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REVIEW

Advances in diagnostic and treatment options in patients with fibromyalgia syndrome

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Abstract: Fibromyalgia (FM) is characterized as a chronic, painful, noninflammatory syndrome affecting the musculoskeletal system. In addition to pain, common co-morbid symptoms associated with FM include sleep disturbances, fatigue, morning stiffness, affective disorders, chronic daily headache, dyscognition, irritable bowel syndrome, and irritable bladder. Fibromyalgia is usually classified by application of the American College of Rheumatology (ACR) criteria. Although these criteria are accepted among investigators who agree with the concept of fibromyalgia, they do so with some reservations. Tender points and widespread pain alone does not describe the esence of fibromyalgia. New diagnostic tools including either clinical or radiological components are studied to diminish these problems. Although various pharmacological solutions have been studied for treating fibromyalgia, no single drug or groups of drugs have proved to be useful in treating fibromyalgia patients. Recently, three drugs, pregabalin, duloxetine and milnacipran, were approved for the treatment of FM by the US Food and Drug Administration (FDA). Novel therapeutic approaches to the management of FM include cannabinoids, sodium channel blockade and new generation antiepileptics. This review evaluates both new diagnostic tools, including clinical or radiological regimes, and tries to highlight the efficacy of medicinal and nonmedicinal treatments with new therapeutic approaches in the management of FM with a wide perspective.

Keywords: diagnosis, fibromyalgia, rehabilitation, treatment

Introduction

Fibromyalgia (FM) is a chronic, musculoskeletal pain condition associated with some co-morbid symptoms. The American College of Rheumatology (ACR) recommends that patients meet two specific criteria in the diagnosis of FM; a history of widespread pain for at least three months and pain in 11 of 18 specific anatomical sites described as tender points on digital palpation with an approximate force of 40 N (equivalent to 4 kg weight force) for classification of FM.[1] This definition, however, does not include the large number of other symptoms associated with fibromyalgia, including fatigue, nonrestorative sleep, morning stiffness, headache, cognitive disturbances, anxiety, and parasthesias. Depressive syptoms are also quite common in FM patients.[2]

ACR criteria are accepted among investigators who are in agreement with the concept of fibromyalgia, although with some reservations. In practice the diagnosis is often made without the formal tender point examination. Although patients may have the required number of appropriate tender points and these tender points are widespread, pain alone is insufficient to diagnose fibromyalgia.[3,4] In a series of focus groups, clinical experts and patients agreed that while pain is an important symptom of FM, it is also

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necessary to assess other co-morbid symptoms as mentioned above.[5] Despite extensive clinical study, there is no distinct consensus on the optimal management of FM. Previous guidelines for the management of fibromyalgia recommended an approach that integrates pharmacological and nonpharmacological therapies, selected according to the symptoms experienced by individual patients. Therefore, assessing the effectiveness of new therapies requires accurate documentation of a multidimensional array of clinical manifestations. This review analyzes the problems associated with ACR classification criteria for FM and presents new diagnostic methods related with this syndrome. We also evaluate the medicinal and nonmedicinal treatments with new therapeutic approaches in FM with a wide perspective. Articles were identified in the PubMed database by using the following search terms, alone or in combination: "fibromyalgia", "new therapies", "diagnosing methods", "treatment". No date restriction was placed on the search. Original articles from the bibliographies of these primary articles were also reviewed.

Fibromyalgia syndrome

Clinical features

FM is characterized as a chronic, painful, noninflammatory syndrome affecting the musculoskeletal system. This disease affects 2% of the population: 0.5% of men and 3.4% of women.[6] The etiology and pathophysiology of the disease remains unclear. Current hypotheses center on atypical sensory processing in the CNS and dysfunction of skeletal muscle nociception and the hypothalamic–pituitary–adrenal (HPA) axis.[7] Patients seem to have a generalized abnormality in pain perception, with a decline in pain threshold and tolerance to an assortment of stimuli, such as pressure, cold, and heat.[8] In addition to pain, common co-morbid symptoms associated with FM include sleep disturbances, fatigue, morning stiffness, affective disorders, chronic daily headache, dyscognition, irritable bowel syndrome, and irritable bladder.[6]

Pathogenesis

Central sensitization and windup

It was suggested that the pathogenesis of FM involves aberrations in central nervous system (CNS) function that result in abnormal pain perception.[9] Central sensitization of nociceptive neurons in the dorsal horn that are due to activation of N-methyl-D-aspartic acid (NMDA) receptors and disinhibition of pain, that is a result of deficient function of the descending inhibitory system, are probably pathogenic factors for hypersensitivity to all kind of stimuli.[10] In a another definition central sensitization is described as hyperexcitability of the CNS neurons in response to peripheral noxious stimuli, coressponding to an exaggerated response to normally painful stimulus (hyperalgesia), increased duration of response following a brief stimulus (persistent pain) and a response of pain following a normally nonnociceptive stimulus, for example, touch or rubbing (allodynia).[11] One of the hypothesis that hyperalgesia in patients with FM is due to an upregulation in the central nociceptive system.[12]

Important CNS mechanisms relevant for FM pain include temporal summation of pain (windup) and central sensitization.[13,14] Windup (WU) represents an important pain mechanism that can result in both short and long-term changes of neuronal responsiveness, including central sensitization. WU occurs during repetitive nociceptive stimuli of sufficient intensity or frequency to remove the magnesium block of the NMDA receptor. This event is followed by calcium influx into the cell and subsequent triggering of signaling cascades that can result in amplification of nociceptive input and long-term central sensitization. Importantly, once central sensitization has occurred only minimal nociceptive input is required to maintain the sensitized state and clinical pain. Many studies have indicated evidence for abnormal WU and central sensitization in patients with FM.[15,16] It is therefore conceivable that acute or chronic triggers such as trauma or infections can result in the chronic widespread pain of FM.[13,17]

Diagnosing of FM

In the late 1980s, the Fibromyalgia Multicenter Criteria Committee was formed under the auspices of the American College of Rheumatology. Its classification criteria, adopted in 1990, provided a starting point from which to standardize the study of patients with this condition.[1] The publication of the ACR criteria was a great step forward in the understanding of the syndrome.

