Fibromyalgia is a multisymptomatic syndrome defined by the core feature of chronic widespread pain (Bennett 1981, Yunus et al 1981, Goldenberg 1987). 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 (White et al 1995). Contemporary research implicates abnormalities of sensory processing and neuroendocrine dysfunction as being related to the symptomatology of these patients.

Historical perspective
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 interstitium of muscle bundles, the so-called 'myalgic 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 twentieth century. The description of an objective sleep abnormality in these patients by Moldofsky in 1976 and the rediscovery of defined tender areas by Smyth in 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 those seeing rheumatologists. This led the American College of Rheumatology (ACR) to commission a multicenter study to provide diagnostic guidelines. The results of this study were published in 1990 (Wolfe et al 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.

Diagnosis
The 1990 American College of Rheumatology's guidelines for making a diagnosis of fibromyalgia are the most widely used criteria in current use (Wolfe et al 1990). They comprise one historical
feature and one physical finding. The historical feature is widespread pain of 3 months or more. Widespread is defined as pain in an axial distribution plus pain on both left and right sides of the body, and pain above and below the waist. The physical finding is the presence of 11 or more out of 18 specified tender points. A tender point is defined in terms of its location and the patient's experience of pain on digital palpation with an approximate force of 4 kg (the amount of pressure required to blanch a thumbnail). The locations of the 18 tender points are shown in Fig. 7.1.

Epidemiology

Chronic musculoskeletal pain is common encountered in the general population. In the no of England, prevalence rates of 11.2% for chronic widespread pain and 43% for regional pain were found (Croft et al. 1993). In a Kansas study (Wc et al. 1995) the prevalence of chronic widespread musculoskeletal pain was more common in women and increased progressively from ages 18 to 71 with a 23% prevalence in the seventh decade. There appears to be a tendency for some subjects with regional pain syndromes to develop the widespread pain of fibromyalgia (Forseth et al. 1999). The overall prevalence of fibromyalgia in the Kan population was 2%, with a prevalence of 3.4% women and 0.5% men. All epidemiological studies have reported that chronic widespread pain is more prevalent than the ACR defined diagnosis of fibromyalgia, and it is conceptualized that fibromyalgia is at one end of a continuous spectrum of chronic pain (MacFarlane 1999).

Clinical features

Pain

The core symptom of the fibromyalgia (FM) syndrome is chronic widespread pain (Wolfe et al. 1990). The pain is usually perceived as arising in muscle; however, many fibromyalgia patients report joint pain (Reilly and Littlejohn 1984). Stiffness, worse in the early morning, is a prominent symptom of most FM patients; along with perception of articular pain this may reinforce the impression of an arthritic condition. Fibromyalgia pain and stiffness typically have a diurnal variation, with a nadir during the hours of about 11.00 am to 3.00 pm (Moldofsky 1994).

Fatigue

Easy fatigability from physical exertion, mental exertion, and psychological stressors are typical fibromyalgia (Yunus et al. 1981). The etiology of fatigue in fibromyalgia is multifaceted and 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 (Bennett et al 1997). Patients with the chronic fatigue syndrome (CFS) have many similarities with patients (Aaron and Buchwald 2001). About 75%
patients meeting the diagnostic criteria of CFS also meet the criteria for diagnosis of FM (Goldenberg et al 1990).

Disordered sleep

Fibromyalgia patients usually report disturbed sleep (Moldofsky et al 1975). Even if they sleep continuously for 8 to 10 h 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, which would explain their never getting into the restorative stages 3 and 4 of non-REM sleep (Moldofsky 1989). However an alpha intrusion rhythm in delta sleep is not invariable in fibromyalgia nor is it specific (Hauri and Hawkins 1973). The experimental induction of alpha–delta sleep in healthy individuals has been reported to induce musculoskeletal aching and/or stiffness as well as increased muscle tenderness (Moldofsky and Scarisbrick 1976). A poor night’s sleep is often followed by a worsening of fibromyalgia symptoms the next day (Affleck et al 1996).

