



FIBROMYALGIA: PRESENT AND FUTURE! WHERE WE STAND

Anaesthesiology

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ABSTRACT

Fibromyalgia typically presents in young or middle-aged females as persistent widespread pain, stiffness, fatigue, disrupted unrefreshing sleep, and cognitive difficulties, often accompanied by multiple other unexplained symptoms, anxiety and/or depression, and functional impairment of daily living activities. Management of Fibromyalgia at the present time is very difficult as it has multiple etiological factors and psychological predispositions; however, a patient centered approach is essential to handle this problem. Many adjunctive interventions have been implemented in fibromyalgia treatment, but few are supported by controlled trials. Only three drugs, pregabalin, duloxetine, and milnacipran are currently FDA-approved for Fibromyalgia treatment, but many other agents have been tested over the years, with varying efficacy.

KEYWORDS

INTRODUCTION

Pain with its devastating and demoralizing effects remains a challenging problem for both patients and care givers.[1] Fibromyalgia is one of the most common diseases affecting the muscles manifested with pain, stiffness, and tenderness of the muscles, tendons, and joints. The painful tissues involved are not accompanied by tissue inflammation.[2,3] Therefore, despite potentially disabling body pain; patients with fibromyalgia do not develop tissue damage or deformity.[4,5] Factors resulting from living with chronic pain (e.g., poor sleep, reduced physical activity, social withdrawal) are the very same factors that put one at risk for even greater physical pain. Patients with fibromyalgia (FM) bear the additional burden of battling long-held misconceptions that FM is a psychiatric illness. As with most chronic pain conditions, co-morbid mood and anxiety disorders commonly occur in FM (29% and 27%).

The pain of fibromyalgia is generally widespread, involving both sides of the body. Pain usually affects the neck, buttocks, shoulders, arms, the upper back, and the chest. "Tender points" are localized tender areas of the body that can bring on widespread pain and muscle spasm when touched.[6,7]

FMS typically presents in young or middle-aged females as persistent widespread pain, stiffness, fatigue, disrupted unrefreshing sleep, and cognitive difficulties, often accompanied by multiple other unexplained symptoms, anxiety and/or depression, and functional impairment of daily living activities.[8,9] There is an overall 6% to 15% prevalence rate in the United States with a five times greater incidence among women than men. In rheumatology clinics, the rate of new diagnosis is approximately 10% to 20%, whereas in non-specialized settings, the rate is 2.1% to 5.7%.[10,11]

Clinicians should be familiar with the signs and symptoms of fibromyalgia and diagnose the condition with minimum investigation.[12] Since the symptoms of fibromyalgia wax and wane related to stresses,[13] treatment (as with that of other chronic diseases) is an ongoing process rather than management of a single episode.

In terms of conditions associated with fibromyalgia; there are certain conditions associated with fibromyalgia.

Pathophysiology

Although the etiology remains unclear, characteristic alterations in the pattern of sleep and changes in neuroendocrine transmitters such as serotonin, substance P, growth hormone and cortisol suggest that regulation of the autonomic and neuro-endocrine system appears to be

the basis of the syndrome. Fibromyalgia is not a life-threatening, deforming, or progressive disease. Anxiety and depression are the most common association.[14] Aberrant pain processing, which can result in chronic pain, may be the result of several interplaying mechanisms. Central sensitization, blunting of inhibitory pain pathways and alterations in neurotransmitters lead to aberrant neurochemical processing of sensory signals in the CNS, thus lowering the threshold of pain and amplification of normal sensory signals causing constant pain.[15-18]

Assessment of Fibromyalgia

Although fibromyalgia is the most common chronic widespread pain condition, it is often under diagnosed. The diagnosis of fibromyalgia has been shown to increase patient satisfaction and reduce healthcare utilization.

The assessment of Fibromyalgia is based on the criteria for the Classification of Fibromyalgia by the American College of Rheumatology, (ACR) 1990.[19,21] The criterion involves:

- History of widespread pain has been present for at least three months.
- Pain in both sides of the body pain above and below the waist. Pain is considered widespread when all of the following are present:
- Pain in 11 of 18 tender point sites on digital palpation (both side of the body): Occiput (2) Low cervical (2), Trapezius (2), Supraspinatus (2), Second rib (2), Lateral epicondyle (2), Gluteal (2), Greater trochanter (2), Knee (2).

