BJMP 2012;5(2):a522

Editorial

Fibromyalgia, psychiatric comorbidity, and the somatosensory cortex

Francis J Dunne and Ciaran A Dunne

In rheumatology clinics chronic painful conditions are the norm. Although many pain syndromes are associated with low mood and sometimes clinical depression, the mood disorder often goes unrecognised. Fibromyalgia is one such chronic pain syndrome, 'chronic' arbitrarily defined as lasting longer than six months. It is a common, poorly understood, musculoskeletal disorder which more often affects women between the ages of 25-50 years generally.

In nearly all patients three symptoms predominate, namely, neuropathic pain (nerve injury pain), fatigue and non-restorative sleep disturbance. The chronic neuropathic diffuse pain, described as whole body pain, is felt particularly in deep tissues such as ligaments, joints, and muscles of the axial skeleton in mainly the lower cervical and lumbar spine. The pain is often characterised by an exaggerated and prolonged response to a noxious stimulus (hyperalgesia). Patients may be considered to be malingering because there is no obvious explanation for the symptoms. Anxiety, stress and depression caused by fibromyalgia add insult to injury, with personality and cognitive factors coming into play in addition.[1] Paraesthesiae (abnormal sensory sensations) or dysaesthesiae (painful sensations) of the extremities may also occur. There is no objective muscular weakness or neurological disorder to account for the symptoms, which adds to the diagnostic dilemma. For example, fibromyalgia affecting the supraspinatus muscle of the shoulder would limit initial abduction of the arm because of pain, not because of any muscle weakness. Cognitive function is sometimes described as 'fibrofog' or 'conscious confusion' and may be a primary symptom of fibromyalgia, reflecting impairments in working memory (a form of short-term memory), episodic (memory for events), and semantic memory (memory for words, rules, language).

Nociception refers to the process of information about harmful stimuli conveyed by neuronal activity up to the point of perception in the dorsal horn of the spinal cord where primary afferents synapse.[2] Evidence is accumulating which shows that atypical sensory processing in the central nervous system (CNS) and dysfunction of skeletal muscle nociception are important in the understanding of fibromyalgia and other chronic pain syndromes[-3]. The concept of 'central pain sensitization' or 'central sensitivity syndrome' considers fibromyalgia to be a disturbance of nociceptive processing which causes a heightened experience of pain or pain amplification.[4] Because pain signals are subject to variation in amplitude, the modulation of sensory processing may be the key to understanding the pain response not only in fibromyalgia but also in other conditions, such as irritable bowel syndrome. Descending spinal noradrenergic and serotonergic neurons inhibit the neurotransmitters noradrenaline and serotonin, released from primary afferent neurons and dorsal horn neurons. Therefore, when descending inhibition is decreased, irrelevant nociceptive stimuli are more readily felt. Put another way, in patients with chronic pain syndromes descending inhibition may not be functioning adequately to prevent or mask irrelevant pain stimuli. When appropriate medication is used this normal descending inhibition is enhanced and pain is no longer troublesome.

The release of neurotransmitters (ligands) also requires a mechanism that involves voltage-sensitive calcium and sodium channels. Repetitive action potentials cause the calcium channels to open with the ensuing release of neurotransmitters into the synaptic cleft. The postsynaptic neurons are thus stimulated leading to molecular and structural changes (sprouting) which cause neuropathic pain. Drugs such as Pregabalin and Gabapentin bind to voltage-sensitive calcium channels and reduce calcium influx, which in turn diminishes pain. The concept of central pain sensitization now incorporates affective spectrum disorders and functional somatic syndromes. It seems that the more painful symptoms one has which are difficult to explain, the more likely the patient is suffering from a mood disorder. Dopamine may be involved in the regulation of cognition in the dorsolateral prefrontal cortex and could account for the cognitive deficits.[5]Because cingulate and prefrontal cortices are particularly implicated in pain modulation (inhibition and facilitation of pain), structural changes in these systems could contribute to the chronic pain associated with fibromyalgia.[6]

Many patients with fibromyalgia have an increased sensitivity to sensory stimuli that are not normally or previously painful (allodynia). In other words, minor sensory stimuli that

ordinarily would not cause pain in most individuals induce disabling, sometimes severe pain in patients with fibromyalgia.[7] In normal individuals 4 kg/square cm^2pressure (approximately the pressure needed to blanch the skin at the top of one's thumb) causes patients with fibromyalgia to wince with pain or suddenly withdraw when the tender point is palpated. This indicates that pain occurs at a lower pain threshold in fibromyalgia sufferers when this pressure is applied.

