

# Psychosomatic Approach to Fibromyalgia Syndrome: Concept, Diagnosis and Treatment

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Fibromyalgia syndrome (FMS) has chronic widespread pain (CWP) as a core symptom and a variety of associated somatic and psychological symptoms such as fatigue, sleep problems, cognitive disturbances, multiple somatic pain, and depression. FMS is the subject of considerable controversy in the realm of nosology, diagnosis, pathophysiology, and treatment. Moreover, the fact that FMS and mental illness are closely associated with each other might intensify the confusion for the distinction between FMS and mental disorders. This narrative literature review aims to provide the concept, diagnosis, and treatment of FMS from the integrative biopsychosocial and psychosomatic perspective. This article first explains the concepts of FMS as a disease entity of biopsychosocial model, and then summarizes the changes of diagnostic criteria over past three decades, differential diagnosis and comorbidity issue focused on mental illnesses. In addition, an overview of treatment of FMS is presented mainly by arranging the recommendations from the international guidelines which have been developed by four official academic associations.

**Key Words:** Biopsychosocial model, Comorbidity, Fibromyalgia, Psychosomatic medicine

Fibromyalgia syndrome (FMS) is characterized by the core symptom of chronic widespread pain (CWP) and associated symptoms of fatigue, unrefreshing sleep, cognitive disturbances, headaches, low abdominal pain, and depression.<sup>1,2</sup> The quality of life (QoL) of patients with FMS is significantly impaired, and the disease-associated economic burden is substantial.<sup>3,4</sup> FMS occurs in 2–4% of the general population worldwide and increases with age.<sup>5</sup> The rates of prevalence differ according to the diagnostic criteria used, but FMS is reported to occur 2.3 to 13.7 times

more frequently in women than in men.<sup>1</sup> However, confirmation bias and object group selection bias in epidemiological studies might have reduced the count of male FMS patients.<sup>6</sup> According to epidemiological studies of the Korean population, the prevalence rate of FMS using the 1990 classification criteria of the American College of Rheumatology (ACR) was 2.2% in the general population of Kyoung-buk province,<sup>7</sup> and using the modified 2010 ACR criteria, it was 11.0% in patients visiting pain clinics at 14 university hospitals,<sup>8</sup> with female

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predominance.

FMS is the subject of considerable controversy in the realm of nosology, diagnosis, pathophysiology, and treatment.<sup>1,9-13</sup> The definition and diagnostic criteria of FMS have changed during the past three decades.<sup>1</sup> However, debates continue about this disease entity and diagnostic accuracy,<sup>9,11,12,14</sup> and physicians struggle to appropriately diagnose FMS.<sup>15,16</sup> The pathogenesis of FMS is assumed to involve extensive mechanisms, including genetics, neuroimaging abnormalities, central hypersensitivity to pain, sympathetic nervous system dysfunction, personality, early life trauma, stress/environmental factors, subtle immunological and inflammatory changes, small nerve fiber dysfunction, activation of homeostatic neural programs, trauma, and certain types of infection (e.g., Epstein-Barr virus, Lyme disease, Q fever, viral hepatitis).<sup>1,10</sup> The effectiveness of pharmacotherapy for FMS is only modest,<sup>2</sup> and a variety of treatments, including complementary and alternative medicine (CAM), are used in the absence of gold standard treatments.<sup>2,17</sup>

One of the reasons for the confusion would be the vague distinction between FMS and mental illness. Some researchers insisted that FMS is just an alternative name of psychiatric disorder like masked depression, somatoform disorder, or anxiety disorder,<sup>18</sup> or FMS does not exist.<sup>11,19</sup> However, not all FMS patients show significant psychopathology.<sup>20,21</sup> And the fact that central hypersensitivity in patients with FMS has been con-

sistently reported makes people accept “the reality” of FMS.<sup>22,23</sup> Some proposed that FMS is a brain disease or a small fiber neuropathy, rather than psychologically or socially constructed illness.<sup>24</sup> This biological suggestion about the essence of FMS has not seemed to be plausible to explain the complexity of FMS because the psychosocial aspects are still proven to be critical in treatment of chronic pain or FMS.<sup>3,25</sup>

Hence, the comprehensive review about the relationship of FMS and psychiatric disorders is needed to understand the heterogeneous and complex properties of FMS. This narrative literature review aims to provide the concept, diagnosis, and treatment of FMS from the integrative biopsychosocial and psychosomatic perspective. The author first explains the concepts of FMS, which are closely associated with but distinguished from psychiatric disorders, and then summarizes the diagnosis and treatment of FMS to help clinicians understand that FMS requires multidisciplinary and integrative approaches.

