

Contemporary Management Strategies for Fibromyalgia

On March 21, 2009, *The American Journal of Managed Care* (AJMC) held a roundtable of clinical, patient advocacy, and managed care experts to explore issues in the diagnosis and management of fibromyalgia. The attendees reached a consensus on the following issues:

1. The prevalence, patient burden, and economic burden associated with fibromyalgia merit earlier diagnosis and treatment, additional education for the medical community (particularly primary care physicians), and appropriate management by health plans, including patient access to US Food and Drug Administration (FDA)-approved fibromyalgia medications.
2. Physicians, payers, and patient advocates should work to satisfy 3 critical outcome domains for fibromyalgia patients: *clinical*—decreased symptoms and improved physical function; *economic*—lower fibromyalgia-related healthcare costs; and *quality of life*—continued involvement in employment, family, and social activities.
3. The current treatment and diagnostic guidelines for fibromyalgia attempted to identify treatment options for an often misunderstood disease state, but are not commonly used by physicians or payers as a treatment algorithm. The guidelines have limited utility to physicians and payers because they precede or do not consider recent FDA approvals of 3 pharmacologic agents for fibromyalgia; their recommendations for other treatments used for fibromyalgia are based on data mainly from uncontrolled, small, open-label trials of short duration; they lack a straightforward treatment algorithm (although an algorithm might be problematic given the idiosyncratic nature of the disease); and they need to be updated as advances in disease management are made.
4. The development of a therapeutic category for “fibromyalgia” on payer formularies would benefit patients, physicians, and payers as a step toward further legitimizing the disease state, raising awareness of fibromyalgia, educating physicians and patients on available FDA-approved treatments, enhancing patient access through improved and appropriate recognition of FDA-approved treatments, and improving understanding of disease-specific drug utilization by payers.

Abstract

A roundtable meeting that comprised clinical, patient advocacy, and managed care experts discussed issues regarding the diagnosis and management of fibromyalgia. The panel agreed that earlier diagnosis and treatment, additional education for the medical community, and appropriate management by health plans, including patient access to US Food and Drug Administration–approved fibromyalgia medications, are needed. In addition, physicians, payers, and patient advocates must work to improve clinical, economic, and quality-of-life outcomes for fibromyalgia patients. Finally, treatment and diagnostic guidelines must be updated as advances in disease management are made (including approvals of 3 new pharmacologic agents), and development of a therapeutic category for “fibromyalgia” on payer formularies is needed.

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For participant information and disclosures, see end of text.

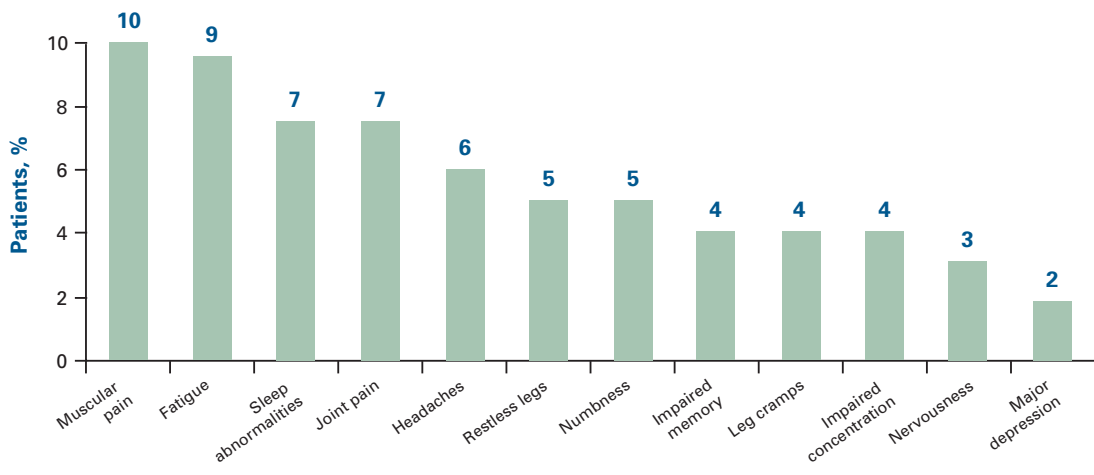
SECTION 1. FIBROMYALGIA: CLINICAL OVERVIEW AND ECONOMIC BURDEN

Fibromyalgia (FM) is a multisymptom condition characterized by chronic widespread pain (CWP) and usually accompanied by a multitude of additional symptoms.¹⁻⁷ Most people with FM suffer from decreased physical function,^{2,3,8-10} which can lead to disability.^{6,11,12} Sleep disturbances, fatigue, and morning stiffness are present in more than 73% of FM patients.¹ Many patients have headaches, cognitive impairment, decreased well-being, depressed mood,

paresthesias, irritable bowel or bladder symptoms, anxiety, temporomandibular joint pain, restless legs, and/or hypersensitivity to noise, heat, and cold.^{1-7,13} Comorbidities, which are far more common in FM patients than controls, may include other neuropathic or gastrointestinal (GI) disorders, migraine, respiratory or circulatory conditions, and mental and mood disorders (Figures 1A and 1B).⁴

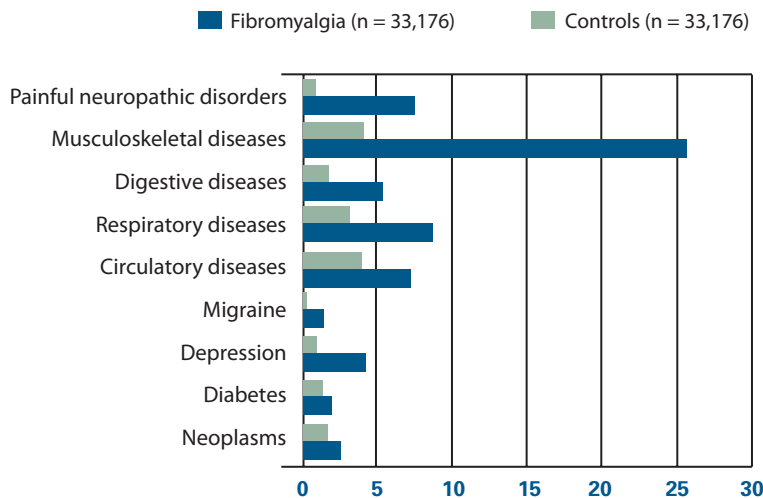
The pain of FM is distinctive. Patients with FM have CWP for 3 months or longer in all 4 quadrants of the body, but not centered in the joints, as

■ **Figure 1A. Patient-Reported Symptoms at Diagnosis of Fibromyalgia**



Adapted from Kranzler JD, et al. *Psychopharmacol Bull.* 2002;36(1):165-213.

■ **Figure 1B. Comorbidities Associated With Fibromyalgia**



Adapted from Berger A, et al. *Int J Clin Pract.* 2007;61(9):1498-1508.

with rheumatoid arthritis.^{14,14,15} FM patients have a lower pain threshold than healthy control subjects⁹; generalized tenderness includes allodynia (pain from normally nonnoxious stimuli) and hyperalgesia (increased response to painful stimuli).^{6,16} Although they cannot detect pressure, electrical, or thermal stimuli at lower levels than controls, the stimulus level that causes pain is lower.^{9,14,17} This phenomenon is independent of psychological factors such as expectancy and hypervigilance.¹⁷ The pain of FM may even persist after stimuli cease.¹⁸

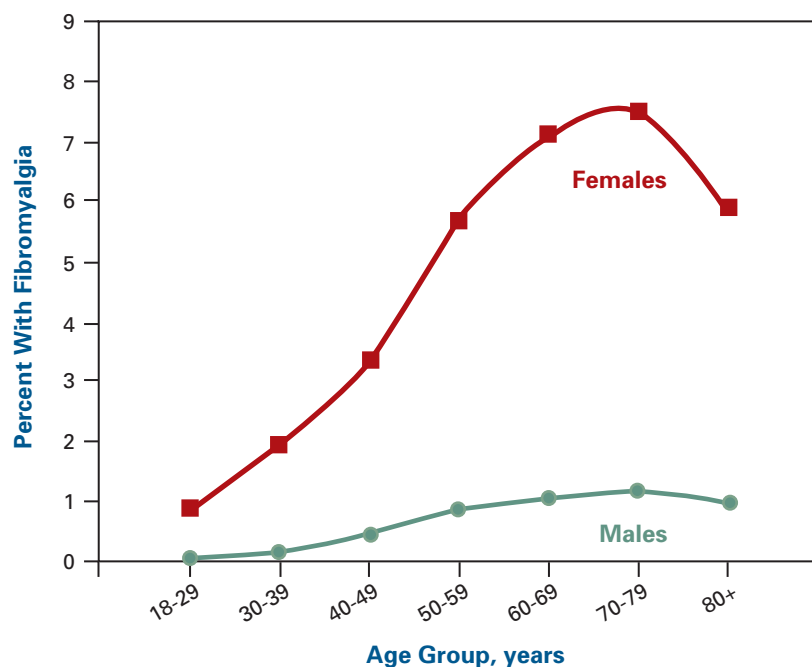
FM is more widespread than many are aware (Figure 2) and is believed to be underdiagnosed and undertreated. In the United States the prevalence is 2% to 4%^{2,4,19-21} with onset usually at 20 to 55 years,⁴ but prevalence increases with age.²¹ The female-to-male ratio is up to 9:1.^{4,21} FM is the second most common disorder treated by rheumatologists, after osteoarthritis.²⁰ Managed care participants in the roundtable were surprised by the prevalence and said patients were difficult to track due to use of a broad range of diagnoses and varied drug utilization. Since prescription claims data do not consistently include *International Classification of Diseases (ICD-9 or -10)* diagnosis information (although the data can be included, it is not typically

required by payers, thus not captured), pharmacy utilization data cannot be used with certainty to identify patients with FM, because many of the drugs and drug classes prescribed are also used for a variety of other medical conditions.

