

Is there a relationship between fibromyalgia and rhinitis?

Marianne Frieri, M.D., Ph.D.,¹ and Antigone Argyriou, M.D.²

ABSTRACT

Fibromyalgia (FM) is a common chronic pain disorder characterized by diffuse musculoskeletal pain and stiffness. It is recognized as a common syndrome affecting 2–4% of the population that may present with several ambiguous and seemingly unrelated symptoms. A broad variety of complaints and lack of tests to accurately identify the disease challenges physicians with confirming this elusive diagnosis. FM has significant overlap with several other systemic diseases including those of sensory hypersensitivity, autonomic deregulation, neurological dysfunction, migraine, and related chronic rhinitis. Current research suggests a relationship between allergic disease especially allergic and NAR and sinusitis. The pathogenesis of FM is related to aberrant pain processing and immunoregulatory abnormalities that may occur in autoimmune disorders with increases in immunologic signaling molecules such as ILs, cytokines, nerve growth factor, which is linked with rhinitis, TNF-alpha, and L-selectin suggesting that pathophysiology is a product of the inflammatory response system. Central nervous system cytokine activation through viral neurotropism and subsequent glial activation is speculated as a possible mechanism. Allergists-immunologists and other specialists such as rheumatologists and rehabilitation and psychiatric physicians may be able to more accurately diagnose and treat these debilitated and often stigmatized patients. The complexity of this disorder must be tackled by a multidisciplinary approach to ensure the successful management of this multifaceted syndrome.

(Allergy Asthma Proc 33:443–449, 2012; doi: 10.2500/aap.2012.33.3596)

Fibromyalgia (FM) is a chronic pain syndrome characterized by diffuse musculoskeletal aching, stiffness, and exaggerated tenderness at 18 specified tender points.¹ American College of Rheumatology 1990 criteria² for FM for classification purposes include widespread pain present for at least 3 months and the presence of a second clinical disorder does not exclude the diagnosis of FM. (Table 1). Listing a history of widespread pain and in 11 of 18 tender point sites on digital palpation is listed. Trigger points are listed in Fig. 1

PATHOPHYSIOLOGY OF FM

Although the current opinion among most investigators is that FM is not a disorder of the peripheral tissues, many studies have suggested that FM may manifest as abnormal histopathological findings in peripheral muscle.³ FM researchers studying muscle pathology have focused on altered muscle metabolism such as high-energy phosphate metabolites. Bengtsson suggested that these metabolites such as adenosine triphosphate and adenosine diphosphate were lower in tender points of muscle than in the same anatomic locations in control participants.⁴ However, researchers have since indicated that various central nervous

system processes in the brain and the spinal cord manifest abnormalities in patients with FM.¹ Glial cells, long thought to be metabolically inactive support cells in the nervous system, are now recognized as playing a substantial role in modulating pain signaling.⁵ Glial cells and astrocytes are activated by stimuli that induce pain, such as nerve trauma, subcutaneous irritation, and i.p. inflammation and by neurotransmitters.⁶

Glial cells release many neuroactive substances on activation by painful stimuli, including nitric oxide, prostaglandins, leukotrienes, nerve growth factor (NGF), excitatory amino acids, and reactive oxygen species.⁷ Activated glia up-regulate release of substance P (SP) and other excitatory amino acids from primary afferent neurons in the spinal cord and enhance the excitability of pain transmission neurons.

In addition, microglia and astrocytes release proinflammatory cytokines, such as IL-1, IL-6, and TNF- α .⁸ Blocking the actions of these cytokines prevents or reverses exaggerated pain states.⁶

ASSOCIATION OF ALLERGIC AND NAR AND NEUROPEPTIDES

Allergic and NAR can occur in patients with FM along with sinusitis. Chronic rhinitis has been reported to have an underrecognized association with FM.⁹ NGF has been linked with FM and has been shown to be consistently expressed in the epithelium and in the submucosa of subjects with allergic rhinitis, preferentially localized in eosinophils and mast cells. The preferential NGF localization in mucous cells of the epithelial lining and in the submucosal glands suggests a

From the ¹Department of Medicine, Nassau University Medical Center, East Meadow, New York, and ²Department of Physical Medicine and Rehabilitation, Montefiore Medical Center, Bronx, New York

The authors have no conflicts of interest to declare pertaining to this article

Address correspondence and reprint requests to Marianne Frieri, M.D., Ph.D., Department of Medicine, Nassau University Medical Center, 2201 Hempstead Turnpike, East Meadow, New York, NY 11554

E-mail address: mfrieri@numc.edu

Copyright © 2012, OceanSide Publications, Inc., U.S.A.

