Fibromyalgia: A Clinical Update

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Fibromyalgia is a common chronic syndrome defined by core symptoms of widespread pain, fatigue, and sleep disturbance. Other common symptoms include cognitive difficulty, headache, paresthesia, and morning stiffness. Fibromyalgia is increasingly understood as 1 of several disorders that are referred to as central sensitivity syndromes; these disorders share underlying causes and clinical features. Tender points are often detected in patients with fibromyalgia and were formerly required for diagnosis. Newly proposed criteria, however, rely on patients' reports of widespread pain and other somatic symptoms to establish the diagnosis of fibromyalgia. The management of fibromyalgia requires a multidimensional approach including patient education, cognitive behavioral therapy, exercise, and pharmacologic therapy. The present review provides an update on these various aspects of treating a patient with fibromyalgia.

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Fibromyalgia is a chronic, potentially disabling condition defined by core symptoms of widespread pain, stiffness, fatigue, sleep disturbance, and cognitive dysfunction.[1,2] As a condition that affects 2% of the US population and is 7 times more prevalent in women than in men,[3] fibromyalgia is one of the most common disorders seen by primary care physicians. Patients with fibromyalgia often have a bewildering array of symptoms and a paucity of objective findings, which can frustrate the diagnostic efforts of their health care providers. Test results for diseases of muscle and nerve are normal; serologic studies for autoimmune and infectious diseases are nonrevealing. Given the prevalence of and difficulty in diagnosing fibromyalgia, it is important that primary care physicians be aware of newly proposed diagnostic criteria and advances in the recognition and management of fibromyalgia.

The previous lack of a clear organic basis for fibromyalgia and the increased prevalence of affective disorders in fibromyalgia led some observers to consider it a nondisease or a psychosomatic illness. Recent research, however, has illuminated our understanding of the neurobiological basis of chronic pain syndromes. The current model of understanding fibromyalgia is that it is 1 phenotype of several overlapping syndromes that demonstrate disordered pain regulation referred to as *central sensitization*.[4-6] In the present review, I describe the pathologic process of fibromyalgia and provide current understandings of the diagnosis, comorbid conditions, and management of this challenging disorder.

Pathophysiologic Process

Fibromyalgia replaced the previous term "fibrositis" in the 1980s after exhaustive efforts to prove the existence of inflammatory or other abnormalities of muscle and connective tissue had failed.[2,5,7] By then, attention had turned to the central nervous system and the concept of central, or non-nociceptive, pain. More recently, it has been appreciated that fibromyalgia shares similar abnormalities of causation with, and clinical features of, several other disorders.[4-6] This new understanding led to the concept of a group of conditions that make up central sensitivity syndrome (CSS) (*Figure 1*). Rather than being a discrete illness, fibromyalgia is now considered 1 phenotype of a much larger spectrum of disorders that overlap substantially in individual patients.

Predisposing Factors for CSS

The underlying cause of CSS disorders is still being explored, but unifying theories have been proposed.[4,6] A schematic suggesting the possible relationship between the biopsychosocial mechanisms is shown in *Figure 2*. Genetic, sleep, nervous system, infection, and psychological factors are all potential contributors to the presence of fibromyalgia.

Genetic and Familial Predisposition

There appears to be a strong familial component to fibromyalgia and other CSS disorders. First-degree relatives of patients with fibromyalgia are 8.5 times more likely to have the disorder than the general population.[8] In addition, certain genetic markers for serotonin, dopamine, and catecholamine methyltransferase polymorphisms may be associated with heightened pain sensation.[9]

Sleep Abnormalities

In sleep laboratories, patients with fibromyalgia typically display "alpha-delta intrusion," as demonstrated by electroencephalography. The resultant loss of restorative delta wave sleep leads to increased fatigue and pain.[10] This cause and effect relationship, however, goes both ways. Normal individuals who are deprived of sleep develop fibromyalgia symptoms, so sleep disturbance can be an inciting pathway to fibromyalgia, as well as a self-sustaining symptom of the condition.[4]

Autonomic Nervous System Dysfunction

Emotional and physical stress activates the hypothalamic-pituitary-adrenal (HPA) axis. Patients with fibromyalgia have hyperactivity of the HPA axis and the

