co-morbidities in a sample population of patients with irritable bowel syndrome. Eur. J. Intern. Med. 2006;17(8):567–571.
72. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann. Intern. Med. 1994;121(12):953–959.
73. Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Board on the Health of Select Populations, Institute of Medicine. Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. Washington (DC): National Academies Press (US); 2015. Available at: http://www.ncbi.nlm.nih.gov/books/NBK274235/. Accessed December 16, 2019.
74. Brandt LJ, Chey WD, Foxx-Orenstein AE, Schiller LR, Schoenfeld PS, Spiegel BM, Talley NJ, Quigley EMM. An evidence-based position statement on the management of irritable bowel syndrome. Am. J. Gastroenterol. 2009;104 Suppl 1:S1-35.
75. Hanno PM, Burks DA, Clemens JQ, Dmochowski RR, Erickson D, Fitzgerald MP, Forrest JB, Gordon B, Gray M, Mayer RD, Newman D, Nyberg L Jr, Payne CK, Wesselmann U, Faraday MM. AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. J. Urol. 2011;185(6):2162–2170.
76. Abeles AM, Pillinger MH, Solitar BM, Abeles M. Narrative review: the pathophysiology of fibromyalgia. Ann. Intern. Med. 2007;146(10):726–734.
77. Simms RW, Roy SH, Hrovat M, Anderson JJ, Skrinar G, LePoole SR, Zerbini CA, de Luca C, Jolesz F. Lack of association between fibromyalgia syndrome and abnormalities in muscle energy metabolism. Arthritis Rheum. 1994;37(6):794–800.

78. Häkkinen A, Häkkinen K, Hannonen P, Alen M. Force production capacity and acute neuromuscular responses to fatiguing loading in women with fibromyalgia are not different from those of healthy women. J. Rheumatol. 2000;27(5):1277–1282.
79. Lund E, Kendall SA, Janerot-Sjøberg B, Bengtsson A. Muscle metabolism in fibromyalgia studied by P-31 magnetic resonance spectroscopy during aerobic and anaerobic exercise. Scand. J. Rheumatol. 2003;32(3):138–145.
80. Yunus MB. Central sensitivity syndromes: a new paradigm and group nosology for fibromyalgia and overlapping conditions, and the related issue of disease versus illness. Semin. Arthritis Rheum. 2008;37(6):339–352.
81. Suzuki R, Rygh LJ, Dickenson AH. Bad news from the brain: descending 5-HT pathways that control spinal pain processing. Trends Pharmacol. Sci. 2004;25(12):613–617.
82. Cagnie B, Coppieters I, Denecker S, Six J, Danneels L, Meeus M. Central sensitization in fibromyalgia? A systematic review on structural and functional brain MRI. Semin. Arthritis Rheum. 2014;44(1):68–75.
83. Truini A, Tinelli E, Gerardi MC, Calistri V, Iannuccelli C, La Cesa S, Tarsitani L, Mainero C, Sarzi-Puttini P, Cruccu G, Caramia F, Di Franco M. Abnormal resting state functional connectivity of the periaqueductal grey in patients with fibromyalgia. Clin. Exp. Rheumatol. 2016;34(2 Suppl 96):S129-133.
84. Fallon N, Chiu Y, Nurmikko T, Stancak A. Functional Connectivity with the Default Mode Network Is Altered in Fibromyalgia Patients. PLoS ONE 2016;11(7):e0159198.
85. Kaplan CM, Schrepf A, Vatansever D, Larkin TE, Mawla I, Ichesco E, Kochlefl L, Harte SE, Clauw DJ, Mashour GA, Harris RE. Functional and neurochemical disruptions of brain hub topology in chronic pain. Pain 2019;160(4):973–983.
86. Martucci KT, Weber KA, Mackey SC. Altered Cervical Spinal Cord Resting-State Activity in Fibromyalgia. Arthritis & Rheumatology (Hoboken, N.J.) 2019;71(3):441–450.
87. Schweinhardt P, Sauro KM, Bushnell MC. Fibromyalgia: A Disorder of the Brain? Neuroscientist 2008. doi:10.1177/1073858407312521.
