

The rational management of fibromyalgia patients

Robert M. Bennett, MD, FRCP, FACP

Department of Medicine (OP09)
Oregon Health and Science University
3181 SW Sam Jackson Park Road
Portland, OR 97201, USA

The rational management of fibromyalgia (FM) calls for a holistic approach based upon a bio–psycho–social approach to management. The biologic component of this approach requires an understanding of the physiology and biochemistry of chronic pain in terms of different levels of targeted intervention, and strategies for managing dysfunctional sleep, fatigue, deconditioning, psychologic distress, cognitive dysfunction and FM associated disorders ^[1]. The physician treating FM patients must have a wide-ranging interdisciplinary knowledge base coupled with an understanding and empathy for the existential crisis experienced by many FM patients. A structured multidisciplinary approach to managing FM patients requires an appreciation of the parts that make up the whole. One cannot successfully manage FM patients if one treats the diagnosis of FM as a unified entity. There are 12 separate management issues that usually require attention in most FM patients seeking medical help ([Table 1](#)). The remainder of this article provides an overview of relevant management issues, which are then covered in depth in the following articles.

Table 1. The components of a structured fibromyalgia treatment program

1. Diagnosis
2. Education
3. Pain
4. Fatigue
5. Sleep
6. Psychologic disorders
7. Endocrine dysfunction
8. Dysautonomia
9. Deconditioning
10. Cognitive dysfunction
11. The existential crisis
12. Associated syndromes

Diagnosis and evaluation

The diagnosis of FM is usually based on 1990 recommendations of the American College of Rheumatology classification criteria ^[2]. However, it is increasingly evident that many patients with widespread pain have less than the recommended 11 out of 18 tender points. It should be remembered that there are over 600 muscles in the human body, each of which theoretically might contain a tender point. Thus the 18 tender points to be routinely sampled in arriving at diagnosis FM represent only about 3% of the total available tender points. If a patient has widespread pain and tenderness in many other areas, he or she is unlikely to have a different neurophysiologic basis for their pain than patients with strictly ACR defined FM. Thus it is important to look at other sites that commonly harbor myofascial trigger points. The reason for this more extensive evaluation is two-fold: (1) to establish a probable diagnosis of FM in patients with less than 11 tender points, and (2) find pain generators relevant to myofascial peripheral pain that would benefit from trigger point therapy. The article by Yunus in this issue for in-depth coverage.

Taking a general medical history and performing a routine physical examination is unlikely to pick up many of the issues that are critical to formulating a rational structured treatment plan. Rather, a FM focused history and examination is an important requisite in structuring an effective management program. The history and examination will probably suggest certain problems that need further evaluation in terms of specialist referral or investigations. The particulars are discussed in depth in the articles by Yunus, Turk, and Borg-Stein.

FM is not a diagnosis of exclusion and thus laboratory tests and imaging studies play no role in establishing the diagnosis according to the 1990 ACR criteria. However, FM patients may have other painful conditions, indeed FM is a common accompaniment of lupus, rheumatoid arthritis and osteoarthritis ^{[3] [4] [5]}. The role for further investigations in FM patients has not been well established, but there are clearly some associated and/or concomitant problems that will only be elucidated by an investigational approach. These ancillary problems and the usual investigations are shown in [Table 2](#). Whether to proceed with any of these investigations is based on taking a FM-focused history and the findings on an attentive examination.

Table 2. Possible investigations

Suspected problem	Initial investigation
Endocrine	
Thyroid disorder	TSH
Estrogen status	FSH
HPA axis status	AM Cortisol
Testosterone status	Free testosterone
Growth hormone status	IGF-1
DHEA status	DHEAS

Table 2. Possible investigations

Sleep disorder

Sleep apnea	
Narcolepsy	Sleep study
Sleep phase disorder	
α - δ Sleep pattern	
Periodic limb movement	Trial of L-DOPA / Carbidopa

Infectious diseases

Hepatitis C	Hepatitis C antibody
HIV infection	HIV screening test
Lyme disease	Lyme ELISA / Western blot

Psychologic stress

Depression	Beck depression inventory
Anxiety	Beck anxiety inventory
Coping style	Coping strategies questionnaire
Overall impact on life activities	Quality of life questionnaire

Peripheral pain generators

Osteoarthritis	Radiographs
Peripheral neuropathy	NCV / EMG
Spinal stenosis	MRI spine
Disc herniation	MRI spine
Chiari I malformation	MRI foramen magnum
Endometriosis	Gynecologic referral
Migraine	Response to 5HT _{1D} blocker

Autonomic dysfunction

Neurally mediated hypotension	Tilt table test
Postural orthostatic tachycardia syndrome	Tilt table test

Education

There is a wealth of evidence that higher educational attainments are associated with a better prognosis in many chronic diseases ^[6]. There are several studies that support the value of education in FM patients ^{[2] [7] [8] [9] [10] [11] [12]}. Indeed, education has several components common to cognitive behavioral techniques, such as goal setting and reassessment of priorities. The major elements of an educational program are shown in Table 3 and covered in the articles by Burckhardt and Goldenberg in this issue.

Table 3. The components of a fibromyalgia educational program

Table 3. The components of a fibromyalgia educational program

1. Validate symptoms
2. Emphasize nondestructive (not necessarily benign) nature of FM
3. Focus on improving function, not complete eradication of symptoms
4. Discuss importance of mind–body relationships—teach meditation and relaxation techniques
5. Discuss drug and nondrug therapy options
6. Discuss “touted cures” for FM
7. Explain the importance of gentle life-long exercise
8. Inform about principles of sleep hygiene
9. Discuss pacing of activities, feeling of guilt, and improved assertiveness
10. Emphasize patient's active role in any treatment

Pain

It is increasingly evident that pain perception in FM is due in part to changes in the central nervous system (CNS) that result in amplification of nociceptive impulses ^{[13] [14] [15]}. This is generally referred to as “central sensitization” and is thought to result from the plasticity of neuronal synapses in response to past pain experiences. There are presumably different levels of central sensitization, accounting for the wide experience of pain in FM. A prominent psychologic input often “colors” the suffering component of the pain experience. There is now an extensive literature describing the neurophysiology and biochemistry of pain perception and amplification. Based on this contemporary scientific background, it is now possible to formulate a rational approach to managing FM related pain. The four major sites in the pain system that are potentially amenable to modification are shown in [Fig. 1](#). In considering the rational management of pain in FM it is logical to focus on each of these four areas, namely peripheral pain generation, dorsal horn sensitization, psychologic influences, and the modulating influences of the descending pain pathway. An overview of this approach to managing FM related pain is given in the article by Rao in this issue.

