To quote the University of California San Diego psychiatrist Stephen Stahl, “fibromyalgia is emerging as a diagnosable and potentially treatable syndrome” (Stahl 2001). While acknowledging that psychological influences are powerful modulators of pain related suffering and dysfunction, there is now a growing understanding that fibromyalgia cannot be “written off” as a somatoform pain disorder. Fibromyalgia is a multi-symptomatic syndrome defined by the core feature of chronic widespread pain (Smythe et al. 1977; Bennett 1981; Yunus et al. 1981; Goldenberg 1987; Wolfe et al. 1990). Many of these patients also have severe fatigue and associated symptoms related to visceral hyperalgesia, such as irritable bowel and bladder. This population accounts for about 20% of patients consulting rheumatologists in North America (Marder et al. 1991; White et al. 1995). Contemporary research implicates abnormalities of sensory processing and neuroendocrine dysfunction as being related to the symptomatology of these patients. This refresher course will: 1) trace the historical evolution of the fibromyalgia concept, 2) present the evidence for fibromyalgia being, in part, a manifestation of central sensitization, 3) provide an overview of the clinical features of fibromyalgia, 4) discuss the rational management of fibromyalgia patients.

Historical Evolution of the Fibromyalgia Concept

The first use of the word “fibrositis” is attributed to Sir William Gowers in a lecture on the subject of lumbago that was published in the British Medical Journal in 1904 (Gowers 1904). To quote from this lecture: “I think we need a designation for inflammation of the fibrous tissue ---we may conveniently follow the analogy of 'cellulitis' and term it 'fibrositis'”. Ralph Stockman, a Glasgow pathologist, described foci of inflammation in the interstitial of muscle bundles, the so-called “magic nodules”, that very same year (Stockman 1904). These histological findings were never verified and the diagnosis of “fibrositis” became equated with the concept of “psychogenic rheumatism” for much of the middle third of the 20th century. The description of an objective sleep abnormality in these patients by Moldofsky in 1976 (Moldofsky et al. 1975) and the rediscovery of defined tender areas by Smythe in 1977 (Smythe and Moldofsky 1977) led to a re-evaluation of the “fibrositis concept” in the 1980s. It became evident that these patients made up a substantial proportion of patients seeing rheumatologists. This led the American College of Rheumatology (ACR) to commission a multi-center study to provide diagnostic guidelines. The results of this study were published in 1990 (Wolfe, Smythe, Yunus, Bennett, Bombardier, Goldenberg, Tugwell, Campbell, Abeles, Clark, Fam, Farber, Fiechtner, Franklin, Gatter, Hamaty, Lessard, Lichtbroun, Masi, McCain, Reynolds, Romano, Russell, and Sheon 1990) and are generally referred to as the 1990 ACR guidelines. They adopted the name of fibromyalgia as the old
name of “fibrositis” was considered to represent a pathological notion that was now discredited. The contemporary etiological paradigm for fibromyalgia is that of a complex hyperalgesic pain syndrome, in which abnormalities of central sensory processing interact with peripheral pain generators and neuro-endocrine pathways to generate a wide spectrum of patient symptomatology and distress (Pillemer et al. 1997). It is now thought that both peripheral and central factors contribute in varying degrees to the expression of symptoms labeled as fibromyalgia.

For most of the 20th century fibrositis/fibromyalgia was considered to be a muscle disease. It is now appreciated that there are no distinctive muscle changes that can define fibromyalgia in terms of a specific tissue pathology (Simms 1996). However, this does not mean that non-pathological muscle pain problems, such as exertional muscle microtrauma, are of no relevance to the pathogenesis. Indeed, it is hypothesized that any tissue generated cause of pain (a peripheral pain generator) can accentuate and/or perpetuate central pain mechanisms. Focal loci of muscle pain are referred to as myofascial trigger points. These are hyperalgesic zones in muscle that often feel indurated on palpation. Prolonged pressure over these areas may cause a pattern of pain that is referred distally - hence the name of "trigger points" (Travell et al. 1992). Kellgren pioneered studies using hypertonic saline to evaluate the correlates of painful foci within muscle (Kellgren 1938). Graven-Nielsen has demonstrated that hypertonic saline induced muscle pain demonstrates temporal and spatial summation that are influenced by central facilitatory and inhibitory mechanisms (Graven-Nielsen et al. 1997) (Basbaum et al. 1984). These experiments highlight the importance of focal muscle pain in inducing a state of central sensitization and are postulated to be relevant to abnormal sensory processing in fibromyalgia patients (Henriksson 1994b) (Bennett 1996b).

