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Fibromyalgia Pathogenesis and Treatment Options Update

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Abstract This review article presents and summarizes up-to-date literature on the clinical manifestations, diagnosis, pathophysiological mechanisms, and treatment options for fibromyalgia patients. First, the most recent diagnostic criteria for fibromyalgia, as put forth by the American College of Rheumatology will be summarized. Clinical features, including chronic widespread pain, hyperalgesia, mood disorders, anxiety, and disturbed sleep patterns will be explored in-depth. The pathogenesis and pathophysiology of fibromyalgia involves alterations in multiple ascending and descending central nervous system pathways, as well as peripheral pathways, leading to heightened pain sensitivity. Risk factors have been studied extensively, and the most recent research focuses on various genetic influences and the contributions of stress and poor sleep. Lastly, the discussion in this article focuses on treatment options for fibromyalgia; some have been mainstay options for many years. Pharmacological agents include tricyclic antidepressants, anti-epileptic drugs, selective serotonin reuptake inhibitors, norepinephrine/serotonin reuptake inhibitors, as well as some investigational agents. The evidence behind non-pharmacologic treatments, including massage therapy, exercise, and acupuncture, are discussed.

Keywords Fibromyalgia · Fibromyalgia, pathogenesis · Fibromyalgia, treatment · Fibromyalgia, sleep disturbance · Fibromyalgia · Central sensitivity syndrome · Fibromyalgia, massage · Fibromyalgia, acupuncture · Fibromyalgia

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Introduction

Fibromyalgia syndrome is a disease entity characterized primarily by multi-focal pain, but the disease definition has been broadened over the past 2 decades to encompass components of fatigue, cognitive dysfunction, and sleep disturbances, among other symptoms. The pain is variable, with location and intensity changing over time and course of the disease [1]. There are no specific tests or pathologies which are specific for, or pathognomonic of, the disease [2•]. In fact, fibromyalgia has been deemed the "medicalization of misery," in an editorial by Hadler [3]. It was formerly called "fibrositis" syndrome, a name constructed to implicate the significant role of *peripheral* inflammation in the pathogenesis [4]. Currently, we have moved beyond those earlier theories, and believe that the abnormal pain processing is mainly centrally driven, with *central sensitization* being the primary driver of the disease. It is part of a group called *central sensitivity syndromes*, which also includes chronic fatigue syndrome, functional dyspepsia, Gulf War syndrome, interstitial cystitis, irritable bowel syndrome (IBS), temporomandibular joint (TMJ) dysfunction, myofascial pain, post-traumatic stress disorder, and restless leg syndrome [5]. Fibromyalgia may co-exist with these disorders or any of the other regional musculoskeletal pain syndromes. Mood and anxiety disorders are also common co-morbid conditions. The prevalence of the disease within the general population appears to range from 1.3–8 % [1, 5, 6] and is the second most common rheumatologic disorder, behind osteoarthritis. It is more common among middle-aged women and is the most common cause of musculoskeletal pain in women aged 20–55 years [7]. The incidence of

fibromyalgia is 6.88 cases per 1000 person-years and 11.28 cases per 1000 person-years for men and women, respectively. The impact on quality of life (QOL) is significant, with a lower QOL compared to such conditions as chronic obstructive pulmonary disease and rheumatoid arthritis. Approximately 35 % of persons diagnosed with fibromyalgia report difficulties in performing activities of daily living [1]. Economically, per the US Center for Disease Control, the annual healthcare cost per patient is US $9573. Treatment is both pharmacologic and non-pharmacologic, with most established guidelines advocating for a multi-modality approach. This article serves as an update on literature concerning the pathogenesis of the disease, as well as current and new treatments.

