FIBROMYALGIA -
THE CONTROVERSY CONTINUES

MEDICAL GRAND ROUNDS
THE UNIVERSITY OF TEXAS SOUTHWESTERN
MEDICAL CENTER

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In 1990, the American College of Rheumatology published criteria for the classification of fibromyalgia, a term adopted to designate a chronic syndrome characterized by widespread pain, tenderness to palpation at multiple points, and debilitating fatigue.[1] Although there is continued controversy over whether or not fibromyalgia represents a discrete condition, it is now reported to be one of the most common diagnoses in ambulatory practice.[2]

The purpose of these Grand Rounds is to review the evolution of the concept of fibromyalgia, discuss the clinical features associated with this disorder and how to differentiate it from other problems, and to summarize literature on pathophysiology and treatment.

History

The concept of tender points, that is anatomic sites of excessive tenderness on palpation, found at characteristic locations and associated with chronic pain, is generally credited to Balfour in 1824.[3] Subsequently, in 1943, Froriep of Germany coined the term *muskelschwiele* (muscle callus) to denote painful hard places in the muscle of patients with "rheumatism". Although many of these palpable areas were exquisitely sensitive to pressure, others were not.[4] Fifty years later, Strauss would report relief of the pain associated with "rheumatic muscle callus" via removal or treatment with heat and massage[4]. The importance of tender, muscular nodules in nonarticular rheumatism was emphasized by Stockman in 1904 who described their histologic appearance as "inflammatory hyperplasia of the connective tissue in patches".[4] The term "fibrositis" was introduced by Gowers shortly thereafter, although he and subsequent investigators were unable to demonstrate significant histologic abnormalities of any kind in affected muscle[4], and others questioned the existence of discrete nodules in general. In 1931, Lange reported the location of thirty-two paired points where hardening commonly occurred within muscle and which were tender to palpation, so called "tender points".[4] Subsequently, Reichart

would note that palpation of circumscribed muscular hardenings or "geloses" could also produce referred pain, and thus offered the first description in the literature of what has become known as "trigger points".[4] Over the next forty years, the literature continued to report findings of tender points and trigger points in patients with either local or generalized soft tissue pain, although in the absence of definite histologic abnormalities, the term "fibrositis" assumed a highly controversial place in the medical literature.[4-7]

Gradually, investigators began to differentiate between those patients with one or a few areas of pain and local tenderness versus those with generalized pain, other systemic symptoms, and multiple tender locations on examinations. Myofascial pain syndrome was the term popularized by Janet Travell for the former condition and the presence of one or more trigger points was considered essential to make a clinical diagnosis.[8,9]

In contrast, Moldofsky and Smythe (1975) published findings on a small group of patients felt to have a generalized "fibrositis syndrome" associated with chronic aching and stiffness, fatigue, poor work tolerance, and sleep disturbance. Areas of tenderness elicited by dolorimeter examination applied to thirteen pairs of bilaterally symmetrical soft tissue sites characterized this disorder, as did the presence of an abnormal sleep pattern on EEG.[10] Moldofsky felt that "fibrositis" was common and accounted for many of the cases previously labeled as neurasthenia, one of the most popular diagnoses of the 19th Century and felt to be a "functional nervous disorder in which the demands of civilization predisposed the patient to exhaustion of nervous system energy in a manner much akin to a battery losing its electric charge".[10] They further postulated that the sleep abnormalities they noted were the etiology of the problem and recommended a reclassification of the symptom complex from the obvious misnomer of "fibrositis syndrome" to a "nonrestorative sleep syndrome".[10] Over the next decade, several studies sought to verify and expand the clinical features of this syndrome.

Prevalence

While the prevalence of fibromyalgia is not clearly known, it appears to be a common disorder in clinic populations.[11] Accurate estimates have been hampered by the variability of diagnostic criteria, confusion with other disorders and overlap between

"primary" and "secondary" fibromyalgia. The former refers to the presence of the syndrome in the absence of a known cause or associated contributory disorder and normal laboratory and radiographic studies. "Secondary" fibromyalgia refers to an identical clinical syndrome concurrent with other disorders such as rheumatoid arthritis or osteoarthritis.[12] Table 1 summarizes several authors' figures. It is notable that the data from Campbell was obtained by requesting all patients attending the general medical and medical subspecialty clinics (excluding Rheumatology) at the Oregon Health Sciences University to complete a questionnaire as opposed to the others where the patients were being evaluated specifically for their fibromyalgic complaints.

TABLE 1. Prevalence of Fibromyalgia in Various Clinical Settings (Adapted from Wolfe[15])

Setting	Prevalence (%)
Primary fibromyalgia syndrome	
Family practice clinic	
Hartz[14]	2.1
General medicine clinic	
Campbell[16]	5.7
Rheumatology clinic	
Wolfe[11]	3.7
Yunus[12]	20.0
Secondary fibromyalgia syndrome	
Rheumatology clinic[12]	10.9

Clinical Studies

Defining specific criteria for diagnosis of a disease or syndrome is required prior to initiating any meaningful clinical study. Designing these criteria, however, is a difficult task for a disorder in which even the physical findings appear subjective.[13] Yunus developed diagnostic criteria for fibromyalgia by comparing presumed fibromyalgic patients with matched control subjects.[12,14] Fifty consecutive patients were diagnosed with fibromyalgia at the outpatient Rheumatology Clinic at the University of Illinois using criteria similar to those previously published by Moldofsky and Smythe. "All patients had symptoms of either generalized aching or stiffness, involving thirty or more areas for a minimum of three months duration, and at least four well-defined tender points" from a total of thirty-four bilaterally paired points examined. All "relevant" laboratory and radiographic studies were normal and there was no evidence of any organic systemic illness with an otherwise normal physical examination.

Tender points were defined as "areas of prominent localized tenderness elicited on firm palpation of specific anatomic sites. An area of tenderness was accepted as a tender

point only if there was evidence of verbal response to pain, ('Oh, it really hurts'), physical withdrawal of the part, expression of pain on the face, or the characteristic recoil out of proportion to the amount of pressure exerted by the examiner, i.e., the jump sign". The control subjects were 50 age, sex, and race matched healthy volunteers recruited from staff, students, or their families. The study was not blinded.

Yunus found that the age range of patients at presentation was from 14-61 years with a mean of 34 years. Age of onset ranged from 9-55 years with a mean of 29 years. Eighty-six percent were females, and all were Caucasian.

Symptoms reported by patients with a frequency significantly higher than controls are shown in Table 2.[12]

TABLE 2. Frequency (%) of Selected Symptoms in Patients with Primary Fibromyalgia and Controls (Adapted from Yunus[12])

Symptoms	Patients	Controls	P Value
Generalized Aches and Pains	98	_*	
Tiredness	92	10	< 0.001
Stiffness	64	_*	
Anxiety	70	18	< 0.001
Sleep Problem	56	12	< 0.001
Bothersome Headache	44	16	< 0.01
Irritable Bowel Syndrome	34	8	< 0.01
Subjective Swelling	32	6	< 0.01
Numbness	26	4	< 0.01

* Individuals with significant aches, pains, or stiffness were excluded from control group

On examination, he found that patients had a mean of 12 tender points versus 1.1 for controls (<0.001) (range of 4-28 for patients, 0-4 for controls). The frequency of tenderness to palpation at a specific site in a patient versus control is shown in Table 3.

Yunus concluded that fibromyalgia was a legitimate syndrome with historical and physical differences which could distinguish these patients from others. He recommended the following scheme to diagnose these patients (Table 4).

Campbell selected 22 patients with fibromyalgia from a general medical outpatient population by a screening questionnaire and subsequent examination, and compared them with age, sex, and clinic matched patients who did not meet "possible" criteria on the initial screening questionnaire.[17] Patients and controls were obtained from the total population seeking care in the clinic for any complaint, not specifically a "fibromyalgic" complaint.

Forty-two patients met initial criteria on the screening questionnaire that was completed appropriately by 596 of the 1,100 consecutive individuals requested to do so. Of these, 27 ultimately returned for further evaluation and 22 received a diagnosis of definite fibromyalgia. This study defined fibromyalgia on the basis of a positive initial questionnaire and the development of objective tenderness at dolorimeter pressures less than 4 kg/1.54 cm^2 in at least 12 of 17 "tender points" tested.

TABLE 3. Frequency (%) of Common Sites of Tender Points in 50 Patients with Fibromyalgia vs. 50 Normals (Adapted from Yunus[12])

Location of Tender Points	Present in Patient	Present in Control
Upper border of trapezius	84	16
Medial knee	74	10
Lateral elbow	62	26
Posterior iliac crest	60	10
Lumbar spine	58	0
Medial elbow	50	2
Sternocleidomastoid	46	16
Dorsal spine	42	0
Costochondral junction	32	0
Bicipital tendon	30	0
Sacroiliac joint	30	0
Cervical spine	28	2
Medial scapula	28	0
Greater trochanter of hip	24	0
Suboccipital muscle insertion	20	2

$p < 0.001$ for all differences except sternocleidomastoid ($p < 0.01$).

