## Introduction

## Fibromyalgia and Its Related Disorders

## Don L. Goldenberg, M.D.

**D** uring the past 20 years, fibromyalgia has emerged as a prominent but poorly understood illness. Conservative estimates are that 3 to 6 million Americans have fibromyalgia.<sup>1</sup> Historically, fibromyalgia has been classified as an inflammatory musculoskeletal disease, and, until 1980, the condition was often termed *fibrositis*. However, fibromyalgia is currently considered to be an illness that primarily affects the central nervous system rather than a peripheral pain disorder. Because investigators never found any significant pathologic changes in the muscle or soft tissue regions where fibromyalgia patients complain of pain, research logically turned to the brain and the spinal cord to explain the pain perception abnormalities so characteristic of this illness.

As discussed in the article by Laurence A. Bradley, Ph.D., abundant evidence,<sup>2,3</sup> especially with imaging studies, has shown neural dysregulation in patients with fibromyalgia. Furthermore, alterations in stress regulation, including the hypothalamic-pituitary-adrenal axis<sup>4,5</sup> and the autonomic nervous system,<sup>6,7</sup> have been noted in a number of studies in fibromyalgia. Many of these abnormalities are similar to those described in comorbid illnesses such as irritable bowel syndrome, chronic fatigue syndrome, atypical facial pain and jaw pain disorders, and irritable bladder syndrome and vulvodynia.<sup>8</sup> Thus, it is not surprising that fibromyalgia clinically overlaps with these other functional illnesses.

Exhaustion, sleep disturbances, and cognitive disturbances are an integral part of fibromyalgia. However, these symptoms have been underappreciated and, until recently, not well characterized. Jennifer M. Glass, Ph.D., reviewed this information in detail, especially in regard to cognitive disturbances in patients with fibromyalgia and related dis-

This article is derived from the planning teleconference series "Understanding Fibromyalgia and Its Related Disorders" that was held in October and November 2007 and supported by an educational grant from Eli Lilly and Company.

4

orders. Standard neuropsychological testing has not captured the absence of cognitive disturbances in fibromyalgia, and currently, no specific treatment for cognitive disturbances exists, yet they have been frustrating to large groups of patients.

The overlap of fibromyalgia with mood disturbances, in particular with major depressive disorder, has been appreciated and actively studied for the past 25 years. Lesley M. Arnold, M.D., highlighted the genetic and physiologic relationship of chronic pain disorders like fibromyalgia with comorbid mood disturbances. Fibromyalgia has a significant familial predisposition (p = .0002) as well as a modest genetic co-aggregation with mood disturbances.<sup>9</sup> Dr. Arnold also provided guidelines for the diagnosis of fibromyalgia in the psychiatric setting.<sup>10,11</sup> Questions regarding standardized diagnostic testing and whether mental health professionals should perform a physical examination and a tender point examination remain unanswered. A stepwise treatment approach for mental health professionals includes careful diagnostic evaluation with attention to comorbid disorders and individualized therapy, including medicinal and nonmedicinal treatments.

Specific recommendations regarding choices of medications and nonpharmacologic approaches to treat fibromyalgia are discussed in the last 2 articles. As Daniel J. Clauw, M.D., indicated, the medications that have been most helpful, not surprisingly, affect pain regulation, mood, and sleep. Tricyclic antidepressants have been found to be effective and have been used in low doses, primarily at night time.<sup>12,13</sup> Although the serotonin reuptake inhibitors have a limited analgesic impact, efficacy has been demonstrated when they are used as combination therapy with the tricyclic agents.<sup>14</sup> The dual reuptake inhibitors have recently been evaluated in randomized clinical trials.<sup>15–17</sup> A number of studies<sup>15,18</sup> have demonstrated that duloxetine is effective in treating fibromyalgia, and other medications are currently under investigation. Medications classified as anticonvulsants have substantial analgesic effects. The first medication approved by the U.S. Food and Drug Administration for the treatment of fibromyalgia is pregabalin. Both gabapentin and pregabalin have been useful for the management of pain as well as for sleep disturbances in patients with fibromyalgia.<sup>18,19</sup> Finally, with the exception of tramadol, analgesics or anti-inflammatory agents have little evidence<sup>13,20</sup> of efficacy in fibromyalgia.

From the Department of Medicine and the Department of Rheumatology, Newton-Wellesley Hospital, Newton, Mass.

Dr. Goldenberg is a consultant for Eli Lilly, Pfizer, Merck, Cypress Bioscience, and Forest.

Corresponding author and reprints: Don L. Goldenberg, M.D., 2000 Washington St., Suite 304, Newton, MA 02462 (e-mail: dgoldenb@massmed.org).