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 (Glass and Park 2001). Currently, defects have been described in terms of working memory, episodic memory, and verbal fluency. These decreases in cognitive performance has 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, such as irritable bowel syndrome, restless leg syndrome, dysautonomia, cognitive dysfunction, chemical hypersensitivity, and irritable bladder (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 (Burckhardt et al 1994, Yunus 1994). Importantly fibromyalgia is not common in patients with major depression, even those depressed individuals who complained of pain did not multiple tender points (Fassbender et al 1997). Psychological distress in fibromyalgia may in part determine who becomes a patient (Aaron et al 1996). There is increasing acceptance that post-traumatic stress disorder may be associated with fibromyalgia (Amur 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 1999b). 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 (Buckila et al 1997). A striking familial prevalence of fibromyalgia has been reported by Buckila et al 1996). This suggests that subjects destined to develop fibromyalgia either are 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 impairs a patient’s quality of life (Burckhardt et al 1993). An analysis of 1604 fibromyalgia patients followed in academic centres reported that pain, fatigue, sleep disturbance, functional status, anxiety, depression, and
Clinical pain states

health status were essentially unchanged after 7 years of follow-up (Wolfe et al. 1997a). There is some evidence that fibromyalgia patients seen in the community, rather than tertiary care centres, have a better prognosis (Granges et al. 1994). The consequences of pain and fatigability influence motor performance; everyday activities take longer in fibromyalgia patients, they need more time to get started in the morning, and they often require extra rest periods during the day (Henriksson CM 1994). 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). The adaptations that fibromyalgia patients have to make in order to minimize their pain experience often has a negative impact on both vocational and avocational activities.

Disability

Despite the superficial appearance of normality many fibromyalgia patients have difficulty with remaining competitive in the work force (Bennett 1996a). Most FM patients report that chronic pain and fatigue adversely affect the quality of their life and negatively impact their ability to be competitively employed (Henriksson 1995). The extent of reported disability in FM varies greatly from country to country—probably reflecting differences in political philosophies and socio-economic realities. A survey of fibromyalgia patients seen in academic centres reported that 71% perceived themselves as being disabled. Sixteen percent were receiving Social Security benefits (SSD); this compares to 2.2% of the US population (Wolfe et al. 1997b).

Pathogenesis

The contemporary aetiological 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. It is now thought that both peripheral and central factors contribute in varying degrees to the expression of symptoms labelled as fibromyalgia.

For most of the twentieth 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 ‘trigger points’ (Travell and Simons 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 summations influenced by central facilitatory and inhibitory mechanisms (Bassbaum and Fields 1984, Graven-Nielsen et al. 1997). 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 KG 1994, Bennett 1996c).

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 can cause trauma. However, NMR spectroscopy can evaluate living untraumatized 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 muscular dystrophies (Younkin et al. 1987) and also with increasing age (Saitusugui et al. 1980). They are thought to result from the lipid peroxidation of sarcoplasmic 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.

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).

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 transcutaneous 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 (Wali and Crondy-Dillon 1960). This effect, known as diffuse noxious inhibitory control (DNIC), is defective in fibromyalgia subjects (Lautenbacher and Rollman 1997), thus supporting the notion that they have a defective descending inhibitory pain system (Mense 2000).

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 (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 two 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 and Cohen 1993).

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 thalamic blood flow, 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).

Elevated levels of substance P in the CSF

Substance P is an important nociceptive neurotransmitter. There are three definitive studies that have shown a threefold increase of substance P in the CSF of fibromyalgia patients compared to that in controls (Vaeroy et al, 1988, Russell et al 1994, Liu et al 2000). Animal models of hyperalgesia and hypoalgesia have implicated substance P as a major aetiological 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. Giovena et al have reported a fourfold elevation of NGF in the CSF of patients with primary fibromyalgia compared with that of healthy controls and other pain patients (Giovena et al 1999). The intravenous administration of recombinant nerve growth factor in humans results in a muscle pain syndrome resembling fibromyalgia that 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 2001).

