CHAPTER 8

FIBROMYALGIA

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INTRODUCTION

Fibromyalgia (FM) is characterized by chronic common pain, sleep disorders, physical exhaustion, and cognitive difficulties. FM is a heterogeneous condition that is often associated to specific diseases such as infections, psychiatric or neurological disorders, diabetes and rheumatic pathologies. The primary driver of FM is sensitization, which comprises central sensitivity syndromes usually referred to joint stiffness, chronic pain at multiple tender points, and systemic symptoms comprising cognitive dysfunction, sleep disturbances, anxiety, fatigue, and depressive episodes. FM is more frequent in females, where it matters musculoskeletal pain and affects significantly the quality of life, often requiring an unexpected healthcare effort and consistent social costs (Wang SM & et al. ,2015)(Chinn S & et al., 2016) (Blanco I. & et al. , 2010).

Table 1. Characteristics and Associated Features of Fibromyalgia
Characteristic features
Chronic widespread pain for at least three months
Tender points in 11 of 18 specific anatomic locations
Associated features
Anxiety
Cognitive difficulties
Fatigue
Headache
Paresthesias
Sleep disturbance

Generally, a patient-tailored approach requires a pharmacological treatment by considering the risk-benefit ratio of any medication. Being the third most common diagnosis in rheumatology clinics. (Cabo-Meseguer A. & et al., 2017),

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(Williams D.A. & et al., 2009)Although the prevalence of FM is reported to be between 0.5 and 5.8 %, the prevalence increases as the education level and socioeconomic level decreases. The incidence of FM increases with age. It increases with age and is most common between the ages of 40-60. Incidence in women 4-9 times more than men (Rahman A. & et al., 2014)(McBeth J. & et al., 2007)(Ozkan O, Yildiz M and Köklükaya E, 2011) (Solitar BM,2010)(Forbes D &Chalmers A, 2004)(Wolfe F. & etal., 2011)(Recla JM, 2010)(Jones GT & et al., 2011).

The pathophysiology of fibromyalgia is unclear. Fibromyalgia clusters in families, suggesting a genetic predisposition. Environmental and psychological factors, which could impact various members of the same family, may contribute to the symptomatology of the disease. Present theories of pathogenesis include central sensitization and hypothalamic-pituitary-adrenal axis dysregulation; however, more research is needed to determine a definite pathophysiology (Bennett R. 2004).

To date there are no specific tests specific for FM. FM is currently recognized by the widespread pain index (which divides the body into 19 regions and scores how many regions are reported as painful) and a symptom severity score (SSS) that assesses cognitive symptoms, unrefreshing sleep and severity of fatigue. The diagnosis of FM might take >2 years, with patients seeing an average of 3.7 different physicians during that time (Choy E & et al., 2010). Many health care providers, especially in primary care, report unclear diagnostic criteria, a lack of confidence in using existing criteria for diagnosis, insufficient training or skill in diagnosing FM, and a lack of knowledge of treatment choices (Hadker N & et al., 2011).

Early efforts focused on FM as a chronic common pain disorder with other associated symptoms (Smythe HA, 1972) (Steingrimsdottir OA & et al., 2017). The American College of Rheumatology (ACR) 1990 classification criteria (Wolfe F & et al., 1990) eliminated associated symptoms and focused solely on chronic widespread pain (CWP) (defined as pain in the left side of the body, pain in the right side of the body, pain above the waist, pain below the waist, and axial skeletal pain [cervical spine or anterior chest or thoracic spine or low back]) and tenderness (defined as pain on palpation of ≥11 of 18 specific tender point sites on the body) (Figure 1). Although the ACR 1990 criteria helped to advance research studies of FM, the criteria were not intended for use in clinical practice, did not include commonly associated symptoms, and required a tender point exam, which was impractical for use in the clinical setting (Gracely RH, Grant MA & Giesecke T, 2003). With the publication of the 2010 and 2011 criteria,(Wolfe F & et al., 2011) (Wolfe F & et al., 2010) the definition of FM moved from a predominantly chronic pain disorder to a multi-symptom disorder and eliminated the tender point

exam as a requirement for diagnosis. Although the authors of the 2010/2011 criteria re-emphasized the importance of associated symptoms, there may have been too much movement away from chronic pain as the core symptom of FM (Jones GT & et al., 2010). Studies of alternative criteria evaluated a variety of associated symptoms along with various definitions of common pain in the diagnosis of FM (Arnold LM & et al., 2012) (Bennet RM & et al., 2014). The authors of the revised 2016 criteria187 addressed the problem with the 2010/2011 criteria regarding misclassification of patients who did not have generalized pain (Wolfe F & et al., 2011), which happened because the 2010/2011 criteria do not consider the spatial distribution of painful sites. The 2016 criteria now require that patients have pain in 4 of 5 regions, called "generalized pain" to distinguish it from the 1990 definition of "widespread pain." Even though there are different definitions of widespread pain and associated symptoms, most of the previous FM criteria appear to identify a similar group of patients most clinicians would agree have FM.

