Fibromyalgia

Regina P Gilliland, MD, Department of Internal Medicine; Division of Rehab Medicine, Mobile Infirmary Medical Center
Updated: Jan 5, 2009

Introduction

Background

Fibromyalgia is a complex disorder that was not defined until the late 20th century. It was, however, discovered much earlier, with the condition having been described in medical literature dating as far back as the early 17th century. Many physicians question the existence of fibromyalgia and prefer not to deal with patients who have this complicated disorder. In the past, poor recognition and lack of treatment for fibromyalgia could be explained by a lack of meaningful research. Today, abundant research and medical evidence support the diagnosis of this disease.

Some experts propose that physicians make a paradigm shift in their approach to successfully caring for patients with fibromyalgia. We can no longer rely on the technological advances of science. Even with advanced imaging and laboratory tests, none of the findings confirm the diagnosis of fibromyalgia. A physician skilled in taking a careful history, listening to the patient's concerns, and performing a thorough examination remains the foundation for diagnosing and treating fibromyalgia. The physician must remain a scientist and practice evidence-based medicine without abandoning the Hippocratic principles in the Physician's Oath. We must keep our promises to care for and serve sick and suffering individuals, without prejudicial views.

Definition of fibromyalgia

Fibromyalgia, a common disorder, is a syndrome composed of a specific set of signs and symptoms. Fibromyalgia has long been considered a "wastebasket" diagnosis. However, in 1987, the American Medical Association (AMA) acknowledged fibromyalgia as a true illness and a potential cause of disability. Many well-respected organizations, such as the AMA, the National Institutes of Health (NIH), and the World Health Organization (WHO), have accepted fibromyalgia as a legitimate clinical entity.[1] Fibromyalgia is now recognized as one of many central pain-related syndromes that are common in the general population. Research advances have lead to the conclusion that disturbances within the central nervous system (CNS) known as central sensitization represent the most likely source.[2]

Patients with fibromyalgia generally see many physicians before receiving a correct diagnosis. Patients may seek medical advice for more than 5 years before a correct diagnosis is made, and more than 50% of patients receive a misdiagnosis and may undergo unnecessary surgery.

Nomenclature

Although the syndrome has been known by other names, the word fibromyalgia was first introduced in 1976. This word is derived from the Latin roots *fibro* (fibrous tissue), *my* (muscles), *al* (pain), and *gia* (condition of). Fibromyalgia was most commonly known by the misnomer fibrositis, where "itis" implied an inflammatory component. Chaitrow asserts that no inflammatory process has ever been found to be part of this disease.[3]

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Pathophysiology

The sequence of events that causes fibromyalgia remains unknown, but advances and discoveries may help to unravel the mysteries of this disease. Research shows biochemical, metabolic, and immunoregulatory abnormalities associated with fibromyalgia.

Although the pathogenesis of fibromyalgia is not completely understood, the currently known abnormalities substantiate the proposal that fibromyalgia can no longer be considered a subjective pain condition. The biochemical changes seen in the CNS, the low levels of serotonin, the 4-fold increase in nerve growth factor, and the elevated levels of substance P all lead to a whole-body hypersensitivity to pain and suggest that fibromyalgia may be a condition of central sensitization or of abnormal central processing of nociceptive pain input.[2] Ongoing research will continue to provide a clearer picture of the pathophysiology of this complex syndrome.

Central processes

Clinicians can enhance their approach to diagnosis and treatment by broadening their knowledge of these biochemical and immunoregulatory abnormalities, which may be involved in how nociceptive signals to the CNS are interpreted and how individuals physiologically respond to stress.

Our current understanding of the pathophysiology of fibromyalgia is that the disease is a disorder of central pain processing or a syndrome of central sensitivity. Daniel Clauw, a rheumatologist and fibromyalgia researcher, describes the syndrome as a diffuse problem of sensory volume control that alters the patient's threshold of pain and of other stimuli, such as heat, noise, and strong odors. He also suggests that patients may have hypersensitivity because of neurobiologic changes that affect the perception of nociceptive pain or because of expectancy or hypervigilance, which may be related to psychological factors.[4]

Plasticity in the function of N-methyl-D-aspartate (NMDA) subtype glutamate receptors is necessary for central sensitization to occur. Increased sensitivity of central NMDA receptors were implicated in earlier studies as playing a primary role in fibromyalgia. However, subsequent evidence has suggested that suppression of the normal activity of dopamine-releasing neurons in the limbic system is the primary pathology in fibromyalgia. Increasing evidence indicates that fibromyalgia may represent a dysregulation of dopaminergic neurotransmission.

Serotonin

The most widely acknowledged biochemical abnormality associated with fibromyalgia is abnormally low serotonin levels. Many studies have linked serotonin, a neurotransmitter, to sleep, pain perception, headaches, and mood disorders. Lower-than-normal levels of serotonin have been observed in patients with fibromyalgia. A low platelet serotonin value is believed to be the cause of the low serum levels, which have been correlated with painful symptoms.

Serotonin levels in the CNS are thought to be low because of low levels of tryptophan (amino acid precursor to serotonin) and 5-hydroxyindole acetic acid (metabolic by-product) in the spinal fluid. Investigators have proposed a link between low serotonin levels and symptoms of fibromyalgia.[5] Moreover, many propose that low serotonin levels may cause fibromyalgia in whole or in part.

Substance P

In support of the idea of a systemic biochemical abnormality in fibromyalgia, investigators from 4 independent studies reported levels of substance P that were 2-3 times higher than normal.[6]

Substance P, the neuropeptide in spinal fluid, is a neurotransmitter that is released when axons are stimulated. Increased levels of substance P increase the sensitivity of nerves to pain or heighten awareness of pain. The elevated levels in the spinal cord cause fairly normal stimuli to result in exaggerated nociception. Some authors believe that neither elevated substance P levels nor low serotonin levels alone can be primary cause. Instead, the dual dysfunction may be responsible for fibromyalgia.

Adenosine triphosphate

Researchers also have found low levels of adenosine triphosphate (ATP) in red blood cells of patients with fibromyalgia. Although the significance is unknown, it has been suggested that low platelet serotonin levels can be explained if platelet ATP levels are also low. ATP is necessary to move and then hold serotonin in platelets.[7] More investigation into ATP and the link to serotonin is needed.

Dysfunction of the hypothalamic-pituitary-adrenal axis

Some investigators have studied the neuroendocrine aspects of fibromyalgia and have found dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis.[8] The HPA axis is a critical component of the stress-adaptation response. In a normally functioning system, corticotropin-releasing hormone (CRH) stimulates the anterior pituitary to release adrenocorticotropic hormone (ACTH). ACTH then stimulates the adrenal cortex to produce glucocorticoids, which are powerful mediators of the stress-adaptation response.

Circadian regulation and the stress-induced stimulation of the HPA axis are, in part, regulated by serotonin. Perturbations in serotonin metabolism (as well as premorbid abnormalities of the HPA axis) may explain the abnormalities of the HPA axis in fibromyalgia.

Dysfunction of the HPA axis may exaggerate the effects of abnormal serotonin metabolism. Hypoactivity of the HPA axis may cause low central serotonin levels.

Some authors have noted that 5 main measurable neuroendocrine abnormalities are associated with dysfunction of the HPA axis.[9] These are as follows:

- Low free cortisol levels in 24-hour urine samples
- Loss of the normal circadian rhythm, with elevated evening cortisol level (when it should be at its lowest level)
- Insulin-induced hypoglycemia associated with an overproduction of pituitary ACTH
- Low levels of growth hormone
- Stimulated ACTH secretion leading to insufficient adrenal release of glucocorticoids

Growth hormone

Growth hormone, produced during delta sleep, is involved in tissue repair. Therefore, disrupted stage 4 (delta) sleep associated with fibromyalgia may account for low levels of growth hormone. Growth hormone stimulates

the production of insulinlike growth factor I (IGF-I) in the liver. Some authors have found that most patients with fibromyalgia have low levels of IGF-I and that low levels are specific and sensitive for fibromyalgia.[10]

Nerve growth factor

In some studies, nerve growth factor was found to be 4 times higher in the spinal fluid of patients with fibromyalgia than it was in the spinal fluid of individuals without the condition. This factor is important in the pathophysiology of fibromyalgia, because the process enhances the production of substance P in afferent neurons, increasing an individual's sensitivity to or awareness of pain. Nerve growth factor also may play a role in spreading or redistributing perceived pain signals.

Genetic predisposition

Increasing evidence suggests that genetic and environmental factors play a role in the etiopathology of fibromyalgia. The most probable mode of inheritance is polygenic. According to Olson, early results of studies involving more than 140 families may confirm that the genes associated with serotonin play a role in fibromyalgia.[11] Some evidence indicates that the etiology of fibromyalgia may involve polymorphisms of genes in the serotonergic, catecholaminergic, and dopaminergic systems.[12] Future genetic studies are needed in the fields of fibromyalgia and related conditions.