88. Staud R, Godfrey MM, Robinson ME. Fibromyalgia Patients Are Not Only Hypersensitive to Painful Stimuli But Also to Acoustic Stimuli. J Pain 2021;22(8):914–925.
89. Clauw DJ, Crofford LJ. Chronic widespread pain and fibromyalgia: what we know, and what we need to know. Best Pract Res Clin Rheumatol 2003;17(4):685–701.
90. Salemi S, Aeschlimann A, Wollina U, Gay RE, Michel BA, Gay S, Sprott H. Up-regulation of delta-opioid receptors and kappa-opioid receptors in the skin of fibromyalgia patients. Arthritis Rheum. 2007;56(7):2464–2466.
91. Harris RE, Clauw DJ, Scott DJ, McLean SA, Gracely RH, Zubieta J-K. Decreased central mu-opioid receptor availability in fibromyalgia. J. Neurosci. 2007;27(37):10000–10006.
92. Watkins LR, Hutchinson MR, Rice KC, Maier SF. The “toll” of opioid-induced glial activation: improving the clinical efficacy of opioids by targeting glia. Trends Pharmacol. Sci. 2009;30(11):581–591.
93. Mhalla A, de Andrade DC, Baudic S, Perrot S, Bouhassira D. Alteration of cortical excitability in patients with fibromyalgia. Pain 2010;149(3):495–500.
94. Foerster BR, Petrou M, Edden RAE, Sundgren PC, Schmidt-Wilcke T, Lowe SE, Harte SE, Clauw DJ, Harris RE. Reduced insular γ-aminobutyric acid in fibromyalgia. Arthritis Rheum. 2012;64(2):579–583.
95. Harris RE, Sundgren PC, Craig AD, Kirshenbaum E, Sen A, Napadow V, Clauw DJ. Elevated insular glutamate in fibromyalgia is associated with experimental pain. Arthritis Rheum. 2009;60(10):3146–3152.
96. Valdés M, Collado A, Bargalló N, Vázquez M, Rami L, Gómez E, Salamero M. Increased glutamate/glutamine compounds in the brains of patients with fibromyalgia: a magnetic resonance spectroscopy study. Arthritis Rheum. 2010;62(6):1829–1836.
97. Haas L, Portela LVC, Böhmer AE, Oses JP, Lara DR. Increased plasma levels of brain derived neurotrophic factor (BDNF) in patients with fibromyalgia. Neurochem. Res. 2010;35(5):830–834.
98. O’Mahony LF, Srivastava A, Mehta P, Ciurtin C. Is fibromyalgia associated with a unique cytokine profile? A systematic review and meta-analysis. Rheumatology (Oxford) 2021;60(6):2602–2614.
99. Uçeyler N, Häuser W, Sommer C. Systematic review with meta-analysis: cytokines in fibromyalgia syndrome. BMC Musculoskelet Disord 2011;12:245.
100. Salemi S, Rethage J, Wollina U, Michel BA, Gay RE, Gay S, Sprott H. Detection of interleukin 1beta (IL-1beta), IL-6, and tumor necrosis factor-alpha in skin of patients with fibromyalgia. J. Rheumatol. 2003;30(1):146–150.
101. Üçeyler N, Valenza R, Stock M, Schedel R, Sprotte G, Sommer C. Reduced levels of antiinflammatory cytokines in patients with chronic widespread pain. Arthritis & Rheumatism 2006;54(8):2656–2664.
102. Sturgill J, McGee E, Menzies V. Unique cytokine signature in the plasma of patients with fibromyalgia. J Immunol Res 2014;2014:938576.
103. Sommer C, Kress M. Recent findings on how proinflammatory cytokines cause pain: peripheral mechanisms in inflammatory and neuropathic hyperalgesia. Neurosci. Lett. 2004;361(1–3):184–187.