Finally, I addressed the nonpharmacologic therapy of fibromyalgia, which should include exercise, education, and cognitive-behavioral therapy. Cardiovascular fitness training has been the best studied in clinical trials<sup>21,22</sup> in fibromyalgia, and some evidence<sup>23,24</sup> suggests that strength training and techniques such as manipulation and acupuncture may have an adjunctive therapeutic role. Formal patient education enhances the impact of and compliance with exercise.<sup>22</sup> Cognitive-behavioral therapy has included group and individual therapy with a focus on the appropriate adaptation to a chronic illness.<sup>22,25</sup>

As with many chronic pain disorders, such as headaches, the spectrum of fibromyalgia ranges from mild, requiring no medical attention, to severe, with disabling widespread pain and exhaustion. Unfortunately, the progression from mild to severe symptoms is not well understood but certainly involves personal psychosocial factors. Therefore, mental health professionals must understand fibromyalgia and its related disorders and need to become more involved in the diagnosis and management of this illness.

*Drug names:* duloxetine (Cymbalta), gabapentin (Neurontin and others), pregabalin (Lyrica), tramadol (Ultram and others).

*Disclosure of off-label usage:* The author has determined that, to the best of his knowledge, duloxetine, gabapentin, and tramadol are not approved by the U.S. Food and Drug Administration for the treatment of fibromyalgia.

## REFERENCES

- Lawrence RC, Felson DT, Helmick CG, et al, for the National Arthritis Data Workgroup. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: pt 2. Arthritis Rheum 2007;58:26–35
- Wolfe F, Russell IJ, Vipraio G, et al. Serotonin levels, pain threshold, and fibromyalgia symptoms in the general population. J Rheumatol 1997;24:555–559
- Offenbaecher M, Bondy B, de Jongs S, et al. Possible association of fibromyalgia with a polymorphism in the serotonin transporter gene regulatory region. Arthritis Rheum 1999;42:2482–2488
- McCain GA, Tilbe KS. Diurnal hormone variation in fibromyalgia syndrome: a comparison with rheumatoid arthritis. J Rheumatol Suppl 1989; 19:154–157
- 5. Crofford LJ, Pillemer SR, Kalogeras KT, et al. Hypothalamic-pituitary-

adrenal axis perturbations in patients with fibromyalgia. Arthritis Rheum 1994;37:1583-1592

- Martínez-Lavín M, Hermosillo AG, Mendoza C, et al. Orthostatic sympathetic derangement in subjects with fibromyalgia. J Rheumatol 1997;24: 714–718
- Ulas UH, Unlu E, Hamamcioglu K, et al. Dysautonomia in fibromyalgia syndrome: sympathetic skin responses and RR interval analysis. Rhematol Int 2006;26:383–387
- Staud R, Rodriguez M. Mechanisms of disease: pain in fibromyalgia syndrome. Nat Clin Pract Rheumatol 2006;2:90–98
- Arnold LM, Hudson JI, Hess EV, et al. Family study of fibromyalgia. Arthritis Rheum 2004;50:944–952
- Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33:160–172
- 11. Pope HG Jr, Hudson JI. A supplemental interview for forms of "affective spectrum disorder." Int J Psychiatry Med 1991;21:205–232
- Arnold LM, Keck PE Jr, Welge JA. Antidepressant treatment of fibromyalgia: a meta-analysis and review. Psychosomatics 2000;41:104–113
- Dadabhoy D, Clauw DJ. Therapy insight: fibromyalgia: a different type of pain needing a different type of treatment. Nat Clin Pract Rheumatol 2006;2:364–372
- Cantini F, Bellandi F, Niccoli L, et al. Fluoxetine combined with cyclobenzaprine in the treatment of fibromyalgia. Minerva Med 1994;85:97–100
- Arnold LM, Lu Y, Crofford LJ, et al, for the Duloxetine Fibromyalgia Trial Group. A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. Arthritis Rheum 2004;50:2974–2984
- Arnold L. Duloxetine and other antidepressants in the treatment of patients with fibromyalgia. Pain Med 2007;8(suppl 2):S63–S74
- Vitton O, Gendreau M, Gendreau J, et al. A double-blind placebocontrolled trial of milnacipran in the treatment of fibromyalgia. Hum Psychopharmacol 2004;19(suppl 1):S27–S35
- Arnold LM, Goldenberg DL, Stanford SB, et al. Gabapentin in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled, multicenter trial. Arthritis Rheum 2007;56:1336–1344
- Crofford LJ, Rowbotham MC, Mease PJ, et al. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2005;52:1264–1273
- Goldenberg DL. Pharmacological treatment of fibromyalgia and other chronic musculoskeletal pain. Best Pract Res Clin Rheumatol 2007;21: 499–511
- Gowans SE, de Hueck A, Voss A, et al. Effect of a randomized, controlled trial of exercise on mood and physical function in individuals with fibromyalgia. Arthritis Rheum 2001;45:519–529
- Goldenberg DL, Burckhardt C, Crofford L. Management of fibromyalgia syndrome. JAMA 2004;292:2388–2395
- Busch A, Schachter CL, Peloso PM, et al. Exercise for treating fibromyalgia syndrome. Cochrane Database Syst Rev 2002;3:CD003786
- Duncan B, White A, Rahman A. Acupuncture in the treatment of fibromyalgia in tertiary care: a case series. Acupunct Med 2007;25:137–147
- Williams DA, Cary MA, Groner KH, et al. Improving physical function status in patients with fibromyalgia: a brief cognitive behavioral intervention. J Rheumatol 2002;29:1280–1286