

# Speculative trends in the future drug treatment of fibromyalgia

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Fibromyalgia is a common although ill understood condition, overlapping with several other diffuse conditions that might provide clues to its pathogenesis. Low-dose amitriptyline remains the mainstay of treatment, although other tricyclics appear to be effective, as do some other antidepressants in doses lower than those used for depression. Tramadol may have a specific place amongst analgesics. Hormonal factors may be important and drugs used in combination appear more effective than a single drug, particularly if they block different CNS transmitters. Physiotherapy might help, particularly if more applied and modest improvements have been claimed for a wide variety of other drugs. Amongst cytokines, interleukin-6 and -8 appear to be the most useful targets for drug action.

Fibromyalgia, a common condition affecting up to 4% of the population [1] and more common in women [2], was well described 150 years ago, but it has only recently gained acceptance as a discreet clinical condition. Box 1 shows the diagnostic features of fibromyalgia, although it will be noted that many of the characteristic features overlap considerably with other conditions. Prominent amongst these are irritable bowel syndrome and depression. More contentious is an association with chronic fatigue syndrome, migraine headache, irritable bladder and even Gulf War syndrome, should that condition exist. In the absence of signs of inflammation in the musculoskeletal system, there was a need for diagnostic features on clinical examination. The pioneering work of Smythe and Moldofsky led to the description of tender points at which pressure produced disproportionate pain [3]. Inevitably, it remains hard to quantify the degree of pressure (although a dolorimeter has been suggested as a means of doing this) [4] and it is also conceded that since the condition displays fluctuance, on any one day a variable number of pressure points will be affected; on some days hardly any.

The arguments for and against the existence of the condition as a discrete entity have once again recently been aired [5–8], arguably with a consensus that even if the pain is real, fibromyalgia may not be.

The onus remains on the clinician to exclude important diagnoses that might mimic the symptoms but for which quite separate and adequate treatment is available. These include hyperthyroidism, systemic lupus erythematosus, inflammatory myopathy, hypoparathyroidism, osteomalacia and, even occasionally, myeloma

and carcinomatosis amongst the most important. Once such diagnoses are excluded there remains a pool of patients in which the diagnosis of fibromyalgia needs to be considered. Discussion then centers on the distinction between 'true' fibromyalgia and regional myofascial pain syndromes (sometimes termed repetitive strain disorder). Myofascial pain syndrome is characterized by the aggravation of perceived pain by palpation of a trigger point deep within the muscle [9,10]. By contrast, fibromyalgia is felt to be defined by points that are specifically tender, defined as tender points, although the relationship between these two entities is controversial. Myofascial pain syndromes may be precipitated by ergonomic stress, such as that encountered in the workplace [11].

Psychological factors are also of importance. Some of us have concluded that fibromyalgia is a psychiatric illness [12]. Major depression has been found in up to 30% of patients and a degree of anxiety disorder in around 15% [13,14]. Others have failed to find a specific personality type and have argued that any psychiatric illness present is related to healthcare-seeking behavior [15]. Cynics have suggested that the unsolicited list of problems and symptoms, often annotated with pictures illustrating the site of the pain, clinches the diagnosis providing that it is at least two or three pages long.

This speculative article draws on personal experience of such patients, 20 years in clinical pharmacology associated with rheumatology and experience with other separate groups of patients that increasingly have seemed to resemble some aspects of fibromyalgia. These include patients seen, often for medico-legal purposes, under the banner 'repetitive strain' or 'over-use' syndrome,

**Keywords:** analgesics, combination therapy, cytokines, fibromyalgia, sympathetic nervous system, tricyclics

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**Box 1. Diagnostic features of fibromyalgia.**

Cardinal features

- Chronic widespread pain
- Widespread tender points on examination

Characteristic features

- Fatigue
- Sleep disturbances
- Stiffness
- Paraesthesiae
- Headaches
- Irritable bowel syndrome
- Raynaud's-like symptoms
- Depression
- Anxiety

*For the classification criteria, patients must have pain for at least 3 months involving the upper and lower body, right and left sides, as well as the axial skeleton and pain in at least 11 of 18 tender points on digital examination.*

patients with inherited joint hypermobility who seem particularly prone to symptoms similar to fibromyalgia and patients with mild variant complex regional pain syndrome type 1 (previously called reflex sympathetic dystrophy), which often presents after injury, as does the onset of fibromyalgia.