## **CONCEPTS AND MODEL OF FIBROMYALGIA SYNDROME**

According to Wolfe,<sup>26</sup> the article entitled “Two contributions to understanding of the fibrositis syndrome” by Smythe and Moldofsky (1977) provided an important opportunity for FMS to be given an independent diagnostic code in the International Classification of Disease-10 (M79.7). That article was listed in the *Bulletin of the Rheumatic Diseases* published by the US Arthritis

Foundation for general practitioners and rheumatologists in North America and helped to establish FMS as a rheumatic disease. Since then, FMS has fit into the postmodern illness trend of the 21st century that considers the cultural factors of disease to be important, and the efforts of stakeholders — patients, patient support organizations, pharmaceutical companies, academic physicians, the pharmaco-academic complex, professional organizations, attorneys, and governments — have contributed to the popularization of the diagnosis.<sup>11</sup> In a way, the popularization of FMS can be considered as an example of the medicalization of non-medical problems, and its side effects include a high misdiagnosis rate, which increases the number of unnecessary patients, costs, and disability; the distortion of scientific research; many unnecessary treatments; and making psychosomatic diseases look like diseases that can be compensated. Therefore, careful attention is warranted in the diagnosis and treatment of FMS.<sup>11</sup> Before FMS can be accurately diagnosed, the concepts of FMS need to be defined in detail, which can best be done using the biopsychosocial model.

### **Concepts of FMS**

The study published by Häuser et al. in 2009 is helpful in understanding the concept of the disease called FMS. They measured physical/psychological/social distress in 2,524 people age 14 years or older in the general population in Germany and conducted a cluster analysis. They found that FMS was distributed throughout the German population according the severity of peo-

ple's physical/psychological/social distress and that respondents could be classified into four clusters.<sup>27</sup> Cluster 1 (58.0%) was a healthy group of patients who had no discomfort in any of the three distress domains. Cluster 2 (28.6%) patients showed localized pain and borderline depression, but they did not have many physical symptoms. Cluster 3 (7.5%) patients were classified as a generalized pain group that reported multiple pains but did not show high levels of fatigue or any symptom of depression. Cluster 4 (5.8%) patients reported pain in various parts of the body, high fatigue, moderate physical symptoms, and moderate depression. Both the Cluster 3 and 4 patients reported systemic pain, but unlike Cluster 3 patients, the Cluster 4 patients showed high psychological and social discomfort that met the diagnostic criteria of FMS. In other words, within the general population, FMS patients reported high levels of fatigue, depression, and social discomfort along with systemic pain, which indicates that the group of patients showing only systemic or local pain was excluded from FMS. That study also suggests that FMS is not a categorical condition, such as cancer or trauma, but a continuum disorder diagnosed according to severity, such as hypertension or DM. In other words, people who did not have FMS in the past could develop the disease over time, and people who did not have the syndrome could be classified as having the syndrome due to changes in diagnostic criteria. It is therefore necessary to remember that patients who show major symptoms of CWP and FMS might meet the diagnostic criteria for FMS in the future, even if they do not

completely meet the diagnostic criteria for FMS at present.<sup>9,27</sup>

### **Disease Model of FMS**

The biopsychosocial model of disease best explains FMS. It assumes that FMS is created and maintained by complex interactions of biological factors such as genetics, neuroelectrophysiology, brain metabolism, functional impairment, abnormal neurotransmission, HPA axis dysregulation, and autonomic dysfunction; psycho-behavioral factors such as depression, anxiety, anger, catastrophizing, pessimism, and avoidance behavior; and social factors such as interpersonal conflicts, chronic environmental stress, and economic problems.<sup>25,28</sup> Robust evidence indicates that FMS can be conceptualized as abnormal central pain processing rather than damage to a peripheral organ. (i.e., FMS is a central sensitization syndrome).<sup>29</sup> Hyperalgesia and allodynia in FMS are clear signs of central sensitization. Additionally, the expansion of the receptive pain field, sustained electrophysiological discharge, referred pain across multiple spinal segments, and a variety of pain complaints (e.g., burning, throbbing, tingling, or numbness) in patients with FMS can be explained by central sensitization.<sup>23</sup> Adverse childhood experiences as a psychosocial factor might alter stress-related neurobiological substrates, including the HPA axis, monoaminergic neurotransmitter systems, and immune system and the activities of the amygdala, hippocampus, and thalamus.<sup>23,30,31</sup> Thus, early life adversity might contribute to the dysfunction of pain processing and central hypersensitivity.<sup>32</sup>

Developmental adversity and genetic vulnerability could thus act as predisposing factors that lower the threshold for the onset of FMS. Similarly, physical injury, infection, psychosocial stress, interpersonal conflicts, depression, anxiety, and insomnia also act as precipitating factors that create FMS. The onset of FMS further reduces the ability to control new stresses and creates a vicious cycle that makes pain control more difficult. In addition, irritability, nervousness, mental disorder, and maladaptive thoughts and behaviors such as catastrophizing, and avoidance, as well as social withdrawal, secondary gain, and medico-legal disputes act as perpetuating factors and contribute to making the disease chronic.<sup>2,18,33</sup> Distinguishing between nociception and pain reinforces the importance of psychological and behavioral factors, as well as biological factors, in FMS. In other words, a stimulus that induces nociception is perceived by the brain only after the completion of the transduction, transmission, and modulation process. During that process, cognitive appraisal, primary and secondary emotions, and avoidance behavior influence how people subjectively experience pain.<sup>25</sup> Therefore, psychological and behavioral factors play an important role when people experience nociception as pain.

