Multidisciplinary approach to Fibromyalgia: What are we learning from updated evidence-based medicine?

Jiu-Haw Yin[1,2], Giia-Sheun Peng[1,2], Long-Sun Ro[3]

Abstract

Fibromyalgia (FM) is a disease characterized by amplified pain responses; here, hyperalgesia occurs in response to noxious stimuli, and allodynia occurs in response to non-noxious stimuli. The diagnosis of FM is often time consuming because it overlaps with psychosomatic symptoms. Indeed, most cases of FM are combined with other comorbidities, such as rheumatological diseases, mental disorders, or gastrointestinal disorders. The main symptoms of FM, which include pain, fatigue, and sleep disturbance, are poorly discriminatory and, thus, greatly increase the difficulty of diagnosis. The 2017 European League Against Rheumatism treatment guidelines of FM recommend that non-pharmacological therapies based on exercise should first be attempted after a diagnosis of FM. Although drug treatments appear to be effective, evidence supporting the use of this treatment modality is relatively weak. Obtaining a broad understanding of FM can help clinicians formulate individualized treatment to improve patient functions and quality of life.

Keywords: fibromyalgia, diagnostic criteria, non-pharmacological therapy.

Acta Neurol Taiwan 2022;31:134-144

Fibromyalgia (FM) is a disease characterized with amplified pain responses; here, hyperalgesia occurs in response to noxious stimuli, and allodynia occurs in response to non-noxious stimuli[(1)]. The diagnosis of FM is often delayed by an average of 5–7 years because the condition was previously considered an exclusion diagnosis and partially overlapped with depression accompanied by psychosomatic symptoms; moreover, a gray area between FM, rheumatoid arthritis (RA), trigeminal neuralgia, and other diseases has been noted[(2)]. The main symptoms of FM, including pain, fatigue, and sleep disturbance, are poorly discriminatory, which greatly increases the difficulty of diagnosis.

From the [1]Department of Neurology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan; [2]Division of Neurology, Department of Internal Medicine, Taipei Veterans General Hospital, Hsinchu Branch, Hsinchu County, Taiwan; [3]Department of Neurology, Chang-Gung Memorial Hospital Linkou Medical Center and College of Medicine, Chang-Gung University, Linkou, Taoyuan, Taiwan.

Received April 16, 2021.
Revised and Accepted April 21, 2021.

Correspondence to: Long-Sun Ro, MD, PhD. Department of Neurology, Chang-Gung Memorial Hospital Linkou Medical Center and College of Medicine, Chang-Gung University, Linkou, Taoyuan, Taiwan, No. 5, Fuxing St., Guishan Dist., Taoyuan City 333012, Taiwan.
E-mail: cgrols@adm.cgmh.org.tw

History of Fibromyalgia

Webster's Dictionary included the term "fibromyalgia" for the first time only in 1980; in fact, however, similar terms appeared earlier in the 16th century[3]. In 1592, French physician Baillou first referred to muscle pain and acute rheumatic fever as rheumatism. In the 18th century, rheumatism was further divided into articular rheumatism with joint deformation and muscular rheumatism without joint deformation. Prior to the 19th century, the descriptions of this type of pain generally involved local characteristics, such as tender points, trigger points, and muscle nodules. Beard proposed the

Table 1. Fibromyalgia Diagnostic Criteria—2016 ACR Revision

Criteria:

A patient satisfies modified 2016 fibromyalgia criteria if the following three conditions are met:

(1) Widespread pain index (WPI) ≥7 and symptom severity scale (SSS) score ≥5 OR WPI 4–6 and SSS score ≥9.

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

(3) Symptoms have been generally present 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? Scores will be between 0 and 19

Left upper region (region 1)	***Right upper region (region 2)***	***Axial region(region 5)***
Jaw, left*	Jaw, right*	Neck
Shoulder girdle, left	Shoulder girdle, right	Upper back
Upper arm, left	Upper arm, right	Lower back
Lower arm, left	Lower arm, right	Chest*
		Abdomen*
Left lower region (region 3)	***Right lower region (region 4)***	
Hip (buttock, trochanter), left	Hip (buttock, trochanter), right	
Upper leg, left	Upper leg, right	
Lower leg, left	Lower leg, right	

2) Symptom Severity Scale (SSS) score:

Fatigue

Waking unrefreshed

Cognitive symptoms

For the each of the three symptoms above, 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

The Symptom Severity Scale (SSS) score:

Refers to the sum of the severity scores of three symptoms (fatigue, waking unrefreshed, and cognitive symptoms) (0–9) plus the sum (0–3) of the number of the following symptoms the patient has been bothered by that occurred during the previous 6 months:

1) headaches (0–1)

2) pain or cramps in lower abdomen (0–1)

3) depression (0–1).

The final Symptom Severity Score is between 0 and 12.

The Fibromyalgia Severity Scale is the sum of the WPI and SSS.