Beneficial response to an NMDA receptor antagonist

The excitatory amino acid glutamine reacting with NMDA (N-methyl-D-aspartic acid) receptors plays...
Clinical pain states

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 s. 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).

Management

The management of fibromyalgia patients is an exercise in symptom palliation and maintenance of physical and emotional functionality. The successful management of fibromyalgia patients requires a thorough analysis in terms of the bio-psycho-social model of disease. The major management issues that usually require attention are shown in Table 7.1.

Diagnosis and evaluation

The diagnosis of fibromyalgia is usually based on 1990 recommendations of the American College of Rheumatology classification criteria (Wolfe et al 1990). 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 harbour 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) to find relevant myofascial pain generators that would benefit from trigger point therapy (Borg-Stein and Stein 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 programme. The history and examination will probably suggest certain problems that need further evaluation in terms of specialist referral or investigations.

Education

There is good evidence that higher educational attainments are associated with a better prognosis in many chronic diseases (Ramos-Reus et al 2000). There are several studies that support the value of education in fibromyalgia patients (Gowans et al 1999, Mannerkorpi et al 2000). Indeed, education has several components common to cognitive-behavioural techniques, such as goal setting and reassessment of priorities. Important educational issues are shown in Table 7.2.
The components of a fibromyalgia educational gramme

1. Validate symptoms
2. Emphasize non-destructive (not necessarily benign) nature of FM
3. Focus on improving function, not complete eradication of symptoms—as in many other chronic diseases
4. Discuss importance of mind-body relationships—teach meditation and relaxation techniques
5. Discuss drug and non-drug 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, feelings of guilt and improved assertiveness
10. Emphasize patient's active role in any treatment plan

Table 7.3 Peripheral pain generators

<table>
<thead>
<tr>
<th>Myofascial trigger points</th>
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<tr>
<td>Degenerative joint disease</td>
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<tr>
<td>Inflammatory joint disease</td>
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<tr>
<td>Bursitis</td>
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<tr>
<td>Tendinitis</td>
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<tr>
<td>Developmental defects (e.g., scoliosis)</td>
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<td>Hypermobility syndrome</td>
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<tr>
<td>Neuropathic pain</td>
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<tr>
<td>Injuries/trauma</td>
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<tr>
<td>Repetitive strain</td>
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<tr>
<td>Visceral pain (e.g., IBS, endometriosis)</td>
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<tr>
<td>Herniated discs</td>
</tr>
<tr>
<td>Spinal stenosis/Chiari malformation</td>
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<tr>
<td>Recurrent headaches (e.g., migraine)</td>
</tr>
</tbody>
</table>