A dolorimeter is a spring-loaded gauge which applies a specified pressure in a range of 0-9 kg.[18] The value of 4 kg/1.54 cm^2 was chosen on the basis of the authors' prior experience with fibromyalgia patients.

Patients and controls were then subjected to further evaluation with a second questionnaire, physical examination, and psychologic testing. Examiners were blinded to the original classification of their subject, as well as to the results of each section of the three part evaluation. No fibromyalgia patient had previously received a diagnosis of fibromyalgia, and most had received no specific diagnosis.

Campbell reported that patients with fibromyalgia had a greater number of, and more sensitive tender points than did controls, but that pressure tolerance between groups did not differ over selected control or "nontender" points (Table 5). Symptomatology by virtue of inclusion definition was similar to that reported by Yunus. Patients were somewhat older, but females again predominated (71%).

TABLE 4. Yunus Criteria for Diagnosis of Primary Fibromyalgia (Adapted from Yunus[12])

I.	Necessary Criteria	
	A.	Generalized aches and pains, or stiffness involving three or more anatomic sites for at least three months
	B.	Absence of secondary cause
II.	Main Criteria	
	Presence of at least five typical and consistent tender points	
III.	Minor Criteria	
	A.	Modulation of symptoms by physical activity
	B.	Modulation of symptoms by weather
	C.	Aggravation of symptoms by anxiety or stress
	D.	Sleep disturbance
	E.	Fatigue
	G.	Chronic headache
	H.	Irritable
	I.	Subjective swelling
	J.	Paresthesias

Patients must satisfy I and II plus three (3) minor criteria. If the patient had only three tender points, then five (5) minor criteria are recommended.

Wolfe applied a 17-item symptom questionnaire modified from Campbell to 155 patients previously diagnosed as having fibromyalgia at 3 different centers each using different criteria for the original diagnosis, as well as 136 patients with a variety of rheumatic diseases and 58 normals.[19]

TABLE 5. Dolorimeter pressure required to elicit "pain" over tender and nontender points. (Adapted from Campbell[16])

	Mean Pressure ± SD (kg/1.54 cm^2)	
Location of Tender Point	Patient	Control
Occiput	2.6 ± 1.5	65 ± 22
Intertransverse	1.8 ± 1.3	51 ± 27
Trapezius	2.7 ± 1.1	69 ± 21
Paraspinous	3.4 ± 1.4	77 ± 17
Costochondral	2.3 ± 1.1	59 ± 25
Lumbar	4.7 ± 2.0	62 ± 23
Elbow	2.6 ± 1.2	84 ± 16
Gluteus	4.5 ± 1.4	82 ± 17
Knee	2.9 ± 1.3	69 ± 26
(All differences significant at $p < 0.001$)		
Location of Nontender Point		
Upper back	7.3 ± 2.3	76 ± 19
Forearm	7.3 ± 2.1	78 ± 17
Thumb	7.8 ± 2.2	81 ± 19
Shin	7.6 ± 2.3	71 ± 20
Forehead	6.5 ± 2.6	72 ± 25
(None of these differences were statistically significant)		

They reported that symptom frequency was very similar between groups of patients diagnosed at the various centers, but that this alone was insufficient to separate these patients from others with rheumatic diseases such as rheumatoid arthritis, osteoarthritis, and low back pain. Wolfe then compared the results of the tender point count at his own institution in the patients with fibromyalgia, rheumatoid arthritis, osteoarthritis, and low back pain. His results are shown in Table 6.[18] He concluded that the tender point count (not determined in a blinded fashion) was a highly effective tool in separating patients with fibromyalgia with those from other rheumatic diseases.

More recently, Goldenberg reviewed his experience with 118 fibromyalgia patients seen in the Arthritis Section of Boston University

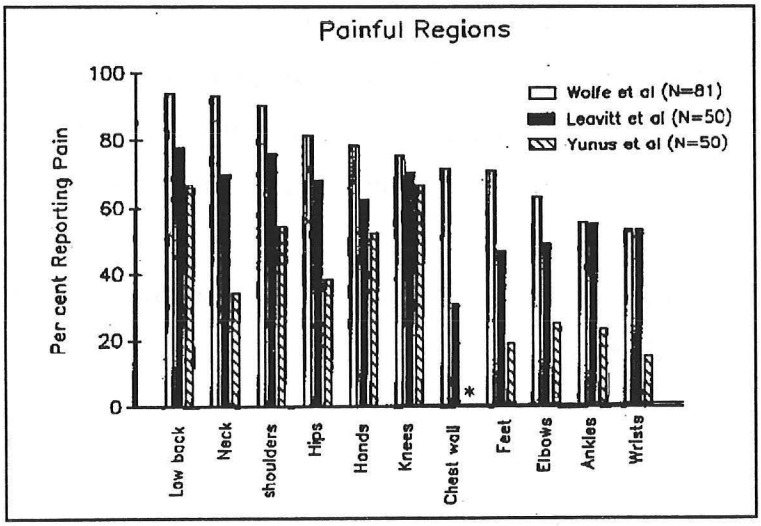
Medical Center and followed prospectively for one year. All had at least six tender points and fulfilled all major and four of six minor criteria as outlined by Yunus.[2] He reports results for symptomatology and tender count examinations comparable to those of Yunus.[20]

The aforementioned studies form the bulk of the clinical information available on fibromyalgia prior to a recently published multicenter trial. Before discussing the latter, it is appropriate to review what have been felt to be "core" features, "characteristic" features, and "associated" features of this syndrome, as well as its natural history and overlap with chronic fatigue syndrome.

Core Features

Widespread pain is generally considered to be the dominant feature of the fibromyalgia syndrome.[14] Figure 1 delineates the percentage of patients reporting pain at various sites, by various investigators. Leavitt noted that over 50% of patients reported pain in 15 of 25 areas studied and 25% reported pain in essentially all areas.[21] The most common areas of involvement are the axial skeleton, shoulders, and pelvic girdle. It is unusual for patients with fibromyalgia not to have neck or low back pain. Wolfe notes that patients frequently concentrate on one or a few areas that hurt the most, and the generalized nature of the pain complaint may be missed without specific questioning by the physician.

Figure 1. Percentage of fibromyalgia patients reporting pain in various body regions.[15]



Leavitt found that patients with fibromyalgia reported pain of equal intensity to those he studied with rheumatoid arthritis. However, pain reported by the former group was significantly more diffuse and radiating, and these patients used an average of 4.5 more

TABLE 6. **Tender point count in patients with fibromyalgia versus other rheumatologic conditions (Adapted from Wolfe[19])**

Tender point count	Fibromyalgia (% patients) n = 55	RA (% patients) n = 51	OA Knee (% patients) n = 54	Low Back Pain (% patients) n = 111
4 or >	96	22	17	23
7 or >	94	12	11	23
12 or >	54	8	2	6

words to describe their pain, suggesting a more complex pain experience. Four words that best distinguished patients with fibromyalgia from those with rheumatoid arthritis were radiating, steady, spreading, and spasms.

The second core feature is the presence of widespread tender points.[15] The latter has been considered a "gold standard" for diagnosis of the syndrome by most investigators although the minimum number and location has varied widely as has the recommended technique for quantitating "tenderness". It is noted that tender points may be unknown to the patient and located in areas outside their areas of pain complaint. They are reported to be frequently bilateral, but asymmetry is not uncommon. A variety of structures lie beneath these points (muscle, fat, tendinous insertions, ligaments, cartilage, and bone), and no reproducible abnormalities have been demonstrated on histopathologic examination of these areas. Indeed, some have questioned their validity.[23] Campbell suggested the following criteria to determine "construct validity" in the absence of histopathologic abnormalities.

(1) Tender points need to be present when fibromyalgia symptoms are present and absent if symptoms are absent.

(2) They need to allow distinction between patients with fibromyalgia and normals.

(3) They need to allow distinction between patients with fibromyalgia and other rheumatic diseases.

(4) Changes in symptoms need to correlate with changes in number and severity of tender points.

(5) **The measurement of tender points should be reliable from one observer to another and from one time to another if all other conditions are stable.[23]**

The clinical studies previously reported by Yunus, Wolfe, and Goldenberg all utilized specific anatomic regions as previously described by Smythe to palpate for tenderness in patients with fibromyalgia.[24] Goldenberg did not evaluate a control group. Wolfe compared current patients with fibromyalgia and rheumatoid arthritis with retrospective data on patients with low back pain and osteoarthritis. Yunus compared patients with fibromyalgia and matched normal subjects. No study was blinded, and only Yunus defined the term "tenderness to palpation". All described severe tenderness at many sites in

TABLE 7: Percentage of patients with a specific tender point present (Adapted from Goldenberg[20])

Tender Point	Goldenberg[20] (N=118)	Yunus[12] (N=50)
Midpoint, upper trapezius	90	84
Medial fat pad knee	90	74
Distal to lateral epicondyle	86	62
Middle to upper outer quadrant of buttock	65	60
Midpoint, sternocleidomastoid muscle	65	46
Distal to medial epicondyle	57	50
Second costochondral junction	42	32

patients with fibromyalgia versus controls, although only Yunus reported this to be statistically significant. Table 7 demonstrates the percentage of patients in whom a specific area was tender from the two studies in which it was reported.

