REVIEW ARTICLE

Fibromyalgia Management

Veronica Ridpath, OMS III & Ronald Januchowski, DO

Edward Via College of Osteopathic Medicine-Carolinas Campus

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Fibromyalgia can be a debilitating syndrome that can frustrate patients and physicians alike. Understanding the etiology and methods for diagnosis can allow for improved patient interactions and better introduction of an overall care plan for the patient. Management of the the patient with fibromyalgia requires an osteopathicapproach, integrating a multidisciplinary approach with a patient-centered focus. The Osteopathic Primary Care physician plays a valuable role in incorporating both pharmacological and non-pharmacological methods of treatment. Goals for treatment should be improvement in health related quality of life and improved patient function. Using a collaborative approach to treatment will produce increased patient satisfaction with care with reduced medical utilization and better long-term clinical outcomes.

INTRODUCTION

Fibromyalgia (FM) is a syndrome primarily consisting of widespread chronic pain, transient cognitive difficulties, non-restorative sleep, and fatigue. Other symptoms such as headaches, vertigo, tinnitus, Raynaud's phenomena, pelvic pain, palpitations and paresthesias have also been reported. The disorder is relatively common with a prevalence in the general population of about 3%. Fibromyalgia most commonly presents between the ages of 30-50 years old, however the incidence increases with age. The female to male ratio of diagnosed patients is approximately 9:1.

Historically, FM was a diagnosis of exclusion. The wide variety of presentations and lack of definitive serological or imaging tests has led to confusion on the pathophysiology of the syndrome and skepticism of its validity as a diagnosis. Concomitant diagnosis with DSM Axis I disorders such as generalized anxiety or major depression have further confounded the accurate diagnosis of FM. Multiple hypotheses on pathophysiology exist, but the prevailing theory is that FM is at least in part a neurosensory disorder of central sensitization.

ETIOLOGY & PATHOPHYSIOLOGY

Evidence for Central Sensitization

Multiple factors are thought to contribute to the development and perpetuation of FM. The current prevailing hypothesis is that it is a disorder of central sensitization and aberrant pain signaling.[1] Compared to healthy controls and even other chronic pain patients, FM patients report increased pain perception to noxious stimulus in healthy tissue. Referred pain patterns also tend to be more widespread and distressing to the FM patient. Increased nociceptive response to stimulus compared to other chronic pain populations suggests a failure of endogenous pain inhibition and the descending pain pathways.[2] On PET scan, FM patients show decreased mu-opioid receptor binding potentials compared to healthy controls. The degree of decreased binding potential in the cingulate and striatum is inversely proportional to perception of pain.[3]

Sleep dysfunction is also exceptionally common in FM. Poorer sleep quality and duration is associated with increased physical debility and psychological distress.[4] There is conflicting evidence as to whether this association is bidirectional, or whether sleep dysfunction is merely a result of other FM symptoms.

Musculoskeletal differences

Even when accounting for the historic "tender points" in the 1990 ACR guidelines for diagnosis, a higher number of myofascial trigger points have been found in FM patients.[5] Manipulation of these trigger points reproduces the spontaneous pain patterns encountered in FM. Further research has shown that FM tender points have a high correlation to discrete myofascial tender points, which may be part of the etiology of peripheral pain.

Patients with FM show a dysfunctional response to exercise, one of the mainstay lifestyle changes suggested to patients with chronic pain. Compared to controls, FM patients have decreased blood flow to muscles in response to aerobic demand.[6] There is also a decreased anti-inflammatory response during recovery after exhaustive exercise.[7] These physiological differences may explain why many patients with FM have difficulty tolerating exercise regimens. Given the other positive benefits of exercise on quality of life such as increased stamina and physical function, awareness of its effects on muscle tissue can help providers educate patients and counsel on exercise regimens that are tolerable.

CORRESPONDENCE:
Ronald Januchowski, DO | rjanuchowski@carolinas.vcom.edu

DIAGNOSIS

The American College of Rheumatology (ACR) in 1990 presented the first standardization of FM diagnosis with research led by Frederick Wolfe, MD. The diagnostic criteria included physical examination as well as a test of 18 bilateral tender points. A presence of tenderness to 4-kilogram pressure applied in 11 of the 18 tender points was considered a positive result.[8] The criteria was revised in 2010 to eliminate the tender point test and introduce two measures of both physician assessment and patient self-reporting. The Widespread Pain Index (WPI) measured the extent of pain across the body and Symptom Severity Scale (SSS) measured symptoms related to sleep, fatigue, and cognition. The reasoning behind the revision includes difficulty in standardization of tender point measurement and the temptation to use tender points as a definitive diagnostic tool. More important measures in diagnosing FM include sleep, fatigue, pain, and general impact on patient quality of life.[9]

