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Critical Review

AAPT Diagnostic Criteria for Fibromyalgia

Lesley M. Arnold,[*] Robert M. Bennett,[†] Leslie J. Crofford,[‡] Linda E. Dean,[§] Daniel J. Clauw,[¶] Don L. Goldenberg,[||] Mary-Ann Fitzcharles,[**] Eduardo S. Paiva,[††] Roland Staud,[‡‡] Piercarlo Sarzi-Puttini,[§§] Dan Buskila,[¶¶] and Gary J. Macfarlane[§]

[*]*Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, Cincinnati, Ohio*
[†]*Department of Medicine, Oregon Health and Science University, Portland, Oregon*
[‡]*Division of Rheumatology and Immunology, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee*
[§]*Epidemiology Group and Aberdeen Centre for Arthritis and Musculoskeletal Health, School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Scotland, United Kingdom*
[¶]*Departments of Anesthesiology, Medicine (Rheumatology), and Psychiatry, University of Michigan Medical School, Ann Arbor, Michigan*
[||]*Department of Medicine, Tufts University School of Medicine, Boston, Massachusetts, and Departments of Medicine and Nursing, Oregon Health and Science University, Portland, Oregon*
[**]*Division of Rheumatology, Department of Medicine, McGill University, Montreal, Quebec, Canada*
[††]*Division of Rheumatology, Department of Medicine, Universidade Federal do Parana, Curitiba, Brazil*
[‡‡]*Division of Rheumatology, Department of Medicine, University of Florida, Gainesville, Florida*
[§§]*Division of Rheumatology, Department of Medicine, Milan University, Milan, Italy*
[¶¶]*Department of Medicine, H. Soroka Medical Center, Ben Gurion University of the Negev, Beer Sheva, Israel*

Abstract: **Fibromyalgia (FM) is a common chronic pain disorder that presents diagnostic challenges for clinicians. Several classification, diagnostic and screening criteria have been developed over the years, but there continues to be a need to develop criteria that reflect the current understanding of FM and are practical for use by clinicians and researchers. The Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks (ACTTION) public-private partnership with the U.S. Food and Drug Administration (FDA) and the American Pain Society (APS) initiated the ACTTION-APS Pain Taxonomy (AAPT) to develop a diagnostic system that would be clinically useful and consistent across chronic pain disorders. The AAPT established an international FM working group consisting of clinicians and researchers with expertise in FM to generate core diagnostic criteria for FM and apply the multidimensional diagnostic framework adopted by AAPT to FM. The process for developing the AAPT criteria and dimensions included literature reviews and synthesis, consensus discussions, and analyses of data from large population-based studies conducted in the United Kingdom. The FM working group established a revised diagnosis of FM and identified risk factors, course, prognosis, and pathophysiology of FM. Future studies will assess the criteria for feasibility, reliability, and validity. Revisions of the dimensions will also be required as research advances our understanding of FM.**

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Address reprint requests to Lesley M. Arnold, M.D., Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine, 260 Stetson Street, Suite 3200, Cincinnati, Ohio 45219. E-mail address: lesley.arnold@uc.edu
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Perspective: ***The ACTTION-APS FM taxonomy provides an evidence-based diagnostic system for FM. The taxonomy includes diagnostic criteria, common features, comorbidities, consequences, and putative mechanisms. This approach might improve the recognition of FM in clinical practice.***

Key Words: *Fibromyalgia, diagnosis, criteria, AAPT, dimensions.*

Over many decades, there have been efforts to develop diagnostic criteria for the condition we now recognize as fibromyalgia (FM). The multiple symptoms and comorbidities associated with FM make it difficult to diagnose, and FM is still underdiagnosed and undertreated.[7,34,79] The diagnosis of FM might take >2 years, with patients seeing an average of 3.7 different physicians during that time.[34] Many health care providers, particularly in primary care, report unclear diagnostic criteria, a lack of confidence in using existing criteria for diagnosis, insufficient training or skill in diagnosing FM, and a lack of knowledge of treatment options.[79] Therefore, despite progress in the understanding and management of FM, there remain barriers in the recognition and diagnosis of FM in clinical practice.

To address problems related to the diagnosis of different chronic pain disorders, the Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations Opportunities and Networks (ACTTION) public-private partnership with the U.S. Food and Drug Administration (FDA) and the American Pain Society (APS) initiated the ACTTION-APS Pain Taxonomy (AAPT) to develop a diagnostic system that would be clinically useful and consistent across chronic pain disorders. Fillingim et al[61] provides more information about the rationale and background for the AAPT. In 2013, the AAPT Steering Committee invited L.M.A., R.M.B., and L.J.C. to be co-chairs of the Fibromyalgia Working Group. The co-chairs subsequently selected international FM experts as members of the working group. The goal of the Fibromyalgia Working Group was to apply the multidimensional diagnostic framework adopted by AAPT to FM and evaluate new approaches to the diagnosis of FM that might improve the recognition of FM in clinical practice. Briefly, in the AAPT taxonomy, there are 5 dimensions: dimension 1: core diagnostic criteria; dimension 2: common features; dimension 3: common medical co-morbidities; dimension 4: neurobiological, psychosocial, and functional consequences; and dimension 5: putative neurobiological and psychosocial mechanisms, risk factors, and protective factors.[61]

As part of the AAPT process, the Fibromyalgia Working Group members held in-person meetings, teleconferences, and email communications to review the literature on FM symptoms and diagnostic criteria and establish consensus on the approach to FM diagnosis. This article details the development of the dimensions for FM.

Dimension 1

Core Diagnostic Criteria

There have been many efforts to improve the identification of patients with FM, and several classifications, diagnostic and screening criteria have been developed over the years.[11,16,126,162,187-189,193,197] Early efforts focused on FM as a chronic widespread pain disorder with other associated symptoms.[162,197] The American College of Rheumatology (ACR) 1990 classification criteria[193] eliminated associated symptoms and focused solely on chronic widespread pain (CWP) (defined as pain in the left side of the body, pain in the right side of the body, pain above the waist, pain below the waist, and axial skeletal pain [cervical spine or anterior chest or thoracic spine or low back]) and tenderness (defined as pain on palpation of ≥11 of 18 specific tender point sites on the body). Although the ACR 1990 criteria helped to advance research studies of FM, the criteria were not intended for use in clinical practice, did not include commonly associated symptoms, and required a tender point exam, which was impractical for use in the clinical setting.[74] With the publication of the 2010 and 2011 criteria,[188,189] the definition of FM moved from a predominantly chronic pain disorder to a multi-symptom disorder and eliminated the tender point exam as a requirement for diagnosis. Although the authors of the 2010/2011 criteria re-emphasized the importance of associated symptoms, there may have been too much movement away from chronic pain as the core symptom of FM.[95] Studies of alternative criteria evaluated a variety of associated symptoms along with various definitions of widespread pain in the diagnosis of FM.[11,16] The authors of the revised 2016 criteria[187] addressed the problem with the 2010/2011 criteria regarding misclassification of patients who did not have generalized pain,[57] which occurred because the 2010/2011 criteria do not consider the spatial distribution of painful sites. The 2016 criteria now require that patients have pain in 4 of 5 regions, called "generalized pain" to distinguish it from the 1990 definition of "widespread pain." Even though there are different definitions of widespread pain and associated symptoms, most of the previous FM criteria appear to identify a similar group of patients most clinicians would agree have FM.