104. Staud R. Fibromyalgia pain: do we know the source? Curr Opin Rheumatol 2004;16(2):157–163.

105. Tsigos C, Chrousos GP. Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. J Psychosom Res 2002;53(4):865–871.
106. Mastorakos G, Pavlatou M, Diamanti-Kandarakis E, Chrousos GP. Exercise and the stress system. Hormones (Athens) 2005;4(2):73–89.
107. Beiner E, Lucas V, Reichert J, Buhai D-V, Jesinghaus M, Vock S, Drusko A, Baumeister D, Eich W, Friederich H-C, Tesarz J. Stress biomarkers in individuals with fibromyalgia syndrome: a systematic review with meta-analysis. Pain 2023;164(7):1416–1427.
108. Crofford LJ, Young EA, Engleberg NC, Korszun A, Brucksch CB, McClure LA, Brown MB, Demitrack MA. Basal circadian and pulsatile ACTH and cortisol secretion in patients with fibromyalgia and/or chronic fatigue syndrome. Brain Behav. Immun. 2004;18(4):314–325.
109. Wingenfeld K, Heim C, Schmidt I, Wagner D, Meinlschmidt G, Hellhammer DH. HPA axis reactivity and lymphocyte glucocorticoid sensitivity in fibromyalgia syndrome and chronic pelvic pain. Psychosom Med 2008;70(1):65–72.
110. Crofford LJ, Pillemer SR, Kalogeras KT, Cash JM, Michelson D, Kling MA, Sternberg EM, Gold PW, Chrousos GP, Wilder RL. Hypothalamic-pituitary-adrenal axis perturbations in patients with fibromyalgia. Arthritis Rheum. 1994;37(11):1583–1592.
111. Wingenfeld K, Wagner D, Schmidt I, Meinlschmidt G, Hellhammer DH, Heim C. The low-dose dexamethasone suppression test in fibromyalgia. J Psychosom Res 2007;62(1):85–91.
112. Jones KD, Deodhar P, Lorentzen A, Bennett RM, Deodhar AA. Growth hormone perturbations in fibromyalgia: a review. Semin. Arthritis Rheum. 2007;36(6):357–379.
113. Ablin J, Neumann L, Buskila D. Pathogenesis of fibromyalgia - a review. Joint Bone Spine 2008;75(3):273–279.
114. Riva R, Mork PJ, Westgaard RH, Okkenhaug Johansen T, Lundberg U. Catecholamines and heart rate in female fibromyalgia patients. J Psychosom Res 2012;72(1):51–57.
115. Kadetoff D, Kosek E. Evidence of reduced sympatho-adrenal and hypothalamic-pituitary activity during static muscular work in patients with fibromyalgia. J Rehabil Med 2010;42(8):765–772.
116. Lerma C, Martinez A, Ruiz N, Vargas A, Infante O, Martinez-Lavin M. Nocturnal heart rate variability parameters as potential fibromyalgia biomarker: correlation with symptoms severity. Arthritis Res. Ther. 2011;13(6):R185.
117. Cohen H, Neumann L, Shore M, Amir M, Cassuto Y, Buskila D. Autonomic dysfunction in patients with fibromyalgia: application of power spectral analysis of heart rate variability. Semin. Arthritis Rheum. 2000;29(4):217–227.
118. Cohen H, Neumann L, Alhosshle A, Kotler M, Abu-Shakra M, Buskila D. Abnormal sympathovagal balance in men with fibromyalgia. J. Rheumatol. 2001;28(3):581–589.
119. Torpy DJ, Papanicolaou DA, Lotsikas AJ, Wilder RL, Chrousos GP, Pillemer SR. Responses of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis to interleukin-6: a pilot study in fibromyalgia. Arthritis Rheum. 2000;43(4):872–880.
120. Maekawa K, Twe C, Lotaif A, Chiappelli F, Clark GT. Function of beta-adrenergic receptors on mononuclear cells in female patients with fibromyalgia. J. Rheumatol. 2003;30(2):364–368.
121. Giesecke T, Gracely RH, Williams DA, Geisser ME, Petzke FW, Clauw DJ. The relationship between depression, clinical pain, and experimental pain in a chronic pain cohort. Arthritis Rheum. 2005;52(5):1577–1584.