The 2010 criteria were further revised in 2011 to focus entirely on patient self-reported symptoms. The FM Survey Questionnaire (FSQ) is a 31 item-screening tool based on these criteria and developed by Hauser that requires no objective exam or symptom evaluation by the clinician. This allows it to be used in any practice setting without special training. The FSQ has been shown to have similar sensitivity and specificity to both the 1990 ACR Criteria as well as the 2010 ACR revised criteria.[10] A Spanish-language version of the FSQ has been shown to be as reliable as the original FSQ, which provides useful cross-cultural relevancy to the survey.[11]

FM is diagnosed primarily through the history and physical exam, and there are no laboratory tests that can definitely diagnose fibromyalgia. While blood testing is not required for the diagnosis of fibromyalgia, many practitioners will order lab work to exclude other primary diagnoses. However, fibromyalgia can be comorbid with other rheumatologic diseases, so a positive diagnosis of another disease does not automatically exclude fibromyalgia. Commonly ordered tests include complete blood count (CBC), vitamin D, calcium/phosphate levels, thyroid-stimulating hormone (TSH), and C-reactive protein. Ruling out and correcting anemias, thyroid pathology, inflammatory processes, and vitamin deficiencies can help reduce the complicated clinical presentation of FM syndrome. At this time, there are no laboratory tests that are specifically suggested by any organization.

There is some correlation to genetic markers HLA-B27, HLA-B51 and FMF but there is insufficient evidence to use them for exclusion.[12] Current recommendations by the ACR do not advise routine screening for FM in asymptomatic patients.

MANAGEMENT IN THE PRIMARY CARE SETTING

As of publication, there is no 'gold standard' management for fibromyalgia syndrome. Different modalities have variable levels of success, and improvement in pain and health-related quality of life (HRQOL) from pharmacological agents alone is minimal.[13] Adjuvant non-pharmacological treatments are critical for effective management of symptoms and pain and debility-related psychosocial correlates. Providers must be straightforward with patients to communicate realistic expectations of continual symptom management, as full remission is rare.

Clinical trials of FM medications have historically excluded patients with long-standing injuries or other rheumatological disorders. We now know that FM often presents concomitantly with chronic pain conditions, so these study populations may not be representative of patients who will present to the primary care office.

MEDICATION MANAGEMENT

Centrally Acting Drugs

Currently, there are three FDA-approved drugs for the treatment of FM on the market. The first approved was pregabalin (Lyrica) in 2007, followed by duloxetine (Cymbalta) in 2008, and finally milnacipran (Savella) in 2009. Drug monotherapy with one of the FDA-approved agents along with patient lifestyle modification is considered first line treatment. Amitriptyline is also widely used for FM treatment, although it is not FDA-approved for this indication.

Duloxetine is one of the commonly used SSRIs used in the treatment of FM. It has been shown to reduce pain and stiffness, but the majority of benefit comes from decreased fatigue and anti-depressive and anxiolytic effects.[14] Many patients find benefit at lower than recommended dose (30 mg vs 60 mg). Patients prescribed duloxetine also show greater compliance and reduced inpatient and outpatient service utilization.[15]

Milnacipran is an SNRI with similar effects on pain and functioning as compared to duloxetine. The benefit milnacipran has over duloxetine is the longer time to diminished therapeutic response: approximately three years. However, it has been associated with more adverse events and one meta-analysis has called into question whether the number of patients who benefit from milnacipran: (40% in the test groups vs 30% in the placebo groups) is worth the adverse effect profile.[16]

Lyrica (pregabalin) provides distinct benefit in pain and sleep quality, as well as significant anxiolytic effects with a low risk of dependence. Compared to other drugs used to treat FM, pregabalin has been shown to have a longer time to diminished therapeutic response in the domains of sleep and fatigue,[17] allowing patients to maintain significant relief without constant medication changes. With pregabalin also being used for the treatment of nerve pain disorders like diabetic neuropathy and post-herpetic neuralgia, this treatment may provide relief in patients whose predominant pain pattern is neuropathic or characterized as "burning" or "electric". Side effects include weight gain, dizziness, and edema. Once-daily dosing before bedtime can minimize somnolence associated with pregabalin treatment.