Muscle microtrauma, a normal occurrence in healthy individuals, has been postulated to be one cause of peripheral nociceptive input in fibromyalgia patients (Bennett 1993). It is difficult to diagnose this phenomenon as the act of biopsying a muscle cause trauma. However NMR spectroscopy can evaluate living un-traumatized muscle. Three NMR studies have reported an increase in phosphodiester peaks in fibromyalgia compared to controls (Jubrias et al. 1994) (Park et al. 2000) (Sprott et al. 2000). Phosphodiester peaks occur in musculo-dystrophies (Younkin et al. 1987) and also with increasing age (Satrustegui et al. 1988). They are thought to result from the lipid peroxidation of sarcolemmal membrane proteins. This process occurs in calcium activated muscle damage (muscle microtrauma) (Armstrong et al. 1991). There are several lines of evidence to suggest that the pain experience of fibromyalgia patients is in part the result of disordered sensory processing at a central level.

**Diagnosis and Evaluation**

The diagnosis of fibromyalgia is usually based on 1990 recommendations of the American college of rheumatology classification criteria (Wolfe, Smythe, Yunus, Bennett, Bombardier, Goldenberg, Tugwell, Campbell, Abeles, Clark, Fam, Farber, Fiechtner, Franklin, Gatter, Hamaty, Lessard, Lichtbroun, Masi, McCain, Reynolds, Romano, Russell, and Sheon 1990).

Firstly, these patients have widespread body pain - defined as pain in at least 3 quadrants of the body that has persisted for at least 3 months. Patients describe their pain in different ways but commonly they
use adjectives such as aching, stabbing, knife-like, or lancinating. There is usually an associated feeling of stiffness in muscles and an increase in pain after exertion. In reality, these symptoms are seldom found in any other medical condition. Exceptions being polymyalgia rheumatica in elderly patients, severe hypothyroidism, and widespread bone pain due to neoplasia or osteomalacia. Other pain states such as widespread arthritis have symptoms predominantly referred to joints. Most primary muscle diseases, such as the muscular dystrophies and polymyositis, have weakness, not pain, as the predominant symptom. Having the patient fill out a pain diagram is a simple and effective way of screening for a history of widespread pain.

The second step in making a diagnosis of FM is to systematically palpate the muscles for “tender points.” This is done with a pressure of about 4 kg - enough to blanch a thumbnail. In general, tender points are located towards one end of a muscle where it is narrowing to join a tendon or bone. For instance, common tender point locations are: the insertion of the extensor muscles of the hand at the (1) insertion of nuchal muscles into occiput; (2) upper border of trapezius-mid-portion; (3) muscle attachments to upper medial border of scapula; (4) anterior aspects of the C5, C7 intertransverse spaces; (5) 2nd rib space - about 3 cm lateral to the sternal border; (6) muscle attachments to lateral epicondyle; (7) upper outer quadrant of gluteal muscles; (8) muscle attachments just posterior to greater trochanter; (9) medial fat pad of knee proximal to joint line.

A total of eleven or more tender points in conjunction with a history of widespread pain is characteristic of the fibromyalgia syndrome.
lateral epicondyle of the elbow, the insertion of the nuchal muscles into the occiput, the origin of the gluteus medius muscle from the pelvic brim and its insertion into the greater trochanter... The American College of Rheumatology (ACR) fibromyalgia criteria recommend palpation of 9-paired tender-point areas (i.e., 18 points in all) see Figure 1.

A diagnosis of fibromyalgia demands the finding of 11 or more tender points. However, it is increasingly evident that many patients with widespread pain have less than the recommended 11 out of 18 tender points. If a patient has widespread pain and tenderness in many other areas, they are unlikely to have a different neuro-physiological basis for their pain than patients with strictly ACR defined fibromyalgia. Thus it is important to look at other sites that commonly harbor myofascial trigger points. The reason for this more extensive evaluation is twofold: 1) to establish a probable diagnosis fibromyalgia in patients with less than 11 tender points, and 2) find relevant myofascial pain generators that would benefit from trigger point therapy (Borg-Stein et al. 1996).

Fibromyalgia 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, fibromyalgia patients may have concomitant conditions that are relevant to overall management in terms of peripheral pain generators that can accentuate and maintain central sensitization. In many cases these concomitant problems investigational approach to diagnosis. A fibromyalgia-focused history and examination is an important requisite in obtaining data for an effective management program. The history and examination will probably suggest certain problems that need further evaluation in terms of specialist referral or investigations.

**Central Pain Mechanisms in Fibromyalgia**

Patients with severe fibromyalgia have clinical features commonly observed in states of central sensitization; namely: a reduced pain threshold (alldynia), an increased response to painful stimuli (hyperalgesia) and an increase in the duration of pain after nociceptor stimulation (persistent pain). In 1965 Mendell and Wall (Mendell et al. 1965) noted that when stimulation of a peripheral nerve at sufficient intensity to activate C-fibers was performed repetitiously there was a progressive build up of the amplitude of the electrical response recorded in the corresponding dorsal horn neurons of the spinal cord. Interestingly this phenomenon was more marked when muscle nerves were stimulated than when skin nerves were stimulated; this is in keeping with the notion that muscle pain may be a potent; but non-specific; peripheral generator. They termed this phenomenon "wind-up. It is now appreciated that the phenomenon of wind-up is crucial to understanding central sensitization. Furthermore the biochemical basis for this neurophysiological phenomenon is now being unraveled at a molecular level.
in terms of the activation of NMDA receptors. There is good evidence that central sensitization is relevant to the pain experience in fibromyalgia patients (Bennett 1999).

