Fibromyalgia syndrome: An approach to pathogenesis, current and novel treatments

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Abstract
Introduction
Understanding the pathophysiology of fibromyalgia and therefore the establishment of effective treatments have been complex arguments. This review discusses ideas that have become accepted as well as novel associations under consideration regarding the pathogenesis of fibromyalgia and the current and emerging therapeutics for its treatment.

Conclusion
The findings of recent studies related with central pain processing, genetic abnormalities, and external factors have led to the use of new therapies that have shown beneficial effects on symptoms.

Introduction
Fibromyalgia is a syndrome characterized by chronic, widespread pain in combination with tenderness to palpation at specific tender point sites on the body, in the absence of otherwise apparent organic disease. It is a chronic manifestation of diffuse musculoskeletal pain that is more commonly encountered in women (9:1 female: male ratio) and is present in all ethnic groups, climates and cultures. Despite the high prevalence of fibromyalgia (approximately 2% of the population and 3.4% of females in the United States) as well as the increasing public awareness and the United States) as well as the increasing public awareness and physician acceptance of the syndrome, understanding its clinic, pathophysiology and finding effective treatments continues to be a complex endeavor.

The introduction of the American College of Rheumatology fibromyalgia classification criteria 20 years ago heralded two decades of professional acceptance and enhanced interdisciplinary research in the pathogenesis and therapy of fibromyalgia.

Whereas the initial criteria included tenderness on pressure (tender points) in at least 11 of 18 defined anatomic sites with the presence of widespread pain, in the 2010 set of proposed criteria it is clear that apart from the pain other seminal features of the disorder – namely cognitive dysfunction, unrefreshing sleep, fatigue and mood disorders – play an important role in the diagnosis. These symptoms are leading to limitations in vocational tasks in patients with fibromyalgia so; understanding the clinic presentation, resulting functional disability and the establishment of effective and new treatments are very important.

In the following paper we will review discussion about ideas that have become accepted as well as novel associations under consideration in regard to the pathogenesis of fibromyalgia and the current and emerging therapeutics for its treatment.

Discussion
Pathogenetic aspects of fibromyalgia
Until now, many advances have been made in unravelling its pathogenesis. Firstly, a deficiency of serotonin and a surplus of substance P have been recorded in the cerebrospinal fluid of patients with fibromyalgia.

Serotonin deficiency may be related to the altered sleep patterns, especially during stage 4 sleep (deep sleep), on the other hand, a surfeit of substance P, a brain and spinal cord neuropeptide released from the terminals of specific sensory nerves, plays a role in pain signalling, integration and modulation, suggesting that fibromyalgia patients have an enhanced sensitivity to pain.

In addition, central sensitization is another mechanism to explain this increased perception of pain in fibromyalgia patients. This pathway involves triggering an N-Methyl-D-aspartate (NMDA) receptor, which is thought to be involved in this abnormal temporal summation of pain stimuli.

Muscular pathology has also been implicated in the pathophysiology of tender points in the fibromyalgia syndrome. Decreased growth hormone concentration, which is essential for muscle function, may explain the extended muscle pain seen after exercise in fibromyalgia patients.

It is currently recognized that familial aggregation is often encountered in fibromyalgia. Several candidate genes have been suggested to mediate this association. Early research into the genetic basis of fibromyalgia was directed towards the possibility of linkage to human leukocyte antigens. Burda and collaborators reported that the HLA1 DR4 antigen was detected in 64% of patients with fibromyalgia versus 30% of healthy controls. Several teams observed a higher frequency of the S/S genotype of the serotonin transporter gene (5-HTT) promoter region in fibromyalgia patients compared to healthy controls.

Some studies show that infections also such as hepatitis B virus, hepatitis C virus, human immunodeficiency virus and Lyme disease triggered fibromyalgia.

Past history of negative life events has often been described among patients with fibromyalgia, and increased rates of post-traumatic stress disorder associated with childhood abuse, trauma or anxiety have been reported.

Recently, increasing attention has been given to novel factors that have not classically been thought to play a...
role in the development of fibromyalgia. While several associations have been suggested among these factors, their role in the pathophysiology of disease has yet to be clarified.