A tender point hurts only at the area where pressure (enough to cause the examiner's nail bed to blanch, or about 4 kg) is applied, and there is no referred pain. An instrument known as a dolorimeter can be used to apply exactly 4 kg of pressure over the tender points during the examination.[22]

New Diagnostic Criteria

Recently, ACR is proposing a new set of diagnostic criteria for fibromyalgia that includes common symptoms such as fatigue, sleep disturbances, and cognitive problems, as well as pain. The tender point test is being replaced with a widespread pain index and a symptom severity (SS) score. The new criteria appear in a one-page symptom checklist format that will hopefully be more suitable for use in the primary-care setting.[23]

A tender point evaluation is no longer required although a full physical exam is still recommended along with other diagnostic tests to identify causes for the patients' symptoms besides fibromyalgia. In place of the tender point count, patients (or their physician) may endorse 19 body

regions in which pain has been experienced during the past week. One point is given for each area, so the score is between 0-19. This number is referred to as the Widespread Pain Index (WPI) and it is one of the two required scores needed for a doctor to make a diagnosis of fibromyalgia.

The second part of the score required to assess the diagnosis of fibromyalgia involves the evaluation of a person's symptoms. The patient ranks specific symptoms on a scale of 0-3. These symptoms include: Fatigue, Waking unrefreshed, Cognitive symptoms, Somatic (physical) symptoms in general (such as headache, weakness, bowel problems, nausea, dizziness, numbness/tingling, hair loss). The numbers assigned to each are added up, for a total of 0-12.

The diagnosis is based on both the WPI score and the SS score either:

- WPI of at least 7 and SS scale score of at least 5, **OR**
- WPI of 3-6 and SS scale score of at least 9.

Laboratory Investigations

Laboratory testing, such as complete blood count, erythrocyte sedimentation rate, rheumatoid factor, antinuclear antibody, thyroid-stimulating hormone, T3, T4, creatinine phosphokinase, a serum muscle enzyme, vitamin D, ESR, CRP, renal function, and liver function tests are necessary to rule out other disorders. X-rays, blood tests, specialized scans such as nuclear medicine and CT scan muscle biopsy are normal in cases of fibromyalgia.

FM/A Blood

The FM/a Test is a blood test used for the diagnosis of fibromyalgia. It is available for use in patients of any age who have at least four of the typical symptoms of fibromyalgia. The FM/a Test is a cytokine assay of in vitro stimulated peripheral blood mononuclear cells. Production of cytokines by stimulated immune cells in patients with fibromyalgia has been shown to be significantly different from that of healthy control patients. Based on the concentrations of four cytokines, a cytokine/chemokine composite score, calculated as $1 / (1 + e^{-x}) * 100$, on a scale of 0 to 100 was developed. A score greater than 50 is considered positive for fibromyalgia. [24]

Management of Fibromyalgia

By the time many fibromyalgia patients reach the primary care setting or practice, they may have been seen by multiple healthcare providers. Patients are often frustrated or discouraged after receiving inadequate answers or diagnosis of their chronic ailments. Many are relieved to learn that there is an actual diagnosis and possible treatment options for their symptoms. [25-26]

Patients should participate in developing and initiating a care plan. Being a participant in their care will help the patient to assume control of their lives and focus on positive lifestyle changes rather than on chronic dysfunction. Patients must try to avoid exacerbating factors and limit anxiety and stress. [27-28]

A great majority of FMS patients can be managed well by Family Physicians in ambulatory care by managing stress, depression, pain and life style modification. [29] CNS agents, antidepressants, muscle relaxants, or anticonvulsants are the most successful pharmacotherapies.

Therapeutic Measures In FMS

Medications have a limited role in FMS treatment to limit symptoms, so patients can participate in non-pharmacologic modalities that provide long-term disease management such as exercise, behavioral and education. Non pharmacologic therapies should be used when possible. [30]

Pharmacotherapeutic Agents Used for FMS.

Only three drugs, pregabalin, duloxetine, and milnacipran, have been approved for use in the treatment of FMS by the FDA.

Tricyclic Antidepressants (TCAs)

It is recommended by all various clinical practice guidelines. Different TCAs have been used in the treatment of chronic pain, the largest body of evidence on therapeutic utility in FMS exists regarding amitriptyline. [31-33].

Serotonin-Noradrenaline Reuptake Inhibitors (SNRIs)

Various clinical trials published evaluating duloxetine showed a

significant improvement in FMS-associated pain and depressive symptoms [34]. The vast majority of clinical trials evaluating milnacipran have shown a significant improvement in pain levels, in addition to fatigue.