Fig. 1. Neural impulses destined to result in the sensation of pain arise in peripheral nociceptors and travel in unmyelinated type C fibers to the dorsal horn of the spinal cord. After crossing the midline, ascending impulses travel to the thalamus. A projection from the lateral thalamus goes to the somatosensory cortex. A second projection from the medial hypothalamus travels to several subcortical nuclei—especially those making up the limbic system. The cognitive activity of the prefrontal cortex and the subconscious activation of subcortical nuclei influence the activity of structures in the midbrain (the PAQ and RVM), which, in turn, modulate the activity at the dorsal horn by way of the descending tract.

The periphery

There is no specific tissue pathology, at least in peripheral tissues, that can be said to be characteristic of FM ^[16]. However, this fact should not be taken as negating the importance

of peripheral nociceptive mechanisms. Once the CNS is sensitized, peripheral pain generators will not only be perceived as being more painful, but a persistent barrage of nociceptive impulses will prolong and amplify the biochemical machinery of central sensitization. The most common peripheral pain generators in FM are myofascial trigger points. Although trigger points can be discerned with precision clinically, their underlying pathology is still not well established. Common peripheral pain generators are shown in [Table 4](#)

Table 4. Common peripheral pain generators

- Myofascial trigger points
- Degenerative joint disease
- Inflammatory joint disease
- Bursitis
- Tendinitis
- Developmental defects (eg, scoliosis)
- Hypermobility syndrome
- Neuropathic pain
- Injuries / trauma
- Repetitive strain
- Visceral pain (eg, IBS, endometriosis)
- Herniated discs
- Spinal stenosis / Chiari malformation.
- Recurrent headaches (eg, migraine)

Although some peripheral pain generators, notably arthritic disorders, may be helped by nonsteroidal anti-inflammatory drugs (NSAIDs), central pain is not usually very responsive to these agents. Thus the use of NSAIDs is usually adjunctive to the use of centrally acting analgesics. Specific treatments for other pain generators would include, for example, gabapentin in neuropathic pain and 5-HT_{1D} antagonists in vascular headaches. Some pain generators, such as osteoarthritis of the knees or the hips, and endometriosis, may be helped by surgery. As the most common pain generator in most FM patients is myofascial trigger points, it is imperative that these be identified and effectively managed by pacing, stretching, improved physical conditioning, self help techniques such as acupressure and spray and stretch, and by physician intervention with procaine or botulinum toxin injections. The search for these pain generators is a critically important and often neglected aspect of treating FM. This topic is covered in depth in the article by Borg-Stein ^[5] in this issue.

The dorsal horn

The synapse of first and second order neurons in the spinal cord is the site of dynamic state-dependent modulation of nociceptive impulses leading to central sensitization ^{[13] [17] [18]}

. The critical pathophysiologic event leading to sensitization of the dorsal horn WDR neurons is “wind-up.” This term refers to the fact that repetitious activation of C fibers results in an exponential increase in the magnitude of the response recorded in the second order neurons in the dorsal horn. An important molecular event in the initiation and maintenance of central sensitization is activation of NMDA receptors (N-methyl-D-aspartate). Activation of NMDA receptors induces a long lasting activation potential in the stimulated neuron that results in functional neuroplasticity. With more persistent activation of NMDA receptors, structural reorganization of the dorsal horn synapse may occur; this leads to long lasting changes that result in amplified efferent sensory activity in the spinothalamic tracts ^{[19] [20]}. The release of excitatory amino acids such as glutamate and their interaction with cognate receptors is enhanced by neuropeptides such as substance P (SP) and nerve growth factor (NGF). This mechanism may be relevant to abnormal sensory processing in FM, as the CSF levels of both SP and NGF have been reported to be elevated in FM ^{[21] [22] [23]}. It is also important to note that the activity of dorsal horn neurons is modified by the descending pain system. The concept that the somatosensory system can operate at several different levels of activity, which are dependent upon the variation of afferent input, is important in the rational pharmacotherapy of chronic pain states.

Reducing “nociceptive amplification” that occurs at the first synapse is mainly accomplished through pharmacologic means ^[24]. Currently the only FDA approved drugs that modulate dorsal horn cell reactivity are those that activate or amplify the descending pain system.

The descending system originates in the midbrain and terminates at the level of dorsal horn neurons; thus influencing spinal cord sensitization ^{[25] [26] [27]}. It is now increasingly appreciated that this descending system is responsible for such diverse events such as the placebo effect, fear induced hypoalgesia, anticipatory hyperalgesia, the benefits of cognitive behavioral therapy, the action of opioids and inflammation-induced hyperalgesia. Much of the research on the descending modulatory system has focused on the reduction of dorsal horn activity. Most of the drugs used to treat pain act at the level of the descending inhibitory system, working to modulate the activity of the dorsal horn. These include opioids, tramadol, GABA agonists, antidepressants, $\alpha 2$ adrenergic agonists and 5-HT₃ antagonists. These medications are discussed in the articles by Rao, Barkhuizen, and Spaeth in this issue.

The ascending system would logically be targeted by inhibition of substance P release or blocking its interaction with the NK 1 receptors. However, clinical trials of a first generation substance P antagonist have been disappointing in chronic pain states ^[28]. To date NGF antagonists have not been used in human clinical trials. There is good experimental evidence that blocking NMDA receptors ameliorates pain in FM subjects. Most of this work has been performed using ketamine—a dissociative anesthetic ^{[29] [30] [31]}. Dextromethorphan is a weak NMDA receptor antagonist that has been successfully used in neuropathic pain ^{[32] [33] [34]} and more recently as an adjunct to tramadol and treatment of FM ^[35]. These topics are discussed in depth in the articles by Rao, Barkhuizen, Russell, and Henriksson in this issue.

The brain

FM patients are sometimes told, but more often given subliminal cues, that their problem is “all in your head.” There is now overwhelming scientific evidence that the higher cortical centers do in fact influence the experience of pain ^{[36] [37] [38] [39]}. However, there is no conclusive evidence, to date, that a pain experience can be exclusively generated by activity of the higher cortical centers. The critical role of the central nervous system in modulating the subjective experience of pain can now be described in terms of abnormal brain scans, the neurophysiology of central sensitization, disorders of neurotransmitters and their receptors and the remarkable clinical efficacy of drugs that target and transmitters and their receptors. This molecular pharmacologic approach to etiology is well exemplified by the success of serotonergic agents in diseases such as depression and migraine. Targeting the brain in this new era of understanding “symptoms without pathology” is now seen as one part of a multimodal approach to management ^[40]. Drug therapy, transcranial magnetic stimulation, hypnotherapy and cognitive behavioral therapy are some of the current tools commonly used to target the brain in the management of chronic pain problems. A detailed discussion of the psychologic aspects of managing FM patients is found in the articles by Turk and Burckhardt in this issue.