**Deficient pain modulation in response to repeated thermal stimuli**

An up-regulation of pain threshold can be demonstrated in normal individuals by subjecting them to repeated non-noxious skin stimulation. This is the basis for the use of trans-cutaneous nerve stimulators (TENS) in the management of chronic pain states. The physiological basis for this effect is the inhibition of dorsal horn neuron excitability by persistent stimulation of type A myelinated axons (Wall et al. 1960). This effect, known as diffuse noxious inhibitory control (DNIC) is defective in fibromyalgia subjects (Lautenbacher et al. 1997), thus supporting the notion that they have a defective descending inhibitory pain system (Mense 2000).

**Elevated levels of substance P in the CSF**

Substance P is an important nociceptive neurotransmitter. There are 3 definitive studies that have shown a 3 fold increase of substance P in the CSF of fibromyalgia patients compared to controls (Vaeroy et al. 1988) (Liu et al. 2000) (Russell et al. 1994). Animal models of hyperalgesia and hypoalgesia have implicated substance P as a major etiological factor in central sensitization and have highlighted the relevance of substance P in human pain states (Abbadie et al. 1996).

**Elevated levels of nerve growth factor**

Nerve growth factor (NGF) is required for the normal development of sympathetic and sensory neurons. Giovengo has reported a 4 fold elevation of NGF in the CSF of patients with primary fibromyalgia compared with healthy controls and other pain patients (Giovengo et al. 1999) (Fig 2).

The intravenous administration of recombinant nerve growth factor in humans results in a muscle pain syndrome resembling fibromyalgia which lasts for up to a week after the initial injection. The mechanism whereby NGF causes hyperalgesia is hypothesized to be related to its stimulation of protein synthesis in the CNS (Bennett 2001a).

**Figure 2.** Several neurotransmitter and modulators such as substance P, dynorphin and nerve growth factor (NGF) have been found to be elevated in the CSF of fibromyalgia patients. The graph here shows a study on CSF levels of NGF. Interestingly patients with secondary fibromyalgia were found to have normal values (not shown in this figure).
Qualitative differences in pain

An objective measure of applied force to a tender point can be obtained by dolorimetry (Campbell et al. 1983). A study using an electronic dolorimeter recorded the subject's assessment of pain intensity on a 0 to 10-cm visual analogue scale (VAS) at varying levels of applied force (Bendtsen et al. 1997). Distinctly different response curves were obtained for controls and fibromyalgia patients. Similar abnormalities of pain processing in fibromyalgia patients have also been reported for heat and cold (Kosek et al. 1996).

Abnormalities on SPECT imaging

Pain induced changes in brain blood flow or metabolism can now be visualized by several different imaging techniques (Bradley et al. 2000). There are reports of reduced thalamic blood flow in fibromyalgia subjects (Mountz et al. 1995) (Kwiatek et al. 2000). It is interesting that chronic pain states have been associated with, whereas acute pain increases thalamic blood flow. The reason for this difference is postulated to be a disinhibition of the medial thalamus which results in activation of a limbic network (Craig 1998).

Hyper-responsive somatosensory induced potentials

Somatosensory induced potentials refer to the electrophysiological activity in the brain that can be measured by skull electrodes in response to peripheral sensory stimulation. Gibson et al reported an increased late nociceptive (CO2-laser stimulation of skin) evoked somatosensory response in 10 FM patients compared to 10 matched controls (Gibson et al. 1994). Lorenz et al (Lorenz et al. 1996) have reported increased amplitude of the N170 and P390 brain somatosensory potentials in fibromyalgia compared to controls evoked by laser stimulation of the skin. Furthermore they observed a response in both hemispheres, whereas in controls the response was localized to one side of the brain. These 2 studies provide objective evidence that fibromyalgia patients have an altered processing of nociceptive stimuli in comparison to pain free controls.

Secondary hyperalgesia on electrocutaneous stimulation

Primary hyperalgesia is the normal perception of pain from nociceptor stimulation in an injured tissue. Secondary hyperalgesia refers to pain elicited from uninjured tissues (Magerl et al. 1998). Arroyo and Cohen, while attempting to treat fibromyalgia patients with electrical nerve stimulation reported sensory phenomena characteristic of secondary hyperalgesia (Arroyo et al. 1993).

Beneficial response to an NMDA receptor antagonist

The excitatory amino acid glutamine reacting with NMDA (N-Methyl-D-Aspartic acid) receptors plays a central role in the generation of non-nociceptive pain. Two studies have reported that intravenous ketamine (an NMDA receptor antagonist) attenuates pain and increases pain threshold, as well as improving muscle endurance in FM patients (Sorensen et al. 1995). The experimental induction of pain
summation and referral by intramuscular hypertonic saline in fibromyalgia is attenuated by the use of ketamine (Graven-Nielsen et al. 2000).