With its many and variable symptoms, some of which can occur in other disorders, FM can be difficult to identify. Recent laboratory, positron emission tomography,²² voxel-based morphometry,²³ and functional magnetic resonance imaging (fMRI) research has supported the legitimacy of FM as a genuine disorder.^{6,7,20} Nevertheless, legitimacy as a discrete entity is still not universally accepted,^{5,20,24,25} which can result in problems for patients afflicted with FM, from stigma to difficulty obtaining accurate diagnosis and treatment.

Dr. Goldenberg (Rheumatology): I discuss this as a problem with pain volume control, that there is a decrease in threshold to various noxious stimuli. It's not just pain. It's all stimuli. So you hear these weird symptoms from people that smells, sounds, or bright lights bother them. If they have a CNS hypersensitivity or hyperirritability, it makes perfect sense.

■ **Figure 2.** Epidemiology of Fibromyalgia in the General Population



Reprinted with permission from Wolfe F, et al. *Arthritis Rheum.* 1995;38(1):19-28.

The predominant theory of pathogenesis in FM is central sensitization due to dysregulation of pain pathways.^{10,12,18} Brain imaging has demonstrated this altered pain processing, with FM patients reporting pain at half the pressure required to register pain in controls.^{7,14,20} At the different pressures required to report similar pain, fMRI showed the same brain areas were involved in pain processing, indicating the FM patients and controls experienced the pain similarly while the stimuli were different.⁷ Although the exact etiology is unknown,^{3,5} genetics appears to play a major role in susceptibility.⁹ First-degree relatives of FM patients have 8 times the risk for FM as the general population.⁹ FM has been associated with polymorphisms in the serotonin transporter gene and the catecholamine-O-methyltransferase enzyme that inactivates catecholamines.^{9,20} These polymorphisms affect the metabolism or transport of the monoamine neurotransmitters serotonin and norepinephrine.⁹ Compared with controls, FM patients have been found to have lower levels of metabolites of serotonin and norepinephrine in their cerebrospinal fluid.^{7,9} Serotonin and norepinephrine are antinociceptive⁹; that is, they decrease the sensitivity of pain processing systems through

the descending central nervous system (CNS) pain pathways.^{7,9} Low levels indicate dysregulation of pain impulses through decreased activity in descending antinociceptive pathways, resulting in hyperalgesia and allodynia.^{7,9} The low levels of serotonin and norepinephrine metabolites prevalent in FM subjects⁹ suggest that serotonin and norepinephrine reuptake inhibitors (SNRIs) might help realign altered pain processing in descending CNS pain pathways. Whereas SNRIs have had analgesic effects in animal models of hyperalgesia and allodynia, selective serotonin reuptake inhibitors (SSRIs) have not, which highlights the particular importance of norepinephrine in pain modulation.¹⁹ On the other hand, FM subjects are reported to have increased levels of pronociceptive transmitters substance P and glutamate that amplify pain impulses in the ascending pain pathway.^{7,9} Drugs such as anticonvulsants are thought to function by reducing the release of pronociceptive transmitters in the ascending pathway.

FM Causes Functional Impairment

FM is associated with functional disability. The chronic, impairing symptoms of FM can lead to loss of function, which negatively affects

Table 1. Fibromyalgia (FM) Is Associated With Functional Disability

Employment and Productivity	Other Functional Impacts	Health-Related Quality of Life (HRQOL)
20%-50% of patients can work few or no days	Limitations in activities of daily living are as high as in rheumatoid arthritis	Before-treatment HRQOL scores are significantly impaired compared with the general population
36% are absent from work ≥ 2 d/mo	Sleep impairment scores are well above those in other chronic illnesses; sleep deficits exacerbate fatigue and functional limitation	HRQOL has been reported to be worse than in patients with congestive heart failure, rheumatoid arthritis, osteoarthritis, permanent ostomies, chronic obstructive pulmonary disease, and type 1 diabetes
31% have lost employment due to FM	Social and family activities may be curtailed due to fatigue, pain, and/or depression; sports and physical exercise may become difficult or impossible	
26%-55% receive disability or Social Security payments	Social difficulties due to chronic pain can lead to maladaptive illness behaviors (reduced activities and exercise, involvement in disability and compensation systems), which can help perpetuate functional decline	

Sources: Busch A, et al. *J Rheumatol*. 2008;35(6):1130-1144. Bennett R, et al. *Arthritis Rheum*. 2005;53(4):519-527. Mease P. *J Rheumatol*. 2005;32(suppl 75):6-21. Dadabhoy D, Clauw DJ. *Nat Clin Pract Rheumatol*. 2006;2(7):364-372.

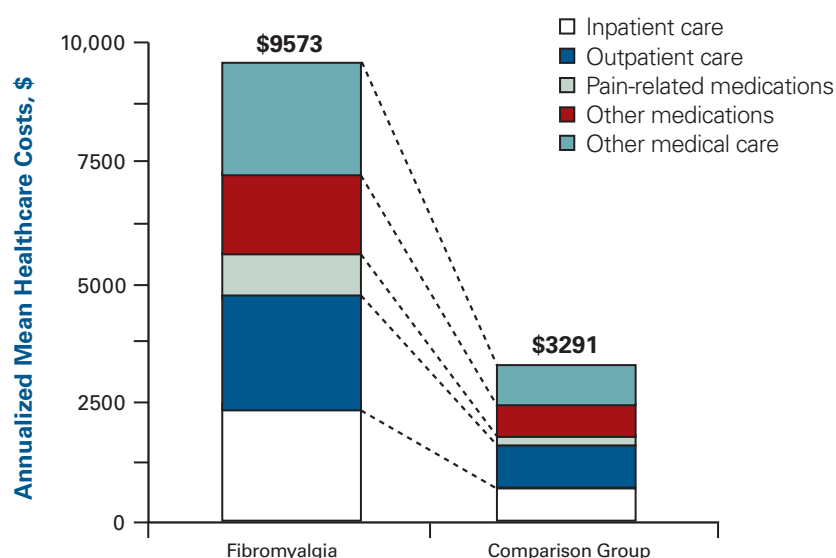
work and leisure activities,²⁶ may increase over time, and reduces health-related quality of life (QOL).^{13,25} Up to 50% of patients can work only a limited number of days because of the disorder,²⁶ and up to 55% receive disability or Social Security payments.^{13,26} Participation in family and social activities may decrease because of fatigue, pain, and/or mood symptoms, and inadequate restorative sleep increases the overall fatigue. Eventually, some FM patients become completely disabled and incapable of continuing employment (Table 1).