Table 1 Center for disease control and prevention CFS criteria

Clinicians should consider a CFS diagnosis with these criteria:

- Unexplained, persistent fatigue that is not caused by ongoing exertion, is not substantially relieved by rest, is of new onset (not lifelong), and results in a significant reduction in previous levels of activity
- Four or more of the following symptoms are present for 6 mo:
 - Impaired memory or concentration
 - Postexertional malaise (extreme, prolonged exhaustion and sickness after physical or mental activity)
 - Unrefreshing sleep
 - Muscle pain
 - Multijoint pain without swelling or redness
 - Headaches of a new type or severity
 - Sore throat that is frequent or recurring
 - Tender cervical or axillary lymph nodes

Source: Centers for Disease Control and Prevention.⁴⁷
CFS = chronic fatigue syndrome.

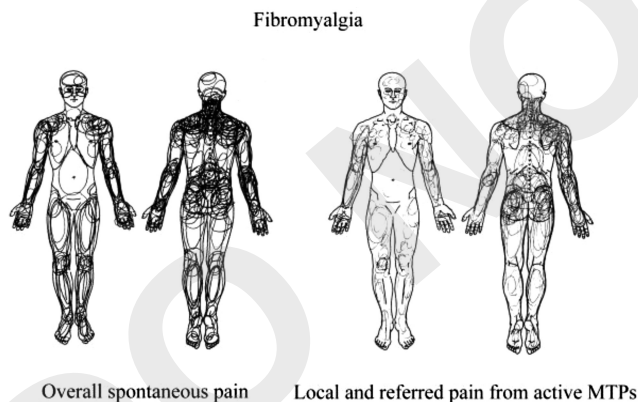


Figure 1. Spontaneous and evoked pain in FM patients. The overall spontaneous pain pattern and local and referred pain pattern from key active myofascial trigger points (MTP). The referred pain was lightly shaded on purpose to denote the induced pain from key active MTPs. (Source: from Ge H-You et al.⁴⁸ with permission.)

possible role for NGF in modulating secretion in allergic rhinitis and possibly other allergic diseases.¹⁰

NGF binds to trkA tyrosine kinase receptors. NGF released during occupational exposure may mediate SP up-regulation in airway sensory neurons, innervating the nasal cavity.¹¹

Several studies have reported that migraine headaches are more common in patients with allergic rhinitis.¹² Migraine is associated with rhinitis and chronic forms of migraine show a high frequency of FM comorbidity, suggesting that factors facilitating the wors-

ening of migraine may also predispose to diffuse musculoskeletal pain.¹³ Cleveland reviewed symptoms of rhinitis and FM. Patients were examined for tender points and a history of congestion was present in 91%, rhinorrhea was present in 87%, and postnasal drip was present in 83%. A history of diffuse, aching pain or tiredness for at least 3 months was found in 49 and 79% who were skin test positive to inhalant allergens. Although positive skin tests alone did not correlate with the number of tender points or criteria for FM, rhinitis, rather than atopy, is associated with FM and may be an underdiagnosed, but important, causative factor.⁹

Baraniuk reviewed nasal secretion analysis in allergic rhinitis, cystic fibrosis, and nonallergic FM/chronic fatigue syndrome (CFS) subjects.¹⁴ Rhinitis symptoms are present in ~70% of subjects with FM/CFS and only 35–50% have positive allergy skin tests; therefore, non-allergic mechanisms may also play a role. Nasal lavages were performed, and markers of vascular permeability, glandular secretion, and neutrophil and eosinophil infiltration were measured in 27 nonallergic FM/CFS, 7 allergic rhinitis, 7 cystic fibrosis, and 9 normal subjects. Allergic rhinitis subjects had significantly increased vascular permeability (immunoglobulin G [IgG]) and eosinophil cationic protein levels. Although there were no significant differences between FM/CFS, normal lavage fluids analysis of the constituents of nasal mucus provides information about the ongoing secretory processes in rhinitis. There were no differences in the basal secretion of these markers of vascular permeability, submucosal gland serous cell secretion, eosinophil, and neutrophil degranulation in nonallergic FM/CFS subjects. Future studies should examine alternative mechanisms such as inducible, irritant-activated, or reflex-mediated effects.¹⁴

Wang evaluated the role of proinflammatory cytokine IL-8 and its clinical relevance in patients with FM who fulfilled clearly defined inclusion and exclusion criteria and underwent a 3-week inpatient multidisciplinary pain therapy.¹⁵ Before and during the inpatient therapy, the serum level of IL-8 was significantly higher in patients with FM compared with controls but did not correlate with pain intensity and medication. In patients with FM, IL-8 serum level correlated with nicotine consumption. Their results suggested that the IL-8 level contributes in patients with FM whose pain intensity and back function can be improved under influence of multidisciplinary pain therapy without need of an anti-IL-8 therapy. Our division evaluated the effect of macrolide therapy on specific *Streptococcus pneumoniae* cytokine and nitric oxide production in patients with acute sinusitis and noted that IL-8 levels were decreased in patients with sinusitis.¹⁶