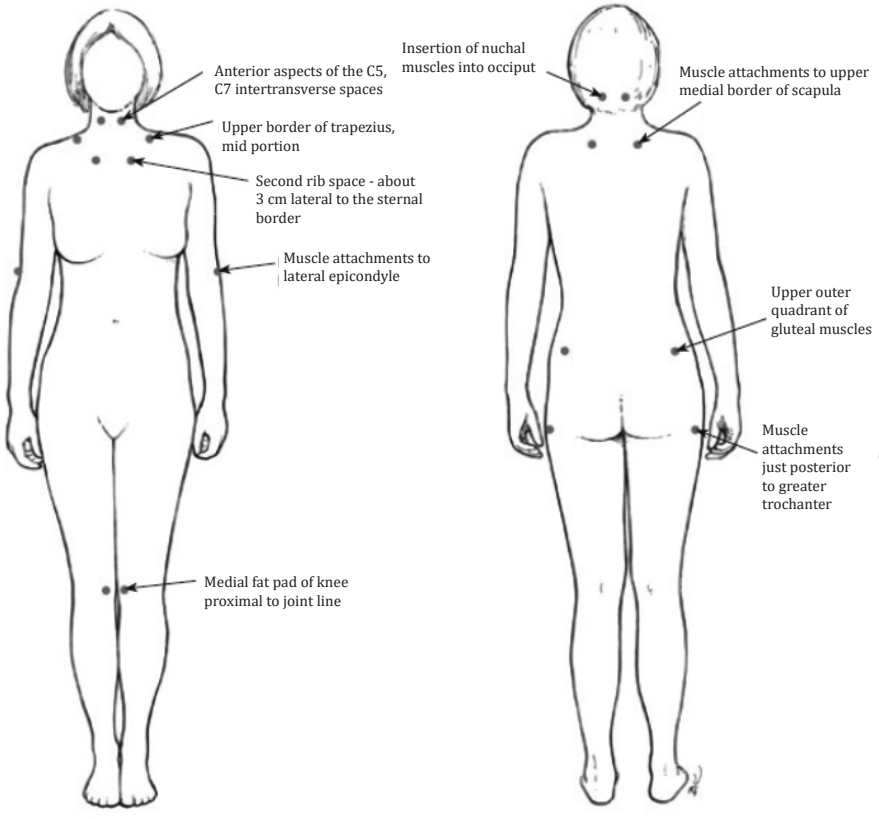

Figure 1. The American College of Rheumatology 1990 Criteria recommended anatomic tender point locations for diagnosis of fibromyalgia.

Comorbid Conditions

Fibromyalgia is associated with sleep disorders. Polysomnographic findings in fibromyalgia patients include an alpha frequency rhythm, termed alpha-delta sleep anomaly. Sleep pattern is altered in these patients and there is sign of an increase in stage 1 sleep, a reduction in delta sleep, and an increased number of arousals.

Anxiety and depression are two of the most widespreadly encountered comorbid conditions in patients with fibromyalgia. Evidence in the medical literature indicates underdiagnosis and inadequate treatment of mood disorders in patients with chronic pain, including fibromyalgia (Perez-Stable EJ & et al., 1990).

Headaches are present in more than one half of all patients with fibromyalgia (Marcus DA, Bernstein C & Rudy TE, 2005). The high prevalence of migraine in patients with fibromyalgia suggests a common pathogenesis. Migraine has been characterized by a defect in the serotonergic and adrenergic systems. A parallel dramatic failure of serotonergic systems and a defect of adrenergic transmission also have been shown to affect patients with fibromyalgia (Nicolodi M & Sicuteri F., 1996).

Patients with fibromyalgia often also have irritable bowel syndrome (IBS) (Sperber AD & et al, 1999). IBS is a functional disorder of the gastrointestinal tract. Patients suffer from chronic abdominal pain and disturbed bowel function without evidence of structural or laboratory abnormalities on routine testing. An increased sentience of the clinical impact of fibromyalgia on patients with IBS, and vice versa, and recognition of the implications of this association for quality of life should enable physicians to rearten their patients regarding the nature and severity of their symptoms and to provide appropriate treatment. This may lead to a reduction in referrals and unnecessary tests for these patients.