FM is also associated with a significant cost burden on all involved, including patients and their families, employers, and payers. The condition imposes substantial direct medical costs²⁷ and indirect costs of lost work productivity.²⁷⁻²⁹ Large US claims database analyses have demonstrated these high costs.^{4,30,31} In a US insurance database analysis of more than 60,000 FM patients and age- and sex-matched controls, FM patients had mean total healthcare costs approximately 3 times higher and median costs 5 times higher than controls (\$9573 vs \$3291 and \$4247 vs \$822, respectively, $P < .001$ for both comparisons) (Figure 3).⁴ FM patients had

4 times as many doctors' office and emergency department visits as control patients.⁴ FM patients were almost 4 times as likely to receive pain-related prescription medications (including antidepressants) and also significantly more likely to receive non-pain-related medications.⁴ Almost half of the FM patients also had healthcare encounters for symptoms other than CWP, including headache, abdominal pain, chest pain, fatigue, and GI symptoms; psychiatric comorbid diagnoses were also significantly higher than in controls.⁴

Another claims database analysis of more than 15,000 privately insured US employees (FM, $n = 8513$; control, $n = 7260$) found that total annual medical, prescription drug, and indirect costs of FM patients were almost double those of controls (\$10,199 vs \$5274, $P < .0001$).³⁰ Total direct costs (medical utilization plus prescription drugs) were 86% higher for employees with FM versus controls (\$7286 vs \$3915, $P < .0001$).³⁰ Total costs for FM approached those of osteoarthritis (\$10,199 vs \$10,861, $P = .3758$), and indirect costs were significantly higher in FM than osteoarthritis (\$2913 vs \$2537, $P < .0001$).³⁰ Compared with osteoarthritis, FM was associ-

■ **Figure 3. Healthcare Costs Are Higher Among Fibromyalgia Patients**



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ated with more claims for comorbidities such as psychiatric diagnoses, chronic fatigue syndrome, and most pain disorders.³⁰

A single-employer US administrative claims database of 4699 employees with at least 1 FM claim found significantly higher total annual costs for FM claimants compared with typical beneficiaries (\$5945 vs \$2486, $P < .001$).³¹ Medical utilization and prescription drug costs were significantly higher in FM claimants ($P < .001$).³¹ Disability prevalence was twice as high among employees with FM ($P < .001$).³¹ Employees with FM who filed disability claims incurred \$6669 in healthcare costs and \$5654 in disability costs for total annual costs of \$14,100 per employee.³¹ Each dollar spent by the employer on FM-specific claims was matched by \$57 to \$143 spent on other direct and indirect costs.³¹ The authors concluded that the employer burden was substantially increased by hidden costs of comorbidities and disability.³¹

Dr. Fouts (Family Medicine): I think I'm the type of person who needs to be educated. I'm the type of doctor who needs to be on the forefront of treating it. I would compare the situation with FM similar to depression 10 to 15 years ago where somebody went into their family doctor, and they just didn't want to talk about it. But if you did get them to talk about it, often their doctor didn't really want to take care of it. I think education will help overcome these situations.

Studies in Europe and Canada have shown similar high direct and indirect costs associated with FM.^{27,29} In addition, these types of claims database analyses do not include the costs of over-the-counter medications and uncovered alternative treatments, which could bring total costs even higher. The roundtable participants agreed that FM imposes high costs on the US healthcare system and speculated that the costs in the published studies likely underestimate reality.

Diagnosis of FM

The FM diagnosis can be difficult to diagnose and often is delayed. Although the leading

theory of pathogenesis—central sensitization from dysregulated pain pathways—is supported by neurotransmitter, neurohormone, and sleep physiology irregularities, objective biomarkers of disease activity have not been validated.¹⁰ Because no objective laboratory test or marker exists, diagnosis is based on history and physical examination.¹³ FM should be diagnosed by its own clinical characteristics. Differential diagnosis is subtle, as FM can be difficult to distinguish from conditions with similar symptoms that may or may not be present as comorbidities.^{1,4,13,20} The roundtable participants observed that many patients self-diagnose FM and then initiate discussion of the diagnosis with their doctor. They said that physician familiarity with the disorder has been improving in recent years, but the current state of FM recognition among primary care physicians (PCPs) is low and corresponds to that of depression about 10 to 15 years ago. Nevertheless, it has been documented that PCPs are capable of diagnosing FM with similar accuracy to specialists. A retrospective analysis of 646 consecutive rheumatology patients at an academic medical center in Israel found that of the 196 patients referred with an initial diagnosis of FM, 71% had that diagnosis confirmed by the consultant rheumatologist.³² The kappa statistic demonstrated a good level of agreement between the family practice physicians and rheumatologists ($\text{kappa} = .70, P < .001$).³² Sensitivity of the FM diagnosis by the family physicians was 87% and specificity was 88%.³² The authors said PCPs in the area were well-informed about FM because of ongoing FM research at the medical center. They speculated that the strong results of the study may be related to this knowledge base among the generalists.³² The Israeli study highlights the need for additional education about FM in the US medical community, particularly the primary care community. If FM can be diagnosed accurately by a PCP without referral to specialists, then the extended time and effort commonly spent in obtaining an accurate diagnosis can be reduced, and an effective treatment plan can be initiated earlier.

Diagnosis of FM entails assessment of pain and other symptoms. In 1990 the American College of Rheumatology (ACR) established

diagnostic criteria for FM including CWP for at least 3 months and pain on at least 11 of 18 specified muscle tendon sites of focal tenderness (“tender points”; **Figure 4**) on digital palpation using a force of approximately 4 kg/cm².^{1,4,7,9,17,20}

Although tender points were the most powerful discriminator between FM patients and controls, tenderness is subjective and depends on the examiner’s strength of palpation.¹ ACR diagnostic criteria are sensitive (88.4%) and specific (81.1%) and can distinguish FM pain from other rheumatologic conditions,¹ but were originally intended as a research tool. The cutoff of 11/18 tender points is considered by many to be somewhat arbitrary. Tender points may be associated with distress rather than pressure pain threshold,^{9,17} and some patients have fewer than 11 tender points but still have FM.^{15,33} Women are 11 times more likely than men to exceed 11 tender points on physical examination.⁹

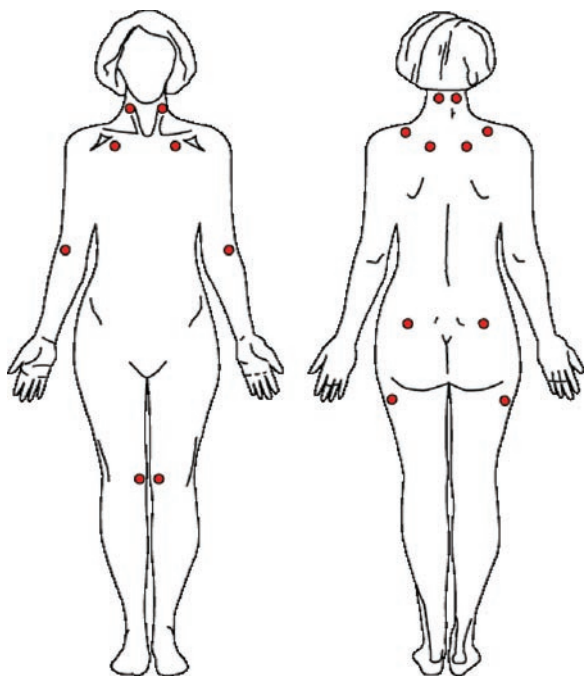
Other domains besides pain must be assessed for an accurate FM diagnosis. Some authors have suggested the use of a structured interview with questions about generalized fatigue, headache,

sleep disturbance, neuropsychiatric complaints, numbness or tingling, and irritable bowel symptoms.^{7,34} More recently, expert panels have recommended additional core domains of FM for study investigation, including multidimensional function, cognitive dysfunction, and health-related QOL.¹⁰ A need exists, especially in the primary care community, for better diagnostic criteria and objective tools to assess illness severity.

Delays in Diagnosis

It is possible that difficulty in diagnosing FM may have contributed to its underrecognition and underdiagnosis. Diagnosis and treatment can be delayed for years with many healthcare visits, referrals, diagnostic tests, a variety of diagnoses, and little impact on symptoms.^{4,5,28} Roundtable participants noted that according to the American Pain Foundation (APF), chronic pain disorders including FM take 2 to 3 years and 8 to 13 healthcare professionals to be diagnosed accurately. Diagnostic delay may result from physician skepticism of the disease state, despite objective evidence and recognition of FM by key organizations including the ACR, Social Security Administration,

■ **Figure 4.** Illustration of Tender Points for Diagnosis of Fibromyalgia



Adapted from Wolfe F, et al. *Arthritis Rheum.* 1990;33(2):160-172

and World Health Organization.^{1,35} Some physicians still believe FM is a manifestation of another underlying disorder,^{5,25} and others question the ACR criteria and therefore the validity of the diagnosis.⁶ Roundtable participants stated that diagnostic delay may also result from lack of confidence on the part of PCPs due to the need for an objective diagnostic test or confusion about the role of tender points. Regardless of the reason, participants acknowledged that delayed diagnosis increases costs for insurance companies while adding to burden on patients.

