Fibromyalgia Syndrome: Review of Clinical Presentation, Pathogenesis, Outcome Measures, and Treatment

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ABSTRACT. Fibromyalgia syndrome (FM) is a common chronic pain condition that affects at least 2% of the adult population in the USA and other regions in the world where FM is studied. Prevalence rates in some regions have not been ascertained and may be influenced by differences in cultural norms regarding the definition and attribution of chronic pain states. Chronic, widespread pain is the defining feature of FM, but patients may also exhibit a range of other symptoms, including sleep disturbance, fatigue, irritable bowel syndrome, headache, and mood disorders. Although the etiology of FM is not completely understood, the syndrome is thought to arise from influencing factors such as stress, medical illness, and a variety of pain conditions in some, but not all patients, in conjunction with a variety of neurotransmitter and neuroendocrine disturbances. These include reduced levels of biogenic amines, increased concentrations of excitatory neurotransmitters, including substance P, and dysregulation of the hypothalamic-pituitary-adrenal axis. A unifying hypothesis is that FM results from sensitization of the central nervous system. Establishing diagnosis and evaluating effects of therapy in patients with FM may be difficult because of the multifaceted nature of the syndrome and overlap with other chronically painful conditions. Diagnostic criteria, originally developed for research purposes, have aided our understanding of this patient population in both research and clinical settings, but need further refinement as our knowledge about chronic widespread pain evolves. Outcome measures, borrowed from clinical research in pain, rheumatology, neurology, and psychiatry, are able to distinguish treatment response in specific symptom domains. Further work is necessary to validate these measures in FM. In addition, work is under way to develop composite response criteria, intended to address the multidimensional nature of this syndrome. A range of medical treatments, including antidepressants, opioids, nonsteroidal antiinflammatory drugs, sedatives, muscle relaxants, and antiepileptics, have been used to treat FM. Nonpharmaceutical treatment modalities, including exercise, physical therapy, massage, acupuncture, and cognitive behavioral therapy, can be helpful. Few of these approaches have been demonstrated to have clear-cut benefits in randomized controlled trials. However, there is now increased interest as more effective treatments are developed and our ability to accurately measure effect of treatment has improved. The multifaceted nature of FM suggests that multimodal individualized treatment programs may be necessary to achieve optimal outcomes in patients with this syndrome. (J Rheumatol 2005;32 Suppl 75:6-21)

Key Indexing Terms:

NEUROTRANSMITTER	PAIN	NEUROHORMONE
FIBROMYALGIA	SLEEP	FATIGUE

FIBROMYALGIA: THE CLINICAL SYNDROME

Fibromyalgia (FM) is one of several relatively common overlapping syndromes characterized by otherwise unexplained chronic pain and fatigue[1,2]. The cardinal features of FM are chronic widespread pain in the presence of multiple tender points throughout the body on physical examination. Clinical descriptions of what we now call FM have been reported since the mid-1800s. Various terms, including "neurasthenia" and "muscular rheumatism" had originally been applied. In 1904, Gowers created the term "fibrositis"[3], which was used until the 1970s and 1980s, when it was recognized that the etiology of this syndrome lay in the central nervous system (CNS). Pioneering studies by Smythe and Moldofsky[4] shed light on associated sleep pathology and opened the door to our current concept of the condition as caused by both central and peripheral pain sensitization mechanisms, which contribute to the constellation of symptoms that define FM[5-7].

Diagnosis is made by a combination of patient history, physical examination, laboratory evaluations, and exclusion of other causes for symptoms attributed to FM. In 1990, the American College of Rheumatology (ACR) defined 2 major diagnostic criteria for classifying FM in adults. The first criterion is a history of widespread pain for at least 3 months. The second criterion requires patient report of tenderness in at least 11 of 18 defined tender points when digitally palpated with about 4 kg per unit area of force (Figure 1)[8]. The diagnostic utility of tender points was supported by reports in the 1980s, including ability to distinguish FM from controls[9,10]. The

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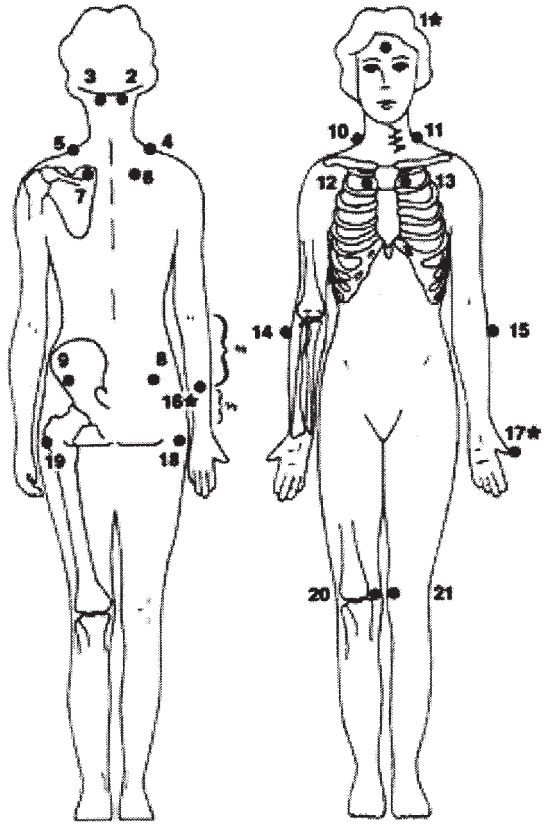

Figure 1. Location of tender points[8]. * Represents "control" points.

pain is often described as a deep, widespread, gnawing or burning ache, frequently radiating and quite variable. Pain self-rating may well be more severe than rheumatoid arthritis (RA)[11]. Virtually all patients describe severe fatigue, significant in the morning, despite adequate sleep, and worsening again by mid-afternoon. Fatigue may be described as being physically or emotionally draining[11]. Patients usually describe poor sleep patterns, either difficulty with falling asleep or frequent wakening. Additional features of FM often include stiffness, skin tenderness, postexertional pain, irritable bowel syndrome, cognitive disturbance, irritable bladder syndrome or interstitial cystitis, tension or migraine headaches, dizziness, fluid retention, paresthesias, restless legs, Raynaud's phenomenon, and mood disturbances[11,12]. Three key features, pain, fatigue, and sleep disturbance, are present in virtually every patient with FM[13,14].

The ACR tender point criteria for a diagnosis of FM have been accepted as adequate for diagnosis of this condition in the clinical setting[15], but have also been criticized. Many patients with chronic widespread pain have less than the 11 of 18 tender points specified in the ACR criteria[6]. Clauw and Crofford have pointed out that the tender point requirement in the ACR criteria may artificially increase the female predominance of FM, and select for individuals with higher levels of disease-related distress[16]. It has also been noted that the ACR classification criteria focus only on pain and disregard other important symptoms of FM, including fatigue, cognitive disturbance, sleep disturbance, and psychological distress, and that focusing strictly on pain may fail to capture the "essence" of this syndrome[17].

About 10%–11% of the population has chronic widespread pain at any given time and about one-fifth of these individuals have the 11 of 18 tender points specified in the ACR classification criteria[16,18]. Chronic regional pain is present in 20%–25%. Even when defined according to the highly focused criteria set forth by the ACR, FM is a very common condition that has been estimated to affect about 2% of the adult (18 years of age) population in the USA. FM has a prevalence of 3.4% in women versus only 0.5% in men[19]. It occurs in 5%–6% of adult patients presenting at general medical and family practice clinics and in 10%–20% of adult patients presenting to rheumatologists, making it one of the most common diagnoses in office-based rheumatology practices[19,20].

To differentiate symptom characteristics of FM from those present in other patients with chronic pain, it is important that assessments used in the evaluation be sensitive to differences between this condition and other chronic pain states, as they may have similar symptoms[21-4]. As many as 80% of patients with FM also fulfill criteria for chronic fatigue syndrome, up to 80% have headaches, 75% have temporomandibular disorders, and up to 60% may have irritable bowel syndrome[14]. The extensive overlap between FM and chronic fatigue syndrome is underscored by results from a recent analysis demonstrating that these 2 syndromes share a large number of symptoms, including muscle pain, sleep disturbance, fatigue, cognitive dysfunction, abdominal pain, muscle weakness, reduced activity, and migratory arthralgias[13]. The high comorbidity found in patients with FM and the similarity between the cardinal symptoms of this and other closely related diseases make specific assessment of effects of treatment on FM symptoms challenging.

Many patients with FM suffer significant disability and reduced quality of life. Results from one survey carried out in the mid-1990s indicated that 25.3% of patients received disability payments. However, only 25% of these were specifically for the diagnosis of FM[25]. Results from a small cohort of 127 patients with FM indicated substantially greater disability. Overall, 31% of patients employed prior to onset of their FM reported loss of employment due to their disease[26].

The disability associated with FM does not change substantially over time. For example, in a large cohort of 538 patients followed for 7 years and evaluated with the Health Assessment Questionnaire (HAQ) every 6 months, functional disability worsened slightly over this period. Further, measures of pain, global severity, fatigue, sleep disturbance, anxiety, and depression were

all abnormal at study entry (an average of 7.8 yrs after disease onset) and were essentially unchanged over the study period[27].

The pain, disability, and other symptoms of FM result in significantly reduced quality of life for patients with this disease. Results from one comparison of women with FM versus healthy women and others with RA, osteoarthritis, permanent ostomies, chronic obstructive pulmonary disease, or type 1 diabetes indicated that those with FM had consistently lower scores than all others for nearly all the domains evaluated[28]. Results from a more focused comparison of 44 women with FM and 41 with RA indicated that the 2 diseases resulted in similar degrees of disability and negative impact on quality of life[29].

PATHOPHYSIOLOGY OF FIBROMYALGIA

Our understanding of the pathophysiology of FM has evolved significantly in recent years, but remains incomplete. The following sections briefly summarize information about alterations in neurotransmitters, neurohormones, cytokines, and regional CNS blood flow that have been documented in patients with FM.

