

Focused Review

Fibromyalgia: An Afferent Processing Disorder Leading to a Complex Pain Generalized Syndrome

Howard S. Smith, MD¹, Richard Harris, PhD², and Daniel Clauw, MD²

From: ¹Albany Medical College, Department of Anesthesiology, Albany, NY; ²University of Michigan, Ann Arbor, MI.

Dr. Smith is Associate Professor & Academic Director of Pain Management, Albany Medical College, Department of Anesthesiology, Albany, NY. Dr. Harris is Research Assistant, Professor of Anesthesiology, The University of Michigan, Ann Arbor, MI. Dr. Clauw is Professor of Anesthesiology, Medicine (Rheumatology) and Psychiatry; and Director, Chronic Pain and Fatigue Research Center, The University of Michigan, Ann Arbor, MI.

Address correspondence:
Howard S. Smith, MD
Associate Professor & Academic Director
of Pain Management
Albany Medical College
Department of Anesthesiology
47 New Scotland Avenue; MC-131
Albany, New York 12208
E-mail: smithh@mail.amc.edu

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Fibromyalgia is a condition which appears to involve disordered central afferent processing. The major symptoms of fibromyalgia include multifocal pain, fatigue, sleep disturbances, and cognitive or memory problems. Other symptoms may include psychological distress, impaired functioning, and sexual dysfunction. The pathophysiology of fibromyalgia remains uncertain but is believed to be largely central in nature. In 1990 the American College of Rheumatology (ACR) published diagnostic research criteria for fibromyalgia. The criteria included a history of chronic and widespread pain and the presence of 11 or more out of 18 tender points. Pain was considered chronic widespread when all of the following are present: pain in the left side of the body; pain in the right side of the body; pain above the waist; pain below the waist. In addition, axial skeletal pain must be present and the duration of pain must be more than 3 months. A tender point is considered positive when pain can be elicited by pressures of 4 kg/cm² or less. For tender points to be considered positive, the patient must perceive the palpation as painful; tenderness to palpation is not sufficient.

However, over the next 20 years it became increasingly appreciated that the focus on tender points was not justified. In 2010 a similar group of investigators performed a multicenter study of 829 previously diagnosed fibromyalgia patients and controls using physician physical and interview examinations, including a widespread pain index (WPI), a measure of the number of painful body regions. Random forest and recursive partitioning analyses were used to guide the development of a case definition of fibromyalgia, to develop new preliminary ACR diagnostic criteria, and to construct a symptom severity (SS) scale. The most important diagnostic variables were WPI and categorical scales for cognitive symptoms, un-refreshed sleep, fatigue, and number of somatic symptoms. The categorical scales were summed to create an SS scale. The investigators combined the SS scale and the WPI to recommend a new case definition of fibromyalgia: (WPI \geq 7 AND SS \geq 5).

Although there is no known cure for fibromyalgia, multidisciplinary team efforts using combined treatment approaches, including patient education, aerobic exercise, cognitive behavioral therapy, and pharmacologic therapies (serotonin norepinephrine reuptake inhibitors [e.g., duloxetine, milnacipran] and alpha 2-delta receptor ligands [e.g., pregabalin]) might improve symptoms as well as function in patients with fibromyalgia.

Key Words: Pain, fibromyalgia, fatigue, sleep, duloxetine, pregabalin, milnacipran

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Fibromyalgia is a medical condition that appears to involve disordered afferent processing and which might be associated with multiple symptoms, the hallmarks being chronic widespread pain (in any bodily region including visceral organs), fatigue, sleep disturbances, and cognitive alterations. Many individuals

also experience psychological distress and impaired function, including sexual dysfunction (Fig. 1).

The core symptoms seen in individuals with fibromyalgia as well as many other closely related "central" pain syndromes are multifocal pain, fatigue severe enough to limit daily activities, sleep disturbances,

cognitive or memory problems, and, in many cases, psychological distress (1,2). Some individuals in the population only have one of these symptoms but more often individuals have many, and the precise location of the pain, and predominant symptom at any given point in time, may change over time. Thus, in clinical practice, it is useful to consider a fibromyalgia-like or central pain syndrome when individuals have multifocal pain combined with other somatic symptoms.

The presence and severity of these symptoms occur over a very wide continuum in the population. All of our current diagnostic labels are at some level arbitrary because there is no objective tissue pathology or gold standard to which "disease" can be anchored. These symptoms and syndromes occur approximately 1.5 – 2 times more commonly in women than men. The sex difference appears more apparent in clinical samples (especially tertiary care) than in population-based samples (3,4). There is a strong familial predisposition to these symptoms and illnesses, and studies clearly show that these somatic symptoms and syndromes are separable from depression and other psychiatric disorders (5,6). A variety of biological stressors seem to be capable of either triggering or exacerbating fibromyalgia, including physical trauma, infections, early life trauma, and deployment to war, in addition to some types of psychological stress (e.g., there was no increase in somatic symptoms or worsening of fibromyalgia following the terrorist attacks of 9/11) (7-10).

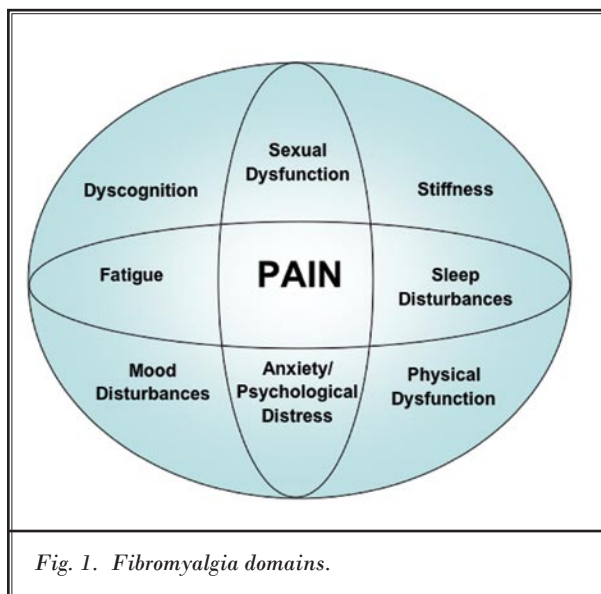


Fig. 1. Fibromyalgia domains.

HISTORY OF FIBROMYALGIA AND ITS EVOLUTION

Although there are clear descriptions of individuals with what we now call fibromyalgia going back centuries in the medical literature, Sir William Gowers coined the term "fibrositis" in 1904, which was considered a form of muscular rheumatism caused by inflammation of fibrous tissue overlying muscles (11). Although other terms such as "psychogenic rheumatism" were proposed and used in the mid-20th century, the term fibrositis remained the most widely used term to describe individuals with chronic widespread pain and no alternative explanation.

Several authors began to suggest that this term was a misnomer because there was no inflammation of the muscles. Smythe and Moldofsky (12) helped to establish current concepts regarding fibromyalgia in the mid-1970s (12). Moldofsky and colleagues, in addition to others, performed seminal studies showing that individuals with fibrositis suffered from objective sleep disturbances, and showed that these same symptoms could be induced in healthy individuals deprived of sleep (13-16). Hudson and colleagues (17,18) were arguably the first investigators to note the strong familial tendency to develop fibromyalgia, and proposed that this condition is a variant of depression, coining the term "affective spectrum disorder." In parallel during this same period of time, Yunus (19) similarly began to note the high frequency of associated functional somatic syndromes such as irritable bowel syndrome and headache with fibromyalgia, again steering the focus away from skeletal muscle. Nonetheless, the theories positing a pathophysiologic role of skeletal muscle took time to fade, persisting into the mid-1990s (20-22).

Just as spastic colitis became irritable bowel syndrome, temporomandibular joint syndrome became temporomandibular disorder (when it was recognized that the problem was not in the joint), chronic Epstein-Barr virus syndrome became chronic fatigue syndrome (CFS) (when it was realized that this syndrome occurs commonly after many viral illnesses and without infection with this pathogen), fibrositis became fibromyalgia.

It has also become clear that fibromyalgia is not just fibromyalgia. There is now significant evidence that fibromyalgia is part of a much larger continuum that has been called many things, including functional somatic syndromes, medically unexplained symptoms, chronic multisymptom illnesses, somatoform disorders, and perhaps most appropriately, central sensitivity syndromes. Yunus et al (19) showed fibromyalgia to be

Table 1. *Clinical entities currently considered parts of the spectrum of Central Sensitivity Syndrome (CSS)*

Clinical Syndromes
Fibromyalgia
Chronic Fatigue Syndrome (CFS)
Irritable Bowel Syndrome (IBS) and other functional GI disorders
Temporomandibular Disorder (TMD)
Restless Leg Syndrome (RLS) and Periodic Limb Movements in Sleep (PLMS)
Idiopathic Low Back Pain (LBP)
Multiple Chemical Sensitivity (MCS)
Primary Dysmenorrhea
Headache (tension, migraine, mixed)
Migraine
Interstitial Cystitis/Chronic Prostatitis/Painful Bladder Syndrome
Chronic pelvic pain and endometriosis
Myofascial Pain Syndrome / Regional Soft Tissue Pain Syndrome

associated with tension type headache, migraine and irritable bowel syndrome (IBS). Together with primary dysmenorrhea, these entities were depicted by Yunus in a Venn diagram in 1984, emphasizing the epidemiological and clinical overlap among the syndromes (19). The more recent term Central Sensitivity Syndromes (CSS) as proposed by Yunus is the preferred term to globally group these entities together, because it is felt that this might represent the best nosological term at present for these syndromes (23) (Table 1).

There is also a clear overlap between the CSS disorders and a variety of psychiatric disorders. This overlap likely occurs at least in part because of the same neurotransmitters (albeit in different brain regions) that are operative in psychiatric conditions. The presence of co-morbid psychiatric disturbances is somewhat more common in individuals with CSS seen in tertiary care settings than primary care settings (3,4). Figure 2 demonstrates the overlap among fibromyalgia, CFS, and a variety of regional pain syndromes as well as psychiatric disorders – and shows that the common underlying pathophysiological mechanism seen in most individuals with fibromyalgia, and large subsets of individuals with these other syndromes, is central nervous system (CNS) pain or sensory amplification.