The study by Campbell of 22 patients with fibromyalgia and 22 controls differed in that (1) no patient carried a prior diagnosis of fibromyalgia, (2) control patients had a variety of medical problems and had high incidence of musculoskeletal complaints (41%), (3) a dolorimeter was used to assess tenderness, (4) tender point locations were loosely defined - i.e. "lumbar" or "knee", (5) control points were studied in both groups, and (6) the study was blinded. They reported a significant difference in tenderness between controls and patients at the "tender points" but no difference at "control points".[17]

Other literature relevant to the validity of the tender point concept has also been published. Wolfe performed tender point examination at sites previously designated by Smythe in 1,520 consecutive patients with various rheumatic diseases. The mean tender point count was 2.1 with 4 or more tender points found in 22.9%, 7 or more in 13.6%, 12 or more in 4.3%. 60.1% had no tender points. The tender point count increased gradually with age, women had more tender points than men, and Caucasians more than blacks or Hispanics. A rheumatologic history was obtained during a structured interview at each visit. The correlation between tender points and clinical variables typically associated with fibromyalgia, however, was poor (≤ 0.26 for all but neck pain, 0.34).[25]

Simms studied tenderness at 75 unilateral anatomic locations in 10 fibromyalgia patients and 10 normal control subjects to determine which sites best identified patients with fibromyalgia.[18] In this nonblinded study which utilized a dolorimeter, the mean amount of pressure required to elicit tenderness was significantly lower in patients than in controls at 19 sites ($p < .001$). Of previously proposed tender points, however, only 2 were included in the 19. While some points were excluded on the basis of the p value chosen ($p < .001$ vs .05) it is interesting to examine their data in detail. Fibromyalgia patients experienced pain at lower pressures than controls at almost all of the 75 sites. Of 5 control sites previously evaluated by Campbell, one fell into the tender point range for both patients and controls and 2 approached this range for the fibromyalgia patients. Control patients had mean values diagnostic of fibromyalgia at 4 of 23 previously proposed tender points and the p value between patients and controls was > 0.12 at 5 of these points.

Scudds used a variable pressure dolorimeter to evaluate patient responsiveness, using threshold and tolerance measures at a nontender point on the arm of patients with fibromyalgia, matched patients with rheumatoid arthritis and normal controls (not blinded).[26] He also conducted similar tests with a pressure algometer and with constant current pulse trains to test the generality of the predictions to time varying pressure pain and pain produced by direct activation of afferent nerves. Patients with fibromyalgia had lower pain threshold and pain tolerance than controls for all 3 forms of nociceptive stimulation and values for the rheumatoid arthritis group were intermediate. The data

were variable, however, and reached significance only for the variable pressure dolorimeter.

Tunks evaluated 10 patients with fibromyalgia (satisfying Yunus criteria) and 10 normal controls with a pressure algometer to establish inter-rater and test-retest reliability at tender points.[27] There was significantly lower tenderness thresholds of tender points in fibromyalgia compared to normals and inter-rater and test-retest reliability were high (0.85). A further 10 normals and 10 fibromyalgia subjects were then examined for 5 paired tender points and 5 paired nontender points. There was an even larger difference between fibromyalgia and normal subjects observed on nontender points. They postulated a generalized lowering of the tenderness threshold to explain these results. Similar results were reported by Bloch et al. in abstract form.[28] In addition, symptomatology did not correlate with the number of tender points, but did correlate with lower general pressure point pain tolerance.

Additional information regarding tender points can be obtained from studies evaluating various therapeutic modalities. Goldenberg reported that treatment with 25 mg of amitriptyline resulted in significant short term improvement in all outcome parameters, including tender point score.[29] Scudds reported similar results as well as a generalized improvement in pain threshold levels.[30] Carette reported that patients receiving 75 mg of amitriptyline at bedtime noted significant short term improvement in stiffness and pain analog scores but minimal change on tender point evaluation.[31]

TABLE 8: Percentage of patients with fibromyalgia reporting modulating factors on symptoms (Adapted from Yunus[15])

Factors that worsen symptoms	%	Factors that relieve symptoms	%
Cold or humid weather	92	Hot shower	92
Fatigue	78	Being active	92
Sedentary state	78	Warm, dry weather	80
Anxiety	68	Massage	64
Overactivity	62		

Finally, each of the four major investigators in this field have published their views on tender points. Wolfe noted that in clinical practice patients with "all-over" tenderness

were "often encountered" and constitute a subgroup within the construct of fibromyalgia. He recommended that at the present time they should be thought of as having fibromyalgia. Conversely, Yunus noted that "some patients have typical fibromyalgia symptoms, including diffuse aching at many sites, but no tender points. In our opinion, there is no reason that these patients cannot be diagnosed as having fibromyalgia for patient management purposes."[32] Goldenberg and Campbell limit the designation "fibromyalgia syndrome" to only include those patients with demonstratable tender points.

Characteristic features

Wolfe notes that these features are present in more than 75% of patients.[15]

(1) Sleep abnormality - Although specific EEG abnormalities have been reported, clinically this refers to a "non-restorative" sleep pattern, where a patient awakens feeling tired or unrefreshed. There may, however, be no difficulty getting to sleep or staying asleep.[33]

(2) Fatigue - This can be a major or a minor complaint and depending on the definition, is present in 55-100% of patients. 55% of patients report they are too fatigued "to do what they want".[15,34]

(3) Morning stiffness - This is reported in 75-91% of patients in various series.[15] Wolfe found a mean duration of 2.4 hours, a value approaching that in rheumatoid arthritis (3.3 hours).[34]

(4) Modulating factors - Yunus noted the presence of one or more modulating factors in all patients and 5 or more in 90%.[12] Table 8 summarizes his findings. Wolfe states that the prevalence of such factors in these patients is approximately equal to that in patients with other rheumatic conditions, but not in normals.[15]

Associated Features

These features have been reported in more than 25% of patients.[15]

(1) Subjective swelling - 32% of patients evaluated by Yunus reported swelling in a periarticular location or diffusely in the fingers.[12] Campbell noted no

difference between patients with fibromyalgia and control subjects, 41% of whom had chronic musculoskeletal symptoms. Objective swelling on examination is not a feature of this syndrome.

(2) Neurovascular symptoms and signs - Symptoms such as coldness, numbness, paresthesias, mottled skin, and reticular skin pattern are common. Numbness was reported by 26% of patients in the Yunus series[12]. Wolfe noted that 27% of patients reported cold hands and 21% reported mottling[34]. Symptoms suggestive of Raynaud's syndrome have been reported in 9 to 38% of patients and may reflect the definition of Raynaud's used in the various studies. All authors report that virtually none of the patients with a Raynaud's-like phenomena go on to develop other manifestations of systemic connective disease.[15,34,35]

Reactive hyperemia is a phenomenon in which an area that has been palpated becomes hyperemic.[34] Yunus reported that marked cutaneous erythema following pressure over tender points was observed in patients with fibromyalgia or rheumatoid arthritis significantly more frequently than controls.[12] Wolfe notes that this phenomena occurs frequently in patients with fibromyalgia but can also be found in many patients with other rheumatic diseases.[34] Littlejohn et al. compared 13 patients with fibromyalgia to 14 normal controls in a nonblinded study and found a significantly reduced threshold for both mechanically and chemically induced flare responses[36].

(3) Headaches - Headaches were reported by over 40% of patients in the Yunus series, equally divided between migraine and nonmigrainous headache.[12] Campbell noted headaches in 55% of patients versus 9% of controls.[17] Wolfe reported severe headaches in 52%, roughly half of these being migraines.[34]

(4) Irritable bowel syndrome - Irritable bowel syndrome was diagnosed in 34% of patients reported by Yunus vs 8% of controls and 50% of patients reported by Campbell vs 5% in controls. Wolfe reported 46% of patients describing abdominal pain and 36% labeled with a diagnosis of "bowel problems".

(5) Psychologic abnormalities - A more extensive discussion of the psychologic status of patients with fibromyalgia will follow shortly in the pathophysiology section. Smythe, however, described a "fibrositic personality" with patients being demanding and perfectionistic.[24] Other investigators have noted a spectrum of abnormalities ranging from anxiety to depression.[12,15,34] Yunus found a significant association between those patients who were depressed or anxious and the presence of associated functional complaints such as headaches or irritable bowel syndrome.[20] Others have reported that the majority of these patients are psychologically normal.

