Pain in fibromyalgia patients

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Fibromyalgia is defined by widespread pain and 11 of 18 tender points, often accompanied by symptoms such as fatigue, sleep disturbance, headache, irritable bowel syndrome and mood disorder. Fibromyalgia's diagnosis is eminently clinical, and currently there are no specific laboratory or technical tests. The major role in pathogenesis appears to be central and available evidence points toward dysregulation of neurotransmitter function and central pain sensitization as fundamental mechanisms. There is no evidence of abnormalities in muscle and tendon. The goal of therapy in fibromyalgia is to treat pain, and reduce physical function and sleep disturbance. The treatment of patients with fibromyalgia is difficult, and no single treatment has been successful. Here, actual evidence of the effects of pharmacological and nonpharmacological interventions on pain is summarized. Tricyclic agents, selective serotonin-reuptake inhibitors, muscle relaxants, anti-epileptics drugs, aerobic exercises, psychological treatment, patient education and combined therapies can reduce symptoms and disability effectively.

Fibromyalgia (FM), as defined in the 1990 American College of Rheumatology (ACR) criteria [1], is a chronic, generalized pain condition with characteristic tender points on physical examination (11 of 18 tender points), often accompanied by a number of associated symptoms, such as fatigue, sleep disturbance, headache, irritable bowel syndrome and mood disorder. FM affects 3–6 million people in the USA, with a prevalence in the general population estimated at 2–3% and an increased frequency among women [2,3]. The etiology and pathogenesis of FM are not well understood, but they are probably multifactorial [4]. Evidence shows that the syndrome is influenced by factors such as stress, medical illness, physical stress (especially in early childhood), endocrinological genetic factors and pain conditions in some, but not all patients, as well as a variety of neurotransmitter and neuroendocrine changes (available evidence points toward dysregulation of neurotransmitter function and central pain sensitization as fundamental mechanisms) [5–7]. There is no evidence of abnormalities in muscle and tendon.

The diagnosis of FM is eminently clinical, and no specific complementary test currently exists, therefore, it is difficult to value and measure the magnitude of the problem in each patient. Thus, the treatments applied for FM are very diverse and, in some cases, the evaluation of their effectiveness is very difficult.

Patient quality of life (QoL) is broadly affected [8] and a significant number of people present with chronic pain that intensely affects QoL, leading to a partial or complete loss of labor activity in 25–50% of patients [9].

The goal of therapy in FM is to treat pain, reduced physical function and sleep disturbance [6]. The treatment of patients with FM is difficult and no single treatment has been successful or demonstrated consistent efficacy across all symptom domains [10]. Therefore, multimodal treatment programs have been developed. These programs usually include lifestyle modifications and pharmacological interventions based on neuromodulatory medications such as tricyclic compounds, selective serotonin-reuptake inhibitors (SSRIs) and serotonin–norepinephrine-reuptake inhibitors (SNRIs), antidepressants, opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), sedatives, muscle relaxants and antiepileptic hypnotics intended to relieve pain, improve sleep quality and treat mood disorders [10,11]. Nonpharmacologic therapies include education, physical therapy, massage and exercise-based treatments [7,10,11,12], and psychological- or cognitive-based therapies [13]. Finally, multiple modalities of alternative and complementary medicine have also been proven in the treatment of FM.

However, owing to the complexity of the symptoms of FM and the fact that there are currently no appropriate tools to measure the

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effectiveness of the different therapeutic options, the results of the published clinical research are, occasionally, difficult to value.

Treatment

Pharmacological treatment

Our ignorance of the etiology of FM currently prevents a completely effective pharmacological treatment for pain. Multiple drugs have been examined, although only a minority have been demonstrated to have certain effectiveness [14].

NSAIDs & opiates

A randomized study evaluated the effectiveness of the association of tramadol 300 mg and paracetamol 2600 mg, compared with placebo, in 313 patients with FM [15]. A smaller interruption of the treatment rate was observed in the active intervention group, as well as an improvement in pain and in the measures of general impact on health. As co-intervention, the patients received other medications (the SSRIs zolpidem and flurazepam).