Selective noradrenaline reuptake inhibitors (NRIs), such as reboxetine and its enantiomer esreboxetine, were also suggested as possible treatments for FMS, while the body of evidence regarding the efficacy of reboxetine is rather sporadic and is based mostly on case reports [35], esreboxetine was shown to reduce pain, fatigue, and improve overall quality of life in a randomized, double-blind, placebo-controlled trial [36].

Selective Serotonin Reuptake Inhibitors (SSRIs)

Among the SSRIs investigated for the treatment of FMS were citalopram, escitalopram, fluoxetine, paroxetine, and sertraline. Despite the theoretical assumption, that the combined inhibition of serotonin and noradrenaline is more efficacious than selective serotonin augmentation vis-à-vis the inhibition of pain [37], the use of this class of drugs is recommended in practice guidelines.

Cyclobenzaprine

Cyclobenzaprine is a 5-HT₂ receptor blocker, which acts on a subfamily of serotonin receptors, and causes muscle relaxation [38].

Mirtazapine

Mirtazapine is an atypical antidepressant with noradrenergic and specific serotonergic activity. A meta-analysis held by Welsch et al. did not find the drug effective for pain relief in FMS nor for any other associated mental or functional symptoms related to it (depression, sleep problems, fatigue, etc.) [39].

Gabapentinoids

The two main members of this family of drugs, pregabalin and gabapentin, act by binding to the alpha₂delta subunit of voltage-gated calcium channels in the CNS. Originally used as anticonvulsants, they are currently mainly used for the treatment of chronic pain. Lacosamide is another anticonvulsant that has been evaluated as a therapeutic modality for neuropathic pain. [40].

A newer gabapentinoid, mirogabalin (DS-5565) was shown to have analgesic qualities in animal models of both central and peripheral neuropathies [41]

Opioids

Endogenous descending antinociceptive activity is postulated to be reduced in FMS. In humans, such two descending pain inhibitory pathways exist: the noradrenaline/serotonin-mediated pathway and the opioid-mediated one [42]. Naltrexone, a competitive opioid receptor antagonist, was proposed as potential new means of treating chronic pain. The beneficial effect of naltrexone on fibromyalgia symptoms was shown by Youner and Mackey in a pilot study in 2009 [43].

Dopamine Receptor Agonists

Evidence indicating involvement of dopaminergic pathways in the pathophysiology of FMS has led to attempts to develop medications intervening in dopaminergic metabolism [44]. With most evidence about the benefit of dopaminergic agonists being sporadic, it is worth mentioning tergulide, which in a randomized, double-blind placebo-controlled trial, was found to improve FMS symptoms in a subgroup of patients with spinal stenosis (as opposed to the comparing all tergulide-assigned patients to the placebo group, where no significant improvement was found) [45].

Cannabinoids

There are two major active components in cannabinoids: tetrahydrocannabinol (THC) and cannabidiol (CBD). The former is the psychoactive component, which affects pain (as well as emotions) and works through CB₁ and CB₂ receptors. The latter has anti-inflammatory and analgesic traits. The THC:CBD therefore determines the product's overall effect [46].

CB₁ cannabinoid receptors are found predominantly in the CNS and peripheral nervous system. Their agonists act along sensory pathways as modulators of pain [47]. With regard to the complex function of the endocannabinoid system in pain modulation, FMS is hypothesized to be induced, among other factors, by a lack of endocannabinoid activity [48].

NMDA Antagonists

Glutamate is the most abundant excitatory neurotransmitter in the nervous system. Central sensitization of pain transmission pathways is associated with hyperexcitability of the glutamatergic system, which leads symptoms observed in persons suffering from chronic pain [49]. Ketamine, an NMDA antagonist, was found to reduce muscular and referred pain in FMS patients [50]. Memantine, another receptor antagonist, was suggested to be useful because of its ability to reduce neurotoxicity caused by high levels of glutamate found in different brain areas of FMS patients [51,52].

Novel Therapeutic Approaches

NYX-2925((2S,3R)-3-hydroxy-2-((R)-5-isobutyryl-1-oxo-2,5-diazaspiro[3,4]octan-2-yl) butanamide) is a new NMDA receptor modulator which was shown by Khan et al. to affect NMDA receptor synaptic plasticity. This finding led to the hypothesis that it would be effective in NMDA receptor-associated CNS disorders [53].