Some investigators suggest that the genetic predisposition manifests when the person reaches a critical age or when he/she sustains an external insult, such as trauma or illness.

Frequency

United States

Conservative estimates suggest that at any given time, 2% of the general population meet the criteria for the diagnosis of fibromyalgia; this percentage, which includes children, translates into 3.4% of women and 0.5% of men.

As a result, fibromyalgia the second most common disorder that rheumatologists encounter. Physicians may find that approximately 8% of their patients have fibromyalgia. In a rheumatology and physiatry practice, however, as many as 15% of evaluated patients have fibromyalgia. This incidence implies that 1 of every 10 patients evaluated in a medical practice has fibromyalgia.

International

Cases of fibromyalgia have been reported by researchers from around the world.

Mortality/Morbidity

The social, emotional, economic, and functional effects of fibromyalgia on an individual's life have been compared with those of rheumatoid arthritis. Research indicates that the socioeconomic impact of fibromyalgia includes the following[13]:

- Approximately one third of patients with fibromyalgia reportedly modify their work to keep their job. Some patients shorten their workday and/or workweek, and many persons with fibromyalgia change to a job that is less physically and mentally taxing than their previous one. Patients have also reported an inability to achieve career or educational advancement, and some have reported career loss. Such

changes often lead to a decreased income and increased financial burdens.

- One study on patient perspectives confirmed that fibromyalgia has a significant negative impact on the quality of social and economic functions in patients' lives.
- One report suggested that approximately 15% of the people with fibromyalgia are receiving disability benefits. Disability rates as high as 44% are reported.
- It has been estimated that overall, fibromyalgia costs the American economy over $9 billion annually.

Race

Fibromyalgia exhibits no race predilection. Researchers have reported the condition in all ethnic groups and cultures.

Sex

Fibromyalgia is 4-7 times more common in women than in men. No universally accepted explanation exists for this predilection, since differences between boys and girls are hardly recognized.

Age

Fibromyalgia can occur in individuals of all ages. Symptoms usually arise in persons aged 20-55 years, but the condition may be diagnosed in childhood.

Clinical

History

Although insurance reimbursement and other aspects of the medical infrastructure are often barriers to giving patients the necessary examination time, a thorough and detailed history saves time in the long run, reduces the potential for litigation, helps to prevent incorrect diagnosis, and eliminates inappropriate or unnecessary treatments. Without a thorough history, it is impossible to develop a complete list of comorbid illnesses, with the inevitable result that treatment is incomplete and often inappropriate. Patients with fibromyalgia do significantly better when they receive a comprehensive, individualized treatment regimen than when they do not, and a thorough history is the first step toward developing that regimen.

Start the evaluation by identifying the chief complaint, which usually is pain. However, avoid treating patients based on the chief complaint alone. Premature treatment may lead to symptom chasing and ineffective treatment. Patients with fibromyalgia experience changes in symptoms from day to day, a feature that may not reflect the global nature of their disorder. This waxing and waning or fluctuating pattern of symptoms is common in fibromyalgia.

Next, expand on the chief complaint by asking specific questions about the patient's pain. Question the patient about the distribution of pain (eg, ask whether the pain is regional or generalized). Ask about the duration and onset of the pain. Patients can usually remember a sudden onset of pain. If the pain began gradually, determining the exact time of onset is difficult. Inquire about aggravating and alleviating factors. Record the description or characteristics of the pain (eg, ask whether the pain is migratory, burning, tender, sore, aching, sharp, or radiating).

Question the patient about his/her sleep habits and environment. If possible, ask the patient's sleeping partner

if the patient snores or kicks while asleep. Inquire as to how long it takes for the patient to fall asleep and how many times he/she awakens. Ask patient how he/she feels in the morning.

Pellegrino and the present author suggest that physicians obtain information about the patient's diet, particularly about the individual's caffeine and carbohydrate intake.[14, 15]

The history should include any symptoms that may indicate the presence of 1 or more coexisting conditions (see Associated conditions, below). Information on medications, exercise, and fatigue is also important. List any allergies and perpetuating factors. (See Clinical presentation, below.)

The patient's history of pain can be summarized as follows:

- Widespread pain
    - Right and left sides of the body
    - Above and below the waist
    - Along the axial skeleton
- Duration of pain
    - Constant
    - More than 3 months

Diagnostic criteria

Before 1990, no guidelines for evaluating and diagnosing fibromyalgia existed, and for a long time, no medical or imaging tests were available to definitely diagnose the condition. However, a blood test involving antipolymer antibodies has been developed. Approximately 50% of patients with fibromyalgia have these antibodies. This blood test provides objective evidence for the identification of a subgroup of people with fibromyalgia. Routine laboratory tests and radiography can help to evaluate suspected coexisting conditions or to rule out other possible diseases.

To reduce misdiagnosis and confusion, the American College of Rheumatology (ACR) recognized the need to establish a clear definition and guidelines. They sponsored a multicenter study to develop these criteria. In 1992, at the Second World Congress on Myofascial Pain and Fibromyalgia, the diagnostic criteria for fibromyalgia were expanded and refined.

The diagnostic criteria include 2 basic requirements. The first is the presence of pain in all 4 quadrants of the body, as well as in the axial skeleton on a more or less continuous basis for at least 3 months. The pain often is described as widespread or global.

The second criterion is the presence of at least 11 of 18 anatomically specific tender points (see Physical, below). A tender point hurts only at the area where pressure (enough to cause the examiner's nail bed to blanch, or about 4 kg) is applied, and there is no referred pain. An instrument known as a dolorimeter can be used to apply exactly 4 kg of pressure over the tender points during the examination. The 18 possible tender points exist as 9 pairs. Tender points may be found in any palpable muscle, but 18 sites are consistently present in patients with fibromyalgia and are used for diagnosis. The ACR criteria describe 4 pairs of tender points on the anterior of the body and 5 pairs on the posterior of the body.[16]

Clinical presentation

Before receiving a correct diagnosis, the typical patient with fibromyalgia has seen an average of 15 physicians and has had the condition for approximately 5 years. Many cases are misdiagnosed, and many patients endure costly treatments that provide little benefit. At some point, most patients have been told that nothing is medically wrong with them and that the condition is imagined. Therefore, many patients become frustrated and skeptical. Although most patients are relieved when a correct diagnosis is finally made, the patient may need to be convinced that the clinician actually knows what is wrong and that a treatment plan has been formulated.

Most patients with fibromyalgia are female and do not appear chronically ill, although they may look fatigued or agitated. Their chief complaint is often "I hurt all over all the time." The quality of their constant pain is described as burning, aching, and soreness. They may feel as if they are bruised all over, even though there are no physical signs of this. Although the pain is constant, the location migrates and the intensity varies. Many patients may complain of only a single painful area, such as the low back or neck.

A careful history reveals that the individual's pain is global, not focal, in its distribution. Patients may initially complain of pain at 1 site because they are primarily concerned about their worst pain. Because many patients do not understand that their symptoms are connected, they provide a fragmented history. The physician must ask the right questions to develop a complete understanding of the patient's distribution of pain.

Patients generally do not tell the physician that they have a sleeping disorder. Again, a carefully taken history reveals unrefreshing sleep in about 65% of patients and morning fatigue in about 80%. Patients awaken as tired as they were before sleeping. Most patients awaken frequently throughout the night, and some have difficulty falling asleep. They finally fall asleep in the early morning hours, describing this as their best sleep. Many patients fall asleep immediately, deny sleep onset problems, and report only infrequent awakenings. Sleep onset this rapid is abnormal and should not be overlooked.[17]

Most patients complain of morning stiffness of variable duration. Question the patient's sleeping partner about leg movements. Approximately 20% of persons with fibromyalgia have concomitant restless legs syndrome, which may lead the physician to choose or add medications other than antidepressants.

The patients report their fatigue is second only to pain. The fatigue is worse in the morning and early evening. By 10 or 11 o'clock in the morning, the fatigue subsides somewhat. Several investigators, including the present author, have found that poor sleep, physical activity, and diet can worsen the patient's fatigue.

Patients may not admit to feeling depressed or anxious; therefore, the physician must inquire about these conditions. The source of the patient's emotional stress may be multifactorial.

Approximately 50% of patients with fibromyalgia present with complaints of tissues feeling swollen and of numbness and tingling in the extremities. These symptoms generally are more common in the upper extremities than in the lower ones. Objective swelling, sensory changes, and other neurologic findings are usually absent.