* Not included in the generalized pain definition

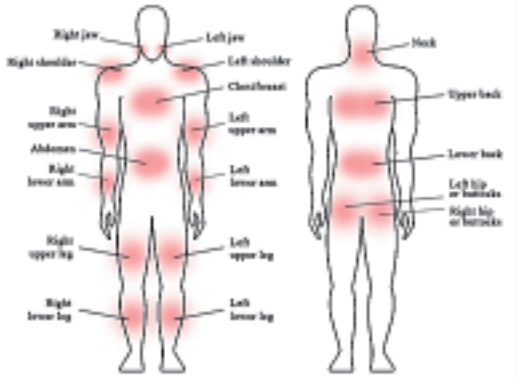
concept of neurasthenia in 1880, while Gower proposed the term fibrositis in 1904. These different terms provide new theories with which to interpret the disease. In 1976, American rheumatologist Kahler Hench named the disease "fibromyalgia," which implies that its cause is related more to pain than to inflammation. In 1981, Muhammad Yunus proposed diagnostic criteria with data support and found strong associations among tension-type headache, primary FM, primary menstrual pain, and irritable bowel syndrome (IBS). The 1990 American College of Rheumatology (ACR) diagnostic criteria formulated an updated description of FM and posited that the existence of other clinical diagnoses does not exclude the diagnosis of FM[3]. In 2000, the concept of central sensitization was proposed to provide a new explanation for FM and other diseases[4]. After several revisions, the ACR published the latest diagnostic criteria of FM in 2016, including pain in at least four quadrants of the body, symptoms lasting 3 months, and widespread pain index (WPI) ≥ 7 plus symptom severity scale (SSS) ≥ 5 or WPI 4–6 plus SSS ≥ 9 (Table 1, Figure 1). The greatest difference between this version and the 2010 version of the definition of FM is that the disease was originally diagnosed by exclusion; in the 2016 version, FM was not considered mutually exclusive with other diagnoses[5].

Prevalence and risk factors of fibromyalgia

The prevalence of FM based on the 2010/2011 ACR diagnostic criteria is approximately 2%–8%; the disease is known to affect more women than men and increase in prevalence with age. Besides age and gender, other risk factors include genetics, sleep disorders, low activity,

Widespread Pain Index
(1 point per area; score range: 0-19 points)

1) Please indicate if you have had pain or tenderness **over the past 7 days** in the areas shown below.
Check the areas in the diagram for each in which you have had pain or tenderness.



Symptom Severity
(score range: 0-12 points)

2) For each symptom listed below, use the following scale to indicate the severity of the symptom **over the past 7 days**.
- **No problem**
- **Slight or mild problem**: generally mild or intermittent
- **Moderate problem**: considerable problem; often present and/or at a moderate level
- **Severe problem**: continuous, life-disturbing problems

	No problem	Slight or mild problem	Moderate problem	Severe problem
Points	0	1	2	3
A. Fatigue	☐	☐	☐	☐
B. Trouble thinking or remembering	☐	☐	☐	☐
C. Waking up tired (unrefreshed)	☐	☐	☐	☐

3) During the **the previous 6 months** have you had any of the following symptoms?

Points	0	1
A. Pain or cramping in lower abdomen	☐ No	☐ Yes
B. Depression	☐ No	☐ Yes
C. Headache	☐ No	☐ Yes

(1) Widespread pain index (WPI) ≥7 and symptom severity scale (SSS) score ≥5 OR WPI 4–6 and SSS score ≥9.
(2) Generalized pain, defined as pain in at least 4 of 5 regions, must be present. Jaw, chest, and abdominal pain are not included in generalized pain definition.
(3) Symptoms have been generally present 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.

Figure 1. 2016 ACR clinical fibromyalgia diagnostic criteria

obesity, and the presence of other painful diseases[6]. Eighty percent of all cases of FM are combined with other comorbidities, such as other rheumatological diseases, mental disorders, or gastrointestinal disorders[7]. During differential diagnosis, FM must be physically differentiated from chronic fatigue syndrome, RA, and hypothyroidism, among other disorders; psychologically, it must be differentiated from depression, generalized anxiety disorder (GAD), and physical symptoms[8]. Therefore, the components of FM must be carefully considered if the patient has a history of chronic widespread pain, frequent headache, menstrual pain, temporomandibular joint problems, IBS, fatigue, or shoulder and neck pain[6].

Pathophysiology of fibromyalgia

The potential pathophysiological mechanisms of FM include central sensitization, impaired descending pain suppression pathway, abnormal neurotransmitters, and dysfunction of the hypothalamic–pituitary gland–adrenal (HPA) axis[9]. Sensory neurons in the dorsal root ganglia (DRG) of patients with FM release adenosine triphosphate (ATP) to activate satellite glial cells, which then secrete interleukin (IL) 1 beta, ATP, nerve growth factor, and other substances to sensitize sensory neurons. Resident T cells and macrophages in DRG release IL-1, IL-6, and tumor necrosis factor, thereby triggering more macrophages and T-cell recruitment. These two events affect the Na^+ and K^+ channels of sensory neurons, leading to neuronal hyperexcitability[10]. Presynaptic neurons in the dorsal horn of the spinal cord of FM patients release excessive substance P and excitatory amino acids. When post-synaptic neurons receive excessive information, calcium ions enter the cells and cause nitric oxide (NO) production, which simultaneously stimulates the pre- and post-synapses of neurons (Figure 2). Overstimulation triggers glial cells around the synapses to release NO, prostaglandins, and other substances, resulting in pain sensitization[11]. Under normal circumstances, pain inhibitory neurons release gamma-aminobutyric acid (GABA) and glycine at the synapses, which reduce the transmission of pain by activating GABA receptors and increasing K^+ currents. However, in patients with FM, the function of pain inhibition is decreased because of the activation of microglia[10]. At the genetic level, the risk of a person developing FM increases eightfold if a first-degree relative is diagnosed with FM; this observation may be related to the neurotransmitter-related gene mutations described above[12, 13].

