

Advances in fibromyalgia treatment: understanding endogenous pain modulation

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Fibromyalgia (FM) is a multisymptomatic pain syndrome that is characterized by widespread pain, tenderness, fatigue and disturbed sleep. The classification of FM is based on the presence of widespread pain for more than 3 months and a generalized allodynia to pressure (assessed by a standardized palpation of so-called tender points) [1]. Thus, the classification of FM relies entirely on the patient's subjective report of pain and tenderness and this has raised a lot of controversy. FM has been described in terms of a 'virtual disease', medicalizing ordinary psychosocial problems resulting in unwarranted economical burdens to society [2]. By contrast, the advocates of FM have stressed that there is convincing evidence of an objectively verifiable dysfunction of central pain processing [3], and that although FM is associated with depressive and anxiety symptoms [4], these comorbidities only affect a minority of FM patients [5]. Furthermore, recent studies have demonstrated a reduction in healthcare costs following the diagnosis of FM [6,7].

The pain associated with FM is continuous, with few pain-free intervals [8]. It is mainly muscular and is exacerbated during and following physical activity [9]. Muscle ischemia [10], possibly caused by a deficient regulation of muscle blood flow during physical activity [11], could form the basis of peripheral sensitization in FM. Dysregulation of the autonomic nervous system – increased sympathetic activity at baseline and hyporeactivity during exercise and stress [12,13] – could contribute to muscle ischemia as well as to the exercise intolerance. Increased afferent input from sensitized muscle nociceptors has been suggested to initiate and maintain the central dysfunction, that is, pain amplification, in FM patients [14].

The notion of FM as a pain amplification syndrome dates back to Smythe in 1979 [15] and was later supported by findings of generalized, multimodal allodynia and hyperalgesia [16] and a dysfunction of endogenous pain inhibitory mechanisms [17,18]. This view has

recently gained objective support from imaging studies demonstrating enhanced transmission and/or processing of nociceptive input in FM patients [19,20]. In addition, aberrant concentrations of transmitter substances implicated in pain regulation – decreased levels of serotonin, noradrenalin and dopamine [21] and elevated concentrations of substance P [22], glutamate, nerve growth factor and brain-derived neurotrophic factor (BDNF) [23] – have been found in the cerebrospinal fluid of FM patients, which is in accordance with a CNS dysfunction in FM.

Although the controversies regarding FM have been said to also extend into the field of FM treatment [24], this is not evident. Currently, there are two evidence-based guidelines regarding the management of FM that are published in English, those of the American Pain Society (APS) [25] and those of the European League Against Rheumatism (EULAR) [26]. Both guidelines stress the importance of a multidisciplinary approach to FM treatment using a combination of nonpharmacological (mainly physical exercise and cognitive behavioral therapy [CBT]) and pharmacological modalities. They differ in that the APS criteria assign strong evidence to cardiovascular exercise, CBT and amitriptylin, but only modest evidence to serotonin-noradrenaline-reuptake inhibitors (SNRIs) and pregabalin, while the EULAR guidelines assign strong evidence to pharmacological treatments (including amitriptylin, SNRIs and pregabalin) but only weak evidence to exercise and CBT. The differences are likely to be explained by the fact the EULAR guidelines are only based on controlled trials whereas the APS guidelines also take meta-analysis and uncontrolled trials into account. Furthermore, although the authors of the APS guidelines foresaw the likelihood of a US FDA approval of pharmacotherapy for FM, the guidelines were published before such approval and before the publication of some major pharmacotherapy FM trials.



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The mechanisms of action of the non-pharmacological treatments, exercise and CBT are not well understood. Exercise has been demonstrated to improve muscle blood flow [27] and to permit more intensive physical activity during the same level of sympathetic nervous system activation in healthy subjects [28]. Furthermore, pain inhibitory mechanisms are normally activated during exercise [29,30]; however, these have been demonstrated to be dysfunctional in FM patients [31,32]. Prospective studies are needed to establish whether exercise can normalize muscle blood flow, autonomic tone and/or endogenous pain modulation in FM patients. The pain-relieving mechanisms of CBT are not known in sufficient detail to permit further discussion, although studies in FM patients are underway.

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Several drugs have been demonstrated to have beneficial effects on pain in FM: tramadol [33–35], amitriptylin [36], duloxetine [37–39], milnacipran [40–43], pregabalin [44–48] and gabapentin [49]. Currently, three drugs are approved for the treatment of FM in the USA (and also in some non-European countries) – the SNRIs duloxetine and milnacipran and the anti-convulsant pregabalin. Importantly, the pain relieving effect of SNRIs [38,39] and pregabalin [45] in FM has been demonstrated to be independent of the baseline levels of depression/anxiety as well as the degree of improvement of mood during treatment. Therefore, the pain relieving effects of these drugs are not mediated by improvements in mood.