Experimentally induced central hyperexcitability
Temporal summation of nociceptive impulses at the level of the spinal cord normally occurs when unmyelinated C fiber input exceeds a rate of one impulse every 2-3 seconds. There is good experimental evidence that this neurophysiological process is a critical event in the development of central sensitization (Koltzenburg et al. 1994). An amplification of temporal summation has been demonstrated after repetitive thermal stimulation of the palmar skin in fibromyalgia patients (Staud et al. 2001) and after intramuscular electrical stimulation of muscle (Sorensen et al. 1998).

Clinical Features

Pain
The core symptom of the FM syndrome is chronic widespread pain (Wolfe, Smythe, Yunus, Bennett, Bombardier, Goldenberg, Tugwell, Campbell, Abeles, Clark, Fam, Farber, Fiechtner, Franklin, Gatter, Hamaty, Lessard, Lichtbroun, Masi, McCain, Reynolds, Romano, Russell, and Sheon 1990). The pain is usually perceived as arising from muscle, however many fibromyalgia patients also report joint pain (Reilly et al. 1992). Stiffness, worse in the early morning, is a prominent symptom of most FM patients; along with the perception of articular pain this may reinforce the impression of an arthritic condition.

Fatigue
Easy fatigability from physical exertion, mental exertion and psychological stressors are typical of fibromyalgia. The etiology of fatigue in fibromyalgia is multifaceted and is thought to include non-restorative sleep, deconditioning, dysautonomia, depression, poor coping mechanisms and secondary endocrine dysfunction involving the hypothalamic pituitary adrenal axis and growth hormone deficiency (Crofford et al. 1994; Bennett et al. 1997; Pillemer, Bradley, Crofford, Moldofsky, and Chrousos 1997).

Disordered sleep
Fibromyalgia patients usually report disturbed sleep (Moldofsky, Scarisbrick, England, and Smythe 1975). Even if they sleep continuously for 8 to 10 hours they awake feeling tired. This is referred to as non-restorative sleep. Most relate to being light sleepers, being easily aroused by low-level noises or intrusive thoughts. Many exhibit an alpha-delta EEG pattern, that would explain their never getting into the restorative stages 3 and 4 of non-REM sleep (Moldofsky 1989).

Cognitive dysfunction
Cognitive dysfunction is a major problem, according to self-reports, for many fibromyalgia patients (Park et al. 2001). Patients commonly describe difficulties with short-term memory, concentration, logical
analysis and motivation. Problems with cognitive function are being increasingly recognized in fibromyalgia patients and are the subject of increasing research efforts (Grace et al. 1999; Glass et al. 2001). Currently, defects have been described in terms of working memory, episodic memory and verbal fluency. These decreases in cognitive performance and been estimated to be equivalent to 20 years of aging (Glass and Park 2001).

**Associated disorders**
It is not unusual for fibromyalgia patients to have an array of somatic complaints other than musculoskeletal pain (Bennett 1989; Clauw 1995). It is now thought that these symptoms are in part a result of the abnormal sensory processing and the neuroendocrine effects of chronic stress.

**Psychological distress**
As in many chronic conditions there is an increased prevalence of psychological diagnoses in fibromyalgia patients. Depression is more common in fibromyalgia patients than in healthy controls (Yunus 1994; Burckhardt et al. 1994b). Importantly fibromyalgia is not common in patients with major depression; even those depressed individuals who complained of pain did not have multiple tender points (Fassbender et al. 1997). Although psychiatric disorders are more prevalent in fibromyalgia patients than fibromyalgia non-patients, they do not seem to be intrinsically related to the pathophysiology of the fibromyalgia syndrome, but rather appear to be a result of symptom severity (Aaron et al. 1996).

**Initiation and maintenance of fibromyalgia**
Fibromyalgia seldom emerges out of the blue. Most patients relate an acute injury, repetitive work related pain, athletic injuries or another pain state. It is not uncommon for a regional pain syndrome to evolve into fibromyalgia (Forseth et al. 1999). Others attribute stress, infections and toxins to its onset. Fibromyalgia is commonly found as an accompaniment of rheumatoid arthritis, low back pain, SLE, Sjogren's and inflammatory bowel disease and osteoarthritis (Morand et al. 1994; Urrows et al. 1994; Lapossy et al. 1995; Bennett 1997; Sperber et al. 1999). There is a reported 22% prevalence of fibromyalgia, one year after whiplash injuries (Buskila et al. 1997). A striking familial prevalence of fibromyalgia has been reported by Buskila (Buskila et al. 1996). This suggests that subjects destined to develop fibromyalgia are either genetically predisposed (nature), or have past life events or experiences that favor its later development (nurture).