122. Lee YH, Choi SJ, Ji JD, Song GG. Candidate gene studies of fibromyalgia: a systematic review and meta-analysis. Rheumatol Int 2012;32(2):417–426.
123. Smith SB, Maixner DW, Fillingim RB, Slade G, Gracely RH, Ambrose K, Zaykin DV, Hyde C, John S, Tan K, Maixner W, Diatchenko L. Large candidate gene association study reveals genetic risk factors and therapeutic targets for fibromyalgia. Arthritis Rheum 2012;64(2):584–593.
124. Arnold LM, Fan J, Russell IJ, Yunus MB, Khan MA, Kushner I, Olson JM, Iyengar SK. The fibromyalgia family study: a genome-wide linkage scan study. Arthritis Rheum 2013;65(4):1122–1128.
125. Docampo E, Escaramís G, Gratacòs M, Villatoro S, Puig A, Kogevinas M, Collado A, Carbonell J, Rivera J, Vidal J, Alegre J, Estivill X, Rabionet R. Genome-wide analysis of single nucleotide polymorphisms and copy number variants in fibromyalgia suggest a role for the central nervous system. Pain 2014;155(6):1102–1109.
126. Dutta D, Brummett CM, Moser SE, Fritsche LG, Tsodikov A, Lee S, Clauw DJ, Scott LJ. Heritability of the Fibromyalgia Phenotype Varies by Age. Arthritis Rheumatol 2020;72(5):815–823.
127. Offenbaecher M, Bondy B, de Jonge S, Glatzeder K, Krüger M, Schoeps P, Ackenheil M. Possible association of fibromyalgia with a polymorphism in the serotonin transporter gene regulatory region. Arthritis Rheum. 1999;42(11):2482–2488.
128. Cohen H, Buskila D, Neumann L, Ebstein RP. Confirmation of an association between fibromyalgia and serotonin transporter promoter region (5- HTTLPR) polymorphism, and relationship to anxiety-related personality traits. Arthritis Rheum. 2002;46(3):845–847.
129. Gursoy S. Absence of association of the serotonin transporter gene polymorphism with the mentally healthy

subset of fibromyalgia patients. Clin. Rheumatol. 2002;21(3):194–197.
130. Buskila D, Dan B, Cohen H, Hagit C, Neumann L, Lily N, Ebstein RP. An association between fibromyalgia and the dopamine D4 receptor exon III repeat polymorphism and relationship to novelty seeking personality traits. Mol. Psychiatry 2004;9(8):730–731.
131. Gürsoy S, Erdal E, Herken H, Madenci E, Alaşehirli B, Erdal N. Significance of catechol-O-methyltransferase gene polymorphism in fibromyalgia syndrome. Rheumatol. Int. 2003;23(3):104–107.
132. Zhang L, Zhu J, Chen Y, Zhao J. Meta-analysis reveals a lack of association between a common catechol-O-methyltransferase (COMT) polymorphism val^{158}met and fibromyalgia. Int J Clin Exp Pathol 2014;7(12):8489–8497.
133. Finan PH, Zautra AJ, Davis MC, Lemery-Chalfant K, Covault J, Tennen H. Genetic influences on the dynamics of pain and affect in fibromyalgia. Health Psychol 2010;29(2):134–142.
134. Solak Ö, Erdoğan MÖ, Yıldız H, Ulaşlı AM, Yaman F, Terzi ESA, Ulu S, Dündar Ü, Solak M. Assessment of opioid receptor μ1 gene A118G polymorphism and its association with pain intensity in patients with fibromyalgia. Rheumatol. Int. 2014;34(9):1257–1261.
135. Vargas-Alarcón G, Fragoso J-M, Cruz-Robles D, Vargas A, Martinez A, Lao-Villadóniga J-I, García-Fructuoso F, Vallejo M, Martínez-Lavín M. Association of adrenergic receptor gene polymorphisms with different fibromyalgia syndrome domains. Arthritis Rheum. 2009;60(7):2169–2173.