Baraniuk also reviewed relationships between rhinitis, FM, and chronic fatigue.¹⁷ (Fig. 2). This article

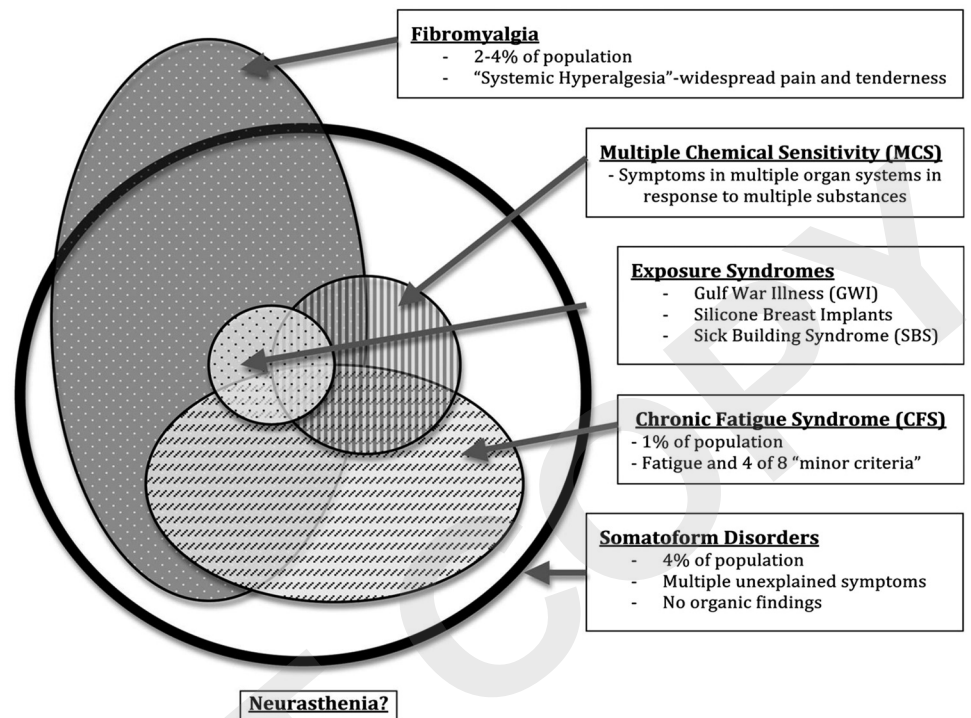


Figure 2. Overlap of fibromyalgia (FM) with other neurasthenic disorders. (Source: Adapted with permission from Baraniuk JN.¹⁷)

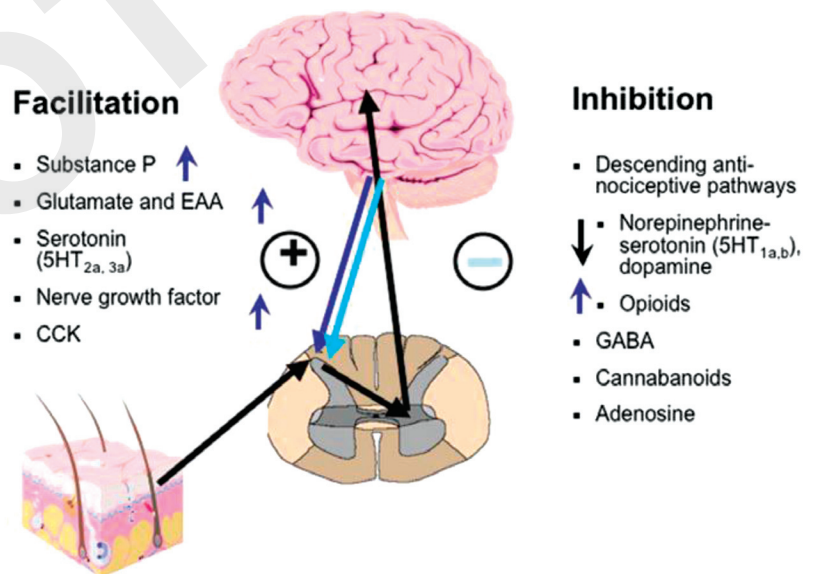


Figure 3. Neural influences on pain and sensory processing. (Source: from Smith HS, et al.¹⁸ with permission.)