Diagnosis

In 1990, the American College of Rheumatology (ACR) published the first set of classification criteria for fibromyalgia syndrome [8•]. A positive diagnosis required the presence of at least 11 or 18 pre-defined tenderness points on the body, along with widespread pain. The physician should apply a standardized amount of pressure of 4 kg, enough to turn a thumbnail white [9], and these symptoms must have been present for at least 3 months. However, after 2 decades, the ACR proposed new criteria in 2010, which removed the tender points. Instead, a scoring system took its place. A positive diagnosis is defined as a (1) widespread pain index (WPI) ≥ 7 and severity score (SS) ≥ 5 or WPI 3–6 and SS ≥ 9, and (2) symptoms being present for at least 3 months. The modifications have improved the sensitivity and specificity for the criteria to 90.2 and 89.5 %, respectively [10]. Another screening tool, the Fibromyalgia Survey Questionnaire has also shown a sensitivity and specificity of 93.1 and 91.7 %, respectively, for a score ≥ 12 [11]. The reasons for the change were multi-faceted. The majority of fibromyalgia diagnoses are done in primary care settings, where it is believed the practitioners did not document tender point counts or performed the assessments incorrectly. Thus, for a disease without objective lab or image testing, detection using the 1990 criteria was highly dependent on clinical setting. And again, there is now the association of more clinical symptoms, including fatigue and cognition, which was not known when the 1990 criteria were developed.

Clinical Features

Generalized pain with variable pain severity and anatomical location has also been and will continue to be the defining feature of the disease. The pain is characterized by an increased sensitivity to pressure and light touch, which causes allodynia (perceived pain to non-noxious stimuli) and hyperalgesia (disproportionate pain to painful stimuli). Fatigue, up to 70 % in some patients, is a common symptom. Co-morbid depression is very common among fibromyalgia patients, with a lifetime prevalence of 62–86 % [12]. Major sleep disturbance is very common, seen in up to 90 % of patients, and the severity correlates with pain severity. Morning tiredness and daytime somnolence then ensue; although, insomnia is not a common feature [2•]. Therefore, the impetus to modify diagnostic criteria was centered on the shift in belief that fibromyalgia is not a discrete entity, but exists on a continuum with multiple types of symptoms. This same approach, of widening our current definitions of the disease, has been applied to uncovering new aspects of the disease pathogenesis.

Differential Diagnosis

As can be expected, the differential diagnosis of fibromyalgia is very large. The musculoskeletal pain or fatigue associated with other disorders may mimic those of fibromyalgia and vice versa. Additionally, there are many similar disorders, which are not exclusive of fibromyalgia, and will overlap concomitantly. The broad categories are the following:

- Inflammatory and autoimmune disorders, including rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, polymyalgia rheumatica, and spondyloarthritides
- Muscle disorders and myalgias
- Endocrinopathies, including hypothyroidism and hyperparathyroidism
- Neurologic disorders, including peripheral neuropathies, nerve entrapment syndromes, multiple sclerosis, and myasthenia gravis
- Myofascial pain syndrome, TMJ dysfunction, lower back pain
- Headache disorders

As fibromyalgia does not present with any of the specific laboratory abnormalities found in the other disorders, normal results may help to rule out incorrect diagnoses. Thus, the diagnosis can become manageable with a thorough and detailed history and physical exam, along with limited laboratory testing and imaging studies [13].

Pathogenesis

As we know today, the development of fibromyalgia results from augmented sensory and pain processing, whereby the exact mechanisms are unknown. There is a decreased

threshold to pain by nociceptive receptors, but also to heat, cold, electrical, and auditory stimuli [1]. The pathogenesis involves some components of the peripheral, central, and autonomic nervous systems; the mechanisms being elucidated via functional imaging studies (e.g., fMRI) and biochemical studies [5]. In normal healthy subjects, the body has multiple important descending inhibitory pain pathways, which carry output from higher brain centers towards the dorsal horn to synapse with ascending second-order neurons. The output inhibits further progression of pain transmission along those second-order neurons. The effect of this processing is such that an intense, painful stimulus should produce a partial whole body analgesic effect. However, c*entral sensitization* is an umbrella term which can describe various dysfunctions of the CNS involving ascending and descending neural pathways, all of which lead to an increased response to mechanical stimulation, mediated by amplification of CNS signaling [14]. At the same time, it is important to note that some degree of central sensitization can be deemed as normal, as it promotes protective behavior to shield injured tissue from further injury and maximize healing. However, these descending pathways, as part of diffuse noxious inhibitory controls, are attenuated or absent in fibromyalgia patients. This leads to the characteristic tenderness, manifested as allodynia and hyperalgesia, as indicated by lowered pain-pressure threshold [15].