Natural History

Although individual symptoms may improve with treatment, the syndrome is usually chronic. Hawley evaluated 75 patients with fibromyalgia at monthly intervals for 1 year and found minimal change in sleep disturbance, pain or functional status.[34] Felson used telephone interviews to follow 39 consecutive patients with fibromyalgia over a 2 year period. More than 60% of patients had moderate to severe continuing symptoms, and almost all took medications regularly to control symptoms. Those taking medication did not differ from other patients with respect to global symptoms or pain.[37] Wolfe evaluated 81 patients in 1985. Only 23% reported having a complete remission of symptoms (no pain or aching for at least 2 months) during a mean disease duration of 12.7 years. The mean length of remission was 34 months. Wolfe noted that repeat remissions were reported by 5% and the longest remission lasted 20 years.[34]

Functional Ability and Socioeconomic Impact

Cathey tested patients with fibromyalgia and rheumatoid arthritis for ability to do standardized work tasks. Neither group was able to perform more than 60% of the work done by controls. The Standford Heath Assessment Questionnaire was found to be the best predictor for work ability in both groups and suggests that self-assessed disability parallels ability to perform.[34,38] While days lost from work were in excess of those reported by the National Center of Health Statistics for that year (9.8 vs 5.2) they were comparable to

figures for patients with osteoarthritis, but less than those for low back pain patients. 30% reported changing jobs because of their disability and 10% actually quit working.

Association with Chronic Fatigue Syndrome

Goldenberg addressed the similar clinical and demographic features of fibromyalgia and chronic fatigue syndrome (CFS) in several papers.[39-42] They first evaluated the clinical similarity by giving a questionnaire used in patients with CFS to 50 consecutive unselected patients with fibromyalgia. Chronic fatigue and myalgias, as predicted, were present in almost all patients from both groups. They also found, however, that symptoms considered typical of CFS were also common in fibromyalgia, including recurrent pharyngitis (54%), chronic cough (40%), recurrent adenopathy (33%) and recurrent low grade fever (28%). 55% of the fibromyalgia patients felt that their fibromyalgia symptoms had followed a viral illness; antibody titers to Epstein-Barr virus were not significantly different from controls.

Subsequently, they administered a standardized history questionnaire used for possible patients with fibromyalgia and performed a tender point examination on 27 patients with debilitating fatigue of at least 6 months duration seen in a primary care practice, as well as on 20 patients with fibromyalgia. 16 of 27 patients with chronic fatigue met full criteria for CFS. Eight patients with chronic fatigue denied significant musculoskeletal pain and had tender point scores similar to 10 normal controls. 19 patients (70%) had persistent, diffuse musculoskeletal pain and the results of their tender point examinations were similar to those of patients with fibromyalgia.

The American College of Rheumatology
1990 Criteria for the Classification of Fibromyalgia[1]

It becomes clear upon review of the literature to 1990 that the term "fibromyalgia" has been used to designate a group of patients with a chronic generalized pain complaint that is poorly understood. Because pain, by definition, is a subjective complaint, and the only physical abnormality in these patients is the presence of tender points, also subjectively determined, many have questioned whether fibromyalgia is a discrete condition, and if so, how it should be diagnosed.

Prior studies had generally not been blinded and frequently the definitions for historical features and assessment of tender points were imprecise. Moreover, it was felt that prior criteria for diagnosis were circular, that is to say that the criteria confirmed the definition of fibromyalgia that was held by the investigators who developed them, a confirmation likely assisted by the unblinded status.[1]

TABLE 8a Scoring system utilized for grading the severity of tender points in the American College of Rheumatology study.[1]

Grade	Complaint
0	No pain
1	Complaint of pain without grimace, flinch, or withdrawal
2	Pain plus grimace or flinch
3	Pain plus marked flinch or withdrawal
4	Patient "untouchable", withdraws without palpation

A grimace was a "facial expression".
A flinch was defined as a "slight body movement".
A marked flinch was defined as an "exagerated body movement".
Withdrawal was defined as "moving the body part away".

Because of this, in 1986 a multicenter criteria committee interested in the fibromyalgia syndrome began a study to develop criteria for the classification of this disorder. 558 consecutive patients were studied at 16 centers: 293 patients diagnosed with fibromyalgia according to the usual criteria at their center and 265 controls. Controls for the group with primary fibromyalgia were matched for age and sex and limited to those with disorders that could be confused with primary fibromyalgia. Control patients for the group with secondary fibromyalgia were matched for age, sex, and concomitant rheumatic disorders.

Interviews and examinations were performed by trained, blinded assessors and well-defined scales were used to quantitate symptoms including pain. Dolorimetry was performed at six "active" sites and three "control" sites. Twelve pairs of typical "tender points" were also examined by palpation. The scoring system used for grading the severity of tender points is shown in Table 8A.

The difference in pain complaints and symptoms for patients and controls is summarized in Table 8B. Dolorimetry and tender point scores are shown in Table 8C. Highly significant differences were reported for most of the symptoms previously reviewed in these Grand Rounds. The investigators also reported that tender points were the most powerful discriminator between fibromyalgia patients and controls. A combination of

TABLE 8b **Pain complaints and symptoms for primary and secondary-concomitant fibromyalgia patients and their control patients (Adapted from Wolfe[1]) ***

Variable	Patients	Controls	P
Primary fibromyalgia			
No. of patients	158	135	—
Pain complaints			
15+ painful regions	59.5	13.3	< 0.001
Widespread pain	97.5	71.1	< 0.001
Symptoms			
General symptoms			
Sleep disturbance	75.6	31.1	< 0.001
Fatigue	78.2	38.1	< 0.001
Morning stiffness	76.2	59.3	< 0.001
Other symptoms			
Paresthesias	67.1	32.3	< 0.001
Anxiety	44.9	21.6	< 0.001
Headache	54.3	30.5	< 0.001
Irritable bowel	35.7	13.3	< 0.001
Interpretive symptoms			
"Pain all over"	68.8	21.7	< 0.001
Secondary-concomitant fibromyalgia			
No. of patients	135	130	—
Pain complaints			
15+ painful regions	51.1	12.3	< 0.001
Widespread pain	97.8	66.9	< 0.001
Symptoms			
General symptoms			
Sleep disturbance	73.3	22.7	< 0.001
Fatigue	85.2	40.3	< 0.001
Morning stiffness	78.0	55.1	< 0.001
Other symptoms			
Paresthesias	57.9	38.5	< 0.001
Anxiety	51.1	21.5	< 0.001
Headache	51.1	24.2	< 0.001
Irritable bowel	22.4	11.6	< 0.001
Interpretive symptoms			
"Pain all over"	64.8	16.3	< 0.001

* Values are the precentage of patients with the pain complaint or symptoms.

widespread pain complaint and mild or greater tenderness in ≥ eleven of eighteen tender point sites yielded a "sensitivity" of 88.4%, a "specificity" of 81.1%, and an "accuracy" of 84.2%.

What conclusions then can be drawn from this study?

(1) Review of the dolorimetery data for patients and controls demonstrates that there is a significant difference not only over proposed "tender points" but also over "control" sites. Controls as well as patients are more tender over tender points than other sites. This suggests that tender points are areas of increased sensitivity in normals and that fibromyalgia patients rather than having unique tender points have a reduced threshold for pressure pain. A potential confounding factor, however, is that at least half of these patients carried a prior diagnosis of fibromyalgia and it is possible, even likely, that

TABLE 8c. **Dolorimetry and tender point scores for patients with primary and secondary fibromyalgia syndrome, as well as their age- and sex matched control patients* (Adapted from Wolfe[2])**

	Patients	Controls	p
Primary fibromyalgia			
No. of patients	158	135	< 0.001
Dolorimetry scores			
Active sites (0-6.5 scale)	3.5 (0.10)	4.9 (0.12)	< 0.001
Control sites (0-6.5 scale)	5.1 (0.11)	5.7 (0.11)	< 0.001
Tender point palpation scores and counts			
Average tenderness (0-4 scale)	1.6 (0.05)	0.6 (0.06)	< 0.001
Mild or greater (0-24 sites)	20.0 (0.34)	8.3 (0.64)	< 0.001
Moderate or greater (0-24 sites)	13.0 (0.54)	4.0 (0.54)	< 0.001
Severe (0-24 sites)	5.2 (0.47)	1.4 (0.27)	< 0.001
Skinfold tenderness	65.1	17.6	< 0.001
Secondary-concomitant fibromyalgia			
No. of patients	135	130	< 0.001
Dolorimetry scores			
Active sites (0-6.5 scale)	3.4 (0.11)	4.9 (0.12)	< 0.001
Control sites (0-6.5 scale)	5.0 (0.12)	5.8 (0.96)	< 0.001
Tender point palpation scores and counts			
Average tenderness (0-4 scale)	1.5 (0.06)	0.5 (0.05)	< 0.001
Mild or greater (0-24 sites)	19.3 (0.38)	7.7 (0.61)	< 0.001
Moderate or greater (0-24 sites)	12.0 (0.61)	3.1 (0.45)	< 0.001
Severe (0-24 sites)	4.7 (0.45)	1.1 (0.22)	< 0.001
Skinfold tenderness	54.8	15.7	< 0.001

* Values are the mean (SEM) except for skinfold tenderness, which is the percentage positive.