Association between fibromyalgia and rheumatic diseases

FM can be categorized as primary FM without obvious pain cause and secondary FM with an exact pain source, such as osteoarthritis (OA) and immune disease[12, 13]. The symptoms of FM, including fatigue, myofascial pain, dry mouth, lower back, and pain, are highly reminiscent of RA, ankylosing spondylosis (AS), systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), and other diseases. Thus, whether to merge or perform differential diagnosis is an important consideration in the clinical setting. Studies demonstrate that 21% (range 4.9%–52.4%) of patients with RA actually have FM[14]. Up to 50% of all patients with RA have pain that persists even after receiving proper treatment and inflammation is relieved. Thus, the concept of FM–RA was developed[15, 16]. The prevalence of FM in patients with AS is approximately 12%–25%[17-19]. Patients with both AS and FM have higher disease activity and are mostly female[19, 20]. Neuropsychiatric lupus erythematosus manifesting as headache, cognitive impairment, and memory loss has been observed in some FM patients, which means immune abnormality may be a factor triggering central sensitization[21]. Raynaud's phenomenon, skin rash, fever, easy bruising, and hair loss are the main symptoms and signs of SLE; by comparison, muscle pain, weakness, cognitive problems, fatigue, and headache are more likely to be associated with FM[22]. The prevalence rate of FM in primary SS (pSS) is 14.6%, and fatigue, arthralgia, and systemic symptoms are highly likely to coexist in pSS–FM patients[23].

Association between fibromyalgia and psychiatric problems

Stress, emotions, and physical pain symptoms are often inseparable. Some patients demonstrate emotional disorders, such as GAD, major depressive disorder (MDD), or post-traumatic stress disorder, when under stress; others show physical symptoms, such as FM, lower back pain, or chronic generalized pain. Both populations tend to experience fatigue, sleep disorders, and cognitive

impairments[24]. The brain areas activated in the functional MRI of chronic widespread pain, anxiety, and depression are very similar, which suggests the possibility of comorbidities[25]. Some studies have shown that the lifetime prevalence rates of depressive and bipolar disorders among patients with FM are 65% and 21%, respectively[26, 27]. A study from the National Health Insurance Database in Taiwan confirmed these associations. Patients with FM have a significantly increased risk of developing subsequent depression (HR = 7.46, 95% CI = 6.77–8.22), and patients with depression have a significantly increased risk of developing subsequent FM (HR = 6.28, 95% CI = 5.67–6.96)[28]. In terms of genetics, FM shows greater associations with heredity than depression [29, 30]. Twin