Descending Pathways

One of the descending inhibitory pathways originates from the rostral ventromedial medulla (RVM) and nuclear raphe magnus and contains serotonergic (5-hydroxytryptaminergic, 5-$HT_{1,2}$) and GABAergic neurons, which synapse in the spinal cord to inhibit transmission in the dorsal horn [16]. A second pathway originates from the dorsolateral posterior tegmentum (DLPT) containing noradrenergic (containing norepinephrine) neurons that send inhibitory signals [2•]. Cerebrospinal fluid (CSF) analysis in fibromyalgia patients has consistently found decreased levels of serotonin and norepinephrine.

Another area of interest is the rostral anterior cingulate cortex (rACC), which has decreased activity to pain provocation, based on functional MRI studies. The rACC contains high levels of μ-opioid receptors, but in fibromyalgia patients, these receptors show decreased binding potential to opioids [17]. Other studies show that CSF levels of endogenous opioids, enkephalins, are actually increased in patients fibromyalgia as well as other idiopathic musculoskeletal pain syndromes [18]. These findings seem to suggest a *decreased* sensitivity towards opioids and corroborate the evidence that opioids are generally ineffective in treating fibromyalgia.

A third descending pathway involves the subnucleus reticularis dorsalis (SRD) of the caudal medulla. This inhibitory conditioned pain modulation (ICPM), is responsible for "heterotopic noxious conditioning," and describes the phenomenon whereby pain from one part of the body reduces the noxious stimulus from another body region. This mechanism is distinct from the two aforementioned pathways. And as suspected, aberrant ICPM processing is found among fibromyalgia patients [2•, 19].

Ascending Pathways

Conversely to abnormal descending inhibitory pathways which have been dampened, there is also abnormal function of ascending pain-facilitating pathways. There is a "wind-up" mechanism whereby levels of excitatory amino acids, glutamate, substance P, and nerve growth factor are increased by two- to threefold in CSF and second-order neurons [1, 20–22].

Non-CNS Mechanisms

Current research and evidence point toward aberrations of the peripheral nervous system present in fibromyalgia and other chronic pain syndromes. These mechanisms involve an antidromal axonal reflex of C-fibers in response to a stimulus, which activate neuroendocrine processes. Vascular permeability and vasodilation occurs. Mediators of innate immunity, including mast cells and dendritic cells, are activated, as well as the main protagonists of adaptive immunity, T-lymphocytes. Neuropeptides, such as glutamate, substance P, calcitonin gene related peptide (CGRP), neurokinin A, NGF, and brain-derived neurotrophic factor (BDNF) are released. Mast cells further release bradykinin, histamine, serotonin, and tumor necrosis factor (TNF). T-lymphocytes release an assortment of cytokines and interleukins. All these processes encompass the phenomenon of "neuro-inflammation," which can be described as classic (involving a mechanical nociceptive stimulus) or "neurogenic," in which stress and other psychological factors induce these neural responses to amplify the pain perception. As a result, the presence of certain signs and physical exam findings in fibromyalgia patients corroborate the role of peripheral mechanisms, such as peripheral swelling, reticular skin discoloration, dermatographism, cutaneous dysesthesia, and even Raynaud's phenomenon [23•]. Triggers that upregulate these abnormal mechanisms include trauma, as well as psychological factors, such as emotional stress. It is well known that catastrophizing is common among fibromyalgia patients [5, 23•].

Therefore, the abnormal "circuitry" of fibromyalgia involves some contributions from peripheral mechanisms, but predominately, central mechanisms, whereby central sensitization is a combination of increased pain facilitation and decreased pain inhibition; however, which one is more

prominent in the pathogenesis of the disease remains unclear at the moment.