According to the ACR's criteria; FM is defined as widespread pain of at least three months duration and pain on palpation of at least 11 of 18 specific tender sites on the body. The dual criteria of widespread pain and tender points results in 88.4% sensitivity and 81.1% specificity for diagnosing FM.[1] There are, however, limitations to the ACR diagnostic criteria. They are entirely subjective and qualitative, centering on the patient's report of pain and the physician's interpretation of behaviors related to pain, such as withdrawing from the stimulus, grimacing, or crying.[18] Improved methods that present stimuli in a random, unpredictable fashion (for example, multiple random staircase) tend to minimize the

influence of these factors.[19] There is no viable method to blind either the subject or the examiner.

Another significant problem with the ACR criteria is the diagnostic method regarding the palpation of the 18 points[20] with a finger pressure of "approximately" 40 N/cm^2 (equivalent to 4 kg/cm^2 weight force).[4] This method has produced questionable inter-examiner reliability[21–23] although this problem has been partially improved by the use of the algometer.[23–25] However, there remains the problem that 19% of patients with at least 11 tender points may not have fibromyalgia syndrome. Additionally, tender points don't correlate well with other measures of illness activity, such as the fibromyalgia impact questionnaire.[26] As a result of such diagnostic difficulties require further study to clarify the diagnosis of fibromyalgia syndrome.

Symptom intensity scale: A new diagnostic tool

The symptom intensity scale (SIS), a relatively new diagnostic tool, offers to assess both regional pain and fatigue in a patient. It can be used to establish the diagnosis of fibromyalgia syndrome and measure its severity in daily clinical practice without the need to count tender points.[27] The SIS questionnaire consists of two parts: a list of 19 anatomical areas (jaws, chest, abdomen, forearms, upper legs, lower legs, upper arms, upper back, hips, shoulders, neck, low back) in which the patient is asked if he or she feels pain (the total number of affirmative answers being the regional pain scale [RPS] score), and a visual analog scale in which the patient makes a mark somewhere along a 10 cm line to indicate how tired he or she feels. Subsequently, the clinician measures the position of the mark from the left end of the line with a ruler. According to the survey criteria, a diagnosis of fibromyalgia can be established if the RPS score is 8 points or higher and the fatigue visual analog scale score is 6 cm or greater. (A score of 5.0 cm or greater on the fatigue visual analog scale is probably consistent with a diagnosis of fibromyalgia syndrome.) The SIS score is calculated according to the following formula:

$$\frac{\text{(Fatigue visual analog scale} + \frac{\text{regional pain scale score)}}{2}}{2}$$

A score ≥5.75 is diagnostic for FM and differentiates fibromyalgia syndrome from other rheumatic conditions.[27]

Katz and colleagues compared ACR criteria, survey criteria and clinician diagnosis. They suggested that clinical diagnosis, ACR and survey criteria were moderately concordant (72%–75%) and addressed a common pool of symptoms and physical findings. They also suggested the survey method had the advantage as it did not require physical examination.[28]

Imaging techniques

Functional MRI (fMRI)

fMRI is a noninvasive brain imaging technique that relies on changes in the relative concentration of oxygenated to deoxygenated hemoglobin within the brain. In response to neural activity, oxygenated blood flow is increased within the local brain area. This causes a decrease in the concentration of deoxygenated hemoglobin. Since deoxygenated hemoglobin is paramagnetic, this in turn causes a change in the magnetic property of the tissue.[29]

In a study by Gracely and colleagues[30] of 16 fibromyalgia patients with 16 matched controls, both sets were exposed to painful pressures during the fMRI experiment. The authors found increased neural activations (ie, increases in the blood oxygenation level dependent signal) in FM patients, compared to the pain-free controls, when stimuli of equal pressure were administered.

At the present time, functional brain imaging in FM has revealed the following insights. 1) FM patients differ from healthy controls in baseline levels of neural activity, specifically in the caudate nucleus. 2) administration of a noxious pressure or heat stimulus results in changes in brain activity consistent with the verbal reports of patients' pain intensity.[19]

Lutz and colleagues[31] combined diffusion tensor magnetic resonance imaging (DT-MRI) and voxel-based morphometry analyses of MRI to study patients with fibromyalgia syndrome to determine micro-structural and volume changes in the central neuronal networks involved in the sensory discriminative and affective-motivational characteristics of pain, anxiety, memory, and regulation of the stress response. Lutz and colleagues found decreases in gray matter volume, in the postcentral gyri, amygdalae, hippocampi, superior frontal gyri, and anterior cingulate gyri. They recognized that increased pain intensity scores were correlated with changes in DT-MRI measurements in the right superior frontal gyrus and increased fatigue was correlated with changes in the left superior frontal and left anterior cingulate gyrus, self-perceived physical impairment was correlated with changes in the left postcentral gyrus.[31] They suggested that DT-MRI may serve as an additional diagnostic technique in FM and probably other dysfunctional pain syndromes.

Magnetic resonance spectroscopy

Magnetic resonance (MR) spectroscopy obtains spectra of multiple selected regions and determines the ratio of

concentrations of metabolites such as N-acetyl-aspartate, creatine, choline, lactate, glucose and glutamate. Abnormalities in the levels of these metabolites are related to a number of pathological changes in brain tissue.[19] In a recent study, to test the levels of these metabolites, in patients with FM, proton MR spectroscopy (H-MR spectroscopy) was used. It was suggested that there were baseline differences in the variability of the relative concentrations of brain metabolites, between patients with FM and healthy controls, in the right dorsolateral prefrontal cortex. Significant correlations between metabolite ratios and clinical and experimental pain parameters in patients with FM were also observed.[32]

Single photon emission computed tomography (SPECT) and positron emission tomography (PET)

Mountz[33] used SPECT to evaluate baseline levels of regional cerebral blood flow (rCBF) in 10 patients with fibromyalgia and in seven healthy control subjects. In this initial study, patients received infusions of approximately 25 mCi of ^{99m}Tc-HMPAO, a radioactive tracer that facilitates the imaging of rCBF. Results from this early study suggested that patients with FM had lower rCBF (suggesting lower neural activity) than healthy control subjects during a quiescent resting state. Reduced neural activity was found both in the right and left thalamus and in the right and left caudate nucleus.[33]

Kwiatek and colleagues[34] used SPECT to assess resting rCBF in 17 patients with FM and in 22 healthy control subjects. These investigators observed decreased rCBF in the right thalamus, the inferior pontine tegmentum and near the right lentiform nucleus but, unlike the Mountz study, no decreases in either the left thalamus or in the caudate nuclei were noted.[34]

In a further study Gur and colleagues[35] studied 19 young women with fibromyalgia and 20 healthy women, they also evaluated differences in rCBF between subject using SPECT. This study indicated a significant increase in rCBF of the caudate nuclei, a reduction in the pons, and some cortical region activity.