Amitriptyline is another centrally acting drug, and is the most commonly prescribed tricyclic antidepressant in the treatment of FM. The mechanism of action in pain improvement is thought to be activation of the descending inhibitory pain pathways. Patients report a modest decrease in tenderness and stiffness, with increased duration and quality of sleep. Amitriptyline also has significant effects on depression and mood symptoms. Many patients who discontinue this medication do so because of the prevalent side effects of weight gain and exacerbated fatigue. The best response is found with low doses administered at bedtime, as this reduces daytime fatigue. Although the use of the FDA- approved drugs duloxetine, pregabalin, and milnacipran have increased, they show no increased benefit in fatigue or functioning over amitriptyline.[18]

The patient's predominant symptoms and concerns about functioning and adverse effects should guide treatment choices. Patients whose primary concern is pain may benefit more from pregabalin, while those who struggle more with cognitive symptoms and poor sleep often do better on duloxetine. Given the higher drug costs and significant side effect profile, providers must carefully weigh the benefits of each drug's use based on individual patient presentation and treatment goals.

Analgesics

Treatment of FM with analgesics is not considered first line, as symptoms are thought to be due to excess pain sensitivity rather than increased rate of pain signal transmission. Research on the treatment of peripheral pain in FM is sparse and many of the studies available have limitations from prior treatment or medical comorbidity exclusion criteria.

The only analgesic that has shown positive effects in the treatment of FM is tramadol, particularly when prescribed with acetaminophen.[19] Opioid analgesics such as hydrocodone and oxycodone are often used in the treatment of other chronic pain conditions; however, there is currently no evidence to suggest that opioid analgesics improve HRQOL in FM. While gross pain may decrease, the patient-oriented measures of pain-related disability and distress show little benefit. Given the side effects and dependence risk, there is no place for them in the routine treatment of FM.[20]

Non-steroidal anti-inflammatory medications such as ibuprofen and naproxen show no increased efficacy over placebo in the treatment of FM-specific pain, and given the gastrointestinal and cardiovascular risk factors of long-term maintenance therapy, they should be avoided unless used for the treatment of comorbid osteoarthritis.

Muscle Relaxants

While not FDA-approved for the indication, low dose cyclobenzaprine given daily at bedtime has been shown to improve quality and duration of sleep, a significant contributor to FM symptoms.[21] Effects on pain are not as significant, with decreased pain peaking early in treatment and eventual habituation approaching baseline levels. With an estimated number needed to treat (NNT) of 4.8, many patients will find significant relief with this drug alone.[22] Side effects are generally mild and include somnolence and dizziness. Physicians should be aware of the slightly increased risk of serotonin syndrome when prescribing cyclobenzaprine with SSRI/SNRIs, and educate patients on the signs and symptoms of serotonin toxicity.

There have been few studies on other muscle relaxant agents in the treatment of FM, and their improvement measures have been based on the old ACR 1990 criteria focusing on tender point pain. A small-scale study on carisoprodol-acetaminophen-caffeine showed moderate reduction in tender point pain in FM, although there was no HRQOL improvement.[23] There is little data on the role of other muscle relaxants on the treatment of FM.

Complementary Medicine & Alternative Therapies

As a relatively common syndrome of unknown etiology, FM has become a ripe target for alternative medicines, special diets, and treatment programs based in little scientific evidence. Providers must be cautious when discussing alternative treatments with patients, as many of these are difficult to monitor and control. At this time, there is no strong evidence to suggest that complementary or alternative therapies such as homeopathy, reiki, supplements, or mindfulness-based meditation provide any measurable benefit.[24] Acupuncture shows no benefit over placebo.[25] Routine supplementation of iron in FM patients without clinical anemia is also not recommended.[26] There is no correlation between FM severity and serum levels of vitamin A, C, E, or magnesium.[27]

While not specific to FM syndrome, hypovitaminosis D has been correlated to diffuse and persistent musculoskeletal pain without any other identifiable cause.[28] With a negligible side effect profile and affordable treatment, close monitoring of vitamin D levels and necessary supplementation should be considered for any patient presenting with nonspecific fatigue and musculoskeletal pain.

Whole-body warmth therapy has shown significant benefit in pain and symptom relief in multiple studies, and was reported as the first most effective treatment intervention in the German Fibromyalgia consumer reports.[29] Variations of warmth therapy such as warm baths were also reported as effective. Patients can be advised to take warm showers or baths for symptom relief, or utilize devices such as electric blankets or heating pads. Patients using contact heat therapy should be counseled on the risks of developing erythema ab igne secondary to prolonged exposure, particularly given the dysfunctional pain processing inherent in FM.

Equally effective to whole-body warmth therapy is transcutaneous electric nerve stimulation (TENS).[30] The advantage of using TENS therapy is the portability of TENS devices and the temporary restoration of central pain inhibition.[31] Benefits of treatment last as long as the stimulator is active, and patients are able to control the intensity and duration of the treatments. Perceived pain-related self-efficacy and locus of control in treatment reduce anxiety and increase response to intervention in other chronic pain conditions.