Based on the review of existing criteria, the consensus of the Fibromyalgia Working Group was to devise core diagnostic criteria (dimension 1) that would reflect the current understanding of FM and be practical for use by clinicians and to provide a basis for clinical trial inclusion and exclusion criteria. The multidimensional diagnostic framework of the AAPT allowed the group to identify the core symptoms of FM and include other associated symptoms and signs in dimension 2. The group members agreed that dimension 1 would include only a core set of diagnostic symptoms, and that signs such as tender points would be relegated to dimension 2.

Definition of FM Pain in Dimension 1

The Fibromyalgia Working Group members agreed that dimension 1 should identify FM as predominantly a chronic pain disorder. In other words, all patients would be required to have chronic pain to be diagnosed with FM. However, the members raised a question about how to define FM pain, that is, whether FM-related pain should be defined by the 1990 ACR criteria (CWP) or by multisite pain (MSP) as in the ACR 2010/2016 criteria. The main distinguishing feature between CWP and MSP is that MSP is a simple count of the number of body sites with pain, whereas CWP requires a specific anatomical distribution of the pain reported. To address this question, members of the working group analyzed data from large population-based studies of 34,818 subjects conducted in the United Kingdom.

The first previously published study[48] investigated whether associations between pain and the additional symptoms associated with FM are different in persons with CWP as defined by the ACR 1990 criteria compared to MSP, with or without joint areas. Briefly, 6 studies were used: the National Child Development (1958 British birth cohort),[13] the Epidemiology of Functional Disorders (EpiFund),[129] the Kid Low Back Pain (Kid LBP),[181] the Managing Unexplained Symptoms (Chronic Widespread Pain) in Primary Care: Involving Traditional and Accessible New Approaches (MUSICIAN),[122] the Study of Health and its Management (SHAMA),[63] and the Women's Health Study (WHEST).[15] In all of the population studies, participants were asked "Have you experienced pain in the past month lasting at least a day?"; those responding positively shaded the sites of pain on 4-view body manikins and indicated whether pain had been present for ≥3 months. Manikins were coded for pain at 35 individual sites. The number of pain sites were determined, including whether the subjects met the ACR 1990 criteria for CWP. MSP was defined as the number of pain sites needed to reach a prevalence similar to that of CWP (as defined by the ACR 1990 criteria) from the same population. As there are no gold-standard definitions of FM, and the prevalence differs depending on the criteria used,[95] a prevalence of 2 to 5% was chosen to reflect both this variability and the expected prevalence using the ACR 1990 criteria. Information was also collected across at least 2 studies on each of the following symptoms: fatigue (Chalder fatigue[32] or SF-36 vitality scale[22]), sleep (Sleep Problem Scale[91] or 2010 modified preliminary ACR criteria question), mood (General Health Questionnaire,[72] Hospital Anxiety and Depression Scale,[200] PROMIS Global Mental Health score,[85] and SF-36 mental health[22]), and the presence of somatic symptoms.[143] Relationships with pain were determined by multiple binary logistic regression models, specifically comparing among those with MSP, and subjects with and without CWP. Among those reporting the nonpain symptoms associated with FM (fatigue, sleep disturbance, somatic symptoms, and mood impairment), there was an increased likelihood of reporting pain, the magnitude of which was similar regardless of the pain definition used. Additionally, there were no indications of differences in the magnitude of the associations by sex. The findings support the continued collection of both pain and associated symptoms when classifying FM and highlight that pain may not require the definition of CWP as used in the 1990 ACR criteria. Classification of pain simply by self-reported number of sites distributed throughout the body, including joint sites, is sufficient when defining the pain of FM. The number of pain sites needed to define MSP in FM was found to be ≥8, which is consistent with previous studies.[184]

Nonpain FM Symptoms in Dimension 1

The Fibromyalgia Working Group proposed a reduction in nonpain symptoms for inclusion in dimension 1 as core diagnostic criteria to reduce the complexity of diagnosis and make the FM criteria easier to use in practice. The Fibromyalgia Working Group identified fatigue and sleep problems as 2 key associated symptoms for several reasons. First, these symptoms, along with chronic pain, occur in most patients with FM.[7] Second, pain, sleep disturbance, and fatigue were identified by OMERACT as core symptoms of FM.[133,196] Finally, responder definitions using fatigue and sleep problems, in combination with pain and physical function, were shown to be responsive to change in FM clinical trials.[12] Other nonpain symptoms and signs are included in dimension 2 and may be considered when evaluating a patient but are not required for diagnosis. However, more study was required to determine whether the presence and severity of fatigue and sleep problems along with MSP would suffice for the core diagnostic criteria.

A second study was conducted using data from the UK population-based studies to address this issue and answer the following questions: 1) What is the prevalence of CWP or MSP in conjunction with the key symptoms of fatigue and/or sleep problems? Is this similar to the prevalence we would expect for FM? and 2) If fatigue and/or sleep problems are present in addition to pain, how many pain sites would it take to result in the same prevalence as CWP or FM without the presence of these symptoms? "Any pain" was defined as a positive response to the following pain stem question that was collected across all of the study populations: "Thinking back over the past month, have you had any aches or pains that have lasted for 1 day or longer?" The prevalence of "any pain" in conjunction with fatigue and/or sleep problems[48] was estimated and subsequently recalculated after the addition of each pain site as indicated by body manikin (eg, 1 site or more, 2 sites or more) until a similar prevalence of CWP or FM was reached.

There were a total of 28,789 subjects across the studies (mean age 42–55 years; males 43–52% [WHEST was conducted only in females]) included in this second study. The prevalence of CWP (defined per the ACR 1990 criteria) across studies was 12 to 17%, and in each study the equivalent prevalence was obtained by defining MSP as ≥8 sites, as noted in Dean et al.[48] In separate analyses using manikins without joint areas included, MSP was consistently defined as reporting ≥8 sites.

Therefore, joint areas were included in all subsequent analyses in this study.