Adiguzel and colleagues used SPECT imaging to assess changes in rCBF following administration of amitriptyline in 14 fibromyalgia patients. After three months of treatment with amitriptyline, they noted increases in rCBF in thalamus bilaterally and the basal ganglia.[36] This study is important as it compares rCBF in both the diagnosis of FM and in evaluating its treatment.

PET has been used in a few studies related to fibromyalgia. Wood and colleagues used PET to indicate that attenuated dopaminergic activity may be playing a role in pain transmission in fibromyalgia.[29,37]

Developments in novel imaging methods promises to increase our knowledge of the mechanisms that initiate and maintain FM, and may improve both diagnosis and treatment strategies.

Treatment

FM is a complex syndrome associated with significant functional and quality-of-life impairments. There is emerging evidence that fibromyalgia is associated with aberrant central nervous system processing of pain.[38] Current treatments for fibromyalgia include medical, self-management and alternative therapies. Although recommendations (eg, European League Against Rheumatism [EULAR] and American Pain Society [APS]) for FM management have been published, a universally accepted treatment algorhythm or approach is often lacking.[39–41]

Pharmacologic treatment

Antidepressants

Amitriptyline

Amitriptyline is the most widely prescribed pharmacologic agent for treatment of FM[42] and has consistently been found to alleviate FM symptoms.[17] A large number of randomized clinical trials (RCTs) have demonstrated that clinically important improvement occurs in 25%–45% of FM patients given this drug.[43–45] Amitriptyline was significantly better than placebo or than naproxen, 500 mg twice daily, in pain reduction.[46] One trial showed that when amitriptyline and fluoxetine were taken together, they were twice as effective as when either was taken alone.[47] In general, pooled analyses demonstrate that the improvement with tricyclics was mild for fatigue and moderate for pain, sleep and overall well-being. The doses of tricyclics have been low, and most studies have been of short duration, such as 6–12 weeks. The doses of amitriptyline have been 25–50 mg, usually given as a single bedtime dose.[48]

Cyclobenzaprine

Cyclobenzaprine shares its tricyclic structure with amitriptyline and nortriptyline but does not function as an antidepressant. Instead, cyclobenzaprine acts at the brain stem to induce skeletal muscle relaxation.[49] The idea that muscle spasm may play a role in fibromyalgia pain (despite electromyographic studies showing no evidence of spasm) led to investigations of cyclobenzaprine.[44,50] Short-term (12-week) studies suggest that 10–40 mg per day of cyclobenzaprine reduces fibromyalgia pain and sleep disturbance.[44,50]

Fluoxetine

There is moderate evidence that the selective serotonin reuptake inhibitor (SSRI) fluoxetine is effective in FM. In one study of 42 patients with fibromyalgia, there was no significant benefit of FM administering fluoxetine (20 mg/day) when compared with placebo over a six-week period.[51] However, a flexible placebo-controlled dose study of fluoxetine (<80 mg/day) demonstrated significant efficacy in 60 women with fibromyalgia[52] improvement was noted on a fibromyalgia impact questionnaire (FIQ) total score as well as subscores for pain, fatigue, and depression. Pain in tender points and total myalgic scores were not significantly improved. There was no difference in the measures of mood disturbances in the two groups and the effect of fluoxetine on pain was still significant after adjustment for change in depression score.[53]

Citalopram

Citalopram was used by Norregaard and colleagues[54] to study its effect on a SSRI, in a placebo-controlled study of FM patients. The results demostrated there was no improvement in the patients who had received citalopram, when compared to the patients who had received placebo, of pain or other main symptoms such as; depression scores, fatigue or insomnia, after eight weeks of treatment.

In a study by Anderberg and colleagues,[55] FM patients had 30–40 mg citalopram/day for four months. In the global judgment of improvements, no significant differences occurred between the citalopram and placebo groups. However, in a more detailed analysis of the patients who completed four months of treatment there were benefits in some areas. Regarding pain, there was a significant reduction of pain scores after two months of treatment in the patients receiving citalopram compared to the patients receiving placebo. However the difference diminished at the end of the trial. The FIQ showed improvement at four months.[55] This study also assessed depressive symptoms, which improved in the citalopram group after one month and increased further over the duration of the trial

Venlafaxine

Venlafaxine is a generic serotonin and norepinephrine reuptake inhibitor (SNRI) that has efficacy in fibromyalgia management at a dosage of 75 mg per day, and is a reasonable alternative for patients who cannot afford branded SNRIs.[56] It significantly improved pain, fatigue, sleep quality, morning stiffness, depression, anxiety and patient global assessment of fibromyalgia in a small, open label clinical trial.[57]

Reboxetine

Reboxetine, a SNRI, has resulted in an increase of interest in the catecholamine pathway for the treatment of chronic pain. Double-blind, placebo-controlled studies indicate that as an antidepressant, reboxetine is more effective than placebo and similar in efficacy to other SSRIs and tricyclic antidepressants in reducing depressive symptoms, with a relatively benign side effect profile and may help stimulate physical activity and vitality.[58]

Dopamine-related agents

Sibutramine

Sibutramine, a serotonin/noradrenaline/dopamine reuptake inhibitor reduces presynaptic dopamine metabolism in FM, as demonstrated by positron emission tomography, and supports a disruption of dopaminergic neurotransmission involved in the pathophysiology of FM.[37] In addition, it has been reported that patients with FM have an abnormal dopamine response to pain.[59] Sibutramine has been reported to improve pain, sleep and fatigue in patients with FM in a pilot retrospective study; when sibutramine was stopped, FM symptoms returned within 3–7 days.[60] Further studies with sibutramine are required to determine the value of such a combined pharmacological profile in the treatment of FM.[61]

Pramipexole

Pramipexole, a second-generation dopamine agonist developed for the treatment of Parkinson's disease was tested in patients with fibromyalgia in a 14-week, single center, randomized, placebo-controlled study in which pramipexole was added on to existing pharmacological and nonpharmacological therapies.[62] The rationale for testing a dopamine D3 agonist in fibromyalgia is based on evidence that excessive adrenergic arousal may fragment sleep, and enhancement of dopaminergic neurotransmission at the D3 receptors in the mesolimbic hippocampus may reduce expression of arousal and improve sleep. Compared with the placebo group, those patients receiving pramipexole titrated over 12 weeks to 4.5 mg every evening had gradual and significant improvement in pain, fatigue, function, and global status.[63] The mechanism by which pramipexole improved the symptoms of fibromyalgia is unclear.