Venlafaxine

Venlafaxine was quite promising in alleviating the pain and disability associated with fibromyalgia. This effect seems to be independent of its anxiolytic and antidepressant properties. Blockade of both norepinephrine and serotonin reuptake might be more effective than blockade of either neurotransmitter alone in the treatment of fibromyalgia. [54]

Life Style Modifications

Stress Management:

Many patients with fibromyalgia have increased levels of stress and feelings of depression, anxiety, and frustration. Several treatment options are available such as cognitive behavioral therapy; including relaxation training, group therapy, and biofeedback, which are some of the useful options.

Exercise:

Physical activity can be taken in many ways, including activities such as walking, jogging or sports. Exercise is a way of responding to stress which allows the discharge of the energy the body is anticipating. [55]

Alternative Therapies:

Chinese herbal medications, Chinese herbal tea, acupuncture, Tai-chi are the different modalities available but more research is required in these fields. [56-59] It has also been suggested that acupuncture triggers the release of endorphins into the blood stream and are body's natural pain relievers. [60]

Treating patients with chronic pain conditions has long held challenges and been rife with pitfalls for healthcare professionals. Pain is a complex and dynamic phenomenon influenced by genetic, physiological, cognitive, affective, behavioral and social factors. Melzack and Wall's gate-control theory revolutionized the understanding of and treatment for chronic pain.

The overview of these techniques and the evidence for their inclusion as fundamental elements of FM treatment.

Educational Approaches

Most experts agree that an educational or psycho educational treatment component is useful if not necessary when treating FM [61]. Such educational programs target increasing understanding of the complex nature of the interactions between neurobiological processes, behaviours such as sleep and/or activity levels, and symptoms. These programs have varied foci, but usually try to allay the stigma often attached to FM and similar disorders. Goldenberg [62] has recently set out recommendations regarding education that seem well founded.

Cognitive-Behavioral Therapy (CBT)

CBT combines interventions from both cognitive and behavior therapies. Cognitive therapy is based on the premise that modifying maladaptive thoughts results in changes in both affect and behavior [63]. Therefore, errors in thinking such as over generalizing, magnifying negatives, minimizing positives and catastrophizing are challenged and replaced with more realistic and effective thoughts, thus decreasing emotional distress and self-defeating behavior.

More specific to FM, catastrophizing, or the belief that the worst possible outcome will occur, has been associated with pain severity, decreased functioning and affective distress in FM.

Effective CBT interventions for FM will likely target the modification of maladaptive thoughts and expectations, thus improving mood, perceived stress, pain coping and problem solving, while including behavioral interventions that specifically address ameliorating FM symptoms (e.g., sleep hygiene, relaxation training, activity pacing). In FM, the primary goal of CBT treatment is to increase self-management which includes moving patients toward more adaptive beliefs regarding their ability to cope with and control pain and other symptoms, as well as taking action to decrease FM symptoms and stress resulting in increased functioning.

Relaxation Techniques

There is substantial overlap between CBT and behavioral interventions. Most CBT includes one or more forms of behavioral relaxation; although, some of these techniques have evidence for efficacy in the absence of a cognitive therapy component. Relaxation techniques likely to be helpful for FM symptoms include, but are not limited to, progressive muscle relaxation, autogenic training, guided imagery and meditation. Biofeedback can also be subsumed under this umbrella but possessing multiple types and having been the recipient of more empirical attention, biofeedback will be described at greater length in the following section.

Heart Rate Variability Biofeedback

Martinez-Lavin has championed this approach and with others, has produced a substantial body of data. There is reasonably good evidence that autonomic nervous system functioning in some FM patients can be characterized by elevated sympathetic tone, by poor parasympathetic tone, and by an abnormal 24-hour autonomic cycle [64-68].

Other Biofeedback Approaches

Several studies exist using other biofeedback approaches. Buckelew and colleagues conducted a randomized controlled trial comparing electromyogram (EMG) biofeedback (n = 29), exercise training (n = 30), combination treatment (biofeedback and exercise) (n = 30) and an educational/attention control (n = 30) [69].

Complementary And Alternative Medicine (CAM) Interventions

FM patients overwhelmingly have sought CAM interventions [70]. Yet, as is the case for so many disorders, very little scientific evidence exists for the efficacy of such approaches. Furthermore, deciding what treatments fall into this category is a perilous endeavor; however, a few treatments have been investigated.