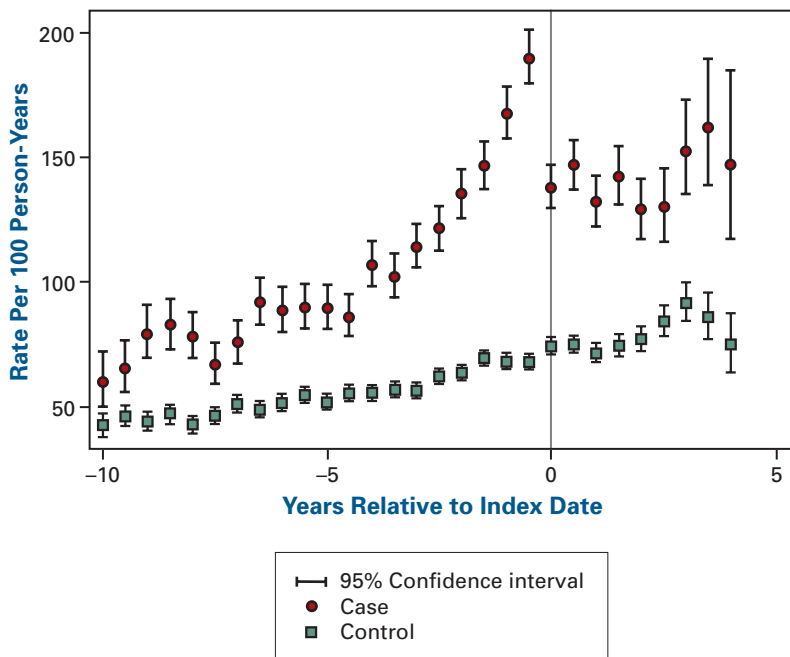
The impact of a delayed diagnosis of FM is greatest on the patient. According to the roundtable participants, patients with undiagnosed, untreated FM feel frustrated and vulnerable, do not know what is wrong with them, and may quit working. The participants agreed that delayed diagnosis adversely affects outcomes, because the disease state is more advanced by the time patients receive adequate management. Years can be wasted with misdiagnosis or no diagnosis while disease progression continues. Early diagnosis and treatment do not occur often enough, but would be beneficial.^{5,9,20} Studies have shown that symptoms

and health satisfaction improve after diagnosis of FM.^{9,20} Diagnosis rules out other more serious conditions, and treatment gives patients hope and a sense of control.⁵ After diagnosis, patients' well-being may improve, in part, simply because of the recognition about their pain and illness.⁵

Dr. Beltran (Managed Care): One of the biggest challenges in healthcare management is treating chronic care illnesses like FM. It sounds like an opportunity for a team approach. One of the reasons there is delay in diagnosis is that patients are referred to different specialists in different temporal time frames as opposed to approaching the problem as a team, where you are getting all the key specialists, whether it be the rheumatologists, neurologists, pain management, and psychiatry, in the same room.

Delayed diagnosis can also increase costs to payers and patients.^{5,28} Retrospective database analyses revealed that earlier diagnosis of FM was associated

■ **Figure 5.** The Impact of a Fibromyalgia Diagnosis on Utilization of Diagnostic Testing



Reprinted with permission from Hughes G, et al. *Arthritis Rheum.* 2006;54(1):177-183.

with cost savings.^{5,28} After diagnosis of FM, medical resource utilization decreased, including visits for comorbidities.^{5,28} Decreases occurred in related testing and laboratory costs (Figure 5), medication costs, referrals, physician visits, and emergency department visits.^{5,28} One author concluded that healthcare providers might "...be legitimately concerned not only with the costs of diagnosing FM but also with the costs of not diagnosing FM."²⁸ The roundtable participants speculated that the documented costs of delayed diagnosis are probably even higher in reality, with more advanced disease feeding into higher costs after later diagnosis.

Dr. Garber (Managed Care): I was truly shocked that we had as many [fibromyalgia] cases diagnosed as we had.... I think it would be worthwhile for us to look into the cost of taking care of FM.

The Need for Education About FM

The roundtable participants agreed that an understanding of the FM disease state and an accurate diagnosis of FM by the medical community still requires considerable education, especially for PCPs. Better understanding of FM should begin with more exposure to it in medical school. Universally accepted diagnostic and treatment algorithms do not exist, but evidence-based information is available and should be more widely disseminated. Patient advocacy groups, health plans, and pharmaceutical companies can help disseminate this information, especially to PCPs and nurse case managers, and facilitate interaction of community specialists with PCPs.

Dr. Draud (Psychiatry): From a cost perspective... people are much more expensive to treat after they have had 2 years of disease state progression.

The participants agreed that greater awareness and understanding of FM among providers, especially PCPs, can lead to earlier, appropriate diagnosis and treatment. Accurate diagnosis can reduce emergency department and office visits, diagnostic tests, and the use of ineffective medications. Patients feel relieved after receiving an

accurate diagnosis, which lifts the burden of uncertainty about their health. They may therefore reduce the number of drugs they continue taking. Earlier, more effective treatment can arrest or minimize further decline of function, enabling continued employment and greater health-related QOL. The participants concluded that identifying patients earlier in the disease continuum would improve patient outcomes and help control costs.

Ms. Gleason (Patient Advocacy): So many of the healthcare providers are uneducated about FM as a whole. Even for medications that have been approved by the FDA, providers may not have a treatment regimen in mind or know what they are going to do with the patient.

Another Need for Patients and Providers: Treatment Access

Access to treatment for FM is sometimes restricted, and is most visibly seen with respect to utilization of specific drug therapies. The roundtable participants expressed concern that these restrictions could impede effective treatment, but also noted these issues are common to many medical areas, not just FM.

Dr. Garber (Managed Care): I think there is a paucity of information both among our nurse care managers and our PCPs about the general sense of what FM is. I think that is one place we can use some help.

As an example, some managed care plans mandate step-edits, prior authorization, or other programs to manage utilization of specific drugs or drug classes. Participants with managed care backgrounds noted that these are meant to promote either guideline-driven therapy or fiscally responsible medication use. Often these programs require use (and failure) of generic drug products before authorizing branded agents. With respect to FM, this translates to use of drugs "off-label" before use of agents that are FDA-approved for treatment of FM.

From the perspective of the clinicians at the roundtable, new medications with FDA indica-

tions for FM can be difficult to obtain because of these requirements, resulting in frustration for both physicians and patients, after having spent years seeking an accurate diagnosis and treatment.

Dr. Flood (Rheumatology): It is very frustrating—I think for everybody involved—trying to take care of patients, and lots of confusion is generated when we are asked to use medicines off-label for a condition. So we are sending a lot of mixed messages, I think, through these step-edits. I think there is a good opportunity to rehabilitate that whole process.

Given the variability of symptoms and presentation of FM among patients and the lack of clear treatment guidelines, an optimal situation would be to provide physicians with better flexibility to recommend and provide the most appropriate treatment. This consideration was tempered by the continuing need for evidence of efficacy and cost-effectiveness for all agents used for the treatment of FM.

The roundtable participants agreed that attention and appropriate management by health plans is needed. A major challenge of managed care is management of chronic diseases, and FM presents opportunities for disease management with a “center of excellence” multidisciplinary team treatment approach. Recognizing the costs of FM and the added costs of delayed diagnosis and ineffective treatments, health plans can alter policies to encourage best practices, including:

- Recognition of the diagnosis of FM
- Assistance in provider education for the diagnosis and treatment of FM
- Coverage of pharmacologic and nonpharmacologic treatments that have been shown to be effective
- Appropriate formulary placement and utilization management of effective medications, particularly drugs with FDA approval.

Summary

FM is a disorder for which early, accurate diagnosis and appropriate treatment are crucial to improve clinical outcomes (ie, prevent loss of function), reduce costs, and maintain or improve

QOL. Evidence and experience suggest that improved awareness and education about FM for both patients and healthcare providers is an unmet need. Managed care organizations can play a role in addressing this unmet need.

Dr. Agin (Pain Specialist): When I prescribe a medication for my patient, and the patient attempts to fill the prescription, the prescription may be denied by their pharmacy plan outright or may require prior authorization. A tedious process begins. My office calls for authorization; the pharmacy plan sends paperwork; our office completes the paperwork and returns it. If the patient actually fits their criteria and can get the medication, the process can delay starting the medications by days to weeks, or they can still be denied after all of the paperwork is submitted. If the patient is scheduled to follow up with the prescribing physician in 2 weeks to see how they are tolerating the medication, this becomes an unnecessary office visit for both the patient and the physician as the patient has not yet had an adequate trial.