136. Üçeyler N, Zeller D, Kahn A-K, Kewenig S, Kittel-Schneider S, Schmid A, Casanova-Molla J, Reiners K, Sommer C. Small fibre pathology in patients with fibromyalgia syndrome. Brain 2013;136(Pt 6):1857–1867.
137. Giannoccaro MP, Donadio V, Incensi A, Avoni P, Liguori R. Small nerve fiber involvement in patients referred for fibromyalgia. Muscle Nerve 2014;49(5):757–759.
138. Grayston R, Czanner G, Elhadd K, Goebel A, Frank B, Üçeyler N, Malik RA, Alam U. A systematic review and meta-analysis of the prevalence of small fiber pathology in fibromyalgia: Implications for a new paradigm in fibromyalgia etiopathogenesis. Semin Arthritis Rheum 2019;48(5):933–940.
139. Clauw DJ, Chrousos GP. Chronic pain and fatigue syndromes: overlapping clinical and neuroendocrine features and potential pathogenic mechanisms. Neuroimmunomodulation 1997;4(3):134–153.
140. Buskila D, Atzeni F, Sarzi-Puttini P. Etiology of fibromyalgia: the possible role of infection and vaccination. Autoimmun Rev 2008;8(1):41–43.
141. Buskila D, Neumann L, Vaisberg G, Alkalay D, Wolfe F. Increased rates of fibromyalgia following cervical spine injury. A controlled study of 161 cases of traumatic injury. Arthritis Rheum. 1997;40(3):446–452.
142. Wynne-Jones G, Jones GT, Wiles NJ, Silman AJ, Macfarlane GJ. Predicting new onset of widespread pain following a motor vehicle collision. J. Rheumatol. 2006;33(5):968–974.
143. Peterson EL. Fibromyalgia--management of a misunderstood disorder. J Am Acad Nurse Pract 2007;19(7):341–348.
144. Sarzi-Puttini P, Buskila D, Carrabba M, Doria A, Atzeni F. Treatment strategy in fibromyalgia syndrome: where are we now? Semin. Arthritis Rheum. 2008;37(6):353–365.
145. Macfarlane GJ, Kronisch C, Dean LE, Atzeni F, Häuser W, Fluß E, Choy E, Kosek E, Amris K, Branco J, Dincer F, Leino-Arjas P, Longley K, McCarthy GM, Makri S, Perrot S, Sarzi-Puttini P, Taylor A, Jones GT. EULAR revised recommendations for the management of fibromyalgia. Ann. Rheum. Dis. 2017;76(2):318–328.
146. Burckhardt CS, Bjelle A. Education programmes for fibromyalgia patients: description and evaluation. Baillieres Clin Rheumatol 1994;8(4):935–955.
147. White KP, Nielson WR, Harth M, Ostbye T, Speechley M. Does the label “fibromyalgia” alter health status, function, and health service utilization? A prospective, within-group comparison in a community cohort of adults with chronic widespread pain. Arthritis Rheum. 2002;47(3):260–265.
148. Ehrlich GE. Pain is real; fibromyalgia isn’t. J. Rheumatol. 2003;30(8):1666–1667.
149. Atzeni F, Alciati A, Salaffi F, Di Carlo M, Bazzichi L, Govoni M, Biasi G, Di Franco M, Mozzani F, Gremese E, Dagna L, Batticciotto A, Fischetti F, Giacomelli R, Guiducci S, Guggino G, Bentivegna M, Gerli R, Salvarani C, Bajocchi G, Ghini M, Iannone F, Giorgi V, Farah S, Bonazza S, Barbagli S, Gioia C, Marino NG, Capacci A, Cavalli G, Cappelli A, Carubbi F, Nacci F, Riccucci I, Cutolo M, Sinigaglia L, Sarzi-Puttini P. The association between body mass index and fibromyalgia severity: data from a cross-sectional survey of 2339 patients. Rheumatol Adv Pract 2021;5(1):rkab015.
150. Busch AJ, Webber SC, Brachaniec M, Bidonde J, Bello-Haas VD, Danyliw AD, Overend TJ, Richards RS, Sawant A, Schachter CL. Exercise therapy for fibromyalgia. Curr Pain Headache Rep 2011;15(5):358–367.