Some investigators list many other common complaints, including chronic headaches and tenderness of the scalp to the touch. Complaints of chest pain, shortness of breath, and palpitations are common. Serious cardiac problems should be considered and may require extensive evaluation. Many symptoms in patients with fibromyalgia are related to mitral valve prolapse syndrome.

Approximately 40% of patients with fibromyalgia describe having alternating bouts of diarrhea and

constipation, and also experience bloating, cramping, and an increased urge to defecate. These symptoms are most likely related to irritable bowel syndrome. Some patients also may complain of symptoms that include urgency, frequency, and a sense of incomplete voiding. Pelvic pain and dysmenorrhea may be present as well.

Associated conditions

Several medical conditions and diseases frequently occur with fibromyalgia. In 1984, Yunus used a Venn diagram to depict the interrelationships of these syndromes. He proposed that the syndromes are interconnected, similar, and overlapping, with a probable common pathophysiologic mechanism.[18, 19] Ironically, they have been described as functional syndromes. This is a misnomer, because their pathophysiology is based on the dysfunction of the neuroendocrine system. Central sensitization is likely the common pathophysiologic pathway.

These coexisting conditions can aggravate and perpetuate the patient's symptoms. If unrecognized, the physician might inadvertently prescribe an ineffective or even harmful treatment regimen, leading to costly and unnecessary testing.

The conditions most commonly associated with fibromyalgia include the following:

- Irritable bowel syndrome
- Tension/migraine headaches
- Dysmenorrhea
- Nondermatomal paresthesia
- Temporomandibular joint syndrome
- Mitral valve prolapse
- Interstitial cystitis, vulvodynia
- Female urethral syndrome
- Vulvar vestibulitis
- Hypermobility syndrome
- Restless legs syndrome
- Allergy
- Multiple chemical sensitivity syndrome
- Enthesopathies
- Vestibular disorders
- Esophageal dysmotility
- Ocular disturbances

- Anxiety disorders
- Pulmonary symptoms
- Raynaud phenomenon
- Thyroid dysfunction
- Lyme disease
- Silicone breast implant syndrome
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Sjögren syndrome
- Infections
- Osteoarthritis
- Chronic fatigue syndrome
- Carpal tunnel syndrome
- Hyperventilation
- Premenstrual syndrome (PMS)
- Depression (see Depression, below)
- Myofascial pain syndrome (see Myofascial pain syndrome, below)
- Cognitive dysfunction (see Cognitive dysfunction, below)
- Sleep disorders[17, 20]
    - Sleep is not a state of massive system shutdown. On the contrary, the brain is active during sleep, constantly communicating with the body. Many neurohormones, antibodies, and other molecules are synthesized during sleep; therefore, when sleep is disrupted, biochemical abnormalities can occur, leading to multisystem disturbances.
    - Sleep studies have shown that patients with fibromyalgia have disordered sleep physiology. Most of these patients experience unrefreshing sleep, with morning fatigue.
    - To understand abnormal sleep architecture, it is essential to know the basics of normal sleep. Sleep can be divided into 2 main parts: nonrapid eye movement (NREM) and rapid eye movement (REM), which alternate cyclically through the night, always starting with NREM sleep. In each successive cycle through the night, NREM sleep decreases, and REM sleep increases. Each cycle, NREM plus REM, lasts about 90 minutes.
    - NREM is divided into 4 stages: stage 1 is initial drowsiness; stage 2, light sleep; and stages 3 and 4, progressively deeper levels of sleep. In stages 3 and 4, an electroencephalogram (EEG) will show delta waves, which are high-amplitude (>75 mV) waves that move slowly (0.5-2 Hz). Much of the body's regulatory work, as well as the synthesis of many substances (eg,

antibodies, growth hormone, other neurochemicals), occurs during NREM sleep.

- REM sleep has a low-voltage, mixed-frequency pattern on EEGs and is considered dream sleep. In this stage, the body has a complete loss of muscle tone, known as flaccid paralysis, and it cannot move. During this part of sleep, consolidation of memories may occur, but disagreement still exists as to what takes place with regard to memory during REM sleep. Some investigators have found that during waking hours, the brain generates alpha waves with a frequency of 7.5-11 Hz.
- Sleep dysfunction is considered an integral feature of fibromyalgia. About 70% of patients recognize a connection with poor sleep and increased pain, along with feeling unrefreshed, fatigued, and emotionally distressed. Several studies have linked abnormal sleep with these symptoms.
- Researchers have studied fibromyalgia and sleep, confirming the disordered sleep physiology in fibromyalgia. This abnormality has been identified as a sleep anomaly of alpha-wave intrusion, which occurs during NREM stage 4 sleep. This intrusion into deep sleep causes the patient to awaken or to be aroused to a lighter level of sleep.
- Some investigators describe the altered sleep physiology and somatic symptoms as a nonrestorative sleep syndrome. This dysfunction is believed to be linked to the numerous metabolic disturbances associated with fibromyalgia, including abnormal levels of neurotransmitters (serotonin, substance P) and neuroendocrine and immune substances (growth hormone, cortisol, interleukin-1). These metabolic imbalances are thought to be responsible—through impairment of tissue repair and disturbance of the immunoregulatory role of sleep—for the increased symptoms associated with this sleep disorder of alpha-wave intrusion.
- Most alpha-wave intrusions occur during the first few hours of sleep, decreasing throughout the night to normal levels by early morning. This hypothesis has been well correlated with patients' frequent reporting that their best sleep is obtained in the early morning hours, just before arising.

- Depression [21]
  - Depression in fibromyalgia is a controversial topic. In support of the contention that fibromyalgia is not a psychiatric illness, some authors believe that the symptoms of fibromyalgia are not connected with psychological factors. Others have determined that fibromyalgia is not a psychiatric disorder. The depression associated with fibromyalgia is believed to result from pain, sleep deprivation, and dysfunction.
  - Depression in fibromyalgia may be treated with a regimen that includes nonpharmaceutical therapies. Treating depression alone does not cure fibromyalgia. Antidepressants may help, but the clinician also should address other symptoms, such as fatigue or pain. Modifying diet and practicing good sleep hygiene are crucial. Starting a rehabilitation exercise program is important. Behavioral modification techniques and stress management may also be used.

- Myofascial pain syndrome [1, 22, 23, 24]
  - Fibromyalgia and myofascial pain syndrome may coexist, creating a complex clinical picture. However, fibromyalgia and myofascial pain syndrome are not the same condition. Some authors assert that fibromyalgia and myofascial pain syndrome can each magnify and perpetuate the symptoms of the other.
  - Fibromyalgia is a generalized amplification of pain or a hypersensitivity condition associated with

tender points in the muscles. These points are exquisitely tender and painful to compression where pressure is applied; the pain is not referred to distant areas.

- Narrowly defined, myofascial pain syndrome is a disorder of trigger points. Similar to tender points, trigger points are discreet areas in muscle tissue and/or its associated fascia that are exquisitely tender to compression; however, pain occurs at the site of the applied pressure and also at a distant site (zone of pain referral). Trigger points are found in taut bands (firm, elongated bands) in muscle fibers and are associated with the local twitch response. This response is an involuntary, transient contraction of the taut bands and can be elicited by snapping or pinching the band.
- Several differences have been noted between fibromyalgia and myofascial pain syndrome; the table below lists a few of these differences. A more detailed review of the similarities and differences in the 2 syndromes is found in *Acupuncture, Trigger Points, and Musculoskeletal Pain: a Scientific Approach to Acupuncture for Use by Doctors and Physiotherapists in the Diagnosis and Management of Myofascial Trigger Point Pain* (2nd ed, 1993), by Baldry, a leading British physician and acupuncturist.[25]

Feature	Fibromyalgia	Myofascial pain syndrome
Sex prevalence	Mostly affects females	No sex difference
Location of pain	Generalized	Localized or regional
Association with fatigue	Common	No
Other associated conditions	Many systemic diseases or conditions, such as mitral valve prolapse, irritable bowel syndrome, and genitourinary disorders	No
Prognosis	Generally chronic	Can be resolved with manual muscle therapies

- Cognitive dysfunction[26]
  - Cognitive function can be considered the ability to think, reason, image, remember, or learn words. The available research on cognition in fibromyalgia suggests that cognitive actions are faulty. This impact on cognition may cause some patients with fibromyalgia the most disability.
  - The euphemism "fibro-fog" is often used to describe the memory problems and unclear thinking (cognitive dysfunction) that occur in patients with fibromyalgia. Decades of research have shown elucidated several memory systems: short term, working, episodic, semantic (predominantly verbal memory), and procedural (memory for different skills).
  - Symptoms include confusion and forgetfulness, an inability to concentrate and recall simple words and numbers, and the transposition of words and numbers. Cognitive functions are often so impaired that patients cannot perform the activities of daily living (ADL), getting lost in familiar places or losing the ability to communicate effectively. Patients who work may fear losing their job, and many pediatric patients drop out of school because of their inability to complete their

schoolwork.