**Prognosis and Impact**
Fibromyalgia symptomatology often persists over many years (Bengtsson et al. 1994). Chronic musculoskeletal pain often severely impacts a patient's quality of life (Burckhardt et al. 1993). An analysis of 1604 fibromyalgia patients followed in academic centers reported that pain, fatigue, sleep disturbance, functional status, anxiety, depression, and health status were essentially unchanged after 7 years of follow up (Wolfe et al. 1997). The consequences of pain and fatigability influence motor
performance; every-day activities take longer in fibromyalgia patients, they need more time to get started in the morning and often require extra rest periods during the day (Henriksson 1994a). They have difficulty with repetitive sustained motor tasks, unless frequent time-outs are taken. Tasks may be well tolerated for short periods of time, but when carried out for prolonged periods become aggravating factors (Waylonis et al. 1994). Prolonged muscular activity, especially under stress or in uncomfortable climatic conditions aggravates the symptoms of fibromyalgia (Waylonis, Ronan, and Gordon 1994). The adaptations that fibromyalgia patients have to make in order to minimize their pain experience, often has a negative impact on both vocational and vocational activities.

Management of Fibromyalgia
A structured multi-disciplinary approach to managing fibromyalgia patients requires an appreciation of the parts that make up the whole. One cannot successfully manage fibromyalgia patients if one treats the diagnosis of fibromyalgia as a unified entity. There are 12 separate management issues that usually require attention in most fibromyalgia patients seeking medical help:

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

Education
There is a wealth of evidence that higher educational attainments are associated with a better prognosis in many chronic diseases (Ramos-Remus et al. 2000). There are several studies that support the value of education in fibromyalgia patients (Wolfe, Smythe, Yunus, Bennett, Bombardier, Goldenberg, Tugwell, Campbell, Abeles, Clark, Fam, Farber, Fiechtner, Franklin, Gatter, Hamaty, Lessard, Lichtbroun, Masi, McCain, Reynolds, Romano, Russell, and Sheon 1990;Rikli et al. 1991;Jensen et al. 1991;Burckhardt et al. 1994a;Vlaeyen et al. 1996;Gowans et al. 1999;Mannerkorpi et al. 2000). Indeed, education has several components common to cognitive behavioral techniques, such as goal setting and reassessment of priorities.

Pain
It is increasingly evident that pain perception in fibromyalgia is in part due to changes in the central nervous system that result in amplification of nociceptive impulses (Friis et al. 1997;Bennett 1999;Staud, Vierck, Cannon, Mauderli, and Price 2001). 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 psychological 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 now possible to formulate a rational approach to managing FM related pain. The 4 major sites in the pain system, which are potentially amenable to modification, are shown figure 3.

1. The Periphery

There is no specific tissue pathology, at least in peripheral tissues that can be said to be characteristic of fibromyalgia (Simms 1996). 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.

Although some peripheral pain generators, notably arthritic disorders, may be helped by 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 commonest pain generator in most fibromyalgia patients is myofascial trigger points it is imperative that these be identified and effectively managed in terms of pacing, stretching, improved physical conditioning, self help techniques such as acupressure and spray and stretch and physician intervention in terms of procaine or botulinum toxin injections. The search for these pain generators is a critically important and often neglected aspect of treating fibromyalgia.

2. 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 (Dickenson 1995; Mannion et al. 2000). 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 maybe relevant to abnormal sensory processing in fibromyalgia, as the CSF levels of both SP and NGF have been reported to be elevated in fibromyalgia (Vaeroy, Helle, Forre, Kass, and Terenius 1988) (Russell, Orr, Littman, Vipraio, Alboukrek, Michalek, Lopez, and MacKillip 1994; Giovengo et al. 1999). 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 pharmacological (Bennett 2001b).
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 mid-brain and terminates at the level of dorsal horn neurons; thus influencing spinal cord sensitization (Bishop 1980; Willis, Jr. 1988; Willis et al. 1997). 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 acting to modulate the activity of the dorsal horn. These include opioids, tramadol, GABA agonists, antidepressants, alpha 2 adrenergic agonists and 5-HT3 antagonists.

Opioids are effective in most acute and chronic pain states. The usual cited concerns regarding addiction are now known to be unfounded – only occurring in about 0.5 percent of opioid treated chronic pain patients (Portenoy 1996; Pappagallo et al. 1997; Bannwarth 1999; Passik et al. 2000). The main problems related to long-term use of opioids are the effects on cognition, reduced motivation to pursue non-pharmacological treatment modalities, aggravation of depression and negative stigmatization by the medical profession and society in general (Savage 1996). All patients taking opioids can be expected to develop dependency; this however is not the same as addiction, but implies that this class of medications cannot be abruptly stopped without the patient experiencing withdrawal symptoms. Nearly all patients develop constipation and this must be dealt with proactively. Other common problems include pruritis, drowsiness and nausea. Although opioids are fairly commonly used in the treatment of fibromyalgia, there have been no controlled clinical trials.