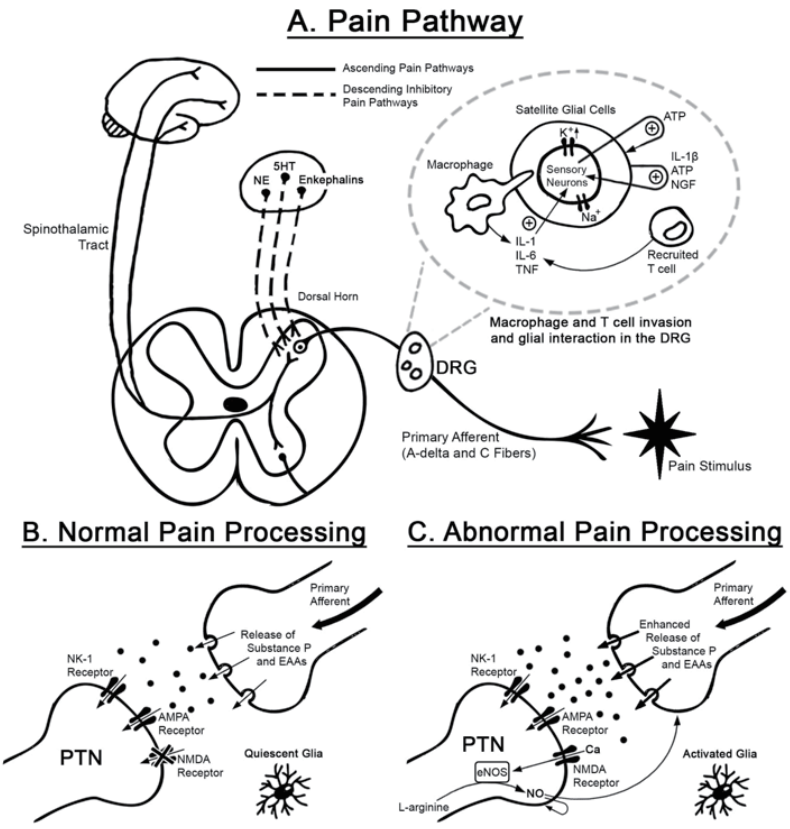


Figure 2. Pain regulation in FM patients. (A) In the classical model of acute pain, painful stimuli are transmitted from the periphery to the dorsal horn via primary afferent fibers and from the dorsal horn to the brain via the spinothalamic tract. Pain perception is modulated by the activation of descending inhibitory pathways and the release of neurotransmitters. The sensory neurons in the DRG of patients with FM release ATP to activate satellite glial cells. After activation, glial cells secrete IL-1β, ATP, NGF, and other substances to sensitize sensory neurons. Resident T cells and macrophages in the DRG release IL-1, IL-6, and TNF, thereby triggering more macrophages and T-cell recruitment. These two events affect the Na^+ and K^+ channels of sensory neurons, leading to neuronal hyperexcitability. (B) During normal pain processing, incoming afferent pain signals induce the dorsal horn to release substance P and EAAs, which bind to activate post-synaptic receptors on PTNs. Glia are present but quiescent. (C) In FM patients, presynaptic neurons in the dorsal horn of the spinal cord release excessive substance P and EAAs. When post-synaptic neurons receive excessive information, calcium ions enter the cells and cause NO production, which simultaneously stimulates the pre- and post-synapses of neurons.

DRG, dorsal root ganglia; ATP, adenosine triphosphate; IL-1β, interleukin 1 beta; NGF, nerve growth factor; EAAs, excitatory amino acids; PTNs, pain transmission neurons; 5-HT, serotonin; NE, norepinephrine; NMDA, N-methyl-D-aspartic acid; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NK-1, neurokinin; cNOS, constitutive nitric oxide synthase; NO, nitric oxide.

studies have found that unsubstantiated somatic distress in anxiety and depression is strongly correlated with genetic and environmental risks[30].

Patients with FM often complain of slow reaction, poor concentration, and memory. The term "fibro fog" has been included in the 2010 FM diagnostic criteria as a symptom that can affect life and work performance[31]. The mechanism of this symptom may be related to the HPA axis. Chronic pain or stress could activate the HPA axis, increase the secretion of cortisol, cause gray matter atrophy in the brain, and affect cognitive function[24]. A study employing near-infrared spectroscopy to measure the function of the frontal lobe found that the activation of the frontal lobe of FM patients is significantly lower than that of the control group during the verbal fluency test; this study also showed that the depression index (Beck Depression Inventory) and degree of prefrontal lobe activation are negatively correlated[32]. Aside from impaired cognitive function, the hypofunction of the frontal lobe of FM patients may also be related to central sensitization[33].

Association between GAD and Fibromyalgia

According to the diagnostic guidelines of DSM-5, GAD involves excessive anxiety, uncontrollable worrying emotions over multiple events or activities for at least 6 months, and meets at least three other manifestations, including restlessness, inattention, fatigue, sleep disturbance, and muscle tightness[34]. The course of GAD is chronic and often exacerbated by stress, which may be continuous or repetitive and last for over 10 years[35]. The factors affecting GAD include stressful life events, sensitivity to anxiety, negative impacts, female gender, and other comorbidities[35]. According to the Anxiety Research Project, which was jointly conducted by Harvard University and Brown University, the probability of recovery from GAD is 58% lower than that of MDD 73%. GAD combined with other anxiety or depression disorders greatly reduces the likelihood of recovery. When combined with major depression, for example, the recovery rate of GAD is reduced to half; when combined with panic disorder, the recovery rate is reduced to one-third[36]. A strong association between GAD and unexplained pain has been reported. According to a previous study, 61% of GAD patients seek medical attention for pain; in a Spanish study, up to 93.5% of all newly diagnosed GAD patients showed painful physical symptoms[37, 38]. A large study enrolling 94,516 participants indicated that patients with chronic fatigue syndrome, FM, and IBS are more likely to have mood or anxiety disorders than patients without functional physical symptoms[39]. Another study revealed that up to 74.8% of FM patients suffer from mental disorders[40]. These studies indicate that GAD and FM are very likely to exist at the same time; thus, the possibility of coexistent FM and GAD should not be ignored in clinical practice.