- Advances in noninvasive technology have made it possible to visualize the brain. Various modalities, such as single-photon emission computed tomography (SPECT) scanning, have helped to define some of the abnormalities linked to the cognitive dysfunction. SPECT shows decreased blood flow in the right and left caudate nuclei and thalami. Functional magnetic resonance imaging (fMRI) can show brain activity by depicting increased blood flow to areas actively engaged in a task. Increased blood flow, and hence increased oxygenation, has different magnetic properties. These properties can be detected and measured using fMRI.
- CNS imbalances have been linked to cognitive dysfunction. Abnormal levels of such neurotransmitters as substance P, serotonin, dopamine, norepinephrine, and epinephrine may cause cognitive dysfunction. Neuroendocrine imbalance of the HPA axis may play a role in fibro-fog.
- Another possible cause of cognitive dysfunction is the distracting quality of pain in fibromyalgia. Cognitive performance of patients with fibromyalgia is correlated with their reported level of pain. Researchers are looking at tissue volumes in areas of the brain (hippocampus) that may be damaged by the effects of stress hormones. Others studies have implicated yeast overload, water retention, and glial cell abnormalities as causes of cognitive dysfunction in fibromyalgia.
- One study showed that the working memory and episodic memory scores of patients with fibromyalgia were similar to those of healthy control subjects who were 20 years older. Patients were matched for age and education.
- In another study, brain fMRI was performed while participants were shown a string of 3 or 4 letters. These letters were presented in jumbled, nonalphabetical order and then in a maintenance condition in which they were alphabetized. The participants were asked to mentally organize the letters into alphabetical order and then press one key if they were in the correct order or another key if they were not. Patients with fibromyalgia performed almost as well as controls, but more of their brain areas were activated during the memory task than were activated in the controls, because the task was harder for the patients to perform. This finding was consistent with the results found in adults who were older than the patients.
- Additional research is needed to determine the brain systems involved, why patients have cognitive problems, and what to do about these problems.

Physical

The goal of the physical examination is to confirm the diagnosis, rule out concomitant systemic diseases, and recognize common coexisting conditions.

The physical examination can be quickly summarized as follows:

- Palpate the muscles by using 4 kg of pressure.
- To meet the diagnostic criteria, pain must occur in 11 of 18 paired tender points.
- The tender-point examination should be performed first during the physical examination, because a number of factors may influence the sensitivity of the tender points during the examination.

The diagnostic criteria include 2 basic requirements. The first diagnostic criterion is the presence of pain in all

4 quadrants of the body and in the axial skeleton on a more or less continuous basis for at least 3 months. The pain often is described as widespread or global. The second diagnostic criterion is, as mentioned above, the presence of at least 11 of 18 anatomically specific tender points. A tender point hurts only at the area where pressure (enough to cause the examiner's nail bed to blanch, or about 4 kg) is applied, and the patient has no referred pain.[27] Additional examination details are as follows:

- Procedure for the tender-point examination - The thumb pad of the examiner's dominant hand is used to apply pressure to the evaluation sites during the tender-point examination. This allows the examiner to use important tactile cues and is as reliable as the use of a dolorimeter. (A dolorimeter can be used to apply exactly 4 kg of pressure over the tender points during the examination.) Because the sequence in which the sites are examined may influence the patient's responses, a standardized procedure for evaluating the tender points enhances interobserver reproducibility and reliability in reporting the findings.[16]
    - First, visually locate the evaluation site.
    - Then, with the thumb pad, press perpendicularly into the evaluation site for 4 seconds.
    - Press the site only once to avoid sensitization.
    - Four kilograms of pressure should be applied to the site; this is enough force to blanch the examiner's nail bed.
    - Have the patient wear a standard gown to allow for easy access to the evaluation sites.
    - Always examine the 18 diagnostic sites and 3 control sites (sites 1, 16, and 17; see Site locations, below) in the designated order. The 3 control points should be palpated and recorded to provide baseline documentation of the patient's pain perception.
    - Examine the right site and then the corresponding left site.
    - The patient should sit on the examination table for the evaluation of the first 17 sites. The individual should lie on his/her side contralateral to the site for the testing of sites 18 and 19, and should lie on his/her back for the evaluation of sites 20 and 21.
    - Other tender points may be present and also should be recorded, but they are not necessary for diagnosis. Some patients may present with fewer than 11 tender points. Experts contend that fibromyalgia can be diagnosed with as few as 8 or 9 tender points if the patient has other symptoms, such as sleep problems, fatigue, and any of the characteristic coexisting conditions.
    - The patient should respond with a "yes" or "no" if he/she has any pain at the site being examined. If the patient's response is "yes," have the individual rate the pain on a scale of 0 (no pain) to 10 (worst pain), and record each response.
    - The patient's position during examination, the amount of force applied at the evaluation site, the number of times the evaluation site is palpated, and the method of applying force (dolorimeter vs finger pad) may influence tender-point sensitivity.
- Site locations - The 18 possible tender points exist as 9 pairs. Tender points may be found in any palpable muscle, but 18 sites are consistently present in patients with fibromyalgia and are used for diagnosis. The ACR criteria describe 4 pairs of tender points on the anterior of the body and 5 pairs on the posterior of the body.[28]
    - 1, control site - Forehead
    - 2 and 3 diagnostic sites - Occiput at the nuchal ridge

- 4 and 5 diagnostic sites - Trapezius
- 6 and 7 diagnostic sites - Supraspinatus
- 8 and 9 diagnostic sites - Gluteal
- 10 and 11 diagnostic sites - Low cervical
- 12 and 13 diagnostic sites - Second rib
- 14 and 15 diagnostic sites - Lateral epicondyle
- 16, control site - Distal middle third of the right forearm
- 17, control site - Nail of the left thumb
- 18 and 19 diagnostic sites - Greater trochanter
- 20 and 21 diagnostic sites - Medial knee

- The 1990 ACR criteria for the location of tender points are as follows:
  - Anterior body - Bilateral
    - At the fifth through seventh intertransverse spaces of the cervical spine
    - In the pectoral muscle, at the second costochondral junctions
    - Approximately 3 finger breadths (2 cm) below the lateral epicondyle
    - At the medial fat pad, proximal to the joint line
  - Posterior body - Bilateral
    - At the upper border of the shoulder in the trapezius muscle, midway from the neck to the shoulder joint
    - At the craniomedial border of the scapula, at the origin of the supraspinatus
    - In the upper outer quadrant of the gluteus medius
    - Just posterior to the prominence of the greater trochanter at the piriformis insertion

- Other evaluations - After completing the tender-point examination, the physician should include neurologic, joint, and musculoskeletal evaluations. Note the presence of swelling, deformities, and erythema. Examine the patient's gait, joint range of motion (ROM), and posture for structural asymmetry and skeletal deficiencies. Palpate the soft issues for tone or spasm. Check for taut bands, twitch responses, and trigger points; their presence signals the coexistence of a myofascial pain syndrome.

Causes

No cause for fibromyalgia has been accepted universally, although many theories have been proposed. Some authors suggest that an inheritance factor may be involved.

- The frequent comorbidity of fibromyalgia with mood disorders suggests a major role for the stress response and for neuroendocrine abnormalities.
- Fibromyalgia is associated with polymorphisms in the catechol-O-methyltransferase enzyme that inactivates catecholamines and the serotonin transporter gene.[5]
- Basal and stimulated activity of several neuroendocrine axes are altered, and dysfunction of the autonomic nervous system is demonstrated in fibromyalgia.

- Psychosocial factors contribute to the expression of fibromyalgia.

The question remains as to whether these abnormalities are causes or effects of fibromyalgia. Ongoing research may soon provide the answer.

Workup

Laboratory Studies

- No tests accurately identify fibromyalgia.
- A new blood test involving antipolymer antibodies was developed.
    - These antibodies are present in approximately 50% of people with fibromyalgia.
    - This biologic marker may provide conclusive evidence for a subgroup of people with fibromyalgia.
- Routine laboratory studies and radiographs are helpful in ruling out other diseases or in diagnosing coexisting conditions.

Imaging Studies

- Regarding the diagnosis of fibromyalgia, some investigators state that imaging studies are helpful only in ruling out other diseases or in diagnosing coexisting conditions.

Treatment

Rehabilitation Program

Physical Therapy

Some investigators believe that a successful fibromyalgia rehabilitation program involves a multidisciplinary team of professionals and various modalities individualized for each patient.[14] The team should include the physician, a medical psychologist, physical and massage therapists, and an exercise physiologist. These professionals should have expertise in the treatment of soft-tissue disorders.

