Editorials

Treating fibromyalgia

Fibromyalgia is a common musculoskeletal disorder, characterized by widespread pain combined with tenderness at multiple tender points. Associated features often include fatigue, unrefreshing sleep, psychological distress, irritable bowel, headaches, paraesthesia and morning stiffness. Although not universally accepted as a discrete entity [1], such patients can be readily classified by using the American College of Rheumatology (ACR) 1990 criteria [2] which require the presence of widespread pain for at least 3 months and pain on palpation of at least 11 of 18 tender points. The syndrome has replaced the label fibrositis and there is a large degree of overlap with other medically unexplained syndromes such as chronic fatigue syndrome. In all cases, a medical explanation for the pain and fatigue needs to be sought, with appropriate investigations undertaken dependent on the presentation. However, despite being the second commonest syndrome seen in some rheumatology clinics [3], treatment has been regarded as unsatisfactory, many patients suffering a chronic or rarely remitting course with significant disability and handicap.

The National Arthritis Data Workgroup recently reviewed six prevalence studies in the North American population and estimated the overall prevalence at 2% (over 3.7 million) [4]. It is commonly associated with poor psychological health: in a British community survey over 25% of individuals with widespread generalized pain had some concomitant mental disorder, most commonly depression [5]. In general, prognosis is poor. In a naturalistic follow-up of UK patients 4 yr after diagnosis, Ledingham et al. [6] found 97% of patients still had typical fibromyalgia symptoms, with 85% still fulfilling the ACR 1990 diagnostic criteria. Sixty per cent felt they were worse and only 20% better than at presentation, while half had stopped work because of their condition. Studies from Denmark, Canada and the USA have all reported similar findings, with high rates of reliance on social security payments or disability pensions.

Many theories about the causation of fibromyalgia have been proposed, although as yet there is neither evidence nor consensus on the importance of these various factors. Proposed aetiological factors include the role of sleep disturbance, loss of fitness, psychiatric disorder, endocrine, traumatic, infective and other factors in the onset of the condition, and also the role of behavioural and cognitive responses in its perpetuation and chronicity. Most of these elements have been used as a basis for treatment. Interpreting the results of clinical research into fibromyalgia must take account of the many potential confounders, biases and methodological weaknesses. These include studies being underpowered or lacking appropriate control groups, selection bias, poor compliance and the potentially confounding Hawthorne effect.

First, the role of sleep disturbance has received much attention. An influential theory was based on the observation that, not only was non-rapid eye movement sleep disturbed in fibromyalgia [7], but also typical symptoms of fibromyalgia could be induced in healthy controls by artificially provoking such sleep disturbance [8]. However, randomized controlled trials of zopiclone [9], temazepam [10], zolpidem [11] and melatonin have all shown that, whilst sleep quality can be improved, there is no concomitant improvement in pain or fatigue symptoms.

Second, there is some evidence that there is a substantial loss of fitness [12, 13] in fibromyalgia patients, although not all studies confirm this [14]. It is clear, however, that there is decreased muscle strength [15] and an increase in the perception of fatigue (or sense of effort) at any given exercise level compared with controls [16]. It is not clear whether these factors are a primary cause or an effect of fibromyalgia, although Moldofsky et al. [7, 8] did find that athletically fit individuals were less prone to develop fibromyalgia-type symptoms in response to selective sleep deprivation than those who were less fit. This led to the proposal that exercise training might serve as a protective factor against developing fibromyalgia and that, by extrapolation, improving patients’ aerobic fitness might improve their symptoms.

Subsequent randomized controlled trials have helped clarify the effects of exercise. Four studies have shown significant improvement in pain and fitness and reduced tender point count at the end of an exercise programme, but have failed to show long-term benefit [17–20], probably because patients had stopped exercising. Not all exercise studies had a positive outcome: one small study failed to show any improvement in symptoms compared with a control group, despite significantly improving physical fitness [21].

There are some difficulties with exercise treatment: in particular, compliance is a significant problem and drop out rates are high. Reasons for this include the initial increase in pain and stiffness in the days following exercise and patients’ subsequent beliefs that exercise worsens the condition. This increase in delayed onset muscle soreness is most probably caused by microtrauma induced by unaccustomed exercise and exacerbated by increased eccentric muscle contraction during exercise [22, 23]. A further hypothesis is that this is exacerbated by impaired healing related to relative deficiency in growth hormone and insulin-like growth factor 1 (somatomedin C) [24].
The third main treatment strategy is of educational programmes including several components: information about the condition; cognitive behavioural therapy and communication skills. Cognitive behavioural therapy can involve a number of strategies [25] such as modifying unhelpful coping behaviours (e.g. excessive use of rest or avoidance of activity, over-monitoring of bodily symptoms), employing relaxation techniques, changing unhelpful illness attributions and trying to improve the confidence in one’s ability to manage one’s symptoms (‘self-efficacy’) [26]. One study looking at group cognitive behavioural therapy resulted in two-thirds of patients reporting benefit but there was no change in quality of life or health status measures [27] over 1 yr. Another randomized controlled trial of a short 10-week course of cognitive behavioural therapy led to marked improvement in pain, fatigue and disease impact [28]. A variety of programmes have studied the combination of education and exercise treatments compared with a control group [18, 29, 30]. Such interventions improve self-efficacy and physical activity in the short term, but long-term benefits have again not been proven.