Non-pharmacological therapy of fibromyalgia

The 2017 European League Against Rheumatism (EULAR) treatment guidelines of FM recommend that non-pharmacological therapies based on exercise should be first attempted after a diagnosis of FM. If the condition is not completely relieved, personalized treatment, including psychotherapy for emotions, is recommended[41]. Severely disabled patients may be recommended a multi-professional team rehabilitation plan (Figure 3). Aerobic and intensive exercises in non-pharmacological therapy are the only items strongly recommended. Other approaches, including cognitive behavioral therapy (CBT), acupuncture, hydrotherapy, and meditation, are weakly recommended[41]. Studies have shown that simply establishing a diagnosis can improve FM patients' satisfaction with their health status because these patients' uncertainty decreases while their confidence increases after a diagnosis is established and treatment can be initiated. Therefore, detecting and treating this group of patients clinically is very important[42]. Exercise can be divided into aerobic exercise, strengthening exercise, stretching exercise, and other special exercises, such as Tai Chi and yoga; these exercises have been shown to relieve FM to some extent[43, 44]. Although no evidence supporting the best type of exercise is available, the most suitable exercise may be selected according to the patient's individual situation so that it can be developed into a daily habit[45]. CBT is generally considered to be helpful for FM; although it cannot relieve pain, it can help patients understand the nature of pain and allow them to accept and address the symptom[46]. Some countries have developed self-directed CBT tools, such as allowing patients to interact with smartphones and chatbots, to achieve

the goals of education and psychological support[47]. Probiotic therapy is also a potential trend. Some scholars believe that the stomach is the second brain of humans and that intestinal bacteria such as Lactobacillus and Bifidobacterium secrete neurotransmitters[48]. Future research may involve studies on the treatment of mental illness by changing the intestinal flora. Studies have shown that the degree of dysautonomia is related to the severity of FM and can be evaluated by measuring a patient's nighttime heart rhythm variability[49]. Studies have also found that sympathetic nerves in patients with FM are abnormally activated; on the contrary, increasing the activity of the vagus nerve can increase pain thresholds and reduce pain sensitivity[50]. Non-invasive brain stimulation, such as transcranial direct current stimulation and repetitive transcranial magnetic stimulation, has shown some ability to improve pain in FM patients[51]. Both types of stimulation appear to be equally effective in FM patients and have different effects depending on the location of the stimulation. For example, stimulating the primary motor cortex can relieve pain, while stimulating the dorsolateral prefrontal lobe can improve depression[52].

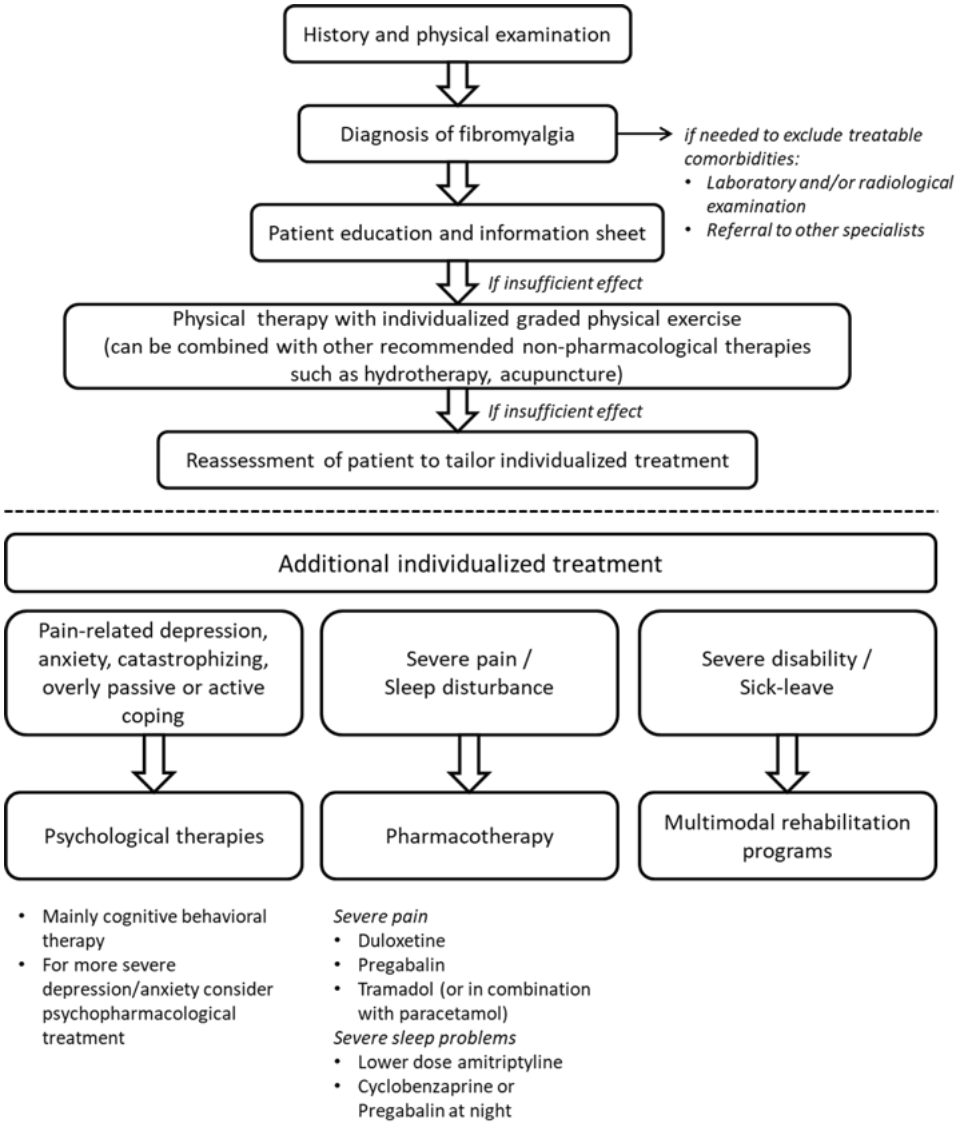


Figure 3. Management recommendations for fibromyalgia (adapted from the 2017 EULAR revised recommendations for the management of fibromyalgia[41]).