Fatigue

Tiredness is a major complaint of nearly all FM patients. Indeed if it is the predominant complaint, these patients may be diagnosed as having chronic fatigue syndrome (CFS). There are many potential causes for excessive fatigue in FM patients (see [Table 5](#)). Many of these causative factors are most amenable to nonpharmacologic interventions. However, sleep problems, depression and other psychologic stressors, some features of dysautonomia, and endocrine dysfunction are appropriately treated with drugs. The pharmacologic treatment of these problems is dealt with in the other sections of this review. Recent studies using the 5-HT₃ receptor antagonist tropisetron reported benefits both in FM related fatigue and in chronic fatigue syndrome ^{[41] [42]}. There are increasing anecdotal reports that modafinil (Provigil), a nonamphetamine drug used in narcolepsy and sleep deprivation situations, is of some benefit in improving nonspecific fatigue ^{[43] [44] [45] [46]}. See the article by Guymer and Clauw in this issue for more in-depth coverage of managing fatigue.

Table 5. Common causes of fatigue

Anemia

Nonrestorative sleep

Concurrent disease

Dysautonomia

Endocrine dysfunction

Inappropriate workload

Chronic inflammation

Medication side-effects

Hemochromatosis

Deconditioning

Table 5. Common causes of fatigue

Primary sleep disorders

Major depression

Anxiety states

Chronic stressors

Sleep

Most FM patients report being light sleepers, being easily aroused by low-level noises or intrusive thoughts. Many exhibit an α - δ EEG pattern, which would explain why they never get into the restorative stages 3 and 4 of non-REM sleep^{[47] [48]}. The experimental induction of α - δ sleep in healthy individuals has been reported to induce musculoskeletal aching and/or stiffness as well as increased muscle tenderness^[49]. A poor night's sleep is often followed a worsening of FM symptoms the next day^[50]. Poor sleep is a major contributor to fatigue. Management of disturbed sleep in FM patients involves a careful analysis of causative factors, including primary sleep disorders such as sleep apnea and periodic limb movement disorder. Important nonpharmacologic aspects of sleep management include ensuring an adherence to the basic rules of sleep hygiene and regular low-grade exercise. The use of low dose tricyclic antidepressants (amitriptyline, trazadone, doxepin, imipramine, etc.)^[51] has been the mainstay of sleep pharmacotherapy in FM patients^{[52] [53]}. Cyclobenzaprine, a TCA analog, has also been used in some success in some FM patients, with positive effects on sleep more than on other features of FM^{[52] [54]}. However, some FM patients cannot tolerate TCAs due to unacceptable levels of daytime drowsiness or weight gain. In these patients benzodiazapine-like medications such as aprazolam^[55], zolpidem^[56] and zopiclone^[57] have been shown to be beneficial in a few trials. γ -Hydroxybutyrate (GHB) was used in a one-month polysomnographic study in 11 FM patients. There was a significant improvement in both fatigue and pain, with an increase in slow wave sleep and a decrease in the severity of the α anomaly^[58]. A subset of FM patients suffer from a primary sleep disorder, which requires specialized management. About 25% of male and 15% of female FM patients have sleep apnea. Unless specific questions about this possibility are asked, sleep apnea will often be missed. Patients with sleep apnea usually require treatment with positive airway pressure (CPAP) or surgery. By far the commonest sleep disorder in FM patients is restless leg syndrome/periodic limb movement disorder. Treatment is usually with L-Dopa/carbidopa (Sinemet 10/100 mg at supertime) or clonazepam (Klonopin 0.5 or 1.0 mg at bedtime)^[59]. More recently other dopamine agonists such as pergolide, tolixepole and pramixepole have been proven to be effective^{[60] [61] [62]}. In recalcitrant cases of restless legs, methadone (10–30 mg/hs) usually provides relief. The management of sleep problems in FM is covered in depth in the article by Moldofsky in this issue.

Psychologic distress

Increased levels of psychologic distress resulting in psychiatric syndromes are a common accompaniment of many painful chronic illnesses^{[39] [63] [64]}. Approximately 30 percent of FM patients have significant current depression and about 60% have a lifetime prevalence of depressive illness^{[65] [66] [67]}. Primary depressive illness can be helped by psychotherapeutic techniques as well as pharmacotherapy. In that FM patients often develop stressors

related to psychosocial/economic issues, therapy focusing on problem solving techniques and cognitive restructuring may be beneficial in addition to drug therapy. Patients with very severe depression and suicidal ideation, bipolar disorder, and psychotic features should be referred to a psychiatrist. Although antidepressant medications are commonly used in the treatment of pain and sleep in FM patients, the doses used are usually suboptimal for treating depressive illness. There has not been a single trial to specifically address the issue of treating depression in FM patients, although one recent article addressed this issue in a useful review^[68]. It is generally assumed that treating depression in these patients is no different than treating primary depressive illness. This may be correct, but it must be born in mind that FM patients may be taking many other medications with the potential for adverse interactions and are more sensitive to medication side-effects. For instance, most of the antidepressant drugs lower the epileptogenic threshold and this theoretically could result in problems with other agents, such as tramadol, that also lower this threshold. Single doses of more than 200 mg of bupropion or a total daily dose of more than 450 mg poses an increased risk of seizures. Selective serotonin–reuptake inhibitors may cause drug interactions because of their inhibition of the cytochrome P-450 system. Since the cardiovascular effects of tricyclic antidepressants include postural hypotension (a common problem in FM patients with dysautonomia), cardiac conduction abnormalities, and arrhythmias, the use of these drugs should be avoided in patients with symptomatic hypotension, ischemic heart disease and known arrhythmias. Nearly all antidepressant medications are eliminated through the liver, so they should be used with caution in patients with hepatic dysfunction. The evaluation and management of psychologic issues are covered in the articles by Turk, Burckhardt, and Goldenberg in this issue.

Endocrine dysfunction

There is no good evidence that FM is primarily due to endocrine dysfunction. However common problems such as hypothyroidism and menopausal symptoms will often aggravate pain and fatigue and appropriate replacement therapy is usually indicated. There has been much interest in abnormalities of the hypothalamic–pituitary–adrenal axis (HPA) in FM patients^{[69] [70]}. The general impression is that FM patients have a somewhat reduced HPA responsiveness. However, replacement therapy with Prednisone 15 mg/day was not shown to be therapeutically useful^[71]. About one third of FM patients are growth hormone deficient^{[72] [73]} and replacement therapy is of benefit to many growth hormone deficient FM patients^[74]. See the article by Genen et al in this issue for in-depth coverage.