Traditional therapy or rehabilitation may worsen the patient's symptoms. Monitor the progress of the patient in rehabilitation. As goals are met and symptoms change, modify the rehabilitation prescription to meet the individual's current needs.

- A number of randomized, controlled trials of multidisciplinary treatment and exercise, combined with education and/or cognitive behavioral therapy showed that patients with fibromyalgia had improvements on a 6-minute walk, with significant decreases in pain and beneficial efficacy. One randomized, controlled trial of multidisciplinary rehabilitation showed improvement in health-related outcomes in a nonclinical, community-based setting at 15-month follow-up. A published study that evaluated the impact of a physical therapy–based educational program on patients with fibromyalgia

found that the program had a positive impact on patients' well-being.[29] The study found that the program had no effect on the other symptoms of fibromyalgia.

- Numerous modalities, including electrotherapy, cryotherapy, and therapeutic heat, can reduce pain. Teach patients how and when to use therapeutic modalities as part of their maintenance program. One investigator recommends muscle energy treatments, positional release methods, and massage as part of the rehabilitation program to decrease stiffness and pain.
- Some investigators have found that daily aerobic and flexibility exercises are an essential component of the rehabilitation program.[30] Exercise was first recognized to have therapeutic benefits 20 years ago. At that time, patients were randomized to receive 20 weeks of high-intensity exercise or flexibility training. Improvements in fitness, global assessment ratings, and tender-point pain thresholds were greater in the high-intensity group than in the flexibility group. Subsequent clinical trials have confirmed the benefits of aerobic exercise and muscle strengthening on mood and physical functioning.
- Patients should begin with gentle warm-up, flexibility exercises and progress to stretching all of the major muscle groups. Low-impact aerobic exercise is necessary at least 3 times weekly. Patients should always start at low levels of exercise and progress slowly. The goal is to exercise safely without increased pain. The patients' target exercise regimen is 4-5 times a week for at least 20-30 minutes each time; this may take the patient months to achieve.
- Some patients with fibromyalgia may never be able to achieve this level of exercise; encourage them to exercise at the highest level possible without worsening their symptoms. Some investigators believe that aquatic exercise may be the safest and gentlest aerobic conditioning exercise available for this group. Aquatic therapy enables aerobic conditioning and also flexibility, strengthening, and stretching exercise. Aquatic exercise is well tolerated and is especially helpful for some patients.

Other Treatment

Trigger-point injection is an important technique for providing mechanical disruption (myolysis) of the trigger point. Disruption leads to a reduction in pain and an increase in ROM, exercise tolerance, and circulation. Therefore, trigger-point injection is a valuable tool in the treatment of patients with tender points and trigger points.[22, 31] Long-term outcomes improve when these injections are used in conjunction with physical therapy, massage therapy, or stretching exercises done at home.

Dry needling and needling with infiltration are effective in eliminating trigger points and tender points. Many authors report that needling with infiltration is most effective. Patients with fibromyalgia who receive trigger-point injections have had significant improvement in pain intensity, pain threshold, and ROM. Patients may have a delayed improvement in pain but an immediate improvement in ROM. They may also experience severe soreness that develops soon after the injection and that lasts for a long period.

- A number of materials and techniques are used for needling with infiltration. Most physicians prefer 1% lidocaine without epinephrine or 0.5% procaine. Lidocaine is often chosen over procaine because it has fewer allergic reactions, a faster onset of action, and greater potency. Steroids are generally not indicated or recommended for trigger-point injections in patients with fibromyalgia. Sterile saline can be used in patients who are allergic to local anesthetics.

- When performing a trigger-point injection, use a sufficiently long needle. In most cases, an extensive area must be infiltrated; therefore, a relatively large volume of 2-12 mL is injected. Before injecting the local anesthetic, make certain that the needle is in the trigger point. Localization of the trigger point is ascertained when the needle causes a marked increase in pain with referral pain and/or a fasciculation is seen or felt.
- Several contraindications to trigger-point injections must be observed. Avoid giving these injections to patients with local or systemic infection. Patients with bleeding disorders or those who are taking anticoagulation medication should not receive trigger-point injections without proper medical evaluation, and they should receive these injections only after the risks and benefits are explained clearly to them.

Medication

Patients with fibromyalgia have difficulty tolerating regular doses of most medications and supplements. They are sensitive to medications, and adverse effects are common. To avoid these problems, use the lowest dose available or perhaps one half to one quarter of the lowest recommended dose.

Several medications should be avoided or used carefully. To date, the US Food and Drug Administration has not approved any drug for the specific treatment of fibromyalgia.

Avoid complications and confusion by providing written instructions and drug information. These instructions need to be easy to understand. Patients should be instructed to consult their physician before starting any over-the-counter (OTC) medications or supplements, to avoid potentially harmful drug interactions.

Classes of drugs

Most investigators recommend using narcotics sparingly. In fibromyalgia without concomitant rheumatic illnesses, steroids are not helpful and should be avoided.

CNS agents, antidepressants, muscle relaxants, or anticonvulsants are the most successful pharmacotherapies. These medications affect serotonin, substance P, norepinephrine, and other neurochemicals that have a broad range of activities in the brain and spinal cord, including the modulation of pain sensation and tolerance.

Nonsteroidal anti-inflammatory drugs (NSAIDs) have not been shown to be effective analgesics when used alone, but when combined with tricyclic agents, they may be useful as analgesics. Guaifenesin had significant benefits in decreasing pain, improving other symptoms, or laboratory parameters in a 12-month, randomized, controlled study.

Data from randomized, controlled trials have not supported the use of thyroid hormones, melatonin, calcitonin, or dehydroepiandrosterone in the treatment of fibromyalgia.

Medications to improve sleep

An effective medication to improve sleep-onset problems is zolpidem. The patient must be given instructions on proper dosing.

Sleep-maintenance disorders are more difficult to manage than are sleep onset problems. In general, antidepressants are most commonly used because of their effect on serotonin. Tricyclic antidepressants have

the strongest evidence for efficacy. The criterion standard is amitriptyline, but many patients cannot tolerate this drug.

Trazodone is inexpensive, well-tolerated, and effective. The starting dose is 25 mg, and it should be taken at 8 pm. If necessary, the dose can be slowly up-titrated. If the patient is not staying asleep, adding a serotonin-selective reuptake inhibitor (SSRI) may be helpful.

If the patient has concomitant restless legs syndrome or mitral valve prolapse, clonazepam may be the drug of choice. The starting dose is 0.125 or 0.25 mg taken at 8 pm. Titrate the dose to the lowest effective dose.

Tiagabine increases sleep efficiency with a marked increase in slow-wave sleep in healthy elderly patients. Tiagabine titrated from 2 mg to 12 mg may improve sleep maintenance in some patients.

Gabapentin is being studied. It may also aid in sleep maintenance.

In 1998, pramipexole was described as an excellent treatment for restless legs syndrome. At the 2000 ACR meeting in Philadelphia, the use of pramipexole at bedtime to treat fibromyalgia was first reported. This medication may aid in sleep maintenance in patients with fibromyalgia and restless legs syndrome.

Summary

Medications useful for treating fibromyalgia include the following:

- Sleep problems
    - Antidepressants (eg, trazodone, SSRIs, dual-reuptake inhibitors [SNRIs], tricyclic antidepressants)
    - Anticonvulsants (eg, clonazepam, gabapentin, tiagabine)
    - Nonbenzodiazepine hypnotics (eg, zolpidem, zaleplon, eszopiclone)
    - Muscle relaxants (eg, cyclobenzaprine, tizanidine)
    - Dopamine agonists (eg, pramipexole)
- Depression - Antidepressants
- Pain
    - NSAIDs
    - Muscle relaxants
    - Analgesics (eg, tramadol)
- Other
    - Vitamins and minerals
    - Malic acid and magnesium combination
    - Antioxidants
    - Amino acids
    - Herbs and supplements

Antidepressants

These drugs are used not only to treat depression but also to improve sleep and pain. Antidepressants increase CNS serotonin. Delta-wave sleep also improves. The result is an improvement in the symptoms experienced by patients with fibromyalgia.

Trazodone (Desyrel)

Antidepressant most helpful in patients with anxiety and sleep disturbances.

Dosing

Adult

Starting dose: 25 mg PO qd, preferably at 8 pm with food; increase dose q3wk but only to lowest effective dose

Pediatric

Not established

Interactions

May enhance response to alcohol, barbiturates, and other CNS depressants; digoxin and phenytoin serum levels may increase with concurrent trazodone; may decrease hypoprothrombinemic effects of warfarin

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Priapism; orthostatic hypotension and syncope; dizziness if taken with empty stomach

Duloxetine (Cymbalta)

Indicated for diabetic peripheral neuropathic pain. Potent inhibitor of neuronal serotonin and norepinephrine reuptake.