### **DIAGNOSIS**

FMS can be either underdiagnosed or overdiagnosed. The reasons for underdiagnosis include a lack of knowledge about FMS, the perception that FMS occurs only in women or is malingering-

ing, difficulty making a diagnosis based on symptoms without objective findings, and failing to recognize the independent existence of FMS as a disease entity and instead regarding it as masked depression or a somatoform disorder.<sup>9</sup> The underdiagnosis of FMS can incur high personal and social costs and increase the subjective pain of patients who must wait several years for their FMS to be properly diagnosed and managed.<sup>34</sup> There is also a tendency for FMS to be overdiagnosed, which could be the result of medicalization, social construction, and the influence of interest groups.<sup>9,11,35</sup> This chapter reviews the diagnostic process, changes in diagnostic criteria, and the issue of comorbidity with mental disorders to help properly diagnose FMS.

### **History taking**

When patients complain of chronic pain that lasts for more than 3 months, it is necessary to distinguish whether the pain is CWP or regional pain.<sup>9</sup> For that purpose, the Widespread Pain Index (WPI) can be used. The quality of pain varies and can be described as deep, throbbing, stabbing, or burning, and it can worsen during the change of seasons or physical activity.<sup>36</sup> Patients might also complain of allodynia, lethargy, muscle stiffness, and a feeling of joint swelling that makes them feel pain with even a light touch or pressure.<sup>1,36</sup>

Properly diagnosing FMS requires a comprehensive evaluation of the degree of functional impairment and psychosocial issues as well as pain.<sup>3</sup> Therefore, major symptoms other than pain, such as fatigue, unrefreshing sleep, and

cognitive dysfunction, should be evaluated along with CWP. The Fibromyalgia Survey Questionnaire (FSQ) can be used for that evaluation.

### **Physical examinations**

Physical examinations are used to examine structural arthropathy, muscle atrophy, neurologically abnormal findings, and symptoms of endocrinological disease. Although patients might report generalized pain in their soft tissues, the tender point examination (TPE) presented in the 1990 ACR has low validity and reliability, so it is not a mandatory item in a physical examination for FMS.<sup>9</sup>

### **Diagnostic laboratory findings**

No biomarkers, such as confirmatory blood or imaging tests, are available for diagnosing FMS, so tests are performed mainly for differential diagnosis. The basic tests and diseases to be identified are: 1) blood sedimentation rate, C-reactive protein, counts of red and white blood cells to rule out polymyalgia rheumatica and rheumatoid arthritis (RA); 2) creatinine kinase to rule out myopathy; 3) serum calcium concentration to rule out hypercalcemia; and 4) thyroid stimulating hormone to rule out hypothyroidism. If patients show no clinical symptoms consistent with RA, systemic lupus erythematosus (SLE), or arthropathy, antibody tests and radiological tests to identify rheumatic diseases are not recommended.<sup>9</sup>

### **Diagnostic criteria**

FMS requires a descriptive diagnosis based on

expert consensus, not an etiological diagnosis.<sup>37</sup> In the past, diagnosis used the classification criteria presented by the ACR in 1990. However, new diagnostic criteria were released in 2010 and 2016. In 2011, a self-administered questionnaire that slightly modified the 2010 diagnostic criteria was published, although it was not part of the official ACR diagnostic criteria. The 2010 and 2011 diagnostic criteria are similar to each other and are often used together, so they are sometimes called 2010/2011 ACR criteria. Examining changes in the diagnostic criteria is helpful for understanding the concepts and symptoms of FMS.

#### 1) 1990 ACR classification criteria.<sup>38</sup>

The ACR criteria published in 1990 were developed to help classify research, not for diagnosis, but FMS has nonetheless been diagnosed based on them.<sup>39</sup> These criteria are meaningful because they introduced the concept of CWP by presenting the location, number, and a test method to differentiate FMS pain from regional pain syndrome and inflammatory rheumatic diseases.<sup>1,39</sup> In their definition, chronic meant pain that lasted for more than 3 months, and widespread meant pain that occurred in the upper and lower back, the right and left sides of the body, and the axial skeleton (cervical, thoracic, and lumbar vertebrae and anterior chest). The presence or absence of pain was determined during an objective examination, with pain considered to be present if the patient complained in a TPE (palpation with a finger with a weight of

4 kg). If patients complained of pain in more than 11 of the 18 tender points presented, they were diagnosed with FMS pain. However, the TPE was difficult to perform and unreliable unless it was performed by a rheumatologist. Furthermore, the 1990 ACR criteria overlooked symptoms other than pain, such as sleep problems, fatigue, and cognitive impairments.

#### 2) 2010 ACR preliminary diagnostic criteria.<sup>26</sup>

In the ACR diagnostic criteria published in 2010, the TPE was deleted, and the number of physical areas of pain reported by the patient was counted and scored with 0–19 points (WPI). In other words, the method for proving pain was changed from an objective physical exam to taking a history of subjective complaints. In addition, the severity of symptoms of fatigue, unrefreshing sleep, and cognitive decline, which are core symptoms other than pain, was measured during the past week and scored from 0 points (no problem) to 3 points (serious problem: general, persistent, causing impairment in everyday life). A list of 40 physical symptoms was also presented, and the subjective degree of each symptom was scored from 0 points (no problem) to 3 points (a significant number of symptoms). Then, the score of the three core symptoms of fatigue, unrefreshing sleep, and cognitive decline (0–9 scores) and the degree or severity of general physical symptoms (0–3 points) were summed onto a 0–12 point Symptom Severity Scale (SSS). Symptom severity on the SSS was de-

terminated by the examiner after a thorough interview with the patient.<sup>40</sup> An FMS diagnosis was possible if the WPI was 7 or more and the SSS was 5 or more, or if the WPI was 3 to 6 and the SSS was 9 or more.