The current thinking about these overlapping symptoms and syndromes is as follows:

- Groups of individuals with these conditions (e.g., fibromyalgia, irritable bowel syndrome [IBS], headaches, temporomandibular joint disorder [TMJD], etc.) display diffuse hyperalgesia (increased pain in response to normally painful stimuli) and/or allodynia

(pain in response to normally non-painful stimuli). Many of these conditions have also been shown to demonstrate more sensitivity to many stimuli other than pain (e.g., auditory, visual), and the aggregate data suggest that these individuals have a fundamental problem with pain or sensory amplification rather than a structural or inflammatory condition in the specific body region where the pain is being experienced. In fact, the expanded relevance of the fibromyalgia construct relates to the idea that all individuals (with and without pain) have different “volume control” settings on their pain and sensory processing. As such, their position on this bell-shaped curve of pain or sensory sensitivity determines to a large part whether they will have pain or other sensory symptoms over the course of their lifetime and how severe these symptoms will be. In addition to pain and sensory amplification, other shared mechanisms and/or epiphenomena include neurogenic inflammation, especially of mucosal surfaces, leading to increased mast cells and the appearance of a mild inflammatory process; dysfunction of the autonomic nervous system; hypothalamic pituitary dysfunction.

- Furthermore, similar types of therapies are efficacious for all of these conditions, including both pharmacological (e.g., tricyclic compounds such as amitriptyline) and non-pharmacological treatments (e.g., exercise and cognitive behavioral therapy). Conversely, individuals with these conditions typically do not respond to therapies that are effective when pain is due to damage or inflammation of tissues (e.g., NSAIDs, opioids, injections, surgical procedures).

Role of Environmental Stressors as Triggers

As with most illnesses that might have a genetic underpinning, environmental factors might play a prominent role in triggering the development of fibromyalgia and related conditions. Environmental “stressors” temporally associated with the development of either fibromyalgia or CFS include early life trauma, physical trauma (especially involving the trunk), certain infections such as hepatitis C, Epstein-Barr virus, parvovirus, Lyme disease, and emotional stress. The disorder is also associated with other regional pain conditions or autoimmune disorders (10,30,31). Of note, each of these stressors only leads to CWP or fibromyalgia in approximately 5 – 10% of individuals who are exposed; the overwhelming majority of individuals who experience these same infections or other stressful events regain their baseline state of health.

Wolfe’s “Symptom Inventory”

Although an early advocate of the fibromyalgia construct, Wolfe (32) later became critical of the construct, arguing that fibromyalgia is not a discrete illness but rather the end of the continuum. A contrary opinion is that fibromyalgia is both a discrete illness (i.e., an individual with fibromyalgia) and the end of a continuum of pain processing. Wolfe (33) has performed seminal work in showing that the degree of “fibromyalgia-ness” an individual with any rheumatic disorder has (including individuals with osteoarthritis, rheumatoid arthritis, regional pain syndromes, etc.), as measured by his Symptom Inventory, is closely correlated with their level of pain and/or disability, even if they do have a “peripheral” cause for their pain. The Symptom Inventory (or other measures of the current or lifetime level of somatic symptoms or “somatization”) is a very good measure for whether individuals have a CSS or an element of central sensitivity, whether or not they also have a peripheral cause for their pain or not. We predict that genetic factors such as those discussed below will be shown to be highly predictive of these measures, and that functional imaging (e.g., hyperactivity or increases in excitatory neurotransmitters in brain regions such as the insula that code for the intensity of all sensory information) and other research methods will similarly show that these self-report measures will have strong biological underpinnings (34-37).

Genetic and Familial Predisposition

Evidence exists for a strong familial component to fibromyalgia and all other CSS. Arguably, this component has been best studied in twin studies comparing a variety of functional somatic syndromes, and in fibromyalgia. Regarding the development of fibromyalgia, Arnold and colleagues (6) showed that the first degree relatives of individuals with fibromyalgia had an 8-fold greater risk of developing fibromyalgia compared with those in the general population. Family members of individuals with fibromyalgia are more sensitive to pressure stimulation (i.e., have a lower pain threshold) than family members of controls, irrespective of the presence of pain. Furthermore, family members of individuals with fibromyalgia are also much more likely to have other pain syndromes, such as IBS, TMD, headaches, and other regional pain syndromes (38,39). Similarly, strong genetic predisposition to chronic pain, and to nearly all of the CSS syndromes, have been noted. These observations are congruent with the twin studies that suggest that approximately 50% of the risk of developing one of these disorders is genetic, and 50% is environmental.

THE IMPACT OF FIBROMYALGIA SYNDROME ON FUNCTIONING AND QUALITY OF LIFE

Fibromyalgia affects all aspects of daily physical functioning. Women with fibromyalgia consistently scored among the lowest in quality of life measures versus women with rheumatoid arthritis (RA), osteoarthritis (OA), chronic obstructive pulmonary disease (COPD), or insulin-dependent diabetes mellitus (IDDM) (40). Patients with fibromyalgia have reported difficulty with multiple activities (41,42). Sixty-two percent have difficulty climbing stairs, 55% have difficulty walking 2 blocks, and 35% have difficulty with activities of daily life (41). It has also been reported that fibromyalgia has a negative impact on personal relationships, career, and mental health (43).

The burden of illness for fibromyalgia is substantial and comparable to RA. Patients with fibromyalgia incurred direct costs approximately equal to RA patients. Patients with fibromyalgia had more emergency department (ED), physician, and physical therapy visits than RA patients (44). Mean annual expenditures for fibromyalgia patients were \$10,911 (SD = \$16,075). RA patient annual expenditures were similar to fibromyalgia: \$10,716 (SD = \$16,860) (44).

Fibromyalgia places a significant cost, absence, and productivity burden on employers (45). Total health ben-

efit costs for fibromyalgia were \$8,452 versus \$11,253 ($P < 0.0001$) for OA and \$4,013 ($P < 0.0001$) for patients without fibromyalgia, with burden of illness = \$4,439 (44). Total days absent were 16.8 versus 19.8 ($P < 0.0001$) and 6.4 ($P < 0.0001$), respectively (45). Fibromyalgia is associated with substantial direct and indirect health care costs in the US. The mean (SD) annual direct costs per patient for fibromyalgia were \$7,973 (\$7,341), including physician office visits \$1,528 (\$1,953), diagnostic tests \$435 (\$1,859), prescription medications \$3,419 (\$3,667), emergency room visits \$43 (\$323), and out-of-pocket costs incurred by individuals for fibromyalgia treatments \$1,798 (\$3,056) and home healthcare services \$650 (\$1,756) (45). The mean (SD) annual indirect costs per person for fibromyalgia were \$10,697 (\$20,463), including \$1,228 (\$4,904) related to absenteeism and \$9,470 (\$20,446) related to disability due to fibromyalgia, including both disability payments and the opportunity cost of not working (46). Annemans et al (47) found that failure to diagnose a true case of fibromyalgia has its own costs, mostly from excess general practitioner visits, investigations, and prescriptions.

PATHOPHYSIOLOGY OF FIBROMYALGIA

Evidence of Augmented Pain and Sensory Processing as the Most Reproducible Pathogenic Feature of These Illnesses

Once fibromyalgia is established, by far the most consistently detected objective abnormalities involve pain and sensory processing systems. Since fibromyalgia is defined in part by tenderness, considerable work has been performed exploring the potential reason for this phenomenon. The results of 2 decades of psychophysical pressure pain testing in fibromyalgia have been very instructive (48).

One of the earliest findings in this regard was that the tenderness in fibromyalgia is not confined to tender points, but instead extends throughout the entire body (49,50). Theoretically, such diffuse tenderness could be either primarily due to a psychological factor (e.g., hypervigilance, where individuals are too attentive to their surroundings), or neurobiological influence factors (e.g., the plethora of factors that can lead to temporary or permanent amplification of sensory input).

Early studies typically used dolorimetry to assess pressure pain threshold, and concluded that tenderness was in large part related to psychological factors, because these measures of pain threshold were correlated with levels of distress (32,50,51). To minimize the

biases associated with "ascending" (i.e. the individual knows that the pressure will be predictably increased) measures of pressure pain threshold, Petzke and colleagues (52-54) performed a series of studies using more sophisticated paradigms using random delivery of pressures. These studies showed that the random measures of pressure pain threshold were not influenced by levels of distress of the individual, whereas tender point count and dolorimetry exams were; fibromyalgia patients were much more sensitive to pressure even when these more sophisticated paradigms were used; fibromyalgia patients were not any more "expectant" or "hypervigilant" than controls; pressure pain thresholds at any 4 points in the body are highly correlated with the average tenderness at all 18 tender points and 4 "control points" (the thumbnail and forehead).

In addition to the heightened sensitivity to pressure noted in fibromyalgia, other types of stimuli applied to the skin are also judged as more painful or noxious by these patients as well. Fibromyalgia patients also display a decreased threshold to heat (54-57), cold (5,58), and electrical stimuli (59).

Gerster and colleagues (60) were the first to demonstrate that fibromyalgia patients also display a low noxious threshold to auditory tones, suggesting that this was a more global problem in sensory processing in some. A recent study by Geisser and colleagues (61) used an identical random staircase paradigm to test fibromyalgia patients' threshold to the loudness of auditory tones, and to pressure. This study found that fibromyalgia patients displayed low thresholds to both types of stimuli, and the correlation between the results of auditory and pressure pain threshold testing suggested that some of this was due to shared variance, and some unique to one stimulus or the other. The notion that fibromyalgia and related syndromes might represent biological amplification of all sensory stimuli has significant support from functional imaging studies that suggest that the insula is the most consistently hyperactive region (see below). This region has been noted to play a critical role in sensory integration, with the posterior insula serving a purer sensory role, and the anterior insula being associated with the emotional processing of sensations (36,62,63). Similar findings of hyperalgesia and allodynia have been noted in most of the other conditions acknowledged to be part of this continuum, including IBS, TMD, tension type headache, idiopathic low back pain, vulvodynia, and interstitial cystitis (26,64-69).

NEUROIMAGING

Brain imaging studies also support the existence of central pain augmentation in fibromyalgia, IBS, low back pain, and several other of these conditions (70-73). Gracely et al (70) performed the first functional magnetic resonance imaging (fMRI) study of fibromyalgia patients in 2002. When stimuli of equivalent pressure magnitude were administered to fibromyalgia patients and controls, Gracely and colleagues found increased regional cerebral blood flow in fibromyalgia patients compared to control participants who did not have fibromyalgia. Regions of increased activity included the primary and secondary somatosensory cortex, the insula, and the anterior cingulate cortex, commonly observed regions in fMRI studies of individuals without fibromyalgia undergoing painful stimuli (70). When the pain-free control participants were subjected to pressures (about 4kg/cm²) that evoked equivalent pain ratings in the fibromyalgia patients (about 2kg/cm²), similar activation patterns were seen, suggesting fibromyalgia patients perceive an increased gain or “amplitude set-

ting” in brain sensory processing systems (70) (Fig. 3).