"education" about their problem could alter test responses.

(2) The predictive ability of these criteria alone, including tender point count, to "diagnose" a discrete syndrome, i.e. fibromyalgia, and exclude other disease states is low. The positive predictive value of these recommended criteria in this population (i.e. 50% of patients were felt to have the syndrome in question) was 84%. Since predictive value depends heavily on disease prevalence, however, it falls dramatically as prevalence falls. Thus, in an average rheumatologists' office where maybe 10% of patients are likely to have this problem, the positive predictive value of these criteria alone is 23%.

(3) Finally, it is clear from the sensitivity data that are reported for dolorimetry and tender point counts alone that there are a number of patients with chronic pain and other systemic complaints virtually indistinguishable from patients with fibromyalgia that do not have "diagnostic" tender point examinations. It may well be reasonable in the

clinical setting to treat these patients, as Yunus does for "fibromyalgia", a term that does in fact accurately describe their complaint.

Pathophysiology

A variety of factors have been suggested to be of potential etiologic significance in this syndrome. Four major lines of investigation have been pursued extensively.

(1) Primary Muscle Abnormalities - Kalyan-Raman published muscle biopsy findings in 12 patients diagnosed with fibromyalgia according to the Yunus criteria. Specimens were taken from a prominent tender point at the upper medial portion of the trapezius in all 12 patients. Light microscopic findings consisted of mild nonspecific abnormalities in 9 of 12 cases. None demonstrated inflammatory changes, including edema or inflammatory cells.[43,44]

Bengtsson compared 77 muscle biopsies from 57 patients with fibromyalgia (diagnosed according to the Yunus criteria) to 17 biopsies from 9 healthy controls. The study was not blinded. 42 biopsies from patients were deemed normal or borderline; while 35 were said to show discrete pathologic changes (denervation, regeneration, inflammatory infiltrates, ragged red fibers, and "moth-eaten" fibers). Biopsies from controls were normal or borderline in 14 and showed mild abnormalities in 3. The frequency of type I and type II fibers, as well as capillary density was the same between groups. Bengtsson concluded that these changes, while not sufficient to constitute a diagnostic test for fibromyalgia, indicated that this condition has an organic basis.[45,46]

Bartels and Danneskiold-Samoe compared quadriceps muscle biopsy findings from a nonblinded study of 7 healthy controls and 13 patients with fibromyalgia. They reported that muscle fibers from the fibromyalgia patients had distinctive rubber band-like structures around the diameter at varying intervals, producing constriction at these sites which was likely to cause pain. These findings have not been reproduced to date.[47]

Yunus reported the results of a controlled and blinded electron microscopic study of muscle biopsies in fibromyalgia syndrome. They found that mild EM changes were frequent in the trapezius muscles of both fibromyalgia patients and controls with no significant difference between the two groups, and they speculated that various mechanical

and psychologic stresses of daily life caused these abnormalities. They also stressed the importance of controlled and blinded observations since it is likely that many of the reported "abnormalities" found in fibromyalgia patients were spurious.[48]

Since a feeling of muscle tension is commonly reported by patients with fibromyalgia, it was a commonly held belief that much of the pain in fibromyalgia was caused by increased muscle tension. Surprisingly, however, surface electrodes over muscles self-described as tense and painful showed no evidence of muscle activity.[46] EMG demonstrated no significant difference between 22 fibromyalgia patients and 9 healthy controls.[49]

Decreased muscle tissue oxygen pressure and reduced high-energy phosphate levels have been noted in nonblinded studies of patients with fibromyalgia when compared with controls.[50,51] Bengtsson has proposed that these abnormalities reflect relative tissue hypoxia from decreased circulation.[46,50,51] Kemp, however, was unable to demonstrate a statistically significant difference at rest between the muscle blood flow in the trapezius muscle of 12 fibromyalgia patients and 12 healthy controls.[52] Recently, Bennett compared exercising blood flow (estimated by ^{133}xenon clearance) between 16 patients with fibromyalgia and 16 matched sedentary controls, and found significantly lower values for the former group. They emphasized, however, that differences in blood flow, oxygen pressure, and high-energy phosphate levels may well represent a peripheral detraining effect in fibromyalgia patients secondary to disuse of specific muscles that cause pain.[53]

(2) <u>Immunologic Abnormalities</u> - In 1984, Caro reported the presence of a reticular skin discoloration in 16 of 25 patients with fibromyalgia. 19 of 25 had a band-like, granular deposition of IgG at the dermal-epidermal junction.[54] A subsequent controlled and blinded study performed at several centers revealed an incidence of 53% for the latter finding, a significant difference from controls[55]; although Dinerman reported this to be present in only 11% of patients prospectively evaluated, a value lower than that for controls in the previous study.[56] McBroom was unable to identify IgG at the dermal-epidermal junction of patients with fibromyalgia, but reported IgM in blood vessels of the superficial dermis.[57]

Dinerman prospectively evaluated 118 patients with fibromyalgia to evaluate the prevalence of Raynaud's phenomenon, sicca symptoms, ANA, and low complement levels.

They reported a history of Raynaud's in 30% and sicca symptoms in 18% and noted that patients with the latter abnormalities were more likely to have positive ANA's.[56]

Jacobsen screened for autoantibodies in patients with fibromyalgia and matched normal controls, and reported that 55% of patients had low titer anti-smooth muscle antibodies and 40% had anti-striated muscle antibodies. Bengtsson, however, reported that there was no difference in the incidence of positive antibodies between 223 patients with fibromyalgia and 255 random blood donors.

As Powers has noted, anecdotal evidence for an immunoregulatory defect includes the report of induction of a fibromyalgia-like syndrome following treatment with interleukin-2 and reports of the presence of abnormal T-cell populations in some patients.[14] The evidence that fibromyalgia represents a form of collagen vascular disease, however, is weak and patients with symptoms, signs, or laboratory abnormalities suggesting a collagen-vascular problem likely represent patients with as yet undiagnosed collagen vascular disease.

(3) <u>Sleep Abnormalities</u> - Hauri and Hawkins (1973) first reported anomalous alpha interference in the delta EEG activity of non-REM sleep of nine psychiatric patients with somatic malaise and fatigue. Subsequently, Moldofsky and Smythe reported ten patients with fibromyalgia that had evidence of alpha-delta sleep. Moreover, when six normal volunteers were deprived of stage 4 sleep, they developed temporary musculoskeletal and mood symptoms comparable to those seen in the patients with fibromyalgia.[60] Subsequent studies found that the latter group also developed significant tenderness when examined with a dolorimeter at typical tender point sites. It is notable, however, that neither these nor subsequent studies have been blinded.[61]

Moldofsky went on to advance a hypothesis that the etiology of fibromyalgia was in fact a recurrent non-restorative sleep abnormality and speculated that this might result from a disorder of serotonin metabolism. To test this hypothesis he treated seven patients with L-tryptophan and eight patients with chlorpromazine, both of which had been reported to improve non-REM sleep. Patients treated with chlorpromazine reported improved sleep and decreased musculoskeletal symptomatology, those treated with L-tryptophan did not.[62,63]

Subsequent studies by Moldofsky have centered on exploring the prevalence of alpha-sleep intrusion in the non-REM sleep of patients with other disorders. He has reported that patients with rheumatoid arthritis experiencing a "flare" and patients with nocturnal myoclonus and fibromyalgic complaints both exhibit this sleep anomaly.[64,65] Conversely, normal subjects who were "physically fit" did not experience musculoskeletal symptomatology despite experimental stage 4 sleep deprivation.

While all investigators agree that non-restorative sleep is a common historical complaint of patients with the fibromyalgia syndrome, documented sleep abnormalities have not been reproduced by others. Horne and Shackell reported no significant difference in the percentage of alpha-like activity in sleep stages 2, 3 or 4 between eleven patients with fibromyalgia and fifteen symptom-free controls.[67] Golden found that only one patient out of thirteen satisfying the Yunus criteria for fibromyalgia demonstrated alpha-delta sleep.[68]

(4) Psychologic Abnormalities - Fibromyalgia has been considered by many to be a psychiatric order. This is not surprising given that patients with fibromyalgia appear healthy and have normal laboratory tests. Moreover, diagnosis relies on the use of "subjective" examination skills. In addition, symptoms of fibromyalgia such as fatigue and sleep disturbance occur in depression and other psychiatric disease states.[69]

Some have felt that fibromyalgia represents a manifestation of psychogenic rheumatism, however, the latter is characterized by bizarre, fluctuating musculoskeletal complaints that are frequently associated with obvious psychopathology.[69]

Goldenberg recently reviewed the studies reported since 1982 that have applied a variety of psychologic and psychiatric techniques to the evaluation of patients with fibromyalgia. As noted by Power, most studies have had significant methodologic flaws frequently utilizing tests that rely on positive responses to somatic complaints, pain, anxiety, and sleep disturbance despite a potential medical or "organic" basis for these complaints. Furthermore, most studies have selected very different patient and control groups.[69] Patients with nonpainful medical conditions, hospitalized patients, and patients with chronic pain syndromes have an increased incidence of psychiatric disorders in general.[70,71] Many studies also do not specify how the patients with fibromyalgia were selected to participate. Table 9 adapted from Powers, summarizes the relevant literature to date on this subject.[14]