### 3) *Modified 2010 ACR diagnostic criteria.*<sup>41</sup>

Using the 2010 ACR criteria, a doctor basically interviewed a patient, marked each area of pain, and asked the patient about various physical symptoms, which required a considerable amount of time and effort. However, the symptoms evaluated by doctors were also fundamentally subjective. Therefore, in situations in which detailed patient interviews were difficult due to the research environment, cost, or time, the doctor's evaluation was replaced with a patient self-report questionnaire (FSQ), which is the modified 2010 ACR criteria. In the modified 2010 ACR criteria, the WPI scale is the same as in the 2010 ACR criteria, but some of the SSS was changed. Among the SSS items in the 2010 ACR criteria, the methods for measuring fatigue, unrefreshing sleep, and cognitive decline are maintained as they were, but the 40 general symptoms in the list were limited to three categories: headache, lower abdominal pain and convulsions, and depression for 6 months prior to the examination. Patients were asked to rate those three symptoms as yes (0 point) or no (1 point), instead of evaluating various types of physical symptoms on a 0–3 point scale. As a result, the scores remained the same, so the WPI (0–19 points) and the SSS (0–12 points) were

combined and renamed the Fibromyalgia Symptom (FS) scale (0–31 points). The FS is also called the Fibromyalginess scale. However, diagnosis using only the FSQ was prohibited; the interpretation and final diagnosis of FSQ can only be made by a doctor.<sup>26</sup>

### 4) *2016 revisions to the 2010/2011 diagnostic criteria (2016 ACR criteria).*<sup>42</sup>

The 2016 revised version was published after the 2010/2011 ACR criteria had been used and researched for about 5 years. The major revisions are as follows. First, the 2010/2011 ACR criteria were combined. Second, the 2010/2011 ACR criteria contained a provision that no other disease that could explain the pain should be present, but the 2016 ACR criteria deleted that exclusion criterion. That made it easier for medical personnel with little experience with FMS to diagnose it and made it possible to diagnose FMS in patients with other diseases such as somatic symptom disorder, depressive disorder, and pain disorder.<sup>43</sup> Third, the 2016 ACR diagnostic criteria recommend that the FS score always be used as a scale to indicate the severity of FMS.<sup>1,6</sup> Fourth, it added the requirement of generalized pain, which means pain in at least four of the five regions: the upper and lower sides of the right and left waist and the axial skeleton, excluding the jaw, chest, and abdomen. As a result, the possibility of including patients with regional pain syndrome was reduced. When Ablin et al. applied the 2011 ACR criteria and the 2016 ACR criteria to 16,987 pa-

tients enrolled in the US National Data Bank for Rheumatic Diseases, the consistency rate between the two criteria was 96.2%, and the discrepancy rate was 3.9%. The discrepancy cases in which patients were diagnosed with FMS by the 2011 ACR criteria but not by the 2016 ACR criteria were due to the exclusion of localized pain syndrome.<sup>37</sup> Fifth, the minimum WPI score required for diagnosis was increased from 3 points to 4 points.

Along with the changes in diagnostic criteria, CWP was better distinguished from regional pain and specified as a core symptom of FMS. The deletion of the TPE and introduction of the FSQ contributed to the popularization of the FMS diagnosis to some extent, though allowing only a doctor to perform the diagnosis was an effort to prevent misdiagnosis or excessive diagnosis. In addition, the heterogeneity of FMS was reflected in the diagnostic criteria by firmly establishing the diagnostic status of symptoms other than CWP (e.g., fatigue, sleep problems, cognitive impairment, headache, low abdominal pain and convulsions, and depression).

### **Differential diagnosis**

Differential diagnosis can be largely divided into rheumatic, non-rheumatic, neurological, substance-induced diseases, and psychiatric disorders. 1) Rheumatic diseases: generalized pain, fatigue, and muscle weakness can occur in early RA before clinical symptoms such as joint edema appear. Similarly, non-regional pain also occurs in spondyloarthritis. When elderly patients have

newly developed pain, polymyalgia rheumatica is suspected. In that case, stiffness in the limb girdle is prominent. Non-inflammatory musculoskeletal diseases such as myofascial pain syndrome and hypermobility syndrome also need to be differentiated. 2) Non-rheumatic diseases: endocrinological (hypothyroidism, hyperparathyroidism, acromegaly, vitamin D deficiency), gastrointestinal (celiac and non-gluten sensitivity), infectious (Lyme disease, hepatitis C, immunodeficiency syndrome), and cancer (early stage of multiple myeloma, bone metastasis, leukemia/lymphoma). 3) Neurological diseases: multiple sclerosis, Parkinson's disease, peripheral neuropathy, and spinal stenosis. In myopathy, muscle weakness is the main symptom, but some patients complain mainly of diffuse pain rather than muscle weakness. Patients with those diseases show a claudicant type of pain without accurately describing it. 4) Substance-induced diseases: Pain caused by drugs such as statins (myalgia), opioid analgesia (hyperpathia), anticancer drugs (peripheral neuropathy), aromatase inhibitors (arthropathy), and bisphosphonates (bone pain) also needs to be differentiated from FMS.<sup>9,44</sup> 5) Psychiatric disorders: FMS is considered as one of other medical conditions without clear pathophysiology (i.e., functional syndromes) in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5.<sup>45</sup> Dual diagnosis of FMS and mental disorder is possible according to the 2016 ACR criteria.<sup>42</sup> However, it is reasonable to be diagnosed with the psychiatric disorder like mood disorder, anxiety disorder, somatic symptom and related disorder or sleep-wake disorder when symptoms