Ichesco et al (74) studied 57 individuals (mean age 45) satisfying American College of Rheumatology criteria for fibromyalgia and 20 healthy controls (mean age 42). During a 10 min fMRI scan, 2 kg of pressure (mild pressure) was applied 3 times to the left thumbnail in random sequence for 25 seconds (74). In fibromyalgia patients, 2 kg of pressure resulted in significant neural activity in insula ($Z = 3.21$), bilateral inferior parietal lobes (BA 40, $Z = 4.48-4.81$), primary somatosensory cortex ($Z = 4.03$) and secondary somatosensory cortex ($Z = 4.69$), putamen ($Z = 3.27$) and caudate ($Z = 3.24$). Additional activations were observed in the cerebellum ($Z = 4.95$) and the middle frontal gyrus ($Z = 4.37$). The healthy controls only had significant activation in the contralateral inferior parietal lobe (BA 40, $Z = 3.18$) using the same stimulus intensity (74). In contrast to them, mild pressure stimuli resulted in more extensive activation of pain matrix regions in individuals with fibromyalgia. This study reconfirms an augmented involvement of the “pain matrix” in the processing of

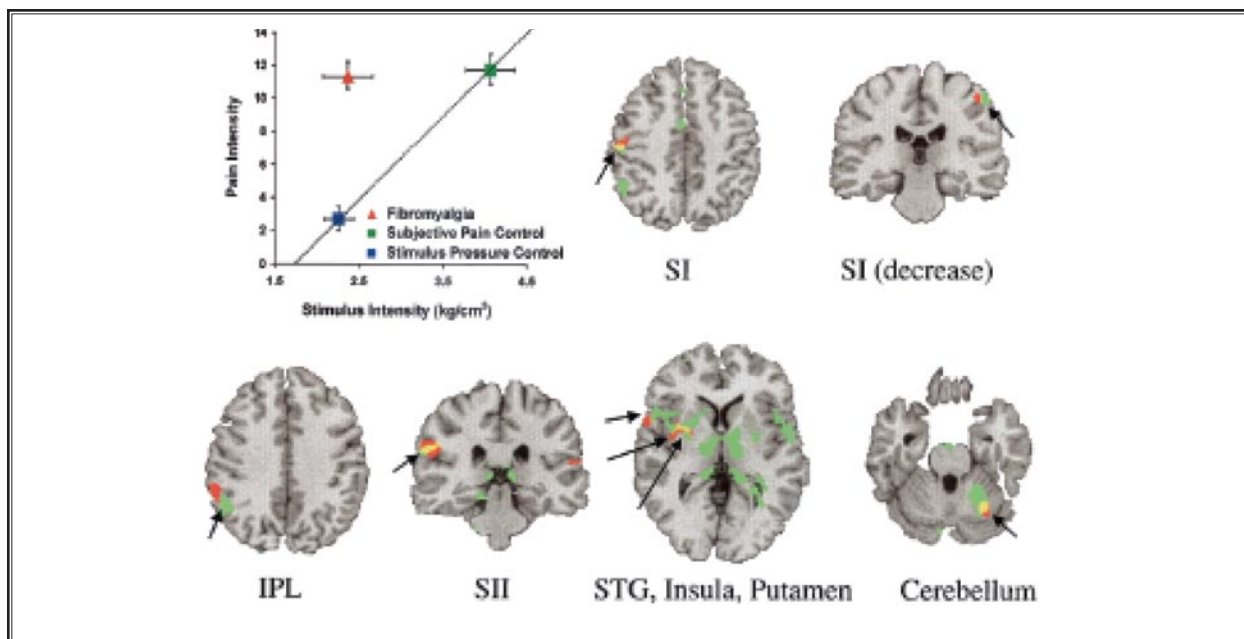


Fig. 3. Stimuli and responses during pain MRI scans. Gracely RH, et al. *Arthritis Rheum.* 2002; 46:1333-1343.

The similar pain intensities, produced by significantly less pressure in fibromyalgia patients, resulted in overlapping or adjacent activations in the contralateral primary somatosensory cortex (SI); inferior parietal lobule (IPL); secondary somatosensory cortex (SII); superior temporal gyrus (STG), insula, and putamen; and in the ipsilateral cerebellum.

In the fibromyalgia condition, a relatively low stimulus pressure (2.4 kg/cm²) produced a high pain level (mean [SD] 11.30 [0.90]). In the stimulus pressure control condition, administration of a similar stimulus pressure (2.33 kg/cm²) to control participants produced a very low level of rated pain (mean [SD] 3.05 [0.85]). In the subjective pain control condition, administration of significantly greater stimulus pressures to the control participants (4.16 kg/cm²) produced levels of pain (mean [SD] 11.95 [0.94]) similar to those produced in patients by lower stimulus pressures.

evoked pain in fibromyalgia and supports the role of central mechanisms being responsible for the pain of fibromyalgia (74). Utilizing other neuroimaging technology, Harris et al (75), utilizing positron-emission tomography (PET), demonstrated evidence of decreased mu-opioid receptor (MOR) availability in fibromyalgia perhaps secondary to increased occupation of MORs by high levels of endogenous opioids in fibromyalgia (75).

The Role of Specific Neurotransmitters

Nearly all bodily physiological processes, such as the control of the immune system or of blood pressure, are controlled by homeostatic processes that can either increase or decrease overall activity of the system. Using the immune system analogy, high levels of pro-inflammatory cytokines, or low levels of anti-inflammatory cytokines, can move an individual towards hyperimmune function. Similarly, there are neurotransmitters that are similarly known to either increase or decrease pain transmission in the CNS. Overall, the analogy of an increased "volume control" or "gain" setting on pain and sensory processing is supported by studies from a variety of sources. Similar to essential hypertension, where a variety of root causes can lead to elevated systemic blood pressure, these disorders represent "essen-

tial hypertension of pain and sensory processing pathways." Elevated levels of neurotransmitters that tend to be pro-nociceptive (Fig. 4 [left side]) or reduced levels of neurotransmitters that inhibit pain transmission (i.e., on the right side of the figure) 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. 4 indicate the direction of the abnormalities in these neurotransmitter levels (either in the cerebrospinal fluid [CSF] or brain) that have been identified to date in fibromyalgia. As noted, in fibromyalgia, there is evidence for increases in the CSF levels of substance P (76-79), glutamate, nerve growth factor, and brain derived neurotrophic factor (80), and low levels of the metabolites of serotonin, norepinephrine, and dopamine (81), any of which could lead to an "increase in the volume control" and augmented pain and sensory processing (77,80-83). The only neurotransmitter system that has been studied to date and not found to be out of line in a direction that would cause augmented pain transmission is the endogenous opioid system. Both CSF levels and brain activity by functional neuroimaging

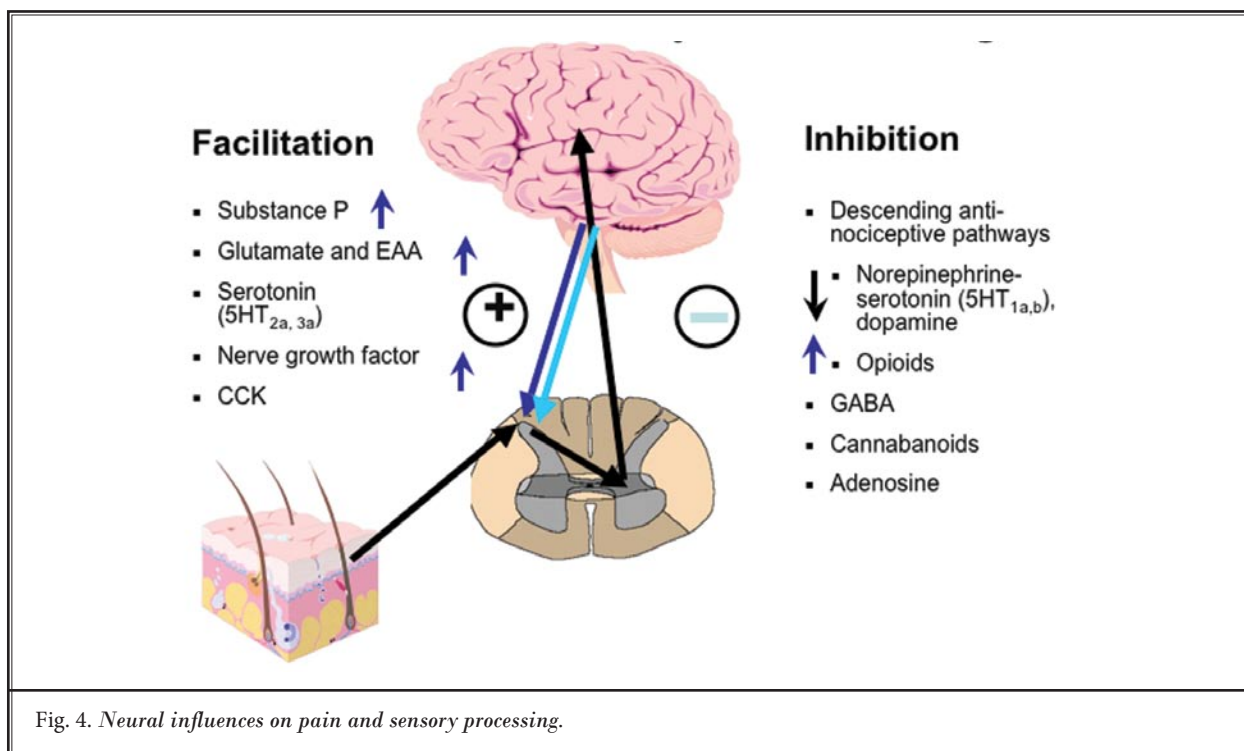


Fig. 4. Neural influences on pain and sensory processing.

appears to be augmented, not reduced (as would cause augmented pain processing) in fibromyalgia, which may be why opioidergic drugs do not appear to work well to treat fibromyalgia and related pain syndromes (75,84).

DIMINISHED EFFICACY OF ENDOGENOUS PAIN INHIBITORY SYSTEMS

Goffaux and coworkers (85) report the results of an experiment in fibromyalgia where they demonstrate a diminished efficacy of descending pain inhibitory mechanisms. This is based on their previously published method where degree of inhibition at the spinal level is estimated by the proxy of an electromyograph-measured withdrawal reflex produced by a painful stimulus and an estimate of the nociceptive signal from a standard stimulus, using somatosensory evoked potentials (SEP) methodology (86). Expectations of analgesia reduce subjective pain ratings and decrease SEP amplitudes, confirming that expectations influence thalamo-cortical processes. However, even when analgesia was experienced, the spinal activity of fibromyalgia patients was abnormal, showing heightened reflex responses. This demonstrates that, unlike healthy individuals, the modulation of pain by expectations in fibromyalgia fails to influence spinal activity. Jensen et al (87) found that the descending pain system activation by a noxious stimulus was reduced in fibromyalgia patients. The stimulus intensity was calibrated to the same subjective level of experienced pain, but the stimulus evoked less activation of the descending system originating in the rostral anterior cingulate cortex (87).