Gentle exercise is also a common suggestion, from both a general health and a pain reduction perspective. Yoga specifically has been shown to reduce the impact of fibromyalgia pain on a patient's quality of life, and decrease pain perception over time.[32] Beyond the physical benefit, formalized yoga programs that focus on mindfulness and stress reduction have also been shown to improve maladaptive pain-related behaviors such as catastrophizing and pain-related anxiety.[33]

NEW, EXPERIMENTAL TREATMENT

With the vast array of contributing factors and new research into mechanisms of FM symptoms, there have been many targets of new pharmacologic therapy. The hypothesis that mu-opioid receptor dysfunction leads to some FM symptoms has led to trials of naltrexone, an opioid-receptor antagonist, in an effort to increase pain inhibition.[34] While pilot studies show an improvement in symptoms, the paucity of research and small sample sizes of existing studies make it impossible to generalize these results to the greater population at this time.

Cannabinoids such as nabilone and medical cannabis show some preliminary positive benefit on sleep quality and duration with modest effects on pain; however, there have not been any studies on FM patients specifically.[35] Furthermore, this option is not legally available in most areas and there have been few studies on the

long term effects of cannabinoids. Legal clarification of the medical validity of cannabinoids and THC derivatives is necessary before recommending them as a treatment option.

OMT & MANUAL THERAPY

There is limited research on the role of osteopathic manipulation in the interdisciplinary treatment of FM, perhaps in part because there is no standard presentation and therefore no clear target for treatment interventions. Empiric treatment of specific dysfunctions may be warranted in individual cases; however, FM patients have a lower threshold for pressure than other chronic pain patients. This mechanical hyperalgesia may warrant the use of gentler and more indirect techniques. In one German consumer report, osteopathy was listed as the ninth most effective intervention in the treatment of fibromyalgia.[29] However; the lack of a true clinical trial makes it difficult to recommend specific treatments.

Massage is often sought by patients seeking relief of FM pain, however, targeted myofascial release shows significant benefit over Swedish massage in treatment of neck and back pain in FM.[36] Connective tissue massage has shown some temporary benefit in FM symptomology, although benefits are short-lived and treatments must be repeated every 3-6 months.[37] In the general population, manual therapies including spinal manipulation and spinal mobilization have measurable effects on the areas of the brain responsible for sensory integration and modulation of the pain experience.[38] Further research would be necessary to determine if this effect extends to the FM population, as patients have aberrant integration and processing of pain.

There is evidence that FM has some features of dysautonomia and sympathetic dysfunction.[39] Osteopathic treatments used to normalize sympathetic activity such as rib-raising could have positive benefits on symptom severity or duration. If future research were conclusive, this would be an area where Osteopathic physicians are uniquely suited to manage this aspect of the FM patient's care. There have been some studies showing OMT as an effective adjunct to medical management of FM,[40] and with new diagnostic criteria and an evolving understanding of the nature of FM, more research is necessary to develop effective treatments for pain control.

MENTAL HEALTH

Mental health is a primary concern with FM. Even patients with no initial presentation of psychiatric symptoms can develop anxiety and depression related to long-term uncontrolled pain and loss of independence. Withdrawal from favored activities and support networks can compound this issue. Providers should encourage patients to maintain community engagement as much as possible, and address mental health concerns as they arise. Control of depression and anxiety is associated with better health-related quality of life (HRQOL) outcomes and decreased duration and impact of pain.[41]

Psychological counseling services may also be beneficial, as poor coping skills can increase perception of pain and functional debility related to symptoms. Catastrophizing, pain anticipation, overgeneralization, and avoidance of situations that might exacerbate pain are all factors in lower HRQOL.[42]

CONCLUSION

It is the opinion of this author that the goal of FM treatment should focus not on a cure, but rather patient education and a collaborative approach to symptom management. A patient-centered approach improves pain-related anxiety and pain intensity,[43] both of which are significant contributors to debility and lower HRQOL. Evidence suggests that an intensive interdisciplinary approach to FM management leads to better quality of life.[44] However, we must consider the burden placed upon the patient using such an approach. If the goal is to improve independence and minimize the effects of FM, it may be a disservice to the patient to shuttle them from specialist to specialist or place them in an intensive program. Symptom relief may occur, but the patient's overall quality of life may suffer.

By providing care with a holistic approach to treatment and applying the Osteopathic tenets, primary care providers can provide integrated care in biological, psychological, and social dimensions of care. Physical therapy, occupational therapy, and specialized psychological services are only valuable pieces of the plan when they are properly integrated into the overall care for the patient.

Further research into the effects of specific manual treatments is necessary to characterize presentations of FM and identify treatment targets. With a broader clinical picture, Osteopathic physicians will be able to manage medication and manual treatment within a single visit, therefore increasing patient access to interventions and leading to better long-term clinical outcomes.

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