Predisposition to FM and Triggering Events

Genetic factors may predispose individuals to FM. Sibship analysis has demonstrated possible genetic linkage of FM to the HLA region[9], and a recent analysis of genetic polymorphism for catechol-O-methyltransferase, an enzyme that inactivates catecholamines, indicated that the LL and LH genotypes occurred more often in patients with FM than in controls. In addition, the HH genotype was seen less often in patients with FM than in healthy patients[30]. Possibly unique autoantibody patterns have been observed in patients with FM, compared to controls, but to date, none have been documented to have diagnostic or clinical relevance. For example, significant differences between serotonin antibodies have been noted between patients with FM and controls[31,32], but were not considered diagnostically relevant when correlated with clinical manifestations[32].

Environmental factors may play a role in triggering the development of FM, and a number of "stressors" have been temporally correlated with the onset of the syndrome, including trauma, infections (e.g., hepatitis C virus, HIV, and Lyme disease), emotional stress, catastrophic events (e.g., war), autoimmune disease, and other pain conditions[16,33].

FM has been reported to coexist in 25% of patients with RA, 30% of patients with lupus, and 50% of patients with Sjögren's syndrome[34-36]. It is important for the clinician to distinguish the symptoms and signs of a coexistent rheumatic disease from those of FM in order to educate the patient about the potential for these conditions to coexist, and to make proper decisions about therapy. This said, it is not always possible to make these distinctions, and thus observing the results of therapeutic trials helps our understanding of the mechanisms contributing to the symptoms. The possibility exists that pain or immunologic factors contribute to the development of FM in these associations.

Several groups have documented the occurrence of distinct triggering events in patients with FM. Results from one retrospective analysis indicated that 23% of a cohort of 127 patients with FM had a potential precipitating event (trauma, surgery, or medical illness) before onset of disease[26]. Results from a second prospective trial of 161 patients with trauma indicated that 14.4% developed FM and that it was particularly common after neck injury[37]. While these results are consistent with the view that there may be a distinct triggering event for many patients with FM, those of Greenfield and colleagues also underscore the point that such an event is not apparent for many patients with this condition. No triggering event was noted for 72% of patients included in their analysis[26].

Biochemical, Physiologic, and Psychiatric Abnormalities Underlying FM

Biogenic amines. The biogenic amines 5-HT and norepinephrine (NE) have a significant modulatory effect on peripheral and central pain processing[38]. Levels of primary metabolites of NE and 5-HT are both reduced in patients with FM[39]. Serum 5-HT concentrations are also abnormally low in these patients[40]. The decrease in 5-HT noted for patients with FM is particularly interesting because this amine is involved in several processes and disease states that may contribute to the overall symptomatology in patients with FM. First, 5-HT acts to presynaptically inhibit release of neurotransmitters involved in pain processing (e.g., substance P, excitatory amino acids) from the terminals of primary afferent neurons[41]. Serotonin also plays an important role in the regulation of mood, and dysregulation of the 5-HT system has been associated with both depression and anxiety[42,43]. Serotonin is also known to be involved in the regulation of sleep and pain perception, both of which may be altered in patients with FM[43].

Substance P and amino acid neurotransmitters. The level of substance P is elevated in the cerebrospinal fluid of patients with FM[44,45]. Measures of pain intensity in these individuals are positively correlated with levels of the metabolites of the excitatory amino acid neurotransmitters glutamate and aspartate[46]. Both excitatory amino acids and substance P contribute to the transmission of pain signals via primary afferent neurons, and glutamate is probably the most common excitatory neurotransmitter in the CNS[46,47]. Concentrations of glycine and taurine were shown to be correlated with pain levels in patients with FM. Glycine is an inhibitory transmitter as well as a

positive modulator of the N-methyl-D-aspartate (NMDA) receptor[46]. The NMDA receptor has been suggested as playing a key role in the nervous system reorganization thought to be involved in the maintenance of chronic pain[45,48].

The increased levels of substance P and other excitatory neurotransmitters in patients with FM may be related to reduced 5-HT and the resultant decrease in presynaptic inhibition of pain-related primary afferent neurons. This view is supported by the report that there are significant negative correlations between levels of substance P and 5-HT, its precursor tryptophan, and its primary metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the serum of patients with FM. Moreover, reduced levels of 5-HIAA and tryptophan were associated with increased pain in these patients, and low levels of 5-HIAA and high concentrations of substance P were both positively correlated with more severe sleep disturbance[49].

The hypothalamic-pituitary-adrenal axis and autonomic nervous system. A large body of evidence supports the relationship between stress and altered activity in both the sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) axis[50,51], and results from a number of studies have documented significant dysregulation of the HPA axis in patients with FM. Such patients have elevated basal values of adrenocortical trophic hormone (ACTH) and follicle-stimulating hormone and decreased levels of insulin-like growth factor 1 (IGF-1), free triiodothyronine, growth hormone (GH), estrogen, and urinary cortisol[52,53]. The normal circadian rhythm for plasma cortisol levels is also disrupted in patients with FM due to abnormally elevated plasma concentrations in the evening[54]. Because the 5-HT system significantly influences the HPA axis, some, if not all, endocrine abnormalities observed in FM may be related to reduced levels of 5-HT observed in these patients[52]. It has also been suggested that the decreased levels of IGF-1 in patients with FM may be the result of a decrease in stage 4, sleep-dependent release of GH[52].

Patients with FM also exhibit marked hypersecretion of ACTH in response to severe acute stressors or insulin-induced hypoglycemia, and this has been suggested to result from chronic hyposecretion of corticotrophin-releasing hormone[45,53,55]. The abnormal hormonal and autonomic responses in FM appear to reflect impairment in the hypothalamic or CNS response to stimuli rather than a primary defect at the level of the pituitary or peripheral endocrine glands[56].

HPA abnormalities reported for patients with FM may be related to depressed autonomic nervous system function. Patients with FM have reduced plasma levels of neuropeptide Y, a peptide colocalized with NE in the sympathetic nervous system[57]. However, interactions between the autonomic nervous system and the HPA axis have not been clearly delineated in patients with FM[45].

Cytokines. Alterations of the cytokine network are correlated with many pain states[58], and cytokine abnormalities have been observed in patients with FM. Wallace and colleagues reported that levels of interleukin 1 receptor antibody (IL-1Ra) and IL-8 were significantly higher in the sera of FM patients and that IL-1Ra and IL-6 were significantly elevated in stimulated and unstimulated peripheral blood mononuclear cells from individuals with this disease[59]. Salemi and colleagues detected IL-1, IL-6, and tumor necrosis factor-α in about 30% of skin biopsies from 53 patients with FM, as compared to none in healthy controls[60]. The significance of these observations is unknown.

Regional CNS blood flow. A range of abnormalities in regional cerebral blood flow (rCBF) have been reported in patients with FM, including: flow decreases in the dorsolateral frontal cortical areas of both hemispheres[61], thalamus and head of the caudate nucleus[62], inferior pontine tegmentum[63], superior parietal cortex, and the gyrus rectalis[64]. Although results of these studies support the view that patients with FM have abnormalities in rCBF, it is not clear how they relate to the pain or other symptoms experienced by these patients. Moreover, nearly all the studies that have evaluated rCBF in patients with FM are limited by very small sample sizes, and contradictory results are present in the literature. Nevertheless, neuroimaging studies will likely enhance our understanding of abnormal pain sensitivity in FM and contribute to the development of interventions aimed at altering CNS function in patients with this disease[65].

Behavioral and psychologic factors. Behavioral and psychological abnormalities may also contribute to symptom maintenance in patients with FM[1]. The most common psychiatric conditions observed in patients with FM include depression (22%), dysthymia (10%), panic disorder (7%), and simple phobia (12%)[66].

Summary

Despite extensive research, understanding of the etiology and pathophysiology of FM remains incomplete. Results from different studies have implicated a range of biologic abnormalities, including abnormal levels of peripheral and CNS neurotransmitters and dysregulation of the HPA axis. We do not know if these abnormalities play a causal role in the syndrome or are secondary phenomena. We also do not know if there is a specific "common denominator" trigger for the syndrome or multiple triggers, nor do we clearly understand perpetuating factors. No single abnormality or constellation of derangements accurately identifies all patients with FM.

Despite significant gaps in our knowledge, our understanding of pathogenesis has advanced through basic research and deductions from observing patient responses to neurophysiologically targeted therapies. A current unifying hypothesis is that there may be multiple factors that contribute to and perpetuate sensitization of the CNS, so it stands to reason that multiple approaches that lead to improvement of this state may be helpful in treatment[6,7,16,17].

ASSESSMENT OF PATIENTS WITH FIBROMYALGIA

The development of specific and sensitive tools for a differential diagnosis or for assessing the effects of treatment in patients with FM is still in its infancy. Tools currently used are dimension-specific and symptom-specific and include both patient-rated and physician-rated measurements of pain, sleep, fatigue, and overall well being that also encompass mood.

Pain Assessment

Chronic generalized pain is a core feature of FM. A number of tools are available for the assessment of pain, including the daily pain diary, the Short Form-McGill Pain Questionnaire (SF-MPQ), the Brief Pain Inventory, and the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS). Important issues that may influence assessment of pain in patients with FM include recall bias, use of paper versus electronic diaries to assess pain experiences, and pain scaling methods[67].

A daily diary has been used to assess the impact of pain in patients with FM and has been reported to be useful for demonstrating the manner in which pain influences activities of daily living in these individuals[68].