There is certainly a hereditary, familial component to developing fibromyalgia. It has been shown that first-degree relatives have an eightfold risk of developing fibromyalgia compared to the general population. The sibling risk ratio for developing fibromyalgia is 13.6 according to a study by Arnold et al. [24]. In general, all family members exhibit some increased risk of developing other central sensitivity syndromes [25]. Kato et al.'s twin studies suggest half the risk is due to genetic factors, while half the risk is due to environmental factors [26]. And the list of specific genes that confer increased risk of fibromyalgia is ever growing. Specific genes which have been implicated include polymorphisms linked to chromosome 17p11.2-q11.2 [24], the serotonin receptor 2A region of chromosome 13, the serotonin transporter gene regulatory region, and the HLA region of chromosome 6. Polymorphisms of the catecholamine methyltransferase (COMT) gene are linked to the decreased pain threshold vulnerability seen in both depression and fibromyalgia. There is also evidence of dopamine-D-3 receptor and adrenergic receptor gene polymorphisms linked to fibromyalgia [27]. The presence of the latter infers a role of the sympathetic nervous system in the development of disease and the fact that many patients exhibit sympathetic hyperactivity [28]. As proposed by Ablin et al., there is a shift in the conceptualization of fibromyalgia from a discrete entity to a disease continuum with many phenotypes. As such, the role of genetic analysis has changed from the historical strategy of finding target genes and identifying specific genetic polymorphisms for those genes. Now, the focus is towards "incorporating genetic data relevant to the processing pain and to pain centralization into the spectrum of centralized pain" [29]. In this way, the genetics of fibromyalgia may be inferred from genetic data of TMJ disorder or IBS, and vice versa.

Stress

Another emerging concept is the role of oxidative stress, as patients are found to have an increased oxidative stress index, increased prolidase levels, and increased mitochondrial reactive oxygen species [30]. Levels of catalase and coenzyme Q_{10}, which is a mitochondrial electron transport carrier molecule, as well as an important anti-oxidant, are decreased in fibromyalgia, depression, and chronic fatigue [31]. Treatment with CoQ_{10} supplements has found some success for the treatment of clinical symptoms [5].

Sleep Disturbance

Historically, it was believed that pain preceded and exhibited a causal relationship with sleep disturbances and the poor sleep present among most fibromyalgia patients. In fact, the prevalence of sleep abnormalities exceeds 90 % in multiple studies [2•]. In a questionnaire study of 600 of mostly women (95 %), the presence of sleep disturbances was present in 96 % of participants at baseline and 94.7 % at 1 year. Surveys utilized included the McGill Pain Questionnaire, Pittsburgh Sleep Quality Index (PSQI), and the Fibromyalgia Impact Questionnaire (FIQ). In the same study, depression was also assessed and found in 50 % of participants at baseline and 30.5 % at 1 year [32]. Currently, it is believed that pain and abnormal sleep exist in a cycle, in that one may cause the other; the severity of sleep disturbance correlates with the severity of the pain and vice versa. Sleep deprivation will enhance pain sensitivity [6]. There is a cumulative effect between poor sleep quality, pain, and fatigue. Common complaints include nocturnal restlessness, involuntary leg movements, frequent awakenings, non-refreshing sleep, and daytime somnolence [2•].

Slow wave sleep (SWS) represented by stages 3 and 4 of non-REM sleep normally comprises approximately 20 % of total sleep time. This stage represents an essential aspect of restorative sleep, during which heart rate, blood pressure, cortisol levels, glucose consumption, and sympathetic nervous system activity decrease. REM sleep comprises 25 %, and the remainder of non-REM sleep, stages 1 and 2, comprise a total of 50 %. Only about 5 % is spent in a wakefulness stage, during which α-waves (7–12 Hz) predominate [2•, 33]. However, recent studies have shown decreased amounts of SWS in fibromyalgia patients compared to healthy controls. Under normal conditions, the body's homeostatic drive will increase the amount of SWS with any prior extended wakefulness. However, despite poor sleep the night before, fibromyalgia patients still exhibit decreased SWS, indicating impairment of this homeostasis [34]. Multiple studies have reported the phenomenon of α-intrusion in the sleep EEG, in which α waves overlap with δ waves during SWS to cause abnormal arousal. But other measurements from polysomnography (PSG) have not found any unique or pathognomonic patterns for fibromyalgia. Some PSG studies have shown low sleep efficiency, long wake time after sleep onset, increased percentage of stage 1 non-REM sleep; but others have not shown these patterns [6].