Potential Role of Cytokines in These Illnesses

Although the CSS conditions all were originally felt to be autoimmune or inflammatory diseases, and then later felt not to be, recent findings are leading to a reconsideration of whether subtle inflammatory changes might be responsible for some of the symptoms seen. Immunological cascades have a role in the maintenance of central sensitivity and chronic pain which is enhanced through release of pro-inflammatory cytokines by CNS glial cells; thus, the traditional paradigm regarding inflammatory versus non-inflammatory pain could gradually become less dichotomic.

FIBROMYALGIA AND OTHER SYMPTOMS

Although pain and fatigue are 2 of the most common fibromyalgia symptoms, sleep disturbances and sexual dysfunction occur very frequently as well in fibromyalgia patients.

Fibromyalgia And Sleep

A report of some form of sleep disturbance is extremely common in fibromyalgia. Moldofsky et al (16) as well as Older et al (88) have shown that selective sleep deprivation led to symptoms of fibromyalgia in healthy individuals.

Belt and colleagues (89) studied 37 patients with fibromyalgia from rehabilitation courses at the Rheumatism Foundation Hospital, Finland. There were 37 patients with fibromyalgia and 31 patients with RA. The fibromyalgia patients reported more insomnia-related symptoms than either RA patients or the population sample. The higher prevalence of insomnia-related symptoms among fibromyalgia patients was not explained by depression or pain (89).

Osorio and colleagues (90) concluded that the Pittsburgh Sleep Quality Index (PSQI) is a useful instrument for characterizing and quantifying sleep disturbances in patients with fibromyalgia. Standard measures of sleep, a gold-standard measure of sleepiness, quantified alpha-delta EEG power, auditory arousal thresholds, and urinary free cortisol largely failed to distinguish between fibromyalgia and control individuals (91). However, decreased short-term heart rate variability (HRV), and especially ratio-based HRV among those with fibromyalgia, suggested diminished parasympathetic and increased sympathetic activity, respectively. Other HRV measures suggested decreased complexity of HRV among those with fibromyalgia. Larger clinical trials of cognitive-behavioral therapy (CBT) for insomnia with fibromyalgia patients are warranted; although cognitive-behavioral therapy for insomnia (CBT-I) may represent a promising intervention for sleep disturbance in fibromyalgia patients.

Fibromyalgia and Sexual Dysfunction

Orellana et al (92) studied 31 consecutive women with fibromyalgia versus 20 aged-matched healthy women and 26 patients with RA. Sexual dysfunction was more frequent among fibromyalgia patients (97%) than in RA patients (84%). Orellana and colleagues (92) concluded that sexual function was very frequently and severely affected in patients with fibromyalgia. Kalichman (93) reviewed the associa-

tion between fibromyalgia and sexual dysfunction in women. All reviewed studies showed that fibromyalgia is associated with sexual dysfunction in women. The major findings were decreased sexual desire and arousal, decreased experience of orgasm, and increased pain with intercourse (93).

THE DIAGNOSIS AND ASSESSMENT OF FIBROMYALGIA

The American College of Rheumatology (ACR) criteria (94) have also been criticized for their failure to recognize the presence of associated fibromyalgia symptoms that must be addressed to optimally manage the disorder (95). ACR criteria are not used by a third of rheumatologists diagnosing fibromyalgia, and 25.5% of patients being treated for fibromyalgia by rheumatologists do not satisfy these criteria (96). Current fibromyalgia criteria aggregate and confound diagnostic status and symptom severity, features that should be separated to enable more adequate fibromyalgia evaluation and management (96). Two decades have passed since the 1990 ACR fibromyalgia criteria were published (94) and over that time, the intense focus on tender points in fibromyalgia has begun to wane. The Manchester criteria (97) used a whole body pain diagram to indicate areas of pain, obviating the need for tender points and showed good agreement with the ACR criteria. The London Fibromyalgia Epidemiology Study Screening Questionnaire (98) was designed as an epidemiologic tool to estimate the prevalence of the syndrome; it included both pain and fatigue.

Wolfe (99) mailed a survey to 12,799 patients who had RA, OA, or fibromyalgia syndrome. The questionnaire asked respondents if they had pain in 38 articular and nonarticular anatomic regions and to complete a 10-cm Fatigue Visual Analogue Scale. He observed that pain in a subset of 19 primarily nonarticular sites differentiated fibromyalgia syndrome from the other 2 diseases (99,100).

Wolfe (99) also showed that a score of at least 8 points on the Regional Pain Scale, combined with a score of at least 6 cm on the Fatigue Visual Analogue Scale, provided the best diagnostic precision consistent with a diagnosis of fibromyalgia syndrome (99). The combination of these 2 measures became known as the Survey Criteria (100). Katz, Wolfe, and Michaud (101) compared the diagnostic precision of the Survey Criteria, the ACR criteria, and a physician's clinical diagnosis in 206 patients and found that they are moderately concordant (72-75%) and address a common pool of

symptoms and physical findings.

Patients with fibromyalgia often have significant and multiple somatic complaints with multiple areas of pain. Clinicians need to evaluate all these pain complaints in a comprehensive manner, since: A) patients may have multiple pain complaints due to multiple causes and not have fibromyalgia, B) patients may have fibromyalgia and complain of spinal pain "as part of their fibromyalgia," or C) patients may have spinal pain originating from other sources (e.g., disc herniation/degeneration, zygapophyseal joints, etc.) as well as fibromyalgia (102-104). In this case it is important not to "automatically assume" that the spinal pain is "part of fibromyalgia." A comprehensive appropriate "diagnostic work-up" which may include imaging and/or diagnostic nerve blocks may be warranted since many of these etiologies of spinal pain may be effectively treated.

Wolfe and Rasker (33) devised the Symptom Intensity Scale. The Symptom Intensity Scale score is derived from two distinct measures:

- The Regional Pain Scale score, which is the number of anatomic areas — out of a possible 19 — locations that the patient notes there is pain
- A Fatigue Visual Analogue Scale score, in which a patient makes a mark somewhere along a 10 cm line to indicate their current level of fatigue. Subsequently, the clinician measures the position of the mark from the left end of the line with a ruler (100).

The Symptom Intensity Scale score is calculated as the Fatigue Visual Analogue Scale score plus half the Regional Pain Scale score, all divided by 2. The scale scores can range from 0 to 9.75. The questionnaire was given to 25,417 patients who had various rheumatic diseases and found that a score of 5.75 or higher was a good "cut-off score" able to discriminate fibromyalgia from other rheumatologic conditions, and identifying 95% of patients who would satisfy the Survey Criteria for fibromyalgia (99,100). Vargas et al (105) conducted a prospective multicenter study which demonstrated that the generation of pain during blood pressure testing (sphygmomanometry-evoked allodynia) was strongly associated with the diagnosis of fibromyalgia.

Recently proposed diagnostic criteria that assess widespread pain along with the severity of symptoms of fatigue, sleep disturbance, cognitive dysfunction, and the extent of somatic symptoms should improve diagnosis and treatment of fibromyalgia (106). Wolfe and colleagues (106) have proposed simple clinical criteria for fibromyalgia that do not require the use of

tender points, expanding the definition of fibromyalgia to include symptoms other than pain, and providing a measure to assess fibromyalgia symptoms related to severity. Wolfe et al (106) performed a 2-stage, 55-site multicenter study of 1,002 fibromyalgia patients and pain controls to develop simple clinical criteria for fibromyalgia. Patients underwent a detailed interview and examination, including tender points (TP) examination and assessment of the extent of widespread pain using a 0-19 widespread pain index (WPI), and completed a detailed questionnaire (106). The WPI was the best predictor of fibromyalgia. Analyses excluding WPI identified unrefreshed sleep, fatigue, cognitive difficulties, and the extent of somatic symptom reporting as the key fibromyalgia predictors. Wolfe and colleagues (106) combined the 4 categorical symptom variables into a 0-12 Symptom Severity (SS) scale. The SS scale correlated with the TP count ($r=0.688$) and the WPI (0.733). Wolfe et al (106) proposed that fibromyalgia can be diagnosed when $(WPI > 6 \text{ AND } SS > 4) \text{ OR } SS \geq 9$. These criteria correctly identified 80.9% of ACR (+) cases and reflect disagreement related to the expanded definition and removal of the tender point criterion, while physician diagnosis agreed with ACR criteria in 84.1% of cases. New diagnostic criteria agreed with an SS scale ≥ 7 in 93% of cases (106). The SS scale correlated with a wide series of fibromyalgia severity measures and was effective in describing fibromyalgia severity and the severity status of persons previously diagnosed with fibromyalgia, but now not satisfying ACR criteria. In the second phase of the study, a simple categorical form, suitable for use in the clinic, was used and performed as well as Phase 1 variables (106). Wolfe et al (106) proposed that the 1990 ACR classification criteria continue to be used for their intended purpose (to identify individuals for research studies), but that these new criteria might be more applicable in clinical settings, or research settings (e.g., epidemiological studies) where a TP count is not feasible.

A 3-item model (pain, fatigue, sleep disturbance) was judged to have adequate validity (93 to 100% agreement among the clinicians; 91 to 100% among the patients), and constituted the Fibromyalgia Assessment Status (FAS) index (107). The 3 items include the following questions: What number between 0 and 10 best describes the average level of pain you have experienced in the past week (0 = no pain; 10 = pain as bad as it can be)?; What number between 0 and 10 best describes the average level of fatigue you have experienced in the past week (0 = no fatigue; 10 = fatigue

as bad as it can be)?; and How much of a problem has sleep been in the past week (0 = no problem; 10 = severe problem)? (107).

The Self-Assessment Pain Scale (SAPS) considers the pain "experienced during the past week" in 16 non-articular sites. The patient is instructed to rate the pain at each of these sites on a scale of 0-3 (0 = none, 1 = mild, 2 = moderate, and 3 = severe). The scale scores range from 0 to 48, but in order to integrate them into one scale they were transformed to a scale of 0 to 10. The FAS index is a short and easy to complete self-administered index combining a set of questions relating to non-articular pain (SAPS range 0 to 10), fatigue (range 0 to 10), and the quality of sleep (range 0 to 10) that provides a single composite measure of disease activity ranging from 0 to 10. The final score is calculated by adding the 3 sub-scores and dividing the result by 3. All 3 measures are printed on one side of one page for rapid review, and scored by a health professional without the need for a ruler, calculator, computer, or website (107).