The prevalence of CWP in conjunction with fatigue was 6% within WHEST and 7% within SHAMA. Using the multisite definition of pain (ie, ≥8 of 35 pain sites), the prevalence of MSP in conjunction with fatigue was 7% in both populations. The prevalence of CWP and sleep problems was 6% within WHEST, 6.5% within SHAMA, and 7% within EpiFund. The prevalence of MSP in conjunction with sleep problems was 7% across all populations. Thus, the prevalence of CWP or MSP (≥8 pain sites) in addition to either fatigue or sleep problems was between 6 and 7% and was greater than the prevalence expected for FM (2–5%). To reach a similar population prevalence expected for FM, ≥10 pain sites are needed in addition to either fatigue or sleep problems.

The prevalence of CWP in conjunction with fatigue and sleep problems was 3% within WHEST and 5% within SHAMA, which is in line with the prevalence expected for FM. Using an MSP definition of ≥8 of 35 sites, the prevalence of MSP in conjunction with fatigue and sleep problems was 4% within WHEST and 5% within SHAMA. Therefore, the prevalence of CWP or MSP in addition to both fatigue and sleep problems was between 3 and 5%, similar to the prevalence for FM established by prior studies.

Additional analyses were conducted to examine the number of pain sites required to reach expected FM prevalence using different combinations of pain, fatigue, and sleep problems. Using the WHEST, SHAMA, EpiFund, and 1958 databases, at least 13 to 15 pain sites were needed if the subject had no sleep or fatigue problems. Using SHAMA, WHEST, and EpiFund, at least 10 to 11 pain sites were needed if the subject had sleep problems, but no fatigue. In the SHAMA and WHEST databases, at least 10 to 11 pain sites were needed if the subject had fatigue but no sleep problems. Finally, if both sleep problems and fatigue were present in the SHAMA and WHEST databases, at least 6 to 8 sites were needed to reach the expected FM prevalence.

Number of Pain Sites

Based on the results of the analyses conducted on the population-based databases and the consensus of the Fibromyalgia Working Group, the proposed criteria for FM dimension 1 require ≥11 pain sites be endorsed on the 35-point body manikin. However, the working group considered that the 35-point manikin would likely be impractical for use by most clinicians and researchers. To reduce the number of possible sites, appropriate sites were grouped together, while keeping key body areas separated such as arms and legs. This resulted in a new body manikin that had only 9 defined sites: head, left arm, right arm, chest, abdomen, upper back and spine, lower back and spine (including buttocks), left leg, and right leg. Another analysis was then conducted using the 4 studies (SHAMA, WHEST [women only], 1958 Birth Cohort, and EpiFund) to determine a new definition of MSP based on the 9-point body manikin that produced the same prevalence as the ACR 1990 CWP definition from the same population. The results indicated that the minimum number of sites required to reach a similar prevalence to that of CWP was between 5 and 6 sites depending on the study used. A conservative approach was taken to define MSP as the reporting of ≥6 pain sites using the 9-point body manikin. Further analysis was undertaken to assess the association between the new definition of MSP and the additional nonpain factors associated with FM, compared with the original MSP definition. This analysis demonstrated that the associations between the new definition of MSP using a 9-point manikin were generally comparable to those using the original MSP definition using a 35-point manikin (data summarized in Supplementary Tables 1 and 2).

Duration of Symptoms and Presence of Other Disorders in Dimension 1

When considering the necessary duration of symptoms that are required for diagnosis of FM, the working group consensus was to maintain the 3-month time frame, which best reflects the chronicity of FM. The group also agreed that the presence of another pain disorder or related symptoms does not rule out a diagnosis of FM, consistent with the 1990 ACR criteria.[193] However, as noted in Bennett et al[16] criteria, a careful clinical evaluation is recommended to identify any condition that could fully account for the patient's symptoms and/or contribute to the severity of the symptoms.

FM Criteria in Dimension 1

Based on the results of the analyses conducted on the population-based databases and the consensus of the Fibromyalgia Working Group, the criteria for FM, dimension 1, are presented in Table 1 and Fig 1. The pre-shaded areas within the body manikin in Fig 1 were included to prevent users from counting the same area twice (for example front and back of the same leg). At

Table 1. AAPT Diagnostic Criteria for Fibromyalgia

Dimension 1: Core Diagnostic Criteria

1. MSP defined as 6 or more pain sites from a total of 9 possible sites (see Fig 1)
2. Moderate to severe sleep problems OR fatigue
3. MSP 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 FM. 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.

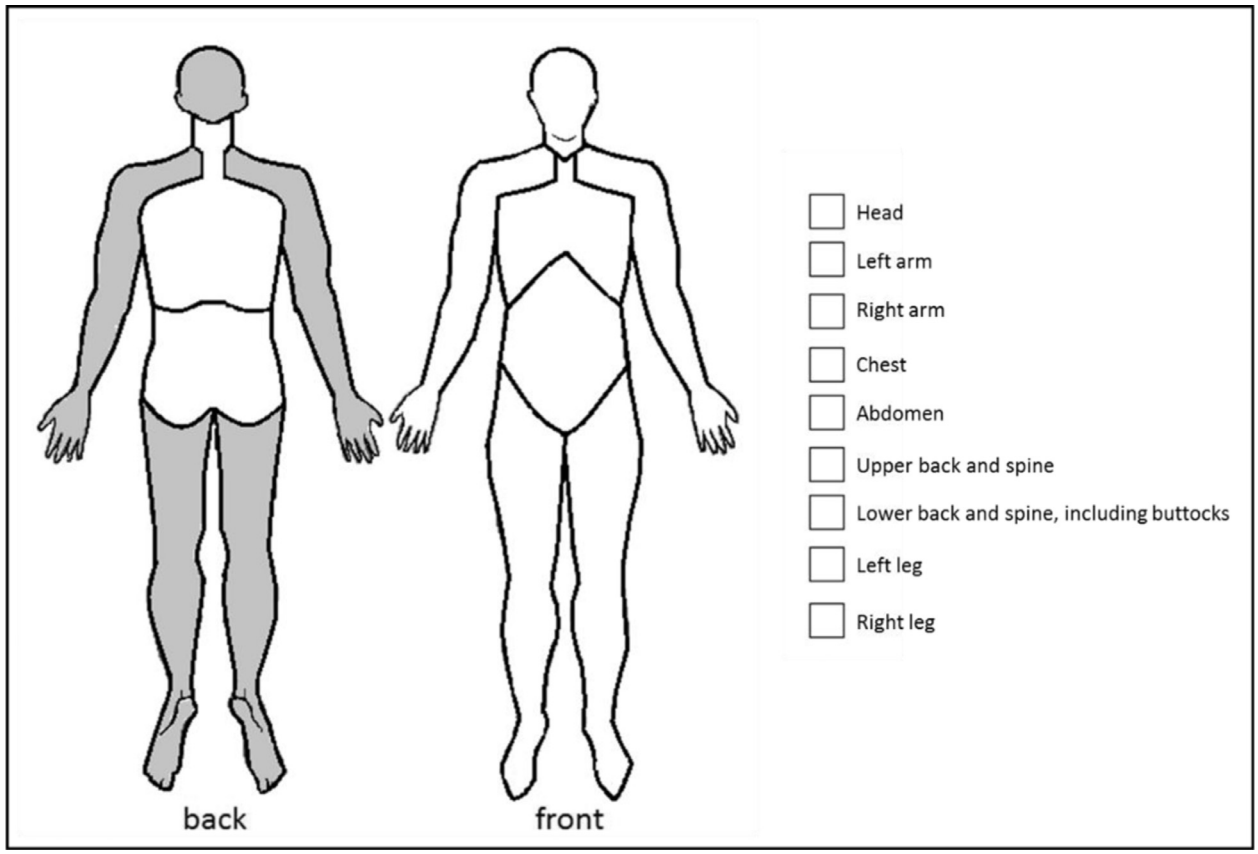

Figure 1. Number of painful body sites.
Patients are asked to check the areas in which they experience pain on the 2-view manikins (ignoring the pre-shaded areas). Alternatively, patients may use the checklist of body sites.
The number of separate sites are summed from a maximum of 9 body sites.