KEY POINTS

- Fibromyalgia is a common disorder seen predominantly in women. The core features of fibromyalgia are widespread pain, sleep disturbance, and chronic fatigue.
- Rather than being a discrete illness, fibromyalgia is considered 1 phenotype of a much larger spectrum of disorders that overlap in individual patients.
- There are objective abnormalities of central nervous system neurotransmitters in fibromyalgia. Central nervous system sensitization appears to underlie the widespread clinical features of fibromyalgia and other disorders of central sensitivity syndrome.
- In patients with fibromyalgia, tender points are common but are no longer required for the diagnosis of fibromyalgia.
- Indiscriminant testing for antinuclear and other autoantibodies should be avoided in the evaluation of a patient with suspected fibromyalgia.
- Pain sensitivity in the general population is represented by a bell-shaped curve. Patients with increased pain but few or less prominent other symptoms may be considered to have a degree of "fibromyalgianess" that may respond to therapy usually reserved for fibromyalgia.
- Fibromyalgia severity varies widely. Patients with marked tenderness, little depression, and good pain-coping skills respond well to treatment and have a favorable prognosis.
- Managing fibromyalgia requires a combination of pharmacologic and nonpharmacologic treatment.
- A philosophy of "start low, go slow" with exercise and drug therapy improves the likelihood of success in managing fibromyalgia.

Chronic fatigue syndrome
Chronic pelvic pain and endometriosis
Fibromyalgia
Headache (tension and migraine)
Idiopathic low back pain
Interstitial cystitis
Irritable bowel syndrome
Multiple chemical sensitivity
Myofascial pain syndrome
Posttraumatic stress disorder
Primary dysmenorrhea
Restless leg syndrome
Temporomandibular joint disorder

Figure 1.
Common conditions in central sensitivity syndrome.[4,5]

sympathetic nervous system, with simultaneous relative hypocortisolism.[11] The causal relationship between HPA dysfunction and fibromyalgia is unclear, but early childhood stress could precipitate the HPA abnormality.[11]

Infection, Inflammation, and Physical Trauma

Inflammatory states may trigger persistent central sensitization in susceptible individuals.[12-15] These states include viral and other infections, chronic autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus, and physical trauma. Pro-inflammatory neurotransmitters, including substance P and glutamate, stimulate peripheral nociceptive fibers, which synapse on spinal neurons and lead to temporary central sensitization in normal individuals. For example, patients with severe osteoarthritis have evidence of elevated cerebrospinal fluid (CSF) substance P levels and lowered widespread pain thresholds.[15] These responses normalize after joint replacement.[15] Individuals with genetic and other susceptibility factors may fail to terminate this transient process, leading to chronic central sensitization.

The evidence for physical trauma as an entry pathway to fibromyalgia has been considered but is controversial, with some studies supporting and others failing to support a relationship.[16,17]

Psychological Factors and Stress

Depression, anxiety, and difficulty coping with stress are common in patients with fibromyalgia. There is an association between childhood abuse and fibromyalgia—McBeth et al[18] suggested that inappropriate learned behavior from living with alcoholic or dysfunctional parents may drive the catastrophizing behavior and learned helplessness that are prevalent in many patients with fibromyalgia. The relationship between these psychological factors and fibromyalgia is bidirectional.

Central Sensitization

Abnormalities in the central nervous system are associated with the intense widespread enhancement of pain in fibromyalgia. For example, Russel and Larson[6] found a sustained 2- to 3-fold elevation of CSF substance P and other neuropeptides that facilitate pain in patients with fibromyalgia, as well as diminished metabolites of CSF serotonin, norepinephrine, and dopamine, which act to inhibit pain perception. Pain is the sine qua non of fibromyalgia, and patients with this disorder experience widespread allodynia (perception of pain caused by a stimulus that should not normally cause pain) and hyperalgesia (exaggerated sense of pain in response to a noxious stimulus).