such as pain, psychological distress, and insomnia are more appropriate for the diagnostic criteria of corresponding psychiatric disorder rather than FMS according to the most recent ACR diagnostic criteria.<sup>45</sup>

### **Comorbidities: Mental disorders**

FMS and mental illness are closely associated with each other in such domains as pathophysiology, clinical symptoms and progress. Therefore, a greater proportion of psychiatric disorders are combined with FMS.<sup>46</sup> In the pathophysiology of FMS, central sensitization plays a more pivotal role than peripheral inflammatory theory, and hypothalamic-pituitary-adrenal (HPA) axis dysregulation, which is a neurobiological substrate of the stress response, is reported to be an important etiological factor.<sup>33</sup> In their clinical progress, mental disorders and FMS can cause the onset or exacerbation of one another, and conversely, improvements in either pain or depression can lead to improvements in other symptoms.<sup>46-48</sup> In this chapter, the author discusses the results of several large-scale epidemiological studies pertaining to comorbidity of FMS and mental disorders.

#### *1) Depressive disorder*

The coexistence of depression and FMS is well known.<sup>49,50</sup> Chang et al. used national health insurance research data over 8 years to compare disease incidence in 25,969 FMS patients without mental illness and 17,142 depression patients who were not diagnosed of FMS. They reported that the risk of developing depression in FMS patients (hazard ratio

[HR] = 7.46, 95% CI = 6.77–8.22) and the risk of developing FMS in depression patients (HR = 6.28, 95% CI = 5.67–6.96) were both significantly higher than the risk of developing either condition in the general population.<sup>48</sup> In addition, Raphael et al. reported that the rate of major depressive disorder in FMS patients was 19.4%, about three times that of those without FMS in their epidemiological study using structural interview.<sup>49</sup>

Polymorphism of the serotonin transporter gene is commonly found in both FMS and major depression, which suggests that the two diseases are genetically associated. Particularly in terms of epigenetics, early developmental adversity might affect pain sensitivity and mood regulation in both diseases. Neuroanatomically, however, FMS is more associated with the right thalamus, whereas depression is more associated with motivation-emotional regions such as the hippocampus and anterior insula.<sup>47</sup> Depression and FMS share commonalities in epidemiology, genetics, neurobiology, clinical manifestations, early life adversity, and psychology, including cognitive distortion and responsiveness to antidepressants, but a theoretical background to explain both of these diseases is still lacking, so it is difficult to regard them as the same disease.<sup>47</sup> Currently, FMS and depression are not considered to be different names for the same disease, but they are understood to be independent diseases that are closely associated with each other in their pathophysiology, onset, clinical symptoms, and progress.<sup>21</sup>

## 2) *Bipolar disorder*

Bipolar disorder (BD) is being studied as one of the most common mental disorders that occurs in FMS.<sup>51</sup> In a meta-analysis, BD could be diagnosed in 21% of FMS patients.<sup>52</sup> In another systematic review, 26.2% of FMS patients were found to have lifetime BD.<sup>50</sup> FMS and BD show some common characteristics in circadian rhythm dysregulation, cognitive impairment, fatigue, and altered stress response.<sup>23</sup> Neurobiologically, dysfunctions in the prefrontal cortex (dorsolateral, ventromedial) and anterior cingulate gyrus that are associated with emotional regulation and pain processing are commonly found in both FMS and BD. The two conditions also share characteristic neuroendocrinological and neuroimmunological findings such as glucocorticoid receptor responsiveness, HPA axis dysregulation, and chronic low-grade inflammation.<sup>51</sup> Clinically, antidepressants such as serotonin and norepinephrine receptor inhibitors (SNRIs) are prescribed as the main drug treatments for FMS. In BD patients, SNRI prescriptions are associated with manic switches that complicate the progressive course of BD, anxiety, agitation and even an increased risk of suicide.<sup>53</sup> Therefore, a sufficient evaluation for BD is necessary before prescribing antidepressants for FMS patients.