showed the importance of FM and allied disorders for and allergy immunology practice. It has an overlap with autonomic dysfunction, irritable bowel syndrome, and migraine headaches that can be associated with chronic rhinitis, sensory hypersensitivity and central nervous system maladaptations (central sensitization) recorded by functional magnetic resonance imaging. Neurological dysfunction may account for the overlap of CFS with idiopathic nonallergic rhinopathy. Scientific advances are in functional magnetic resonance imaging, nociceptive sensor expression, potentially, viral infection (Delete with xenotropic murine

leukemia-related virus) may provide additional insights to novel pathophysiological mechanisms of the "functional" complaints of these patients that are mistakenly interpreted as allergic syndromes. Allergists-immunologists must accept the clinical challenges posed by these complex patients and provide proper diagnoses, assurance, and optimum care even though current treatment algorithms are lacking.¹⁷

Elevated levels of neurotransmitters that tend to be pronociceptive (Fig. 3, left side) or reduced levels of neurotransmitters that inhibit pain transmission (*i.e.*, on the right side of the Fig. 3) have a tendency to

increase the volume control, and drugs that block neurotransmitters on the left or augment activity of those on the right will typically be found to be effective treatments, at least for a subset of individuals with this spectrum of illness. The arrows on Fig. 3 indicate the direction of the abnormalities in these neurotransmitter levels either in the cerebrospinal fluid or brain that have been identified, to date, in FM. In FM, there is evidence for increases in the cerebral spinal fluid levels of SP.¹⁸

Several patients who present with symptoms of allergic rhinitis have absent levels of IgE and TH2 lymphocyte mechanisms. Patients with symptoms of allergic rhinitis but with absent levels of associated inflammatory markers are identified as having nonallergic rhinitis (NAR). The pathogenesis of idiopathic nonallergic, noninfectious, rhinopathy is unclear. Several patients presenting with FM have symptoms corresponding with NAR. This suggests that disorders of neural dysregulation and systemic hyperalgesia are related.¹⁷

A LINK WITH RHINITIS AND FM

Fatigue is a common symptom of chronic rhinosinusitis but the response of fatigue to endoscopic sinus surgery is rarely studied. Sautter evaluated the effects of endoscopic sinus surgery on level of fatigue in patients with chronic rhinosinusitis.¹⁹

Sleep impairment is a significant problem for patients with FM and allergic rhinitis. Allergic rhinitis affects the quality of life of individuals often associated with sleep-disordered breathing, which is thought to be the reason for sleep impairment in individuals with rhinitis.

A survey conducted in >7000 adults showed that sleep disturbance played a major negative role in rhinitis patients.²⁰

The inflammatory mediators such as histamine and cytokines, SP that increases latency to rapid eye movement, and nasal obstruction during allergic reactions may directly affect the central nervous system, which contributes to disturbed sleep and fatigue.²¹

Ravindran reviewed the sinus headache.²² The concept of a sinus headache is problematic from neurology, allergology, and rhinology perspectives. It may be considered the final neurological diagnosis of exclusion when criteria for other craniofacial pain syndromes are not met. Otorhinolaryngologists have a similar exasperation with this cephalgia but tend to attribute idiopathic, nonallergic rhinopathy as the cause. Allergists often evaluate patients who claim to have a sinus headache but instead have perennial allergic rhinitis or NAR. A fresh perspective is required to determine the characteristics, differential diagnosis, and veracity of the sinus headache. Ravindran recom-

mended using the term with caution only if the clinical picture meets the criteria for acute sinusitis-induced headache.²²

PSYCHIATRIC ASPECTS OF FM

Arnold reviewed the relationships among pain and depressive and anxiety symptoms in clinical trials of pregabalin.²³ Patients with FM have an elevated incidence of psychiatric comorbid conditions, and observational studies implicate psychopathology as playing a role in FM in selected patients. Buskila reviewed the comorbidity of FM and psychiatric disorders that includes depression, panic disorders, anxiety, and post-traumatic stress disorder. A link between posttraumatic stress disorder symptoms and FM has been reported, and both conditions share similar symptomatology and pathogenetic mechanisms. Assessment of comorbid psychiatric disorders in FM patients has clinical implications because treatment in these patients should focus both on physical and on emotional dimensions of dysfunction.²⁴ Häuser reviewed emotional, physical, and sexual abuse in FM syndrome: a systematic review with meta-analysis.²⁵ The association of FM syndrome with physical and sexual abuse could be confirmed but is confounded by study quality. Postolache hypothesized that 51 patients with unipolar or bipolar disorder with recurrent mood disorders sensitized to tree pollen by specific IgE antibodies versus those who are not sensitized would report larger negative changes in mood during exposure to tree pollen in spring.²⁵