The pain of fibromyalgia may be aggravated by emotional stress though the latter is difficult to quantify and evaluate. For instance, corticosteroid hormones are released in high amounts after stress yet fibromyalgia is associated in some patients with a decreased cortisol response to stress. Stress may therefore initiate, inhibit or perpetuate alterations in the corticotrophin-releasing hormone (CRH) neuron, with associated effects on the hypothalamic pituitary axis (HPA) and other neuroendocrine axes.[8]

There are many other possible explanations for fibromyalgia pain. One of the major neurotransmitters involved in nociception is substance P, found in high concentrations in the spinal cord, limbic system, hypothalamus, and nigrostriatal system. It is involved in the transmission of pain impulses from peripheral afferent receptors to the central nervous system. Nerve growth factor (NGF), a cytokine-like mediator may indirectly exert its effect through enhancing glutaminergic transmission and could account for sustained central sensitization in fibromyalgia. [9, 10] Another neuropeptide, calcitonin gene-related peptide, a potent vasodilator, present in non-myelinated afferent neurons, may also play a role in pain pathology.[5]

Levels of the neurotransmitter serotonin have been found to be low in some studies in fibromyalgia patients. Although serum levels of serotonin are lower than in some patients with rheumatoid arthritis and healthy controls, the variation is too broad and therefore measurement of serotonin has not proved useful tool in determining a diagnosis of fibromyalgia. [11]

Logically, pharmacologic agents used to treat pain in fibromyalgia would act by either increasing levels of inhibitory neurotransmitters or decreasing levels of excitatory neurotransmitter. In the United States of America (USA), Pregabalin was the first drug to be approved by the Food and Drug Administration (FDA) for the treatment of fibromyalgia and has been shown to improve pain, sleep and quality of life. It is ineffective against depression. The main inhibitory mediator in the brain, gamma amino butyric Acid (GABA), is formed from glutamate (excitatory) by the enzyme glutamate decarboxylase (GAD). It is particularly plentiful in the nigrostriatal pathways. About 20% of CNS neurons are GABAergic and it serves as a neurotransmitter at some 30% of all CNS synapses.[12] Pregabalin increases neuronal GABA levels by producing a dose-dependent increase in glutamate decarboxylase activity. In a meta-analysis of 21 clinical trials to estimate treatment differences vs. placebo, statistically significant improvement was observed with Duloxetine, Milnacipran 200 mg/day, Pregabalin 300 or 450 mg/day, and Tramadol plus Paracetamol. The meta-analysis showed a statistically increased risk of discontinuation because of adverse events related to Milnacipran and Pregabalin.[13]

Antidepressants may improve fibromyalgia symptoms by reducing pain, stabilizing mood and improving sleep, though the effect seems to be modest. If abnormal sleep, and hence subsequent tiredness, precedes the development of fibromyalgia the effect of antidepressants may be primarily associated with improved sleep. However, the efficacy of tricyclic antidepressants is difficult to quantify and their limited superiority over placebo lasts no more than a few months. A meta-analysis of ten randomized double-blinded, placebo-controlled studies revealed only poor to moderate evidence for a beneficial effect at low doses of Amitriptyline (25mg daily) over 6-8 weeks. Even when given in higher doses or prescribed for a longer duration, Amitriptyline did not make a great deal of difference. [14]

The efficacy of Selective Serotonin Reuptake Inhibitors (SSRIs) is also inconclusive. More promising results have been demonstrated with Serotonin and Noradrenaline Reuptake Inhibitors (SNRIs) such as Duloxetine. Both serotonin (5-HT) and noradrenaline (NA) exert analgesic effects via descending pain pathways. Pain is a prominent feature of depression and vice versa and the alleviation of one modifies the other. [15, 16] The reduction in pain reduces fatigue and Duloxetine improves mood.

Other drugs used in this condition include Milnacipran and Cyclobenzaprine (a muscle relaxant structurally related to tricyclic antidepressants). Milnacipran and Cyclobenzaprine are not available in the United Kingdom (UK). Tramadol (a serotonin and noradrenaline reuptake inhibitor) is a weak mu-receptor opioid agonist used to control pain but its adverse effects are those of opiates in general, mainly nausea and dependence.

Although other adjunctive non-pharmacological treatments have been advocated the results are disappointing. Assessments of non-drug treatments are generally mediocre. Aerobic exercises benefit some patients, especially when combined with biofeedback, patient education and cognitive therapy. A whole gamut of treatments such as graded exercises, yoga, dietary advice, balneotherapy (heated pool bathing), homeopathy, massage, acupuncture, patient education, group therapy and cognitive behaviour therapy, have been suggested and tried, but few of them demonstrated clear-cut benefits in randomized controlled trials.Support groups may help some patients. [17, 18, 19]

Fibromyalgia is now considered to be, in part, a disorder of central pain processing. Central sensitization manifests as pain hypersensitivity, particularly allodynia, and hyperalgesia. It is

believed that central sensitization occurs in part through the action of glutamate on the N-methyl-D-aspartate (NMDA) receptor, resulting in an increase in intracellular calcium and kinase activation, leading to hyperalgesia and allodynia.[20]

Response to standard analgesics is erratic and more promising results have emerged with drugs such as the SNRIs Duloxetine and Milnacipran, the anticonvulsants Gabapentin and Pregabalin, either used alone or in combination, or with other agents such as Amitriptyline. There is only modest evidence to support SSRIs and Tramadol. Treatment needs to be holistic and multidisciplinary, focussing on both physical pain management and psychological dysfunction. The multidisciplinary approach, though difficult to measure, may help by imparting a sense of empathy and support for patients. Overall, most patients with fibromyalgia continue to have chronic pain and fatigue with symptoms persisting for many years, but it is not necessarily a progressive disorder and some patients may show moderate improvement.