## 3) *Anxiety disorder*

Because physical or sexual abuse is closely associated with both FMS and chronic pain disorder,<sup>54,55</sup> the correlation between FMS and

PTSD has been studied extensively. When 395 FMS patients were compared with the same number of people from the general population, PTSD could be diagnosed in 45.3% of FMS patients and only 3.0% of the control group. The most distressing traumatic experiences of FMS patients with PTSD were other traumatic experiences that were not included in the trauma list on the research tool, witnessing serious trauma of others, sexual abuse before age 14, severe physical abuse, and rape. In terms of the time of onset, FMS occurred after a traumatic event in 66% of FMS patients with PTSD and did not appear to have been mediated by depression, which indicated that both diseases could be commonly associated with stress.<sup>56</sup> A study by Raphael et al. found that the incidence rate of lifetime obsessive-compulsive disorder, PTSD, and generalized anxiety disorder was five times higher in FMS patients than in the general population.<sup>49</sup>

Anxiety disorder or symptoms are associated with pain severity and the interpretation of pain. If anxiety increases, tolerance to pain decreases and sensitivity increases. It is reported that anxiety and FMS act as mutual risk factors, similar to depression.<sup>23</sup>

## 4) *Somatic symptom disorder*

In the DSM-5, the concept of somatoform disorder in DSM-IV was changed to a new diagnosis called somatic symptom disorder (SSD). Along with the name change, the core symptoms of SSD were changed from medically unexplained physical symptoms

(MUPS) in somatoform disorder in DSM-IV to excessive thoughts, feelings, or behaviors about somatic symptoms or health concerns.<sup>57</sup> Double-diagnosis with SSD and FMS was made possible by the 2016 ACR criteria, which deleted the provision in the 2010/2011 ACR that no other disease that could explain the pain be present.<sup>42</sup> Therefore, SSD might or might not occur with FMS depending on the presence or absence of excessive psycho-behavioral symptoms of somatic pain, not the presence or absence of MUPS. According to the results of large-scale epidemiological studies, an SSD diagnosis was possible in 25.6% ~ 35% of FMS patients.<sup>58-60</sup> Patients with SSD are likely to be immersed in physical symptoms and show health-related anxiety, obsession, and maladaptive health behavior, so psychiatric management might be particularly necessary for patients with both FMS and SSD. However, the terms disproportionate and excessive in the SSD diagnostic criteria that describe the abnormal psychological/cognitive response to physical symptoms are somewhat uncertain, so diagnosing SSD in FMS patients seems to have a problem with reliability and validity.<sup>61,62</sup>

##### 5) *Personality disorders*

According to the study by Attademo et al., personality disorders (PDs) could be diagnosed in 8.7% – 46.7% of FMS patients based on the DSM-IV and DSM-III-R structural review for PD, and most of them were type C obsessive or avoidant PDs.<sup>63</sup> In addition, stud-

ies on the correlation between FMS and borderline personality disorder, which is a type B PD with features such as impulsivity, recurrent interpersonal problems, and suicide attempts, have been conducted.<sup>64,65</sup> When Garcia-Fontanals et al. used the Cloninger R psychobiological model of personality to compare 42 FMS patients who visited a rheumatology department with a normal control group, they found that FMS patients had a significantly higher harm avoidance (HA) temperament score than the control group. Among the sub-items of HA, anticipatory anxiety and pessimism were factors that could predict dysthymia and anxiety disorder.<sup>20</sup> A study using the NEO-Five Factor Inventory 3 found that higher neuroticism (i.e., the tendency of a patient to experience negative emotion) among the five personality factors correlated with poorer health status and greater symptom severity in FMS patients, and that correlation was mediated by depression and anxiety.<sup>66</sup> These results indicate that patients who become greatly anxious and sensitive in the face of FMS (patients with high neuroticism) might have more severe symptoms of FMS. Therefore, PDs are associated with ineffective coping techniques for disease or stress such as avoidance, denial, and disengagement, and those maladaptive coping strategies can aggravate the course of FMS.<sup>67</sup>

##### **Comorbidities: Physical diseases**

FMS can occur in 12 – 20% of RA patients, 5 – 25% of SLE patients, and 11 – 50% of ankylosing

spondylitis patients.<sup>19</sup> Similarly, in a study of 7,233 patients enrolled in the US National Data Bank for Rheumatic Diseases, 21.1% of RA patients, 16.8% of osteoarthritis patients, and 36.7% of SLE patients met the modified 2010 ACR diagnostic criteria for FMS.<sup>41</sup> In addition to rheumatic diseases, diseases such as coronary artery disease, DM, inflammatory bowel disease, and cancer can also occur in FMS patients.<sup>19,46</sup> Functional pain syndromes in specific regions, such as migraine, tension headache, irritable bowel disease, endometriosis, primary menalgia, temporomandibular disease, and atypical chest pain, can also occur in FMS patients.<sup>9,46</sup> Therefore, the treatment of FMS can require a multidisciplinary team approach involving various experts.<sup>9</sup>

## TREATMENT

Several guidelines and review articles pertaining to the treatment of FMS have been published by official academic associations, including the European League Against Rheumatism (EULAR),<sup>3</sup> Israeli Rheumatology Association,<sup>17,68</sup> Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (Germany),<sup>69,70</sup> and Canadian National Fibromyalgia Guideline Advisory Panel.<sup>2</sup> Each guideline has been developed to suit the medical system of its respective country or region, so it is difficult to apply any of them directly to clinical medicine in South Korea. However, because the guidelines mainly describe evidence-based medicine and were written by leading researchers in a multidisciplinary way, they are still useful. In addition, al-

though those four guidelines were developed independently, they commonly identify FMS as a biopsychosocial condition and show considerable commonalities in treatment principles. The differences mainly reflect differences in drug approval requirements or the cultures in each country or continent, particularly CAM. In this chapter, an overview of the four guidelines are mainly presented as a treatment method. A strong recommendation implies that all or almost all informed persons presented with the evidence would recommend for/against the therapy or that the intervention should be offered to most FMS patients.<sup>3,17,70</sup> A weak recommendation implies that most people would recommend for/against the therapy, but a substantial minority would not.<sup>3</sup>