Dysautonomia

Abnormalities of autonomic function appear to be associated with both FM and chronic fatigue syndrome^{[75] [76] [77]}. The most common presentation of dysautonomia in FM patients is the finding of neurally mediated hypotension in about one third of patients^{[78] [79]}. Another manifestation of dysautonomia is the postural orthostatic tachycardia syndrome (POTS). These patients have an exaggerated increase in their heart rate, rather than a pronounced fall in blood pressure, in response to standing and exercise^[80]. Dysautonomia is often associated with severe fatigue^[81]. Treatment involves: (1) education as to the triggering factors and their avoidance, (2) increasing plasma volume (increased salt intake, prescription of Florinef), (3) avoidance of drugs that aggravate hypotension (eg, TCA's, antihypertensives), (4) preventing the ventricle–baroreceptor–reflex (α -adrenergic antagonists or disopyramide), and (5) minimizing the efferent limb of the baroreceptor

reflex (a-adrenergic agonists or anticholinergic agents). See the article by Martinez-Lavin in this issue for in-depth coverage.

Deconditioning

Most FM patients are aerobically unfit and have suboptimal strength and poor flexibility. The notion that “exercise is good for FM patients” is an accepted contemporary truth. There is evidence that acute exercise is associated with reduced pain perception ^{[82] [83]} and a lowered pain threshold ^{[83] [84]}. Although endorphins are secreted in response to acute exercise ^[85], they are probably not the sole mechanism of exercise-induced analgesia ^[86]. During graded exercise, endorphins only start to increase at the anaerobic threshold (ie, lactate production), and in moderate steady state exercise they do not increase until exercise duration exceeds one hour ^[87]. The benefits of exercise are based on reasonable scientific evidence, but exercise may also be deleterious. Whether it is good or bad for FM patients probably depends upon many variables, such as age, current level of conditioning, rate of increase of exercise intensity, frequency of exercise, ratio of eccentric to concentric muscle use, hormonal anabolic status and negative factors such as obesity, arthritis and concomitant muscle disease. FM introduces an important factor into the equation of postexertional pain, that is, amplification of sensory processing (ie, central sensitization). It is hypothesized that for a given intensity of exercise, FM patients will experience more postexertional pain than non-FM patients ^{[88] [89] [90]}. The message is that exercise is a double-edged sword in the management of FM patients. It's just too easy to blame a patient's lack of progress on their poor adherence to a too rigorous exercise regime. A carefully planned individual exercise program is always needed; this is best supervised by an exercise physiologist or a physiotherapist. A structured approach to prescribing exercise in FM patients is given in the article by Jones and Clark in this issue.

Cognitive dysfunction

Cognitive dysfunction is a major problem, according to self-reports, for many FM patients ^{[91] [92] [93]}. Patients commonly describe difficulties with short-term memory, concentration, logical analysis and motivation. Problems with cognitive function are being increasingly recognized in FM patients and are the subject of increasing research efforts ^{[94] [95]}. Currently, defects have been described in terms of working memory, episodic memory and verbal fluency. These decreases in cognitive performance and has been estimated to be equivalent to 20 years of aging ^[94]. Cognitive dysfunction adversely affects the ability to be competitively employed and may cause concern as to an early dementing type of neurodegenerative disease. In practice the latter concern has never been a problem and patients can be reassured. The cause of poor memory and problems with concentration is, in most patients, related to the distracting effects of chronic pain and mental fatigue. Thus the effective treatment of cognitive dysfunction in FM is dependent on the successful management of the other symptoms.

The existential crisis

There is a universal human need for understanding bothersome symptoms in terms of a definitive diagnosis and plans for a cure. Everyone expects a cure until confronted with a chronic and currently incurable disorder. Despite being a common disorder, the term FM does not have widespread public recognition. One might expect that the concept of

chronicity without degeneration would bring sighs of relief, but this is seldom the case. As a rheumatologist I am often struck by the fact that most patients would prefer a diagnosis of lupus or rheumatoid arthritis rather than a diagnosis of FM. And, it is not just the patient who would prefer these diagnoses, so too would many rheumatologists! Having a chronic painful disease, which there is currently no cure, often produces a cascade of emotional reactions that can be likened to an existential crisis^[96]. Needless to say, this crisis is made all the more worse if there is doubt cast on the legitimacy of a diagnosis. Many patients have not heard of FM. Those who are acquainted with this diagnosis are often more medically sophisticated and aware of the apathy and skepticism surrounding the diagnosis of FM; thus they are often reluctant to accept this diagnosis. It often takes many patients a year or more to come to terms with a diagnosis of FM. During this time they typically go through stages of disbelief, anger and frustration, anxiety and depression, before they accept the reality of having such a frustrating and life altering condition. It is only when they fully accept this diagnosis that much progress can be made in terms of a structured approach to management in which the patient themselves becomes an integral part of the treatment team. It's important for physicians treating FM patients to understand that there is a time lag in acceptance, and that during this period little progress may be made. This is time when patience, perseverance, listening, education and empathy are most needed. See the articles by Turk, Burckhardt, and Goldenberg in this issue for further coverage.

Associated disorders

FM has been associated with several distinct syndromes (see [Table 6](#)). In some cases, these syndromes are a significant contributor to the overall symptom morbidity of FM patients. Furthermore, some may aggravate central sensitization by providing peripherally generated nociceptive input.

Table 6. Commonly associated problems

- Irritable bowel syndrome
- Irritable bladder syndrome
- Restless leg syndrome
- Dysautonomia
- Endocrine dysfunction
- Cognitive dysfunction
- Dizziness
- Cold intolerance

Irritable bowel syndrome

Irritable bowel syndrome is a very common associated condition, affecting 30–50% of FM patients^{[97] [98] [99]}. Treatment involves (1) elimination of foods that aggravate symptoms, (2) minimizing psychologic distress, (3) adhering to basic rules for maintaining a regular bowel

habit, (4) prescribing medications for specific symptoms; constipation (stool softener, fiber supplementation and gentle laxatives such as bisacodyl), diarrhea (loperamide or diphenoxylate) and antispasmodics (dicyclomine or anticholinergic/sedative preparations such as Donnatal). There is currently interest in using 5-HT₃ antagonists to help visceral spasm and diarrhea ^[100]. However, the recently introduced 5-HT₃ antagonist, Alosetron, was withdrawn from the market in the United States after some patients developed severe ileus, with several deaths.

Irritable bladder syndrome

Irritable bladder syndrome is increasingly being recognized as a problem for FM patients (213)(1756). Treatment involves (1) increasing intake of water, (2) avoiding bladder irritants such as fruit juices (especially cranberry), (3) pelvic floor exercises (eg, Kegel exercises) and the prescription of antispasmodic medications (eg, oxybutinin, flavoxate, and hyoscamine).

Dizziness

Dizziness is a common complaint of FM patients, but has only been formally studied sporadically. Treatable causes related to FM include: (1) proprioceptive dysfunction secondary to muscle deconditioning, (2) proprioceptive dysfunction secondary to myofascial trigger points in the sterno–cleido–mastoids and other neck muscles, (3) neurally mediated hypotension and (4) medication side effects. Treatment is dependent on making an accurate diagnosis.