Other disorders commonly associated with fibromyalgia include irritable bladder, dysmenorrhea, premenstrual syndrome, restless leg syndrome, temporomandibular joint pain, noncardiac chest pain, Raynaud's phenomenon, and sicca syndrome.

Managing Fibromyalgia

The treatment of patients with fibromyalgia requires a combination of pharmacologic and nonpharmacologic modalities, including exercise, alternative therapies (ozone thrapy, neural therapy, manuel therapy) and cognitive behavioral therapy.

Nonpharmacologic Management

Patient Education

Simply making a diagnosis of fibromyalgia has a positive effect on its management, leading to a reduction in primary care visits, diagnostic testing, and drug prescriptions (White K & et al, 2002) (Hughes G & et al, 2006) (Annemans L & et al, 2008). Patient education is the next step. Emphasizing that the patient does not have a serious or life-threatening disease reduces anxiety. Discussing what is known about the imbalance of central nervous system neurotransmitters and the abnormalities of brain blood flow helps to assure the patient that fibromyalgia is a real illness. One useful metaphor to explain central pain processing abnormalities is an overly sensitive home smoke alarm that goes off every time the oven is turned on. It is a false alarm shrieking "fire" in the absence of fire. An overly sensitive pain processing system will shriek pain in the absence of peripheral pathology, but the perception of pain is very real. Websites hosted by the Arthritis Foundation (http://www.arthritis.org/), the National Fibromyalgia Association (http://fmaware.org/site/), and other reputable organizations can provide patients with useful resources to improve their understanding of fibromyalgia

Setting expectations regarding sickness prognosis and the roles of the patient and physician is significant. It helps to advise patients that fibromyalgia is a chronic disease with good days and bad days; treatment will improve symptoms but usually not eliminate them. The patient can play a major role in adhering to sleep hygiene and exercise programs, as well as other nonpharmacologic modalities.

Cognitive Behavioral Therapy

Cognitive behavioral therapy (to address maladaptive thoughts) and stress-reduction techniques have been shown to be effective in some patients(Häuser W & et al, 2009)(Carville SF & et al, 2008). Recognizing and addressing behavioral issuance of catastrophizing behavior and learned helplessness can aid in focusing treatment on self-management techniques.

Exercise

Aerobic exercise and muscle strength training can reverse deconditioning and improve sleep, pain, and function in patients with fibromyalgia (Carville SF & et al, 2008) (Busch AJ & et al, 2003) (Sprott H, 2003). Patients who choose activities they like (eg, walking, pool exercise, group activities) and who start at gross levels of exercise are more likely to be successful in managing their fibromyalgia in the long term. Exercise intensity should be increased very slowly to avoid injury and flares of pain, which may cause the patient to abandon the activity (Sprott H,

2003). Patients with good coping skills are most likely to adhere to an exercise program (Mease P, 2005).

Complementary and Alternative Medicine

In general, seldom scientific evidence exists to support the use of complementary and alternative medicine in the management of fibromyalgia (Mease P, 2005) (Hassett AL &Gevirtz RN, 2009). Acupuncture, balneotherapy, chiropractic treatment, ozone theraphy and osteopathic manipulative treatment have been used frequently to manage the symptoms of fibromyalgia (Hassett AL &Gevirtz RN, 2009) (Brattberg G, 1999) (Gamber RG & et al, 2002). The results of a controlled trial suggested that profits of massage therapy may last up to 6 months after treatment. In addition, a randomized pilot study revealed that patients who received osteopathic manipulative treatment and medication for fibromyalgia had better outcomes compared with patients who received only medication.

Pharmacologic Management

Fibromyalgia is a syndrome of many symptoms and comorbidities, and there is growing demonstrate of abnormalities of several neural pathways including those mediated by serotonin, norepinephrine, substance P, and glutamate and other neurotransmitters (Yunus MB, 2007) (Smith HS, Harris R & Clauw D, 2011) (Russel IJ & Larson AA, 2009). Patients complain of a variety of seemingly unrelated symptoms. Hence, it is not surprising that there is no single pharmacologic agent capable of effectively addressing all of the potential symptoms of fibromyalgia.