The MPQ can provide detailed information on the characteristics of pain in FM. It includes 78 pain adjectives that are divided into 4 major categories (sensory, affective, evaluative, and miscellaneous sensory). This index takes 10 to 15 minutes to complete. The SF-MPQ, consisting of 15 adjectives (11 sensory, 4 affective) taken from the full MPQ, has been validated[69]. The MPQ did not differentiate pain associated with FM versus that associated with RA, when administered in the standard manner[70]. However, when patients were allowed to select as many words from an adapted MPQ as they wished, significant differences in word choice emerged. Results from another study that used the MPQ to compare patients with FM, RA, or ankylosing spondylitis indicated significantly higher general pain intensity in FM[71].

The Brief Pain Inventory, originally developed for the assessment of cancer pain but now validated in chronic pain states, comprises multiple questions regarding pain intensity, the role of pain in interference in the patient's life, pain relief, pain quality, and patient perception of the cause of pain[72].

The LANSS Pain Scale is an instrument developed to diagnose neuropathic pain and to differentiate it from nociceptive pain. It has been employed in a comparison of patients with FM versus those with RA, and study results showed that thermal pain severity was similar in both groups, but that higher percentages of patients with FM reported dysesthetic, evoked, paroxysmal, or thermal sensory disturbances. The LANSS Pain Scale items may be particularly useful for differentiation of FM pain from nociceptive pain present in RA and other arthritic diseases[73].

Tender point assessment is a demonstrably useful part of the official ACR criteria for the diagnosis of FM[10,74]. However, tender points are not unique to the syndrome. Tenderness is widespread in patients with FM rather than being confined to specific anatomic regions, and these individuals may also demonstrate more hypersensitivity to heat, cold, and electrical stimulation. Some methods of assessing tenderness (e.g., dolorimetry) may demonstrate increased pain sensitivity in patients with FM more objectively than palpation, and are relatively independent of biasing factors or patient distress[75]. In addition to tender point count, assessment of tender point intensity or score has been developed as an assessment tool. The FM Intensity Score (FIS) is obtained by averaging the pain intensity scores (on a 0–10 scale) for the 18 sites assessed in the Manual Tender Point Survey. It has been suggested that the FIS might be helpful when patients are followed through serial examinations over time and for making comparisons among patients[76]. Whereas clinical trials require tender point assessment as part of the diagnostic criteria for trial entry, there have been variable results utilizing tender point count or score as an outcome measure, thus raising questions about its discriminative ability as a pain assessment tool.

Fatigue

Fatigue is one of the core features of FM, and its measurement is important in both the research and clinical settings. The Multidimensional Assessment of Fatigue index is a 16-item instrument developed to provide information about this symptom[69,77]. A variety of other measures exist and have proven useful in measuring fatigue in other rheumatic diseases, such as RA and ankylosing spondylitis. These include the Multidimensional Fatigue Index, which measures various types of fatigue including physical and emotional[78]. Another measure, validated in a number of disease states, is the Functional Assessment of Chronic Illness Therapy system[79], which may be customized to certain disease indications. The Fatigue Severity Scale, originally developed for multiple sclerosis and lupus fatigue assessment, may also prove useful[80].

Sleep

Sleep quality can be assessed on a 100 mm linear scale with "sleep is no problem" at one extreme and "sleep is a

major problem" at the other extreme. Similar scales can be used to rate number of awakenings, and "restedness" on awakening in the morning[69]. The Medical Outcome Study (MOS) sleep scale is an example of an instrument used in an FM trial[81].

Quality of Life and Functional Assessment

Measurement of global sense of well being, quality of life, and functional capacity in multiple dimensions (physical, vocational, social, emotional) is a key area of assessment and is considered essential by regulatory agencies when contemplating approval of medications for chronic pain states[82,83]. Other than the general knowledge that patients with FM are poorly functional relative to healthy individuals and other rheumatic disease patients, our ability to fully measure all dimensions of this dysfunctionality needs refinement. A newer mandate in this arena of assessment that needs to be addressed is that of "participation," requested by the World Health Organization as a measure of the ability of the individual to participate fully in all aspects of life[84].

The Patient Global Impression of Change has been used in evaluations of treatments for FM and is correlated with pain intensity[81].

The MOS Short Form-36 (SF-36) Health Survey is a generic instrument with 8 subscales[85]. Assessment with the SF-36 has shown that patients with FM have reduced physical functioning, physical role functioning, body pain, general health, vitality, and social functioning versus healthy subjects. Results for the SF-36 subscales of physical functioning, body pain, and social functioning in FM patients are highly correlated with functional disability as assessed by the HAQ[86].

The FM Impact Questionnaire (FIQ) is a simple instrument specifically designed to reflect changes in the FM patient's general status over time. It includes 10 questions and takes about 5 minutes to complete. The questions are designed to quantify functional disability, pain intensity, sleep disorder, muscular stiffness, anxiety, depression, and overall sense of well being; visual analog scales (VAS) are used to evaluate pain, fatigue, morning stiffness, stiffness severity, depression, and anxiety[87].

While the FIQ has been used effectively to assess effects of treatment in patients with FM, it does have significant limitations. It was originally developed to assess the current health status of women with this disease, and its validity in men has not been established. However, results from one study of women and men with FM indicated that both genders had decreased physical functioning as demonstrated by the FIQ physical function subscale[88]. The FIQ is also limited because respondents may report items on the physical function subscale as "not applicable," and this may result in underestimation of the functional impact of disease[89]. Finally, the FIQ functional component is aimed at evaluating high levels of disability, and this may limit its ability to detect significant effects of treatment in patients with mild disease. This limitation is supported by the fact that 12% of FM patients in one study scored zero on the FIQ physical function score (i.e., no dysfunction)[89].

Assessment of sexual function is important both as an important domain of human function but also because of the potential for adverse effects of medications on sexual function. An instrument used in an FM trial is the Arizona Sexual Experiences Scale[90].

Psychological and psychiatric assessment.

Psychological evaluation of the patient can provide useful information about the psychological and behavioral features that may influence their pain and dysfunction as well as provide a sense of the impact of pain, fatigue, and other symptoms on their psychological health. It is often presumed that patients with a greater psychological impairment and/or psychiatric pathology may be more symptomatic or resistant to improvement with therapeutic intervention. However, this assumption may be true only in some cases. Both in clinical practice and in drug trials, it is important to diagnose and effectively treat concomitant depression, anxiety, bipolar states, and especially suicidal tendencies. In addition to a careful history, a number of screening tools are available for both clinical and research purposes, including the Beck Depression Inventory[91] and the Mini-International Neuropsychiatric Interview[92]. In clinical practice, diagnosis of such conditions as depression, anxiety, and bipolar disorder can lead to proper therapy of these comorbid conditions and screen for those with suicidal tendencies. In research trials such instruments can be used to either exclude patients with certain psychiatric diagnoses for safety reasons, or stratify patients, e.g., those with and those without major depression, in order to observe if there are differences in treatment outcomes relative to these comorbid conditions. Turk, *et al* have provided a recent review of this area[93].

What constitutes a clinically meaningful response to treatment in a patient with FM?

The wide variety of tools available for assessment of patients with FM has resulted in significant heterogeneity in the manner in which this disease is assessed, and in how potential treatments for it are evaluated in clinical trials. This heterogeneity has made it difficult to determine the relative effectiveness of different medications being developed for treatment of FM. There is now an effort under way to achieve greater standardization of assessment.

One of the main problems in developing an efficacy claim for FM is the lack of consensus about response criteria that could be used as a primary outcome measure in clinical trials. In June 2003, the US Food and Drug

Administration (FDA) Arthritis Advisory Committee met to discuss the development and approval of drugs to treat FM. A transcript of the meeting can be viewed at http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3967T1.htm.

Limitations of current approaches

The primary outcome measure most often used in trials of agents being developed for the treatment of FM is mean reduction in pain intensity. This approach does not adequately address the critical question of whether or not a statistically significant reduction in pain intensity versus placebo with a given treatment is clinically significant or meaningful.

Detection of meaningful change in the condition of patients being treated for FM

Dunkl and colleagues[94] assessed the responsiveness of the FIQ, patient ratings of pain intensity, number of tender points, and total tender point pain intensity score to perceived changes in clinical status in patients with FM enrolled in a clinical trial of magnetic therapy. Individual measures were responsive to perceived improvement in health status, but relatively unresponsive to perceived deterioration. The FIQ total score equaled or outperformed all other measures in its ability to detect clinically important change. However, the patients in this trial were predominately women, and the results may not generalize to men with FM.

Hewett and associates[95] employed a growth curve model approach to estimate reliability of change for data (46 variables) obtained in a randomized clinical trial comparing biofeedback/relaxation, exercise, a combined program, and education in patients with FM. The variables with the best reliabilities for detecting a change in clinical status were the Myalgic Score, the Tender Point Score, the Tender Point Index, the number of words chosen from the MPQ, and 2 anxiety scales from the Symptom Checklist-90-Revised. These findings suggest that measures of tenderness should be responsive to treatment in clinical trials. However, metaanalyses from studies in which antidepressants were used to treat patients with FM revealed that tenderness only minimally improved with active therapy[96]. Further, in the trial of pregabalin in FM, the Manual Tender Point Survey did not significantly improve with pregabalin versus placebo despite improvement in pain, sleep, fatigue, global well being, and function scores[97].

Responder analysis

An alternative approach to defining efficacy is development of a clinically meaningful criterion for a response to therapy. This approach might permit more meaningful comparison from different studies and perhaps also facilitate definition of factors that predict a positive response to therapy[98]. The question of what constitutes a meaningful change in pain scores has been addressed in a pooled analysis of results from patients enrolled in 10 studies of pregabalin for the treatment of osteoarthritis, low back pain, FM, and peripheral neuropathy[99]. In all these trials, pain intensity was measured using an 11-point pain intensity numerical rating scale. Comparison of changes in pain intensity scores with patients' global impression of change over the course of the trial indicated that a reduction of about 2 points or 30% in the pain intensity score represented a clinically important difference, defined as a patient report of "much improved" or "very much improved." A 50% reduction in pain was associated with the highest degree of improvement ("very much improved").