N-methyl-D-aspartate (NMDA) receptor antagonists

Ketamine

Ketamine is a powerful high-affinity NMDA receptor antagonist was initially developed as an anesthetic. NMDA receptors may play a role in the nervous system reorganization

thought to be involved in maintaining chronic pain, and its blockade can relieve pain in patients with FM. Two randomized, controlled trials involving 46 patients fulfilling the 1990 ACR classification criteria for FM showed that ketamine increased endurance and reduced pain intensity, tenderness at trigger points, referred pain, temporal summation, muscular hyperalgesia, and muscle pain at rest.[64] Both studies suggested the presence of central sensitization in FM, that tender points are areas of secondary hyperalgesia, and that the relief of these symptoms by ketamine indicated a reduction in central sensitization. However, the cognitive side effects of NMDA receptor blockade may limit the use of NMDA in FM therapy.

Memantine

Memantine is an amantadine derivative that has been used to treat Parkinson's disease, spasticity, convulsions, vascular dementia, and Alzheimer's disease with an excellent clinical safety record for over 20 years. While decreased NMDA receptor affinity contributes to memantine's safety and efficacy as a neuroprotective agent, it also renders it less effective than high-affinity antagonists (eg, ketamine) in chronic pain management.[65,66] Memantine may also show increased efficacy in the treatment of FM-associated chronic pain. Kim and colleagues[67] reported an increased expression of NMDA receptor subunit 2D in the skin of FM patients with fibromyalgia, which could be indicative of a more generalized increase of the receptor in other peripheral nerves. Memantine may also suppress neuronal excitability and confers neuroprotection in a manner similar to pregabalin.[68]

Atypical antipsychotics

Olanzapine

Olanzapine is a new "atypical" neuroleptic that has been effective for the treatment of many pain conditions, such as cancer pain,[69] headache,[70] and rheumatoid arthritis.[71] Kiser and colleagues[72] described two fibromyalgia patients who benefited from treatment with the atypical neuroleptic olanzapine when other medications have failed.[73]

Ziprasidone

Ziprasidone is a second-generation antipsychotic with potent 5-HT1A and 5-HT1B agonistic properties, a capacity, which has been linked to potential anxiolytic activity.[74] In one study, ziprasidone was administered to 32 fibromyalgia patients at a dose of 20 mg/day, subsequently adjusted according to clinical response and tolerability. It was noted that the conditions of stiffness, anxiety and sadness improved significantly but some side effects were observed like sleep disturbances, headache, tremor, and rigidity so the authors suggested that it could be tried on patients who are markedly anxious and/or depressed.[75]

Antiepileptics

Lacosamide

Lacosamide (LCM) is a third-generation antiepileptic drug. The drug does not mimic the effects as an allosteric modulator of gamma-aminohydroxybutyrate (GABA) A receptor currents.[76] Lacosamide selectively enhances sodium channel slow inactivation with no effect on fast inactivation.[77] The drug displays affinity for the glycine strychnine-insensitive recognition site of the NMDA receptor complex,[76] and allosterically blocks NMDA receptors with a specific action on receptors containing the NR2B subunit.[78] LCM is considered for monotherapy for partial-onset seizures and in patients in migraine prophylaxis or with fibromyalgia syndrome.[79,80]

Zonisamide

Zonisamide (ZNS), a sulphonamide derivative, is a new-generation anticonvulsant with multiple potential mechanisms that contribute to its antiepileptic efficacy and may also explain its currently incompletely assessed utility for nonseizure disorders such as headaches, neuropathic pain, and weight loss. The assessment of LCM and ZNS in patients with FM will provide insight into the potential of sodium channels as therapeutic targets in this condition.[79]

Cannabinoids

The endocannabinoid system shares several similarities with the opioid system.[81] The cannabinoid receptor CB1 and opioid receptors are both found in similar areas of the nervous system involved in pain control, including the periaqueductal gray matter, rostral ventromedial medulla, and the spinal cord.[82] Besides the similarities with the opioid system, cannabinoids have also been shown to inhibit prostaglandin E_2 synthesis,[83] and have an anti-inflammatory effect twice as great as hydrocortisone and 20 times that of aspirin.[84,85]

Nabilone

Nabilone is currently approved for the management of nausea and vomiting during chemotherapy. Other known action of cannabinoids including inhibition of prostaglandin E_2 synthesis.[83] Experimental increases in endorphins[86] and the regulation of substance P and enkephalin mRNA levels in the basal ganglia[87] could all contribute to less pain experienced in the nabilone-treated patients. Research into

oral cannabinoid use in the management of chronic and neuropathic pain has been encouraging.[85,88] Skrabek and colleagues randomized patients into placebo and nabilone receiving groups. After four weeks of treatment patients who received nabilone experienced significant improvements in clinical pain, measured on a visual analog scale, FIQ score and the 10 point anxiety scale of the FIQ. After the wash-out period at the end of the trial all improvements were lost in nabilone group.[85]

Alpha2-delta ligands

Gabapentin

Gabapentin is a GABA analogue that was originally developed for the treatment of epilepsy. The release of neurotransmitters that play a role in pain processing, such as glutamate and substance P, are regulated by calcium influx into nerve terminals within the nociceptive pathways.[89,90] The relevant sites of action include voltage-gated ion channels (ie, sodium and calcium channels), ligand-gated ion channels, the excitatory receptors for glutamate and NMDA, and the inhibitory receptors for GABA and glycine.[91] Block of the presynaptic calcium channels by ligands of the $\alpha 2\delta$ subunit of that channel (eg, gabapentin, pregabalin) will decrease the neurotransmitter release and attenuate abnormal hyperexcitability of neuronal networks such as that associated with chronic pain.[41]