Manual Therapies

Massage is a widely used CAM therapy for patients with FM, and based on patient survey data, the intervention with the highest satisfaction levels. Only one study using a comparison or control was located [71]. Brattberg compared connective tissue massage (n=23) to a no treatment control (n=25) over 15 treatments [71].

Acupuncture

Mayhew and Ernst recently reviewed the evidence concerning acupuncture and FM. They were able to find 5 studies that could be reviewed [72]. They rated their quality as variable, but independent of quality, they found mixed results. They asserted that none of the trials included adequate placebo conditions weakening their scientific value and concluded that acupuncture treatment was not supported by rigorous clinical trials and thus could not be recommended for FM. Since this review, one randomized controlled trial was published.

Hydrotherapy

Several well-controlled studies do exist that evaluated spa type bath therapies that have been used for centuries to ease pain. A recent review [73] found 10 studies of sufficient quality for review. Mean methodological quality was 4.5/9 on the van Tulder scale. Positive outcomes were reported for pain, health-status and tender point count. There is strong evidence for the use of hydrotherapy in the management of FM. However, most studies were short term and few used credible placebo conditions. It does seem, however, that the conventional wisdom that warm water baths relieve pain in the short term is well founded.

Spa Therapy For The Fibromyalgia Syndrome (FMS)

In view of its long history in the treatment of musculoskeletal conditions and in the alleviation of pain in particular, it is not surprising that spa therapy has attracted particular attention for the management of FMS. This common condition, which is characterized by the

presence of chronic widespread pain and tenderness, is considered to represent the clinical manifestation of central nervous system sensitization. Although some progress has been made in the development of pharmacological treatments for FMS, these options are yet hampered by relatively limited response rates versus placebo and frequent (and on occasion severe) side effects as well as the occurrence of tachyphylaxis. In view of these limitations there is growing recognition regarding the importance of integrating nonpharmacological and complimentary approaches into the therapeutic strategy concerning FMS. We will subsequently review existing data regarding the utilization of spa therapy for the treatment of FMS. [74]

Buskila and colleagues [75] evaluated the effectiveness of balneotherapy on patients with FMS at the Dead Sea (Israel). This was a randomized prospective study of a 10-day treatment, including 48 patients randomized to sulfur bath ($n = 24$) or no treatment ($n = 24$). Relief in the severity of FMS-related symptoms (pain, fatigue, stiffness and anxiety) and reduced frequency of symptoms (headache, sleep problems and subjective swelling) were reported in both groups, but lasted longer in the treatment group. It was concluded that treatment of FMS at the Dead Sea was effective and safe.

Qigong and Fibromyalgia

Qigong (Chi Kung, Chi Gong) refers to cultivation (practice, discipline) of qi (life energy, energetic essence) and has a long history in China, extending thousands of years, as a health and wellness practice. Many forms of qigong have developed, reflecting particular contexts for development (martial arts, health practice, and spiritual practice). The modern history of qigong began in China in the 1950s; western interest grew in the 1960s and has further accelerated in recent decades. As a self-practice, internal qigong involves dynamic (movement) and static (quiescent) elements and involves regulation of movement, breath, and awareness. When highly developed by skilled practitioners, qigong can be applied as external qigong, whereby the practitioner directs energy (using hand movements, focused attention) towards an individual to improve the flow of qi. In the past decade, qigong has been characterized as “mindful exercise” or “meditative movement”, and these conceptualizations are useful for considering qigong in relation to other practices such as mindfulness, meditation, and conventional exercise. [76]

CONCLUSION

Fibromyalgia is a common rheumatologic syndrome characterized by heightened pain sensitivity, fatigue, sleep disturbance, and other symptoms as a result of dysregulation of neurophysiologic function. Many theories of etiology are under investigation. With the proper treatment coupled with a caring and well informed physician; patients with fibromyalgia should be able to improve function and reduce pain. The research, as well as our clinical experience, indicates that the addition of education and a behavioral or cognitive-behavioral component to FM treatment protocols is warranted. Especially when combined with other modalities such as exercise, sleep hygiene, or activity pacing, using some form of behavioral intervention seems to add to the efficacy of the treatment. An important caveat however applies: It is important to avoid any suggestion that the symptoms are “all in your head” when recommending these treatments. It is easy to forget the stigmatizing aspects of any mental health diagnosis in our society.

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