It is not known whether improvement in pain intensity alone should define response to treatment in FM, a syndrome characterized by multiple symptoms, including reduced quality of life, impaired physical, social, and emotional function, sleep disturbance, fatigue, and cognitive impairment.

In an attempt to develop a multicomponent criterion for response to treatment in patients with FM, Simms and colleagues[100] proposed that a meaningful response to treatment should be considered to have been achieved if patients met 4 of the 6 following criteria: 50% reduction in pain, sleep, fatigue, patient global assessment, or physician global assessment, and increase of 1 kg in mean total myalgic score. Application of these criteria in a trial that compared amitriptyline, cyclobenzaprine, and placebo in patients with FM indicated that about one-third of patients had at least short-term responses to active treatment[101].

Simms and colleagues[98] attempted to improve the definition for a response to FM therapy by testing criteria with known effective treatment as a gold standard. A set of preliminary criteria was developed using data from a placebo-controlled clinical trial of amitriptyline versus naproxen[102]. In this study, only amitriptyline was significantly more effective than placebo, and the proxy for a response was treatment with amitriptyline. The combination of outcome measures with the highest sensitivity in discriminating between patients receiving amitriptyline versus those treated with placebo or naproxen was change in physician global assessment, change in tender point score, and patient sleep assessment. This analysis resulted in the response criteria composed of physician global assessment, patient-assessed sleep score, and tender point score. For details see Simms, *et al* [98].

These criteria are limited for several reasons. First, reduction in pain, a cardinal feature of FM, did not discriminate between groups and was not included. Second, the trial did not include other possible indicators of response such as functional status or patient global assessment. Third, application of the criteria would require that patients have sufficiently severe symptoms at

Table 1. Proposed preliminary response criteria for fibromyalgia[94].

Improvement in at least 3 of the 4 measures, and at least 3 of the post-treatment scores must satisfy the respective cutoffs:
1. FIQ score < 45 (range 0 = no impact to 80 = maximum impact)
2. Pain intensity rating < 5 (11 point numeric rating scale; 0 = no pain, 10 = very severe pain)
3. Tender point count < 14 [4 kg/cm^2 pressure is applied with a dolorimeter and the patient rates pain from 0 (no pain) to 10 (worst pain ever experienced); positive tender point defined as pain intensity at > 2]
4. Total tender point pain intensity score < 85 (sum of pain intensity scores for the 18 ACR defined sites; range 0 to 180)

FIQ: Fibromyalgia Impact Questionnaire
ACR: American College of Rheumatology

baseline for entry. Finally, response criteria developed from a trial of amitriptyline might not be applicable in patients receiving other treatments.

More recently, Dunkl, *et al*[94] proposed preliminary criteria for identifying responders in FM clinical trials that were based on a study of magnetic therapy in patients with this disease (Table 1). These preliminary criteria identified responders with a sensitivity of 70.5% and specificity of 87.5%. However, they have not been validated in other clinical trials.

The studies reviewed in the preceding paragraphs underscore the need for a single generalizable definition for a response to medical therapy in patients with FM. Although responder analysis necessitates dichotomizing continuous outcome variables and might introduce bias[103], the benefits of this approach outweigh the potential dangers. A response criterion or index provides the advantage of grouping clinically important results into a metric that defines individual response as the primary outcome. Clinical decisions can then be made on the basis of individual response, rather than inference from the patient's response as part of a group mean. This approach also permits combined evaluation of multiple measures of improvement in the same patient[104].

Outcome measures in FM and OMERACT

The large number of instruments briefly reviewed in the preceding sections should make clear that the clinician/researcher is faced with a wide and confusing array of choices for the assessment of disease severity and the effects of interventions in patients with FM. Outcome Measures in Rheumatology Clinical Trials (OMERACT), an informal international network with the goal of improving outcome measurement in rheumatology, has recognized the need to develop consensually approved and validated instruments to assess clinical responses to treatments in patients with FM. An FM working group will be applying the OMERACT "filter" (truth, discrimination, feasability) to develop and refine instruments that yield valid results, are able to discriminate between placebo and treated groups, and are feasible[105]. There is also increased interest in developing a composite outcome measure of such key domains as pain, global sense of well being, function (considered multidimensionally), fatigue, and sleep disturbance.

The work of the OMERACT FM group is analogous to the work being done by chronic pain researchers, the IMMPACT group (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials). IMMPACT is a partnership between researchers, industry, and the FDA to determine which key outcomes should be measured in chronic pain trials. Their current consensus is that these domains should include pain, physical and emotional functioning, patient global ratings of satisfaction, negative health states, adverse events, and patient adherence and disposition[82,83].

TREATMENT OF FIBROMYALGIA

Many patients with FM benefit from a multidisciplinary approach in clinical practice. Nevertheless, pharmacologic treatment remains the primary approach to management for the majority of patients with FM[5]. Despite some success with currently used medications, there is a large unmet need for effective pharmacotherapy in FM. Further, there are presently no treatments for this disease approved by the FDA or the European Registry. The complexity of FM and the presence of multiple symptoms makes it challenging for pharmaceutical companies to mount effective clinical trials to assess emerging pharmacotherapies. However, this is changing, as there have been several recent large trials that have successfully distinguished treatment from placebo in multiple domains in a valid and feasible manner.

Pharmacotherapy for Fibromyalgia

A number of classes of medications have been evaluated in patients with FM (Table 2). Nearly all have demonstrated effectiveness in reducing pain, but fewer have demonstrated significant efficacy in improving the other major symptoms of the disease: fatigue, sleep distur-

Table 2. Efficacy of currently available treatments for fibromyalgia. Adapted from *J Rheumatol 1999*;26:408-12.

Drug class	Fibromyalgia Symptom			
	Pain	Sleep	Fatigue	Mood
TCA	+	+	+	–
SSRI	±	±	±	+
5-HT/NE RI	±	–	±	±
MAO-I	±	±	±	±
NSAID	–	–	–	–
AED	+	+	+	–
Sedatives/hypnotics	–	+	–	–
Muscle relaxants	+	+	±	
Opioids	+			
NMDA antagonists	+			

TCI: tricyclics; SSRI: selective serotonin reuptake inhibitors; 5-HT/NE RI: serotonin/norepinephrine reuptake inhibitors; MAO-I: monamine oxidase inhibitors; NSAID: nonsteroidal antiinflammatory drugs; AED: antiepileptic drugs; NMDA: N-methyl-D-aspartate.

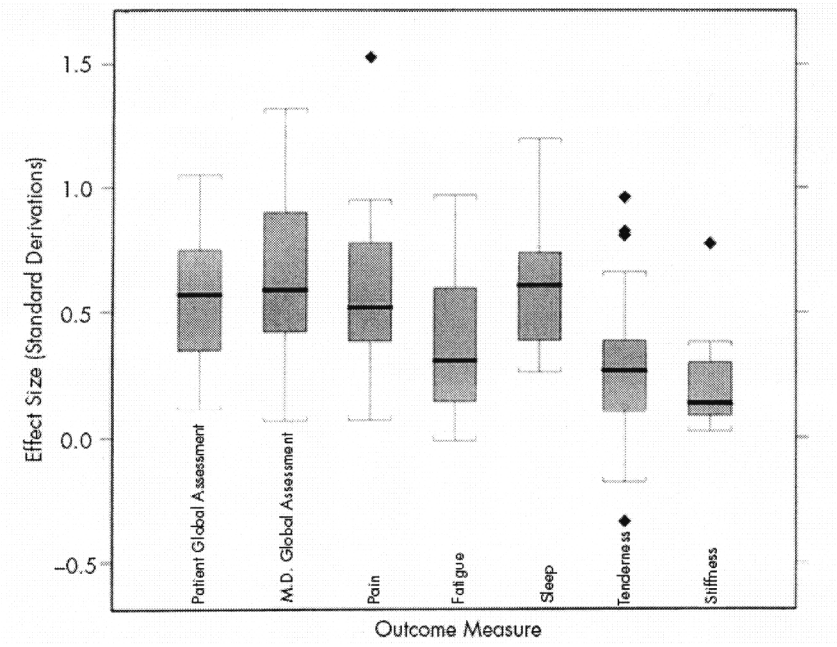

Figure 2. Size of effect by type of outcome measure in 9 controlled studies of tricyclic treatment of FM. From Turk, *et al*. Rheum Dis Clin North Am 2002;28:219-33[96], with permission.

bance, and mood abnormalities[106].

Antidepressants. Given the disturbances in biogenic amines documented for patients with FM, it is not surprising that agents interacting with these aminergic systems have been tested extensively in this disease.

Tricyclics. Amitriptyline, doxepin, and cyclobenzaprine are the most common agents used for FM in the US[88,107]. A metaanalysis of 9 controlled trials of tricyclics (TCA) in the treatment of FM has demonstrated that agents in this class produced significantly greater effects than placebo in physician and patient overall assessments, pain, stiffness, tenderness, fatigue, and sleep quality (Figure 2). The greatest improvements were in measures of sleep quality, and the smallest were for measures of stiffness and tenderness[96].

Selective serotonin reuptake inhibitors. Selective serotonin reuptake inhibitors (SSRI) have shown somewhat disappointing results in FM. Wolfe, *et al* conducted a study with a fixed dose of fluoxetine over 6 weeks, which showed improvement in depression scores but no benefit in other aspects of FM, including pain[108]. On the other

hand, Arnold, *et al* showed that by using a flexible dose of fluoxetine, benefit could be achieved. In a 12-week trial with 51 patients, patients could upwardly titrate their dose of study drug. Statistically significant improvements in FIQ total and MPQ were achieved with a mean dose of 45 mg/day[109]. The combination of fluoxetine and amitriptyline was shown to be more efficacious in FM than either agent alone or placebo[110]. In one randomized, double-blind, placebo-controlled, 4-month trial study of citalopram (2040 mg/day), 40 female patients, 21 in the citalopram and 19 in the placebo group, who fulfilled ACR criteria were enrolled. VAS, the Montgomery Asberg Depression Rating Scale, and FIQ were used to assess pain, depressive symptoms, and physical functioning. The results indicated no significant advantage of active treatment over placebo with respect to pain or well being. However, among those who completed the study, there was a tendency for more patients in the citalopram group (52.9%) to have improved well being versus placebo (22.2%). Citalopram was also significantly superior to placebo in improving depression[111]. A second trial with citalopram also did not show improvement in the pain of FM[112]. Thus, SSRI may play a role in improvement of mood and possibly fatigue, but appear to have little impact on pain or other manifestations of FM.