Tricyclic antidepressants and SNRIs possess analgesic [50–53] and sympathomimetic [54] effects. Therefore, their pain relieving effects in FM could be mediated by a reduction in the afferent input from muscle nociceptors, either as a result of a direct antinociceptive effect and/or through normalizing autonomic tone during exercise with beneficial effects on muscle blood flow. However, although antidepressants have some peripheral analgesic actions [55], their pain relieving effect is likely to be predominantly mediated through the strengthening of serotonergic and noradrenergic endogenous pain inhibitory mechanisms [56]. Recently, we were able to

identify a failure of FM patients to activate the primary link in the descending pain regulating system (i.e., the rostral anterior cingulate cortex) during pressure pain stimulation [20]. Using the same painful pressure stimulation, we found that the sensitivity to pressure pain decreased selectively in FM patients who responded favorably to treatment with milnacipran, as opposed to placebo responders and milnacipran non-responders [57]. The results indicated that the effect of milnacipran was mediated by an analgesic effect, resulting in decreased sensitivity to stimulus-induced pain, either by direct antinociceptive effects and/or by the strengthening of the endogenous pain inhibitory mechanisms. We further addressed this question by assessing the FM patients before and following milnacipran treatment using the same randomized pressure pain stimuli and investigated pain-related cerebral activity with functional MRI. We found that milnacipran treatment increased the activity in brain areas involved in pain modulation [58], which is supportive of a central analgesic effect of milnacipran in FM.

The exact mode of action of pregabalin has not been elucidated. However, it is known that the drug acts at the $\alpha 2\delta$ -subunit of the pre-synaptic, voltage-dependent calcium channels in the central and peripheral nervous system [59]. Pregabalin binds to the $\alpha 2\delta$ subunit and modulates calcium influx at nerve terminals, thereby reducing the release of several neurotransmitters, including glutamate and substance P [59]. The $\alpha 2\delta$ subunits are implicated in hypersensitivity [60] and are upregulated in the dorsal root ganglia and the dorsal horn of the spinal cord in animals with central sensitization [61,62]. The $\alpha 2\delta$ -subunits have been demonstrated to have a minimal effect on physiological transmitter release, but they significantly inhibit release in sensitized neurons [62]. Pregabalin has been demonstrated to suppress allodynia and ectopic discharges [63]. Central sensitization has been suggested in FM based on the presence of generalized allodynia/hyperalgesia [16], increased temporal summation [64,65] and the reduced threshold to elicit the spinal nociceptive flexion reflex [66]. Therefore, it is likely that the pain relieving effects of pregabalin and gabapentin in FM are, at least partially, mediated through inhibition of the sensitized nociceptive pathways.

In recent years, it has become evident that not only neurons, but also activated glia cells are implicated in chronic pain, and that neuron–glia interactions are important for the development of central sensitization and hyperalgesia [67,68].

Glia cells can be activated by nociceptive pathways through the release of substances such as glutamate, substance P and BDNF from presynaptic terminals. In addition to their effects on postsynaptic neuronal receptors, these substances also act on receptors located on microglia and astrocytes, activating glia cells [68]. An alternative way to activate glia is by blood-borne pro-inflammatory cytokines released from peripheral immune cells [69]. Activated glia cells release various substances, such as proinflammatory cytokines (TNF- α , IL-1 β and IL-6), prostaglandins (PGE2), BDNF and glutamate, that have an excitatory effect on the neurons implicated in pain processing [67]. Glia cell activation has been suggested as a possible pathophysiological mechanism in FM [14,70] which is supported by findings of increased levels of proinflammatory cytokines [71,72] and reduced concentrations of anti-inflammatory cytokines in the blood of FM patients [73]. We are not aware of any studies directly assessing glia cell activation in FM patients. However, preliminary data from our laboratory indicate that there is an increased production of proinflammatory cytokines in the cerebrospinal fluid of FM patients, and this would be in accordance with glia cell activation. Further indirect support comes from a recently published pilot study demonstrating the beneficial effects of a low dose of naltrexone on pain and pain sensitivity in FM patients, since it is known that naltrexone can inhibit the activity of microglia and thus, reverse central inflammation [74]. From this perspective, it is important to note that antidepressants have been reported to have an inhibitory effect on glial activation [75,76]. Hypothetically, the inhibitory effect

of pregabalin and gabapentin on the presynaptic release of excitatory transmitter substances with glia-activating effects could also contribute to reduced central inflammation in FM.

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In conclusion, convincing evidence of a dysfunction of pain modulation has been presented in FM and treatments known to modify these mechanisms have pain-relieving effects. However, current treatments are only effective in a limited number of FM patients and this is most likely to be owing to the heterogeneous nature of FM. Mechanistic studies are needed to identify profiles of FM patients, characterizing likely responders with the various treatments. Furthermore, the mechanisms of action of nonpharmacological treatments need to be clarified.

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