Clinical Manifestations

Widespread musculoskeletal pain is the dominant feature of fibromyalgia.[1,2] Proximal regions such as the neck, shoulders, hips, and thighs are most commonly involved, but pain may be felt in the hands and feet.[1,2,19] Statements such as "I hurt all over" often alert the physician to

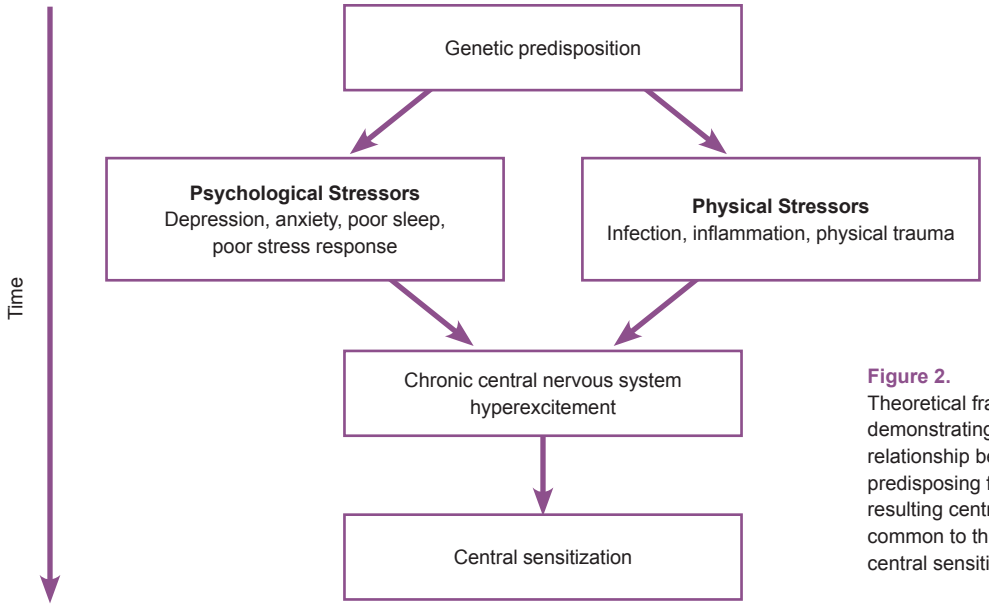

Figure 2.
Theoretical framework demonstrating the possible relationship between the predisposing features and the resulting central sensitization common to the disorders of central sensitivity syndrome.

consider the diagnosis of fibromyalgia. In severe cases, even a gentle hug may be perceived as painful. Patients may complain of swollen joints (subjective swelling), but synovitis is not present on examination. Nondermatomal paresthesia without objective neurologic findings is a frequent complaint.

Fatigue is present in the majority of patients.[1,2,19] Poor sleep, with frequent night-time awakenings and difficulty falling back to sleep, is often reported.[10,19] Exhaustion on awakening may be severe, and morning stiffness is common. "Fibro-fog" describes the symptoms of poor short-term memory and lack of ability to concentrate.[1,19] Poor balance, dry eyes and mouth, and Raynaud phenomenon are occasionally noted.[19]

Patients often have features of the other associated CSS disorders (*Figure 1*).[4,5] Although depression is common in patients with fibromyalgia, it is not universally included in the CSS disorders. There appear to be distinct differences in sleep pathology and neuroendocrine abnormalities between fibromyalgia and depression.[4]

Diagnosis

The diagnosis of fibromyalgia as a discrete entity has typically been made using the American College of Rheumatology (ACR) 1990 classification criteria, which is widespread pain for more than 3 months and the presence of at least 11 of 18 tender points.[2] Widespread pain is defined as pain on both sides of the body, pain above and below the waist, and the presence of axial pain. The examiner identifies tender points by using the thumb to exert 4.0 kg pressure (sufficient to blanch the thumbnail) at each of the discrete tender points to elicit pain.[2]

The ACR diagnostic criteria were developed for research purposes but were gradually adopted for clinical diagnosis. Using these criteria for diagnosis is problematic for more than 1 reason. Few primary care physicians perform tender point examinations (or correctly perform tender point examinations).[19] The same can be said for many rheumatologists.[19] Additionally, the case definition of fibromyalgia has evolved in the past 20 years to include cognitive and other symptoms that are not included in the 1990 ACR criteria.[1] Finally,

tender points are highly correlated with psychological distress and are absent in as many as 25% of patients who have fibromyalgia.[19,20] For these reasons, the ACR introduced a new provisional set of diagnostic criteria for fibromyalgia in 2010.[1] These proposed criteria do not require a tender point examination but rely on patient reports of widespread pain and other somatic symptoms. A patient satisfies the proposed diagnostic criteria if 3 conditions are met:

- The patient has a widespread pain index (WPI) of 7 or greater and symptom severity (SS) scale score of 5 or greater. Alternatively, a patient could meet criteria with a WPI of 3 to 6 and SS scale score of 9 or greater.
- Symptoms have been present at a similar level for at least 3 months.
- The patient does not have a disorder that would otherwise explain the pain.