In the gabapentin in fibromyalgia treatment (GIFT) study, an investigator-initiated, National Institutes of Health-funded study, gabapentin in patient-optimized doses between 1200 and 2400 mg/day was compared with placebo over 12 weeks.[92] The primary outcome, was the measure of pain as estimated by the brief pain inventory (BPI) average pain severity score. Patients treated with gabapentin (median dose 1800 mg/day) had significantly greater improvement in pain severity than patients treated with placebo ($P < 0.015$). Gabapentin compared with placebo also significantly improved the BPI average pain interference score, the FIQ total score, the clinical global impression of severity, and the patient global impression of improvement. There was also improvement in sleep and vitality.[92] Some patients though may have gabapentin associated dose-dependent dizziness and somnolence.[92] Tolerance improves if patients are started on lower doses with incremental increases to the optimal dose. The severity of these adverse effects is generally mild with few discontinuations in clinical trials; however, these and other adverse events, including weight gain and peripheral edema, may limit the utility of these drugs in some patients.[93]

Other pharmacologic medications

Tropisetron

Tropisetron is a 5-hydroxytriptamine 3 (5HT3) serotonin antagonist. The presence of 5HT3 receptors on both the inhibitory dorsal horn interneurons and the primary afferent fibers that relay nociceptive information from peripheral nociceptives to the dorsal horn may explain the pro- and antinociceptive effects of 5-HT3 receptor blockade.[63] In a randomized, placebo-controlled, double blind study patients with FM assessed the efficacy of tropisetron at doses 5 mg, 10 mg, 15 mg per day in a 10-day period. Patients who received 5 mg and 10 mg per day had significant reduction in pain. The effects of a dose of 15 mg per day were not different from placebo.[94] The mechanism by which 5HT3 receptor antagonism reduces FM-associated pain and other symptoms are not understood, although these benefits may be secondary to reduced substance P release.[95]

Tegaserod

Tegaserod, a potent partial agonist of 5-hydroxytryptamine-4 receptors, has been used for the treatment of female irritable bowel syndrome (IBS) patients with constipation (IBS-C). It was shown to improve significantly symptoms of IBS-C within the first week of use.[96] In a study the effect of tegaserod on signs and symptoms of FM in patients treated by this agent, in addition to improvement in IBS status after one month of tegaserod treatment, it was noted that a significant improvement in the general status of the patients, with improvement in their ability to perform daily tasks, and a significant decrease in anxiety and depression scores, together with a suppression of the number of tender points and the intensity of pain while palpating tender points.[97]

Sodium oxybate

Sodium oxybate is the sodium salt of gamma hydroxybutyrate (GHB), an endogenous short-chain fatty acid, and is used for the oral administration of exogenous GHB.[98–100] It is likely that the supraphysiological concentrations induced by exogenous administration lead to qualitatively different neuronal actions from those produced by endogenous GHB. There is evidence suggesting that GHB plays a role as a neuromodulator/neurotransmitter. Sodium oxybate, in narcolepsy has shown dose-related effects on various properties of sleep.[98] A preliminary four-week, double-blind, placebo-controlled crossover trial of 24 woman with FM suggested that sodium oxybate reduced symptoms of pain and fatigue, decreased tender point index, and increased slow-wave sleep and decreased alpha intrusion on polysomnography.[99]

Despite the results GHB is associated with likelihood of abuse.[101] The most frequently reported adverse events included dose-related headache, nausea, dizziness, and somnolence.

Modafinil

Modafinil, unlike amphetamines, is well tolerated, with less peripheral hemodynamic alterations combined with low abuse and tolerance sequelae. It also improves vigilance in sleep-deprived patients.[102] The mechanism by which modafinil might be helpful in the treatment of the fatigue in FM remains unknown. Experimentally, it activates nondopaminergic neurons in contrast with the amphetamines and methylphenidate that exert a significant effect on dopaminergic neurons.[103,104]

Metilphenidate

Metilphenidate has not been specifically studied as a treatment for fibromyalgia, however, it is the most commonly used stimulant in fibromyalgia therapy, owing to its low cost and the lack of insurance restrictions on its use. Psychostimulants could potentially be very helpful in fibromyalgia patients with 'fibrofog', as it can be considered analogous to adult attention deficit/hyper activity disorder and treated similarly.[105]

Growth hormone

Growth hormone (GH) is a polypeptide hormone secreted naturally by the anterior pituitary gland that stimulates cell growth and reproduction. There is some evidence of functional GH deficiency, expressed as low insulin-like growth factor 1 (IGF-1) serum levels, in a subset of fibromyalgia patients.[106] There is a marked decrease in spontaneous integrated GH secretion.[107] GH deficiency in adults has been associated with symptoms that are similar to those described by patients with fibromyalgia: low energy,[108] reduced exercise capacity,[109] muscle weakness, cold intolerance,[108] impaired cognition,[110] dysthymia,[108] and it was theorized that suboptimal levels may be a factor in the impaired resolution of muscle micro-trauma in fibromyalgia.[111,112]

A nine-month study of injectable recombinant human growth hormone in patients with low IGF levels at entry showed an improvement in FM symptoms as assessed by the FIQ total and tender point score.[112] However, enthusiasm for this approach has been dampened by the appearance of adverse effects, the need for frequent injections, and high costs.

Tramadol

Tramadol is a centrally acting analgesic that is useful in the treatment of many pain disorders, including neuropathic pain and fibromyalgia.[113,114] Tramadol has a unique mechanism of action that combines μ-opioid activity with inhibition of serotonin/norepinephrine re-uptake.[115] One or two tramadol–paracetamol (37.5 mg/325 mg) combination tablets taken four times daily can substantially lessen pain, stiffness, and work interference in patients with fibromyalgia.[116] Common adverse effects of this treatment are nausea, pruritis, and constipation.

Anti-Inflammatory medications

Anti-inflammatory medications have not been effective in the treatment of FM. Prednisone 20 mg/day was no better than placebo.[117] Nonsteroidal anti-inflammatory drugs (NSAIDs), including naproxen and ibuprofen, were not effective in FM, although they may have a synergistic effect when combined with medications active on the CNS.[118] They are more likely to be helpful when fibromyalgia is present with associated pain disorders such as osteoarthritis.