Dosing

Adult

Start 30 mg PO qd, then increase to 60 mg PO qd if not effective

Pediatric

Not established

Interactions

Metabolized by CYP1A2 and CYP2D6; coadministration with drugs that inhibit CYP1A2 (eg, fluvoxamine, cimetidine, ciprofloxacin, enoxacin) may increase duloxetine blood levels and toxicity; coadministration with drugs that inhibit CYP2D6 (eg, paroxetine, fluoxetine, quinidine) may increase duloxetine blood levels and toxicity; duloxetine moderately inhibits CYP2D6 and may decrease elimination of CYP2D6 substrates (eg, tricyclic antidepressants, phenothiazines [eg, thioridazine], type 1C antiarrhythmics [eg, propafenone, flecainide]); coadministration with MAOIs may cause serious, sometimes fatal reactions that include hyperthermia, rigidity, myoclonus, autonomic instability, mental status changes including extreme agitation, delirium, and coma
(see Contraindications)

Contraindications

Documented hypersensitivity; uncontrolled narrow-angle glaucoma; within 14 d of stopping MAOI use (do not initiate MAOIs within 5 d of stopping duloxetine)

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Observe closely for clinical worsening and suicidality when initiating treatment or following dosage change; gradually decrease dose when discontinuing, do not abruptly discontinue; caution with hepatic impairment or end-stage renal disease; recommended not to prescribe to patients with substantial alcohol use or evidence of chronic liver disease; may cause slight blood pressure increase; may activate mania or hypomania; common adverse effects include nausea, dry mouth, constipation, decreased appetite, fatigue, somnolence, and increased sweating

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Fluoxetine (Prozac)

Antidepressant that inhibits uptake of serotonin by neurons. Used to improve mood and restore normal sleep patterns.

Dosing

Adult

Starting dose: 10 mg PO qam for 1 wk, then 20 mg PO qam; increase dose q3wk prn in 10-mg increments

Pediatric

Not established

Interactions

Increases toxicity of diazepam and trazodone by decreasing clearance; also increases toxicity of MAOIs and highly protein-bound drugs

Contraindications

Documented hypersensitivity; concurrent MAOIs or use in the last 2 wk

Precautions

Pregnancy

C - Safety for use during pregnancy has not been established.

Precautions

Caution in hepatic impairment and history of seizures; MAOIs should be discontinued at least 14 d before starting therapy

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Venlafaxine (Effexor)

Serotonin/norepinephrine reuptake inhibitor. May treat depression by inhibiting neuronal serotonin and norepinephrine reuptake. In addition, causes beta-receptor down-regulation.

Dosing

Adult

Immediate release: 75 mg/d PO divided bid/tid with food and increase in 75 mg/d increments q4d to 225-375 mg/d
Extended release: 75 mg PO qd with food and increase in 75 mg/d increments q4d to 225 mg/d

Pediatric

Not established

Interactions

Cimetidine, MAOIs, sertraline, fluoxetine class I-C antiarrhythmics, TCAs; phenothiazine may increase the effects of venlafaxine

Contraindications

Documented hypersensitivity; patients taking MAOIs or have taken MAOIs within 14 days of initiating therapy

Precautions

Pregnancy

C - Safety for use during pregnancy has not been established.

Precautions

Patients on this medication may experience hypertension; fatal reaction may occur if venlafaxine is taken concurrently with an MAOI; exercise caution in patients with cardiovascular disorders; the sustained-release formulation should not be divided, crushed, or placed in water

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Amitriptyline (Elavil)

Sedative tricyclic antidepressant helpful in improving mood and restoring sleep. Inhibits uptake of serotonin and norepinephrine.

Dosing

Adult

Starting dose: 5 mg PO qd at 8 pm; increase over 3 wk prn up to lowest effective dose

Pediatric

<12 years: Not established
>12 years: 10 mg PO tid and 20 mg qhs

Interactions

Phenobarbital may decrease effects; coadministration with CYP2D6 inhibitors (eg, cimetidine, quinidine) may increase levels; inhibits hypotensive effects of guanethidine; may interact with thyroid medications, alcohol, CNS depressants, barbiturates, and disulfiram

Contraindications

Documented hypersensitivity; MAOI use in past 14 d; history of seizures, cardiac arrhythmias, glaucoma, or urinary retention

Precautions

Pregnancy

C - Safety for use during pregnancy has not been established.

Precautions

Caution in cardiac conduction disturbances and history of hyperthyroidism, renal or hepatic impairment; avoid in elderly patients

Anticonvulsants

These agents are used to manage pain and provide sedation in patients with neuropathic pain.

Clonazepam (Klonopin)

Effective drug to improve sleep. Should be titrated to lowest effective dose. When discontinuing, slowly taper over 7-14 d.

Dosing

Adult

Starting dose: 0.125-0.25 mg (depending on the patient's history of drug intolerances or drug sensitivities) PO qd at 8 pm; increase to lowest effective dose

Pediatric

<18 years: Not recommended except in seizure disorders
>18 years: Administer as in adults

Interactions

Alcohol, narcotics, barbiturates, nonbarbiturate hypnotics, and tricyclic antidepressants may potentiate effects

Contraindications

Documented hypersensitivity, severe liver disease and acute narrow-angle glaucoma

Precautions

Pregnancy

D - Fetal risk shown in humans; use only if benefits outweigh risk to fetus

Precautions

Caution in renal insufficiency and chronic respiratory disease; can cause hypersalivation; caution patients (especially those receiving long-term high-dose treatment) to avoid abrupt discontinuation

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Tiagabine (Gabitril)

Approved for treatment of seizures. In fibromyalgia, often used for effects on slow-wave sleep. Useful in improving sleep maintenance and decreasing whole-body pain in fibromyalgia.

Mechanism of action in antiseizure effect unknown; believed to be related to ability to enhance activity of GABA, major inhibitory neurotransmitter in CNS. May block GABA uptake into presynaptic neurons, making more GABA available for receptor binding on surfaces of postsynaptic cells; may prevent propagation of neural impulses that contribute to seizures by GABA-ergic action. Modification of concomitant AEDs not necessary unless clinically indicated.

Dosing

Adult

4 mg PO divided bid or qid; increase by 4-8 mg/wk until clinical response or until 56 mg/d total; >56 mg/d PO not systematically evaluated in adequate well-controlled trials

Pediatric

<12 years: Not established
12-18 years: 4 mg PO qd; increase by 4 mg at beginning of wk 2; thereafter, may increase total daily dose by 4-8 mg/wk until clinical response or 32 mg/d;
>32 mg/d PO tolerated in small number of adolescents for relatively short duration

Interactions

Cleared more rapidly in patients treated with carbamazepine, phenytoin, primidone, and phenobarbital than in patients not receiving these drugs

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

C - Safety for use during pregnancy has not been established.

Precautions

Patients receiving valproate monotherapy may require lower doses or a slower dose titration to clinical response; moderately severe to incapacitating generalized weakness reported in <1% of patients with epilepsy; weakness may resolve after reduced dose or discontinuation; should be withdrawn slowly to reduce potential for increased seizure frequency

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Pregabalin (Lyrica)

Structural derivative of GABA. Mechanism of action unknown. Binds with high affinity to alpha(2)delta site (a calcium channel subunit). In vitro, reduces calcium-dependent release of several neurotransmitters, possibly by modulating calcium channel function. FDA approved for neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, or fibromyalgia. Also indicated as adjunctive therapy in partial-onset seizures.

Dosing

Adult

75 mg PO bid initially; increase to 150 mg PO bid within 1 wk based on efficacy and tolerability; may further increase dose to 225 mg bid if needed

Pediatric

Not established

Interactions

May cause additive effects on cognitive and gross motor functioning when coadministered with drugs that cause dizziness or somnolence

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Discontinue gradually (over a minimum of 1 wk) to minimize increased seizure frequency in patients with seizure disorders; may cause insomnia, nausea, headache, or diarrhea with abrupt withdrawal; common adverse effects include dizziness, somnolence, blurred vision, weight gain, and peripheral edema; may elevate creatinine kinase level, decrease platelet count, and increase PR interval; doses >300 mg/d associated with higher rate of adverse effects and treatment discontinuation; decrease dose with renal impairment (ie, CrCl <60 mL/min); angioedema has been reported during postmarketing surveillance

Gabapentin (Neurontin)

Membrane stabilizer, a structural analogue of inhibitory neurotransmitter GABA, which paradoxically is thought not to exert effect on GABA receptors. Appears to exert action via the alpha(2)delta-1 and alpha(2)delta-2 auxiliary subunits of voltage-gated calcium channels.
Used to manage pain and provide sedation in neuropathic pain.
Titration to effect can take place over several days to weeks.