Competing Interests
None declared
Author Details
Francis J Dunne, FRCPsych, Consultant Psychiatrist and Honorary Senior Lecturer, North East London Foundation Trust (NELFT) United Kingdom, & University College London. Ciaran A Dunne, MRCP, Consultant Rheumatologist, Royal Bournemouth and Christchurch Hospitals, Bournemouth, United Kingdom BH7 7DW.
CORRESSPONDENCE: Francis J Dunne, Consultant Psychiatrist, North East London Foundation Trust(NELFT), United Kingdom.
Email: francis.dunne@nelft.nhs.uk

REFERENCES

1. Dunne FJ, Dunne CA. Fibromyalgia and depression: common pathways. Br J Hosp Med. 2012; 73: 211-217.
2. Barker R, Cicchetti F, Neal MJ. Somatosensory system. In: Neuroanatomy and Neuroscience at a Glance, Wiley-Blackwell; 2012: 70-75.
3. Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis & Rheumatism . 2002; 46: 1333–1343.
4. Yunus MB. Role of central sensitization in symptoms beyond muscle pain, and the evaluation of a patient with widespread pain. Best Practice & Res Clin Rheum. 2007;21:481-497.
5. Stahl S. Pain and the treatment of fibromyalgia and functional somatic syndromes. In: Stahl's Essential Psychopharmacology. Neuroscientific Basis and Practical Applications , 3rd edition, 2008; Cambridge University Press: 773-814.
6. Kuchinad A, Schweinhardt P, Seminowicz DA, Wood PB, Chizh BA, Bushnell MC. Accelerated brain gray matter loss in fibromyalgia patients: premature aging of the brain J Neuroscience. 27: 4004-4007.
7. Williams DA, Gracely RH. Biology and therapy of fibromyalgia. Functional magnetic resonance imaging findings in fibromyalgia. Arthritis Res Ther. 2006; 8:224.
8. Gupta A, Silman AJ. Psychological stress and fibromyalgia: a review of the evidence suggesting a neuroendocrine link. Arthritis Res Ther. 2004; 6: 98-106.
9 Russell IJ. Is fibromyalgia a distinct clinical entity? The clinical investigator's evidence. Best Practice & Res Clin Rheum.1999; 13: 445-454.
10. Russell IJ, Alarcón, GS, Bradley LA. Advances in fibromyalgia: possible role for central neurochemicals. Am J Med Sci. 1998; 315: 377-384.
11. Jaschko G, Hepp U, Berkhoff M, Schmet M, Michel BA, Gay S, et al. Serum serotonin levels are not useful in diagnosing fibromyalgia. Ann Rheum Dis. 2007; 66:1267-1268.
12. Rang HP, Dale MM, Ritter JM, Flower RJ. Amino acid transmitters. In: Rang and Dale's Pharmacology. 2007; Churchill Livingstone: Sixth Edition, 479-491.
13. Roskell NS, Beard SM, Yang Z, Kim Le T. A Meta-Analysis of Pain Response in the Treatment of Fibromyalgia. Pain Practice. 2011; 11: 516-527.
14. Nishishinya B, Urrutia G, Walitt B, Rodrigues A, Bonfill X, Alegre C et al. Amitriptyline in the treatment of fibromyalgia: a systematic review of its efficacy. Rheumatology. 2008; 47: 1741-1746.
15. Bair MJ, Robinson RL, Katon W, Konekes K. Depression and pain comorbidity: a literature review. Arch Int Med. 2003;163: 2433-2445.
16. Dunne FJ. Depression and pain. Is there a common pathway? Br J Med Practitioners.org 2011;4(1)a411.
17. Carville SF, Arendt-Nielsen Bliddal SH et al. EULAR evidence-based recommendations for the management of fibromyalgia syndrome. Ann Rheum Dis. 2008; 67: 536-541.
18 Arnold LM. Review: new therapies in fibromyalgia. Arthritis Res Ther. 2006; 8(4):212.
19. Nihalani ND, Schwartz T, Chlebowski S. Fibromyalgia—A review for the psychiatrist. Psychiatry.2006; 3: 44–60.
20. Lee YC, Nassikas NJ, Clauw DJ. The role of the central nervous system in the generation and maintenance of chronic pain in rheumatoid arthritis, osteoarthritis and fibromyalgia. Arthritis Res Ther, 2011;13:211.