least 6 of 9 pain sites are required along with fatigue or sleep problems. Fatigue is defined as physical or mental fatigue judged as at least moderate severity by the health care professional. Physical fatigue may manifest as a complaint of physical exhaustion after physical activity, including an inability to function within normal limits for activities that constitute normal daily activities and the requirement for rest periods after activity. Sleep problems are defined as difficulty falling or staying asleep, frequent awakening that is disturbing during a sleep period, or feeling unrefreshed after sleep. These symptoms must be assessed as at least moderate severity by the health care professional. In assessing the severity of fatigue and sleep problems, the clinician may use multiple sources of information, including patient history and exam, as well as self-reported questionnaires or other corroborating data.

Differential Diagnosis

These new criteria for FM recommend that clinicians evaluate for the presence of other disorders so that appropriate treatments can be initiated. This can be challenging in clinical practice because comorbid disorders, including other chronic pain disorders, are common in patients with FM.[7] Several disorders can mimic FM, such as hypothyroidism and inflammatory rheumatic diseases. In addition, some medications may contribute to pain, such as statins, aromatase inhibitors, bisphosphonates, and opioids (ie, opioid-induced hyperalgesia). However, these conditions and many others (eg, rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus [SLE], spinal stenosis, neuropathies, Ehlers Danlos syndrome,[51] sleep disorders such as sleep apnea, and mood and anxiety disorders[121]) also co-occur in patients with FM. The clinician must determine the possible contribution of various disorders to the patient's presentation. The presence of other disorders does not necessarily exclude a diagnosis of FM, and all disorders will need clinical attention. Table 2 summarizes some of the key medical disorders considered in the differential diagnosis of FM that require additional assessment, tests, and specific treatment. A description of several differentiating signs and symptoms are provided in the table, but a detailed review of the diagnostic tests for each medical disorder is beyond the scope of this article.

In general, extensive laboratory testing is not necessary to diagnose FM.[7] Screening laboratory tests are sometimes obtained to evaluate other possible causes of symptoms or signs. These tests include erythrocyte sedimentation rate and/or C-reactive protein, complete blood count, comprehensive metabolic panel, and thyroid function test. Routine testing for rheumatoid factor or antinuclear antibodies to diagnose FM is not recommended unless the patient has signs or symptoms suggesting an autoimmune disorder, or if initial

Table 2. Differentiating Key Disorders From Fibromyalgia

Medical Disorder	*Differentiating Signs and Symptoms*
Rheumatologic	
Rheumatoid arthritis	Predominant joint pain, symmetric joint swelling, joint line tenderness, morning stiffness >1 hour
Systemic lupus erythematosus	Multisystem involvement, joint/muscle pain, rash, photosensitivity, fever
Polyarticular osteoarthritis	Joint stiffness, crepitus, multiple painful joints
Polymyalgia rheumatica	Proximal shoulder and hip girdle pain, weakness, stiffness, more common in the elderly
Polymyositis or other myopathies	Symmetric, proximal muscle weakness and pain
Spondyloarthropathy	Localization of spinal pain to specific sites in the neck, mid-thoracic, anterior chest wall, or lumbar regions, objective limitation of spinal mobility due to pain and stiffness
Osteomalacia	Diffuse bone pain, fractures, proximal myopathy with muscle weakness
Neurologic	
Neuropathy	Shooting or burning pain, tingling, numbness, weakness
Multiple sclerosis	Visual changes (unilateral partial or complete loss, double vision), ascending numbness in a leg or bandlike truncal numbness, slurred speech (dysarthria)
Infectious	
Lyme disease	Rash, arthritis or arthralgia, occurs in areas of endemic disease
Hepatitis	Right upper quadrant pain, nausea, decreased appetite
Endocrine	
Hyperparathyroidism	Increased thirst and urination, kidney stones, nausea/vomiting, decreased appetite, thinning bones, constipation
Cushing syndrome	Hypertension, diabetes, hirsutism, moon facies, weight gain
Addison disease	Postural hypotension, nausea, vomiting, skin pigmentation, weight loss
Hypothyroidism	Cold intolerance, mental slowing, constipation, weight gain, hair loss

inflammatory indices are abnormal (recognizing that some patients with rheumatoid arthritis or SLE may have normal erythrocyte sedimentation rate and/or C-reactive protein values). Depending on symptoms, medical history and physical exam, other tests such as ferritin, iron-binding capacity and percentage of saturation, and vitamin B12 and vitamin D levels may be indicated.

Dimension 2

Common Features

Features that are not included in dimension 1 but may be used to support a diagnosis of FM are described below.

Tenderness, defined as a generalized sensitivity of soft tissues and muscles to pressure that would not normally be expected to cause pain, is a universal complaint and in the 1990 ACR criteria was codified by the "tender point" examination.[193] Although the tender point evaluation has been eliminated from the more recent criteria, with the exception of the 2012 FM screen,[11,126] the symptom of "tenderness to touch" is included in the 2014 Bennett et al criteria[16] and the 2012 FM screen[11,126]; this question was ranked third in importance as a diagnostic question in the 2014 Bennett et al criteria.[16] A tender point exam, either as part of the 1990 ACR criteria[193] or an abbreviated version,[11,126] may provide valuable information to the clinician about the overall status of the patient's condition[74] and support the diagnosis of FM.