### Goal of treatment

Current treatments cannot cure FMS completely. Therefore, the treatment goal for FMS patients is to reduce the severity of symptoms and help them learn how to control their own symptoms to promote their health-related QoL and functioning.<sup>2,3,28</sup>

### General principles of treatment

1. Self-management strategies such as exercise, regular physical activity, and stress management should be the fundamental treatment.<sup>2</sup> It is important for patients to manage their own symptoms using the self-management strategies.<sup>2,17,70</sup>
2. Patient-centered communication such as shared decision making can be used,<sup>3,70</sup> and patients should actively participate in their treatment.<sup>2,17</sup> Patient-centered communication

can enable the success of non-pharmacological treatment, which is essential,<sup>17</sup> and improve the doctor–patient relationship.<sup>70</sup>

3. Patient education is a basic treatment tool as an element of psychoeducation and CBT.<sup>70</sup>
4. Treatment should be patient-tailored, multidisciplinary, multimodal, and multicomponent.<sup>2,3,17,70</sup> It should include a combination of non-pharmacological and pharmacological therapy or exercise therapy and one or more modes of psychotherapy.<sup>3,17,70</sup>
5. Treatment should be tailored to patients based on their intensity of pain, sleep disturbance, fatigue, depression, level of functional impairment, and comorbidities.<sup>2,3,17,70</sup> Availability, cost, safety issues, and patient preferences should all be considered.<sup>3,70</sup>

### Initiation of treatment

Treatment should begin with patient education and the provision of information. In the initial phase, specific treatment goals should be established for the patient’s health status and QoL,<sup>2,17</sup> with a focus on non-pharmacological therapy.<sup>2,3,17,70</sup> The educational contents should include the fact that FMS is not an organic disease but a functional disorder, that the clinician recognizes the legitimacy of the symptoms, and that the disease will persist but not develop into a more serious condition. In addition, the symptoms should be explained using a biopsychosocial model, and information about recommended and non-recommended treatment methods should be provided. The clinician should emphasize that symptoms can be alleviated through the patient’s

own activities.

### Stepwise approach

Treatment should proceed in a stepwise manner (Table 1).<sup>2,3,17,70</sup> The treatment method varies depending on symptom severity (Germany), comorbidities (Canada), and response to previous treatments (Germany, Israel). Symptom reduction, functional increases, side effects, and cost should be evaluated periodically; if the patient reports positive benefits, the treatment should continue.<sup>2,17,70</sup>

### Pharmacological therapy

1. Medications should be prescribed to treat symptoms that cause the patient to struggle, but they should be used in low doses because the side effects can be similar to FMS symptoms.<sup>2</sup>
2. Anticonvulsants such as gabapentin and pregabalin and SNRIs such as duloxetine and milnacipran are recommended at a strong level in the Canadian and Israeli guidelines, but at a weak level in the German and European guidelines.<sup>3</sup> Those drugs have a high level of evidence in all four guidelines, and all researchers, especially in the EULAR guidelines, agreed to the use of duloxetine, milnacipran, and tramadol. However, differences in permission conditions in each nation and cultural differences made the recommendation levels different.<sup>17</sup>
3. If the benefit versus cost analysis is not positive after 4 weeks of pharmacological therapy, the medication should be suspended.

**Table 1. Stepwise treatment approaches recommended in four guidelines**

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**European League Against Rheumatism.<sup>3</sup>**

- First: Patient education and providing written information about the condition
- Second: Physical therapy with individualized graded physical exercises (can be combined with other recommended non-pharmacological therapies such as hydrotherapy or acupuncture)
- Third: Additional individualized treatment based on reassessment of patients
  - ✓ Pain-related depression, anxiety, catastrophizing, overly passive or active coping: Psychological therapies
  - ✓ Severe pain/sleep disturbance: Pharmacotherapy
  - ✓ Severe disability/sick-leave: Multimodal rehabilitation programs

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**Germany.<sup>70</sup>**

- Mild: Adequate physical and psychosocial activity (e.g., mental activity, maintenance of hobbies and social contacts)
- Severe: Physical therapy, temporary drug therapy, multimodal therapy
- Lack of response to multimodal therapy in severe cases: multimodal programs, disorder-specific psychological or drug therapy for physical comorbidities.
  - ✓ Multimodal complex treatment: (semi-)inpatient multimodal pain therapy, multimodal rheumatologic complex treatment, inpatient psychosomatic-psychotherapeutic hospital treatment