Thus, it has been shown that abnormal sleep disturbance causes enhanced pain, and a study by Moldofsky et al. was the first to show induced sleep disruption caused fibromyalgia symptoms, including fatigue, myalgias, increased tenderness, and reduced pain-pressure threshold [35]. Most recently, in a prospective questionnaire study looking at 4326 adults, 18.5 % developed chronic widespread pain at 3 years [36]. The development of widespread pain was at a higher rate among those with "some" pain at baseline (24.6 %) compared to those with no pain (7.7 %). Multivariate analysis of age, baseline pain, cognitive impairment, anxiety, and non-

restorative sleep, showed that non-restorative sleep was the strongest predictor of widespread pain (OR of 1.9, 95 % 1.2–2.8).

Nutritional Factors

Various vitamin deficiencies have been linked to the presence of widespread or chronic pain. However, there seems to be no definitive conclusions in regards to taking multivitamin supplementation. Vitamin D is implicated in the most recent literature, as it has significant effects on bone, neural tissue, and muscle growth and differentiation. There is a linkage between parathyroid dysfunction (parathyroid hormone regulates the activation of vitamin D into its active form, 1,25-dihydroxyvitamin D) and fibromyalgia, because of two significant factors present in both pathologies: sympathetic hyperactivity and progesterone activity. The latter may help explain why women are more prone to fibromyalgia. However, the clinical data consisting of multiple prospective and cross-sectional trials evaluating blood levels of vitamin D and symptom severity has only yielded controversial and inconclusive results [37].

Thiamine (vitamin B_1) deficiency has been linked to chronic widespread pain and fibromyalgia. In a small trial, Costantini et al. treated three fibromyalgia patients (all women) with high-dose oral thiamine (600–1800 mg/day). After 20 days of treatment, they had significant symptomatic improvements. Their blood levels of thiamine were within normal limits at the onset, but "supra-" normal afterwards. The authors concluded that despite "normal" levels, fibromyalgia patients may manifest symptoms because of a dysfunction of intracellular transport of thiamine, although they could not speculate on the mechanism of action [38].

An association between fibromyalgia and Vitamin B_{12} and folate deficiency has also been explored. Previous research has shown that hypo-methylation is present in immune cells and the DNA-encoding immune cells in patients with chronic fatigue syndrome (CFS) and fibromyalgia. Vitamin B_{12} and folate are fundamental intracellular co-factors for enzymes responsible for providing methyl groups. In a cross sectional survey of 38 patients with CFS and/or fibromyalgia, treated with B_{12} injections and oral folate supplements, those who had better symptomatic improvements, utilized higher doses of oral folate [39].

Other vitamins and minerals have been investigated for their anti-oxidant properties. It has been shown that significant levels of reactive oxygen species cause oxidative stress triggering the local tissue inflammation, which is seen in rheumatologic disease, such as fibromyalgia. Specifically, vitamins A, C, E, and magnesium have been studied; but the studies are few, and the results are controversial [40].

Treatment

Pharmacotherapy

There are multiple evidence-based treatment guidelines for fibromyalgia, put forth by the American Pain Society and the European League Against Rheumatism (EULAR), as well as in national guidelines set forth in Canada, Spain, and Germany. They all recommend common pharmacologic approaches to therapy, which include four broad drug classes—anti-epileptic drugs (AEDs), tricyclic anti-depressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs) [41]. Other drugs include muscle relaxants, 5-HT3 receptor antagonists, dopaminergic agonists, anti-oxidants, and investigational drugs [42•]. However, only *pregabalin*, *duloxetine*, and *milnacipran* have been approved by the Food and Drug Administration (FDA) in the USA for the treatment of fibromyalgia. The use of all other drugs is considered off-label. Even more stringent, Health Canada has only approved pregabalin and duloxetine, while the European Medicines Agency has approved no drugs for this indication.