Dyscognition (eg, trouble concentrating, forgetfulness, and disorganized or slow thinking) is increasingly recognized as a major feature of FM, with dysfunction being seen in working memory and executive function.[70] Self-reported questionnaires are useful to screen for dyscognition in patients with FM, but full neuropsychological testing may be required to delineate the extent of cognitive dysfunction.[163] In brain functional magnetic resonance imaging (fMRI) studies,[71,170] FM patients showed lower activation in the inhibition and attention networks and increased activation in other areas. Because inhibition and pain perception may use overlapping networks, resources taken up by pain processing may be unavailable for other processes.[71]

Musculoskeletal stiffness is experienced, in varying degrees, by all FM patients.[17] Interestingly, stiffness in FM patients is difficult to distinguish from the stiffness in conditions such as rheumatoid arthritis, polymyalgia rheumatica, and ankylosing spondylitis. FM-related stiffness, like that described in these other conditions, is typically more severe in the early morning and improves as the day goes on.[86] However, unlike these other conditions, it is not responsive to corticosteroids.[37] This feature is only used in the 2014 Bennett et al criteria and was ranked fifth in importance as a diagnostic question.[16]

Environmental sensitivity or hypervigilance, manifesting as intolerance to bright lights, loud noises, perfumes and cold, is a common complaint of FM patients. It is probably a reflection of central sensitization.[54,142] A recent study has provided clues as to how sensitivity to bright lights modulates brain connectivity, such that previously innocuous inputs are experienced as being painful.[125] This feature is only used in the 2014 Bennett et al criteria[16] and was ranked second in importance as a diagnostic question.

Epidemiology

The prevalence of FM varies from .5 to 12%, depending on the population sampled and the method of ascertainment.[104,128,138,144,158,177,182,192] Females outnumber

males in a ratio of about 3:1 in studies that do not use tender points as a criterion. Major ethnic variations in prevalence have not been well documented.[151] A survey in 5 European countries (Germany, Italy, Portugal, France, and Spain), using the 1990 ACR criteria,[193] estimated prevalence of FM in the general population and also in 8 participating rheumatology clinics; the overall presence of FM in the 5 countries ranged from 2.9 to 14% in outpatients treated in rheumatology practices.[21]

The prevalence of FM increases with age, rising in middle age (50–59 years) and then dropping off in the oldest age groups (80+ years).[191] The average age of onset is between 30 and 50 years. FM in children is now well recognized. Estimates of the general population prevalence of FM in children and adolescents vary from 1.0% up to 6.2%.[24,27,36,135,199] FM in adolescents is associated with significant impairment in physical function and lower perceived health status compared with peers.[98,101] There is often peer-related discrimination with resulting unpopularity, isolation, and school absenteeism.[99,100] As peer relationships are a key element in the psychological development of children, the occurrence of FM can lead to adjustment problems and other psychopathology in adulthood.[116] The symptoms of FM persist into adulthood for the majority of patients experiencing childhood or adolescent FM.[98]

The incidence of FM was determined in a population-based sample of Norwegian women between the ages of 20 and 49 years who were followed for 5.5 years.[65] The incidence of FM among women who began the observation period without any complaints of musculoskeletal pain was 3.2%, corresponding to an average annual incidence of 583 cases/100,000 women between 20 and 49 years of age. For those with any self-reported pain at the beginning of the study, the incidence was 25%, and risk factors for the development of FM included pain for ≥6 years, self-assessed depression, lack of professional education, and the presence of 4 or more associated symptoms, such as disturbed bowel function, unrefreshing sleep, paresthesia, and subjective swelling. In another cohort of 1,198 early arthritis patients followed by rheumatologists, the incidence of FM was 6.77/100 person-years in the first year after diagnosis of arthritis, and declined to 3.58/100 person-years in the second year. Pain severity and poor mental health predicted FM risk.[114]

Dimension 3

Common Medical and Psychiatric Comorbidities

FM is associated with many comorbidities that may be categorized as other somatic pain disorders, psychiatric conditions, sleep disorders, rheumatic diseases, and other conditions. It is commonly conjectured that many of these associations are a result of central sensitization,[198] but this mechanism cannot explain all associations. Chronic fatigue syndrome is a condition that has considerable overlap with FM, with the predominance of pain an identifier of FM.[134] Among the somatic pain conditions that associate with FM, the best recognized are irritable bowel syndrome, chronic pelvic pain and interstitial cystitis, chronic head and orofacial conditions such as temporomandibular disorder, otologic symptoms, chronic headaches, and migraine disorder.[2,6,90,119,124,152] Psychiatric conditions that associate with FM include major mood disorder (eg, major depressive disorder and bipolar disorder), anxiety disorders (eg, generalized anxiety disorder, panic disorder, posttraumatic stress disorder, social phobia, and obsessive compulsive disorder), and substance abuse disorder.[10,20] Sleep disorders that can occur concomitantly with FM include obstructive and central sleep apnea and restless leg syndrome.[153,166] Various rheumatic conditions, both inflammatory and degenerative, may act as a peripheral pain generator and associate with FM including inflammatory rheumatic diseases such as rheumatoid arthritis, systemic lupus erythematosus, scleroderma, Sjogren's syndrome and others, and osteoarthritis.[14,23,33,59,80,89,137] Joint hypermobility as in joint hypermobility syndrome and Ehler's Danlos syndrome may predispose to recurrent pain and subsequent FM.[31] The association with rhinitis and urticaria is especially interesting, as gene expression profiling in FM has reported an up-regulation of genes involved in allergic responses.[96] Obesity is common in patients with FM and is associated with greater pain severity, poorer sleep, and reduced physical strength and flexibility.[73,141]

Dimension 4

Neurobiological, Psychosocial, and Functional Consequences

General Outcome, Including Cost of FM

Long-term outcome data for FM are limited. Although available studies indicate that symptoms of FM often persist, many patients are able to identify strategies over time that can moderate symptoms. In one of the earliest prospective studies, 538 FM patients from U.S. rheumatology centers that had a special interest in FM were followed every 6 months for 7 years.[185,186] Most outcome measures, including functional disability, did not change or worsened slightly over time. Sixty percent of patients who were diagnosed with FM rated their health as fair or poor. FM patients averaged 1 outpatient visit each month. Costs increased over the 7 years, with a mean yearly per-patient cost of $2,274 in 1996 U.S. dollars.

In single-center prospective reports, there was also little change in symptoms or function over time. In 1 report from Boston, all patients had persistent FM symptoms and 55% reported moderate or severe pain after 10 to 15 years.[60,103] However, 70% of patients reported that their overall FM symptoms were a little or a lot better than when first diagnosed, and 50% reported that they were doing well. Sleep disturbances were the most persistent symptom. In a report from the U.K., 97% of FM patients still had symptoms, and 60% felt worse than their initial visit.[112]

Another multicenter study conducted in the U.S. of 1,555 FM patients found that pain, fatigue, and global well-being had not changed much over 11 years, but there was significant individual variability in outcome measures.[179] In contrast, in a prospective study of FM patients followed in Australian primary care, 47% no longer fulfilled FM criteria and 24% were in remission,[76] and one-third of FM patients in Canada experienced good outcomes at 3 years.[149] An ongoing prospective study from Spain comparing women with FM to matched controls found a greater impact on physical than on psychological outcomes, although both were markedly impaired.[157] That group also noted the combined effect of lack of physical fitness, obesity, and mood disturbances on poor quality of life in FM.[164]