In an effort to investigate the relationship between changes in clinical rating scale items and endpoint Patient Global Impression of Improvement (PGI-I), Hudson et al (108) pooled data from 4 randomized, double-blind, placebo-controlled studies of duloxetine in patients with fibromyalgia.

The PGI-I scale (108) is the most commonly used and validated measure of a patient's response to treatment. This is a categorical scale on which patients provide ratings of their overall impression of how they are feeling since treatment began, with the following choices: 1 = very much better, 2 = much better, 3 = better, 4 = no change, 5 = worse, 6 = much worse, 7 = very much worse (109).

In addition to pain reduction, the factors that might contribute to perceptions of improvement among patients with fibromyalgia might include positive changes in fatigue, physical functioning, mood, and impact on daily living. These domains might be important for outcome assessments in clinical trials of fibromyalgia and in the management of patients with fibromyalgia (109).

The assessment of fibromyalgia is challenging, as is attempting to follow trends longitudinally trying to document overall improvement or in specific domains. Results from a study by Choy et al (110) provide support for the inclusion of the following in the core data set: pain, tenderness, fatigue, sleep, patient global assessment, and multidimensional function/health related quality of life. The core data set was supported by high consensus

among attendees at Outcome Measures in Rheumatology Clinical Trials (OMERACT) (111). Establishing an international standard for randomized controlled trials (RCT) in fibromyalgia should facilitate future meta-analyses and indirect comparisons (110). The OMERACT initiative (111) has helped to resolve the problem of outcomes measurement variability in rheumatic diseases such as rheumatoid and psoriatic arthritis, by establishing core data sets that should be collected and reported in randomized controlled trials (110). The relevant domains for fibromyalgia appear to be pain, patient global, fatigue, health-related quality of life, multidimensional function, sleep, depression, physical function, tenderness, dyscognition (cognitive dysfunction), and anxiety (110). Hudson and colleagues (108) found that in addition to pain reduction, what makes patients with fibromyalgia feel better might include improvement in fatigue, physical functioning, mood, and impact on daily living.

The Fibromyalgia Impact Questionnaire (FIQ) is a validated, disease-specific composite measure that was developed to determine the spectrum of problems related to fibromyalgia and responses to therapeutic intervention (112). It was modified in 1997 and 2002 to reflect experience using the instrument and to clarify the scoring system (113). Bennett et al (114) performed an analysis which indicated that a 14% change in the FIQ total score is clinically relevant and meaningful for patients with fibromyalgia. Thus, a 14% change in the FIQ score represents a minimally clinically important difference, and results of these analyses should enhance the clinical utility of the FIQ in research and practice.

The Revised Fibromyalgia Impact Questionnaire (FIQR) is an updated version of the FIQ that has good psychometric properties, can be completed in less than 2 minutes and is easy to score (115). The FIQR has the same 3 domains as the FIQ (that is, function, overall impact and symptoms). It differs from the FIQ in having modified function questions and the inclusion of questions on memory, tenderness, balance and environmental sensitivity. All questions are graded on a 0-10 numeric scale (114). The total scores of the FIQR and FIQ were closely correlated ($r = 0.88$, $P < 0.001$). Each of the 3 domains of the FIQR correlated well with the 3 related FIQ domains ($r = 0.69$ to 0.88 , $P < 0.01$). The FIQR showed good correlation with comparable domains in the SF-36, with a multiple regression analysis showing that the 3 FIQR domain scores predicted the 8 SF-36 subscale scores (115).

Vallejo and colleagues (116) developed a self-reporting tool which they call the Combined Index of Severity

of Fibromyalgia (ICAF). ICAF is composed of 59 items, offering 4 factors that explain 64% of the variance, and referred to as Emotional Factor (33.7%), Physical-Activity (15%), Active Coping (9%) and Passive Coping (6.3%). The ICAF evaluates emotional aspects: anxiety and depression, and their impact upon social aspects; patient functional capacity, fatigue, sleep quality, and pain; as well as the way in which the patient copes with the disease.

PHARMACOLOGICAL TREATMENT OF FIBROMYALGIA

Evidence supports a multi-faceted program comprising pharmacologic therapy and nonpharmacologic therapy (education, exercise, and cognitive behavioral therapy) (117).

Pharmacologic Approaches to the Treatment of Fibromyalgia

Until 2007, there were no specific agents approved by the US Food and Drug Administration (FDA) for the treatment of fibromyalgia, thus pharmacologic therapy before this was entirely "off-label." Pregabalin, an alpha-2 delta ligand and antiepileptic drug, in 2007 was the first agent the FDA approved for fibromyalgia. In 2008 duloxetine, a selective serotonin norepinephrine reuptake inhibitor (SNRI) drug was the second agent FDA-approved for fibromyalgia, and in 2009 milnacipran (also an SNRI) became the third drug FDA-approved for fibromyalgia.

Antidepressants

The majority of clinical trials for fibromyalgia have involved antidepressants of one class or another. Trials with the oldest class of agents (tricyclic antidepressants) have the most studies. Uçeyler et al (118) performed a systematic review on the effectiveness of treatment with antidepressants for fibromyalgia and included amitriptyline, and 13 RCTs, finding that it was efficient in reducing pain with a moderate magnitude of benefit (pain reduction by a mean of 26%, improvement in quality of life by 30%). Selective serotonin reuptake inhibitors (SSRIs) were studied in 12 RCTs, which also showed positive results, except for 2 studies on citalopram and one on paroxetine. Three RCTs on the dual serotonin and noradrenaline reuptake inhibitors (SNRIs) duloxetine and milnacipran and one of the 2 RCTs using the monoamine oxidase inhibitor moclobemide reported a positive result; however, the longest study duration was 12 weeks (118).

Tricyclic Antidepressants (TCA)

The effectiveness of TCAs, especially amitriptyline and cyclobenzaprine, in treating the symptoms of pain, poor sleep, and fatigue associated with fibromyalgia is supported by RCTs (119). Cyclobenzaprine, a centrally acting muscle relaxant, has been used to treat the musculoskeletal pain and sleep disturbances associated with fibromyalgia syndrome (120-122). The structure of cyclobenzaprine (Fig. 5A) is similar to those of amitriptyline (a tricyclic antidepressant, Fig. 5B) and cyproheptadine (5-HT receptor antagonist, Fig. 5C). Cyclobenzaprine, amitriptyline, cyproheptadine, and ketanserin significantly inhibited facilitatory effects of 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) on flexor reflexes and mono- and polysynaptic spinal reflex potentials in spinalized rats. In intact rats, these drugs significantly reduced the mono- and polysynaptic reflex potentials. 5-HT depletion significantly prevented the depression of the spinal reflex potentials induced by these drugs. These results suggest that the inhibitory effects of cyclobenzaprine, amitriptyline, and cyproheptadine on mono- and polysynaptic reflex potentials are due to the inhibition of descending serotonergic systems through 5-HT₂ receptors in the spinal cord (123). For the purposes of fibromyalgia treatment, cyclobenzaprine can be grouped with TCAs.

Most TCAs increase levels of serotonin and/or norepinephrine by directly blocking their respective reuptake. Many TCAs are considered "dirty" drugs in that they bind to many receptors and thus, may have significant adverse effects, especially at higher doses. In general, secondary amines (e.g., nortriptyline, desipramine) are tolerated somewhat better than tertiary amines (e.g., amitriptyline, imipramine, doxepin). Tolerability can be improved by starting at very low doses (e.g., 10 mg of amitriptyline or 5 mg of cyclobenzaprine), taking the dose a few hours before bedtime, and using a very gradual, slow titration schedule.

Antidepressants can vary considerably in terms of their ability to inhibit the reuptake of serotonin and norepinephrine. Furthermore, the ratio as to their effects on inhibition of serotonin reuptake versus inhibition of norepinephrine reuptake might change with increasing doses. Newer SNRIs such as duloxetine and milnacipran are somewhat more balanced than older antidepressants, but preferential inhibition is still present (e.g., duloxetine has more activity on serotonin reuptake inhibition than norepinephrine reuptake inhibition and milnacipran has more activity on norepinephrine reuptake inhibition than serotonin reuptake inhibition) (Fig. 6).

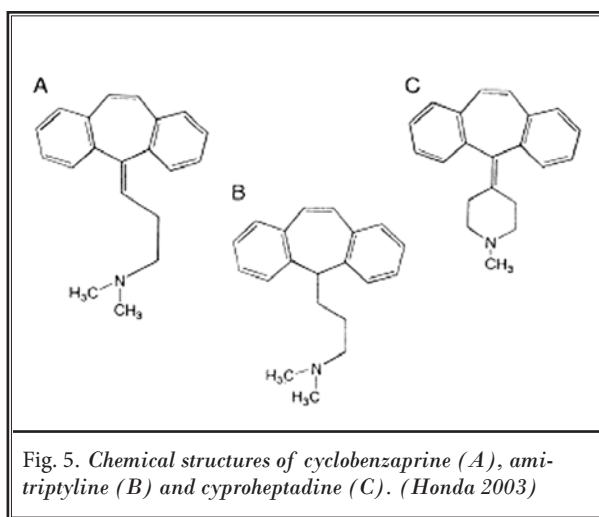


Fig. 5. Chemical structures of cyclobenzaprine (A), amitriptyline (B) and cyproheptadine (C). (Honda 2003)

Selective Serotonin Reuptake Inhibitors (SSRIs)

It is becoming apparent that SSRIs in general are poor agents to provide analgesia in most pain states. Highly selective serotonin reuptake inhibitors (e.g., citalopram, which does not significantly affect reuptake of norepinephrine), do not provide significant analgesia. Otto et al (124) performed a randomized, double-blind, placebo-controlled cross-over trial to see if escitalopram 20 mg once daily would relieve pain in polyneuropathy. Total pain and different pain symptoms were lower during escitalopram treatment ($P = 0.001-0.024$). The Number Needed to Treat (NNT) to obtain one patient with good or complete pain relief was 6.8 (124). Otto and colleagues (124) found a pain-relieving effect of escitalopram in patients with painful polyneuropathy, but a clinically relevant effect was obtained in only a few patients. Therefore, escitalopram cannot be recommended as a standard treatment in neuropathic pain (124). SSRIs which are less selective for serotonin reuptake (fluoxetine, paroxetine, and sertraline), might affect norepinephrine reuptake and thus might provide some analgesia in fibromyalgia, but at higher than average doses as they tend to have less analgesic potency than SNRIs or TCAs (125).

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Serotonin-Norepinephrine reuptake inhibitors (SNRIs) have an effect on norepinephrine reuptake as well as serotonin reuptake, provide analgesia, and are better tolerated than older TCAs. The first SNRI available

in the US, venlafaxine, might have significant effects on norepinephrine reuptake at higher doses and might be beneficial in fibromyalgia when used at these higher doses (126,127).