SECTION 2. CURRENT GUIDELINES FOR THE MANAGEMENT OF FM

Despite years of clinical research and recent FDA approvals, considerable ambiguity remains regarding FM treatment. In addition to pharmacologic treatment, nonpharmacologic therapies have been tried, including patient education, exercise, cognitive-behavioral therapy (CBT), and alternative therapies, often in combination; and most agree that a combination of therapies may be the best approach.^{3,7,9,10,26} Many clinicians, having received little education about FM, have scant awareness of the demonstrated efficacy and safety of treatment options. Each patient is unique and the combinations of symptoms vary widely; therefore, treatment individualization is necessary and a wide range of options should be readily available. However, access to some drugs is limited by formulary restrictions, and some physicians are not aware of the latest evidence or even recent FDA approvals. For all of these reasons, often treatment of FM is not evidence-based, proceeds on a trial-and-error basis, and can continue long term without sufficient efficacy. Many patients take multiple medications for FM symptoms. Guidelines from

organizations such as medical specialty societies help clinicians treat many other disorders; practical guidelines for FM would be welcome.

Several organizations have published guidelines for FM in this decade (Table 2). These guidelines have offered practical guidance about the identification and treatment of a condition that can be difficult to identify. Moreover, the guidelines have spurred discussion among practicing pain specialists, rheumatologists, research investigators, and others as to the nature and treatment of FM and what questions still need to be answered. Establishment of guidelines in an area such as FM is a step toward improved management by providing physicians and patients with a channel to identify potential therapeutic options and a base from which to develop collab-

orative treatment plans. In summary, the current FM guidelines are a substantial early attempt to define an often misunderstood disease state and the treatment options for it.

However, the most recent published guidelines for FM treatment are 2 to 4 years old, which is a relatively long time in an environment of rapidly changing scientific understanding. When assessing the usefulness of the current guidelines, it is necessary to balance their strengths and benefits with some weaknesses, perhaps the most apparent of which is their publication before the FDA approvals and other important new evidence.

Current Guidelines for FM

The American Pain Society (APS) developed evidence-based guidelines for FM diagnosis and

■ **Table 2.** Current Fibromyalgia (FM) Guidelines

Association	Objectives	Methods	Results
APS (American Pain Society)	To provide evidence-based guidelines for diagnosis and management of FM syndrome in children and adults and to improve quality of care	Review of clinical trials and meta-analyses Rating scheme ranked evidence Guidelines reached by consensus of interdisciplinary panel of 13 experts	Guidelines for diagnosis based on American College of Rheumatology criteria and other symptomatic assessments Guidelines for specific pharmacologic and nonpharmacologic interventions
EULAR (European League Against Rheumatism)	To develop evidence-based recommendations for the management of FM syndrome	Systematic review of pharmacologic and nonpharmacologic intervention studies Rating scheme ranked evidence Recommendations reached by consensus of task force of 19 international European experts	2 General recommendations for recognition/diagnosis and multidisciplinary approach to management 4 Recommendations for nonpharmacologic management 4 Recommendations for pharmacologic management
OMERACT (Outcomes Measures in Rheumatology Clinical Trials)	OMERACT 7: To identify and prioritize symptom domains to be consistently evaluated in FM clinical trials and identify domains and outcomes measures for research agenda OMERACT 8: To reach consensus on core domains, evaluate outcomes measures in recent trials, confirm research agenda	Delphi exercise of 23 FM researchers established preliminary prioritization Patient focus groups and Delphi exercise established patient-identified core domains OMERACT 7 and 8 workshop attendees developed prioritized list of core domains and research agenda	Core domains and outcomes measures were identified, including patient global, multidimensional function, dyscognition Composite response (patient improvement in ≥ 2 parameters simultaneously) recommended as outcomes measure for clinical trials/research agenda

Sources: Burckhardt CS, et al. *American Pain Society*; 2005. Goldenberg DL, et al. *JAMA*. 2004;292(19):2388-2395. Carville SF, et al. *Ann Rheum Dis*. 2008;67(4):536-541. Mease PJ, et al. *J Rheumatol*. 2005;32(11):2270-2277. Mease P, et al. *J Rheumatol*. 2007;34(6):1415-1425.

treatment.^{20,36} A consensus panel of 13 experts in pain management disciplines performed a comprehensive review of 505 peer-reviewed clinical trials and meta-analyses from the preceding 25 years.²⁰ Guidelines were reached by expert consensus and the use of a rating scheme ranking the evidence for treatment efficacy as strong, moderate, or weak.²⁰ The clinical trials used ACR criteria for FM and measured pain outcomes on the Fibromyalgia Impact Questionnaire (FIQ).²⁰ The APS guidelines recommended for diagnosis and assessment a complete history and physical examination, including laboratory testing; clinical diagnosis based on ACR criteria, comprehensive pain assessment (type, quality, location, duration) and effect on QOL; assessment of severity of other FM symptoms, impact on physical/emotional function and overall QOL.³⁶ Based on the rated evidence, the APS guidelines recommended multiple strategies for treatment, including both pharmacologic and nonpharma-

cologic therapies, while stressing the importance of patient education (Table 3).²⁰ The panel found strong evidence for CBT, aerobic exercise, and patient education.²⁰ In pharmacologic therapies, the panel found strong evidence for amitriptyline and cyclobenzaprine, and moderate evidence to support the use of SNRIs, SSRIs, tramadol, and pregabalin.²⁰

The APS guidelines have some limitations. The evaluated studies had heterogeneous treatments, short durations, and inconsistent blinding and controls, which limits their generalizability and practical clinical application. All of the evaluated studies occurred before the FDA approvals for FM of pregabalin, duloxetine, and milnacipran. Most of the studies focused on pain reduction to the exclusion of other symptoms and outcomes including patient global improvement and improved physical function. Finally, many of the treatments discussed in the guidelines still lack FDA approval for FM to date and it doesn't

■ **Table 3.** Comparison of APS and EULAR Guidelines for Fibromyalgia (FM) Management

	Nonpharmacologic Therapy	Pharmacologic Therapy	Limitations of Study Analysis
APS (American Pain Society)	<p><i>Strong evidence:</i> Patient education CBT Aerobic exercise Multidisciplinary therapy</p> <p><i>Moderate evidence:</i> Strength training Acupuncture Hypnotherapy Biofeedback Balneotherapy</p>	<p><i>Strong evidence:</i> Amitriptyline 25-50 mg/d Cyclobenzaprine 10-30 mg/d</p> <p><i>Moderate evidence:</i> SNRIs (milnacipran, duloxetine; mixed evidence for venlafaxine) SSRI (fluoxetine 20-80 mg/d) Tramadol 200-300 mg/d Anticonvulsant (pregabalin 300-450 mg/d)</p>	<p>Heterogeneous treatments in studies Study durations generally short term Some studies unblinded and/or uncontrolled Outcomes measures often exclusively pain without assessment of improvements in patient global, physical function, etc All studies predated FDA approvals of 3 FM pharmacotherapies Some agents listed still lack FDA approval for FM</p>
EULAR (European League Against Rheumatism)	<p>Balneotherapy (Grade B) Individually tailored exercise including aerobic and strength training (Grade C) CBT (Grade D) Others: relaxation, rehabilitation, physiotherapy, and/or psychological support (Grade C)</p>	<p>Tramadol (Grade A) Analgesics (paracetamol/acetaminophen, weak opioids) (Grade D) Antidepressants (amitriptyline, fluoxetine, duloxetine, milnacipran, moclobemide, pirlindole) (Grade A) Tropisetron, pramipexole, pregabalin (Grade A)</p>	<p>Outcome measures other than pain by visual analog scale and function by FIQ specifically excluded Other limitations similar to those of APS above</p>

CBT indicates cognitive-behavioral therapy; FDA, US Food and Drug Administration; FIQ, Fibromyalgia Impact Questionnaire; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Sources: Burckhardt CS, et al. *American Pain Society*; 2005. Goldenberg DL, et al. *JAMA*. 2004;292(19):2388-2395. Carville SF, et al. *Ann Rheum Dis*. 2008;67(4):536-541. Lyrica prescribing information.

appear that any of these agents will be submitted to the FDA for consideration of approval.

The European League Against Rheumatism (EULAR) developed guidelines for FM management based on best evidence and expert opinion (Table 3).³⁷ A panel of 19 FM experts from 11 European countries performed a systematic literature review of 146 clinical trials published from 2002 through 2005 that used ACR diagnostic criteria for FM and focused on FM management.³⁷ The panel made 10 recommendations for FM management including 2 general recommendations, 4 on pharmacologic treatments, and 4 on nonpharmacologic treatments; a multidisciplinary treatment approach was emphasized. The panel found strong evidence for antidepressants to decrease pain and improve function, specifying milnacipran, duloxetine, amitriptyline, fluoxetine, moclobemide, and pirlindole. They found strong evidence for pain management with tramadol, pregabalin, tropisetron, and pramipexole, and also recommended considering simple analgesics (paracetamol [acetaminophen]) and weak opioids.³⁷ Several nonpharmacologic treatments were also recommended. Weaknesses of the EULAR guidelines are similar to those of the APS guidelines and include research evidence and approvals since the publication that render some of the information obsolete.