Tricyclic Antidepressants (TCAs)

Amitriptyline is the representative drug in this class and is recommended by all the clinical guidelines. It is well-studied, having been evaluated in 17 trials, many of them placebo-controlled, and most of them over 15 years ago. Amitriptyline improves pain and sleep disturbances in fibromyalgia compared to placebo, but the effect on depression has scarcely been studied [42•]. And in combination with fluoxetine (SSRI) performed better than amitriptyline alone [43]. The typical dose is 10–50 mg daily. The most recent meta-analysis of 10 studies utilizing amitriptyline, duloxetine (a SNRI), and milnacipran (a SNRI) for the treatment of fibromyalgia showed that amitriptyline could improve pain, fatigue, and health-related quality of life (HRQL) in fibromyalgia, and was found superior to duloxetine and milnacipran [44].

Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)

Duloxetine and milnacipran are representative drugs within this class. They are two of the only three FDA-approved drugs for fibromyalgia. Duloxetine has been shown in multiple placebo trials to confer improve pain and depressive symptoms; but there were no effect on fatigue levels and inconclusive results in regards to sleep disturbance. Basically, duloxetine had been shown to improve the impact of fibromyalgia as measured by the FIQ and the mental component of QOL measures [45]. The target dosage is 60 mg daily.

Milnacipran has been similarly been shown in multiple placebo-controlled studies to improve pain and fatigue. However, results have been mixed with regard to depressive symptoms and sleep disturbance. A Cochrane review in 2013 demonstrated both duloxetine and milnacipran had small improvements in pain compared to placebo, but non-substantial changes in fatigue, QOL, and sleep disturbance [46]. The most recent Cochrane review of milnaciprin for adult fibromyalgia (the review did examine fatigue, sleep, cognition, or any other symptoms), further adds that milnacipran is effective only in about 40 % of patients, providing moderate (30 %) pain relief. Effective dosages were 100–200 mg [47].

Selective Serotonin Reuptake Inhibitors (SSRIs)

Of the available SSRIs, citalopram, escitalopram, fluoxetine, paroxetine, and sertraline have been investigated in at least one placebo-controlled trial. The results of the few trials are not are promising as with SNRIs or TCAs. Citalopram, escitalopram, and paroxetine were ineffective for improving pain [42•]. Interestingly, fluoxetine showed some improvements in pain, fatigue, depression, and overall symptomatology, but only for larger than standard dosing (up to 80 mg) [48]. Therefore, the results of the most recent Cochrane review of SSRIs for treatment of fibromyalgia (included studies up to June 2014) are not surprising. The authors concluded that there was no evidence to suggest SSRIs were superior to placebo in treating pain, fatigue, or sleep disturbance. But they *might* be considered for depression in this population [49•]. But as of now, SSRIs are recommended for use in fibromyalgia by the EULAR and Canadian guidelines.

Serotonin (5-HT_3) Receptor Antagonists

Though serotonin is known for its inhibitory role in descending pain inhibition, specific serotonin receptors (5-HT_3) are involved in pain facilitation in the CNS. Several placebo-controlled trials have shown the efficacy of tropisetron (oral) for the treating fibromyalgia pain [50], but no new trials have come out since 2007.

Cannabinoids

Nabilone, a synthetic cannabinoid, has only been studied in two small clinical trials, most recently in 2010. Interestingly, one study demonstrated improved pain and FIQ scores, while the other study showed improvements only in sleep, but not for pain, mood, or QOL [51, 52].

Sodium Oxybate

Sodium oxybate (Xyrem®) is the sodium salt of γ-hydroxybutyrate, which itself is derived from GABA, and binds $GABA_B$ receptors. It is a sleep modifier specifically licensed to increase the slow wave, non-REM sleep in narcolepsy patients [2•, 53]. It has been studied in several placebo-controlled trials [42•]. In the most recent double-blinded, placebo-controlled trial, improvements in multiple symptoms were demonstrated. Of 548 patients, using doses of 4.5 or 6 g daily, sodium oxybate was shown to significantly reduce pain (>30 % reduction) in over 50 % of the patients. Additionally, it has been found to improve fatigue, sleep disturbance, and functioning as per the FIQ score. However, there were no improvements in depressive symptoms or the mental components of QOL surveys [54]. It has been rejected by the FDA for use in fibromyalgia because of high abuse potential, with no plans for resubmission.