Dosing

Adult

Day 1: 300 mg PO qd
Day 2: 300 mg PO bid
Day 3: 300 mg PO tid and titrate prn; not to exceed 1200 mg PO qid

Pediatric

<12 years: Not established
>12 years: Administer as in adults

Interactions

Antacids may significantly reduce bioavailability of gabapentin (administer at least 2 h following antacids); may increase norethindrone levels significantly

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

C - Safety for use during pregnancy has not been established.

Precautions

Caution in severe renal disease

Muscle Relaxant

These agents are helpful in the management of muscle spasm and rehabilitation measures.

Metaxalone (Skelaxin)

Treats muscle spasm and pain in fibromyalgia.

Dosing

Adult

800 mg PO tid/qid

Pediatric

<12 years: Not established
>12 years: Administer as in adults

Interactions

None reported

Contraindications

Documented hypersensitivity; known tendency for drug-induced hemolytic or other anemias; significantly impaired renal or hepatic function

Precautions

Pregnancy

C - Safety for use during pregnancy has not been established.

Precautions

Caution in hepatic impairment

Tizanidine (Zanaflex)

Centrally acting muscle relaxant metabolized in the liver and excreted in urine and feces.

Dosing

Adult

4-8 mg PO q8h prn; not to exceed 36 mg/d

Pediatric

Not established

Interactions

May interact with alcohol (increase somnolence, stupor) and oral contraceptives (which decrease its clearance), and can cause increased hypotensive effects when administered concurrently with diuretics

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

C - Safety for use during pregnancy has not been established.

Precautions

Caution in renal impairment

Baclofen (Lioresal)

Muscle relaxant (central), presynaptic GABA-B receptor agonist that may induce hyperpolarization of afferent terminals and inhibit monosynaptic and polysynaptic reflexes at spinal level. Lessens flexor spasticity and hyperactive stretch reflexes of upper motor neuron origin. Eliminated through renal excretion. Effective in about 20% of patients. Appears to be of dramatic benefit in as many as 30% of children with dystonia, although benefit not always sustained. Well absorbed, with average oral bioavailability of 60% and mean elimination half-life of 12 h; steady state reached within 5 d with multiple dose administration; metabolism occurs in liver (P 450-dependent glucuronidation and hydroxylation); 6 major and a few minor metabolites produced.

Dosing

Adult

5 mg PO tid for 3 d; 10 mg tid for 3 d; 15 mg tid for 3 d; 20 mg tid for 3 d; thereafter, additional increases may be necessary; not to exceed 80 mg/d PO divided qid

Pediatric

10-60 mg/d PO

Interactions

Opiate analgesics, benzodiazepines, alcohol, tricyclic antidepressants, guanabenz, MAOIs, clindamycin, and hypertensive agents may increase baclofen effects

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Caution in patients with history of autonomic dysreflexia and when spasticity is used to obtain increased function; autonomic dysreflexia can result from withdrawal of this medication

Cyclobenzaprine (Flexeril)

Acts centrally and reduces motor activity of tonic somatic origins, influencing alpha and gamma motor neurons. Structurally related to tricyclic antidepressants.
Skeletal muscle relaxants have modest short-term benefit as adjunctive therapy for nociceptive pain associated with muscle strains and, used intermittently, for diffuse and certain regional chronic pain syndromes. Long-term improvement over placebo has not been established. Often produces a "hangover" effect, which can be minimized by taking the nighttime dose 2-3 h before going to sleep.

Dosing

Adult

10 mg PO tid with a range of 20-40 mg/d in divided doses; not to exceed 60 mg/d

Pediatric

Not established

Interactions

Coadministration with MAOIs and tricyclic antidepressants may increase toxicity; cyclobenzaprine may have additive effect when used concurrently with anticholinergics; effects of alcohol, CNS depressants, and barbiturates may be enhanced with cyclobenzaprine

Contraindications

Documented hypersensitivity; have taken MAOIs within the last 14 d

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Caution in angle-closure glaucoma and urinary hesitance; may cause drowsiness, dizziness, and xerostomia

Nonbenzodiazepine Hypnotics

These medications are indicated for insomnia.

Zolpidem (Ambien, Ambien CR)

Indicated for insomnia. Structurally dissimilar to benzodiazepines but similar in activity, with the exception of having reduced effects on skeletal muscle and seizure threshold.
Agents of varying durations of action are used frequently for anxiety and panic and as sleep aids (poor sleep is nearly universal in fibromyalgia).

Dosing

Adult

Starting dose: 10 mg PO qhs
Elderly dose: 5 mg PO qhs
Should be taken on a relatively empty stomach immediately before going to sleep

Pediatric

Not established

Interactions

Increases toxicity of alcohol and CNS depressants; zolpidem's effect on insomnia may be delayed if taken with food or shortly after a meal

Contraindications

Documented hypersensitivity; lactation

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

Monitor elderly for impaired cognitive or motor performance; extended-release dosage form must be swallowed whole (do not divide, chew, or crush)

Eszopiclone (Lunesta)

Nonbenzodiazepine hypnotic pyrrolopyrazine derivative of the cyclopyrrolone class. The precise mechanism of action is unknown but believed to interact with GABA receptor at binding domains close to or allosterically coupled with benzodiazepine receptors. Indicated for insomnia to decrease sleep latency and improve sleep maintenance. Short half-life of 6 h. Higher doses (ie, 2 mg for elderly and 3 mg for nonelderly adults) are more effective for sleep maintenance, whereas lower doses (ie, 1 mg for elderly and 2 mg for nonelderly adults) are suitable for difficulty in falling asleep.

Dosing

Adult

Nonelderly adults: 2 mg PO hs; may increase to 3 mg PO hs prn
Elderly: 1 mg PO hs initially; not to exceed 2 mg PO hs
Severe hepatic impairment: Do not exceed 2 mg PO hs

Pediatric

<18 years: Not established

Interactions

CYP3A4 and CYP2E1 substrate; potent CYP3A4 inhibitors (eg, ketoconazole, itraconazole, clarithromycin, nefazodone, ritonavir, nelfinavir) increases AUC, C_{max}, and $t_{1/2}$ and therefore potential toxicity (decrease dose); potent CYP3A4 inducers (eg, rifampicin) increases clearance; coadministration with alcohol or other CNS depressants may increase effect and toxicity (decrease dose); coadministration with olanzapine may decrease DSST scores; sleep onset may be delayed if taken with or immediately after a high-fat or heavy meal

Contraindications

Documented hypersensitivity

Precautions

Pregnancy

C - Fetal risk revealed in studies in animals but not established or not studied in humans; may use if benefits outweigh risk to fetus

Precautions

May cause dysgeusia, headache, or coldlike symptoms; rare adverse effects associated with hypnotics include short-term amnesia, confusion, agitation, hallucinations, worsened depression, or suicidal thoughts; high doses (ie, 6-12 mg) produce euphoric effects similar to those of diazepam 20 mg; anxiety, abnormal dreams, nausea, and upset stomach may occur within 48 h after discontinuing; alertness may be affected the following day, use caution operating machinery or driving a car

Follow-up

Further Inpatient Care

- A rehabilitation program for fibromyalgia is incomplete without psychological intervention.
- Many patients with fibromyalgia have increased levels of stress and feelings of depression, anxiety, and frustration.
- Several treatment options are available. According to Buckelew, cognitive behavioral therapy, relaxation training, group therapy, biofeedback, and stress management are some of the most useful options.[32]
- Buckelew and colleagues found that patients receiving aerobic training plus biofeedback had significant improvements in tender-point pain, self-reported physical function, and self-efficacy for function, as compared with a control group.[32]

Further Outpatient Care

- Cognitive behavioral therapy (CBT) techniques emphasize changes in thought patterns and behaviors.[33] CBT can be performed in a one-on-one or group setting, with beneficial effects achievable in as few as 10 sessions. These techniques have been used in chronic pain treatment programs that manage patients with fibromyalgia. A study that reviewed the results of 13 programs using CBT found that generally, CBT provided improvements in pain-related behaviors, coping strategies, and overall physical function.[34] However, providing CBT alone is not advantageous over group programs of exercise and/or education.

Complications

Symptoms of fibromyalgia vary as follows:

- Patients may experience few symptoms one day and many the next.
- Some investigators describe a flare-up as a time when the patient experiences an acute intense increase in symptoms that last more than a day. The pain may be amplified to such intense levels that

the patient becomes bedridden.