The Outcome Measures in Rheumatology Clinical Trials (OMERACT) FM workshop, a group of 21 international research and clinical experts, published a consensus statement that made important advances in prioritizing core symptom domains by including patient perspectives (Table 4).¹⁰ The FM workshops at OMERACT 7 in 2004 and OMERACT 8 in 2006 were organized to develop a consensus identifying and prioritizing key FM symptoms as “core domains” and to validate and standardize outcome measures for clinical trials of FM therapies.¹⁰ In addition to well-established criteria such as pain, fatigue, and sleep quality, OMERACT added as essential evaluation criteria patient global, multidimensional function, health-related QOL, dyscognition, and stiffness.¹⁰ OMERACT also emphasized the value of composite response (patient improvement in ≥ 2 parameters simultaneously) as an outcomes measure. The consensus statement noted, “The ability to ensure clinically meaningful change in multiple dimensions of fibromyalgia utilizing a composite responder index is desirable.”¹⁰ When the OMERACT consensus statement was published, most clinical trials of most drugs used for FM had not included composite response. The pivotal trials of milnacipran have included composite outcomes measures, and the roundtable participants hoped that composite response will be included in future FM research as specified by OMERACT.

■ **Table 4.** OMERACT Addressed the Multiple Dimensions of Fibromyalgia

Key Evaluation Criterion	Portion of Respondents Rating Criterion as “Essential,” %
Pain	100
Fatigue	94
Patient global	94
Multidimensional function	86
Tenderness	74
Sleep	66
Health-related quality of life	65
Dyscognition	61
Stiffness	60

OMERACT indicates Outcome Measures in Rheumatology Clinical Trials. Adapted from Mease P, et al. *J Rheumatol.* 2007;34(6):1415-1425.

FM Guidelines and Current Knowledge About Pharmacotherapies

Many experts, including the AJMC roundtable participants, consider the current FM guidelines to have limited utility for practicing clinicians and payers. One important reason is that the guidelines do not reflect the FDA approvals of 3 agents for FM. The guidelines preceded the FDA approv-

als, so the pharmacologic treatments discussed were by necessity off-label (including those that later received approval). Many drugs are used for the control of different FM symptoms, including SNRIs, anticonvulsants, tricyclic antidepressants (TCAs), muscle relaxants, SSRIs, opioids, non-steroidal anti-inflammatory drugs (NSAIDs), and cyclo-oxygenase (COX)-2 inhibitors.^{9,19,38} How-

Table 5. FDA-Approved Agents for Fibromyalgia (FM)

	Lyrica⁴¹ (Pregabalin)	Cymbalta⁴⁰ (Duloxetine Hydrochloride)	Savella³⁹ (Milnacipran Hydrochloride)
Date of FDA approval	Initial: 2004 (as an anticonvulsant) For FM: June 2007	Initial: 2004 (as an antidepressant) For FM: June 2008	January 2009 (indicated only for FM)
Mechanism of action	Alpha ₂ delta ligand	SNRI	SNRI
Indications	Neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, adjunctive therapy for partial-onset seizures, FM	Major depressive disorder, generalized anxiety disorder, diabetic peripheral neuropathic pain, FM	FM
Studies that established efficacy for FM	One 14-wk randomized, double-blind, placebo-controlled trial, one 6-mo randomized withdrawal study	Two randomized, double-blind, placebo-controlled trials (3 mo and 6 mo), 1 randomized, double-blind, dose-comparison trial	Two randomized, double-blind, placebo-controlled trials (6 mo and 3 mo)
Primary end points/outcomes measured in FM pivotal trials	Pain reduction (VAS); improvements in patient global (PGIC) and function (FIQ)	Pain reduction, improvements in patient global (PGIC) and function (FIQ)	Composite end point of pain reduction (VAS) and improvement in patient global (PGIC). Also composite end point of pain (VAS), physical function (SF-36 PCS), and patient global (PGIC)
Recommended dose for FM	150-225 mg bid 75 mg bid May increase to 150 mg bid within 1 wk Maximum dose 225 mg bid	60 mg/d Start 30 mg/d for 1 wk, increase to 60 mg/d	50 mg bid (start 12.5 mg/d, increase on day 2 to 12.5 mg bid, on day 4 to 25 mg bid, after day 7 to 50 mg bid) Maximum dose 200 mg/d
Warnings and precautions	Angioedema, hypersensitivity reactions, peripheral edema	Suicidality in children, adolescents and young adults (all antidepressants); hepatotoxicity, orthostatic hypotension, serotonin syndrome (or neuroleptic malignant syndrome), bleeding, hypomania, seizures, urinary retention, hyponatremia, alterations in blood pressure and blood glucose levels. Interactions with inhibitors of CYP1A2, CYP2D6	Suicidality in children, adolescents, and young adults (all antidepressants); serotonin syndrome, elevated blood pressure and heart rate, seizures, hepatotoxicity, bleeding, hyponatremia, activation of mania, dysuria, narrow angle glaucoma, use with alcohol
Most common adverse reactions	Dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, difficulty with concentration/attention	Nausea, dry mouth, constipation, somnolence, hyperhidrosis, decreased appetite	Nausea, headache, constipation, dizziness, insomnia, hot flush, hyperhidrosis, vomiting, palpitations, heart rate increase, dry mouth, hypertension
Scheduling and dependence	Schedule V controlled substance; rapid discontinuation associated with withdrawal symptoms	Unscheduled; withdrawal symptoms on abrupt discontinuation	Unscheduled; withdrawal symptoms on abrupt discontinuation

FDA indicates US Food and Drug Administration; FIQ, Fibromyalgia Impact Questionnaire; PGIC, Patient Global Impression of Change; SF-36 PCS, Short Form-36 Physical Composite Score; SNRI, serotonin and norepinephrine reuptake inhibitor; VAS, visual analog scale.

ever, only 3 agents have received FDA approval for this indication: Savella (milnacipran),³⁹ Cymbalta (duloxetine),⁴⁰ and Lyrica (pregabalin)⁴¹ (Table 5). FDA approval implies a level of scrutiny and supporting basic research and clinical trial evidence that is lacking for off-label uses of drugs. In the case of the FDA-approved FM drugs, the clinical trials supporting the duloxetine and pregabalin approvals had single-end-point outcomes measures, whereas the primary end points for milnacipran trials were composite measures, a more comprehensive measure of simultaneous efficacy across multiple symptoms versus placebo. Since the current FM management guidelines predate the FDA approvals, they are not mentioned in the recommendations.

Dr. Dunn (Managed Care): When we see [fibromyalgia] patients, they are on generic SSRIs, generic muscle relaxants, generic antidepressants, and opioids. What drives pharmacy costs are [long-acting] opioids, which are known to be generally ineffective.

The FDA-approved drugs for FM belong to classes that have demonstrated efficacy for FM management. Pregabalin is an anticonvulsant, and randomized controlled trials have also supported the efficacy of another anticonvulsant, gabapentin.^{16,41} Milnacipran and duloxetine are SNRIs with demonstrated efficacy and safety in FM; their serotonin- and norepinephrine-reuptake inhibiting actions may correct functional deficits in descending pathway pain processing.^{7,9,39,40} However, 2 other SNRIs, venlafaxine and desvenlafaxine, have not had efficacy for FM established in clinical trials.^{9,42} Some off-label drugs are discussed or recommended in the guidelines,^{2,20,37} but many drugs prescribed off-label for FM may have limited utility for this purpose. Clinical trial evidence for their efficacy and safety in FM is limited or absent. Studies have failed to confirm the efficacy of NSAIDs and COX-2s in FM.¹³ Short-term studies have demonstrated some efficacy with tricyclics, but safety and tolerability concerns have limited their use.^{9,19} Efficacy in FM clinical trials has not been demonstrated with opioids, which also carry the potential for dependence and abuse as well as exacerbating pain as opioid hyperalgesia.^{9,13} Only a few controlled trials have been conducted using muscle relaxants for

FM patients, with mixed results.¹³ Tramadol, which combines some opioid activity with SNRI activity, may have some efficacy, but bears the risk of withdrawal symptoms, abuse, and serotonin syndrome.^{7,9,12,43} Studies of SSRIs have shown efficacy for mood and fatigue in FM, but limited efficacy for pain.¹³ To be optimally useful, guidelines for FM management should consider the FDA approvals, clinical studies of drugs approved for FM, and the latest evidence regarding all agents used commonly on- and off-label.