151. McDowell CP, Cook DB, Herring MP. The Effects of Exercise Training on Anxiety in Fibromyalgia Patients: A Meta-analysis. Med Sci Sports Exerc 2017;49(9):1868–1876.
152. Andrade A, Dominski FH, Sieczkowska SM. What we already know about the effects of exercise in patients with fibromyalgia: An umbrella review. Semin Arthritis Rheum 2020;50(6):1465–1480.

153. Estévez-López F, Maestre-Cascales C, Russell D, Álvarez-Gallardo IC, Rodriguez-Ayllon M, Hughes CM, Davison GW, Sañudo B, McVeigh JG. Effectiveness of Exercise on Fatigue and Sleep Quality in Fibromyalgia: A Systematic Review and Meta-analysis of Randomized Trials. Arch Phys Med Rehabil 2021;102(4):752–761.
154. Bidonde J, Busch AJ, Webber SC, Schachter CL, Danyliw A, Overend TJ, Richards RS, Rader T. Aquatic exercise training for fibromyalgia. Cochrane Database Syst Rev 2014;(10):CD011336.
155. Salaffi F, Di Carlo M, Farah S, Marotto D, Giorgi V, Sarzi-Puttini P. Exercise therapy in fibromyalgia patients: comparison of a web-based intervention with usual care. Clin Exp Rheumatol 2020;38 Suppl 123(1):86–93.
156. Bernardy K, Klose P, Busch AJ, Choy EHS, Häuser W. Cognitive behavioural therapies for fibromyalgia. Cochrane Database Syst Rev 2013;(9):CD009796.
157. Mascarenhas RO, Souza MB, Oliveira MX, Lacerda AC, Mendonça VA, Henschke N, Oliveira VC. Association of Therapies With Reduced Pain and Improved Quality of Life in Patients With Fibromyalgia: A Systematic Review and Meta-analysis. JAMA Intern Med 2021;181(1):104–112.
158. Jensen KB, Kosek E, Wicksell R, Kemani M, Olsson G, Merle JV, Kadetoff D, Ingvar M. Cognitive Behavioral Therapy increases pain-evoked activation of the prefrontal cortex in patients with fibromyalgia. Pain 2012;153(7):1495–1503.
159. Lazaridou A, Kim J, Cahalan CM, Loggia ML, Franceschelli O, Berna C, Schur P, Napadow V, Edwards RR. Effects of Cognitive-Behavioral Therapy (CBT) on Brain Connectivity Supporting Catastrophizing in Fibromyalgia. Clin J Pain 2017;33(3):215–221.
160. Deare JC, Zheng Z, Xue CCL, Liu JP, Shang J, Scott SW, Littlejohn G. Acupuncture for treating fibromyalgia. Cochrane Database Syst Rev 2013;(5):CD007070.
161. Langhorst J, Klose P, Dobos GJ, Bernardy K, Häuser W. Efficacy and safety of meditative movement therapies in fibromyalgia syndrome: a systematic review and meta-analysis of randomized controlled trials. Rheumatol. Int. 2013;33(1):193–207.
162. Langhorst J, Musial F, Klose P, Häuser W. Efficacy of hydrotherapy in fibromyalgia syndrome--a meta-analysis of randomized controlled clinical trials. Rheumatology (Oxford) 2009;48(9):1155–1159.
163. Schmidt-Wilcke T, Clauw DJ. Fibromyalgia: from pathophysiology to therapy. Nat Rev Rheumatol 2011;7(9):518–527.
164. Boomershine CS, Crofford LJ. A symptom-based approach to pharmacologic management of fibromyalgia. Nat Rev Rheumatol 2009;5(4):191–199.
165. Goldenberg DL BC. MAnagement of fibromyalgia syndrome. JAMA 2004;292(19):2388–2395.
166. Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, Blazina I, Dana T, Bougatsos C, Deyo RA. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. Ann Intern Med 2015;162(4):276–286.