**Theories on pathogenesis**  
These are legion. Genetic factors might apply, however the evidence for primary muscular abnormalities, although well researched, remains extremely elusive. Genetics of fibromyalgia have focused on a possible link to human leukocyte antigen (HLA) [16], serotonergic candidates [17], dopamine receptors [18] and substance P receptors [19]. To date, genetic searches have focused on polymorphisms in genes related to neurotransmitters involved in pain transmission and processing, but other genetic mechanisms may become relevant.

A possible link may exist between fibromyalgia and an autonomic and/or CNS abnormality [20] (the skin hyper-reactivity, pain sensitivity and autostatic intolerance common to both conditions) and resulting discussion has centered on abnormal pain processes, perhaps with abnormal levels of substance P [21].

The psychological abnormality is invariably striking. Although this rarely conforms to classical psychiatric illness, only a proportion of patients with fibromyalgia display a major depression or anxiety disorder. This may be related to slow-wave sleep disruption, as first

suggested by Moldofsky [22]. However, the logical link that might follow, which would be of abnormal circadian rhythm even under neuro-endocrine control, has proved elusive, although recent evidence has pointed towards an altered response of the central stress axis [23]. Text-books frequently quote possible pathophysiological models of fibromyalgia, suggesting that precipitating factors might summate with putative pre-existing factors (not necessarily genetic) to produce pain, fatigue and depression manifested through skin hyper-reactivity and muscle imbalance. Local manifestation at the musculoskeletal system might feed back into the spinal cord with increased cutaneous and muscle nociception, possibly with resultant feedback of increased sympathetic outflow at the periphery. Centrally, this might lead to reduced serotonin and increased substance P or some of these features, allowing connection to ascending and descending pathways in the spinal cord, ultimately invoking the hypothalamus with the option of cortical involvement as the icing on the cake. Clearly, there are many points at which pharmacological intervention might occur.

**Overlap in classification**  
My own clinical experience has been striking for the way in which two separate groups of patients, specifically referred to me, often overlap with fibromyalgia.

First, patients with traumatic injury (often a road traffic accident), after the expected period of convalescence during which tissue damage resolves, continue to complain of those elements of fibromyalgia that most resemble reflex sympathetic dystrophy. Recent, careful epidemiological work has argued strongly against whiplash as a cause of persistent fibromyalgia in the population as a whole [24], but this would not necessarily exclude that progression in a small proportion of patients, perhaps just those who had sustained a specific type of whiplash. In turn, it might be that physiotherapy leading to joint stabilization could play a greater part in treatment.

Second, patients with inherited abnormalities of connective tissue manifested by hypermobility syndromes often develop localized symptoms reminiscent of fibromyalgia. This is already well recognized in the literature [25,26]. More precisely, these only occur when joints that are disproportionately supple compared with others are subjected to specific overuse. The classic example is the adolescent with a lax hand who only develops

symptoms when perhaps under slight stress, for example when having to write intensively to complete examination scripts at the end of the year. The severity of symptoms seems to correlate well with ergonomic stress, raising the possibility that physiotherapy in the form of joint protection, perhaps with attention to joint stability and even improvement in proprioception, might play a more important role than it does in the management of fibromyalgia. Certainly, this will escape side effects from drugs, especially when drugs are used in combination. Conventional physiotherapy includes low-impact exercises, group therapy, cognito-behavioral approaches and aerobic exercise. Perhaps some of these should be more refined and more specifically applied to the areas where the patient experiences particular pain.

#### Clues from epidemiology

A condition in which 75% of affected patients are female, in the absence of a firm genetic predisposition, surely suggests an influence of hormones, especially oestrogen and/or progestogen [27,28]. With a mean age of presentation as late as the fifth decade, perhaps it is the loss of these hormones with compensatory overdrive from the pituitary that represents the greater problem. Fatigue is consistently associated [29], which might argue for a cytokine end point since the blockade of tumor necrosis factor (TNF)- $\alpha$  in rheumatoid arthritis seems to be particularly effective in relieving the fatigue of this condition, although this link remains tenuous.