The WPI is calculated by summing up patient reports of pain in 19 separate regions of the body.[1] The SS scale score is calculated by grading several symptoms (eg, pain, fatigue, awaking unrefreshed) on a severity scale from 0 ("no problem") to 3 ("severe, pervasive, continuous, life-disturbing problems").[1]

Comorbid Conditions

The various members of the CSS family listed in *Figure 1* are often referred to as comorbid disorders associated with fibromyalgia, and it is common to find 1 or more of these disorders in patients with fibromyalgia.[5,6] Anxiety and depression are seen in about half of patients with fibromyalgia.[4]

Fibromyalgianess

Rather than insisting on an "either/or" requirement in diagnosing fibromyalgia, there is an emerging and clinically useful concept of considering varying degrees of "fibromyalgianess" in patients.[20,21] This term reflects the growing awareness that pain sensitivity in the general population is represented by a bell-shaped curve.[21,22] Many musculoskeletal diseases appear capable of triggering the phenomenon of central sensitization with an associated increase in sleep disturbance, fatigue, widespread pain, and other symptoms common in fibromyalgia.[11-16] If symptoms are sufficiently severe, a diagnosis of fibromyalgia is usually made and treatment is initiated. Patients with fewer or less-prominent symptoms, however, may respond to therapy usually reserved for "complete fibromyalgia."[20-22]

Differential Diagnosis and Laboratory Testing

The differential diagnosis of fibromyalgia includes disorders that have features of widespread pain and fatigue. These disorders include hypothyroidism, inflammatory and other myopathies, polymyalgia rheumatica, other rheumatic diseases, viral infections, and severe vitamin D deficiency.[19]

Statements such as "I hurt all over" often alert the physician to consider the diagnosis of fibromyalgia

Patients with hypothyroidism often present with substantial fatigue, myalgia, and malaise. Serum creatine kinase (CK) levels may be elevated in patients with hypothyroidism.[23] The usual features of polymyositis are proximal muscle weakness and elevation of serum CK levels.[24] Patients with statin-related myopathy may present with muscle weakness or pain or a combination of both. Serum CK levels are often elevated but may be normal in mild disease.[25] Patients with suspected statin myopathy but with normal serum CK levels often benefit from a trial of observation off of the drug.[25] It may take several weeks after cessation of the drug for improvement to be noted.[25] Polymyalgia rheumatica is usually seen in elderly patients who present with marked proximal muscle stiffness greater than muscle pain.[26] An

elevated erythrocyte sedimentation rate (ESR) and a prompt response to low-dose glucocorticoid treatment aid in confirming the diagnosis. Some chronic viral infections such as Epstein-Barr virus, hepatitis B, hepatitis C, and parvovirus may mimic or trigger fibromyalgia.[4,14]

Individuals with inflammatory rheumatic diseases such as rheumatoid arthritis, systemic lupus erythematosus, or Sjögren syndrome may present with substantial pain and fatigue, but diagnoses are made on the basis of the presence of synovitis, multisystem abnormalities, sicca symptoms, or other objective findings.[13] Tests for antinuclear and other autoantibodies have poor predictive value and should be reserved for patients who demonstrate inflammatory or multisystem disease by medical history and physical examination.[13,27]

It is important to emphasize that fibromyalgia may be triggered by and coexist with many chronic diseases. For example, a patient whose rheumatoid arthritis symptoms are well controlled with appropriate therapy but who continues to complain of pain most likely has secondary fibromyalgia and will likely respond to therapy directed toward fibromyalgia.[4,13]

Subgrouping Fibromyalgia

There is a wide spectrum of symptom severity in fibromyalgia. Using features of degree of tenderness, depression and anxiety, catastrophizing behavior, and cognitive ability to control pain, investigators identified 3 subgroups of patients with fibromyalgia.[28] The most common patient subgroup (group 1) displayed moderate tenderness, moderate depression and anxiety, moderate tendency to catastrophize, and moderate pain-coping skills. The most challenging patient subgroup (group 2) displayed marked tenderness, high depression and anxiety, marked catastrophizing behavior, and poor pain-coping skills. Importantly, a third patient subgroup (group 3) was characterized as having marked tenderness but with little depression/anxiety, little tendency to catastrophize, and good pain-coping skills. The importance of these findings is the recognition that fibromyalgia is a heterogeneous disorder. Group 3 patients often respond well to treatment and have a favorable prognosis. Group 2 patients tend to have a poor response to treatment, and their long-term prognosis is poor.[28]

Managing Fibromyalgia

The treatment of patients with fibromyalgia requires a combination of pharmacologic and nonpharmacologic modalities, including exercise and cognitive behavioral therapy.