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**Israel.<sup>17</sup>**

- Step 1
  - ✓ Education and explanation of the essence of the disorder and the principals of treatment
  - ✓ Instructions regarding graded aerobic exercise adjusted to the functional level and general health of the patient
  - ✓ Referral to hydrotherapy/aquatic exercise
  - ✓ Start low-dose amitriptyline (10–25 mg at bedtime)
  - ✓ Refer for CBT
- Step 2
  - ✓ Treatment with an SNRI medication (duloxetine, milnacipran) instead of amitriptyline or the addition of an SSRI medication (e.g., fluoxetine) to amitriptyline treatment
  - ✓ Start treatment with pregabalin to improve sleep quality and reduce pain
  - ✓ Refer for balneotherapy
  - ✓ Add complimentary medicine modalities: tai chi and yoga

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**Canada.<sup>2</sup>**

- First: Manage in the primary care setting with knowledgeable healthcare professionals and ideally, where possible, augment with access to a multidisciplinary team
  - Second: Specialist consultation, including referral to a sleep specialist or psychologist for selected subjects, but continued care by a specialist is not recommended
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The longest randomized controlled trial of amitriptyline, duloxetine, and pregabalin was 6 months, so suspension of medication should be considered after 6 months of pharmacological therapy.<sup>70</sup>

4. In the European guidelines, non-steroidal anti-inflammatory drugs and serotonin receptor reuptake inhibitors (SSRIs) are not recommended due to their lack of effectiveness. In particular, it is strongly recommended not to use growth hormone, sodium oxybate, high-potency opioid analgesics, or corticosteroids due to their lack of effectiveness and high possibility of side effects.<sup>3</sup>
5. Anxiolytics, hypnotics, ketamine, monoamine oxidase inhibitors (MAOIs), neuroleptics are negatively recommended in German.<sup>70</sup> On the other side, Canadian guideline describes that combinations of simple analgesics, TCA, other antidepressants, gabapentinoids, dopaminergic agents or sleep modifiers are possible pharmacological strategies.<sup>2</sup> Amitriptyline and cyclobenzaprine for treatment of insomnia are weakly recommended in EULAR.<sup>3</sup>

### **Non-pharmacological therapy**

1. Exercise is recommended at a strong level because of it offers pain relief, an increase in physical function, and a sense of well-being, and it is widely available, low cost, and safe. There is still no evidence for a difference in the effectiveness of aerobic exercise and muscle-strengthening exercise.<sup>3</sup>
2. CBT is recommended as the primary treatment in Germany, Canada, and Israel,<sup>17</sup> and receiving CBT for even a short period of time helps to reduce pain and the fear of activity.<sup>2</sup> In the European guidelines, a modest reduction effect and long-term effect of CBT are recognized in the pain, mood, and disability domains. CBT is recommended at a weak level if patients have mood disorders or non-adaptive strategies.<sup>3</sup>
3. Non-pharmacological therapy is preferred in the German guidelines because symptoms worsened again after the suspension of medication, pharmacological therapy induced hepatotoxicity or significant weight gain, and the side effects of the drugs were similar to FMS symptoms.<sup>17</sup>
4. In the European guidelines, mindfulness-based stress reduction (MBSR), acupuncture, and hydrotherapy are recommended at a weak level for the improvement of pain, fatigue, and QoL. However, hydrotherapy and acupuncture can have non-specific effects.<sup>3</sup> Meditation and exercise therapy such as qi gong, yoga, and tai chi MBSR can help improve sleep, fatigue, and QoL,<sup>71</sup> and they are recommended at a weak level in the European guidelines and a strong level in the German guidelines. They are recommended for only a small number of patients in the Israeli guidelines.<sup>17</sup>
5. In the European guidelines, biofeedback, capsaicin, hypnosis, massage, and S-adenosyl methionine are not recommended due to a lack of effectiveness or the quality of research. Moreover, chiropractic is not recommended at a strong level due to safety problems.<sup>3</sup>

In general, CAM treatment has a low level of evidence. However, the differences in the level of recommendations in each country might have been influenced by differences in the definition of CAM and the culture of each country. For example, tai chi is classified as an exercise in Canada and as CAM in Germany and Israel.<sup>17</sup> Hypnotherapy is considered a complementary therapy in the United States,<sup>72</sup> but it is classified as psychotherapy in Canada.<sup>17</sup> Although hydrotherapy and balneotherapy are not recommended in the Canadian guidelines because of a lack of evidence, they are recommended for some patients in the German guidelines because hydrotherapy is more familiar and available in Europe than in Canada. The Canadian guidelines do not recommend any CAM treatment because of a low level of scientific evidence.<sup>2</sup> However, considering that FMS lasts for many years or decades, some CAM could be included in the self-management strategies.<sup>17</sup>

## CONCLUSIONS

FMS is a disease with the core symptom of CWP that is accompanied by various physical ailments that cause inherent mental and social suffering. The concept of FMS should be understood using an integrative biopsychosocial model. The goal of FMS treatment should ultimately be to improve patients' health-related QoL by comprehensively managing their functional levels and psychosocial contexts, including pain reduction. Achieving that goal in

medical reality requires complex, multidisciplinary treatment. Various experts should work together to offer pharmacological therapy and non-pharmacological treatment such as CBT. In the long-term, patients should be motivated to develop and maintain self-management strategies such as exercise and stress management so that they can control their symptoms and improve functioning on their own. That process requires the establishment of a cooperative relationship among medical staff, colleagues, patients, and caregivers to provide patients with scientific and rational treatment.

## CONFLICT OF INTEREST

The author reports no conflicts of interest.

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