Considering the management of pain in FM, it is vital to focus on the major sites of pain generation/processing, namely peripheral pain generation, spinal sensitization, psychological influences, and the descending pain pathway. There is no specific tissue pathology, at least in peripheral tissues, that can be said to be characteristic of fibromyalgia (Simms 1996). However, this should not be taken as negating the importance of peripheral nociceptive mechanisms. Once the somatosensory system is sensitized, peripheral pain generators will only be perceived as being more painful, but persistent barrage of nociceptive impulses will prolong and amplify the biochemical machinery of central sensitization. Common peripheral pain generators are shown in Table 7.3. Although some peripheral pain generators, notably arthritic orders, may be helped by NSAIDs, central pain is usually not very responsive to these agents. Thus, use of NSAIDs is usually adjunctive to the use of centrally acting analgesics. Specific treatments other pain generators would include, for example, gabapentin in neuropathic pain and 5-HT 2A antagonists in vascular headaches. Some pain generators, such as ostearthrosis of the knees, bursitis, and carpal tunnel syndrome, may be helped by local corticosteroid injections. In other instances surgery may be appropriate (e.g., severe ostearthrosis of the hips, Chiari deformity, endometriosis). As the commonest pain generators, in most fibromyalgia patients, are 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 acupuncture and spray and stretch, and physician intervention in terms of procaine or botulinum toxin injections. Most of the drugs used to treat pain act at the level of the dorsal horn. The modulation of the ‘nociceptive amplification’ that occurs at the first synapse is mainly pharmacological (Reveille 2000). The descending pain system originates in the midbrain and terminates at the level of dorsal horn neurons, thus influencing spinal cord sensitization (Willis and Westlund 1997). This descending system is responsible for such diverse events as the placebo effect, fear-induced hypoalgesia, anticipatory hyperalgesia, the benefits of cognitive behavioural therapy, the action of opioids, and inflammation-induced hyperalgesia. Thus cortical and subcortical circuits can modulate dorsal horn activity through emotional states related to attention, motivation, and cognition. Currently the only FDA-approved drugs that modulate dorsal horn cell reactivity are those that activate or amplify the descending pain system; these include opioids, tricyclic antidepressants, and alpha-2 adrenergic agonists. Antidepressants such as amitriptyline have long been a mainstay in the treatment of chronic pain states (Fishbain 2000), including fibromyalgia.
Clinical pain states

(Carette et al. 1986). A meta-analysis of antidepressants in the treatment of fibromyalgia, analysed 13 randomized, placebo-controlled trials (O’Malley et al. 2000). The odds ratio for improvement with therapy was 4.2. Analysing the effect on specific symptoms indicated that antidepressants improved sleep, fatigue, pain, and well-being—in that order. Only one study found a correlation between symptom benefit and improvement in depression. Despite their widespread use, the long-term efficacy of antidepressants in managing fibromyalgia pain has not been well established (Carette et al. 1994).

Opioids are effective in most acute and chronic pain states. Although opioids are fairly commonly used in the treatment of fibromyalgia (Wolfe et al. 1997a), there have been no controlled clinical trials. 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). The usual cited concerns regarding addiction are now known to be unfounded—only occurring in about 0.5% of opioid-treated chronic pain patients (Portenoy 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. Addiction is a dysfunctional state occurring as a result of the unrestrained use of a drug for its mind-altering properties; manipulation of the medical system and the acquisition of narcotics from non-medical sources are common accompaniments. Addiction should not be confused with ‘pseudo-addiction’. This is a drug-seeking behaviour generated by attempts to obtain appropriate pain relief in the face of undertreatment of pain (Weissman and Haddox 1989). Opiates should not be the first choice of analgesia in fibromyalgia, but they should not be withheld if less powerful analgesics have failed.

Tramadol (Ultracet) is proving to be a useful drug to treat pain in chronic conditions, including fibromyalgia (Roth 1998, Schützer et al. 2000). Tramadol has a dual mechanism of acting both as a weak opioid agonist and as an inhibitor of the reuptake of serotonin and noradrenaline (norepinephrine) at the level of the dorsal horn (Lewis and Han 1997). A double-blind 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 patients and other symptoms (Brown et al. 2001).

Alpha-2 adrenergic agonists such as tizanidine (Zanaflex) have been used successfully in chronic pain disorders (Fogelholm and Räisänen 1992). The experimental basis for this adrenergic action is the observation that intravenously administered alpha-2 adrenergic agonists produce powerful analgesia in both experimental animals and man (Nabeshima et al. 1987, Coward 1990). 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 being not nociceptive but it is also an antispasmodic (Smith and Barton 2000), which could draw on a benefit in fibromyalgia patients if it is given evening.