Serotonin/norepinephrine reuptake inhibitors. Newer medicines are capable, as seen in TCA, of inhibiting reuptake of both serotonin and norepinephrine (SNRI), but with fewer side effects. SNRI milnacipran, currently licensed for treatment of depression in Europe and Asia, was used in a placebo-controlled trial based on the postulate that the greater ratio of norepinephrine to serotonin reuptake inhibition effect would render it superior for pain treatment. In this 12-week trial, 125 patients were randomly prompted to record, on an electronic hand-held device, their level of pain, fatigue, and sleep, as well as quality of life information. Patients using the medication twice a day achieved statistically significant improvement in weekly average daily pain scores as well as patient global impression of change, fatigue, and function as measured by components of the FIQ and SF-MPQ. Thirty-seven percent were responders, achieving a 50% Gracely scale improvement in pain. The drug was generally well tolerated[113].

Duloxetine, another new SNRI, was tested at a 60 mg bid dose in a placebo-controlled trial in 207 subjects with FM over 13 weeks. The co-primary outcome measures were the total FIQ and the FIQ pain score. Although treated patients had statistically significant improvements on the total score, they did not improve on the FIQ pain score. However, they did improve on the Brief Pain Inventory score, a secondary outcome measure. Other measures showing improvement included: tender point number and pain threshold, global impression of change, and several quality of life measures. Among the small number of male patients no significant improvement was observed. There were no significant tolerability issues[114].

Venlafaxine, also an SNRI, has been assessed at 75 mg/day in a 12-week study of 15 patients with FM. The primary outcome measures were the FIQ total score and pain score. Anxiety and depression were measured with Beck Depression, Beck Anxiety, Hamilton Anxiety, and Hamilton Depression scales. Venlafaxine treatment significantly reduced pain ($F = 14.3$; $p = 0.0001$) and disability caused by FM ($F = 42.7$; $p = 0.0001$). It also significantly decreased both physician and patient-rated depression and anxiety[115].

Monoamine oxidase inhibitors. Monoamine oxidase inhibitors (MAO-I) block the catabolism of 5-HT and thus increase its level in the brain. Preliminary studies with moclobemide, a second-generation MAO-I, failed to demonstrate significant analgesic activity in patients with FM when compared with amitriptyline. Results from a recent study with another MAO-I, pirlindole, indicated that there were significant beneficial effects on sleep, fatigue, and mood in FM patients[106].

5-HT3 receptor antagonists. Clinical trials have shown that a 5-HT3 receptor antagonist has significant clinical efficacy in patients with FM. Tropisetron, a selective, competitive 5-HT3 receptor antagonist, was tested in a short-term study of 418 patients with FM. Patients were randomly assigned to receive placebo or 5 mg, 10 mg, or 15 mg/day of tropisetron. Clinical response was measured by changes in pain score, VAS, tender point count, and ancillary symptoms. Responders were prospectively defined as patients showing a 35% or higher reduction in pain score. Treatment with the 5 mg dose of tropisetron resulted in a significantly higher response rate (39.2%) than placebo (26.2%) with a mean reduction in pain score of 55.4%. Higher tropisetron doses were not effective[116], which is consistent with the observation that 5-HT3 receptor antagonists may have nociceptive and antinociceptive effects under different circumstances. The mechanism by which 5-HT3 receptor antagonism reduces FM-associated pain and other symptoms is not understood; it has been suggested that these benefits may be secondary to reduced release of substance P[117].

Antiepileptic drugs. Antiepileptic drugs (AED) have been demonstrated to be effective in a variety of different types of neuropathic pain[118] and are widely used as analgesics. It has been suggested that the pain of FM has a neuropathic origin[119]. Gabapentin has been used clinically, and a placebo-controlled trial in FM is being conducted (Arnold LM, personal communication). A newly developed AED, pregabalin, was shown to be effective for treatment of FM[97]. Pregabalin (up to 150 mg tid) was evaluated in an 8-week, randomized, double-blind, place-

bo-controlled, parallel-group trial that included 529 patients. Pregabalin was superior to placebo in reducing scores for pain, SF-MPQ, MOS Sleep Index, fatigue, Patient Global Impression of Change, Clinician Global Impression of Change, and 4 of the 8 domains on the SF-36. Twenty-seven percent of patients achieved a responder status of 50% improvement. The most common adverse events were dizziness and somnolence, and overall tolerability was good[97]. Pregabalin is also effective for postherpetic neuralgia and painful diabetic neuropathy, for epilepsy, and for generalized anxiety disorder[120-123].

Opioids. Opioids have analgesic activity and are used in some patients with FM. However, their use is generally limited because of concern about addictive potential and other adverse effects[106].

Tramadol. Tramadol, a weak μ-opioid receptor agonist that also inhibits reuptake of 5-HT and NE, is effective for treatment of FM-associated pain[112]. In a 6-week, randomized, double-blind, placebo-controlled study to evaluate efficacy of tramadol 50–400 mg/day dose in the treatment of pain of FM, 35 patients were randomized to the tramadol group and 34 to a placebo group. Kaplan-Meier estimate of cumulative probability of discontinuing the double-blind treatment period because of inadequate pain relief was significantly lower in the tramadol group compared to placebo group ($p = 0.001$). Twenty (57.1%) patients in the tramadol group successfully completed the study compared with 9 (27%) in the placebo group[124]. In a more recent trial with the combination of tramadol and acetaminophen, 315 patients were studied in a placebo-controlled fashion for 91 days. The primary endpoint was length of time until discontinuation due to lack of efficacy. This occurred significantly less frequently in the tramadol group, 29 patients as compared to 51, and the overall discontinuation due to any reason was also less in the treated group: 48 versus 62[125].

Muscle relaxants. Muscle relaxant medications are used both chronically for FM as well as on a short-term basis for symptom flares. However, there has been little systematic study of their effectiveness. Cyclobenzaprine, considered to be a muscle relaxant but with significant similarity to tricyclics in chemical structure, has been assessed in 4 randomized trials, 2 of which were positive[101,126-128]. Other muscle relaxants have been used, but have not been subjected to controlled trials in FM.

N-methyl-D-aspartate receptor antagonists. The NMDA receptor may play a key role in nervous system reorganization thought to be involved in maintenance of chronic pain[48], and it has been shown that NMDA receptor blockade can relieve pain in patients with FM[129,130]. However, the cognitive side effects of NMDA receptor blockade may limit use of NMDA as FM therapy[106].

Dopamine agonists. A new dopamine agonist, pramipexole, used for Parkinson's disease and restless leg syndrome, is being tested in a placebo controlled trial in FM, following positive results in a single open-label trial[131].

Sedative hypnotics. Sedative hypnotic agents, including zopiclone and zolpidem, have been used in patients with FM, and have been shown to improve sleep and relieve fatigue. Other agents include gamma hydroxybutyrate (a precursor of gamma-aminobutyric acid with powerful sedative properties), melatonin, and pramipexole, have also been shown to act on symptoms of FM[106]. Several antidepressant agents, such as amitriptyline and trazodone, are used in low dosage for their sedative properties.

Growth hormone. A number of studies have demonstrated that growth hormone or insulin-like growth factor-1 (IGF-1) levels are reduced in patients with FM[53]. Bennett, *et al* employed growth hormone supplementation subcutaneously in a placebo-controlled trial in 45 FM patients for 9 months[132]. The treatment group showed improvement of overall symptoms and tender points. Carpal tunnel syndrome occurred in 7 patients, possibly as an adverse drug event. Despite these positive efficacy results, Geenen, *et al* suggest caution in utilizing this approach in consideration of potential side effects and the potential for hindering endogenous growth hormone production[53]. GH analogs are being studied in FM.

Nonsteroidal antiinflammatory drugs. NSAID (including cyclooxygenase-2 selective agents) and acetaminophen are used in the treatment of FM for their analgesic properties, but there is limited evidence to support their effectiveness in patients with this condition[106].

Pharmacotherapy of associated symptoms. Patients with FM will benefit from selective attention to associated symptoms, which often results in overall improvement by reduction of symptom burden. Fatigue may be improved with the use of SSRI (see above) or modafinil. A small open trial with the latter demonstrated improvement in fatigue but not in pain[129]. A variety of approaches are used to treat irritable bowel syndrome, including dietary fiber, antispasmodics, both laxatives and antidiarrheal agents, and more recently, the 5-HT3 antagonists[5]. Irritable bladder syndrome may be treated with antispasmodics, biofeedback, and forms of physical therapy, as well as urethral dilatation[5]. Various analgesic medications, beta blockers, calcium channel blockers, and other agents may improve headache, and migraine-specific medications aid migraine[5]. It is important not to overmedicate this problem, which may lead to medication-induced chronic headache. Temporomandibular joint dysfunction may be

treated with dental prostheses, biofeedback, and treatment of associated trigger points[5]. Restless leg syndrome may be treated with clonazepam or antiparkinsonian medications at bedtime. These are but a few of the examples of treatment of associated symptoms.