Tramadol (Ultram) is proving to be a useful drug to treat pain in chronic conditions, including fibromyalgia (Roth 1998; Schnitzer et al. 2000). Tramadol has a dual mechanism of action being a week opioid agonists as well as inhibiting the reuptake of serotonin and noradrenaline at the level of the dorsal horn (Lewis et al. 1997). A double-blinded study demonstrated its efficacy and tolerability in the management of fibromyalgia pain at an average dose of 200 mg / day (Russell et al. 1997). A combination of tramadol and acetaminophen (Ultracet) has also been reported to benefit fibromyalgia pain and other symptoms (Bennett R.M. et al. 2001).

Alpha 2 adrenergic agonists such as tizanidine (Zanaflex) have been used successfully in some chronic pain disorders (Fogelholm et al. 1992). The experimental basis for this antinociceptive action is the observation that intrathecally administered alpha 2 adrenergic agonists, but not beta-adrenergic receptor agonists, produce a powerful analgesia in both experimental animals and man (Nabeshima et al. 1987; Coward 1994). There have been no trials of these agents in fibromyalgia. There is anecdotal evidence for tizanidine being useful in FM related pain, as not only is it antinociceptive but it is also an antispasmodic (Smith et al. 2000) which cause drowsiness — a benefit in fibromyalgia patients if it is given in the evening.

5-HT3 antagonists have been the subject of several encouraging short term trials in fibromyalgia patients (Haus et al. 2000; Farber et al. 2000). 5-HT3 receptors are found only in neuronal tissues, both central and peripheral
The complex biochemistry of 5-HT3 receptors suggests that antagonists would have nociceptive and antinociceptive actions under different circumstances. When activated the 5-HT3 receptor causes a rapid membrane depolarization with resultant rise in cytosolic Ca++ which in turn modulates the release of neuro active molecules such as substance P., serotonin, GABA, acetylcholine, cholecystokinin and dopamine (Wolf 2000). Longer term studies in fibromyalgia patients are needed before the efficacy of this class of drugs can be fully evaluated.

Drugs that modulate the ascending pain system are less commonly used. However there is experimental evidence that blocking NMDA receptors with ketamine ameliorates pain in fibromyalgia subjects (Sorensen, Bengtsson, Backman, Henriksson, and Bengtsson 1995; Graven-Nielsen et al. 2000). Dextromethorphan is a weak NMDA receptor antagonist that has been successfully used in neuropathic pain (McQuay et al. 1994) and more recently as an adjunct to tramadol and treatment of fibromyalgia (Clark S.R. et al. 2000). Logically inhibition of substance P release or blocking its interaction with the NK 1 receptor should be beneficial. However, clinical trials of a first generation substance P antagonist were disappointing in chronic pain states (Hill 2000). To date NGF antagonists have not been used in human clinical trials.

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 (Hill 2000). To date NGF antagonists have not been used in human clinical trials. There is good experimental evidence that blocking NMDA receptors ameliorates pain in fibromyalgia subjects. Most of this work has been performed using ketamine - a dissociative anesthetic (Sorensen, Bengtsson, Backman, Henriksson, and Bengtsson 1995; Sorensen, Graven-Nielsen, Henriksson, Bengtsson, and Arendt-Nielsen 1998; Graven-Nielsen, Aspegren, Henriksson, Bengtsson, Sorensen, Johnson, Gerdle, and Arendt-Nielsen 2000b). Dextromethorphan is a weak NMDA receptor antagonist that has been successfully used in neuropathic pain (Price et al. 1994; McQuay, Carroll, Jadad, Glynn, Jack, Moore, and Wiffhe 1994; Nelson et al. 1997) and more recently as an adjunct to tramadol and treatment of fibromyalgia (Clark S.R. and Bennett 2000).

The Brain

Fibromyalgia 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 (Price et al. 1987; Harkins et al. 1989; Rainville et al. 1997; Turk 1999). 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 pharmacological 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 (Sharpe et al. 2001).

**Fatigue**

The common treatable cause of chronic fatigue in fibromyalgia patients are: (1) inappropriate dosing of medications (TCAs, drugs with antihistamine actions, benzodiazepines etc.), (2) depression, (3) aerobic deconditioning, (3) a primary sleep disorder (e.g. sleep apnea), (4) non-restorative sleep (see above), (5) neurally mediated hypotension and (6) growth hormone deficiency (Bennett et al. 1992; Bennett, Cook, Clark, Burckhardt, and Campbell 1997; Bennett et al. 1998). Many of these causative factors are most amenable to non-pharmacological interventions. However, sleep problems, depression and other psychological stressors, some features of dysautonomia and endocrine dysfunction are appropriately treated with drugs. Recent studies using the 5-HT3 receptor antagonist tropisetron reported benefits both in fibromyalgia related fatigue and in chronic fatigue syndrome (Spath et al. 2000). There are anecdotal reports that modafinal (Provigil), a non-amphetamine drug used in narcolepsy and sleep deprivation situations, is of some benefit in improving non-specific fatigue (Lyons et al. 1991).