Pyridostigmine (PYD)

Pyridostigmine is a parasympathomimetic and a reversible cholinesterase inhibitor. Treatment of FM patients with GH has been reported to be of some clinical benefit[112] but GH is seldom prescribed because of its high costs and concerns regarding its long-term usage.[119] GH secretion in FM patients can be acutely increased by the use of PYD in combination with exercise.[120] Jones and colleagues randomized their study participants to one of the following four groups: PYD plus exercise, PYD plus diet recall but no exercise, placebo plus exercise, and placebo plus diet recall but no exercise. The researchers suggested that neither the combination of PYD plus supervised exercise nor either treatment alone yielded improvement in most FM symptoms. However, PYD did improve anxiety and sleep, and exercise improved fatigue and fitness. They speculated that PYD might have improved vagal tone, thus benefiting sleep and anxiety; they also offered a further study.[121]

Melatonin

Melatonin has multiple actions including modulation of the sleep/wake cycle and benzodiazepine-like effects.[122] Thus, melatonin administration improves sleep and rest, and decreases anxiety derived from sleeplessness. Additionally, melatonin also synchronizes neurotransmitter circadian rhythms including those of c-aminobutyric acid, benzodiazepine, dopamine, and glutamate.[122,123] Also, melatonin has antistress properties and influences the HPA axis, which may account for some of its effects in FM. The actions of melatonin in terms of its ability to enhance mitochondrial bioenergetics[124] may be pertinent to its beneficial effects in

these patients. While reduced levels of melatonin have been reported in FM women,[125,126] alterations in its circadian rhythm seem not to be a primary cause of FM.

Approved medications

Until early 2009, only two drugs were approved by the US Food and Drug Administration (FDA) for the treatment of fibromyalgia: pregabalin, approved in June 2007 and duloxetine, approved in June 2008, on January 14, 2009, milnacipran was approved by the FDA for the management of FM.[127] All three drugs have shown similar efficacy in pain management,[128] but their abilities to manage other fibromyalgia symptoms are not the same. Their different pharmacodynamic and safety profiles, often make one a better initial choice than the others for an individual patient.[129]

Pregabalin

Pregabalin, like gabapentin, is an alpha-2delta-subunit ligand that exhibits anti-hyperalgesic, anxiolytic and anticonvulsant properties.[90] Pregabalin's binding affinity for the alpha-2-delta subunit is six times higher than that of gabapentin, rendering pregabalin more clinically effective at lower doses.[130] Vera-Llonch and colleagues[131] also suggest that pregabalin (375 mg/day) may provide better analgesic outcomes than gabapentin (1200 mg/day and 1800 mg/day) over a 12-week period. This increased efficacy, as well as its favorable pharmacokinetic profile, renders pregabalin the preferred anticonvulsant adjuvant analgesic for chronic pain treatment.[130] In two randomized controlled trials (of 8 and 14 weeks, respectively) involving patients with FM, pregabalin significantly reduced the pain score and improved sleep and fatigue demonstrating efficacy against the three major symptoms of the condition.[132,133] Although significantly more patients had ≥50% improvement in pain in the pregabalin than in the placebo group, this level of benefit was in a limited (up to 30%) number of subjects. When ≥30% decrease in pain scores was determined, the number of responders only increased up to 50%. A six-month double-blind, placebo-controlled trial demonstrated durability of the effects of pregabalin on pain, fatigue and sleep disturbance with an onset of effects within one week of treatment.[134] Pregabalin significantly delayed the time to loss of therapeutic response, with 68% of patients maintaining therapeutic response at the end of the trial.

Duloxetine and milnacipran

The prevailing theory is that decreased serotinergic and noradrenergic activity leads to a decrease in activity via descending analgesic pathways, which in turn leads to pain as well as diffuse hyperalgesia and allodynia seen in fibromyalgia and a number of related conditions.[29] For that reason selective SNRIs such as duloxetine and milnacipram demonstrate the greatest promise. Similar to pregabalin, they reduce not only pain, the primary symptom of FM, but also improve other symptom domains, and some aspects of function and global assessments.[135]

Duloxetine is an antidepressant, but is also effective in neuropathic pain independent of its effects on mood. It is a selective serotonin and norepinephrine reuptake inhibitor that is relatively balanced in its affinity for both serotonin and norepinephrine reuptake inhibition. A randomized, double-blind, placebo controlled trial has evaluated duloxetine in patients with FM.[136] In the initial study, men and women stratified for the presence of current major depression were treated with duloxetine 60 mg twice daily compared with placebo.[136] Outcome measures were based on FIQ total and pain scores, patients treated with duloxetine had significant improvement in the FIQ total score, but not the pain score. Significantly more women treated with duloxetine (30%) than placebo (16%), however, had more than 50% reduction in the FIQ pain score.[137] Duloxetine-treated male patients failed to improve significantly.

Similar to duloxetine, milnacipran is a well-characterized small molecule that acts as a selective reuptake inhibitor of both serotonin and noradrenaline,[138] but it is unique in its preference for norepinephrine reuptake inhibition and also binds NMDA receptors. Because of a higher affinity for the norepinephrine transporter than does duloxetine, milnacipran may be better for patients with severe fatigue and/or cognitive dysfunction (the so-called fibrofog).[139] The FDA's approval of milnacipran was based on the results from two US-based phase III clinical efficacy trials – one of 15 weeks' and the other of 27 weeks' duration. In the 15-week study,[140] a significantly greater proportion of patients who received milnacipran (either 100 mg or 200 mg daily) than those who received placebo met the composite criteria for pain response and syndrome response. In some patients, a significant reduction in pain was seen as early as week 1, and persisted to the end of the study. Other significant improvements for both the 100 mg and 200 mg groups were seen in indices of total impact FIQ, disability and fatigue. In addition, the 200 mg dose led to significant improvements in short-form, 36-question health survey (SF-36) mental component scores and Beck Depression Inventory scores.