Nonpharmacologic Management

Patient Education

Simply making a diagnosis of fibromyalgia has a positive effect on its management, leading to a reduction in primary care visits, diagnostic testing, and drug prescriptions.[29-31] Patient education is the next step. Emphasizing that the patient does not have a serious or life-threatening disease reduces anxiety. Discussing what is known about the imbalance of central nervous system neurotransmitters and the abnormalities of brain blood flow helps to assure the patient that fibromyalgia is a real illness. One useful metaphor to explain central pain processing abnormalities is an overly sensitive home smoke alarm that goes off every time the oven is turned on. It is a false alarm shrieking "fire" in the absence of fire. An overly sensitive pain processing system will shriek pain in the absence of peripheral pathology, but the perception of pain is very real. Websites hosted by the Arthritis Foundation (http://www.arthritis.org/), the National Fibromyalgia Association (http://fmaware.org/site/), and other reputable organizations can provide patients with useful resources to improve their understanding of fibromyalgia.

Setting expectations regarding illness prognosis and the roles of the patient and physician is important. It helps to advise patients that fibromyalgia is a chronic

illness with good days and bad days; treatment will improve symptoms but usually not eliminate them. The patient can play a major role in adhering to sleep hygiene and exercise programs, as well as other nonpharmacologic modalities.

Cognitive Behavioral Therapy

Cognitive behavioral therapy (to address maladaptive thoughts) and stress-reduction techniques have been shown to be effective in some patients.[32,33] Recognizing and addressing behavioral issues of catastrophizing behavior and learned helplessness can aid in focusing treatment on self-management techniques.

Exercise

Aerobic exercise and muscle strength training can reverse deconditioning and improve sleep, pain, and function in patients with fibromyalgia.[33-35] Patients who choose activities they like (eg, walking, pool exercise, group activities) and who start at low levels of exercise are more likely to be successful in managing their fibromyalgia in the long term. Exercise intensity should be increased very slowly to avoid injury and flares of pain, which may cause the patient to abandon the activity.[35] Patients with good coping skills are most likely to adhere to an exercise program.[36]

Complementary and Alternative Medicine

In general, little scientific evidence exists to support the use of complementary and alternative medicine in the management of fibromyalgia.[36,37] Acupuncture, balneotherapy, chiropractic treatment, and osteopathic manipulative treatment have been used frequently to manage the symptoms of fibromyalgia.[37-39] The results of a controlled trial[38] suggested that benefits of massage therapy may last up to 6 months after treatment. In addition, a randomized pilot study[39] revealed that patients who received osteopathic manipulative treatment and medication for fibromyalgia had better outcomes compared with patients who received only medication.

Pharmacologic Management

Fibromyalgia is a syndrome of many symptoms and comorbidities, and there is growing evidence of abnormalities of several neural pathways including those mediated by serotonin, norepinephrine, substance P, and glutamate and other neurotransmitters.[4-6] Patients complain of a variety of seemingly unrelated symptoms. Therefore, it is not surprising that there is no single pharmacologic agent capable of effectively addressing all of the potential symptoms of fibromyalgia.

Antidepressants

Antidepressants appear to exert their effects by modulating serotonin and norepinephrine pathways. Tricyclic antidepressants (TCAs) such as amitriptyline, desipramine, and nortriptyline have been shown in short-term studies to improve pain, sleep, fatigue, and overall sense of well-being.[33,36] However, they are associated with more adverse effects when used at higher doses.[5] Tricyclic antidepressants are often prescribed initially for patients with fibromyalgia who do not have depression.