The putative epidemiological association with depression [30] is more contentious and, as in arguments around the sleep disturbance, it is uncertain whether the depression might follow the fibromyalgia or might be the primary event. If a consensus of opinion is against the latter, a recent study on the impact of fibromyalgia on healthcare use in the UK confirms that 81.3% of 2260 patients were female with a mean age of 49 years and that these patients had records of higher rates of illness and healthcare use in the 10 years preceding the fibromyalgia diagnosis than an age-matched control group [31]. The authors conclude that illness behavior may yet be playing a part. Benefit has also been claimed for hypnotherapy and homeopathy, perhaps lending this some support.

#### Antidepressants

Tricyclics, notably amitriptyline [31], are normally held to play a specific role in the management of this condition and have been studied

more than any other class of medication. The fact that benefit can be shown at doses lower than those used when these drugs are prescribed for depression is quoted in support of the argument that these patients are not clinically depressed. Many develop side effects from amitriptyline, even at very low doses. It seems unlikely that there is a specific abnormality of drug metabolism in this condition, raising the possibility of increased sensitivity at the end organ, the symptoms of side effects often typical of those manifested through the autonomic nervous system. Dosulepin (dothiepin) also has proven efficacy [32], perhaps not as good as amitriptyline but with less of a propensity to side effects. Cyclobenzaprine is available in the USA but not in Europe. Perhaps these drugs are affecting neurogenic amines in the brain.

Claims for efficacy have also been made for serotonin-uptake inhibitors [33], including fluoxetine, paroxetine and sertraline.

An important clue comes from the enhanced benefit when low doses of these drugs are used in combination, implying that more than one neurotransmitter may be involved and that both need to be blocked simultaneously [34,35]. Venlafaxine is efficacious [36]; this drug inhibits serotonin and noradrenaline uptake. When drugs are used in combination (notably amitriptyline as a tricyclic with fluoxetine as a selective serotonin-reuptake inhibitor) the benefit is enhanced, and there have been recent claims for benefit from troisetron [37], a serotonin antagonist.

Intriguingly, monoamine-oxidase inhibitors, also effective in depression, are not of value in fibromyalgia [38].

#### Analgesics

There would not seem to be a rational place for the analgesic effect provided by anti-inflammatory drugs. Most investigators agree with this, presumably because there is no inflammation to block. Paracetamol, as the weakest and safest analgesic and available over-the-counter in many countries, tends to be ineffective. UK practice allows access to compound generic analgesics, of which co-codamol (paracetamol with codeine) and co-dydramol (paracetamol with dihydrocodeine) can still be prescribed. Co-proxamol (a low dose of dextropropoxyphene with paracetamol) is in the process of being withdrawn in the UK, partly due to concern over the difference in half-life between the two components and partly because of the

increased fatalities that occurred when this, rather than other drugs, was the choice of a suicidal overdose. Withdrawal of this drug and the subsequent substitution of other analgesics effectively created an informal controlled situation and many patients with fibromyalgia attested to the benefit they gained from it, which was not replicated by the alternative use of co-codamol or co-dydramol. Perhaps the euphoric lift provided by dextropropoxyphene, less marked with codeine or dihydrocodeine, was what was needed [39]. One of our earlier studies had demonstrated the convincing analgesic effect of diethylpropion, an appetite suppressant with CNS-stimulating properties not seen with fenfluramine, an appetite suppressant with depressive properties, when used for painful joints, supporting the desirability of a euphoric lift [40].

Specific claims have been made for tramadol that, as a weak opioid agonist, inhibits the re-uptake of both serotonin and noradrenaline at the level of the dorsal horns [41]. Stronger opioids are rarely prescribed because of concern regarding addiction, although ketamine, which blocks the *N*-methyl-D-aspartate receptor, has also been demonstrated to acutely relieve pain for fibromyalgia.

#### The contenders

These represent the most conventional and proven approaches, although a wide variety of alternatives have been suggested for a number of reasons.

Manipulation of the sympathetic nervous system has perhaps been displayed, but the evidence is contradictory [42,43], thus intravenous guanethidine reduced the distribution of the condition (number of tender points) but did not improve pain. By contrast, complete stellate ganglion blockade using anaesthetic improved both pain and the number of tender points. This would be unrealistic for generalized fibromyalgia but might be considered when the condition was convincingly localized. Benefit from local anaesthetic seems to derive either from the site of their action (the stellate ganglion) or from their use in combination (e.g., lidocaine with ketamine [44]) rather than from a specific individual effect.