In the 27-week study,[141] significantly more patients in the milnacipran treatment groups (100 mg or 200 mg daily) than in the placebo group met the composite criteria for

pain response and syndrome response at three months. At the 27-week end point, however, only the 200 mg milnacipran group had significantly higher pain response rates than the placebo group, and neither milnacipran group had significantly higher syndrome response. Furthermore, cognition was significantly improved at both 15 and 27 weeks in the 200 mg group.[142]

Physical therapies

Transcutaneous electrical nerve stimulation

Transcutaneous electrical nerve stimulation has been attempted and shown to be of little benefit to FM patients. It is more appropriate for localized pain versus the diffuse, generalized pain typically associated with fibromyalgia; this limits its usefulness in the treatment of the disease.[143]

Ultrasound

Ultrasound therapy has achieved recognition as a suitable method in physical medicine in treatment of acute and chronic musculoskeletal disorders.[144] Experimental studies have shown that it is possible to heat deeper structures, such as joints, muscle, and bone, with ultrasound.[145] It was suggested that combined therapy with pulsed ultrasound and interferential current, acting as an electrodiagnostic tool and as modality of physical therapy, provides an effective pain management, with consequent sleep improvement in FM.[17,146,147]

Low level laser

The exact mechanism of pain reduction by low level laser therapy is not completely understood. While underlying mechanism is unknown, it has been demonstrated in animal studies that laser therapy results in a selective reduction of Aβ and C fiber activity.[148] Anti-inflammatory effects have been demonstrated both *in vitro*[149] and *in vivo*[150] and reduction of interstitial fluid at the site of inflammation has been described.[151] It has also been suggested that low level laser therapy has effects on peripheral nerve stimulation and microcirculation regulation, interrupting the pain mechanism and thereby providing analgesia.[152] In some experimental studies pain thresholds have been shown to increase owing to laser application.[153] Analgesia may also occur due to the release of endogenous opioids following laser stimulation.[151,155]

Gur and colleagues[156] previously carried out a randomized, single-blind and placebo-controlled study to evaluate the efficacy of 904 nm gallium arsenide (GaAs) low energy laser therapy in 40 FM patients.[156] It was found that there was no significant difference between the two groups with respect to all parameters before therapy whereas a significant difference was observed in parameters as pain, muscle spasm, morning stiffness and tender point numbers in favor of laser group after therapy. The authors suggest that laser therapy is an effective treatment of these parameters in FM patients and suggest that this therapy method is a safe and effective treatment. Gur and colleagues also carried out a randomized, single blind, and placebo-controlled study to compare the effectiveness of low energy laser therapy and low-dose (10 mg/day) amitriptyline therapy on clinical symptoms and quality of life in 50 patients with FM. In this study the authors concluded that both low dose amitriptyline and low level laser therapy is effective in reducing the clinical symptoms of FM and increasing quality of life (QoL). They conclude that such therapy is also a safe and effective treatment in the patients with FM.[17,157]

Exercise

Exercise, muscle strength, and endurance have been shown to be lower in patients with FM than healthy age-matched controls.[158] A cycle is established, that activity produces micro trauma, increased local pain and generalized pain, so the patients decrease their activity level. Thus, one of the rationales for the exercise interventions in patients with FM is to break the cycle of deconditioning.[159] A better muscular blood flow and less susceptibility to muscular micro trauma, as a result of regular training might improve pain in FM. As many fibromyalgia symptoms are also associated with deconditioning, the effect of various types of exercise, including aerobic dance, stationary cycling, and aerobic walking, have been evaluated.[160,161] Cardiovascular exercise appears to be the most effective form of exercise (as compared to flexibility[162] and relaxation[163] exercises) in which fibromyalgia patients can participate.[6] These studies suggest that aerobic exercise three times a week can reduce tender point tenderness. Overall pain may also decrease, although sleep and level of fatigue are likely to be unaffected.

Magnetotherapy

Magnetotherapy treatment of FM symptoms using static or pulsed magnet fields attached to the surface of the body has been also evaluated. Magnetotherapy can produce positive changes in the immunological condition of the patient, such as vasodilatation of the arterial part of capillaries, analgesia and anti-inflammatory action. Lena and Friol[164] carried out a nonrandomized study with two groups of 25 FM patients. To one of these a pharmacologically conventional treatment was administered for 10 days. The second group completed 10 sessions of magnetotherapy using a magnetic bed, with

solenoid placed in the dorsal region of the patient in prone position. At the end of the treatment, both groups had reduced tender points score, an improvement which lasted for 25 days. However, a greater improvement was observed in the pharmacological group.[165]

Acupuncture

Acupuncture is a treatment in traditional Chinese medicine with more than 2500 years of history for use in chronic pain and has been suggested for use in fibromyalgia.[166] According to traditional Chinese medicine, fibromyalgia is caused by dysfunction of the liver, spleen, and kidney that interrupts or depletes the body's internal energy and blood flow, resulting in clinical symptoms.[167,168]

The National Institute of Health Consensus Conference on Aupuncture concluded that acupuncture may be useful as an adjunct or alternative treatment for FM. However, two recent, randomized, controlled trials found that acupuncture was no better than control interventions in the reduction of pain associated with FM.[169]

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBO) therapy has been used worldwide for the past 30 years to treat many diseases, including conditions caused by local hypoxia or ischemia.[170] HBO therapy involves breathing 100% oxygen via an endotracheal tube, mask or hood in a pressure chamber at pressures higher than 1 atmosphere absolute (ATA). The aim of HBO therapy in patients with FM is to reduce muscle hypoxia and increase levels of high-energy phosphate. Yildiz and colleagues[171] carried out a randomized study exposing a group of 26 FM patients to once daily 90-minute sessions of hyperbaric treatment at 2.4 atmospheres, five days a week for three weeks duration. A second group (n = 24) were administered air at 1 atmosphere and acted as control group. After receiving treatment, the hyperbaric group showed a significant improvement in tender points scores, pain threshold and pain severity.[171]

Hydrotherapy

Hydrotherapy affects muscular tone, joint mobility, and pain intensity by thermal and hydromechanical stimuli, which cause analgesia in the nerve endings that increases the pain threshold, thus resolving the muscular spasms.[172] Moreover, a peripheral vasodilatation takes place, as well as an increase in the tendon extensibility, which benefits the conjunctive tissues. This helps to improve muscular ischemia and reduce the algesic mediators in FM.[173] Another prophylactic property of hydrotherapy is based on the concentration of elements and mineral compounds like carbon dioxide, calcium, magnesium, lithium, and sulphate, which are dissolved in water and can be absorbed through the skin, providing healing effects in several body organs and circulatory system, reducing muscular spasms, pain sensitivity, and increasing joint mobility, as well as peripheral circulation.[174]

During a randomized controlled trial, Buskila and colleagues examined the effects of sulphur bath balneotherapy on 48 patients with FM.[175] Subjects were randomly assigned to receive daily sulphur baths lasting 20 minutes with water from the Dead Sea, or no treatment, over a 10-day period. Blinded assessments revealed that although both groups improved on almost all areas measured, including physical functioning, tender point count, tenderness threshold, pain, fatigue, stiffness and anxiety measured using visual analog scales. The improvements were particularly remarkable in the treatment group and lasted for a minimum of three months.