167. Hwang J-M, Lee B-J, Oh TH, Park D, Kim C-H. Association between initial opioid use and response to a brief interdisciplinary treatment program in fibromyalgia. Medicine (Baltimore) 2019;98(1):e13913.
168. Curtis AF, Miller MB, Rathinakumar H, Robinson M, Staud R, Berry RB, McCrae CS. Opioid use, pain intensity, age, and sleep architecture in patients with fibromyalgia and insomnia. Pain 2019;160(9):2086–2092.
169. Abeles M, Solitar BM, Pillinger MH, Abeles AM. Update on fibromyalgia therapy. Am. J. Med. 2008;121(7):555–561.
170. Liu Y, Qian C, Yang M. Treatment Patterns Associated with ACR-Recommended Medications in the Management of Fibromyalgia in the United States. J Manag Care Spec Pharm 2016;22(3):263–271.
171. Tofferi JK, Jackson JL, O'Malley PG. Treatment of fibromyalgia with cyclobenzaprine: A meta-analysis. Arthritis Rheum. 2004;51(1):9–13.
172. O'Malley PG, Balden E, Tomkins G, Santoro J, Kroenke K, Jackson JL. Treatment of fibromyalgia with antidepressants: a meta-analysis. J Gen Intern Med 2000;15(9):659–666.
173. Arnold LM, Keck PE Jr, Welge JA. Antidepressant treatment of fibromyalgia. A meta-analysis and review. Psychosomatics 2000;41(2):104–113.
174. Carette S, Bell MJ, Reynolds WJ, Haraoui B, McCain GA, Bykerk VP, Edworthy SM, Baron M, Koehler BE, Fam AG. Comparison of amitriptyline, cyclobenzaprine, and placebo in the treatment of fibromyalgia. A randomized, double-blind clinical trial. Arthritis Rheum. 1994;37(1):32–40.
175. Carette S, Oakson G, Guimont C, Steriade M. Sleep electroencephalography and the clinical response to amitriptyline in patients with fibromyalgia. Arthritis Rheum. 1995;38(9):1211–1217.
176. Uçeyler N, Häuser W, Sommer C. A systematic review on the effectiveness of treatment with antidepressants in fibromyalgia syndrome. Arthritis Rheum. 2008;59(9):1279–1298.
177. Häuser W, Petzke F, Üçeyler N, Sommer C. Comparative efficacy and acceptability of amitriptyline, duloxetine and milnacipran in fibromyalgia syndrome: a systematic review with meta-analysis. Rheumatology (Oxford) 2011;50(3):532–543.
178. Alberti FF, Becker MW, Blatt CR, Ziegelmann PK, da Silva Dal Pizzol T, Pilger D. Comparative efficacy of amitriptyline, duloxetine and pregabalin for treating fibromyalgia in

adults: an overview with network meta-analysis. Clin Rheumatol 2022;41(7):1965–1978.
179. Goldenberg D, Mayskiy M, Mossey C, Ruthazer R, Schmid C. A randomized, double-blind crossover trial of fluoxetine and amitriptyline in the treatment of fibromyalgia. Arthritis Rheum. 1996;39(11):1852–1859.
180. Moldofsky H, Harris HW, Archambault WT, Kwong T, Lederman S. Effects of bedtime very low dose cyclobenzaprine on symptoms and sleep physiology in patients with fibromyalgia syndrome: a double-blind randomized placebo-controlled study. J. Rheumatol. 2011;38(12):2653–2663.
181. Arnold LM, Gendreau RM, Palmer RH, Gendreau JF, Wang Y. Efficacy and safety of milnacipran 100 mg/day in patients with fibromyalgia: results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum. 2010;62(9):2745–2756.
182. Branco JC, Zachrisson O, Perrot S, Mainguy Y. A European multicenter randomized double-blind placebo-controlled monotherapy clinical trial of milnacipran in treatment of fibromyalgia. J. Rheumatol. 2010;37(4):851–859.
183. Sayar K, Aksu G, Ak I, Tosun M. Venlafaxine treatment of fibromyalgia. Ann Pharmacother 2003;37(11):1561–1565.
184. Lunn MPT, Hughes RAC, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. Cochrane Database Syst Rev 2014;1:CD007115.