TABLE 9: Psychologic Abnormalities in Fibromyalgia (FM) (Adapted from Powers)[14]

Study	Subjects	Controls	Tests	Results
Payne et al. (1982)[72]	30 FM (hospitalized)	30 RA 30 "arthritis" (hospitalized)	Minnesota Multiphasic Personality Inventory (MMPI)	FM:RA Higher on six scales, but only hypochondriasis and hysteria in the pathologic range.
Ahles et al. (1984)[70]	45 FM (ambulatory)	30 RA (ambulatory) 32 normals (hospitalized)	MMPI Life Events Inventory Assertive-Aggressiveness Inventory	FM:RA Higher scores for hypochondriasis, hysteria, psychasthenia, schizophrenia. Subgrouping according to scores showed: FM: 31% psychologically disturbed; 33% typical chronic pain profile; 36% normal. FM:RA Higher scores. FM:RA No difference.
Wolfe et al. (1984)[73]	46 FM 32 FM/RA (ambulatory)	76 RA (ambulatory)	MMPI	FM:RA Higher on five scales, but especially hypochondriasis and hysteria.
Clark et al. (1985)[74]	22 FM (ambulatory)	22 controls, 44% with "pain" (ambulatory)	Beck Depression Inventory Spielberger State and Trait Anxiety Inventory SCL-90-R	No difference. No difference. No difference.
Hudson et al. (1985)[75]	31 FM (ambulatory)	14 RA (ambulatory) 41 relatives (ambulatory)	National Institute of Mental Health-Diagnostic Interview Schedule (NIMH-DIS) 21-Item Hamilton Rating Scale for Depression	FM:RA Higher rates for major affective and anxiety disorders. Current diagnosis of major depression for 26% FM. Depression preceded diagnosis for 64% FM.
Ahles et al. (1986)[76]	45 FM (ambulatory	30 RA 32 normal controls (ambulatory)	Revised earlier data using contemporary MMPI Norms	Subgrouping according to scores showed: FM: 17.8% psychologically disturbed; 33.3% typical chronic pain profile; 48.9% normal.
Goldenberg (1986)[77]	82 FM (ambulatory)	14 RA 41 relatives (ambulatory)	NIMH-DIS	FM:RA Higher rate of major depression and anxiety.
Ahles et al. (1987)[78]	45 FM	29 RA 31 normal controls (ambulatory)	Zung Self-Rating Depression Scale	FM:RA No difference.
Kirmayer et al. (1988)[79]	20 FM	23 RA (ambulatory)	NIMH-DIS Center for Epidemiologic Studies Depression Scale Symptom Checklist-90-revised (SCL-90-R)	FM:RA No difference in current or past depression. FM:RA More somatic symptoms.
Uveges et al (1990)[80]	25 FM	22 RA (ambulatory)	SCL-90-R Visual Analog Scale McGill Pain Questionnaire Arthritis Impact Measurement Scale (AIMS) Hassles Scale Ways of Coping-Revised Sleep Questions	FM:RA Greater psychological distress on six subscales. FM:RA Higher levels of pain. FM:RA Higher levels of pain. FM:RA Higher pain and psychologic status scores. FM:RA Greater life stress. FM:RA No difference. FM:RA Greater sleep disturbance.
Dailey et al. (1990)[81]	28 FM	28 RA 28 normal controls (ambulatory)	Life Experience Survey Hassles Scale Inventory of Socially Supportive Behaviors AIMS	FM:RA Lower major life stress. FM:RA Higher levels of daily stress. FM:RA No difference. FM:RA No difference.

Payne, Ahles, and Wolfe utilized the Minnesota Multiphasic Personality Inventory (MMPI) and reported significantly higher rates of depression, hysteria, and hypochondriasis in patients with fibromyalgia compared with normal controls and patients with rheumatoid arthritis.[70,72,73] Ahles reported 31% of fibromyalgia patients to be psychologically disturbed, 33% to have a typical chronic pain profile, and 36% as normal.[72] A later study evaluated the same patient data using "contemporary" MMPI norms and found close to 50% of the fibromyalgia patients to be psychologically normal.[76] Wolfe reported that only 28% of patients with fibromyalgia were normal compared with 51% of rheumatoid arthritis controls.

Clark utilized three psychological tests, the SCL-90-R which is a multidimensional psychologic symptom inventory, the Speilburger State and Trait Anxiety Inventory and the Beck Depression Inventory to compare newly diagnosed outpatients with fibromyalgia (not under subspecialty care) with controls who did not meet criteria for fibromyalgia, although 41% had moderate or severe pain. Clark reported no significant difference between groups on any of the tests. This study is the only one to uniformly utilize patients with a new diagnosis of fibromyalgia who were not yet seeing a rheumatologist, avoiding potential confounding factors associated with chronic utilization of health care.[74]

Hudson gave thirty-one patients with fibromyalgia and fourteen patients with rheumatoid arthritis the Diagnostic Interview schedule, which generates current and past diagnoses according to DSM-II criteria. 71% of the fibromyalgia patients compared with 13% of the patients with rheumatoid arthritis and 12% of a normal control group had a lifetime history of major depression. Major depression was present currently in only 26% of the fibromyalgia patients and the onset of the major depression preceded the first symptoms of fibromyalgia in 64%, often by five to ten years. The morbid risk for major depression in first-degree relatives and the percentage of probands with a positive family history of major depression were both significantly greater in fibromyalgia patients. This study was extended to an additional eighty-two patients with similar results, and represents the only data to demonstrate an association of fibromyalgia and depression according to diagnostic criteria.[75] Ahles administered the Zung Self-Rating Depression (SDS) Scale to forty-five fibromyalgia patients, twenty-nine with rheumatoid arthritis, and thirty-one

healthy controls. The mean SDS scores were significantly higher than controls in both fibromyalgia and rheumatoid arthritis patients but did not differ from each other.[78]

Most recently Kirmayer applied the Diagnostic Interview schedule to the three groups of patients described above. While no significant differences were found, the trends were similar.[79]

Other have evaluated the correlation between "stress" and fibromyalgia. Dailey reported that patients with fibromyalgia showed higher levels of stress as measured by daily "hassles" than did patients with rheumatoid arthritis.[81] Similar results were reported by Uveges.[80]

While the role of psychologic factors in fibromyalgia syndrome is at present incompletely defined and there are potentially significant methodologic flaws in virtually every study, it appears the majority of patients do not meet criteria for any of the major recognized psychiatric disorders.

Alterations in Sensitivity to Pain

Results of studies by Scudds[26], Tunks[27], and Bloch[28], previously cited in these Ground Rounds, suggest that a reduction in pain threshold may be important in patients with fibromyalgia, although all 3 studies were flawed; none were blinded and patient numbers were small. Nevertheless, it is intriguing to speculate that such patients may have a peripheral or central abnormality leading to altered pain perception.

Management of Fibromyalgia

Yunus has stressed that management of the patient with fibromyalgia begins with the initial interaction between physician and patient. A physician may have a negative attitude toward a patient who starts "complaining a lot", especially when physical examination and laboratory studies are largely unrevealing. Many of these patients have had their symptoms dismissed by other physicians and others carry an incorrect diagnosis.[86] Yunus notes that successful treatment requires that the physician understand that the patient's pain is "real". The disability caused by, and the socioeconomic impact of, fibromyalgia are substantial and handling of such a patient in a noncaring manner may

contribute to disability, "doctor shopping", and inflated health care costs.[86]

It is clearly important to exclude other disorders that may be confused with fibromyalgia. The differential diagnosis includes early or mild rheumatoid arthritis, osteoarthritis, polymyalgia rheumatica, systemic lupus erythematosus, ankylosing spondylitis and hypothyroidism. Once these have been excluded on the basis of pertinent negative historical, physical examination, and laboratory findings, it is important that the physician communicate clearly that the patient does not have these other problems and that fibromyalgia is a relatively common, nonprogressive disorder whose etiology is at present unknown.

Patient education is an integral part of management. Important contributing factors in fibromyalgia recognized by several investigators include poor sleep, overwork, trauma, anxiety, stress, lack of physical conditioning, and obesity. The relative importance of each of these in an individual needs to be determined by the physician and lifestyle modification recommended.