Summary

A wide range of agents have been employed in the treatment of patients with FM. However, only a small number of these medications have demonstrated effectiveness in controlled clinical trials. Antidepressants, primarily tricyclics, are effective, but they have a relatively narrow therapeutic index, and their use may be limited by poor tolerability[133]. SSRI have better tolerability than TCA, but do not appear to be as effective in relieving the wide range of FM-associated symptoms[106]. Medications that inhibit reuptake of both norepinephrine and serotonin (SNRI), such as milnacipran and duloxetine, show promise in treating both pain of FM and associated symptoms of sleep disturbance and fatigue, yet with fewer side effects than traditional TCA[67,114]. The new antiepileptic pregabalin has been shown to be effective for reducing many of the symptoms associated with FM and is well tolerated[97]. This agent appears to work through binding to the $\alpha_2\gamma$ subunit of voltage-gated calcium channels. Its efficacy for this indication, as well as for neuropathic pain, may shed further light on the pathophysiology of FM[120]. There also is interest in a related compound, gabapentin, which is currently being tested in FM (Arnold LM, personal communication).

Nonpharmacologic Treatment

A variety of nonpharmacologic treatments have been demonstrated to have at least modest efficacy in patients with FM.

Cognitive behavioral therapy. Psychological and behavioral therapies are being used in the treatment of FM with increasing frequency. The rationale for including psychological therapies is improved management of psychological and social factors that may influence perception and maintenance of chronic pain in these patients[134]. It has been suggested that patients with FM experience significantly greater daily stress than individuals without this disease, and it has been shown that inclusion of cognitive behavioral therapy as part of the treatment regimen for patients with FM can improve physical functioning[135].

Exercise. Exercise programs, including strength and flexibility training, have been shown to have positive effects in patients with FM, improving both mood and physical function[136]. A controlled trial of graded aerobic exercises versus relaxation and flexibility training indicated that the former treatment resulted in a significantly greater percentage of participants rating themselves as much or very much better at 3 months. Exercise also resulted in a reduction in the number of patients fulfilling the ACR criteria for FM, decreased tender point counts, and improved FIQ scores[137]. Review of randomized controlled trials has resulted in the recommendation that low intensity aerobic exercise, such as walking, can improve function and symptoms in patients with FM. This exercise should be performed twice weekly at moderate intensity. Because of the highly variable levels of functioning and symptom severity in patients with FM, exercise prescriptions should be individualized[138].

Sleep hygiene. A variety of approaches can be used to improve sleep in patients with FM in addition to pharmacotherapeutic approaches discussed previously. These include behavioral approaches, fitness, and regular proper nutrition that may reduce disturbances in circadian sleep-wake rhythms. Diagnosis and treatment of comorbid conditions such as sleep apnea can be helpful. These and other issues related to sleep physiology have been recently reviewed[139].

Alternative therapies. Complementary and alternative medicine (CAM) has gained increasing popularity, particularly among individuals with FM, for whom traditional medicine has generally provided inadequate benefits. Alternative therapies, including osteopathic manipulation, acupuncture, low-power laser therapy, balneotherapy (20-minute bathing, once a day, 5 times per week, for a 3-week period), and sulfur baths, have all demonstrated beneficial effects in relieving at least some symptoms of FM[136]. In general, there are only very limited data from well controlled trials to support any alternative therapies in patients with FM[140].

Summary

The range of pharmacologic therapies that have efficacy in relieving at least some symptoms in subsets of patients with FM and the fact that no single treatment is completely effective in all patients suggest that multiple pathogenic mechanisms may contribute to FM and that their influence may differ from one patient to another. The multifaceted nature of FM suggests that multimodal, individualized treatment programs that combine pharmacologic and nonpharmacologic therapies may be necessary to achieve optimal outcomes in patients with this syndrome.

CONCLUSION

FM is a relatively common disorder that encompasses symptoms of chronic, widespread pain, often in association with other clinical manifestations such as sleep disturbance, fatigue, and mood disorders. Our understanding of the pathophysiology of this condition is increasingly focused on neurotransmitter and neurohormone

dysregulation and central sensitization of the nervous system. It is anticipated that increased understanding may lead to more targeted therapies. Currently available effective treatments for FM appear to share common mechanisms of modulating neurotransmitters related to perception and pathogenesis of pain. Nevertheless, no single agent is likely to be completely effective in relieving all FM-associated symptoms, and a multifaceted, integrated approach to treatment will continue to be needed to achieve good treatment outcomes in patients with this syndrome. Recent FM-specific studies with emerging medications demonstrate the ability of the medications to be partially effective in multiple symptom domains such as pain, fatigue, sleep disturbance, quality of life, and function. The outcome measures used in these trials have been able to discriminate treatment response. Further refinement of these measures, including development of a composite response measure, is desirable to most accurately assess treatment effect.

REFERENCES

1. Clauw DJ. Elusive syndromes: treating the biologic basis of fibromyalgia and related syndromes. Cleve Clin J Med 2001;68:832-4.
2. Bennett R. Fibromyalgia, chronic fatigue syndrome, and myofascial pain. Curr Opin Rheumatol 1998;10:95-103.
3. Gowers WR. Lumbago: Its lessons and analogues. BMJ 1904;1:117-21.
4. Smythe HA, Moldofsky H. Two contributions to understanding the "fibrositis" syndrome. Bull Rheum Dis 1978;26:928-31.
5. Barkhuizen A. Rational and targeted pharmacologic treatment of fibromyalgia. Rheum Dis Clin North Am 2002;28:261-90.
6. Bennett RM. The rational management of fibromyalgia patients. Rheum Dis Clin North Am 2002;28:181-99.
7. Bennett RM. Emerging concepts in the neurobiology of chronic pain: evidence of abnormal sensory processing in fibromyalgia. Mayo Clin Proc 1999;74:385-98.
8. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Arthritis Rheum 1990;33:160-72.
9. Yunus MB, Khan MA, Rawlings KK, Green JR, Olson JM, Shah S. Genetic linkage analysis of multicase families with fibromyalgia syndrome. J Rheumatol 1999;26:408-12.
10. Campbell SM, Clark S, Tindall EA, Forehand ME, Bennett RM. Clinical characteristics of fibrositis. I. A "blinded", controlled study of symptoms and tender points. Arthritis Rheum 1983;26:817-24.
11. Goldenberg DL. Fibromyalgia and related syndromes. In: Klippel JH, Dieppe PA, Arnett FC, et al, editors. Rheumatology. 2nd ed. St. Louis: Mosby; 1998:15.1-15.12.
12. Bennett RM. Fibromyalgia. In: Wall PD, Melzack R, editors. Textbook of pain. 4th ed. London: Harcourt Publishers, Churchill Livingstone; 1999:579-601.
13. Aaron LA, Burke MM, Buchwald D. Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder. Arch Intern Med 2000;160:221-7.
14. Aaron LA, Buchwald D. A review of the evidence for overlap among unexplained clinical conditions. Ann Intern Med 2001;134:868-81.
15. Wolfe F. The fibromyalgia syndrome: a consensus report on fibromyalgia and disability. J Rheumatol 1996;23:534-9.
16. Clauw DJ, Crofford LJ. Chronic widespread pain and fibromyalgia: what we know, and what we need to know. Best Pract Res Clin Rheumatol 2003;17:685-701.
17. Crofford LJ, Clauw DJ. Fibromyalgia: where are we a decade after the American College of Rheumatology classification criteria were developed? Arthritis Rheum 2002;46:1136-8.
18. Croft P, Rigby A, Boswell R, Schollum J, Silman A. The prevalence of chronic widespread pain in the general population. J Rheumatol 1993;20:710-3.
19. Wolfe F, Ross K, Anderson J. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 1995;38:19-28.
20. Goldenberg DL, Simms RW, Geiger A, Komaroff AL. High frequency of fibromyalgia in patients with chronic fatigue seen in a primary care practice. Arthritis Rheum 1990;33:381-7.
21. Brecher LS, Cymet TC. A practical approach to fibromyalgia. J Am Osteopath Assoc 2001;101 Suppl pt 2:S12-S17.
22. Menninger H. Other pain syndromes to be differentiated from fibromyalgia. Z Rheumatol 1998;57 Suppl 2:56-60.
23. Millea PJ, Holloway RL. Treating fibromyalgia. Am Fam Physician 2000;62:1575-1582;1587.
24. Fassbender K, Samborsky W, Kellner M, Muller W, Lautenbacher S. Tender points, depressive and functional symptoms: comparison between fibromyalgia and major depression. Clin Rheumatol 1997;16:76-9.
25. Bennett RM. Fibromyalgia and the disability dilemma. A new era in understanding a complex, multidimensional pain syndrome. Arthritis Rheum 1996;39:1627-34.
26. Greenfield S, Fitzcharles MA, Esdaile JM. Reactive fibromyalgia syndrome. Arthritis Rheum 1992;35:678-81.
27. Wolfe F, Anderson J, Harkness D, et al. Health status and disease severity in fibromyalgia: results of a six-center longitudinal study. Arthritis Rheum 1997;40:1571-9.
28. Burckhardt CS, Clark SR, Bennett RM. Fibromyalgia and quality of life: a comparative analysis. J Rheumatol 1993;20:475-9.
29. Martinez JE, Ferraz MB, Sato EI, Atra E. Fibromyalgia versus rheumatoid arthritis: a longitudinal comparison of the quality of life. J Rheumatol 1995;22:270-4.
30. Gursoy S, Erdal E, Herken H, Madenci E, Alasehirli B, Erdal N. Significance of catechol-O-methyltransferase gene polymorphism in fibromyalgia syndrome. Rheumatol Int 2003;23:104-7.
31. Klein R, Beansch M, Berg PA. Clinical relevance of antibodies against serotonin and gangliosides in patients with primary fibromyalgia syndrome. Psychoneuroendocrinology 1992;17:593-8.
32. Werle E, Fisher H, Muller A, et al. Antibodies against serotonin have no diagnostic relevance in patients with fibromyalgia syndrome. J Rheumatol 2001;28:595-600.
33. Daoud KF, Barkhuizen A. Rheumatic mimics and selected triggers of fibromyalgia. Curr Pain Headache Rep 2002;6:284-8.
34. Wolfe F, Cathey MA, Kleinheksel SM. Fibrositis (fibromyalgia) in rheumatoid arthritis. J Rheumatol 1984;11:814-8.
35. Middleton GD, McFarlin JE, Lipsky PE. The prevalence and clinical impact of fibromyalgia in systemic lupus erythematosus. Arthritis Rheum 1994;37:1181-8.
36. Bonafede RP, Downey DC, Bennett RM. An association of fibromyalgia with primary Sjögren's syndrome: a prospective study of 72 patients. J Rheumatol 1995;22:133-6.
37. Buskila D, Neumann L, Vaisberg G, Alkalay D, Wolfe F. Increased rates of fibromyalgia following cervical spine injury. A controlled study of 161 cases of traumatic injury. Arthritis Rheum 1997;40:446-52.
38. Dubner R, Hargreaves KM. The neurobiology of pain and its modulation. Clin J Pain 1989;5 Suppl 2:S1-4.
39. Russell IJ, Vaeroy H, Javors M, Nyberg F. Cerebrospinal fluid biogenic amine metabolites in fibromyalgia/fibrositis syndrome and rheumatoid arthritis. Arthritis Rheum 1992;35:550-6.
40. Wolfe F, Russell IJ, Vipraio G, Ross K, Anderson J. Serotonin levels, pain threshold, and fibromyalgia symptoms in the general population. J Rheumatol 1997;24:555-9.
41. Bourgoin S, Pohl M, Mauborgne A, et al. Monoaminergic control