Osteopathic and chiropractic manipulation

Osteopathic and chiropractic manipulation are treatment approaches that utilize joint manipulation. These techniques are intended to reduce pain, enhance muscle strength and joint mobility, provide proprioceptive training, and limit further joint and muscle damage.[176] A common criticism of these techniques is that although they may be effective in reducing pain and increasing mobility, the effects may be short-lived. Chiropractic and osteopathy have become popular in the treatment of acute conditions, though there is little scientific evidence regarding their effectiveness in chronic conditions.[177]

In a study by Gamber and colleagues,[178] 24 patients with FM were randomly assigned to one of four treatment groups: manipulation, manipulation and teaching, moist heat, or a control group (standard medical care). Gamber and colleagues found significant improvements in pain, activities of daily living and chronic pain attributes in the manipulation treatment groups. However the small sample size and lack of follow-up data make it difficult to form definitive conclusions. Thus the evidence for the success of chiropractic and osteopathic intervention is insufficient, additional, larger randomized controlled trials are warranted to resolve its efficacy.[177]

Electromyographic biofeedback training

Electromyographic biofeedback training teaches an individual to become aware of processes and sensations in the body that are not normally apparent and with the use of special equipment bringing them under conscious control. An individual is hooked up to a biofeedback instrument which

measures such physiological variables as skin temperature and heart rate. These measurements are then relayed back to the patient in real time to alter the body functions being measured. Since the equipment is designed to detect minute changes in the body functions being measured, the patients' effort to affect these processes is instantly reinforced by the display of these measurements, no matter how small and the patient is further encouraged to bring these processes into conscious awareness and control. Over time, the goal is to be able to influence these sensations and process without the aid of the biofeedback instruments.[179]

Cognitive behavioral therapy

Cognitive behavioural therapy (CBT) attempts to change physiological responses by manipulating cognitive reasoning and is intended to help patients feel that they are in control of their condition. This includes decreasing feelings of helplessness, reorganizing negative thoughts leading to pain and developing strategies for handling pain.[180] A meta-analysis of CBT in chronic pain patients drew the conclusion that this form of therapy is indeed effective in this patient population.[181] However, in a prospective study comparing a group that received intensive cognitive intervention with a control group that received less structured group discussions about pain and coping, the efficacy of this treatment did not significantly differ between the two groups.[182]

Miscellaneous agents

S-Adenosyl-L-methionine

S-adenosyl-L-methionine (SAMe), administered as a salt, is a naturally occurring active derivative of methionine present in all body tissue. Over the past 25 years, antidepressant, analgesic, and anti-inflammatory properties of SAMe have been identified. In the past 10 years, its role in the treatment of fibromyalgia has been evaluated in several small, short-duration, double-blind studies. A significant improvement of symptoms, including depression, pain, and the number of tender points, has been reported with oral, intravenous, and intramuscular administration of SAMe.[183]

Botanical oils

A single randomized, controlled, investigator-blinded study assessed pine oil and valerian on pain, sleep, and tender point count in patients with FM.[184] Subjects were randomized into one of three whirlbath treatments, each given a total of 10 times (three times per week): valerian bath (n = 12), pine oil bath (n = 7), or plain water bath (n = 11). Valerian baths were associated with improved sleep, pine oil baths with increased sensitivity to pain in certain body areas, and plain water baths appeared to reduce pain intensity. However, both valerian and pine oil baths improved well-being.

Chlorella pyrenoidosa

Chlorella pyrenoidosa is a species of unicellular fresh water green algae rich in proteins, minerals and vitamins. Dietary supplementation with *Chlorella pyrenoidosa* has been associated with symptom relief in FM in two studies by the same research group. In the first study, an uncontrolled open-label trial,[185] subjects with FM supplemented their diets with 10 g of *Chlorella* and 100 ml of *Chlorella* extract for 2 months. The mean number of tender points decreased significantly.[186] A larger, well-designed randomized placebo-controlled, double-blinded crossover clinical trial of 37 FM subjects also observed a significant reduction in the number of tender points among the treatment group compared with a slight increase in placebo subjects in addition to a significant increase in functioning.[187,188]

Surgical treatment

Thimineur and colleagues studied 12 patients with FM who were treated for comorbid chronic daily headaches with peripheral stimulation in the cervical plexus (C2) region of the scalp. They studied headache severity, quality of life, and FM symptoms, particularly diffuse pain, fatigue, and depression. Twelve patients (nine females and three males; mean age 48 years) who met criteria for FM, with a comorbid headache disorder, were implanted with C2 area stimulation technique. The outcome was prospectively studied with standard evaluation tools at baseline, three and six months postimplant. They recorded that visual analog scale pain levels for FM-related pain decreased significantly at six months, chronic fatigue and depression as assessed by the Beck Depression Inventory and fatigue impact scale, overall quality of life as assessed by the Health Survey Short Form 36 (SF-36) were also improved. They suggested that C2 area scalp stimulation might diminish pain and related symptoms in patients with FM.[189]

Conclusion

ACR classification criteria includes tender point count which is central to FM, however, tender points and widespread pain alone do not wholly describe fibromyalgia-a disorder with comorbid symptoms. Patients may have enough and appropriate tender points and yet not have fibromyalgia. However; there are many treatment options for the effective management of this disease that require the identification of

individual symptoms. These symptoms are not limited to pain and tender points. Sleep disorders, cognitive dysfunctions, fatigue, stiffness, depression are also the components of this syndrome. It may be suggested that, revised or new evaluating criteria may help developing new diagnostic methods. Although various pharmacological treatments have been studied for treating FM, no single drug or groups of drugs has proved to be useful in treating these patients. However, three drugs have recently been approved by the US FDA for the treatment of FM; pregabalin, duloxetine, milnacipran. Symptom based treatment for individual therapy with a multidisciplinary approach that includes both pharmacological and nonpharmacological strategies are recommended.

Disclosures

The authors report no conflicts of interest in this work.

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