Cold intolerance

Many FM patients complain of being colder than their partners; indeed, a significant subset of FM patients have cold induced vasospasm ^[101]. Treatment involves: (1) keeping warm, (2) low-grade aerobic exercise (which improves peripheral circulation), (3) treatment of dysautonomia (see above), and (4) the prescription of vasodilators such as the calcium channel blockers (but these may aggravate the problem in patients with hypotension).

Multiple sensitivities

This condition is thought to be a manifestation of central sensitization. Several recent reports have suggested multiple sensitivity is a common accompaniment of FM ^{[102] [103]}. The major management strategy is to avoid the offending agents. There have been no studies of pharmacotherapy of this condition in FM patients. In general, FM patients are unduly sensitive to drug side effects, so new medications should be started at low doses.

Evaluating response to treatment

The primary aim of therapy in chronic incurable disorders is to enable the patient to live as full and productive life as possible. Thus palliation of symptoms combined with improved physical and emotional well-being are the essential goals of effective treatment. Assessing

improvement or worsening in FM has to take into account the plurality of relevant problems as given in [Table 1](#) . In general, questionnaires that provide details about quality of life probably give the best overall self assessment of change, as quality of life is severely impaired in FM patients ^[104] ^[105] . However, there is not necessarily a linear relationship between quality of life and health status. Improved coping, as occurs longer the duration, the older the individual, the more likely the person will report a relatively good quality of life. The short form 36 (SF 36) is a commonly used health questionnaire that has been applied to many chronic disorders and thus has the advantage of enabling comparisons with other disorders. Pain can be assessed with regular use of pain diagrams and visual analog scales (pain VAS) as well as its effect on function. Interestingly, measurement of tender point scores has been reported to bear little relationship to self-reported pain ^[106] . The 6-minute walk distance has proved useful in assessing improved conditioning in FM ^[107] ^[108] . If the patient's main current problem is depression, it would be appropriate to monitor this with a daily diary and/or Beck Depression Inventory. It is evident that the priorities of management will change over time, for instance, an initial focus on pain relief may later be replaced with a focus on fatigue or cognitive dysfunction. A questionnaire that provides an overall view of the plurality of problems in FM is the Fibromyalgia Impact Questionnaire (FIQ) ^[109] . The FIQ has shown a good sensitivity to change ^[107] ^[110] ^[111] and is currently the most widely used FM questionnaire and by one assessment the most useful ^[112] . See the articles by Yunus, Turk, and Goldenberg in this issue for more information.

References

- [1]. Littlejohn GO. A database for fibromyalgia. *Rheum Dis Clin North Am* 1995;21:527-57. [Abstract](#)
- [2]. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia: Report of the Multicenter Criteria Committee. *Arthritis Rheum* 1990;33:160-72. [Abstract](#)
- [3]. Bennett R. The concurrence of lupus and fibromyalgia: implications for diagnosis and management. *Lupus* 1997;6:494-9. [Citation](#)
- [4]. Wolfe F. Determinants of WOMAC function, pain and stiffness scores: evidence for the role of low back pain, symptom counts, fatigue and depression in osteoarthritis, rheumatoid arthritis and fibromyalgia. *Rheumatology (Oxford)* 1999;38:355-61. [Abstract](#)
- [5]. Wolfe F, Cathey MA, Kleinheksel SM. Fibrositis (Fibromyalgia) in rheumatoid arthritis. *J Rheumatol* 1984;11:814-8. [Abstract](#)
- [6]. Ramos-Remus C, Salcedo-Rocha AL, Prieto-Parra RE, Galvan-Villegas F. How important is patient education? *Baillieres Best Pract Res Clin Rheumatol* 2000;14:689-703.
- [7]. Burckhardt CS, Bjelle A. Education programmes for fibromyalgia patients: description and evaluation. *Baillieres Clin Rheumatol* 1994;8:935-55. [Abstract](#)
- [8]. Gowans SE, de Hueck A, Voss S, Richardson M. A randomized, controlled trial of exercise and education for individuals with fibromyalgia. *Arthritis Care Res* 1999;12:120-8. [Abstract](#)
- [9]. Jensen MP, Turner JA, Romano JM. Self-efficacy and outcome expectancies: relationship to chronic pain coping strategies and adjustment. *Pain* 1991;44:263-9. [Abstract](#)
- [10]. Mannerkorpi K, Nyberg B, Ahlmen M, Ekdahl C. Pool exercise combined with an education program for patients with fibromyalgia syndrome. A prospective, randomized study. *J Rheumatol* 2000;27:2473-81.