NSAIDs were not associated with any improvement in the evaluated results. There was an improvement in the symptoms associated with FM and the physical state with the following combinations: cyclobenzaprine–ibuprofen, amitriptyline–naproxen and alprazolam–ibuprofen.

There is no evidence for the effectiveness of the NSAIDs in the treatment of FM.

Opioid agonists (tramadol)

The effectiveness of tramadol was evaluated in intravenous infusion (100 mg/2 ml) compared with placebo. Only nine patients completed both treatment cycles. A decrease in spontaneous pain was observed but there was no improvement in pressure at tender points. It is necessary to consider the small number of patients included in this study [16]. In a 4-year nonrandomized study of opiates compared with baseline, no significant improvement in pain was observed at follow-up and increased depression was reported in the last 2 years of the study [17].

Given the negative effect of opiates, the benefit of tramadol may be due to norephinephrine/serotonin inhibition. Currently, there is no clear evidence on opiate effectiveness.

Muscular relaxant (cyclobenzaprine)

A recent meta-analysis examined five studies to investigate the effectiveness of cyclobenzaprine in FM [18]. The odds ratio for the global improvement with treatment was 3.0 and the number of patients that were necessary to treat for one improvement in symptoms was 4.8 (95% confidence interval [CI]: 3.0–11). Pain improved quickly but the effects did not last long. There were no improvements in tender points. Cyclobenzaprine is chemically very similar to tricyclic antidepressants, thus, it is unclear whether the observed effects occured as a result of the muscle relaxant or via other mechanisms similar to those of the TCAs.

Tricyclic antidepressants

A systematic review evaluated the effectiveness of antidepressants in 14 studies (nine tricyclic, three SSRIs and two *S*-adenosylmethionine) [19,20]. Symptomatic improvement with the antidepressants was observed. The number of patients that were necessary to treat to see an improvement in some FM symptoms was 4 (95% CI: 2.9–6.3). There was a relative improvement in symptoms in the patients receiving the TCAs compared with placebo (fatigue: 14%; tender points: 9%; pain: 26%; sleep: 23%; feeling well: 18%). The most frequent adverse effects were gastrointestinal illness, oral dryness, somnolence and migraines. This meta-analysis demonstrates a greater effectiveness of TCAs compared with other antidepressants.

A randomized study compared the effectiveness of amitriptyline with nortriptyline and placebo in 118 patients with FM for 2 months of treatment [21]. Both drugs showed improvement after treatment (86.5% in the amitriptyline group and 72.2% in the nortriptyline group vs 54.5% in the placebo group). This improvement was significant in the three groups ($p < 0.05$) in relation to the baseline levels, as much in the functional capacity measured by the Fibromyalgia Impact Questionnaire (FIQ) as in the analog scale of pain. No differences were found between amitriptyline and nortriptyline and the reflected improvement was very poor compared with placebo.

In a placebo-controlled meta-analysis, tricyclic agents were associated with effect sizes that were substantially larger than zero for all measurements. The largest improvement was associated with measures of sleep quality [22].

Other antidepressants

SSRIs

In a placebo-controlled study, 42 patients with FM treated with fluoxetine 20 mg/day were evaluated over a period of 6 weeks and no differences

were found between the groups [23]. In a separate study by Goldenberg and colleagues, 19 patients treated with fluoxetine 20 mg/day were evaluated compared with amitriptyline 25 mg/day and placebo; there was an improvement in the active intervention group with regard to pain and FIQ [24]. A third study evaluated 22 patients treated with citalopram 20 and 40 mg/day compared with placebo over 8 weeks. There were no differences found between the groups [25].

Fluoxetine 10–80 mg/day demonstrated significant improvement in a 12-week, flexible-dose, placebo-controlled trial on most outcome measures (pain, fatigue and depression) and although counts for the number of tender points and total myalgic scores improved more in the fluoxetine group than in the placebo group, these differences were not statistically significant [26]. Citalopram 20 mg/day improved depressive symptoms and pain significantly at 2 months, but the effect disappeared after 4 months according to a randomized, double-blind, placebo-controlled study by Auderberg and colleagues [27]. However, these results were not corroborated by others [25].