Pharmacological treatments of fibromyalgia

Severe pain or sleep disorders can be treated with drugs such as pregabalin and duloxetine (Figure 3). Drug treatments, including pregabalin, duloxetine, amitriptyline, cyclobenzaprine, and tramadol, may be effective, but the evidence supporting their use is relatively weak[41]. According to Canadian guidelines, level Ia evidence of the benefits of aerobic exercise, intensive exercise, and CBT has been obtained, and these interventions are strongly recommended as non-pharmacological therapies; similarly, level Ia evidence of the effects of drug treatments, including pregabalin, amitriptyline, SNRIs, and SSRIs, has been collected, and these therapies are also strongly recommended[53]. Some physicians believe that FM treatment should be conducted with stronger painkillers. However, the current evidence does not recommend the use of powerful analgesics, such as local anesthetics, opioids, and other drugs[54]. Pregabalin can bind with α2-δ units in the calcium ion channels of the central nervous system tissue with high affinity, reduce the permeability of calcium ions and release of neurotransmitters, and inhibit central nervous system sensitization[55]. A randomized controlled trial enrolling 197 patients found that FM patients with depression and taking SSRI or SNRI plus pregabalin show significantly reduced pain responses[56]. A follow-up study analyzed this group of patients and found that pregabalin has excellent pain relief effects on patients who were initially diagnosed with FM, who were diagnosed with depression within 10 years, and who took lighter antidepressant doses. Efficacy analysis revealed that pregabalin is significantly better than placebo for moderate to severe pain and has obvious efficacy for anxiety and sleep disorders[57]. Besides pain, patients with FM may suffer from depression, anxiety, fatigue, sleep disorders, and other symptoms[58]. When combined with depression, duloxetine, fluoxetine, naltrexone, dronabinol, and other drugs may be considered; when combined with anxiety, pregabalin, gabapentin, or nabilone may be used. When FM is combined with fatigue or sleep disorders, amitriptyline, pregabalin, gabapentin, and other drugs may be considered. Although the drugs suitable for FM treatment are very limited, clinicians may still formulate personalized prescriptions to improve patient functions and quality of life[59].

REFERENCES

1. Gottschalk A, Smith DS. New concepts in acute pain therapy: preemptive analgesia. Am Fam Physician. 2001;63(10):1979-84.
2. Goldenberg DL. Fibromyalgia syndrome a decade later: what have we learned? Arch Intern Med. 1999;159(8):777-85.
3. Inanici F, Yunus M. History of fibromyalgia: Past to present. Current pain and headache reports. 2004;(8):369-78.
4. Yunus MB. Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. Semin Arthritis Rheum. 2007;36(6):339-56.
5. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Häuser W, Katz RL, et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Semin Arthritis Rheum. 2016;46(3):319-29.
6. Clauw DJ. Fibromyalgia: a clinical review. JAMA. 2014;311(15):1547-55.
7. Queiroz LP. Worldwide epidemiology of fibromyalgia. Curr Pain Headache Rep. 2013;17(8):356.
8. Bair MJ, Krebs EE. Fibromyalgia. Annals of Internal Medicine. 2020;172(5):ITC33-ITC48.
9. Abeles AM, Pillinger MH, Solitar BM, Abeles M. Narrative Review: The Pathophysiology of Fibromyalgia. Annals of Internal Medicine. 2007;146(10):726-34.
10. Xu M, Bennett DLH, Querol LA, Wu L-J, Irani SR, Watson JC, et al. Pain and the immune system: emerging concepts of IgG-mediated autoimmune pain and immunotherapies. Journal of Neurology, Neurosurgery & Psychiatry. 2020;91(2):177.
11. Bradley LA. Pathophysiology of fibromyalgia. Am J Med. 2009;122(12 Suppl):S22-30.
12. Arnold LM, Hudson JI, Hess EV, Ware AE, Fritz DA, Auchenbach MB, et al. Family study of fibromyalgia. Arthritis Rheum. 2004;50(3):944-52.
13. Ablin JN, Cohen H, Buskila D. Mechanisms of Disease: genetics of fibromyalgia. Nat Clin Pract Rheumatol. 2006;2(12):671-8.
14. Duffield SJ, Miller N, Zhao S, Goodson NJ. Concomitant fibromyalgia complicating chronic inflammatory arthritis: a systematic review and meta-analysis. Rheumatology. 2018;57(8):1453-60.