- Flares-ups usually are triggered by a stressor. The stressor may be infection, trauma, or changes in medication, sleep, or exercise. Onset of allergies, changes in diet, and a change in usual activity may bring on a flare-up.

Teach patients about the triggers of flare-ups. On occasion, no trigger can be identified. Patients must learn to identify their triggers and what measures to take to decrease their symptoms.[33] Tips for avoiding and managing flare-ups include the following:

- Educate the patient about flare-ups. (See Patient Education, below.)
- Treat infection quickly.
- Avoid changes in diet.
- Exercise as prescribed (ask patients not to increase their routine without consulting a physician).
- Moderate changes in activity.
- Avoid unnecessary life changes.
- Treat changes in mood or sleep early and aggressively.
- Always start new medications at the lowest possible dose.
- Prepare for situations that have caused flare-ups in the past (situations, for example, that may require an increase in sleep medication or help with housework and child care).
- Encourage patients to pace their activities and know their limits.

Prognosis

- Fibromyalgia is not a life-threatening, deforming, or progressive disease.
- The symptoms of fibromyalgia are variable.
- Without proper diagnosis and treatment, a patient with fibromyalgia may have the illusion of disease progression. This illusion does not occur as a result of disease but is instead caused by sleep deprivation and physical deconditioning.
- Some investigators state that, with the proper treatment and a caring, informed physician, patients with fibromyalgia should be able to improve function and reduce pain.

Patient Education

- History
    - Treatment of fibromyalgia begins with a detailed history and a thorough physical examination. Making a correct diagnosis is crucial, and patients need to know that a name exists for the

mysterious symptoms that they are experiencing.

- No cure
  - The physician should inform the patient that no cure exists for fibromyalgia but that education, lifestyle changes, and proper rehabilitation can help the individual to regain control and achieve significant improvement.
  - Although fibromyalgia has no cure, patients should be reassured that the illness is not life threatening. Some authors suggest explaining the chronic, fluctuating nature of this disorder to patients. When patients with fibromyalgia fully understand the nature of the disease, they are more likely to comply with treatment and to take an active role in managing the disease.
  - At the initial visit, give patients educational materials about fibromyalgia, including a list of resources, such as books, videotapes, newsletters, and brochures, related to the disease. Some authors recommend encouraging patients to attend their local fibromyalgia support group. Provide education and support to the patient's significant family members.

- Sleep
  - Poor sleep worsens and perpetuates symptoms, so aggressive treatment is indicated. Most patients understand little about the nature of sleep; therefore, instruct them on the basics of sleep and proper sleep hygiene. Providing this education is one of the most helpful interventions.[35]
  - The present author suggests asking the patient to keep a sleep diary for 2 weeks before starting any new medications. The diary should include a list of medications taken during the 2 weeks, the time at which patients went to bed, the approximate time at which they fell asleep, the number of awakenings, the number of times they got out of bed, and a general description of how rested they felt. The sleep diary provides useful information for choosing medications.
  - Suggest a few helpful dietary and behavioral changes to the patient. Instruct the patient to avoid caffeine and large evening meals; avoiding alcohol is also helpful. Teach the patient basic relaxation techniques to use before bed. If urinary frequency is problematic, restrict fluids in the evenings.
  - Consider comorbid illnesses, such as restless legs syndrome, periodic limb-movement disorder, or sleep apnea, that may be present. If these disorders are suspected, a sleep study may be needed.
  - After proper education and instruction on sleep hygiene and dietary changes, consider using appropriate medications to improve the patient's sleep. (See Medications to improve sleep.)

- Nutrition
  - Poor diet worsens the symptoms of fibromyalgia. One investigator suggests that this deterioration may be due to impaired glycolysis and carbohydrate metabolism.[36] Dietary changes are essential to improving symptoms and challenging to achieve.
  - Although many dietary choices can be made, some may be no healthier than the patient's existing diet. While no dietary or nutritional approach is universally accepted, increasing evidence reveals that some nutritional changes may improve the symptoms of fibromyalgia. Choose an approach that is nutritionally balanced and safe. Help the patient to set reasonable and attainable goals.[37]
  - Have the patient keep a food journal for 2 weeks. Determine what foods the patient normally

eats. Slowly wean the patient off caffeine, because abruptly stopping caffeine will increase fatigue and pain, headaches, anxiety, and sleep disturbance. Some suggest that all alcohol must be avoided for at least 6 months; if the patient's symptoms are stable, he/she may consume no more than 2 alcoholic drinks a day. Tobacco use should cease, as should the consumption of chemical-laden foods, refined sugars, white flour, aspartame, and monosodium glutamate (MSG). Case studies have shown worsening of symptoms in patients who were challenged with aspartame and MSG and have demonstrated patient improvement when these compounds were removed from the diet.

- Most patients with fibromyalgia consume enormous amounts of carbohydrate-rich foods, which may contribute to their symptoms. Some suggest a diet high in fresh vegetables, fish, and fiber. Green, leafy, and yellow vegetables are preferred because of their low carbohydrate content. Choose fruits carefully; some are more glycemic than others. Fruits such as citrus fruits, apples, berries, cantaloupe, and peaches may be preferred. The rate of carbohydrate absorption decreases if the patient combines it a food containing fiber or fat. Ask the patient to avoid junk foods or processed snack foods, which usually contain large amounts of sugar or salt.
- Patients with fibromyalgia produce more damaging free radicals than do healthy people, and they have a reduced antioxidant capacity. Normal cellular respiration produces free radicals that lead to oxidative stress. The antioxidant defense system normally keeps these free radicals in check. Dietary antioxidants consumed in foods are essential to increasing our antioxidant status and maintaining our antioxidant systems.

  Vitamins (eg, C, E), minerals (eg, selenium, zinc), and phytochemicals are important dietary antioxidants. Vegetarian diets improve some symptoms, in association with an increased intestinal bacterial profile and increased antioxidant status; however, they may be difficult to maintain long term. A vegetarian diet rich in a variety of fruits, vegetables, and nuts may be of some benefit. Moderation may be the key to long-term compliance.
- Physicians must acquaint themselves with the available research on diet and metabolism. Investigate the trend diets and make informed recommendations to each patient on an individual basis. Help patients set attainable goals for dietary modification.

- For excellent patient education resources, visit eMedicine's Muscle Disorders Center; Mental Health and Behavior Center; and Back, Ribs, Neck, and Head Center. Also, see eMedicine's patient education articles Fibromyalgia, Chronic Fatigue Syndrome, Chronic Pain, and Fatigue.

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Keywords

fibromyalgia, myofascial pain, fibromyalgia symptoms, fibromyalgia pain, treatment fibromyalgia, symptoms of fibromyalgia, fibromyalgia syndrome, chronic fibromyalgia, fibromyalgia fatigue, interstitial myofibrositis, muscular hardening, muscular rheumatism, musculorheumatism, myofibrositis, myogelosis, myositism, nodular rheumatism, nonarticular rheumatism, rheumatic muscle callus, rheumatic muscle hardening, rheumatic myalgia, rheumatic pain modulation disorder, tension myalgia, fibromyositis, fibrositis, idiopathic myalgia

Contributor Information and Disclosures

Author

Regina P Gilliland, MD, Department of Internal Medicine; Division of Rehab Medicine, Mobile Infirmary Medical Center
Regina P Gilliland, MD is a member of the following medical societies: American Academy of Physical Medicine and Rehabilitation, Medical Association of the State of Alabama, and Southern Medical Association
Disclosure: Acorda Honoraria for Speaking and teaching; Pfizer Honoraria for Speaking and teaching

Medical Editor

Martin K Childers, DO, PhD, Associate Professor, Department of Neurology, Wake Forest University Health Services
Martin K Childers, DO, PhD is a member of the following medical societies: American Academy of Physical Medicine and Rehabilitation, American Congress of Rehabilitation Medicine, American Osteopathic Association, Christian Medical & Dental Society, and Federation of American Societies for Experimental Biology
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Pharmacy Editor

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Patrick M Foye, MD, FAAPMR, FAAEM is a member of the following medical societies: American Academy of Physical Medicine and Rehabilitation, American Association of Neuromuscular and Electrodiagnostic Medicine, Association of Academic Physiatrists, and International Spine Intervention Society
Disclosure: Nothing to disclose

CME Editor

Kelly L Allen, MD, Regional Medical Director, IMX-Medical Management Services
Disclosure: Nothing to disclose

Chief Editor

Consuelo T Lorenzo, MD, Consulting Staff, Department of Physical Medicine and Rehabilitation, Alegent

Health Care, Immanuel Rehabilitation Center
Consuelo T Lorenzo, MD is a member of the following medical societies: American Academy of Physical Medicine and Rehabilitation
Disclosure: Nothing to disclose