The fourth main approach has been to use pharmacological interventions, either directed at a presumed cause or as symptomatic management. One approach attempts to correct underlying neuroendocrine abnormalities such as the low levels of insulin-like growth factor 1 found in a third of patients [24]. Bennett et al. [24] studied the effect of growth hormone treatment given as daily subcutaneous injections in this subset of individuals. They found that 68% of those receiving active treatment had a good global response compared with 26% of the placebo-treated group at 6 months (although one-third of the treatment arm developed carpal tunnel syndrome).

In a previous study designed to assess the potential benefit of oral corticosteroids there was no benefit derived from 2 weeks of treatment with 15 mg of prednisolone daily [31].

Pain control is an important aim of therapy. However, non-steroidal anti-inflammatory drugs have disappointingly little effect: ibuprofen [32] being no better than placebo and naproxen and only marginally better and adding minimal benefit in combination with amitriptyline [33]. Tramadol, which combines analgesic mechanisms mediated via weak opioid and monoaminergic actions, is widely used and anecdotally highly effective in fibromyalgia, but is yet to be adequately evaluated. A small study of intravenous tramadol was promising, producing a 40% reduction in pain compared with placebo [34]. Tramadol causes minimal respiratory depression, dependence and tolerance and is, therefore, more appropriate for long-term regular administration than other narcotic analgesics.

Tender point injection is widely practised as part of a treatment package but is yet to be subject to a randomized blinded controlled trial, although an open study found significant relief from combined lignocaine and triamcinolone [35].

Tricyclic antidepressants at low doses are thought to have a pain-modifying but not significant antidepressant action. Initial under-powered studies of their use looked promising [36], with 44% of patients on amitriptyline (titrated up to 50 mg a day) gaining more than a 50% reduction in pain at 9 weeks compared with 22% of the placebo group. Subsequent randomized controlled trials confirmed the effectiveness of amitriptyline, but only for 20–30% of patients [33, 37]. Cyclobenzaprine, a tricyclic-type medication without antidepressant but with central muscle relaxant action mediated via reduction in brainstem noradrenergic function [38] has also shown modest benefit, but with no advantage over amitriptyline [39, 40]. In conclusion, the overall degree of benefit of tricyclics is modest although for a minority of patients there is evidence for a persistent benefit in many aspects of their condition.

Studies looking at the effects of the selective serotonin re-uptake inhibitor (SSRI) antidepressants have been largely disappointing. In an open study of 23 patients taking fluoxetine there was no benefit in pain scores or tender point scores [41]. In a randomized controlled trial Wolfe et al. [42] showed only a slight improvement in depression scores over a 6-week treatment period but no benefit in any other aspect of the condition. These findings parallel similarly disappointing results in chronic fatigue syndrome [43]. Citalopram (another SSRI) has also failed to show any significant benefit [44, 45]. The place for SSRIs may be in combination with tricyclics as Goldenberg et al.’s [46] randomized controlled trial of amitriptyline and/or fluoxetine did show most benefit from the combination. However, this result should be viewed with caution as fluoxetine can markedly increase plasma levels of tricyclics; therefore, the improved efficacy could represent a dose-response effect of tricyclics. Two small studies suggest that two other drugs acting on the serotonin system might be efficacious. In a small double blind crossover study of ondansetron, a selective 5HT3 receptor antagonist, individuals on ondansetron 8 mg twice daily gained more than a 40% reduction in pain [47]. In a small open study of venlafaxine, a serotonin and noradrenaline re-uptake inhibitor (SNRI) antidepressant, 55% of patients gained more than 50% improvement in their symptoms [48].

Many patients turn to alternative therapies. In one study, 98% of individuals had used at least one complementary treatment including vitamins (44%), bed rest (33%), exercise (25%), acupuncture [49], hypnosis [50] or prayer (23%) [51].

What, then, can we conclude? The evidence is strongest for the use of supervised graded exercise and/or educational programmes (including cognitive behavioural therapy), although which specific aspects of such regimens are most helpful remains unclear. It is important not to overlook comorbid psychiatric disorders and to treat them appropriately. Pharmacological treatments also have an important role, primarily in the symptomatic treatment of pain and sleep disorder (in combination with sleep hygiene advice). There is a need for well-constructed randomized controlled trials to evaluate a possible role for the newer classes of
antidepressants such as SNRIs and analgesics such as tramadol. Finally, we need to acknowledge that treatments based on current ideas regarding aetiology are of only limited effectiveness. This necessitates the need for the development and testing of new hypotheses of pathogenesis and treatment.

S. Richards and A. Cleare

Department of Rheumatology and 1Psychological Medicine, Kings College Hospital, London, UK

References

33. Goldenberg DL, Felson DT, Dinerman H. A randomised controlled trial of amitryptiline and naproxen in the process...