5-HT3 antagonists have been the subject of several encouraging short-term trials in fibromyalgia patients (Farber et al. 2000). Haus and colleagues found that 5-HT3 receptors are found only in neuronal both central and peripheral (Tecott et al. 1991). The complex biochemical processes of 5-HT3 receptors suggest that antagonists would block nociceptive and non-nociceptive actions in different circumstances. When activated the 5-HT3 receptor causes a membrane depolarization with resultant cytosolic Ca++, which in turn modulates the release of neuropeptide molecules such as substance P, serotonin, GABA, acetylcholine, cholecystokinin and dopamine (Wolf 2000). Longer-term studies in fibromyalgia patients are needed before the clinical efficacy of this class of drugs can be fully evaluated.

Drugs that modulate the ascending pain system are less commonly used. However, there is clinical evidence that blocking NMDA receptors with ketamine ameliorates pain in fibromyalgia subjects (Sorenson et al. 1995). Dextromethorphan, a weak NMDA receptor antagonist that has been successfully used in neuropathic pain (McRae et al. 1994) and more recently as an adjunct to tramadol and treatment of fibromyalgia (Clark et al. 2000). Logically inhibiting the release of substance P does appear to be beneficial in chronic pain trials of a first-generation substance P antagonist were disappointing in chronic pain (Hill 2000). To date NGF antagonists have not been used in human clinical trials.

Sleep

Most fibromyalgia patients relate to sleep difficulties as being easily aroused by minor noises and thoughts. Many exhibit daytime alertness which would explain their difficulty in the restorative stages of sleep (Hawley et al. 1991). The psychological aspects of sleep and disturbed sleep are a central problem in the treatment of fibromyalgia patients. Establishing an adherence to a regular sleep and regular low-to-moderate-intensity tricyclic antidepressants such as amitriptyline, doxepin, imipramine, and fluoxetine are questions that are often asked and are sometimes asked. Although the use of benzodiazepines such as alprazolam (Xanax) and clonazepam (Klonopin) for the treatment of insomnia is controversial, the use of benzodiazepines and other hypnotics such as zolpidem (Ambien), doxepin (Sinequion), clonazepam (Klonopin), and zolpidem (Ambien) has been reported to improve sleep in fibromyalgia patients.
of medications (TCAs, drugs with antihistamine actions, benzodiazepines, etc.), (2) depression, (3) aerobic deconditioning, (3) a primary sleep disorder (e.g. sleep apnoea), (4) non-restorative sleep (see above), (5) neurally mediated hypotension, and (6) growth hormone deficiency (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 modafinil (Provigil), a non-amphetamine drug used in narcolepsy and sleep deprivation situations, is of some benefit in improving non-specific fatigue (Lyons and French 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, which would explain their never getting into the restorative stages 3 and 4 of non-REM sleep (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, trazodone, doxepin, imipramine, etc.) has been the mainstay of sleep pharmacotherapy in FM patients (Goldenberg 1989, 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 be 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 apnoea, which usually requires treatment with positive airway pressure (CPAP) or surgery. For 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 supper.

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 and Gavrin 1999). Approximately 30% of fibromyalgia patients have significant current depression and about 60% have a lifetime prevalence of depressive illness (Okifuji et al 2000). It is generally assumed that treating depression fibromyalgia patients is no different than treating primary depressive illness. There are no trials that have specifically addressed the issue of treating depression in FM patients; however, one 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 is important in such patients. Techniques of cognitive-behavioural therapy seem particularly well suited to effect these changes and may be enhanced when done as a part of group therapy (Goldenberg et al 1994).

Deconditioning

The notion that ‘exercise is good for fibromyalgia patients’ is an accepted contemporary truth (Clark et al 2001) 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 concent-
Clinical pain states

similarities between fibromyalgia symptomatology and the overtraining syndrome. Overtraining 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 programme is always needed to optimize the benefits and minimize increased pain and fatigue (Clark 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 (Croft et al. 1994, Pillmer et al. 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 (Clark et al. 1985). About one-third of fibromyalgia patients are growth hormone deficient (Bennett et al. 1997), and replacement therapy has been reported to benefit such patients (Bennett et al. 1998).

Associated disorders

Recognition and treatment of problems commonly associated with fibromyalgia are important in the overall management scheme.