Abstract

- [11]. Rikli RE, Edwards DJ. Effects of a three-year exercise program on motor function and cognitive processing speed in older women. *Res Q Exerc Sport* 1991;62:61-7. [Abstract](#)
- [12]. Vlaeyen JW, Teeken-Gruben NJ, Goossens ME, Rutten-van Molken MP, Pelt RA, van Eek H, et al. Cognitive-educational treatment of fibromyalgia: a randomized clinical trial. I. Clinical effects. *J Rheumatol* 1996;23:1237-45. [Abstract](#)
- [13]. Bennett RM. Emerging concepts in the neurobiology of chronic pain: evidence of abnormal sensory processing in fibromyalgia. *Mayo Clin Proc* 1999;74:385-98. [Abstract](#)
- [14]. Friis S, Mellemkjaer L, McLaughlin JK, Breiting V, Kjaer SK, Blot W, et al. Connective tissue disease and other rheumatic conditions following breast implants in Denmark. *Ann Plast Surg* 1997;39:1-8. [Abstract](#)
- [15]. Staud R, Vierck CJ, Cannon RL, Mauderli AP, Price DD. Abnormal sensitization and temporal summation of second pain (wind-up) in patients with fibromyalgia syndrome. *Pain* 2001;91:165-75. [Abstract](#)
- [16]. Simms RW. Is there muscle pathology in fibromyalgia syndrome? *Rheum Dis Clin North Am* 1996;22:245-66. [Full Text](#)
- [17]. Doubell TP, Mannion RJ, Woolf CJ. The dorsal horn: state-dependent sensory processing, plasticity and the generation of pain. In: WallPD, MelzackR, editors. *Textbook of pain* London: Churchill Livingstone; 2000. p. 165-81.
- [18]. Willis Jr. WD. Dorsal horn neurophysiology of pain. *Ann N Y Acad Sci* 1988;531:76-89. [Citation](#)
- [19]. Dickenson AH. Spinal cord pharmacology of pain. *Br J Anaesth* 1995;75:193-200. [Citation](#)
- [20]. Mannion RJ, Woolf CJ. Pain mechanisms and management: a central perspective. *Clin J Pain* 2000;16(3 Suppl):S144-56. [Abstract](#)
- [21]. Vaeroy H, Helle R, Forre O, Kass E, Terenius L. Elevated CSF levels of substance P and high incidence of Raynaud phenomenon in patients with fibromyalgia: new features for diagnosis. *Pain* 1988;32:21-6. [Abstract](#)
- [22]. Giovengo SL, Russell IJ, Larson AA. Increased concentrations of nerve growth factor in cerebrospinal fluid of patients with fibromyalgia. *J Rheumatol* 1999;26:1564-9. [Abstract](#)
- [23]. Russell IJ, Orr MD, Littman B, Vipraio GA, Alboukrek D, Michalek JE, et al. Elevated cerebrospinal fluid levels of substance P in patients with the fibromyalgia syndrome. *Arthritis Rheum* 1994;37:1593-601. [Abstract](#)
- [24]. Bennett RM. Pharmacological treatment of fibromyalgia. *Journal of Functional Syndromes* 2001;1:79-92.
- [25]. Bishop B. Pain: its physiology and rationale for management. Part I. Neuroanatomical substrate of pain. *Phys Ther* 1980;60:13-20. [Abstract](#)
- [26]. Willis WD, Westlund KN. Neuroanatomy of the pain system and of the pathways that modulate pain. *J Clin Neurophysiol* 1997;14:2-31. [Abstract](#)
- [27]. Willis Jr. WD. Anatomy and physiology of descending control of nociceptive responses of dorsal horn neurons: comprehensive review. *Prog Brain Res* 1988;77:1-29. [Citation](#)
- [28]. Hill R. NK1 (substance P) receptor antagonists—why are they not analgesic in humans? *Trends Pharmacol Sci* 2000;21:244-6. [Abstract](#)
- [29]. Graven-Nielsen T, Aspegren KS, Henriksson KG, Bengtsson M, Sorensen J, Johnson A, et al. Ketamine reduces muscle pain, temporal summation, and referred pain in fibromyalgia patients. *Pain* 2000;85:483-91. [Abstract](#)
- [30]. Sorensen J, Bengtsson A, Backman E, Henriksson KG, Bengtsson M. Pain analysis in patients with fibromyalgia: effects of intravenous morphine, lidocaine and ketamine. *Scand J Rheumatol* 1995;24:360-5. [Abstract](#)
- [31]. Sorensen J, Graven-Nielsen T, Henriksson KG, Bengtsson M, Arendt-Nielsen L. Hyperexcitability in fibromyalgia. *J Rheumatol* 1998;25:152-5. [Abstract](#)
- [32]. McQuay HJ, Carroll D, Jadad AR, Glynn CJ, Jack T, Moore RA, et al. Dextromethorphan for the treatment of neuropathic pain: a double-blind randomised controlled crossover trial with integral n-of-1 design. *Pain* 1994;59:127-33. [Abstract](#)
- [33]. Nelson KA, Park KM, Robinovitch E, Tsigos C, Max MB. High-dose oral dextromethorphan versus placebo in painful diabetic neuropathy and postherpetic neuralgia. *Neurology* 1997;48:1212-8. [Full Text](#)
- [34]. Price DD, Mao J, Frenk H, Mayer DJ. The N-methyl-D-aspartate receptor antagonist dextromethorphan selectively reduces temporal summation of second pain in man. *Pain* 1994;59:165-74. [Abstract](#)
- [35]. Clark SR, Bennett RM. Supplemental dextromethorphan in the treatment of fibromyalgia: a double-blind,

- placebo-controlled study of efficacy and side-effects. *Arthritis Rheum* 2000;43(Suppl 9):S333.
- [36]. Harkins SW, Price DD, Braith J. Effects of extraversion and neuroticism on experimental pain, clinical pain, and illness behavior. *Pain* 1989;36:209-18. [Abstract](#)
- [37]. Price DD, Harkins SW, Baker C. Sensory-affective relationships among different types of clinical and experimental pain. *Pain* 1987;28:297-307. [Abstract](#)
- [38]. Rainville P, Duncan GH, Price DD, Carrier B, Bushnell MC. Pain affect encoded in human anterior cingulate but not somatosensory cortex. *Science* 1997;277:968-71. [Abstract](#)
- [39]. Turk DC. The role of psychological factors in chronic pain. *Acta Anaesthesiol Scand* 1999;43:885-8. [Abstract](#)
- [40]. Sharpe M, Carson A. "Unexplained" somatic symptoms, functional syndromes, and somatization: do we need a paradigm shift? *Ann Intern Med* 2001;134:926-30. [Abstract](#)
- [41]. Haus U, Varga B, Stratz T, Späth M, Muller W. Oral treatment of fibromyalgia with tropisetron given over 28 days: influence on functional and vegetative symptoms, psychometric parameters and pain. *Scand J Rheumatol* 2000;(Suppl 113)55-8.
- [42]. Späth M, Welzel D, Farber L. Treatment of chronic fatigue syndrome with 5-HT₃ receptor antagonists—preliminary results. *Scand J Rheumatol* 2000;(Suppl 113)72-7.
- [43]. Akerstedt T, Ficca G. Alertness-enhancing drugs as a countermeasure to fatigue in irregular work hours. *Chronobiol Int* 1997;14:145-58. [Abstract](#)
- [44]. Broughton RJ, Fleming JA, George CF, Hill JD, Kryger MH, Moldofsky H, et al. Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness in narcolepsy. *Neurology* 1997;49:444-51. [Full Text](#)
- [45]. Lyons TJ, French J. Modafinil: the unique properties of a new stimulant. *Aviat Space Environ Med* 1991;62:432-5. [Abstract](#)
- [46]. Pigeau R, Naitoh P, Buguet A, McCann C, Baranski J, Taylor M, et al. Modafinil, d-amphetamine and placebo during 64 hours of sustained mental work. I. Effects on mood, fatigue, cognitive performance and body temperature. *J Sleep Res* 1995;4:212-28.
- [47]. Drewes AM, Gade K, Nielsen KD, Bjerregard K, Taagholt SJ, Svendsen L. Clustering of sleep electroencephalographic patterns in patients with the fibromyalgia syndrome. *Br J Rheumatol* 1995;34:1151-6. [Abstract](#)
- [48]. Moldofsky H. Sleep and fibrositis syndrome. *Rheum Dis Clin North Am* 1989;15:91-103. [Abstract](#)
- [49]. Moldofsky H, Scarisbrick P. Induction of neurasthenic musculoskeletal pain syndrome by selective sleep stage deprivation. *Psychosom Med* 1976;38:35-44. [Abstract](#)
- [50]. Affleck G, Urrows S, Tennen H, Higgins P, Abeles M. Sequential daily relations of sleep, pain intensity, and attention to pain among women with fibromyalgia. *Pain* 1996;68:363-8. [Abstract](#)
- [51]. Goldenberg DL. A review of the role of tricyclic medications in the treatment of fibromyalgia syndrome. *J Rheumatol* 1989;(Suppl 19)137-9.
- [52]. Bennett RM, Gatter RA, Campbell SM, Andrews RP, Clark SR, Scarola JA. A comparison of cyclobenzaprine and placebo in the management of fibrositis. A double-blind controlled study. *Arthritis Rheum* 1988;31:1535-42. [Abstract](#)
- [53]. Carette S, Bell MJ, Reynolds WJ, Haraoui B, McCain GA, Bykerk VP, et al. Comparison of Amitriptyline, Cyclobenzaprine, and placebo in the treatment of fibromyalgia. *Arthritis Rheum* 1994;37:32-40. [Abstract](#)
- [54]. Reynolds WJ, Moldofsky H, Saskin P, Lue FA. The effects of cyclobenzaprine on sleep physiology and symptoms in patients with fibromyalgia. *J Rheumatol* 1991;18:452-4. [Abstract](#)
- [55]. Russell IJ, Fletcher EM, Michalek JE, McBroom PC, Hester GG. Treatment of primary fibrositis/fibromyalgia syndrome with ibuprofen and alprazolam: A double-blind, placebo-controlled study. *Arthritis Rheum* 1991;34:552-60. [Abstract](#)
- [56]. Moldofsky H, Lue FA, Mously C, Roth-Schechter B, Reynolds WJ. The effect of zolpidem in patients with fibromyalgia: a dose ranging, double blind, placebo controlled, modified crossover study. *J Rheumatol* 1996;23:529-33. [Abstract](#)
- [57]. Drewes AM, Andreassen A, Jennum P, Nielsen KD. Zopiclone in the treatment of sleep abnormalities in fibromyalgia. *Scand J Rheumatol* 1991;20:288-93. [Abstract](#)
- [58]. Scharf MB, Hauck M, Stover R, McDannold M, Berkowitz D. Effect of gamma-hydroxybutyrate on pain, fatigue, and the alpha sleep anomaly in patients with fibromyalgia. Preliminary report. *J Rheumatol* 1998;25:1986-90. [Abstract](#)
- [59]. Montplaisir J, Lapierre O, Warnes H, Pelletier G. The treatment of the restless leg syndrome with or