Whereas immediate referral to a psychologist or psychiatrist is likely to result in dismissal of the physician by the patient, issues of anxiety, stress, and depression can be approached in the primary physician's office and over time additional counseling may be accepted. Reputable pain clinics offer a multidimensional approach to the treatment of such patients and can be an invaluable aid to the primary care giver.[86] Behavior changes are central and crucial to successful therapy. These changes begin with the patient's acceptance of chronic pain without accepting the disability that chronic pain causes. Thus, the patient should aim to achieve normal or near normal function. Yunus notes that one of the important differences between those who do well in managing their chronic pain and those who do not is that successful patients have a definite goal in mind, particularly in daily life. The idea of an immediate goal is to complete one or more well-defined and achievable tasks on a particular day.[86]

To achieve this, consideration of two aspects of behavior are necessary - operant behavior and pacing of activities.[86,87] Chronic pain behaviors are frequently similar and independent of their underlying etiology. A patient with chronic back pain following surgical repair of a herniated disc may exhibit sick pain behavior identical to the patient

with fibromyalgia. Both patients have unconsciously developed operant behavior defined as voluntary behavior of an individual that is influenced by consequences of that behavior. An example of this could be the patient who is completely disabled because any movement causes pain. A family member rushes to assist her when she moans, as she attempts any activity, and the patient experiences immediate relief. Her unconscious but voluntary moaning prior to any activity is reinforced by her family member's help, so relief of pain reinforces her sick pain behavior.[86]

This behavior can be altered to improve the functional status of the patient but this requires frank discussion of these issues in the presence of family members. Moreover, as emphasized by Yunus, operant behavior is <u>not</u> the equivalent of malingering, and any suggestions that the patient is consciously avoiding duties should be avoided.[86,87] Pacing of activities is also important. A gradual increase in the tolerance of physical activity can be achieved by stopping an activity before the onset of severe pain.[86]

Specific Treatment Modalities

Amitriptyline

Tricyclic medications have been proposed as therapeutic agents for the treatment of fibromyalgia since the reports by Moldofsky and Smythe of objective sleep abnormalities in these patients. Two controlled and one crossover study have demonstrated some short-term benefit to low dose amitriptyline in this syndrome.

Carette randomized seventy patients meeting Smythe's criteria for fibromyalgia to treatment with amitriptyline or a placebo at bedtime for nine weeks. Patients assigned to the amitriptyline group received 10 mg daily for the first week, 25 mg for the second through fourth weeks, and 50 mg for the last five weeks of the trial. Physicians and patients were blinded to treatment status and the same physicians reevaluated a given patient over time. Patients' self-assessments include: (a) duration of morning stiffness, (b) evaluation of overall pain on a scale from 1 to 10, (c) evaluation of sleep quality, and (d) overall assessment of disease compared to baseline. Physician assessments included measurement of point tenderness with a dolorimeter over four paired "tender" points - the midpoint of the upper trapezius, second costochondral junction, 2 cm distal to the lateral

epicondyle and over the medial fat pad of the knee. Individual scores were summed to give a total myalgic score. Physicians were also asked to scale an overall assessment of disease activity over this interval.[88]

Results are shown in Table 10. Eleven patients withdrew from the trial, seven in the amitriptyline group and four in the placebo group. Patients who received amitriptyline improved significantly in their morning stiffness and pain analog scores at five and nine weeks as compared with baseline, however the difference between the two treatment groups was not significant. Total myalgic scores did not improve significantly over baseline in either group. 70% of patients who received amitriptyline believed that the quality of their sleep improved, compared with 34% of patients taking the placebo at five weeks and 40% at nine weeks, a significant difference. In the amitriptyline group, 77% of patients experienced overall improvement at five weeks and 70% at nine weeks. In the placebo group, 43% experienced improvement at five weeks and 50% at nine weeks. These differences were significant at five weeks (p=.008) but not at nine weeks (p=0.11). 70% of amitriptyline treated patients noted side effects such as drowsiness and xerostomia which were felt to unblind the study drug to both patient and physician in a number of cases.[88]

TABLE 10. Morning stiffness, pain analog scores, and total myalgic scores in patients receiving amitriptyline (A) or placebo (P)* (Taken from Carette[88])

	Prestudy	5 weeks	9 weeks
Morning stiffness (minutes)			
A	75 ± 72	41 ± 58†	48 ± 61†
P	78 ± 71	71 ± 80	66 ± 76
Pain analog score			
A	6.3 ± 2.3	3.8 ± 2.3†	4.3 ± 3.0†
P	5.8 ± 2.4	5.3 ± 2.7	5.0 ± 3.0
Total myalgic score			
A	22.2 ± 6.7	27.1 ± 9.0†	25.2 ± 8.1
P	24.8 ± 7.9	26.7 ± 9.0	26.2 ± 8.9

* Values are mean ± SD.
† $P < 0.05$, compared with prestudy value.

Goldenberg randomly assigned sixty-two patients diagnosed with fibromyalgia (using the Yunus' criteria) to one of four regimens in a six week double-blind trial: (1) 25 mg of amitriptyline at bedtime, (2) 500 mg of naproxen twice daily, (3) both the amitriptyline and

naproxen, (4) double placebo. Amitriptyline was associated with significant improvement in all outcome parameters, including tender point score (P<.001) and all outcome measures at the end of the study were significantly lower in patients taking amitriptyline versus those taking placebo.[89,90]

Scudds randomized thirty-six patients with fibromyalgia according to the Smythe criteria to one of two groups. Group 1 received amitriptyline for a period of four weeks, followed by a two week washout period, and then a second period of four weeks during which time they received a placebo. Group 2 followed the same schedule as Group 1 except that they received placebo in the first period and amitriptyline in the second. Patients received 10 mg amitriptyline daily at bedtime for the first week, 25 mg for the second week, and 50 mg daily for the final two weeks. Efficacy was evaluated pre and post treatment via total myalgic score and measurement of pain threshold and tolerance at specified control or nontender points using a dolorimeter. Patients also rated their pain pre and post treatment. Amitriptyline significantly reduced the total myalgic score and pain rating with some increase in pain threshold but not tolerance.[91]

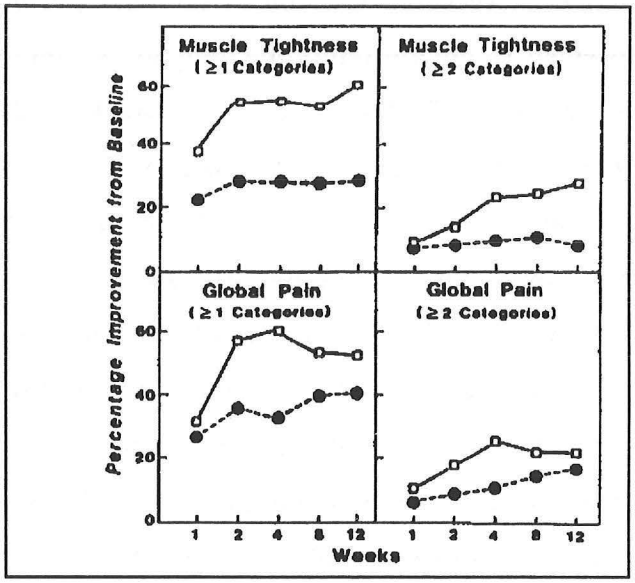
Criticisms of these studies include the problem of effective blinding in a situation where the majority of treated patients experience well-described side effects to the study drug and a significant placebo effect. (50% of patients in the placebo group experienced a significant decrease of pain in the Carette study). Additionally, the clinical impact of the therapy was not felt to be impressive, even by the investigators reporting statistically significant results. Goldenberg found that only a third of his patients chronically treated with amitriptyline achieved a meaningful response defined as fulfilling three of the four following criteria:

- ≥ 50% improvement in patient global assessment
- ≥ 50% improvement in physician global assessment
- ≥ 50% improvement in patient rated pain
- ≥ 25% improvement in tender point score[90]

Cyclobenzaprine

Cyclobenzaprine (Flexeril) is a tricyclic compound with a chemical structure similar to that of amitriptyline but minimal antidepressant effects. Bennett tested the efficacy of cyclobenzaprine as compared with placebo in a twelve-week, double-blind, controlled trial of one hundred twenty patients with fibromyalgia. All patients in the treatment group began with 10 mg of the study drug at night and reached an "optimal" therapeutic dose within the first two weeks of treatment. Effectiveness was evaluated using a patient rated scale for pain, sleep, morning stiffness and duration of fatigue, as well as physician palpation of tender points and assessment of "global" musculoskeletal pain. Patients taking cyclobenzaprine experienced a significant decrease in the severity of pain, a significant increase in the quality of sleep and decreases in the total number of tender points. Control patients likewise improved in each of these areas, in some cases significantly but not to the same degree (See Figure 2). The authors also estimated that at least half of the patients and physicians were unblinded by virtue of side effects of the study drug.[92]

Figure 2 Percentage improvement in tightness in the shoulder girdle musculature and in the assessment of global pain in fibrositis patients treated with cyclobenzaprine (▫) vs. patients treated with placebo (•). (Taken from Bennett[92])