Chronic fatigue

The common treatable causes 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 apnoea), (4) non-restorative sleep (see above), (5) neurally mediated hypotension, and (6) growth hormone deficiency (Bennett et al. 1997, 1998).

Restless leg syndrome

Treatment is simple and very effective—L-dopa/levodopa (Sinemet) in an early evening dose of 10/100 mg (a minority require a higher dose or use of the long-acting preparations). Some patients respond to gabapentin. Recalcitrant cases are 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, and (4) prescribing medications for specific symptoms: constipation (stool softener, fibre supplementation, and gentle laxatives such as bisacodyl), diarrhoea (loperamide or diphenoxylate), and antispasmodics (dicyclomine or 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. Kegel exercises), and (4) the prescription of antispasmodic medications (e.g. oxybutynin, flavoxate, hyoscyamine).

Cognitive dysfunction

This is a common problem for many fibromyalgia patients. It adversely affects the ability to be competitively employed and may cause concern 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.

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 vasoconstrictors 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 sternocleido-mastoids and other neck muscles, (3) neurally mediated hypotension, and their side effects. Upon making an accurate diagnosis or using the principles of psychopharmacology, (4) hyperexcitability in the central nervous system (CNS), (5) minimizing psychological distress, (6) adhering to basic rules for maintaining a regular bowel habit, and (7) prescribing medications for specific symptoms: constipation (stool softener, fibre supplementation, and gentle laxatives such as bisacodyl), diarrhoea (loperamide or diphenoxylate), and antispasmodics (dicyclomine or dicyclomine) or anticholinergic/sedative preparations such as Donnatal.

Neurally mediated hypotension

Treatment involves: (1) eliminating foods that aggravate symptoms, (2) minimizing psychological distress, (3) adhering to basic rules for maintaining a regular bowel habit, and (4) prescribing medications for specific symptoms: constipation (stool softener, fibre supplementation, and gentle laxatives such as bisacodyl), diarrhoea (loperamide or diphenoxylate), and antispasmodics (dicyclomine or dicyclomine) or anticholinergic/sedative preparations such as Donnatal.

Multidisciplinary team

Most of the recommendations assume a one-on-one doctor’s role to accommodate the individual needs of the patient. However, most of these recommendations can be incorporated into a multidisciplinary team programme using professional resources (e.g. psychologists, exercise physiologists, workers, and social workers). Bennett et al. 1996b, Turk et al. 1997. In addition, patients can be seen several times a month. Participation of meeting other patients and the development of a support group can help patients develop a sense of control over their problems. This form of therapy is integral in one 6-month program that showed improvement over a 2-year period (Bennett et al. 1997).

References

neurally mediated hypotension (see below), and (4) medication side effects. Treatment is dependent upon making an accurate diagnosis.

**Neurally mediated hypotension**

Treatment involves: (1) education as to the triggering factors and their avoidance, (2) increasing plasma volume (increased salt intake, prescription of finene), (3) avoidance of drugs that aggravate hypotension (e.g., TCAs, antihypertensives), (4) preventing reflex (β-adrenergic antagonists or diospyramid), and (5) minimizing the efferent limb of the reflex (α-adrenergic agonists or anticholinergic agents).

**Multidisciplinary 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 multidisciplinary treatment programme using a team of interested health professionals (nurse practitioners, clinical psychologists, exercise physiologists, mental health care workers, and social workers) (Goldenberg 1989, Bennett 1996b, Turk et al. 1998). In this way groups of 5–15 patients can be seen in designated sessions several times a month. Patients are usually appreciative of meeting others who share similar problems, and the dynamics of group therapy is often a powerful aid to cognitive-behavioural modifications. Such groups can be encouraged to develop a sense of camaraderie in solving mutual problems. This form of therapy has proved beneficial in one 6-month programme, with continuing improvement out to 2 years after leaving the programme (Bennett et al. 1996).

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