Antidepressants

Antidepressants appear to use their effects by modulating serotonin and norepinephrine pathways. Tricyclic antidepressants (TCAs) such as amitriptyline, desipramine, and nortriptyline have been shown in short-term studies to improve pain, sleep, fatigue, and overall sense of well-being (Carville SF & et al, 2008). No matter how, they are associated with more adverse effects when used at higher doses (Smith HS, Harris R & Clauw D, 2011). Tricyclic antidepressants are often prescribed initially for patients with fibromyalgia who do not have depression.

There is an emerging and clinically useful concept of considering varying degrees of "fibromyalgianess" in patients

It is recommended that TCAs be started at very low doses 2 hours before sleep and titrated upward slowly over various weeks. Despite their initial effectiveness, the long-term durability of TCAs has been questioned (Yunus MB & 2007). Anticholinergic effects (dry mouth and constipation), sedation, and stupor limit their tolerability. Although cyclobenzaprine is classified as a muscle relaxant, it is

structurally a TCA. It has been shown to improve sleep, pain, and overall sense of well-being but appears to have little or no effect on fatigue in patients with fibromyalgia (Smith HS, Harris R & Clauw D, 2011).

Selective serotonin reuptake inhibitors (SSRIs) are useful for the management of depression and fatigue but have been less powerful in improving pain and sleep in patients with fibromyalgia (Yunus MB & 2007) (Smith HS, Harris R & Clauw D, 2011). The selective norepinephrine serotonin reuptake inhibitors (SNRIs) duloxetine and milnacipran have been approved by the US Food and Drug Administration for the management of fibromyalgia and appear to be more effective in relieving fibromyalgia symptoms than are the SSRIs (Yunus MB & 2007). Duloxetine decreased pain and improves a patient's overall sense of well-being. It has relatively little effect on sleep and is usually taken in the morning. The most common adverse effects are nausea and headache, which tend to improve with continued use. Patients with fibromyalgia and comorbid depression may benefit from SNRIs as initial therapy. As with all fibromyalgia treatments, a "start low, go slow" dosing strategy improves patient compliance.

Tramadol combined with acetaminophen improves fibromyalgia pain . This drug has mild SNRI effects in addition to mild opioid effects. Care should be taken to avoid excessive combinations of SSRI and SNRI drugs to avoid serotonin syndrome (Russel IJ & Larson AA, 2009). Features of serotonin syndrome include mental status changes, autonomic hyperactivity, and neuromuscular hyperactivity.

Antiepileptic Drugs

Pregabalin, which is approved by the US Food and Drug Administration for the management of fibromyalgia, and gabapentin appear to suppress the release of pain pathway neurotransmitters, including substance P and glutamate (Häuser W & et al, 2009). They have been demonstrated to improve pain, sleep, fatigue, and overall quality of life in patients with fibromyalgia (Häuser W & et al, 2009). They are not approved for the management of depression. They are much used as adjunctive therapy, being added to drugs affecting other pain pathways. Adverse effects that limit their use include dizziness, somnolence, and weight gain (Smith HS, Harris R & Clauw D, 2011). These symptoms tend to improve with continued use.

Other Drugs

Opioids have not been shown to be effective in the management of fibromyalgia and should be avoided if possible. Opioid-induced hyperalgesia and long-term contrary effects limit the usefulness of this drug class (34,37).

Nonsteroidal anti-inflammatory drugs wield their primary effect on prostaglandin-associated inflammatory pathways and are not very effective in reducing the central pain of fibromyalgia (Mease P, 2005). They are useful, however, in the management of coexisting "pain generators" such as osteoarthritis or degenerative disk disease.

Fibromyalgia is of several overlapping disorders of central sensitivity syndrome. The growing knowledge of the underlying biopsychosocial reasons of these disorders is leading to a more rational approach to treatment. Recognizing the heterogeneous nature of fibromyalgia, with marked individual variation in prognosis and feedback to therapy, aids substantially in its management. An understanding of the different pain-relieving mechanisms of drugs aids in the selection of combinations of therapy that may be more effective in the treatment of patients with fibromyalgia.

The review of the literature suggests that a multidisciplinary therapeutic advance, based on the combination of pharmacologic and alternative therapy (including thermal, light, electrostimulatory and body exercise treatments) could improve the quality of life and reduce pain and other symptoms related to FM. However, sometimes the ability of patients to participate to alternative therapies is impeded by the level of pain fatigue, poor sleep, and cognitive dysfunction. These patients may need to be conducted with medications before initiating nonpharmacologic therapies.

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