FM has been associated with significant direct medical costs.[110] In a large U.S. health care database of >30,000 FM patients, health care costs were 3 times greater than controls.[18] In another survey of 16,000 patients with FM, there were greater comorbidities, physician visits, and costs compared with controls.[111] In Quebec, the mean direct annual cost of FM was estimated to be $3,804, and an average of 6 days were lost due to pain during the prior 3 months.[110] Indirect costs are also high,[110] mainly driven by lost work productivity, with the highest direct annual cost in the U.S. compared to France and Germany. [107] In a recent report from Australia, one-quarter of working FM subjects stopped work within 5 years of the diagnosis and one-third were receiving financial support because of FM.[78]

Compared with controls, patients with CWP had worse quality of life, greater disability, mood and sleep disturbances, cardiovascular comorbidity, and higher mortality rates.[136] In the 2012 U.S. National Health Interview Survey, FM patients had high levels of self-reported pain, physical and psychological comorbidities, and high medical costs, as well as high rates of Social Security and work disability.[180] Fifty-six percent of FM patients <65 years old were unable to work compared with 6% without FM. Disability payments in the prior year were 30% in FM patients compared with 3% in controls.

In a more recent study from Canada, one-third of FM patients were receiving disability payments.[62] Disability compensation was associated with illness severity, number of medications used, and previous employment in physically demanding jobs. Illness burden was evaluated in 125 individuals not complaining of CWP, 176 with CWP, and 171 with FM.[156] The FM patients had more comorbidities, pain-related medications, poorer health status and function, worse sleep, lower productivity, and greater health care costs. Those investigators also reported that over 2 years, about one-quarter of FM patients no longer met criteria for FM and that symptoms wax and wane.[3]

Morbidity and Mortality

In older European men, CWP was associated with slower cognition[113] and increased frailty.[178] There was a 1.25-fold higher risk of stroke in FM compared with controls and a 2.3-fold higher risk in younger subjects.[175] Initial reports suggested that FM and CWP were associated with increased mortality, including from cancer and cardiovascular disease.[130,171] Although there has been variability across studies conducted,[56,190] the largest study that has examined this (UK Biobank)[120] combined into a meta-analysis has confirmed that patients with CWP do have an important excess risk of death. As expected, suicidal ideation and risk of suicide were associated primarily with depression and global mental health and were much greater in patients with FM than in patients with low back pain and controls.[30,94]

Dimension 5

Putative Neurobiological and Psychosocial Mechanisms, Risk Factors, and Protective Factors

Risk Factors and Comorbidities

Individuals who develop FM nearly always have a lifelong history of chronic pain in various regions of the body, as well as other central nervous system symptoms such as fatigue, sleep, memory, and mood difficulties.[7] Often beginning in childhood or adolescence, individuals who eventually go on to develop FM are more likely to experience headaches, dysmenorrhea, temporomandibular joint disorder, chronic fatigue, irritable bowel syndrome and other functional GI disorders, interstitial cystitis/painful bladder syndrome, endometriosis, and other regional pain syndromes (especially back and neck pain).[1,40,88] As a result, many in the field have started to believe that these "centralized" pain states are best thought of as a single, lifelong disease that merely tends to manifest in multiple different bodily regions over time.[173,183,195]

In addition to FM patients frequently having a personal lifetime history of chronic pain, a strong family history of chronic pain is often identifiable. The first-degree relatives of FM patients are 8 times as likely to have this condition as the family members of controls, and also have very high rates of other chronic pain states.[9] This familial and personal co-aggregation of conditions that includes FM was originally collectively termed affective spectrum disorder[87] and, more recently, central sensitivity syndromes,[198] chronic multisymptom illnesses, and chronic overlapping pain conditions. In population-based studies, the key symptoms that often co-aggregate besides pain are fatigue, memory difficulties, and mood disturbances.[66,67] Twin studies suggest that ~50% of the risk of developing FM or related pain conditions such as irritable bowel syndrome and headache is genetic and 50% environmental.[102]

The environmental factors that are most likely to trigger the development of FM are various types of "stressors." These stressors include the following: early lifetime adverse events, medical illness (including infections), trauma, and psychosocial stressors.[131] For example, FM or similar illnesses are found at much higher than expected rates in individuals who have experienced certain types of infections[25,29] (eg, Epstein Barr virus, Lyme

disease, Q fever, viral hepatitis), trauma[26,132] (eg, motor vehicle collisions), and deployment to war.[115] FM also is very commonly seen as a comorbidity in other chronic pain conditions such as osteoarthritis, rheumatoid arthritis, and lupus.[14,59,137] This phenomenon had previously been termed "secondary FM"; however, because this is so common and might occur in a subset of nearly any chronic pain cohort, the preferred terminology is that there has been a centralization of pain that manifests as co-morbid FM. FM, especially the "primary" form, is also very comorbid with early life and current stress, and many, if not most, individuals will have a lifetime history of a psychiatric disorder such as depression or anxiety.[58] There is typically more psychiatric and psychological comorbidity seen in tertiary care settings or in individuals who are refractory to treatment.

Pathophysiology

Although few would purport that there is an animal model that mimics all of the key clinical features of FM, nonetheless animal models can be very helpful in understanding the pathogenesis of this condition.[160] Animals develop the critical features of central sensitization or centralization of pain when exposed to swim stress,[168] neonatal separation from their mothers,[147] and many other nonpainful stimuli.[160] Features of central sensitization and animal pain behaviors consistent with diffuse pain are also seen when central nervous system neurotransmitters are purposefully altered in the direction found in FM. For example, chronic reserpine administration, which depletes bioamines, leads to features consistent with FM,[159,169] as does directly increasing glutamate levels in the insulae.

The strong familial predisposition to FM has led many to study specific genes that may be associated with a higher risk of developing FM. First, candidate gene studies showed that genetic findings such as the serotonin 5-HT2A receptor polymorphism T/T phenotype, serotonin transporter, dopamine 4 receptor, and *COMT* (catecholamine *o*-methyl transferase) polymorphisms all were noted in higher frequency in FM patients than controls. Subsequent studies confirmed some of these associations, whereas others did not.[28,53] Subsequent larger genome-wide linkage and candidate gene studies identified other putative targets.[8,161] Linkage studies confirmed the strong genetic contribution to FM and suggested linkage of FM to the chromosome 17p11.2-q11.2 region.[8] The large candidate gene study identified significant differences in allele frequencies between cases and controls for 3 genes: *GABRB3* (rs4906902, $P = 3.65 \times 10^{-6}$), *TAAR1* (rs8192619, $P = 1.11 \times 10^{-5}$), and *GBP1* (rs7911, $P = 1.06 \times 10^{-4}$). These 3 genes, and 7 other genes with suggestive evidence for association, were examined in a second, independent cohort of FM patients, and evidence of association in the replication cohort was observed for *TAAR1*, *RGS4*, *CNR1*, and *GRIA4*.[161] Because classic genetic studies have not yet identified strong, reproducible polymorphisms or haplotypes associated with FM, and because there is clear evidence of environmental factors such as stress playing a prominent role in the pathogenesis, other groups have postulated that epigenetic findings might be important in FM.[35] There is also emerging evidence of functional genetic polymorphisms affecting pain severity in FM.[109]