Duloxetine and milnacipran are two SNRIs that have undergone multicenter trials showing efficacy in fibromyalgia in multiple outcome domains (independent of their antidepressant effects) and have been approved for the treatment of fibromyalgia by the US FDA (128, 129). Duloxetine decreased self-reported pain and stiffness as well as reducing the number of tender points in fibromyalgia compared to placebo (125). Choy et al (130) analyzed pooled data from 4 double-blind, randomized, placebo-controlled studies (128,131) (2 with 6-month open-label extension phases) (132,133) and a 1-year, open-label safety study (131). Most treatment-emergent adverse effects (TEAEs) emerged early and were mild to moderate in severity (134). The profile of adverse events in patients enrolled at least 6 months, and for patients in the one-year study, was similar to that found in the short-term treatment studies, with no new adverse events emerging at a notable rate. About 20% of patients discontinued due to adverse events in the short-term treatment studies and in the one-year study. Serious adverse effects (SAEs) were uncommon, and none occurred at a significantly higher frequency for duloxetine compared with placebo (134). Arnold and colleagues (135) conducted a pooled analysis of 4 placebo-controlled clinical trials (128,130-132) which provided evidence that 12 weeks of treatment with duloxetine 60-120 mg/d effectively improves fibromyalgia symptoms and might offer benefits beyond pain relief (135). Milnacipran demonstrated overall improvement in fibromyalgia including improvement in level of fatigue, physical function, and discomfort (8,129,136-141). Fatigue data were pooled from 3 phase III pivotal studies (3 to 6 months) in fibromyalgia patients randomized to receive placebo (n=1133), milnacipran 100 mg (n=1139), or milnacipran 200 mg/d (n=837) (139). Among patients with fibromyalgia, 3 months of milnacipran treatment resulted in significant improvements relative to placebo in multiple dimensions of their fatigue (139).

Functional MRI studies in fibromyalgia patients suggest that similar levels of subjective pain result in similar CNS activation in both fibromyalgia patients and control individuals. For a similar stimulus, however, fibromyalgia patients have a greater subjective sensation of pain. This increased sensitivity is accompanied with a decreased activity in brain regions implicated in the descending pain inhibitory pathways. Fibromyalgia

patients treated with milnacipran exhibited a reduction in pain sensitivity and a parallel increase in activity in brain regions implicated in the descending pain inhibitory pathways compared to placebo-treated patients (140). In this study there was no comparable improvement in pain threshold among individuals responding positively to placebo, adding even more evidence to suggest that the hyperalgesia is playing a pathogenic role (i.e. rather than representing an epiphenomenon) in these illnesses.

Häuser et al (141) performed a meta-analysis with 18 randomized controlled trials (median duration, 8 weeks; range, 4-28 weeks) involving 1,427 participants. Overall, there was strong evidence for an association of antidepressants with reduction in pain (standardized mean differences [SMD], -0.43; 95% confidence interval [CI], -0.55 to -0.30), fatigue (SMD, -0.13; 95% CI, -0.26 to -0.01), depressed mood (SMD, -0.26; 95% CI, -0.39 to -0.12), and sleep disturbances (SMD, -0.32; 95% CI, -0.46 to -0.18). There was strong evidence for an association of antidepressants with improved health-related quality of life (SMD, -0.31; 95% CI, -0.42 to -0.20) (138). Effect sizes for pain reduction were large for TCAs (SMD, -1.64; 95% CI, -2.57 to -0.71), medium for monoamine oxidase inhibitors (SMD, -0.54; 95% CI, -1.02 to -0.07), and small for SSRIs (SMD, -0.39; 95% CI, -0.77 to -0.01) and SNRIs (SMD, -0.36; 95% CI, -0.46 to -0.25). Häuser and colleagues (141) concluded that antidepressant medications are associated with improvements in pain, depression, fatigue, sleep disturbances, and health-related quality of life in patients with fibromyalgia.

Alpha-2-delta Ligands

Pregabalin is a gamma-aminobutyric acid (GABA) analog antiepileptic drug which binds to the alpha-2-delta subunit of calcium channels, which is how it is thought to produce its beneficial effects. The FREEDOM trial (Fibromyalgia Relapse Evaluation and Efficacy for Durability of Meaningful Relief) (142) evaluated the durability of effect of pregabalin in reducing pain and symptoms associated with fibromyalgia in 1,051 patients who initially responded to the drug. The patients received 6 weeks of open label treatment with pregabalin and then 26 weeks of double-blind treatment (142). By the end of the double-blind phase, 61% of those in the placebo group had loss of therapeutic response compared with only 32% in the pregabalin group (140). Häuser et al (141) performed a meta-analysis of 4 other studies (143-146) of pregabalin for fibromyalgia. Effects were summarized using SMD. There was strong

evidence for a reduction of pain (SMD -0.28, 95% CI -0.36, -0.20; $P < 0.001$), improved sleep (SMD -0.39, 95% CI -0.48, -0.39; $P < 0.001$), and improved health-related quality of life (HRQOL) (SMD -0.30, 95% CI -0.46, -0.15; $P < 0.001$), but not for depressed mood (SMD -0.12, 95% CI -0.30, 0.06; $P = 0.18$) (147). The magnitude of all these beneficial effects in the entire cohort of groups of patients was small when using Cohen's measure of effect size, ranging from approximately 0.2 to 0.4 (148). Side effects such as dizziness and somnolence were common in individuals taking either of these drugs, each occurring in nearly one of 5 patients, whereas other side effects such as weight gain, confusion, and euphoria occurred less commonly (148). However, many analgesics used for chronic pain conditions have low effect sizes and frequent adverse effects. Even analgesics that are classically felt to be effective in treating chronic pain (e.g., NSAIDs or acetaminophen in osteoarthritis of the knee) have similar or even lower effect sizes for pain relief (149). They also raise concerns regarding the external validity of the studies, noting that patients with severe co-morbid depression or on disability were generally excluded from participation in the trials (148).

Gabapentin is an older and structurally similar alpha-2-delta ligand and antiepileptic drug which is not FDA approved for the treatment of fibromyalgia but has shown potential benefit in fibromyalgia. Arnold et al (150) performed a 12-week, randomized, double-blind study designed to compare gabapentin (1,200-2,400 mg/d) ($n=75$ patients) with placebo ($n=75$ patients) for efficacy and safety in treating pain associated with fibromyalgia with the primary outcome measure being the Brief Pain Inventory (BPI) average pain severity score. Arnold and colleagues (150) concluded that gabapentin (1,200-2,400 mg/d) is safe and efficacious for the treatment of pain and other symptoms associated with fibromyalgia.

Other Centrally Acting Agents

Gamma-hydroxybutyrate (also known as sodium oxybate), a precursor of GABA with strong sedative qualities has been shown to be beneficial in improving fatigue, pain, and sleep architecture in patients with fibromyalgia (151). Russell and colleagues (152) randomized 118 patients with fibromyalgia (92 of which completed the study) after discontinuing their prestudy fibromyalgia medications to receive 4.5 gm or 6 gm of sodium oxybate or matching placebo once per night for 8 weeks. The primary outcome variable (POV) was a composite score for changes from baseline in 3 coprimary self-report mea-

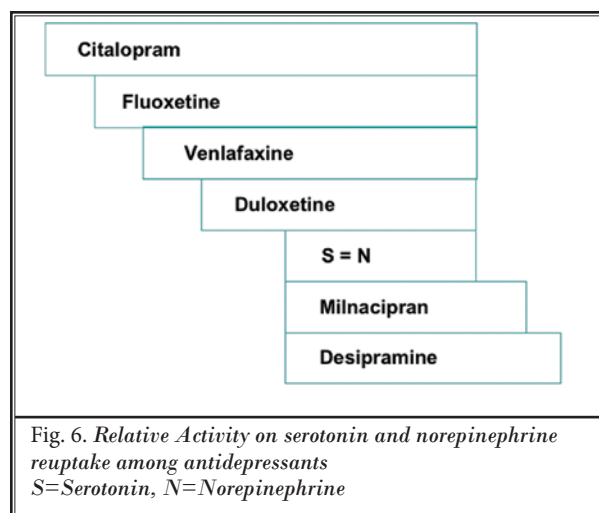


Fig. 6. *Relative Activity on serotonin and norepinephrine reuptake among antidepressants*
S=Serotonin, N=Norepinephrine

asures: patient's pain rating (in daily electronic diaries) on a pain visual analog scale (PVAS), the FIQ score, and the Patient Global Impression of Change (PGI-C) (152). Significant benefit was observed with both dosages of sodium oxybate, according to changes in the POV and subjective sleep quality (152). Improvements in the PVAS score were significantly correlated with sleep outcomes. Sodium oxybate was well tolerated overall; dose-related nausea ($\leq 28\%$ of patients) and dizziness ($\leq 18\%$ of patients) tended to resolve with continued therapy (152).

Pramipexole is a dopamine agonist used for Parkinson's disease that has utility for the treatment of periodic leg movement disorder (153). Pramipexole might improve both pain and sleep in fibromyalgia patients (154).

Tizanidine is a centrally acting alpha-2 adrenergic agonist considered a muscle relaxant which might have beneficial effects on spasticity. Tizanidine might produce significant improvements in several parameters in fibromyalgia including sleep, pain, and measures of quality of life (155). Additionally, tizanidine treatment resulted in a significant reduction in substance P levels in the CSF of patients with fibromyalgia.

There have been no adequate randomized controlled clinical trials of opioids in fibromyalgia, however, anecdotal evidence has not found this class of analgesics to be effective for fibromyalgia. Tramadol is a compound that has some weak analgesic effects by binding to the mu-opioid receptor, but the majority of its analgesic effects are from serotonin/norepinephrine reuptake inhibition. Tramadol appears to possess some beneficial effects in the management of fibromyalgia both alone and as a fixed-dose combination with acet-

aminophen (153,156,157). Tapentadol, an atypical opioid that has some opioid effects as well as inhibits the reuptake of norepinephrine, has not been studied yet for the treatment of fibromyalgia.

Non- Pharmacological Treatment of Fibromyalgia

Educational Approaches To Fibromyalgia Treatment

Upon initial diagnosis of fibromyalgia as well as when symptoms begin to improve, providing education about fibromyalgia and exercise techniques, during visits or group meetings, and through books and Web resources might be clinically useful (158). Goldenberg (159) suggests providing patients with fibromyalgia a detailed discussion of potential pathophysiological mechanisms in the context of the biopsychological model; dispelling the notion that the absence of organic disease means that the symptoms are "psychogenic" (159).