of the release of calcitonin gene-related peptide- and substance P-like materials from rat spinal cord slices. Neuropharmacology 1993;32:633-40.
42. Ressler KJ, Nemeroff CB. Role of serotonergic and noradrenergic systems in the pathophysiology of depression and anxiety disorders. Depress Anxiety 2000;12 Suppl 1:2-19.
43. Juhl JH. Fibromyalgia and the serotonin pathway. Altern Med Rev 1998;3:367-75.
44. Russell IJ, Orr MD, Littman B, et al. Elevated cerebrospinal fluid levels of substance P in patients with the fibromyalgia syndrome. Arthritis Rheum 1994;37:1593-601.
45. Pillemer SR, Bradley LA, Crofford LJ, Moldofsky H, Chrousos GP. The neuroscience and endocrinology of fibromyalgia. Arthritis Rheum 1997;40:1928-39.
46. Larson AA, Giovengo SL, Russell IJ, Michalek JE. Changes in the concentrations of amino acids in the cerebrospinal fluid that correlate with pain in patients with fibromyalgia: implications for nitric oxide pathways. Pain 2000;87:201-11.
47. Hirose K, Chan PH. Blockade of glutamate excitotoxicity and its clinical applications. Neurochem Res 1993;18:479-83.
48. Riedel W, Neeck G. Nociception, pain, and antinociception: current concepts. J Rheumatol 2001;60:404-15.
49. Schwarz MJ, Spath M, Muller-Bardorff H, Pongratz DE, Bondy B, Ackenheil M. Relationship of substance P, 5-hydroxyindole acetic acid and tryptophan in serum of fibromyalgia patients. Neurosci Lett 1999;259:196-8.
50. Carrasco GA, Van de Kar LD. Neuroendocrine pharmacology of stress. Eur J Pharmacol 2003;463:235-72.
51. Goldenberg DL. Fibromyalgia, chronic fatigue syndrome, and myofascial pain syndrome. Curr Opin Rheumatol 1993;5:199-208.
52. Neeck G. Neuroendocrine and hormonal perturbations and relations to the serotonergic system in fibromyalgia patients. Scand J Rheumatol 2000;113 Suppl:8-12.
53. Geenen R, Jacobs JW, Bijlsma JW. Evaluation and management of endocrine dysfunction in fibromyalgia. Rheum Dis Clin North Am 2002;28:389-404.
54. McCain GA, Tilbe KS. Diurnal hormone variation in fibromyalgia syndrome: a comparison with rheumatoid arthritis. J Rheumatol 1989;16 Suppl 19:154-7.
55. Griep EN, Boersma JW, de Kloet ER. Altered reactivity of the hypothalamic-pituitary-adrenal axis in the primary fibromyalgia syndrome. J Rheumatol 1993;20:469-74.
56. Adler GK, Manfredsdottir VF, Creskoff KW. Neuroendocrine abnormalities in fibromyalgia. Curr Pain Headache Rep 2002;6:289-98.
57. Crofford LJ, Engleberg NC, Demitrack MA. Neurohormonal perturbations in fibromyalgia. Baillieres Clin Rheumatol 1996;10:365-78.
58. Couture R, Harrisson M, Vianna RM, Cloutier F. Kinin receptors in pain and inflammation. Eur J Pharmacol 2001;429:161-76.
59. Wallace DJ, Linker-Israeli M, Hallegua D, et al. Cytokines play an aetiopathogenetic role in fibromyalgia: a hypothesis and pilot study. Rheumatology Oxford 2001;40:743-9.
60. Salemi S, Rethage J, Wollina U, et al. Detection of interleukin 1 beta (IL-1 beta), IL-6, and tumor necrosis factor-alpha in skin of patients with fibromyalgia. J Rheumatol 2003;30:146-50.
61. Johansson G, Risberg J, Rosenhall U, Orndahl G, Svennerholm L, Nystrom S. Cerebral dysfunction in fibromyalgia: evidence from regional cerebral blood flow measurements, otoneurological tests and cerebrospinal fluid analysis. Acta Psychiatr Scand 1995;91:86-94.
62. Mountz JM, Bradley LA, Modell JG, et al. Fibromyalgia in women: abnormalities of regional cerebral blood flow in the thalamus and the caudate nucleus are associated with low pain threshold levels. Arthritis Rheum 1995;38:926-38.
63. Kwiatek R, Barnden L, Tedman R, et al. Regional cerebral blood flow in fibromyalgia: single-photon-emission computed tomography evidence of reduction in the pontine tegmentum and thalami. Arthritis Rheum 2000;43:2823-33.
64. Gur A, Karakoc M, Erdogan S, Nas K, Cevik R, Sarac AJ. Regional cerebral blood flow and cytokines in young females with fibromyalgia. Clin Exp Rheumatol 2002;20:753-60.
65. Bradley LA, McKendree-Smith NL, Alberts KR, Alarcon GS, Mountz JM, Deutsch G. Use of neuroimaging to understand abnormal pain sensitivity in fibromyalgia. Curr Rheumatol Rep 2000;2:141-8.
66. Epstein SA, Kay G, Clauw D, et al. Psychiatric disorders in patients with fibromyalgia. A multicenter investigation. Psychosomatics 1999;40:57-63.
67. Gendreau RM, Mease PJ, Rao SR, et al. Milnacipran: A potential new treatment of fibromyalgia [abstract]. Arthritis Rheum 2003;48 Suppl:S616.
68. Henriksson C, Gundmark I, Bengtsson A, Ek AC. Living with fibromyalgia: consequences for everyday life. Clin J Pain 1992;8:138-44.
69. Littlejohn GO. A database for fibromyalgia. Medical Pain Education Website. [Internet] Accessed April 20, 2005. Available from: http://websites.golden-orb.com/pain-education/100130.php
70. Burckhardt CS, Clark SR, Bennett RM. A comparison of pain perceptions in women with fibromyalgia and rheumatoid arthritis: relationship to depression and pain extent. Arthritis Care Res 1992;5:216-22.
71. Mengshoel AM, Forre O. Pain and fatigue in patients with rheumatic disorders. Clin Rheumatol 1993;12:515-21.
72. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore 1994;23:129-38.
73. Martinez-Lavin M, Lopez S, Medina M, Nava A. Use of the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) questionnaire in patients with fibromyalgia. Semin Arthritis Rheum 2003;32:407-11.
74. Yunus M, Masi AT, Calabro JJ, Miller KA, Feigenbaum SL. Primary fibromyalgia (fibrositis): clinical study of 50 patients with matched normal controls. Semin Arthritis Rheum 1981;11:151-71.
75. Gracely RH, Grant MA, Giesecke T. Evoked pain measures in fibromyalgia. Best Pract Res Clin Rheumatol 2003;17:593-609.
76. Sinclair D, Starz TW, Turk DC. The Manual Tender Point Survey. National Fibromyalgia Association Web site. [Internet] Accessed April 20, 2005. Available from: http://fmaware.org/doctor/tenderpt.htm
77. Belza BL, Henke CJ, Yelin EH, Epstein WV, Gilliss CL. Correlates of fatigue in older adults with rheumatoid arthritis. Nurs Res 1993;42:93-9.
78. Smets EM, Garssen B, Bonke B, De Haes JCJM. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res 1995;39:315-25.
79. Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. Health Qual Life Outcomes 2003;1:79.
80. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989;46:1121-3.
81. Hays RD, Stewart AL. Sleep measures. In: Stewart AL, Ware JE, editors. Measuring functioning and well-being: The Medical Outcomes Study approach. Durham, NC: Duke University Press; 1992:235-59.
82. Turk DC, Dworkin RH, Allen RR, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. Pain 2003;106:337-45.
83. Turk DC, Dworkin RH. What should be the core outcomes in chronic pain clinical trials? Arthritis Res Ther 2004;6:151-4.
84. Ehrlich GE, Khaltaev NG. Low back pain initiative. Geneva: World Health Organization; 1999.
85. Ware JEJ, Sherbourne CD. The MOS 36-Item Short Form Health Survey (SF-36): Conceptual framework and item selection. Medical Care 1992;30:473-83.
86. Neumann L, Berzak A, Buskila D. Measuring health status in