SNRIs

Milnacipran has been shown to be effective in treating the core symptoms of FM, including pain, fatigue and mood [28]. In this trial, robust improvements were observed in the Patient Global Impression of Change, with modest effects on fatigue and functioning (measured by FIQ) and small effects on sleep. Patients demonstrated improvements in pain regardless of baseline major depressive episode status, but patients with depression had the largest placebo response on pain scales [29]. Duloxetine, another SNRI, was tested in FM patients. In the first of two studies, significant improvement was demonstrated in the treated group using the total FIQ score, but there was no significance in the coprimary outcome of FIQ pain score, nor was improvement noted in male subjects [30]. A secondary outcome measure of pain, the Brief Pain Inventory (BPI), did show statistically significant improvement in the treated group. Duloxetine also improved several other symptoms associated with FM, including stiffness and tender points (measured by dolorimetry), as well as global assessment and several QoL measures. Duloxetine improved pain symptoms regardless of baseline major depressive disorder status [30]. A second study, using the BPI as a primary pain end point and excluding male patients, did show statistically significant improvement [31].

Venlafaxine, another dual SNRI, was more effective than blockade of either neurotransmitter alone in a 2003 study by Sayer and colleagues [32]. Although the two studies have conflicting results, one showed efficacy using a higher dose. The presence of lifetime psychiatric disorders, particularly depressive and anxiety disorders, predicted a positive response to venlafaxine [33].

Since TCAs (and high doses of certain SSRIs, e.g., fluoxetine) that have the most balanced reuptake inhibition are the most effective analgesics and many have concluded that dual-receptor inhibitors, including SNRIs and norepinephrine reuptake inhibitors, might be of more benefit than pure serotonergic drugs. These drugs are pharmacologically similar to some TCAs in their ability to inhibit the reuptake of both serotonin and norepinephrine, but differ from TCAs in being generally devoid of significant activity in other receptor systems. This selectivity results in diminished side effects and enhanced tolerability.

In summary, there is moderate evidence of the effectiveness of this group of agents.

Serotonin (5-HT)$_3$ receptor antagonists (Tropisetron & ritanserin)

In two studies of very short duration (between 5 and 10 days), the effectiveness of intravenous tropisetron was compared with placebo [34,35]. In the first, an improvement in pain was observed in the 21 patients receiving medication [34]. In the other study, the effectiveness of tropisetron at different doses (5, 10 and 15 mg/day) was evaluated and compared against placebo in 418 patients with FM [35]. The results were better (improvement of 35% or more in the punctuation of pain) with 5 mg/day than with the highest doses of 10 and 15 mg/day. This was accompanied with an improvement in the number of tender points.

Ritanserin does not improve pain or fatigue, nor do analgesics, but it produced a significant improvement with respect to migraine and the sensation of morning wellbeing ($p < 0.05$), according to another randomized, 16-week study where ritanserin was evaluated compared with placebo in 51 patients [36].

Other drugs

Sodium oxybate

According to one study, a significant benefit exists with the use of sodium oxybate in pain, global fatigue and sleep quality [37].

Recombinant human growth hormone.

The use of growth hormone in FM is based on studies showing that levels of insulin-like growth factor (IGF)-1, the mediator of growth hormone activity in patients with FM, are lower than in age-matched controls. Whether lower IGF-1 is a result of FM or is involved in the causative pathway is not known; however, IGF-1 does play a role in muscle repair and, thus, could conceivably be involved in the pathogenesis of FM pain [38]. A 9-month study of injectable recombinant human growth hormone in patients with a low IGF-1 at entry showed improvements in FM symptoms, as assessed by the FIQ total and tender points score [39,40].