Postolache hypothesized that differences between high and low tree pollen periods in self-reported allergy symptoms would correlate positively with differences in self-reported depression scores and confirmed the hypothesized positive relationship between the changes in allergy symptoms and in subjects' depression scores. This was consistent with previous epidemiological evidence connecting allergy with depression and reports of increased expression of cytokines in the prefrontal cortex in victims of suicide and in experimental animals sensitized and exposed to tree pollen.²⁶ Manalai also reported on pollen-specific IgE positivity is associated with worsening of depression scores in bipolar disorder patients during high pollen season.²⁷

FM is also frequent in systemic lupus erythematosus (SLE) patients and contributes to worsening health status in SLE patients. Allergic disorders commonly occur in patients with SLE. Sequeira found a high prevalence of rhinitis and asthma in their families.²⁸

Psychiatric disorders such as anxiety and depression are also present in many SLE patients.¹⁸ Torrente-Se-garra reviewed the association between FM and psychiatric disorders in SLE.²⁹ Cardiovascular complica-

tion also occurs in SLE, which could contribute to anxiety and depression.³⁰

POSSIBLE PRECIPITANTS OF FM

Despite the difficulty inherent in addressing cause in the absence of a defined pathogenesis, many researchers have attempted to examine the triggers that lead to FM infection. Several studies suggested that viral infection may precipitate FM in some patients such as hepatitis C and human immunodeficiency virus, which have been found to have higher rates of FM than the general population.³¹ Luczkowiak studied the presence of xenotrophic murine related virus and polytropic murine leukemia virus-related retroviruses in a group of patients with FM.³² FM does not appear to be associated with xenotrophic murine related virus or polytropic murine leukemia virus-related viruses. The role of these new agents in human disease and, specifically, in CFS remains to be clearly confirmed in multicenter and standardized studies.³² It is presently unclear how viruses might trigger FM, but central nervous system cytokine activation *via* viral neurotropism and subsequent glial activation may play a role. Several retrospective studies suggest that physical trauma can precipitate FM. Trauma and infection are recognized FM triggers. Martinez-Lavin reviewed when distress becomes (un)sympathetic pain.³³ Both physical and emotional stressors are frequent FM triggers and bodily trauma, particularly a whiplash injury during automobile accident, is a recognized trigger.³³ FM patients are often immersed in a stressful lifestyle and anxiety and depression are frequent companions.³³

However, the problem with retrospective studies is that of selective memory. Indeed, accumulating evidence suggests that FM probably results from abnormal central pain processing rather than a dysfunction in the peripheral tissues where such pain is perceived. Several mechanisms may be involved, including central sensitization, suppression of descending inhibitory pathways, excessive activity of glial cells, and abnormalities of neurotransmitter release or regulatory proteins or both. In patients with prolonged exposure to pain, the incoming afferent signals are increased, and presynaptic release of SP and excitatory amino acids is enhanced. An influx of calcium ions increases the production of nitric oxide, which causes nerves to become hyperexcitable and further release SP.³⁴

Ablyn studies biomarkers in FM.³⁵ Increased serum brain-derived neurotrophic factor (BDNF) levels have been recently reported in FM, suggesting an involvement in the syndrome. BDNF is involved in neuronal survival and synaptic plasticity of the central and peripheral nervous system, and it appears to modulate nociceptive sensory inputs and pain hypersensitivity.³⁵

Mucosal expression of NGF and BDNF has also been reported in chronic rhinosinusitis. Thus, increased expression of NGF may contribute to neural hyperresponsiveness in chronic rhinosinusitis mucosa, particularly those patients with nasal polyps and/or allergies.³⁶ Allergic rhinitis is characterized by allergic airway inflammation and a hyperresponsiveness to nonspecific stimuli, which is partly neuronally controlled.³⁷ BDNF and NGF exert immunomodulatory functions on eosinophils of patients with allergic rhinitis and, eosinophils of patients with allergic rhinitis are capable of BDNF and NGF production.³⁷

Lee evaluated the role of the central nervous system in the generation and maintenance of chronic pain in FM and other rheumatologic conditions.³⁸ In FM, the importance of central nervous system pain mechanisms as loss of descending analgesic activity and central sensitization is well documented. When central pain is identified, different classes of analgesics (*e.g.*, serotonin-norepinephrine reuptake inhibitors, $\alpha 2\delta$ ligands) may be more effective than drugs that treat peripheral or nociceptive pain (*e.g.*, nonsteroidal anti-inflammatory drugs and opioids).³⁸ Descending pain pathways and central sensitization modulate the pain response in the dorsal horn of the spinal cord. Patients with FM have a diffuse hyperalgesic state of central augmentation of processing pain which has been identified using neuroimaging techniques and may be partially caused by specific defects such as loss of descending analgesic activity and central sensitization.³⁸

Bradley reviewed evidence for genetic abnormalities in FM.³⁹ Genetic markers have been discovered within the D4 dopamine gene, which showed a significant decrease in a specific 7-repeat allele in FM patients.