Brain-derived neurotrophic factor (BDNF) is involved in neuronal survival and synaptic plasticity of the central and peripheral nervous system, and it appears to modulate nociceptive sensory inputs and pain hypersensitivity. Increased serum BDNF levels have been recently reported in fibromyalgia, suggesting an involvement in the syndrome.15

Serum ferritin levels were found to be significantly lower in FMS patients, perhaps due to the role of iron as a cofactor in enzymes involved in neurotransmitter synthesis.17 Levels of magnesium and zinc were also found to be decreased in 32 FMS patients (selenium was not). Association between serum zinc level and number of tender points and between fatigue and magnesium level was also found to be meaningful.18 Serum IL-8 levels were elevated in fibromyalgia patients as well, and these levels were reduced to near normal levels within 6 months after brief inpatient multidisciplinary pain therapy.19

The role of oxidative stress in the pathophysiology of fibromyalgia also has been studied, and Cordero and colleagues evaluated mitochondrial function in affected patients by examining their blood mononuclear cells. They noted reduced levels of coenzyme Q10, decreased mitochondrial membrane potential, increased levels of mitochondrial superoxide, and increased lipid peroxidation, as well as increased autophagy and mitophagy. These findings may support the role of oxidative stress and mitophagy in FMS.

While studies attempting to localize the pathology in FMS to peripheral tissues have failed in showing any abnormalities in muscle tissue, Staud and coworkers did show that enhanced central pain processing can occur via continued peripheral muscle afferent input.21,22 Their study demonstrated that muscle lidocaine injections increased local pain thresholds and decreased remote secondary heat hyperalgesia in fibromyalgia patients, emphasizing the important role of peripheral impulse input in maintaining central sensitization.

**Treatments**

Given the unclear aetiology of fibromyalgia, and the heterogeneous presentations of the disease, it has become clear that no one therapy is broadly efficacious.

Besides non-steroidal anti-inflammatory drugs and opioids, antidepressants are the most frequently used drugs by FMS patients.23 Antidepressants have been recommended by evidence-based guidelines for the treatment of fibromyalgia.23 In terms of pharmacologic treatments, the tricyclic antidepressants (TCAs) were the initial drugs studied for fibromyalgia.

Several trials have shown short-term improvement in pain and sleep, but long-term studies have not been as efficacious.23,24 Adverse reactions that may limit effectiveness include fatigue, sedation, cognitive difficulties, dry mouth, and cardiac arrhythmias, although agents such as nortriptyline may have better side effect profiles at higher doses than the traditional drug used, amitriptyline.24

Monoamine oxidase inhibitors (MAOIs), noradrenaline reuptake inhibitors (NRIs) and selective serotonin reuptake inhibitors (SSRIs) are not approved for FMS in Europe.23 The serotonin noradrenaline inhibitors (SNRIs) duloxetine and milnacipran have been approved by the US FDA for FMS.23 For selective serotonin reuptake inhibitors (SSRIs), studies have shown that fluoxetine can be as effective as amitriptyline, with the two in combination having greater efficacy than either alone.25

One trial using higher doses of fluoxetine demonstrated a reduction in pain regardless of effect on depression.25 Other SSRIs, although regularly used in practice, have not been studied effectively for FMS. Serotonin-norepinephrine reuptake inhibitors (SNRIs, or dual-reuptake inhibitors) may have greater antinociceptive properties than pure SSRIs. Arnold and associates pooled four placebo-controlled trials using duloxetine in FMS patients, assembling 797 patients receiving treatment and 535 controls; patients were followed after a 12-week treatment period. Pain was significantly reduced in treated patients, and improvements were also noted on depression and global functioning scales.26 Milnacipran is an SNRI that is somewhat selective for norepinephrine reuptake inhibition. U.S. and European studies have shown its effectiveness over placebo in pain reduction after 1 week, as well as with pain, fatigue, and cognition at 15 weeks, and with overall response (including use of the Fibromyalgia Impact Questionnaire (FIQ) total score) of FMS at 3 months.27 Patients continuing on milnacipran demonstrated a durable efficacy in pain reduction and FIQ over a 12-month period. The medication appears to be well tolerated, with headache and nausea as the most common adverse effects. On functional MRI studies, milnacipran treated patients exhibited a reduction in pain sensitivity and a parallel increase in activity in brain regions implicated in the descending pain inhibitory pathways, compared to placebo-treated patients.28 Duloxetine became the second drug approved for the treatment of fibromyalgia in 2007, and milnacipran became the third in 2009. According to recent quantitative analysis (meta-analysis) providing the efficacy and harms of antidepressants in the management, although the TCA amitriptyline and the SNRIs duloxetine and milnacipran were first-line options, physicians and patients were advised to be realistic about the potential benefits of antidepressants in FMS.