There is an emerging and clinically useful concept of considering varying degrees of "fibromyalgianess" in patients

It is recommended that TCAs be started at very low doses 2 hours before sleep and titrated upward slowly over several weeks (*Table*).[40] Despite their initial effectiveness, the long-term durability of TCAs has been questioned.[40] Anticholinergic effects (dry mouth and constipation), sedation, and grogginess limit their tolerability. Although cyclobenzaprine is classified as a muscle relaxant, it is structurally a TCA. It has been shown to improve sleep, pain, and overall sense of well-being but appears to have little or no effect on fatigue in patients with fibromyalgia.[41]

Selective serotonin reuptake inhibitors (SSRIs) are useful for the management of depression and fatigue but

Table.
Drugs Commonly Used in the Management of Fibromyalgia

Drug	Starting Dose[a]	Target Dose	Common Adverse Effects
Amitriptyline	5-10 mg 2 h before bedtime	25-50 mg	Drowsiness, dry mouth, dizziness
Desipramine	5-10 mg 2 h before bedtime	25-50 mg	Drowsiness, dry mouth, dizziness
Cyclobenzaprine	5-10 mg 2 h before bedtime	10-30 mg	Drowsiness, dry mouth, dizziness
Duloxetine	20-30 mg every morning	30-60 mg	Nausea, headache, dizziness, insomnia
Milnacipran	12.5 mg every morning	50-100 mg twice daily	Nausea, headache, dizziness, insomnia
Pregabalin	25 mg at bedtime	100-450 mg	Dizziness, somnolence, weight gain, blurred vision
Tramadol-acetaminophen	50 mg every morning or at bedtime	50-200 mg	Nausea, headache, dizziness, insomnia

[a] A "start low, go slow" approach to drug therapy is recommended to improve likelihood of success in managing fibromyalgia.

have been less impressive in improving pain and sleep in patients with fibromyalgia.[5,40] The selective norepinephrine serotonin reuptake inhibitors (SNRIs) duloxetine and milnacipran have been approved by the US Food and Drug Administration for the management of fibromyalgia and appear to be more effective in relieving fibromyalgia symptoms than are the SSRIs.[33,36,40] Duloxetine reduces pain and improves a patient's overall sense of well-being. It has relatively little effect on sleep and is usually taken in the morning. The most common adverse effects are nausea and headache, which tend to improve with continued use. Patients with fibromyalgia and comorbid depression may benefit from SNRIs as initial therapy. As with all fibromyalgia treatments, a "start low, go slow" dosing strategy improves patient compliance.

Tramadol combined with acetaminophen improves fibromyalgia pain.[33,36] This drug has mild SNRI effects in addition to mild opioid effects.[5] Care should be taken to avoid excessive combinations of SSRI and SNRI drugs to avoid serotonin syndrome.[42] Features of serotonin syndrome include mental status changes, autonomic hyperactivity, and neuromuscular hyperactivity.

Antiepileptic Drugs

Pregabalin, which is approved by the US Food and Drug Administration for the management of fibromyalgia, and gabapentin appear to inhibit the release of pain pathway neurotransmitters, including substance P and glutamate.[43] They have been demonstrated to improve pain, sleep, fatigue, and overall quality of life in patients with fibromyalgia.[5,36,43] They are not approved for the management of depression. They are often used as adjunctive therapy, being added to drugs affecting other pain pathways. Adverse effects that limit their use include dizziness, somnolence, and weight gain.[43] These symptoms tend to improve with continued use.

Other Drugs

Opioids have not been shown to be effective in the management of fibromyalgia and should be avoided if possible.[33,36] Opioid-induced hyperalgesia and long-term adverse effects limit the usefulness of this drug class.[33,36]

Nonsteroidal anti-inflammatory drugs exert their primary effect on prostaglandin-associated inflammatory pathways and are not very effective in reducing the central pain of fibromyalgia.[36] They are useful, however, in the management of coexisting "pain generators" such as osteoarthritis or degenerative disk disease.

Conclusion

Fibromyalgia is 1 of several overlapping disorders of central sensitivity syndrome. The growing knowledge of the underlying biopsychosocial causes of these disorders is leading to a more rational approach to treatment. Recognizing the heterogeneous nature of fibromyalgia, with marked individual variation in prognosis and response to therapy, aids substantially in its management. An understanding of the different pain-relieving mechanisms of drugs aids in the selection of combinations of therapy that may be more effective in the treatment of patients with fibromyalgia.

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