The role of oxidative stress in the pathophysiology of FM was studied by Cordero who evaluated mitochondrial function in affected patients by examining their blood mononuclear cells.⁴⁰ They noted reduced levels of coenzyme Q10, decreased mitochondrial membrane potential, increased levels of mitochondrial superoxide, and increased lipid peroxidation, as well as increased autophagy and mitophagy. Their findings may support the role of oxidative stress in the pathophysiology of FM.⁴⁰

TREATMENT

Cyclobenzaprine shares pharmacologic properties with tricyclic antidepressants but acts on the brainstem to induce skeletal muscle relaxation *via* reduction of tonic activity of α - and γ -neurons. Anticholinergic side effects are associated with cyclobenzaprine. The anticholinergic agent ipratropium bromide for rhinitis is not considered effective in relieving nasal congestion; however, limited data suggest that sleep and quality of life may be improved after treatment.²¹

Short-term studies showed improvement in pain and fatigue with cyclobenzaprine, but longer-term studies did not show an advantage over placebo. Carette compared the relative efficacy and tolerability of amitriptyline, cyclobenzaprine, and placebo in the treatment of FM and to identify predictors of response to amitriptyline and cyclobenzaprine.⁴¹ Their data confirmed the short-term efficacy of amitriptyline and cyclobenzaprine in a small percentage of patients with FM.⁴¹ Pregabalin was the first medication the Food and Drug Administration approved for FM, after the drug was initially approved for diabetic neuropathy and post-herpetic neuralgia. Pregabalin disrupts neuronal signaling by binding to the α -2-delta-subunit of voltage-gated calcium channels in the central nervous system. Multiple double-blind placebo-controlled trials have shown significant reductions in pain score, as well as decreased fatigue, improved sleep, and health-related quality of life.⁴²

Gabapentin is another centrally acting agent that is approved for multiple neurological diseases and inhibits the same voltage-gated calcium channels as pregabalin.⁴³ Naltrexone, in addition to antagonizing opioid receptors on neurons, also inhibits microglia activation. It is proposed that this mechanism may explain the improvements in FM symptoms in a pilot study of 10 patients treated with the medication.⁴⁴

Vierck reviewed a mechanism-based approach to prevention of and therapy for FM.⁴⁵

Physical exercise has been shown to counteract peripheral vasoconstriction and to attenuate stress, depression, and fatigue and improve mentation and sleep quality. Thus, exercise can interrupt the reciprocal interactions between psychological stress and each of the multiple-system disorders of FM. The large literature supporting these conclusions indicates that exercise should be considered strongly as a first-line approach to therapy.⁴⁵

Mease reviewed pharmacotherapy of FM.⁴⁶ Several different medications, including the serotonin and norepinephrine reuptake inhibitors, duloxetine and milnacipran and the α (2) δ -modulator pregabalin have been used for management based on their clinically meaningful and durable effect on pain in monotherapy trials. They also have been shown to beneficially effect patient global impression of change, function, and variably other key symptom domains, such as fatigue, sleep disturbance, and cognition which can also occur in allergic rhinitis. Adjunctive therapy with medicines targeted at specific symptom domains such as sleep, as well as treatments aimed at common comorbid conditions such as allergic rhinitis and NAR, sinusitis and irritable bowel syndrome, or disease states such as rheumatoid arthritis should be considered for the purpose of reducing the patient's overall symptom burden. Current therapies neither completely treat FM

symptoms nor benefit all patients. Thus, further research on new therapies with different mechanisms and side effect profiles is needed.⁴⁶

DISCUSSION

The pathophysiology of FM continues to elude researchers. There appears to be a link of FM with allergic rhinitis, NAR, sinusitis, and migraine because of the role of sleep disturbances, quality of life, irritants, and neuropeptides. For physicians, finding objective ways to evaluate for and definitively diagnose FM remain important. The complexity of the illness has created obstacles in discovering its pathophysiology. Several mechanisms have been proposed to explain the pain hypersensitivity associated with this disease, but additional research is necessary to explain this multi-system syndrome.

Once questioned as a true disorder, recent research suggests this disease indeed stems from an organic cause. Although acceptance is the first step to understanding, many questions remain unanswered. It is likely that the proposed mechanisms of pathophysiology are all intertwined to contribute to the disease collectively and not exclusively.

The overlap between FM and several other diseases of immunologic dysfunction suggests a link between the immune system, chronic rhinitis, and the body's pain response. The inflammatory molecules used as chemical signals throughout the nervous system related to neuropeptides in chronic rhinitis and migraine have provided much insight into altered levels of pain sensation related to FM and sleep disturbances in chronic rhinitis.