$\gamma$ -hydroxybutyrate, an active metabolite in the human CNS, is thought to aid sleep. When administered in fibromyalgia it produces significant improvement in fatigue and pain associated with an increase in slow-wave sleep and a

reduction in the severity of the  $\alpha$ -sleep anomaly [45]. Melatonin is also thought to be a hormone with an effect on sleep control and a small open study has suggested benefit, presumably through a neuroendocrinological pathway, with the need to proceed to double-blind studies [46]. By analogy with antidepressants, the combination of these two mediators might be even more effective.

Pregabalin has been introduced for the control of neuropathic pain, where it gives proven benefit. Empirically, it was logical to evaluate it in fibromyalgia where it seemed to be effective at a dose of 450 mg/day [47]. Other drugs are in development for the management of neuropathic pain that may also play a role in fibromyalgia. One of these is capsaicin, unashamedly a topically applied counterirritant rather than a drug, which is thought to have specific effects on the nerve cells, although this appears to be less effective, despite reducing muscle tenderness [48], and this drug has not been further developed for this indication.

Cytokine blockade inevitably merits consideration in an era of biologic agents, although this remains speculative in this condition. Recent studies have strongly suggested that cytokines might have a role in the pathogenesis of fibromyalgia, a finding that was not previously suspected, with interleukin (IL)-6 and perhaps IL-8 the most relevant.

IL-6 is capable of blocking hypothalamic corticotrophin release and, when administered to patients with fibromyalgia, it produces higher noradrenalin levels than in controls [49]. That it might have a specific pathogenetic role in fibromyalgia is supported by its ability to increase the heart rate in this condition more than in age-matched controls. In turn, the specific blocker IL-6 might be beneficial. Biologic blockers, although specific, would be expensive. Some drugs that never reach the market place (e.g., tenidap) have also had less specific effects and added action in blocking IL-6. A return to analogs of this type might provide a cheaper alternative.

IL-8 is also recognised as a mediator of sympathetic pain and so would naturally come under scrutiny in fibromyalgia. Endogenous levels of IL-8 in patients with fibromyalgia are higher than in controls but a rise in IL-6 is not so marked [50]. This might remain an exciting, although more expensive, option in treating fibromyalgia at its most fundamental level.

### Future perspective

With genetic, neuroendocrine, neurotransmitter and cytokine pathogenetic links already reasonably established, it seems unlikely that the next 5–10 years will identify further quite separate pathogenetic mechanisms. There is more than enough to warrant study here and it is probable that therapy simultaneously directed to more than one mechanism may be more effective than therapy directed at a single mechanism. Indeed, fibromyalgia may be a collection of different conditions masquerading under the same name.

In spite of a familial association, genetic manipulation seems unrealistic in the next decade. The cytokine drive is clearly of topical interest, given the increasing number of drugs

available to manipulate cytokines but those so far incriminated are relatively lowly and nonspecific in the pathogenetic cascade. Even if the prime cause of the cytokines were identified, the expense of treating this is likely to be prohibitive for such a common condition.

Therefore, management may be better directed towards chemical mediators. Neurotransmitters offer the easiest solution and further clinical benefits may accrue from blocking more than one transmitter simultaneously. Manipulation of the pituitary–adrenal axis is also quite feasible and relatively inexpensive but this option is arguably less specific, perhaps inducing compensatory hormonal change for a condition that itself may be aggravated by incorrect hormonal balance.

### Executive summary

- Fibromyalgia is a common although ill understood condition.
- Although diagnostic criteria exist, there is probably some substantial overlap with other conditions.
- The chance that fibromyalgia may therefore be more than one discrete condition opens up the possibilities for novel drug treatment.
- Tricyclic antidepressants provide specific benefits, and analogs without side effects would be of value.
- There is clear evidence that very low doses of antidepressants, when used in combination, enhance benefit, providing they each block a separate transmitter.
- Psychoactive drugs blocking more than one transmitter may therefore provide added value.
- Some analgesics (such as tramadol) appear to have specific activity, offering further clues to their mechanism of action.
- In addition to analgesics, up to 20 different drugs from a variety of backgrounds have shown efficacy in small, sometimes controlled, trials.
- Manipulation of the sympathetic nervous system, hormones effective in altering sleep and drugs effective in the control of neuropathic pain all have advocates.
- Cytokine blockade is attracting interest; current evidence suggests that manipulation of interleukin -6 and, possibly -8, could have therapeutic potential.

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