Pregabalin

Pregabalin is a three-substituted analogue of γ-amino butyric acid (GABA) that binds to the α-2δ subunit of the voltage-gated calcium channel in the CNS. It is structurally related to gabapentin and is being developed for the treatment of FM and other indications. Pregabalin was studied in an 8-week, randomized, controlled trial in FM and, at 450 mg/day, was efficacious in the treatment of pain, sleep disturbance and fatigue [41]. Dizziness and somnolence were the most frequent adverse events. Rates of discontinuation due to adverse events were similar across all four treatment groups. The primary outcome was pain measured by an 11-point numeric rating score recorded in a daily pain diary. Pregabalin 450 mg/day significantly reduced the average severity of pain compared with placebo (-0.93 on a 0–10 scale; $p \leq 0.001$) and significantly more patients in this group had 50% or greater improvement in pain at the end point (29 vs 13% in the placebo group; $p = 0.003$). Other symptoms, such as fatigue and sleep disturbance, were improved over an 8-week period. There was significant improvement in pain at the highest dose studied. As such, it is possible that improvements in pain scores reported by patients could be a by-product of a positive anxiolytic effect. Patients taking pregabalin also experienced a higher incidence of peripheral edema than those taking placebo, although the mechanism of pregabalin-induced peripheral edema is unclear. Furthermore, pregabalin monotherapy was effective in improving health-related QoL for patients with longstanding FM. The data presented in this report suggest that pregabalin provides clinically significant benefits in patients with FM, and these data support further study of this agent for treatment of patients with this prevalent and often disabling syndrome.

There is no evidence for the effectiveness of steroids [42], calcitonin [43], gabapentin [44], ketamine [45], interferon-α [46] and thyroid hormone [47] in patients with FM.

In a review with meta-analysis that defines four categories of results (physical state, symptoms of FM defined by the patient, psychological state and daily functionality) regarding effectiveness of the pharmacological and nonpharmacological interventions in FM [48], muscle relaxants and antidepressants improved the evaluated parameters, and were more effective than the antidepressants in benefiting physical state ($p = 0.003$). *S*-adenosylmethionine was associated with an improvement in the physical state, the symptoms associated with FM and the psychological state, except in a study that observed a psychological deterioration. Finally, no pharmacological treatment improved daily activities.

Rehabilitative & physical treatment

This treatment modality varies with the type and intensity of each patient's clinic. Clinically, the therapeutic priorities are pain, the muscular malfunction and the functional disorder of muscle secondary to the pain. The treatment should be individualized and adapted to each patient [48,50]. It is necessary for the patient's active participation. Therapy is based fundamentally on procedures with the objective of reducing the muscular hypertonia and relaxation to palliate the myofascial pain. It is of interest to act in a concomitant way regarding behavior factors of overload, eliminating the appearance of exogenous factors, such as cold, humidity, positional overload and stress. Diverse methods have been proved successful and the conclusion is that patients subjected to strengthening and stimulating exercises, carried out under aerobic conditions, in or outside the water (but not exhausting), have an improvement in pain and fatigue superior to control patients or those that carry out stretching exercises. Tolerance to pain is also increased [50]. Exercise should be supervised in cases with moderate or serious affection [51]. Initially, therapy requires a gradual setting-up and control of the conditions in which it is carried out [52].

Psychological treatment

Many authors point out the possibility that psychological factors can play a role in the initiation as well as in the progression of FM [52].

The psychological treatment of pain pursues the modification of the emotional state and behavior with the purpose of increasing the patient's functionality and maintaining their social interactions. A complete psychological intervention should include:

- Programs of behavior modification [53]
- Training in biofeedback techniques [54]
- Behavioral–cognitive therapy [55,56]

Feeding in FM

The nutrients recommended for patients with associated feed disorders who endure this pathology are cereals and vegetables (e.g., rice, maize, bread and nutritional pastes) that represent the most important source of complex carbohydrates (starches), fibers and proteins of vegetable origin. Vegetables and fruits are an important source of vitamins, mineral salts, fibers and sugars. Milky products, such as milk, cheese and yogurts, are rich in calcium, magnesium and good-quality proteins [57].