Anti-Epileptic Drugs (AEDs)

Pregabalin and gabapentin are AEDs, which work via binding to the α_2-subunit of voltage gated calcium ion channels within the CNS. Despite positive results with regard to pain and impact scores, gabapentin has only been studied in one placebo-controlled trial, which improved pain using 1200–2400 mg daily dosing [55]. Pregabalin was the first drug to be FDA approved for fibromyalgia in 2007. Short-term placebo-controlled trials have shown improvements with pain and sleep disturbances. Even more promising was a 6-month, long-term, placebo trial (FREEDOM), which showed pregabalin improved all outcomes: pain, sleep, fatigue, and QOL [56•]. But the most recent Cochrane review on AEDs in fibromyalgia reported more conservative results. The authors concluded that pregabalin demonstrated a small benefit in reducing pain and sleep problems, but had insubstantial effects of fatigue [57•].

Investigational and New Drugs

Other anti-depressants studied in clinical trials include mirtazapine (pre-synaptic α_2-antagonist), esreboxetine (NRI), and desvenlafaxine (SNRI), but the development of the latter two has been halted [42•].

Testosterone in the form of a transdermal gel has been shown to decrease pain responses in animal models. At the onset of a painful stimulus, levels of substance P increase in facilitation pathways, which activates aromatase to convert testosterone to estradiol and subsequently causes a release of endogenous enkephalins in descending inhibitory pathways to downregulate substance P. In fibromyalgia patients, particularly women, deficient amounts of testosterone lead to increased substance P and induce "wind up." [58]. However, the role of opioids is complex, as exogenous opioids are generally ineffective for treating fibromyalgia [10], and so further research is warranted.

Non-Pharmacologic Treatment

Exercise

Exercise, in the form of aerobic exercise, resistance training, or flexibility training, has been shown in trials to provide benefits in fibromyalgia patients. In a 2007 meta-analysis of 2276 subjects in 34 studies designed to evaluate the effectiveness of different exercise modalities, aerobic-only exercise was shown to improve global well-being, physical function, and pain. Strength testing and flexibility training were not evaluated in this review [59].

In 2014, another meta-analysis evaluating 219 women in five different studies comparing resistance training (weight training) to no exercise or other types of training. Moderate intensity resistance training when compared to no exercise was shown to improve pain, tenderness, physical functioning, and not surprisingly, muscle strength. However, the evidence was rated as low quality, and 8 weeks of aerobic exercise alone was shown to have better pain outcomes than resistance training [60]. Aquatic exercise, defined as performing exercise in waist-deep or chest-deep water, has also been demonstrated in another meta-analysis of 881 subjects in 16 studies, to be effective in improving pain, stiffness, muscle strength, and overall well-being compared to no exercise; however, these results were similar to standard land-based exercise [61].

Mind and Body Therapy

The label of "mind and body therapy" is a heterogeneous term which some consider as "meditative movement therapy" or "complementary and alternative exercise." Within these umbrella terms, *qigong* refers to the cultivation of *qi* (life energy). The goal is to improve the flow of *qi* through the body with purposeful hand and body movements. The most recent review of trials demonstrated improvements after 6 months compared to baseline, in all domains of fibromyalgia. However, the studies had significant methodological issues and variability. Ultimately, the amount of quality of qigong practice (daily self-practice) matters significantly and can lead to long-term benefits (≥6 months) [62]. *Tai chi* is another mind-body technique, with specific movements, postures, and breathing techniques. A meta-analysis in 2014 of seven studies evaluating tai chi for fibromyalgia showed improvements in symptoms of pain and sleep quality [63].