185. Arnold LM, Zhang S, Pangallo BA. Efficacy and safety of duloxetine 30 mg/d in patients with fibromyalgia: a randomized, double-blind, placebo-controlled study. Clin J Pain 2012;28(9):775–781.
186. Russell IJ, Mease PJ, Smith TR, Kajdasz DK, Wohlreich MM, Detke MJ, Walker DJ, Chappell AS, Arnold LM. Efficacy and safety of duloxetine for treatment of fibromyalgia in patients with or without major depressive disorder: Results from a 6-month, randomized, double-blind, placebo-controlled, fixed-dose trial. Pain 2008;136(3):432–444.
187. Welsch P, Üçeyler N, Klose P, Walitt B, Häuser W. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia. Cochrane Database Syst Rev 2018;2:CD010292.
188. Häuser W, Petzke F, Sommer C. Comparative efficacy and harms of duloxetine, milnacipran, and pregabalin in fibromyalgia syndrome. J Pain 2010;11(6):505–521.
189. Schmidt-Wilcke T, Ichesco E, Hampson JP, Kairys A, Peltier S, Harte S, Clauw DJ, Harris RE. Resting state connectivity correlates with drug and placebo response in fibromyalgia patients. Neuroimage Clin 2014;6:252–261.
190. Häuser W, Bernardy K, Uçeyler N, Sommer C. Treatment of fibromyalgia syndrome with antidepressants: a meta-analysis. JAMA 2009;301(2):198–209.
191. Derry S, Cording M, Wiffen PJ, Law S, Phillips T, Moore RA. Pregabalin for pain in fibromyalgia in adults. Cochrane Database Syst Rev 2016;9(9):CD011790.
192. Arnold LM, Choy E, Clauw DJ, Oka H, Whalen E, Semel D, Pauer L, Knapp L. An evidence-based review of pregabalin for the treatment of fibromyalgia. Curr Med Res Opin 2018;34(8):1397–1409.
193. Arnold LM, Emir B, Pauer L, Resnick M, Clair A. Time to improvement of pain and sleep quality in clinical trials of pregabalin for the treatment of fibromyalgia. Pain Med 2015;16(1):176–185.
194. Harris RE, Napadow V, Huggins JP, Pauer L, Kim J, Hampson J, Sundgren PC, Foerster B, Petrou M, Schmidt-Wilcke T, Clauw DJ. Pregabalin rectifies aberrant brain chemistry, connectivity, and functional response in chronic pain patients. Anesthesiology 2013;119(6):1453–1464.
195. Ichesco E, Peltier SJ, Mawla I, Harper DE, Pauer L, Harte SE, Clauw DJ, Harris RE. Prediction of Differential Pharmacologic Response in Chronic Pain Using Functional Neuroimaging Biomarkers and a Support Vector Machine Algorithm: An Exploratory Study. Arthritis Rheumatol 2021;73(11):2127–2137.
196. Arnold LM, Goldenberg DL, Stanford SB, Lalonde JK, Sandhu HS, Keck PE Jr, Welge JA, Bishop F, Stanford KE, Hess EV, Hudson JI. Gabapentin in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled, multicenter trial. Arthritis Rheum. 2007;56(4):1336–1344.
197. Cooper TE, Derry S, Wiffen PJ, Moore RA. Gabapentin for fibromyalgia pain in adults. Cochrane Database Syst Rev 2017;1(1):CD012188.
198. Perrot S, Russell IJ. More ubiquitous effects from non-pharmacologic than from pharmacologic treatments for fibromyalgia syndrome: a meta-analysis examining six core symptoms. Eur J Pain 2014;18(8):1067–1080.
199. Roskell NS, Beard SM, Zhao Y, Le TK. A meta-analysis of pain response in the treatment of fibromyalgia. Pain Pract 2011;11(6):516–527.
200. MacLean AJB, Schwartz TL. Tramadol for the treatment of fibromyalgia. Expert Rev Neurother 2015;15(5):469–475.