- without periodic leg movements in sleep. *Sleep* 1992;15:391-5. [Abstract](#)
- [60]. Earley CJ, Yaffee JB, Allen RP. Randomized, double-blind, placebo-controlled trial of pergolide in restless legs syndrome. *Neurology* 1998;51:1599-602. [Full Text](#)
- [61]. Inoue Y, Mitani H, Nanba K, Kawahara R. Treatment of periodic leg movement disorder and restless leg syndrome with talipexole. *Psychiatry Clin Neurosci* 1999;53:283-5. [Abstract](#)
- [62]. Montplaisir J, Nicolas A, Denesle R, Gomez-Mancilla B. Restless legs syndrome improved by pramipexole: a double-blind randomized trial. *Neurology* 1999;52:938-43. [Full Text](#)
- [63]. Gamsa A. The role of psychological factors in chronic pain. II. a critical appraisal. *Pain* 1994;57:17-29. [Abstract](#)
- [64]. Penny KI, Purves AM, Smith BH, Chambers WA, Smith WC. Relationship between the chronic pain grade and measures of physical, social and psychological well-being. *Pain* 1999;79:275-9. [Abstract](#)
- [65]. Goldenberg DL. Psychological symptoms and psychiatric diagnosis in patients with fibromyalgia. *J Rheumatol* 1989;16(Suppl. 19):127-30.
- [66]. Hudson JI, Goldenberg DL, Pope Jr. HG, Keck Jr. PE, Schlesinger L. Comorbidity of fibromyalgia with medical and psychiatric disorders. *Am J Med* 1992;92:363-7. [Abstract](#)
- [67]. Okifuji A, Turk DC, Sherman JJ. Evaluation of the relationship between depression and fibromyalgia syndrome: why aren't all patients depressed? *J Rheumatol* 2000;27:212-9. [Abstract](#)
- [68]. Arnold LM, Keck Jr. PE, Welge JA. Antidepressant treatment of fibromyalgia. A meta-analysis and review. *Psychosomatics* 2000;41:104-13. [Abstract](#)
- [69]. Chrousos GP. The role of stress and the hypothalamic-pituitary-adrenal axis in the pathogenesis of the metabolic syndrome: neuro-endocrine and target tissue-related causes. *Int J Obes Relat Metab Disord* 2000;24(Suppl 2):S50-5. [Abstract](#)
- [70]. Pillemer SR, Bradley LA, Crofford LJ, Moldofsky H, Chrousos GP. The neuroscience and endocrinology of fibromyalgia. *Arthritis Rheum* 1997;40:1928-39. [Citation](#)
- [71]. Clark S, Tindall E, Bennett RM. A double blind crossover trial of prednisone versus placebo in the treatment of fibrositis. *J Rheumatol* 1985;12:980-3. [Abstract](#)
- [72]. Bennett RM, Clark SR, Campbell SM, Burckhardt CS. Low levels of somatomedin C in patients with the fibromyalgia syndrome. A possible link between sleep and muscle pain. *Arthritis Rheum* 1992;35:1113-6. [Abstract](#)
- [73]. Bennett RM, Cook DM, Clark SR, Burckhardt CS, Campbell SM. Hypothalamic-pituitary-insulin-like growth factor-I axis dysfunction in patients with fibromyalgia. *J Rheumatol* 1997;24:1384-9. [Abstract](#)
- [74]. Bennett RM, Clark SR, Walczyk J. A randomized, double-blind, placebo-controlled study of growth hormone in the treatment of fibromyalgia. *Am J Med* 1998;104:227-31. [Abstract](#)
- [75]. Martinez-Lavin M, Hermosillo AG. Autonomic nervous system dysfunction may explain the multisystem features of fibromyalgia. [editorial; comment] *Semin Arthritis Rheum* 2000;29:197-9. [Citation](#)
- [76]. Martinez-Lavin M, Hermosillo AG, Mendoza C, Ortiz R, Cajigas JC, Pineda C, et al. Orthostatic sympathetic derangement in subjects with fibromyalgia. *J Rheumatol* 1997;24:714-8. [Abstract](#)
- [77]. Raj SR, Brouillard D, Simpson CS, Hopman WM, Abdollah H. Dysautonomia among patients with fibromyalgia: a noninvasive assessment. *J Rheumatol* 2000;27:2660-5. [Abstract](#)
- [78]. Bou-Holaigah I, Calkins H, Flynn JA, Tunin C, Chang HC, Kan JS, et al. Provocation of hypotension and pain during upright tilt table testing in adults with fibromyalgia. *Clin Exp Rheumatol* 1997;15:239-46. [Abstract](#)
- [79]. Wilke WS, Fouad-Tarazi FM, Cash JM, Calabrese LH. The connection between chronic fatigue syndrome and neurally mediated hypotension. *Cleve Clin J Med* 1998;65:261-6. [Abstract](#)
- [80]. Karas B, Grubb BP, Boehm K, Kip K. The postural orthostatic tachycardia syndrome: a potentially treatable cause of chronic fatigue, exercise intolerance, and cognitive impairment in adolescents. *Pacing Clin Electrophysiol* 2000;23:344-51. [Abstract](#)
- [81]. Karas B, Grubb BP, Boehm K, Kip K. The postural orthostatic tachycardia syndrome: a potentially treatable cause of chronic fatigue, exercise intolerance, and cognitive impairment in adolescents. *Pacing Clin Electrophysiol* 2000;23:344-51. [Abstract](#)
- [82]. Chase TN, Murphy DI. Serotonin and central nervous system function. *Annu Rev Pharmacol Toxicol* 1983;13:181-97.
- [83]. Koltyn KF, Garvin AW, Gardiner RL, Nelson TF. Perception of pain following aerobic exercise. *Med Sci Sports Exerc* 1996;28:1418-21. [Abstract](#)
- [84]. Guieu R, Blin O, Pouget J, Serratrice G. Nociceptive threshold and physical activity. *Can J Neurol Sci*