Israeli patients with fibromyalgia syndrome and widespread pain and healthy individuals: utility of the short form 36-item health survey (SF-36). Semin Arthritis Rheum 2000;29:400-8.
87. Burckhardt CS, Clark SR, Bennett RM. The Fibromyalgia Impact Questionnaire: development and validation. J Rheumatol 1991;18:728-33.
88. Buskila D. Drug therapy. Baillieres Best Pract Res Clin Rheumatol 1999;81:45-55.
89. Wolfe F, Hawley DJ, Goldenberg DL, et al. The assessment of functional impairment in fibromyalgia (FM): Rasch analyses of 5 functional scales and the development of the FM Health Assessment Questionnaire. J Rheumatol 2000;27:1989-99.
90. McGahuey CA, Gelenberg AJ, Laukes CA, et al. The Arizona Sexual Experience Scale (ASEX): reliability and validity. J Sex Marital Ther 2000;26:25-40.
91. Beck AT. A systematic investigation of depression. Compr Psychiatry 1961;2:163-70.
92. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (MINI): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59 Suppl 20:22-33.
93. Turk DC, Monarch ES, Williams AD. Psychological evaluation of patients diagnosed with fibromyalgia syndrome: a comprehensive approach. Rheum Dis Clin North Am 2002;28:219-33.
94. Dunkl PR, Taylor AG, McConnell GG, et al. Responsiveness of fibromyalgia clinical trial outcome measures. J Rheumatol 2000;27:2683-91.
95. Hewett JE, Buckelew SP, Johnson JC, et al. Selection of measures suitable for evaluating change in fibromyalgia clinical trials. J Rheumatol 1995;22:2307-12.
96. Arnold LM, Keck PE Jr, Welge JA. Antidepressant treatment of fibromyalgia: a meta-analysis and review. Psychosomatics 2000;41:104-13.
97. Crofford LJ, Russell J, Mease P, et al. Pregabalin improves pain associated with fibromyalgia syndrome in a multicenter, randomized, placebo-controlled monotherapy trial [abstract]. Arthritis Rheum 2002;46 Suppl:S613.
98. Simms RW, Felson DT, Goldenberg DL. Development of preliminary criteria for response to treatment in fibromyalgia syndrome. J Rheumatol 1991;18:1558-63.
99. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94:149-58.
100. Simms RW, Goldenberg DL, Felson DT, et al. Tenderness in 75 anatomic sites. Distinguishing fibromyalgia patients from controls. Arthritis Rheum 1988;31:182-7.
101. Carette S, Bell MJ, Reynolds WJ, et al. Comparison of amitriptyline, cyclobenzaprine, and placebo in the treatment of fibromyalgia. A randomized, double-blind clinical trial. Arthritis Rheum 1994;37:32-40.
102. Goldenberg DL, Felson DT, Dinerman H. A randomized, controlled trial of amitriptyline and naproxen in the treatment of patients with fibromyalgia. Arthritis Rheum 1986;29:1371-7.
103. Oppenheimer L, Kher U. The impact of measurement error on the comparison of two treatments using a responder analysis. Stat Med 1999;18:2177-88.
104. Witter J, Simon LS. Chronic pain and fibromyalgia: the regulatory perspective. Best Pract Res Clin Rheumatol 2003;17:541-6.
105. OMERACT 7 Website. OMERACT 7 program. [Internet] Accessed April 20, 2005. Available from: http://reuma.rediris.es/omeract/whatis/index.html
106. Rao SG, Bennett RM. Pharmacological therapies in fibromyalgia. Best Pract Res Clin Rheumatol 2003;17:611-27.
107. Bennett RM. Pharmacological treatment of fibromyalgia. J Functional Syndromes 2001;1:79-92.
108. Wolfe F, Cathey MA, Hawley DJ. A double-blind placebo controlled trial of fluoxetine in fibromyalgia. Scand J Rheumatol 1994;23:255-9.
109. Arnold LM, Hess EV, Hudson JI, Welge JA, Berno SE, Keck PE Jr. A randomized, placebo-controlled, double-blind, flexible-dose study of fluoxetine in the treatment of women with fibromyalgia. Am J Med 2002;15:191-7.
110. Goldenberg D, Mayskiy M, Mossey C, Ruthazer R, Schmid C. A randomized, double-blind crossover trial of fluoxetine and amitriptyline in the treatment of fibromyalgia. Arthritis Rheum 1996;39:1852-9.
111. Anderberg UM, Marteinsdottir I, von Knorring L. Citalopram in patients with fibromyalgia – a randomized, double-blind, placebo-controlled study. Eur J Pain 2000;4:27-35.
112. Norregaard J, Volkmann H, Danneskiold-Samsoe B. A randomized controlled trial of citalopram in the treatment of fibromyalgia. Pain 1995;61:445-9.
113. Gendreau M, Hufford MR, Stone AA. Measuring clinical pain in chronic widespread pain: selected methodological issues. Best Pract Res Clin Rheumatol 2003;17:575-92.
114. Arnold LM, Lu Y, Crofford L, et al. A double-blind multicenter trial comparing duloxetine to placebo in the treatment of fibromyalgia with or without major depressive disorder [abstract]. Arthritis Rheum 2003;48 Suppl:S691.
115. Sayar K, Aksu G, Ak I, Tosun M. Venlafaxine treatment of fibromyalgia. Ann Pharmacother 2003;37:1561-5.
116. Farber L, Stratz TH, Bruckle W, et al. Short-term treatment of primary fibromyalgia with the 5-HT3-receptor antagonist tropisetron: results of a randomized, double-blind, placebo-controlled multicenter trial in 418 patients. Int J Clin Pharmacol Res 2001;21:1-13.
117. Stratz T, Muller W. The use of 5-HT3 receptor antagonists in various rheumatic diseases — a clue to the mechanism of action of these agents in fibromyalgia? Scand J Rheumatol 2000;113 Suppl:66-71.
118. Dworkin RH, Backonja M, Rowbotham MC, et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. Arch Neurol 2003;60:1524-34.
119. Zimmermann M. Pathophysiological mechanisms of fibromyalgia. Clin J Pain 1991;7 Suppl 1:S8-S15.
120. Dworkin RH, Corbin AE, Young JP Jr, et al. Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. Neurology 2003;60:1274-83.
121. Arroyo S, Anhut H, Kugler AR, et al. Pregabalin add-on treatment: a randomized, double-blind, placebo-controlled, dose-response study in adults with partial seizures. Epilepsia 2004;45:20-7.
122. Pande AC, Crockatt JG, Feltner DE, et al. Pregabalin in generalized anxiety disorder: A placebo-controlled trial. Am J Psychiatry 2003;160:533-40.
123. Sharma U, Iacobellis D, Glessner C, et al. Pregabalin effectively relieves pain in two studies of patients with painful diabetic peripheral neuropathy (studies 1008-14/-29) [abstract]. 19th Annual Scientific Meeting of the American Pain Society; November 2-5, 2000; Atlanta, Georgia:679.
124. Russell IJ, Kamin M, Bennett RM, Schnitzer TJ, Green JA, Katz WA. Efficacy of tramadol in treatment of pain in fibromyalgia. J Clin Rheumatol 2000;6:250-7.
125. Bennett RM, Kamin M, Karim R, Rosenthal N. Tramadol and acetaminophen combination tablets in the treatment of fibromyalgia pain: a double-blind, randomized, placebo-controlled study. Am J Med 2003;114:537-45.
126. Bennett RM, Gatter RA, Campbell SM, et al. A randomized trial of cyclobenzaprine and placebo in the management of fibrositis. Arthritis Rheum 1988;31:1535-42.
127. Quimby LG, Gratwick GM, Whitney CD, et al. A randomized trial of cyclobenzaprine for the treatment of fibromyalgia. J Rheumatol 1989;16 Suppl 19:140-3.
128. Reynolds WJ, Moldofsky H, Saskin P, et al. The effects of cyclobenzaprine on sleep physiology and symptoms in patients with fibromyalgia. J Rheumatol 1991;18:452-4.
129. Kranzler J, Gendreau J, Rao S. The psychopharmacology of fibromyalgia: a drug development perspective. Psychopharmacol

Bull 2002;36:165-213.
130. Graven-Nielsen T, Aspegren Kendall S, Henriksson KG, et al. Ketamine reduces muscle pain, temporal summation, and referred pain in fibromyalgia patients. Pain 2000;85:483-91.
131. Holman A, Neiman R, Ettlinger R. Pramipexole for fibromyalgia: the first open label, multicenter experience [abstract]. Arthritis Rheum 2002;46 Suppl:S108.
132. Bennett RM, Clark SC, Walczyk J. A randomized, double-blind, placebo-controlled study of growth hormone in the treatment of fibromyalgia. Am J Med 1998;104:227-31.
133. Pachas WN. Modafinil for the treatment of fatigue of fibromyalgia. Clin Rheumatol 2003;9:282-5.
134. Preskorn SH, Jerkovich GS. Central nervous system toxicity of tricyclic antidepressants: phenomenology, course, risk factors, and role of therapeutic drug monitoring. J Clin Psychopharmacol 1990;10:88-95.
135. Williams DA. Psychological and behavioral therapies in fibromyalgia and related syndromes. Best Pract Res Clin Rheumatol 2003;17:649-65.
136. Williams DA, Cary MA, Groner KH, et al. Improving physical functional status in patients with fibromyalgia: a brief cognitive behavioral intervention. J Rheumatol 2002;29:1280-6.
137. Sprott H. What can rehabilitation interventions achieve in patients with primary fibromyalgia? Curr Opin Rheumatol 2003;15:145-50.
138. Richards SC, Scott DL. Prescribed exercise in people with fibromyalgia: parallel group randomised controlled trial. BMJ 2002;325:185.
139. Mannerkorpi K, Iversen MD. Physical exercise in fibromyalgia and related syndromes. Best Pract Res Clin Rheumatol 2003;17:629-47.
140. Moldofsky H. Management of sleep disorders in fibromyalgia. Rheum Dis Clin North Am 2002;28:353-65.