REFERENCES

1. Abeles AM, Pillinger MH, Solitar BM, et al. Narrative review: The pathophysiology of fibromyalgia. *Ann Intern Med* 146:726–734, 2007.
2. American College of Rheumatology. Criteria for rheumatic diseases. www.rheumatology.org/practice/clinical/classification/index.asp; accessed March 30, 2010.
3. Simms RW. Fibromyalgia is not a muscle disorder. *Am J Med Sci* 315:346–350, 1998.
4. Bengtsson A, Henriksson KG, and Larsson J. Reduced high-energy phosphate levels in the painful muscles of patients with primary fibromyalgia. *Arthritis Rheum* 29:817–821, 1986.
5. Watkins LR, Milligan ED, and Maier SF. Spinal cord glia: New players in pain. *Pain* 93:201–205, 2001.
6. Watkins LR, Milligan ED, and Maier SF. Glial activation: A driving force for pathological pain. *Trends Neurosci* 24:450–455, 2001.
7. Watkins LR, and Maier SF. The pain of being sick: Implications of immune-to brain communication for understanding pain. *Annu Rev Psychol* 51:29–57, 2000.
8. Watkins LR, and Maier SF. Immune regulation of central nervous system functions: From sickness responses to pathological pain. *J Intern Med* 257:139–155, 2005.
9. Cleveland CH Jr, Fisher RH, Brestel EP, et al. Chronic rhinitis: An underrecognized association with fibromyalgia. *Allergy Proc* 13:263–267, 1992.