The current guidelines also do not reflect updated analyses of FM treatments. Two recent systematic reviews, which were completed after the current guidelines, add substantially to the evidence base and scientific understanding of FM therapy. Nishishinya et al systematically reviewed 10 randomized, placebo-controlled trials of amitriptyline for FM.⁴⁴ Although amitriptyline 25 mg/day was associated with significant improvements in some symptoms, amitriptyline 50 mg did not perform significantly better than placebo.⁴⁴ Of the 10 studies, 8 had durations of only 8 weeks,⁴⁴ and the 8-week efficacy shown for amitriptyline 25 mg was not observed at 12 weeks in the study of that length.⁴⁴ The 10 studies did not report adverse events consistently and rigorously.⁴⁴ The authors concluded that no evidence supports the efficacy of amitriptyline at doses higher than 25 mg/day or for longer than 8 weeks.⁴⁴

Dr. Flood (Rheumatology): We have no data about the safety of any of the [older] nonapproved drugs in FM patients. Whereas for the approved agents, the FDA requires trials to report safety data, and the FDA is watching out to make sure that the safety data are relevant and honest.

Häuser et al performed a meta-analysis of 18 randomized, placebo-controlled trials of antidepressants used for FM, including TCAs, SSRIs, SNRIs, and monoamine oxidase inhibitors.²⁵ The authors found strong evidence for efficacy of some of the agents, but noted patient preferences and comorbidities related to potential adverse effects of these drugs should be considered before initiating treatment.²⁵ The meta-analysis had several limitations. It could not compare classes or individual drugs because of the different combinations of medica-

tions allowed in each study. Most studies were only 8 weeks in duration. A disparity in sample sizes between drug classes (eg, small “n” in TCA trials and large “n” in SNRI trials) could affect the rigor of observed effect sizes. Not included were the phase 3 pivotal trials of milnaci-pran, outcomes assessment of composite response or physical function, or discussion of attributes of medications that may affect compliance, such as tolerability and the potential for drug–drug interactions.

Dr. Goldenberg (Rheumatology): I think I use guidelines and most people use guidelines to help with our gestalt about what is an appropriate individual therapy. Of course, the limitations with guidelines in rheumatoid arthritis or in FM are that it’s such an individual condition. So we as clinicians have to be aware of the fact that it just gives us another way to think about the condition.

The current guidelines for FM management predate these 2 analyses, which would appear to weaken the case for some off-label drugs recommended in the guidelines.

Dr. Beltran (Managed Care): In our organization clinical guidelines never replace physicians’ clinical judgment and experience...and ultimately when the guideline doesn’t fit the patient, we defer to the physician’s clinical judgment and expertise.

Challenges for FM Guidelines

The AJMC roundtable participants observed that the current FM guidelines are not commonly used by physicians or payers to make treatment or formulary decisions. Some physicians, especially PCPs, find it difficult to keep current with the latest guidelines for the many disorders they treat and are not familiar with the guidelines for FM. Guidelines in general can sometimes be too restrictive to apply to the unique needs of individual patients with any disorder, and individualization is crucial in FM treatment. Participants noted that clinicians should fit guidelines to the patient, not the patient to the guidelines. Especially if guidelines are followed rigidly in formulary positions, they can be too restrictive to individualize patient care and treat patients early and effectively.

In further discussion, the roundtable participants concluded that the current FM guidelines have limited practical utility. They lack a straightforward recommended treatment algorithm (although an algorithm could be difficult because each FM patient has a unique set of symptoms and requires individualized treatment). More important, the usefulness of the latest published guidelines has been limited by the rapid change in the research and clinical fields of FM. The guidelines precede or do not consider recent FDA approvals of 3 agents for FM or their pivotal trials, and some guidelines may overemphasize TCAs. The guidelines do not include evidence from the latest systematic review analyses. The outcomes measurements in trials cited for the APS and EULAR guidelines do not include evaluation criteria deemed essential by patients and physician experts, as recommended by OMERACT. Participants observed that guidelines can be “double-edged swords,” used not only to encourage the use of certain treatments but to justify discouraging other treatments that may be helpful for individual patients. In the case of FM, physicians may be forced to use unapproved drugs off-label before trying FDA-approved drugs. For lack of guidelines that reflect the latest findings, clinicians, managed care organizations, and other stakeholders have diverse understandings and views on best practices for the treatment of FM. Clinician prescribing practices vary widely, and managed care does not have disease management initiatives in place for FM patients.

Dr. Draud (Psychiatry): When you see real people who have real disease, patients’ symptoms don’t always match the treatment guidelines. I think it’s helpful to have them [guidelines], but I treat symptoms, not rigid diagnostic criteria and guidelines.

Updated guidelines for the diagnosis and management of FM should reflect the rapidly changing landscape of scientific understanding and advances in disease management. They should enhance clinician education as well as clinical practice, because they could further legitimize FM and clarify understanding of the disease process. Health plans could help advance this medical education by dis-

seminating new guidelines to clinicians. Updated guidelines could also encourage the easing of current formulary restrictions on access to effective FM treatments. The current FM guidelines are rarely used in formulary development processes; however, more useful guidelines would be welcome. The new guidelines should be geared toward optimizing the 3 critical outcome domains of FM: clinical, economic, and QOL.

Dr. Flood (Rheumatology): I think in terms of how you develop guidelines and treatment decisions, we are just at the dawn of a new era in American medicine. The president has placed in the stimulus bill billions of dollars to do comparative effectiveness studies. Those are some of the areas that researchers need to latch on to, so we can question whether there is a difference between amitriptyline and a different drug, and whether there are variabilities based on patient characteristics. These are doable trials; we just need the researchers to have the opportunity and the funds to do it. Those funds are available as they have never been before.

To underpin and strengthen new guidelines, more comparative clinical trials are needed to evaluate the efficacy and safety of drug therapies for FM. Already available to include are the FDA-approved agents and their supporting pivotal trials, which should be given due consideration in updated guidelines. Also available are the recent meta-analyses discussed above, which clarify the evidence to date regarding some agents. Additional new head-to-head studies would offer valuable evidence and help resolve controversies over conflicting data. New trials and new guidelines should consider patient perspectives (eg, by using OMERACT criteria and composite response outcome measures). Guidelines should recognize early diagnosis and appropriate treatment, thereby preventing further functional deterioration, preserving QOL, and realizing cost savings.

Guidelines should be used as a tool for optimal patient care, which for FM means individualization of treatment. Often treatment individualization can be best achieved through a collaborative multidisciplinary team, which might include a PCP, rheumatologist, pain specialist, psychiatrist, physical therapist, and/or others. Listening to the

patient's concerns and giving counsel regarding how to have a better QOL with a chronic illness is important for optimal outcomes and can be facilitated by the additional healthcare encounters that occur with team treatment. If the patient does not fit guidelines, the team can defer to clinical judgment and experience. Even when treating patients with FM without a collaborative team, clinicians should be able to assess its progression on the disease continuum and refer to guidelines accordingly. Managed care could develop formularies and initiate chronic-care disease management programs that reference guidelines, the latest evidence in the literature, and a consensus of various specialists while allowing flexibility for patient individualization

Summary

The current guidelines have been and are a good attempt to increase awareness of FM, add legitimacy to the disease state, and outline possible treatment options. However, they have several limitations, including the omission of new treatments and recent evidence. Updated or revised guidelines that include some of the most recent data and information could become an important tool to aid in the successful management of FM.

SECTION 3. CATEGORY MANAGEMENT OF FM AGENTS: IMPLICATIONS FOR PATIENT OUTCOMES AND UTILIZATION MANAGEMENT

Summary of Roundtable Discussions of Issues and Needs Relating to FM

The AJMC roundtable participants agreed that due to the prevalence, patient burden, and costs, all FM patients should be diagnosed and managed appropriately. They also agreed that an opportunity to educate providers about FM diagnosis and management exists; such education could improve patient outcomes and lower costs. The participants noted that physicians have several choices at their disposal to treat FM, including 3 FDA-approved agents, along with nonpharmacologic treatments and some off-label medications. They found current guidelines to be a reasonable attempt to identify appropriate treatments, but noted the guidelines are outdated,

not widely used by plans or providers, and have limitations. Participants agreed the best management approach for FM would allow patients open access to all available treatments, with individualized treatment decisions made jointly between the physician and patient. Participants noted that current access to FDA-approved agents to treat FM is often restricted, allowed only after failure of treatment with other agents (typically generic drugs), for which FM is an off-label use. This is a common practice for many medical conditions, including FM, in managed care environments. Discussion then turned to establishment of an FM category on payer formularies as a step toward legitimizing the disease state and educating providers about FDA-approved and non-FDA-approved treatments.

Dr. Lee (Internal Medicine): With new medications, it's very difficult to get approval [insurance coverage]. There is a lot of paperwork, a lot of step therapy, and it gets the physician and patient frustrated. When they don't get approved, they will often just give up.