1992;19:69-71. [Abstract](#)

[85]. Goldfarb AH, Jamurtas AZ. Beta-endorphin response to exercise. An update. Sports Med 1997;24:8-16.

[Abstract](#)

[86]. Koltyn KF. Analgesia following exercise: a review. Sports Med 2000;29:85-98. [Abstract](#)

[87]. Schwarz L, Kindermann W. Changes in beta-endorphin levels in response to aerobic and anaerobic exercise. Sports Med 1992;13:25-36. [Abstract](#)

[88]. Bennett RM. The contribution of muscle to the generation of fibromyalgia symptomatology. J Musculoskeletal Pain 1996;4:35-59.

[89]. Geel SE. The fibromyalgia syndrome: musculoskeletal pathophysiology. Semin Arthritis Rheum 1994;23:347-53. [Abstract](#)

[90]. Watkins LR, Maier SF, Goehler LE. Immune activation: the role of pro-inflammatory cytokines in inflammation, illness responses and pathological pain states. Pain 1995;63:289-302. [Abstract](#)

[91]. Jennum P, Drewes AM, Andreasen A, Nielsen KD. Sleep and other symptoms in primary fibromyalgia and in healthy controls. J Rheumatol 1993;20:1756-9. [Abstract](#)

[92]. Landro NI, Stiles TC, Sletvold H. Memory functioning in patients with primary fibromyalgia and major depression and healthy controls. J Psychosom Res 1997;42:297-306. [Abstract](#)

[93]. Sletvold H, Stiles TC, Landro NI. Information processing in primary fibromyalgia, major depression and healthy controls. J Rheumatol 1995;22:137-42. [Abstract](#)

[94]. Glass JM, Park DC. Cognitive dysfunction in fibromyalgia. Curr Rheumatol Rep 2001;3:123-7. [Abstract](#)

[95]. Grace GM, Nielson WR, Hopkins M, Berg MA. Concentration and memory deficits in patients with fibromyalgia syndrome. J Clin Exp Neuropsychol 1999;21:477-87. [Abstract](#)

[96]. Chapman CR, Gavrin J. Suffering: the contributions of persistent pain. Lancet 1999;353:2233-7.

[Abstract](#)

[97]. Menon PS, Gupta P, Karmarkar MG. High and low dose clonidine tests for the diagnosis of growth hormone deficiency. Indian Pediatr 1994;31:145-51. [Abstract](#)

[98]. Sivri A, Cindas A, Dincer F, Sivri B. Bowel dysfunction and irritable bowel syndrome in fibromyalgia patients. Clin Rheumatol 1996;15:283-6. [Abstract](#)

[99]. Sperber AD, Atzmon Y, Neumann L, Weisberg I, Shalit Y, Abu-Shakrah M, et al. Fibromyalgia in the irritable bowel syndrome: studies of prevalence and clinical implications. Am J Gastroenterol 1999;94:3541-6. [Abstract](#)

[100]. Farthing MJ. Irritable bowel syndrome: new pharmaceutical approaches to treatment. Baillieres Best Pract Res Clin Gastroenterol 1999;13:461-71.

[101]. Bennett RM, Clark SR, Campbell SM, Ingram SB, Burckhardt CS, Nelson DL, et al. Symptoms of Raynaud's syndrome in patients with fibromyalgia. A study utilizing the Nielsen test, digital photoplethysmography, and measurements of platelet alpha 2-adrenergic receptors. Arthritis Rheum 1991;34:264-9. [Abstract](#)

[102]. Buchwald D, Garrity D. Comparison of patients with chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities. Arch Intern Med 1994;154:2049-53. [Abstract](#)

[103]. Jason LA, Taylor RR, Kennedy CL. Chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities in a community-based sample of persons with chronic fatigue syndrome-like symptoms. Psychosom Med 2000;62:655-63. [Abstract](#)

[104]. Bernard AL, Prince A, Edsall P. Quality of life issues for fibromyalgia patients. Arthritis Care Res 2000;13:42-50. [Abstract](#)

[105]. Burckhardt CS, Clark SR, Bennett RM. Fibromyalgia and quality of life: A comparative analysis. J Rheumatol 1993;20:475-9. [Abstract](#)

[106]. Jacobs JW, Rasker JJ, van der HA, Boersma JW, de Blecourt AC, Griep EN, et al. Lack of correlation between the mean tender point score and self-reported pain in fibromyalgia. Arthritis Care Res 1996;9:105-11. [Abstract](#)

[107]. Bennett RM, Burckhardt CS, Clark SR, O'Reilly CA, Wiens AN, Campbell SM. Group treatment of fibromyalgia: a 6 month outpatient program. J Rheumatol 1996;23:521-8. [Abstract](#)

[108]. King S, Wessel J, Bhambhani Y, Maikala R, Sholter D, Maksymowych W. Validity and reliability of the 6 minute walk in persons with fibromyalgia. J Rheumatol 1999;26:2233-7. [Abstract](#)

[109]. Burckhardt CS, Clark SR, Bennett RM. The fibromyalgia impact questionnaire: development and validation. J Rheumatol 1991;18:728-33. [Abstract](#)

[110]. Goldenberg DL, Mossey CJ, Schmid CH. A model to assess severity and impact of fibromyalgia. J

Rheumatol 1995;22:2313-8. [Abstract](#)

[111]. Worrel LM, Krahn LE, Sletten CD, Pond GR. Treating fibromyalgia with a brief interdisciplinary program: initial outcomes and predictors of response. Mayo Clin Proc 2001;76:384-90. [Abstract](#)

[112]. Dunkl PR, Taylor AG, McConnell GG, Alfano AP, Conaway MR. Responsiveness of fibromyalgia clinical trial outcome measures. J Rheumatol 2000;27:2683-91. [Abstract](#)