Because, although a small number of patients experience a substantial symptom relief with no or minor adverse effects, a remarkable number of patients dropped-out of therapy because of intolerable adverse effects or experience only a small relief of symptoms, which did not outweigh the adverse effects.23 Additionally they...
concluded that amitriptyline should be preferred for co-morbid sleep disturbances and duloxetine for co-morbid major depression. In addition, the importance of potential adverse effects to the patient (e.g. sexual dysfunction by SSRI, weight gain by TCAs) and contraindications (e.g. SNRIs in case of severe liver damage) should be considered.

Also, the costs (amitriptyline is available as a generic and is cheaper than duloxetine and milnacipran) and local availability may be an important issue to consider. Therefore, if antidepressants are considered for FMS therapy, shared decision making of patients and physicians has been recommended and the choice of drug should depend on which symptoms of FMS should be targeted by the drug and on the potential of the drug to reduce the symptoms.

Pregabalin was the first medication the FDA approved for fibromyalgia, after the drug was initially approved for diabetic neuropathy and post-herpetic neuralgia. According to the results of a double-blind placebo-controlled trial, significant reductions in pain score, as well as decreased fatigue, improved sleep, and health-related quality of life. Over 6 months, pregabalin retained its effectiveness in responders, compared to those who went off the drug. Side effects include dizziness, somnolence, and weight gain. It was reported that in the literature, pregabalin may reduce pain in some patients with fibromyalgia.

However, the presenting symptoms can vary significantly, and symptoms can vary even in individual patients over time. They concluded that there was some relief but did not have a cure. Gabapentin is another centrally acting agent that is approved for multiple neurologic diseases. In a 12-week randomized controlled trial (RCT), gabapentin was more effective than the placebo in improving pain scores, sleep quality, and FIQ scores at an average dose of 1800 mg per day. The most common side effects were dizziness, sedation, and light headedness. Although commonly prescribed, there is little objective evidence to assess the efficacy of non-steroidal anti-inflammatory drugs (NSAIDs). And also for opioids, there are no short- or long-term data available to inform the use of pure opiates in fibromyalgia, but there have been some studies to support the use of the mixed opiate tramadol.

FMS should not be treated by drugs alone. The efficacy of aerobic exercise, balneotherapy and multicomponent therapy (combination of physical exercise with psychological therapy) to relieve FMS symptoms has been demonstrated by systematic reviews. These non-pharmacological treatment options are safe and well tolerated, and are alternatives or combination options to drug therapy.

A review by Goldenberg and colleagues suggested strong evidence for efficacy of several interventions, including cardiovascular exercise, cognitive behavioural therapy, and patient education.

However, two other reviews shed light on the fact that most studies of these interventions are of questionable quality, and no meaningful conclusions could be derived from them. Nevertheless, these investigators felt that combination approaches had better outcomes than single interventions.

Several novel therapeutics have been looked at lately as potential future therapies for fibromyalgia. Skrabek and coworkers performed the first RCT to assess the benefit in FMS of nablin, a synthetic cannabinoid, and found significant increases in pain, FIQ score, and anxiety (but not the number of tender points) in 40 patients over a 4-week period. Sodium oxybate, the sodium salt of a metabolite of gamma-aminobutyric acid, was found to help FMS symptoms during its open-label trial for patients with narcolepsy. An 8-week RCT resulted in beneficial responses in composite pain, FIQ, and global health scores, as well as subjective sleep outcomes in 124 patients. Naltrexone, in addition to antagonizing opioid receptors on neurons, also inhibits microglia activation. It is proposed that this mechanism may explain the improvements in fibromyalgia symptoms in a recent pilot study of 10 patients treated with the medication.

Conclusion

The findings of recent studies related with central pain processing, genetic abnormalities, and external factors have led to the use of new therapies that have shown beneficial effects on symptoms.

References


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Review