10. Bresciani M, Lalibert  F, Lalibert  MF, et al. Nerve growth factor localization in the nasal mucosa of patients with persistent allergic rhinitis. *Allergy* 64:112–117, 2009.
11. Wilfong ER, and Dey RD. Nerve growth factor and substance P regulation in nasal sensory neurons after toluene diisocyanate exposure. *Am J Respir Cell Mol Biol* 30:793–800, 2004.
12. Martin VT, Taylor F, Gebhardt B, et al. Allergy and immunotherapy: Are they related to migraine headache? *Headache* 51:8–20, 2011.
13. de Tommaso M. Prevalence, clinical features and potential therapies for fibromyalgia in primary headaches. *Expert Rev Neurother* 12:287–295, 2012.
14. Baraniuk JN, Clauw D, Yuta A, et al. Nasal secretion analysis in allergic rhinitis, cystic fibrosis, and nonallergic fibromyalgia/chronic fatigue syndrome subjects. *Am J Rhinol* 12:435–440, 1998.
15. Wang H, Buchner M, Moser MT, et al. The role of IL-8 in patients with fibromyalgia: A prospective longitudinal study of 6 months. *Clin J Pain* 25:1–4, 2009.
16. Jaimez L, Lai SY, Wang SF, et al. The effect of macrolide therapy on specific *S. pneumoniae* cytokine and nitric oxide production in patients with acute sinusitis. *Ann Allergy Asthma Immunol* 80:Abstract 63a, 1998.
17. Baraniuk JN. Relationships among rhinitis, fibromyalgia, and chronic fatigue. *Allergy Asthma Proc* 31:169–178, 2010.
18. Smith HS, et al. Neural influences on pain and sensory processing. *Pain Physician* 14:E217–E245, 2011.
19. Sautter NB, Mace J, Chester AC, et al. The effects of endoscopic sinus surgery on level of fatigue in patients with chronic rhinosinusitis. *Am J Rhinol* 22:420–426, 2008.
20. Meltzer EO, Nathan R, Derebery J, et al. Sleep, quality of life, and productivity impact of nasal symptoms in the United States: Findings from the Burden of Rhinitis in America survey. *Allergy Asthma Proc* 30:244–254, 2009.
21. Sardana N, and Craig TJ. Congestion and sleep impairment in allergic rhinitis. *Asian Pac J Allergy Immunol* 29:297–306, 2011.
22. Ravindran M, and Baraniuk JN. The sinus headache explained. *Curr Allergy Asthma Rep* 10:202–209, 2010.
23. Arold LM, Leon T, Whalen E, and Barrett J. Relationships among pain and depressive and anxiety symptoms in clinical trials of pregabalin in fibromyalgia. *Psychosomatics* 51:489–497, 2010.
24. Buskila D, and Cohen H. Comorbidity of fibromyalgia and psychiatric disorders. *Curr Pain Headache Rep* 11:333–338, 2007.
25. H user W, Kosseva M,  uceyler N, et al. Emotional, physical, and sexual abuse in fibromyalgia syndrome: A systematic review with meta-analysis. *Arthritis Care Res (Hoboken)* 63:808–820, 2011.
26. Postolache TT, Lapidus M, Sander ER, et al. Changes in allergy symptoms and depression scores are positively correlated in patients with recurrent mood disorders exposed to seasonal peaks in aeroallergens. *Scientific World J* 17:1968–1977, 2007.
27. Manalai P, Hamilton RG, Langenberg P, et al. Pollen-specific immunoglobulin E positivity is associated with worsening of depression scores in bipolar disorder patients during high pollen season. *Bipolar Disord* 14:90–98, 2012.
28. Sequeira JF, Cesic D, Keser G, et al. Allergic disorders in systemic lupus erythematosus. *Lupus* 2:187–191, 1993.
29. Torrente-Segarra V, Carbonell-Abell  J, Castro-Oreiro S, and Manresa Dom nguez JM. Association between fibromyalgia and psychiatric disorders in systemic lupus erythematosus. *Clin Exp Rheumatol* 28(suppl 63):S22–S26, 2010.
30. Frieri M. Accelerated atherosclerosis in systemic lupus erythematosus. Role of proinflammatory cytokines and therapeutic approaches. *Curr Allergy Asthma Rep* 12:25–32, 2012.
31. Buskila D, Atzeni F, and Sarzi-Puttini P. Etiology of fibromyalgia: The possible role of infection and vaccination. *Autoimmun Rev* 8:41–43, 2008.
32. Luczkowiak J, Sierra O, Gonz lez-Mart n JJ, et al. No xenotropic murine leukemia virus-related virus detected in fibromyalgia patients. *Emerg Infect Dis* 17:314–315, 2011.
33. Martinez-Lavin M. Fibromyalgia: When distress becomes (un) sympathetic pain. *Pain Res Treat* 98:1565, 2012.
34. Solitar BM. Fibromyalgia: Knowns, unknowns, and current treatment. *Bull NYU Hosp Joint Dis* 68:157–161, 2010.
35. Ablin J, Buskila D, and Clauw DJ. Biomarkers in fibromyalgia. *Curr Pain Headache Rep* 13:343–349, 2009.
36. Coffey CS, Mulligan RM, and Schlosser RJ. Mucosal expression of nerve growth factor and brain-derived neurotrophic factor in chronic rhinosinusitis. *Am J Rhinol Allergy* 23:571–574, 2009.
37. Raap U, and Braunstahl GJ. The role of neurotrophins in the pathophysiology of allergic rhinitis. *Curr Opin Allergy Clin Immunol* 10:8–13, 2010.
38. Lee YC, Nassikas NJ, and Clauw DJ. The role of the central nervous system in the generation and maintenance of chronic pain in rheumatoid arthritis, osteoarthritis and fibromyalgia. *Arthritis Res Ther* 13:211, 2011.
39. Bradley LA. Pathophysiology of fibromyalgia. *Am J Med* 122: S22–S30, 2009.
40. Cordero MD, De Miguel M, Moreno Fern ndez AM, et al. Mitochondrial dysfunction and mitophagy activation in blood mononuclear cells of fibromyalgia patients: Implications in the pathogenesis of the disease. *Arthritis Res Ther* 12:R17, 2010.
41. Carette S, Bell MJ, Reynolds WJ, et al. Comparison of amitriptyline, cyclobenzaprine, and placebo in the treatment of fibromyalgia. A randomized, double-blind clinical trial. *Arthritis Rheum* 37:32–40, 1994.
42. Mease PJ, Russel IJ, Arnold LM, et al. A randomized, double blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia. *Nat Clin Pract Rheumatol* 4:514–515, 2008.
43. Arnold LM, Goldenberg DL, Stanford SB, et al. Gabapentin in the treatment of fibromyalgia: A randomized, double blind, placebo-controlled, multicenter trial. *Arthritis Rheum* 56:1336–1344, 2007.
44. Younger J, and Mackey S. Fibromyalgia symptoms are reduced by low-dose naltrexone: A pilot study. *Pain Med* 10:663–672, 2009.
45. Vierck CJ. A mechanism-based approach to prevention of and therapy for fibromyalgia. *Pain Res Treat* 2012:951354, 2012.
46. Mease PJ, Dundon K, and Sarzi-Puttini P. Pharmacotherapy of fibromyalgia. *Best Pract Res Clin Rheumatol* 25:285–297, 2011.
47. Centers for Disease Control and Prevention. Chronic fatigue syndrome. www.cdc.gov/cfs/diagnosis/index.html; accessed March 30, 2010.
48. Ge HY, Wang Y, Fern ndez-de-las-Pe as C, et al. Reproduction of overall spontaneous pain pattern by manual stimulation of active myofascial trigger points in fibromyalgia patients. *Arthritis Res Ther* 13:R48, 2011. □

Copyright of Allergy & Asthma Proceedings is the property of OceanSide Publications Inc. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.