**Sleep**

Most fibromyalgia patients relate to being light sleepers, being easily aroused by low-level noises or intrusive thoughts. Many exhibit an alpha-delta EEG pattern, that would explain their never getting into the restorative stages 3 and 4 of non-REM sleep (Moldofsky 1989; Drewes et al. 1995). Important non-pharmacological 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.) has been the mainstay of sleep pharmacotherapy in FM patients (Goldenberg 1989a; Carette et al. 1994). Many fibromyalgia patients cannot tolerate TCAs due to unacceptable levels of daytime drowsiness or weight gain. In these patients’ benzodiazepine-like medications such as aprazolam (Russell et al. 1991), zolpidem (Moldofsky et al. 1996) and zopiclone (Drewes et al. 1991) have been shown to the beneficial in a few trials. A subset of fibromyalgia patients suffer from a primary sleep disorder, which requires specialized management. About 25% of male and 15% of female fibromyalgia patients have sleep apnea which usually require treatment with positive airway pressure (CPAP) or surgery. By far the commonest sleep disorder in fibromyalgia patients is restless leg syndrome/periodic limb movement disorder. Treatment is usually with L-DOPA/carbidopa (Sinemet 10/100 mg at suppertime) or clonazepam (Klonipin 0.5 or 1.0 mg at bedtime) (Montplaisir et al. 1992). More recently other dopamine agonists such as pergolide, tolizepole and pramixepole have been proven to be effective (Montplaisir et al. 1999).

**Psychological Distress**

Having a chronic painful disease, for which there is currently no generally accepted cure, often produces a cascade of emotional reactions that can be likened to an existential crisis (Chapman et al. 1999). Approximately 30 percent of fibromyalgia patients have significant current depression and about 60% have a lifetime prevalence of depressive illness (Goldenberg 1989b; Okifuji et al. 2000). It is generally assumed, that treating
depression fibromyalgia patients is no different than treating primary depressive illness. There are no trial that have specifically addressed the issue of treating depression in FM patients; however one recent article addressed this issue in a useful review (Gruber et al. 1996). Although antidepressant medications are commonly used in the treatment of pain and sleep in fibromyalgia patients, the doses used are usually suboptimal for treating depressive illness. Further FM patients may be taking many other medications with the potential for adverse interactions and are more sensitive to medication side-effects. 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 poor coping strategies often tend to catastrophize adverse life events -- which they perceive as being helpless to influence. Psychological intervention in terms of improving the internal locus of control and more effective problem solving are important in such patients. Techniques of cognitive-behavioral therapy seem particularly well suited to effect these changes and may be enhanced when done as a part of group therapy (Nielson et al. 1992; Goldenberg et al. 1994).

**Endocrine Dysfunction**
There is no good evidence that fibromyalgia is primarily due to an endocrine disorder. 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 fibromyalgia patients (Crofford, Pillemer, Kalogeras, Cash, Michelson, Kling, Sternberg, Gold, Chrousos, and Wilder 1994; Pillemer, Bradley, Crofford, Moldofsky, and Chrousos 1997). The general impression is that fibromyalgia patients have a somewhat reduced HPA responsiveness. However replacement therapy with Prednisone 15 mg/day was not shown to be therapeutically useful in fibromyalgia (Smythe 2000). About one third of fibromyalgia patients are growth hormone deficient (Bennett, Clark, Campbell, and Burckhardt 1992; Bennett, Cook, Clark, Burckhardt, and Campbell 1997) and replacement therapy has been reported to benefit such patients (Bennett, Clark, and Walczyk 1998).

**Deconditioning**
The notion that “exercise is good for fibromyalgia patients” is an accepted contemporary truth (Clark et al. 2001) that is supported by many studies. The benefits of exercise are based on reasonable scientific evidence, but exercise may also be deleterious (Mengshoel et al. 1995). Whether it is good or bad for fibromyalgia 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 comitant muscle disease. There are some similarities between fibromyalgia symptomatology and the overtraining syndrome. Over-training results in a syndrome of chronic fatigue, reduced performance, depression, impaired hormonal stress responses, increased susceptibility to muscle damage and infections (Urhausen et al. 1998). A carefully planned individual exercise program is always needed to optimize the benefits and minimize increased pain and fatigue (Clark 1994).
**Dysautonomia**

Abnormalities of autonomic function appear to be associated with both fibromyalgia and chronic fatigue syndrome (Martinez-Lavin et al. 1997; Martinez-Lavin et al. 2000; Raj et al. 2000). The most common presentation of dysautonomia in FM patients is the finding of neurally mediated hypotension in about one-third of patients (Bou-Holaigah et al. 1997; Wilke et al. 1998). 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 stranding and exercise (Klein et al. 1994; Crofford, Pillemer, Kalogerias, Cash, Michelson, Kling, Sternberg, Gold, Chrousos, and Wilder 1994; Karas et al. 2000a). Dysautonomia is often associated with severe fatigue (Karas et al. 2000b). Treatment involves: education as to the triggering factors and their avoidance, increasing plasma volume (increased salt intake, prescription of florninef), avoidance of drugs that aggravate hypotension (e.g. TCA's, anti-hypertensives), preventing the ventricle-baroreceptor-reflex (α-adrenergic antagonists or disopyramide) and minimizing the efferent limb of the baroreceptor reflex (α-adrenergic agonists or anti-cholinergic agents). See chapter 13 for an in depth coverage of this issue.