The physiological hallmark of FM, centralization of pain or central sensitization, is thought to be augmented central pain processing. This was originally identified in FM (and still can be clinically) by noting that an individual is diffusely tender to palpation. In 1990, when the original classification criteria for FM were first published, this feature of diffuse tenderness was incorporated into the diagnostic criteria by requiring that an individual had a certain number of tender points (≥11), in addition to CWP to qualify for this diagnosis.[193] Subsequent studies using more sophisticated measures of experimental pain testing showed that individuals with FM are more tender everywhere in the body, not just in the 18 regions considered to be "tender points."[145,146] Subsequent experimental pain testing studies have identified multiple potential mechanisms that may be responsible for pain amplification in FM, including a decrease in the activity of descending analgesic pathways,[97,108] an increase in pain facilitatory pathways,[165] and a diffuse increase in the processing of all sensory stimuli (not just pain).[68,69] The notion that FM and related syndromes might represent biological amplification of all sensory stimuli has significant support from functional imaging studies that suggest that the insula is the most consistently hyperactive region, as this region is critical in sensory appraisal, with the posterior insula serving a purer sensory role, and the anterior insula being associated with the emotional processing of sensations.[44,45,49,172,174]

These initial observations that individuals with FM were diffusely tender led to subsequent functional, chemical, and structural brain neuroimaging studies that have been among the best "objective" evidence that the pain in FM is real.[82] These methods, such as fMRI, clearly demonstrate that when individuals with FM are given a mild pressure or heat stimuli, that most individuals would feel as "touch" rather than "pain," they experience pain and similar brain activation patterns in brain areas involved in pain processing.[43,75] fMRI has also proved useful in determining how comorbid psychological factors influence pain processing in FM. For example, in FM patients with variable degrees of comorbid depression, the anterior insula and amygdala activations were correlated with depressive symptoms, consistent with these "medial" and pre-frontal brain regions being involved with affective or motivational aspects of pain processing (and being more closely related to unpleasantness rather than the sensory intensity of pain).[19] A more recent advance in the use of fMRI is to look at the extent brain regions are functionally "connected" to each other, that is, simultaneously activated (or deactivated).[148] The advantage of resting-state connectivity analysis is that it is a window into brain changes associated with the chronic, ongoing spontaneous pain common in FM. Individuals with FM have increased connectivity between brain regions involved in increasing pain transmission and neural networks not normally involved in pain, such

as the default mode network, and the degree of this hyper-connectedness is related to the severity of ongoing pain.[139,140] During a painful stimulus, connectivity is decreased between key antinociceptive regions (eg, the brainstem—the origin of descending analgesic pathways) and a region previously identified to be a potential source of dysfunctional pain inhibition in FM.[92,93] Imaging studies have confirmed quantitative sensory testing studies that these individuals are more sensitive to a number of sensory stimuli other than pain, and that machine-learning paradigms can accurately distinguish FM from non-FM patients with >90% accuracy using these results.[117,118]

Other imaging techniques have been used to identify the neurotransmitter abnormalities that may be driving the pain amplification seen in FM and other chronic pain disorders. Positron emission tomography studies show that attenuated dopaminergic activity may be playing a role in pain transmission in FM, and there is evidence of decreased μ opioid receptor availability (possibly owing to increased release of endogenous μ opioids) in FM.[83,194] This latter finding as well as previous studies showing increases in endogenous opioids in the cerebrospinal fluid of FM patients has been suggested as evidence of why opioid analgesics clinically appear to not be effective in FM. There are increases in brain concentrations of the body's major excitatory neurotransmitter, glutamate, in pain-processing regions such as the insula in FM.[81] This finding has also been noted in the cerebrospinal fluid in FM.[155] Drugs such as pregabalin and gabapentin likely work in FM in part by reducing glutamatergic activity.[123] Individuals with FM that had the highest pretreatment levels of glutamate in the posterior insula were those most likely to respond to pregabalin.[84] When pregabalin led to improvement in symptoms in these individuals, there was normalization of fMRI and connectivity findings, all suggesting that this neurotransmitter is playing a critical role in the pathogenesis of FM in some individuals. Conversely, magnetic resonance spectroscopy has recently been used to demonstrate low levels of GABA in several brain regions.[64] This likely accounts for the efficacy of drugs such as gamma-hydroxybutyrate in FM.[154] This finding may also suggest biological plausibility for the finding that FM patients who have low alcohol consumption (compared to none or high) have fewer symptoms and better functionality.[105]

Because of the link between FM and exposure to stress, and because both the neuroendocrine and autonomic nervous systems could cause many of the symptoms of FM, these factors have been fairly extensively studied.[39,46,50] In fact, for several decades after it was understood that conditions such as FM or chronic fatigue syndrome were not due to inflammation or infection, these areas were receiving considerable attention. The problem is that this research has generally yielded inconsistent findings and treatment studies targeting these systems have failed; therefore, these factors are now generally thought to play a role in some individuals, but not to be central pathogenic factors in all individuals with these conditions.[4,42,47,50,127,150]

Although most agree that the core symptoms of FM are likely because of changes in the central nervous system, peripheral factors also play an important role in both the pathogenesis and treatment of FM. For example, some elements of the processes of central sensitization can be worsened or driven by ongoing nociceptive input. Thus, it is likely that the many individuals with FM that also have comorbid conditions causing ongoing peripheral nociceptive input (eg, myofascial pain, osteoarthritis, obesity[52]) would potentially benefit from therapies aimed at reducing the peripheral drive of central sensitization, as has been shown in a short-term study.[5] In fact, one of the major areas of study needed for these conditions is to try to differentiate which individuals have these phenomena that are being driven from the central nervous system and which may be driven by ongoing peripheral nociceptive input.