15. Fitzcharles MA, Ste-Marie PA, Häuser W, Clauw DJ, Jamal S, Karsh J, et al. Efficacy, Tolerability, and Safety of Cannabinoid Treatments in the Rheumatic Diseases: A Systematic Review of Randomized Controlled Trials. Arthritis Care Res (Hoboken). 2016;68(5):681-8.
16. Pollard LC, Kingsley GH, Choy EH, Scott DL. Fibromyalgic rheumatoid arthritis and disease assessment. Rheumatology (Oxford). 2010;49(5):924-8.
17. Almodóvar R, Carmona L, Zarco P, Collantes E, González C, Mulero J, et al. Fibromyalgia in patients with ankylosing spondylitis: prevalence and utility of the measures of activity, function and radiological damage. Clin Exp Rheumatol. 2010;28(6 Suppl 63):S33-9.
18. Aloush V, Ablin JN, Reitblat T, Caspi D, Elkayam O. Fibromyalgia in women with ankylosing spondylitis. Rheumatol Int. 2007;27(9):865-8.
19. Haliloglu S, Carlioglu A, Akdeniz D, Karaaslan Y, Kosar A. Fibromyalgia in patients with other rheumatic diseases: prevalence and relationship with disease activity. Rheumatol Int. 2014;34(9):1275-80.
20. Wallis D, Haroon N, Ayearst R, Carty A, Inman RD. Ankylosing spondylitis and nonradiographic axial spondyloarthritis: part of a common spectrum or distinct diseases? J Rheumatol. 2013;40(12):2038-41.
21. Hanly JG, Su L, Farewell V, McCurdy G, Fougere L, Thompson K. Prospective study of neuropsychiatric events in systemic lupus erythematosus. J Rheumatol. 2009;36(7):1449-59.
22. Wolfe F, Petri M, Alarcón GS, Goldman J, Chakravarty EF, Katz RS, et al. Fibromyalgia, systemic lupus erythematosus (SLE), and evaluation of SLE activity. J Rheumatol. 2009;36(1):82-8.
23. Torrente-Segarra V, Corominas H, Sánchez-Piedra C, Fernández-Castro M, Andreu JL, Martínez-Taboada VM, et al. Fibromyalgia prevalence and associated factors in primary Sjögren's syndrome patients in a large cohort from the Spanish Society of Rheumatology registry (SJOGRENSER). Clin Exp Rheumatol. 2017;35 Suppl 105(3):28-34.
24. Stahl SM. Stahl's Essential Psychopharmacology. Neuroscientific Basis and Practical Applications. 4th Edition. 2013.
25. Martucci KT, Ng P, Mackey S. Neuroimaging chronic pain: what have we learned and where are we going? Future Neurol. 2014;9(6):615-26.
26. 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;245:1098-105.
27. Kudlow PA, Rosenblat JD, Weissman CR, Cha DS, Kakar R, McIntyre RS, et al. Prevalence of fibromyalgia and co-morbid bipolar disorder: A systematic review and meta-analysis. J Affect Disord. 2015;188:134-42.
28. Chang MH, Hsu JW, Huang KL, Su TP, Bai YM, Li CT, et al. Bidirectional Association Between Depression and Fibromyalgia Syndrome: A Nationwide Longitudinal Study. J Pain. 2015;16(9):895-902.
29. Markkula R, Järvinen P, Leino-Arjas P, Koskenvuo M, Kalso E, Kaprio J. Clustering of symptoms associated with fibromyalgia in a Finnish Twin Cohort. Eur J Pain. 2009;13(7):744-50.
30. Gillespie NA, Gehrman P, Byrne EM, Kendler KS, Heath AC, Martin NG. Modeling the direction of causation between cross-sectional measures of disrupted sleep, anxiety and depression in a sample of male and female Australian twins. J Sleep Res. 2012;21(6):675-83.
31. Walitt B, Čeko M, Khatiwada M, Gracely JL, Rayhan R, VanMeter JW, et al. Characterizing "fibrofog": Subjective appraisal, objective performance, and task-related brain activity during a working memory task. Neuroimage Clin. 2016;11:173-80.
32. Chou PH, Tang KT, Chen YH, Sun CW, Huang CM, Chen DY. Reduced frontal activity during a verbal fluency test in fibromyalgia: A near-infrared spectroscopy study. J Clin Neurosci. 2018;50:35-40.
33. Coppieters I, Ickmans K, Cagnie B, Nijs J, De Pauw R, Noten S, et al. Cognitive Performance Is Related to Central Sensitization and Health-related Quality of Life in Patients with Chronic Whiplash-Associated Disorders and Fibromyalgia. Pain Physician. 2015;18(3):E389-401.
34. Association. AP. Diagnostic and statistical manual of mental disorders (5th ed.). 2013.