Alternative therapies

In a controlled, randomized clinical trial of patients receiving true acupuncture compared with a control group of patients who received simulated acupuncture, fatigue and anxiety were significantly improved. However, activity and physical function levels did not change [58].

Educational programs

The objective of educational programs is the improvement in the confrontation of the chronic illness, in order to raise the behaviors of health's state.

As in other chronic illnesses, in FM, educational programs have been applied jointly with physical supervised exercise [59,60], with benefits on physical function, gravity of the pain, social function, psychological distress and QoL. These programs, used in diverse countries, has been variable, oscillating between 1 and 2 h a week, over a period of 6–12 weeks. They have been carried out interactively in small groups of patients and included aspects such as pain (definition and physiopathological mechanisms), information about FM, pharmacological treatment of pain, stress, pain and depression, confrontation strategies, training, relaxation strategies, importance of physical training, ergonomic principles in daily activities and legislation, among others [48].

Multidisciplinary therapeutic programs

The treatment of FM is more effective when several of the aforementioned therapeutic modalities are used concurrently, especially when the patient is affected by chronic incapacitating pain – a situation in which suffering and difficulty in carrying out daily work are significant [61,62]. As a result, a therapeutic strategy based on the grade of pain is suggested [63]. Lastly, structured interdisciplinary rehabilitation covers elements of cognitive and operant behavioral therapy, exercise and drug therapy [64].

Conclusion & future perspective

The treatment of pain in patients with FM is difficult and no single treatment has been successful or demonstrated consistent efficacy across all symptom domains. As a result, multimodal treatment programs based on lifestyle modification and pharmacological interventions have been developed.

Pharmacological measures

The drugs with more evidence of action and that receive more attention are the antidepressants; mainly, TCAs and SSRIs. Amitriptyline and cyclobenzaprin at low doses are able to improve pain moderately, although with a relative frequency of adverse effects. However, fluoxetine improves pain, fatigue and depression; although, in some studies, their effectiveness has not been fully demonstrated. One of the new promising pharmacological options is pregabalin, a potent neuromodulator that diminishes neuronal hyperexcitability associated with neuropathic pain, reducing the severity of pain and other core symptoms of FM, such as fatigue and sleep disturbance. Finally, studies using drugs such as opioid agonists (tramadol), 5-HT_3 receptor antagonist (tropisetron and ritanserin), human growth hormone, sodium oxybate, calcitonin, ketamin, melatonin, interferon, *S*-adenosylmethionine and 5-hydroxytryptophan, among others, have not demonstrated enough evidence to endorse their regular use in FM.

Nonpharmacologic interventions

The physical, psychological and educational treatment of the patient might have a role in the treatment of FM. Patients subjected to strengthening and stimulating exercises, carried out under aerobic conditions (but not exhausting), have an improvement in pain and fatigue, and an increased pain tolerance. Psychological

treatment of pain pursues the modification of the emotional state and behavior with the purpose of increasing patient functionality and maintaining social interactions.

In conclusion, the treatment of pain in FM is more effective when several of the aforementioned pharmacological and nonpharmacological therapeutic modalities are used together.

Executive summary

- Fibromyalgia (FM) is defined as widespread pain in 11 of 18 tender points, often accompanied by symptoms such as fatigue, sleep disturbance, headache, irritable bowel syndrome and mood disorder.
- The role in pathogenesis appears to be central, with dysregulation of neurotransmitter function and central pain sensitization as fundamental mechanisms.
- There is no evidence of abnormalities in muscle and tendon.
- Diagnosis is eminently clinical, and no specific laboratory or technical test exists at present.
- The goal of therapy in FM is to reduce pain, increase physical function and decrease sleep disturbance.
- Treatment of patients is difficult and no single treatment has thus far been successful.
- Tricyclic agents, selective serotonin-reuptake inhibitors, muscle relaxants and anti-epileptic drugs, combined with aerobic exercise, psychological treatment and patient education, can effectively reduce symptoms and disability.

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