Although the prevailing view is that FM is not an autoimmune disorder and that classic anti-inflammatory agents are not of benefit in this condition, there are some data suggesting that the immune system may be playing a role in its pathogenesis.[77] Some have speculated that diet or obesity could contribute to this low-grade inflammation in FM and might be a potential target for therapy, and others have posited that this may provide evidence of microglia involvement in FM. There is also a current ongoing controversy regarding the meaning of finding decreased intra-epidermal nerve fiber density (ie, small-fiber neuropathy) in FM. There is no question that this has been shown in several studies[38,55,106]; however, it might be that this is a nonspecific finding that has now been noted in >50 different pain and nonpain conditions.[38]

Discussion

A new diagnostic framework was established by the AAPT to improve the diagnosis of chronic pain disorders. The AAPT Fibromyalgia Working Group addressed the current state of FM criteria for diagnosis and determined that an alternative to existing criteria might improve the identification of FM patients. The ACR 1990 classification criteria for FM was considered to be impractical for use owing to problems related to the tender point exam, which was difficult to perform and standardize in clinical settings. The tender point exam was also biased toward women, who are more sensitive to a tender point exam than men, and was not an accurate measure of hyperalgesia due to influence by subjective distress.[74] The ACR 2010/2011/2016 criteria eliminated the tender point exam and instead defined FM as a multi-symptom disorder. The appearance of the 2010 criteria created some controversy and confusion, and since 2010, alternative approaches to the diagnosis of FM have been proposed. The challenge shared by all attempts to define criteria for FM is that there is no gold standard for FM diagnosis. Until the pathophysiology is better understood and biomarkers are identified, the diagnosis relies on patient report and clinical assessment. Although the criteria published to date seem to identify a similar group of patients, the goal of the Fibromyalgia Working Group

members was to make the diagnosis of FM practical for clinicians and useful for researchers, and to capture the key symptoms of the disorder. The AAPT taxonomy offers a new approach by defining core criteria and including other associated symptoms and signs, comorbidities, and impact on function in other dimensions. This taxonomy allows the clinician and researcher to focus on a more limited number of core symptoms for diagnosis, while allowing the many other associated symptoms and signs to be included in dimension 2, which will support the diagnosis of FM.

Based on consensus meetings and analyses of several population-based studies to assess definitions of widespread pain and determine the best combination of pain and symptoms to identify FM patients, the Fibromyalgia Working Group developed new criteria for FM in dimension 1. The group determined that widespread pain was the core symptom of FM and, as in the ACR 1990 criteria, all patients should meet this criterion. Based on the results of the data analysis of multiple population based studies and other studies,[41] the group selected MSP with a minimum number of required sites regardless of their anatomical distribution (instead of the ACR 1990 widespread pain criteria) (Fig 1).

Although pain is the main symptom of FM, other symptoms are reported to be clinically significant by patients and are sometimes more disabling than pain. The new AAPT diagnostic criteria include 2 other symptoms, fatigue and sleep problems, which are most commonly reported by FM patients. Based on the results of the analysis of multiple population-based studies, the presence of MSP in combination with moderate to severe fatigue or sleep problems was sufficient to identify the FM patients. This simplified the criteria so that no scoring of associated symptoms was required. Sleep problems identified by FM patient include difficulty falling and staying asleep and unrefreshing sleep—any or all of these problems can be considered when assessing sleep problems. Similarly, fatigue may include mental and/or physical fatigue. Although the analyses of data from the population-based studies offered several approaches to FM diagnosis, the working group consensus was to focus on at least 6 of 9 sites of pain in combination with either fatigue or sleep problems to allow some flexibility (although most patients will have both sleep problems and fatigue, there are some patients who report only 1 of the symptoms). Relegating other symptom domains and signs to dimension 2 allows them to be considered when evaluating a patient but not be required for diagnosis.

The main goal of the AAPT Fibromyalgia Working Group was to develop the AAPT dimensions for FM. In the process, the group devised new core criteria for the diagnosis of FM with the support of analyses of data from a large-scale population-based post hoc study.[48] There are several limitations to using this approach to identify core symptoms of FM. as detailed in Dean et al[48] In developing the new diagnostic criteria, we attempted to approximate the generally accepted prevalence of FM in the analyses. This would seem to present a logical conundrum for a new diagnostic system. Nevertheless, the prevalence proportions typically reported using the ACR 1990 criteria for FM are considered to have face validity, which seemed a reasonable reference point to adopt. MSP was defined here to identify a population with similar prevalence to CWP, and the resulting overlap may limit the ability to detect differences between the 2 groups. The overlap demonstrated was 60 to 76%, with a substantial number of individuals exclusive to 1 group and with differences in pain chronicity between definitions. This indicates that the similarities demonstrated between the MSP and CWP definitions and their relationship to other symptoms associated with FM cannot be attributed solely to the overlap of individuals.

To assess the relationship between pain and the other associated symptoms of FM, bivariate analyses were conducted across multiple study populations. A fully adjusted model, containing all predictors, could not be performed, as no single study contained all measures. Although this did not prevent the study from assessing these relationships individually, future studies evaluating these in the context of the other symptoms would be beneficial.

CWP was assessed using 4-view body manikins, present across all study populations, primarily because the 2011 modification of the 2010 FM criteria was not present in any of the studies used. The use of a body manikin has become 1 standard way to collect information from subjects on their sites of pain, and has been shown to have construct validity and to be reliable.[176] There has been variability in how authors have defined CWP; but, the greatest consistency has come in the use of the definition of CWP within the ACR 1990 criteria for fibromyalgia. However, because these criteria did not specify how they should be operationalized, there is still possible variation.[120,167] Despite the difference in the methods of ascertaining pain, the resulting number of pain sites needed to define MSP is consistent with other studies.[184]

Despite these limitations, the analyses demonstrated that the features of FM could be defined in multiple ways. The consensus of the AAPT working group was to simplify the diagnostic criteria to facilitate the identification of FM in clinical practice and for the purpose of research. We concluded that chronic pain remains the core symptom of FM, and 2 key associated symptoms (fatigue and sleep disturbance) are important in understanding and treating FM. The AAPT working group considered the question of whether to require both fatigue and sleep disturbance in dimension 1. However, based on the clinical experience of the working group members, individuals with FM may at a single point in time have either fatigue or sleep disturbance; although, if they are followed longitudinally, they typically develop both problems over time.

We gathered a group of international clinical and research experts in the field of FM to have broad input in the process. However, the resulting development of the 5 dimensions will need to be assessed by other groups, and the core diagnostic criteria will require further study and validation. We believe that the criteria

will be useful across all clinical settings, including primary, secondary, and tertiary practices, but will also require additional study. A global alignment of taxonomy for pain disorders is an important long-term goal. The AAPT is multidimensional, which makes it unique compared with other existing and in-development diagnostic criteria. We hope that this multidimensional approach will increase the value of the AAPT for both clinical research and clinical practice. Additional studies are needed to assess the prevalence of FM using the new definition. We have cited many of the key studies relevant to the development of the dimensions; however, owing to the rapidly evolving field, the vast literature on FM, and limitations of space, many studies could not be included in our review. In addition, the review of the literature was not intended to be at the level of a systematic review, but rather to support the consensus discussions and develop the dimensions. Revisions of the dimensions will also be required as research continues and our understanding of the pathophysiology of FM and chronic pain improves.

Supplementary Data

Supplementary data related to this article can be found at https://dx.doi.org/10.1016/j.jpain.2018.10.008.

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