Formulary Categories and Access to Treatment

A specific therapeutic category for FM within payer formularies does not exist within most formularies today. This, along with a lack of diagnosis coding on prescription claims, makes it difficult for health plans to track the prevalence of the disease. This inability to track FM may have helped perpetuate a scant awareness of the disease in managed care and inattention to it in chronic disease management plans, educational programs, and other initiatives. Lack of a category for FM also means that the drugs used (off-label) for FM are found in other categories based on their approved indications. Even 2 of the FDA-approved drugs for FM are classified in 1 or more other categories based on their approvals for other conditions, which often are their primary indication. Duloxetine may be found under depression and/or pain management. Pregabalin may be listed under anticonvulsants and/or pain management. Milnacipran, however, is the first drug with FDA approval for FM only, and no roundtable participant was aware of any formulary with a category for FM.

Category requirements of the United States Pharmacopeia (USP) may influence Medicare Part D formulary development in ensuring that drugs in the categories are included. The USP currently lists duloxetine and pregabalin under their primary therapeutic category only (duloxetine under antidepressants, pregabalin under anticonvulsants). The USP formulary has been updated annually, but in agreement with the Centers for Medicare & Medicaid Services (CMS), USP is going to a 3-year update cycle, leaving milnaci-pran currently without a category. Medicare Part D health plans are not required to follow the USP model formulary for categorization, but they are measured against it. As for commercial formularies, health plans frequently keep their commercial and Medicare formularies consistent, but the plans are free to impose limitations or restrictions. Thus USP requirements may have had an indirect influence on the development of formularies that do not include the FDA-approved treatments in an FM category.

The lack of a category for FM may indirectly affect patient access to appropriate treatments, including treatments indicated by the FDA. Formularies commonly control access to the FDA-approved drugs for FM; duloxetine and pregabalin use is restricted on approximately half of commercial health plans.

Ms. Brown (Patient Advocacy): What a lot of these barriers do...is further delay the appropriate care and management of these patients...making the condition far worse. So, what we need to do is get to early intervention through recognition and care that's appropriate and that doesn't have other burdens from access to care as well as the willingness to pay for that care.

Problems with access to treatment contribute to FM patients' dissatisfaction with their health-care. A national patient survey conducted by the APF and National Fibromyalgia Association (NFA) demonstrated widespread insurance or managed care problems.⁴⁵ Common difficulties included incomplete coverage for pain treatment options, delays in preauthorization and access to FDA-approved medications, prolonged appeals processes, and repetitive denials of coverage.⁴⁵

Some of these problems might be related to the lack of an FM category on formularies. Without a category for FM, health plans may not have a unique, comprehensible FM treatment paradigm that clearly identifies FDA-approved therapies.

Dr. Jain (Psychiatry): Legitimacy is what this disorder is begging for. Anything that can add to the legitimacy will serve everyone's interest here. I look at formularies as one more layer of protection for me, because I know they are watching out or reading the picture at a level that I'm not, maybe. I actually like the fact that if your plan says FM is the category and this drug is approved, I know they have looked at it. I like that. I know clinicians and primary physicians like it too.

Often patients tell their physicians about their drug coverage policies, which can guide prescribing practices. FM patients looking at formularies may not see a drug they can associate with their disease. Lack of a category for FM might lead physicians and patients to look at categories like pain management and possibly choose less appropriate treatments, such as opiates. Physicians can select any drug, but many have limited education on FM or the 3 FDA-approved agents. Thus the lack of a category may leave patients as well as their PCPs without guidance from the health plan for appropriate FM management.

Categorizing FM on Formularies to Benefit Patients, Clinicians, and Payers

Most importantly, the roundtable participants felt that a new category for FM on payer formularies could help legitimize the FM disease state. Patients and physicians would be able to see the disease listed in the formulary rather than having to search through "similar" categories for something that may apply to the situation. Greater legitimacy for FM would encourage more research interest, better public awareness, less stigma for patients, and possibly more government funding for research. Greater legitimacy could therefore further the advancement of medical progress against this chronic, debilitating disease.

A new category would also raise awareness of FM as a diagnosis to consider. It would help

health plans recognize the diagnosis and authorize appropriate treatment. It would also encourage action by clinicians who hesitate to diagnose or treat due to confusion or misunderstanding about the disease. A new category would support the need for intervention in FM, thereby perhaps helping reduce the time and effort wasted on inaccurate diagnoses.

A new FM category would serve as part of a broader initiative to educate the medical community and patients about the FM disease state. The category would support the need for better education identified in Section 1 of this supplement. Better education, in turn, can lead to better outcomes. A new category would offer FM patients the validation and reassurance they need while helping them learn about their disease. A new category would educate providers about FM and help separate clinicians' thinking about treating FM from their thinking about treating pain alone, depression, anxiety, or an unknown diagnosis.

Ms. Brown (Patient Advocacy): If [milnacipran] goes to its own category, it's an opportunity for the patient advocacy groups to design outreach information to our constituents to help them be better informed and how to ask the right questions. Not only would they say, "I saw this in a magazine, can I take this?" They can also look and determine whether it is available through their insurance company. If it isn't, they can ask why not and continue with the inquiry.

A new category would further educate patients and physicians about the drug options available for FM. Options presented under the category in commercial plan formularies would include the 3 FDA-approved agents. (Other agents, such as TCAs, could be listed with notations that they do not have FDA approval.) Listing the FDA approvals within the FM category would encourage appropriate on-label utilization. In particular, appropriate categorization of milnacipran, which is indicated only for FM, would encourage approved on-label utilization and discourage the off-label prescribing that could occur if it were classified in a non-FM category.

A category for FM would contribute to improved management of FM drugs by payers, as

it provides an opportunity to list and delineate agents with proven efficacy and effectiveness.

Dr. Lee (Internal Medicine): The thing is education. Knowing that there is a category for any condition, let alone FM, stimulates the decision to look into the options and the evidence behind it. For the patient, it's actually good, because we can then tell them what the efficacy is. I think this is a way to open up a dialogue.

Although identification of FM by pharmacy data alone is problematic, use of that information combined with medical utilization data can more accurately identify FM patients and provide a platform for outcomes research. With this form of integrated data, assessment of cost-effectiveness becomes a reality and puts payers in position to better guide benefit coverage for FM treatment and disease management plans. This could lead to greater patient access to the most effective treatments and still enable health plans to manage utilization. Implementation of a new FM category would vary by organization, and the process to create such a class or category for FM may include:

- A literature review to establish an evidence base of efficacy and safety data
- Discussion with plan clinicians, including consultation with expert specialists in different areas (pain, rheumatology, neurology, etc)

Dr. Dunn (Managed Care): I think the way it could be used is more of an educational approach, which would be the purpose of having a category.

Dr. Goldenberg (Rheumatology): A responsibility for managed care is determining the most cost-effective care for your clients. And I think we have shown you that making a diagnosis of FM is very important in cost-effectiveness. It saves patients, doctors, and the government money. We know that for sure. There is a lot of data, and categorization might help you with that.

- Consideration of FDA approvals, government guidelines and advisories, and guidelines/statements from medical organizations
- Inclusion of unapproved drugs with effectiveness evidence for FM, but with annotations to their lack of FDA approval
- Cost considerations or cost/benefit analyses for individual drugs to be listed in the formulary.

Dr. Bitton (Managed Care): Guidelines are used in the review of new products; and when those products come up for review annually, we will take into consideration changes to those guidelines, as well as discussions from the community, physicians, and from among fellow pharmacists.

Dr. Draud (Psychiatry): There has been attention with regard to cost versus care versus patient. The fact is we are on the same team, and there shouldn't be this tension against managed care. The bottom line is the patient is supposed to be our primary focus. If, in fact, we raise the level of awareness and education and help everybody get on the same page, costs will go down if we treat the illness earlier.

Summary

The AJMC roundtable participants agreed that a separate category for FM in drug formularies would further legitimize FM as a unique condition and support education for the medical and patient communities. With this step forward, all key stakeholders, including physicians, payers, and patient advocates, can work collaboratively on behalf of their patients to facilitate earlier accurate diagnosis and more appropriate treatment, including improved patient access to the most effective treatments. Accurate diagnosis and safe, effective treatment will satisfy the 3 critical outcomes that frame the unique challenge of FM:

- *Clinical:* alleviating symptoms and improving patients' physical function
- *Economic:* reducing the high direct and indirect costs associated with FM

- *Quality of life:* preventing disability and maintaining employment and social involvement, thereby improving QOL.

Dr. Flood (Rheumatology): I think this is a crucial time in the history of FM and its diagnosis and management. I think and I hope that some of the data that we have covered today will help people understand that if we treat people early, if we diagnose them accurately, then we can save the healthcare system, and we can save patients a lot of money and a lot of suffering.

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