Burckhardt and colleagues (160) assigned patients who had fibromyalgia to an education-only condition, an education plus physical training condition, or a delayed treatment wait list control. Both active treatment groups improved on subjective ratings and reports of physical activity compared with controls.

Rooks and colleagues (161) completed a randomized controlled trial with 207 patients confirmed to have fibromyalgia who were assigned to one of 4 groups: an aerobic and flexibility exercise group; a strength training, aerobic, and flexibility exercise group; the Fibromyalgia Self-Help Course; or a combination of the previous 3 groups.

The combination group showed the greatest improvement. It appears that education is most effective in multimodal interventions. CBT combines interventions from cognitive and behavior therapies. Cognitive therapy is based on the premise that modifying maladaptive thoughts results in changes in affect and behavior (162).

Exercise Approaches to Fibromyalgia Treatment

Seventy exercise interventions in fibromyalgia have been published since the early 1970s. A total of 4,385 participants completed 56 randomized controlled trials from 1998 to 2008 (158). Modalities of exercises studied included aerobics (land and water), strength, flexibility, and various combinations of these. More recently,

"movement therapies," such as Qi Gong, T'ai Chi, and yoga, have been tested with positive results (158).

Multiple exercise reviews, position papers, and clinical guidelines have been published; however, studies on exercise in fibromyalgia have suffered from a high attrition rate (158).

The average attrition rate for studies included in the Cochrane Review was 27%. Some early strength training studies had dropout rates as high as 47% (163). Likewise, programs testing running, calisthenics, and fast dancing have reported up to 67% attrition (164). Similarly, high-intensity exercise has also been shown to provoke pain compared with low intensity exercise (165). Exercise interventions that were lower in intensity and allowed for some individualization in the protocol have yielded attrition rates less than 10% (166).

Eighteen original exercise clinical trials have been recently published (161,166-181). Most were high-quality studies confirming that individualized low-intensity exercise of varying dose and modality was effective at improving function and reducing symptoms (158).

In summary, exercise interventions in fibromyalgia are generally positive, with benefits seen largely in fibromyalgia symptoms and physical functioning. The use of low-intensity low-impact programs and maintenance of the ability to individualize the protocol are crucial for optimal adherence to regimens (158). Evidence for mixed-type or aerobic exercise is strongest, with mounting evidence for beneficial effects from strength training (163,166,171,182-185).

The results of flexibility training, including yoga studies, are positive, but there is not yet a preponderance of evidence that supports the use of flexibility training as a single modality in fibromyalgia (166,168,177,187-190). More research needs to be done to evaluate the effectiveness of movement-based therapies in fibromyalgia, such as Qi Gong and T'ai Chi, because emerging evidence in these modalities is positive (174,179,191-194).

Mannerkorpi and colleagues (176) evaluated the effects of pool exercise in patients with fibromyalgia and chronic widespread pain and to determine characteristics influencing the effects of treatment. They demonstrated that the exercise-education program showed significant, but small, improvement in health status in patients with fibromyalgia and chronic widespread pain, compared with education only (176). Patients with milder symptoms improved most with this treatment (176).

Langhorst and colleagues (195) included 10 out of

13 RCTs with 446 participants, with a median sample size of 41 (range 24-80) and a median treatment time of 240 (range 200-300) minutes, into the meta-analysis of hydrotherapy in fibromyalgia (195). Only 3 studies had a moderate quality score. There was moderate evidence for reduction of pain (SMD -0.78; 95% CI -1.42, -0.13; $P < 0.0001$) and improved health-related quality of life (HRQOL) (SMD -1.67; 95% CI -2.91, -0.43; $P = 0.008$) at the end of therapy (192). There was moderate evidence that the reduction of pain (SMD -1.27; 95% CI -2.15, -0.38; $P = 0.005$) and improvement of HRQOL (SMD -1.16; 95% CI -1.96, -0.36; $P = 0.005$) could be maintained at follow-up (median 14 weeks) (195).

Posture and body alignment work might be helpful in conditions such as fibromyalgia by decreasing peripheral pain generators. Posture prescriptions are generally focused on stretching or strength training without added weights (e.g., isometric muscle contractions). Pain-perpetuating postures are common in fibromyalgia and include shortening of the neck and upper back muscles as the patient assumes a head-forward, shoulders-raised, back-rounded posture (158). It is best in patients with fibromyalgia to avoid causing unnecessary strain on the muscles and thus, it is important to minimize eccentric muscle use (158) (e.g., a load is placed on elongated muscles while walking downhill, creating greater eccentric muscle work).

Exercise should also be modified to minimize aggravation of the peripheral pain generators. It is important to choose a type of exercise that does not exacerbate these peripheral pain generators (i.e. patients who have significant knee osteoarthritis and stiffness may do better with water-based aerobics than land-based aerobics) (158). Patients who prefer treadmill walking should walk at a flat, rather than downward, sloping grade to minimize eccentric muscle use. Use small steps and limited arm extension when walking, mopping, or vacuuming to minimize eccentric work in the hips and thighs. Also keep movements near the midline of the body and minimize overhead work and repetitive motion, particularly of small muscle groups (158).

Aerobic activity in fibromyalgia is best accomplished by moving the large muscle groups of the legs and hips, with lesser involvement of the upper extremities. The program should avoid repetitive movements by alternating limbs, building in rest periods that are individualized by the participant, and changing movement patterns frequently (158).

The Ottawa Methods Group found and synthesized evidence from comparative controlled trials following

Cochrane Collaboration methods and formed the Ottawa Panel, with nominated experts from key stakeholder organizations (196). The Ottawa Panel recommended aerobic fitness exercises for the management of fibromyalgia as a result of the emerging evidence (grades A, B, and C+, although most trials were rated low quality) shown in the literature (196).

To receive a grade of A, an RCT had to have an outcome that was both statistically significant and clinically important (an improvement of more than 15% relative to a control, based on panel expertise and empiric results). Grade A outcomes were found for pain relief (190,197-199), psychological well-being (200), endurance (200), anxiety (200), self efficacy (200), depression (201), quality of life (190,165,198,199,202), muscle strength (force-generating capacity) (197), cardiorespiratory fitness (190,198,199), physical general awareness (198), and flexibility (190). However, applying the Jadad scale only, 6 out of the 16 trials were of high methodological quality (≥ 3), (188,197,199,203-205) with scores ranging from 3 to 5.

There were 5 positive recommendations: 2 grade A and 3 grade C+. All 5 were of clinical benefit (206). The Ottawa Panel recommends strengthening exercises for the management of fibromyalgia as a result of the emerging evidence shown in the literature (206). However, only one trial (166) was of higher methodological quality, with a Jadad scale score of 3 out of 5 (206).

BEHAVIORAL MEDICINE APPROACHES TO FIBROMYALGIA TREATMENT

Catastrophizing, or the belief that the worst possible outcome is going to occur, has been associated with pain severity, (207-209) decreased functioning, (208) and affective distress in fibromyalgia (208,209). In cognitive therapy, catastrophic thoughts, such as "My pain is terrible and there is nothing I can do about it," are reframed to "As bad as my pain might get, there are things I can do to make it at least a little better" (210).

Behavior therapy is rooted in the theory that inner states (thoughts and feelings) are less important than the use of operant behavior change techniques to increase adaptive behavior through positive and negative reinforcement and to extinguish maladaptive behavior by using punishment (210). In fibromyalgia, several behavioral techniques are applicable, including behavioral activation (getting patients moving again), graded exercise (initiating exercise and then slowly increasing activities), activity pacing (not overdoing it on days when patients feel good and remaining active on

days when they feel bad), reducing pain behaviors (not reinforcing behaviors associated with secondary gain), sleep hygiene (identifying and then changing behaviors known to disrupt sleep), and learning relaxation techniques to lower stress (e.g., breathing, imagery, progressive muscle relaxation [PMR]) (210).

All CBT interventions are not equal, with many including only modest elements of cognitive therapy and, instead, relying heavily on behavioral interventions (209). Furthermore, CBT might be somewhat operator-dependent and has specific programs for specific conditions/symptoms (e.g., Insomnia [CBT-I]; Pain [CBT-P]; Stress [CBT-S]).

Williams and colleagues (211) randomly assigned 145 patients who had fibromyalgia to 4 weeks of group CBT (6 sessions) or standard medical care. Twenty-five percent of patients who had fibromyalgia and were receiving CBT met criteria for being a "treatment responder" (i.e., sustained improvement in functional status) compared with 12% of those receiving only standard medical care. Pain scores did not change significantly for either group, but patients considered to be "treatment failures" in the CBT group showed no worsening of symptoms or functional status, unlike the wait list controls, who demonstrated deterioration in energy and physical role functioning.

Thieme and colleagues (212) randomly assigned 125 patients who had fibromyalgia to CBT, operant behavior therapy (OBT), or an attention control group. OBT consisted of behavioral interventions to reduce pain behaviors, whereas CBT addressed modifying maladaptive thoughts, problem solving, decreasing psychological stress, pain-coping strategies, and relaxation. These researchers found that when compared with the attention control, CBT and OBT resulted in greater improvement in pain, decreased emotional distress, and improved physical functioning for up to one year after treatment (212). Patients in both treatment groups also had fewer physician visits compared with those in the control group. Further, the effect sizes for improvement were large for CBT and OBT; however, for the most part, the differences between the 2 active treatments were not significant.

RELAXATION TECHNIQUES

Relaxation techniques are commonly part of CBT for fibromyalgia, (211,213). Relaxation techniques likely to be helpful for fibromyalgia symptoms include but are not limited to PMR, autogenic training, guided imagery, and meditation.

PMR involves the systematic tightening and relax-

ing of various muscle groups with the goal of decreasing muscle tension overall, and thus ameliorating anxiety, which was presumed to be linked to muscle tension (214). Patients with fibromyalgia should be cautioned not to tense their muscles too tightly during this exercise because this could result in exacerbating pain. Autogenic training involves repeating such phrases as "My arms are heavy and warm" and visualizing heaviness and warmth in the arms (215).

Autogenic training includes elements of guided imagery, however guided imagery alone that involves engaging all the senses in experiencing pleasant places or circumstances has proved to be helpful for some who have fibromyalgia.

In a randomized controlled trial of 55 women who had fibromyalgia, it was found that those in the guided imagery arm had less pain compared with the control group (216). In another study comparing a 6-week guided imagery intervention with treatment as usual, patients who had fibromyalgia and were receiving guided imagery demonstrated improved functional status and reported a greater sense of self-efficacy for managing pain, although actual pain reports did not change (217).

Hassett and colleagues (218) treated 12 women over 10 sessions and found the HRV biofeedback group to have improved in most fibromyalgia symptom areas (sleep, pain, fatigue, depression, and overall functioning).