Massage Therapy

Prior studies examining the effects of massage therapy in fibromyalgia patients produced variable and controversial results. However, as the diagnostic criteria of fibromyalgia changed in 2010, there was recognition that symptoms other than pain played a large role in disease severity. More recent studies have evaluated these new therapeutic endpoints. In a 2014 systematic review and meta-analysis, Li et al. included randomized controlled trials conducted after 2006; the authors examined fatigue, anxiety, depression, and sleep disturbance. They also included studies looking at traditional Chinese massage, which was not extensively reviewed previously. Their main conclusion was that massage therapy with duration greater than 5 weeks produced significant improvements in pain, anxiety, and depression [64]. In another review which looked at many of the same trials as Li et al., the authors concluded most styles of massage therapy consistently improved the quality of life for fibromyalgia patients. More specifically, they determined myofascial release techniques were the most beneficial, with decreases in pain, anxiety, and depression. Connective tissue massage and *shiatsu* had limited benefit, while Swedish massage may have no benefits for fibromyalgia [65].

Acupuncture

Acupuncture is a form of traditional Chinese medicine, which involves the placement of fine needles at various defined acupuncture points throughout the body. Of its many intended effects, one is to reduce pain in various pain conditions. It is theorized to work by reducing inflammation, causing the release of endorphins, and creating a calmer mind [66•]. Many studies have shown its usefulness in reducing pain in fibromyalgia and other pain states, when compared to no treatment or sham acupuncture. Stival et al. recently performed a randomized, double-blinded, control trial comparing the immediate VAS scores of adult fibromyalgia patients receiving standard acupuncture treatment versus subjects receiving sham treatments. The reduction in VAS score pre- and post-treatment was 4.36 and 1.7 for acupuncture and sham acupuncture patients, respectively [67]. It has been theorized that acupuncture generates its analgesic effects by causing the release of adenosine triphosphate (ATP), which is metabolized to adenosine, which activates A1 receptors to block inflammatory and neuropathic pain. In a recent animal study, levels of transient receptor potential vanilloid 1 (TRPV1) and TRPV4 were increased in the dorsal horn of mice induced with a fibromyalgia-like pain state. Electroacupuncture was shown to significantly reverse the upregulation of these receptors and mitigate mechanical hyperalgesia [68].

Overall, according to the most recent Cochrane review, there is low to moderate level evidence showing that acupuncture improves pain and stiffness in fibromyalgia; but, it may not be generally more effective than sham acupuncture technique. Also, electroacupuncture is better than

acupuncture for pain and stiffness, but the effects do not last after 6 months [66•].

Conclusion

Fibromyalgia is a chronic pain condition characterized by a constellation of symptoms, including pain, tenderness, fatigue, anxiety, sleep dysfunction, cognitive impairment, and mood disturbances. There is a global sense of being unwell, where negative feelings frequently lead to catastrophizing. As with the clinical manifestations, the diagnosis if fibromyalgia has evolved in the last 20 years to be more representative of a spectrum of disorders rather than a discrete entity. The current diagnosis as put forth by the American College of Rheumatology no longer requires the presence of predetermined "tender points," but on the combined WPI and SS scores. Fibromyalgia is part of a larger group of other conditions, which it is often co-morbid with, including TMJ dysfunction, IBS, chronic fatigue syndrome, and myofascial pain syndrome. Depression and sleep disorders are also very common among fibromyalgia patients. The primary mechanism is central sensitization, in which ascending pain pathways are upregulated, while descending inhibitory pain pathways are downregulated. Of course, recent research has shown that peripheral mechanisms are involved, as well other areas of the brain, affecting sleep regulation. The current treatment involves multiple pharmacologic and non-pharmacologic options. However, only three drugs are approved by the FDA in the US for fibromyalgia: pregabalin, duloxetine, and milnacipran. The current guidelines from multiple agencies, including the FDA, promote the use of multiple agents to target the specific symptoms, which are varied among fibromyalgia sufferers. Common therapeutics include tricyclic antidepressants, SSRIs, SRNIs, anti-epileptic drugs, cyclobenzaprine, among others. Other methods include various exercise modalities, mind and body therapy, and acupuncture. Multiple studies and reviews demonstrate that these alternative methods improve the pain and stiffness associated with fibromyalgia; they can be important adjuncts for treatment. And on the horizon, current research is aimed at: (1) understanding more of the genetic underpinnings of fibromyalgia and (2) uncovering more receptors and biomolecules, which are aberrant in the disease.

Compliance with Ethical Standards

Conflict of Interest Steven Chinn, William Caldwell, and Karina Gritsenko declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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