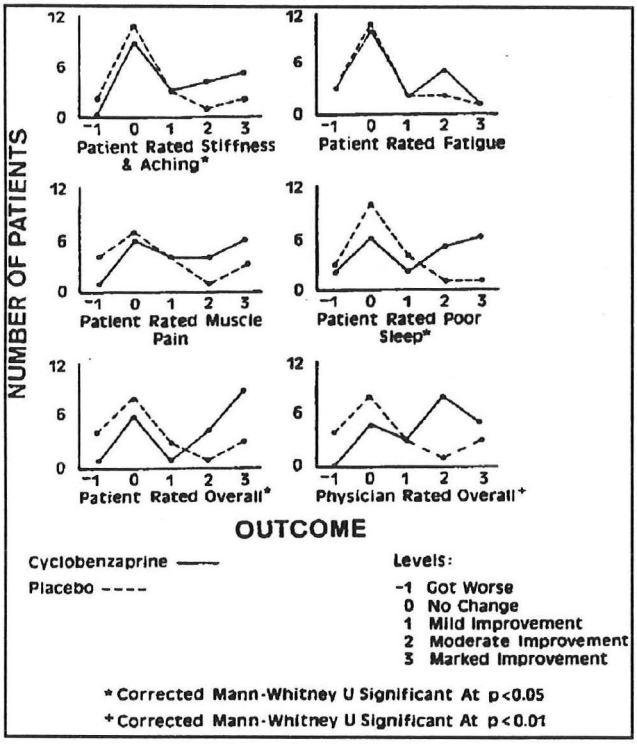


Hamaty enrolled eleven patients into a twenty-one week double-blind, crossover trial comparing cyclobenzaprine and placebo. Seven patients completed the trial and received up to 40 mg of cyclobenzaprine per day as tolerated. They reported no statistically significant reduction in pain but sleep quality was improved ($p < .05$).[93]

Quimby attempted a randomized, double-blind trial of placebo versus cyclobenzaprine in forty female patients from a private rheumatology practice in Maine. Patients and physicians noted significantly more "global" improvement, better sleep, and decreased stiffness in the study drug group (Figure 3), however, the investigators were less

impressed with their results when they found that 69% of the patients and 78% of the physicians recognized the identity of the test drug.[94]

Figure 3. Cyclobenzaprine/placebo 6 week treatment outcome. (Taken from Quimby[94])



Other Drug Therapies

Dothiepin is another tricyclic antidepressant structurally similar to amitriptyline, and results of a randomized double blind, placebo, controlled trial in sixty Italian patients with fibromyalgia were similar to those reported by Goldenberg with amitriptyline. Once again, the majority of study patients could identify the drug.[95] Tavoni also reported benefit to S-adenosyl methionine, a methyl donor in cerebral methylation reactions that seems to have antidepressant properties and few side effects. Dosages of 200 mg per day were used.[96]

Goldberg reported that patients taking a combined naproxen-amitriptyline regimen experienced minor, but not significant, improvement in pain when compared with patients who took amitriptyline alone. Naproxen alone produced no effect whatsoever in this study.[89] Yunus notes that his own experience with NSAIDs in this disorder is that they are not generally effective and recommends that cheaper, safer analgesics such as acetaminophen should be prescribed first. Clark reported that low dose oral steroids produced no improvement in symptoms.[97]

Narcotics and other addictive drugs have not been formally evaluated but their use is strongly discouraged as in all chronic pain situations of this type.[87]

Biofeedback

Biofeedback has received increasing attention as a therapeutic alternative in a variety of chronic painful conditions and has been most successful in treating patients with muscle tension headaches and neck pain.[87] While advocated by several authors, I could find no studies utilizing this form of therapy.

Acupuncture

Acupuncture is a form of hyperstimulation analgesia similar to transcutaneous stimulation, and it has been reported that there is a close correlation between "trigger points" in myofascial pain syndromes and acupuncture sites utilized for pain control.

TABLE 11. Acupuncture Therapy in Fibromyalgia (Adapted from Deluze[98])

Outcomes (means)	Before treatment		After treatment	
	Control (n=27)	Acupuncture (n=28)	Control (n=27)	Acupuncture (n=28)
Pain threshold (kg/cm)	1.47	1.36	1.54	2.32
No. of analgesic tablets during last week	7.93	10.36	10.07	6.86
Regional pain score (1-105)	36.96	43.43	36.26	26.46
Pain on visual analogue scale (1-100 mm)	60.89	56.61	53.78	39.89
Sleep quality (1-10)	4.70	4.11	4.85	5.96
Morning stiffness (minutes)	82.04	57.86	83.15	40.89
Patient's appreciation (1-10)	4.59	4.82	5.07	6.46
Evaluating physician's appreciation (1-10)	4.70	5.21	5.04	7.00

Significant improvement with acupuncture in all outcomes except morning stiffness.

Possible mechanisms by which acupuncture may provide relief of pain include a transcutaneous stimulator like action via the gate control theory and release of endorphins, because acupuncture-induced analgesia can be reversed by naloxone treatment.[87] Recently the results of a double blind, controlled study of acupuncture in seventy patients with fibromyalgia (diagnosed according to the recent recommendations of the American College of Rheumatology) were reported. The patients were randomized to receive either electro-acupuncture or a sham procedure in which acupuncture needles were inserted but somewhat less deeply, at a small distance from prescribed acupuncture sites, and with a

weaker electric current. All but one of the eight outcome measures showed significant improvement in actively treated patients and no change in the placebo group. (Table 11) These results are comparable to those reported for the tricyclic compounds such as amitriptyline.[98]

TABLE 12. Scores on outcome measures in 38 patients with primary fibromyalgia randomized to a 20-week cardiovascular fitness (CVR) or flexibility exercise (FLEX) training program* (Adapted from McCain[100])

Variable	CVR group (n=18)		FLEX group (n=20)		P (CVR vs. FLEX at 20 weeks)
	At study entry	After 20 weeks	At study entry	After 20 weeks	
PWC	27.2 ± 256.0	896.9 ± 395.4	704.6 ± 254.4	689.2 ± 269.0	< 0.001
TMS	125.1 ± 92.5	165.4 ± 98.6	167.4 ± 96.0	158.8 ± 91.2	< 0.02
VAS	70.1 ± 15.8	46.9 ± 30.6	56.3 ± 19.2	47.4 ± 17.0	NS
PDS	14.8 ± 8.2	13.1 ± 13.2	10.2 ± 6.8	10.2 ± 7.3	NS
HPN	6.2 ± 2.0	6.7 ± 1.9	6.0 ± 1.9	6.2 ± 2.0	NS
NPW	4.9 ± 2.2	3.8 ± 2.5	4.5 ± 2.4	3.8 ± 2.4	NS

* Values are the mean ± SD. PWC = peak work capacity, at 170 beats per minute (kilopond-meters); TMS = total myalgic score (kg/cm²); VAS = visual analog scale (pain score, 100-mm scale); NS = not significant; PDS = pain diagram score (percentage of total body area affected); HPN = hours per night of disturbed sleep; NPW = nights per week of disturbed sleep.

Exercise

It has frequently been suggested that a sedentary lifestyle is associated with various musculoskeletal complaints. Moldofsky was the first to suggest that physical fitness training might prove beneficial in fibromyalgia when he reported that athletic subjects were resistant to the development of musculoskeletal pain and fatigue associated with sleep deprivation.[60]

McCain randomized forty-two patients with fibromyalgia (diagnosed utilizing the Smythe criteria) to a 20-week program consisting of either cardiovascular fitness (CVR) training or simple flexibility exercises (FLEX) that did not improve cardiovascular fitness. Patients were supervised by the same instructors and were blinded to the exercises taught to the alternate group. Compliance was 90%, and thirty-eight patients completed the study. Blind assessments were performed by two examiners, standardized during preliminary trials to achieve acceptable inter-rater agreement.

These investigators reported a highly significant improvement in peak work capacity of the patients undergoing CVR, and a clinically and statistically significant improvement in pain threshold scores measured over tender points. (Table 12). 50% of the patients in the CVR group were moderately to markedly improved by their own assessment versus 10% in the FLEX group ($p < 0.01$). (Table 13)

The authors speculate that benefit may have been derived via enhancement of the endogenous opiod system (as in postrun hypalgesia) or by improving mental status, however, it is disheartening that at a mean follow-up of nineteen months, only six patients were involved in regular exercise, and it is unclear whether these were the patients who seemed to benefit from CVR.[99,100]

TABLE 13. Patients' global assessment and physicians' global assessment of disease activity after 20 weeks of CVR training (n=18) or FLEX training (n=20)* (Adapted from McCain[100])

	Patients' assessment		Physicians' assessment	
Category	CVR	FLEX	CVR	FLEX
Worse, unchanged, or minimally improved	9	18	11	19
Moderate - markedly improved	9†	2	7‡	1

* Values are the number of patients in each category. CVR = cardiovascular fitness; FLEX = flexibility exercise.
† $P < 0.01$ versus FLEX group.
‡ $P < 0.005$ versus FLEX group.

CONCLUSION

Fibromyalgia is a common diagnosis in the outpatient setting, but remains poorly understood. It is important to exclude other well-known problems such as hypothyroidism that can result in similar complaints. A multidimensional approach to treatment including a graduated exercise program, acupuncture, and medical therapy utilizing tricyclic agents can prove beneficial.

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