**Deconditioning**

Most fibromyalgia patient are aerobically unfit, have sub-optimal strength and poor flexibility. The notion that "exercise is good for fibromyalgia patients" is an accepted contemporary truth. There is evidence that acute exercise is associated with reduced pain perception (Chase et al. 1983; Koltyn et al. 1996) and a lowered pain threshold (Guieu et al. 1992; Koltyn, Garvin, Gardiner, and Nelson 1996). Although endorphins are secreted in response to acute exercise (Goldfarb et al. 1997), they are probably not the sole mechanism of exercise-induced analgesia (Koltyn 2000). During graded exercise, endorphins only start to increase at the anaerobic threshold (i.e. lactate production), and in moderate steady state exercise they do not increase until exercise duration exceeds one hour (Schwarz et al. 1992). The benefits of exercise are based on reasonable scientific evidence, but exercise may also be deleterious. Whether it is good or bad for fibromyalgia 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. Having fibromyalgia introduces an important factor into the equation of post-exertional pain, that is amplification of sensory processing (i.e. central sensitization). It is hypothesized that for a given intensity of exercise, fibromyalgia patients will experience more post-exertional pain than non-FM patients (Geel 1994; Watkins et al. 1995; Bennett 1996b). The take-home message is that exercise is a two edged sword in the management of fibromyalgia 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 fibromyalgia patients is given in chapter 16.

**Cognitive Dysfunction**
Cognitive dysfunction is a major problem, according to self-reports, for many fibromyalgia patients (Jennum et al. 1993; Sletvold et al. 1995; Landro et al. 1997). Patients commonly describe difficulties with short-term memory, concentration, logical analysis and motivation. Problems with cognitive function are being increasingly recognized in fibromyalgia patients and are the subject of increasing research efforts (Grace, Nielson, Hopkins, and Berg 1999; Glass and Park 2001). Currently, defects have been described in terms of working memory, episodic memory and verbal fluency. These decreases in cognitive performance and been estimated to be equivalent to 20 years of aging (Glass and Park 2001). 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 fibromyalgia 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. That, after all, has been the fulfilled expectation of all individuals until they are confronted with a chronic and currently incurable disorder. Despite its being a common disorder, the term fibromyalgia 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 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 fibromyalgia. 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 (Chapman and Gavrin 1999). 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 fibromyalgia. Those who are acquainted with this diagnosis are often more medically sophisticated and aware of the apathy and skepticism surrounding the diagnosis of fibromyalgia; 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 fibromyalgia. 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 the 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 fibromyalgia patients to understand that there is a time lag in acceptance; during this period little progress may be made. This is time when patience, perseverance, listening, education and empathy are most needed.

Associated Disorders
Recognition and treatment of problems that are commonly associated with fibromyalgia are important in the overall management scheme.
Restless leg syndrome: Treatment is simple and very effective – DOPA / Levodopa (Sinemet) in an early evening dose of 10/100 (a minority require a higher dose or use of the long acting preparations). Some patients respond to gabapentin. Recalcitrant case is often helped by low dose opioid therapy.

Irritable bowel syndrome: Treatment involves (1) elimination of foods that aggravate symptoms, (2) minimizing psychological 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).

Irritable bladder syndrome: Treatment involves (1) increasing intake of water, (2) avoiding bladder irritants such as fruit juices (especially cranberry), (3) pelvic floor exercises (e.g. Kagel exercises) and the prescription of antispasmodic medications (e.g. oxybutinin, flavoxate, hyoscamine).

Cold intolerance: Treatment involves: (1) keeping warm, (2) low-grade aerobic exercise (which improves peripheral circulation), (3) treatment of neurally mediated hypotension (see below), and (4) the prescription of vasodilators such as the calcium channel blockers (but these may aggravate the problem in-patients with hypotension).

Multiple sensitivities: Treatment involves being aware that this is a fibromyalgia-related problem and employing avoidance tactics. Medications often need to be started at half the usual doses.

Dizziness: Treatable causes related to fibromyalgia 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.

Multi-disciplinary team therapy. Most of the recommendations for management assume a one-on-one doctor patient encounter. In the era of cost-effective medicine it is often difficult to accommodate the demands of these patients. However most of these same recommendations can be incorporated into a multi-disciplinary treatment program using a team of interested health professionals (nurse practitioners, clinical psychologists, exercise physiologists, mental health care workers, and social workers) (Goldenberg 1989a; Bennett 1996a). In this way groups of 5-15 patients can be seen in designated sessions several times a month. Multi-disciplinary therapy has proved beneficial in several centers (Turk et al. 1998) (Bennett et al. 1996).

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