Buckelew and colleagues (219) conducted a randomized controlled trial comparing electromyogram (EMG) biofeedback, exercise training, combination treatment (biofeedback and exercise), and an educational/attention control. Patients in the treatment groups showed improvements in self-efficacy for functioning and better tender point index scores (219). Babu et al (220) compared surface EMG biofeedback to a sham feedback condition with patients who had fibromyalgia and found the active biofeedback to reduce tender points and subjective symptoms and to result in improvements on functioning and the 6-minute walk test.

Thieme and Gracely (221) performed a literature search which identified 14 RCTs of CBT and OBT, 5 relaxation RCTs, 5 biofeedback RCTs, 5 hypnotherapy RCTs, and 2 writing intervention RCTs (221). For psychoanalytic therapy in fibromyalgia, no RCTs have been published. The highest effect sizes ($r = 0.53-2.14$) for pain reduction are found after CBT and OBT group treatments (221). Relaxation as a single treatment has not been proven useful. Hypnotherapy and writing intervention have demonstrated mild treatment effects,

whereas psychological treatment is effective in fibromyalgia pain (221).

An internal locus of pain control (I-loc) refers to a belief in pain being an experience that can be modified through personal effort. Actual life experiences might support such beliefs (e.g., success in using behavioral coping skills) (222). Williams et al (222) studied 72 females satisfying ACR criteria for fibromyalgia (mean age = 45.5, [SD = 9.9]) who were randomly assigned to one of 3 treatment arms: exercise, relaxation, or standard case (222). Analysis of covariances (ANCOVA) revealed that even though pain severity was not different, I-loc responders had significant reductions in the number of painful body regions ($F(1.69) = 4.53, P < 0.05$) at post treatment. Responders also demonstrated significant improvements in physical function status as assessed by the SF-36 PCS score ($F(1.69) = 6.55, P < 0.01$) (221). I-loc, a belief in personal pain control, is modifiable through brief nonpharmacological approaches such as exercise and relaxation. Bolstering the belief in I-loc appears to influence pain by influencing perceptions of an illness' effect rather than symptom severity in individuals with fibromyalgia (222).

MULTICOMPONENT TREATMENT OF FIBROMYALGIA

Häuser et al (223) performed a meta-analysis and included 9 (of 14) RCTs with 1,119 participants (median treatment time 24 hours) in the meta-analysis. Effects were summarized using SMDs or weighted mean differences (WMDs). There was strong evidence that multicomponent treatment reduces pain (SMD -0.37; 95% CI -0.62, -0.13), fatigue (WMD -0.85; 95% CI -1.50, -0.20), depressive symptoms (SMD -0.67; 95% CI -1.08, -0.26), and limitations to HRQOL (SMD -0.59; 95% CI -0.90, -0.27) and improves self-efficacy pain (SMD 0.54; 95% CI 0.26, 0.82) and physical fitness (SMD 0.30; 95% CI 0.02, 0.57) at posttreatment. There was no evidence of its efficacy on pain, fatigue, sleep disturbances, depressive symptoms, HRQOL, or self-efficacy pain in the long term. There was strong evidence that positive effects on physical fitness (SMD 0.30; 95% CI 0.09, 0.51) can be maintained in the long term (median follow-up 7 months) (223).

Häuser and colleagues (224) compared the methodology and the recommendations of evidence-based guidelines for the management of fibromyalgia to give an orientation within the continually growing number of reviews on therapy for fibromyalgia. There are currently 3 evidence-based guidelines for the manage-

ment of fibromyalgia published by professional organizations which meet the inclusion criteria of Häuser et al (224): The American Pain Society (APS) (225), the European League Against Rheumatism (EULAR) (226), and the Association of the Scientific Medical Societies in Germany (AWMF) (227).

APS and AWMF ascribed the highest level of evidence to systematic reviews and meta-analyses, whereas EULAR credited the highest level of evidence to randomized controlled studies. Both APS and AWMF assigned the highest level of recommendation to aerobic exercise, cognitive-behavioral therapy, amitriptyline, and multicomponent treatment. In contrast, EULAR assigned the highest level of recommendation to a set of pharmacological treatment. Although there was some consistency in the recommendations regarding pharmacological treatments among the 3 guidelines, the APS and AWMF guidelines assigned higher ratings to CBT and multicomponent treatments (224). Although the search strategies of all 3 guidelines were comparable, EULAR did not include studies on multicomponent treatment, some physical therapies (e.g., acupuncture, massage), or psychological therapies other than CBT. Whereas APS and AWMF used the data of systematic reviews and meta-analyses to support their recommendations, EULAR performed its own statistical analyses by calculating effect sizes of pain visual analog scales (VAS) and function assessed by the FIQ (228).

Similar treatments work for many of the CSS entities. Several drug and non-drug therapies have been shown to be effective for nearly any of the CSS disorders, further reinforcing that this might well be a large overlapping disorder rather than several separate ones. Among classes of drugs, substantial data suggest that tricyclic compounds are effective for treating most of the conditions noted (229-231). Newer serotonin-norepinephrine re-uptake inhibitors such as duloxetine and tramadol have similarly been shown to be effective across a broad range of these conditions (232), and interestingly duloxetine had much earlier been shown to be helpful in treating the pain associated with depression, which is not surprising. The alpha-2-delta ligands such as pregabalin and gabapentin are also being shown to be efficacious in a wide range of these entities (150).

Figure 7 lists the classes of drugs and their level of evidence in fibromyalgia, but in general those drugs with the highest level of evidence in fibromyalgia are also being shown to work in subsets of individuals with CSS. More importantly, drugs such as duloxetine are

being shown to be effective in conditions such as osteoarthritis and low back pain, pointing out that these central mechanisms that are “front and center” in patients with syndromes such as fibromyalgia might be also playing prominent roles in conditions heretofore thought to be peripheral pain syndromes. But we have known for some time that hyperalgesia and other central factors, as well as various other indicators of a wide range of “fibromyaglia-ness” is present in conditions such as osteoarthritis and low back pain.

It is of note that any one of these classes of drugs only works well in about a third of patients, which is entirely consistent that this is a strongly genetic – but polygenic disorder – and thus different treatments are needed in different individuals. Going back to the “essential hypertension of pain processing pathway” analogy, just as we use 8 – 10 classes of drugs acting in different body systems and at different molecular targets to control hypertension, and individuals might respond very well to one class of anti-hypertensive drug but not another, the same is true of CSS syndromes. Individuals might only respond to one of these classes of drugs or might often be on several classes of centrally-acting analgesics (e.g., a low dose of cyclobenzaprine 2 hours before bedtime, pregabalin or gabapentin either just at bedtime or twice daily, and a serotonin-norepineprine reuptake inhibitor such as duloxetine or milnacipran during the day). However, our current pharmacological armamentarium is not nearly as well developed for

central pain as for essential hypertension, which is likely one of the reasons that these syndromes are often still difficult to treat.

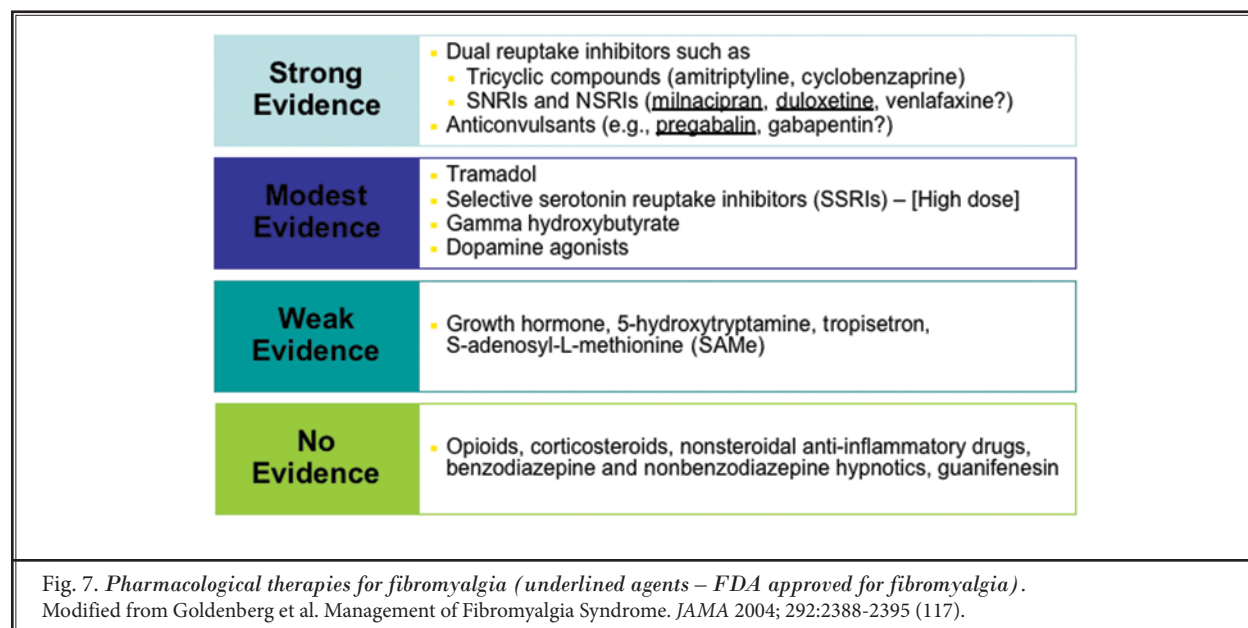
Figure 6 also points out that classes of drugs that are quite effective for “peripheral” or somatic pain due to damage or inflammation in peripheral tissues, such as NSAIDs and opioids, are not nearly as effective analgesics in central pain states.

Just as many pharmacological therapies work across all or most of these conditions, similarly non-pharmacological therapies such as education, exercise, and cognitive behavioral therapy have been demonstrated to be effective across nearly all of the CSS conditions (230-232).

Interventional techniques are generally not well suited for patients with “pure” fibromyalgia, however, patients with fibromyalgia who are also diagnosed with various spinal conditions may be effectively treated with multiple approaches, including interventional techniques (236-253).

CONCLUSION

In the past decades, our understanding of fibromyalgia has evolved tremendously, and the study of fibromyalgia has taught us about the mechanisms that might underlie chronic pain or other somatic syndromes, in individuals without fibromyalgia per se. A better understanding of the underlying mechanisms and most effective treatment for this spectrum of illness is critical to rheumatologists, because as



Wolfe has taught us, many patients with rheumatic disorders have a little, or a lot, of “fibromyalgia-ness.” When this occurs, we need to treat both the peripheral and central elements of pain and other somatic symptoms.

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