35. Keller MB. The long-term clinical course of generalized anxiety disorder. J Clin Psychiatry. 2002;63 Suppl 8:11-6.
36. Bruce SE, Yonkers KA, Otto MW, Eisen JL, Weisberg RB, Pagano M, et al. Influence of psychiatric comorbidity on recovery and recurrence in generalized anxiety disorder, social phobia, and panic disorder: a 12-year prospective study. Am J Psychiatry. 2005;162(6):1179-87.
37. Hartford JT, Endicott J, Kornstein SG, Allgulander C, Wohlreich MM, Russell JM, et al. Implications of pain in generalized anxiety disorder: efficacy of duloxetine. Prim Care Companion J Clin Psychiatry. 2008;10(3):197-204.
38. García-Campayo J, Caballero F, Perez M, López V. Pain related factors in newly diagnosed Generalized Anxiety Disorder patients. Actas Esp Psiquiatr. 2012;40(4):177-86.
39. Janssens KA, Zijlema WL, Joustra ML, Rosmalen JG. Mood and Anxiety Disorders in Chronic Fatigue Syndrome, Fibromyalgia, and Irritable Bowel Syndrome: Results From the LifeLines Cohort Study. Psychosom Med. 2015;77(4):449-57.
40. Thieme K, Turk DC, Flor H. Comorbid depression and anxiety in fibromyalgia syndrome: relationship to somatic and psychosocial variables. Psychosom Med. 2004;66(6):837-44.
41. Macfarlane GJ, Kronisch C, Dean LE, Atzeni F, Häuser W, Fluß E, et al. EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis. 2017;76(2):318-28.
42. 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):260-5.
43. Romero-Zurita A, Carbonell-Baeza A, Aparicio VA, Ruiz JR, Tercedor P, Delgado-Fernández M. Effectiveness of a tai-chi training and detraining on functional capacity, symptomatology and psychological outcomes in women with fibromyalgia. Evid Based Complement Alternat Med. 2012;2012:614196.
44. Langhorst J, Häuser W, Bernardy K, Lucius H, Settan M, Winkelmann A, et al. [Complementary and alternative therapies for fibromyalgia syndrome. Systematic review, meta-analysis and guideline]. Schmerz. 2012;26(3):311-7.
45. Häuser W, Klose P, Langhorst J, Moradi B, Steinbach M, Schiltenwolf M, et al. Efficacy of different types of aerobic exercise in fibromyalgia syndrome: a systematic review and meta-analysis of randomised controlled trials. Arthritis Res Ther. 2010;12(3):R79.
46. Bernardy K, Füber N, Köllner V, Häuser W. Efficacy of cognitive-behavioral therapies in fibromyalgia syndrome - a systematic review and metaanalysis of randomized controlled trials. J Rheumatol. 2010;37(10):1991-2005.
47. Garcia-Palacios A, Herrero R, Belmonte MA, Castilla D, Guixeres J, Molinari G, et al. Ecological momentary assessment for chronic pain in fibromyalgia using a smartphone: a randomized crossover study. Eur J Pain. 2014;18(6):862-72.
48. Galland L. The gut microbiome and the brain. J Med Food. 2014;17(12):1261-72.
49. 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 Research & Therapy. 2011;13(6):R185.
50. Porges SW. The polyvagal theory: new insights into adaptive reactions of the autonomic nervous system. Cleve Clin J Med. 2009;76 Suppl 2(Suppl 2):S86-90.
51. Marlow NM, Bonilha HS, Short EB. Efficacy of transcranial direct current stimulation and repetitive transcranial magnetic stimulation for treating fibromyalgia syndrome: a systematic review. Pain Pract. 2013;13(2):131-45.
52. Hou W-H, Wang T-Y, Kang J-H. The effects of add-on non-invasive brain stimulation in fibromyalgia: a meta-analysis and meta-regression of randomized controlled trials. Rheumatology. 2016;55(8):1507-17.
53. Häuser W, Ablin J, Fitzcharles MA, Littlejohn G, Luciano JV, Usui C, et al. Fibromyalgia. Nat Rev Dis Primers. 2015;1:15022.
54. Kia S, Choy E. Update on Treatment Guideline in Fibromyalgia Syndrome with Focus on Pharmacology. Biomedicines. 2017;5(2):20.
55. Shim JH. Clinical Application of α2-δ Ligand.

Hanyang Med Rev. 2011;31(2):55-62.
56. Arnold LM, Sarzi-Puttini P, Arsenault P, Khan T, Bhadra Brown P, Clair A, et al. Efficacy and Safety of Pregabalin in Patients with Fibromyalgia and Comorbid Depression Taking Concurrent Antidepressant Medication: A Randomized, Placebo-controlled Study. J Rheumatol. 2015;42(7):1237-44.
57. Silverman SL, Backonja M, Pauer L, Landen J, Bhadra Brown P, Scavone JM, et al. Effect of Baseline Characteristics on the Pain Response to Pregabalin in Fibromyalgia Patients with Comorbid Depression. Pain Medicine. 2017;19(3):419-28.
58. Guymer EK, Littlejohn GO, Brand CK, Kwiatek RA. Fibromyalgia onset has a high impact on work ability in Australians. Internal Medicine Journal. 2016;46(9):1069-74.
59. Tzadok R, Ablin JN. Current and Emerging Pharmacotherapy for Fibromyalgia. Pain Res Manag. 2020;2020:6541798.