Expert Opinion

Current concepts in the treatment of fibromyalgia

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Abstract

The treatment of fibromyalgia involves the use of different kinds of therapeutic modalities. Among pharmacologic treatments, several antidepressants and pregabalin, an alfa$_2$delta blocker, are the best studied drugs and have the highest degree of evidence for efficacy. Other drugs that may be used and have at least a positive randomized clinical trial include sodium oxybate, two 5-HT3 receptor antagonists and pramipexole. As it is not an inflammatory disease, NSAIDs are not useful in the long-term management of fibromyalgia, but the combination of tramadol with paracetamol has been shown to be effective. Non-pharmacologic therapies include physical and psychological alternatives. Educating patients to understand their disease is helpful when combined with other non-pharmacologic alternatives, but has little efficacy by itself. Exercise, particularly aerobic exercise, has been shown to improve pain, depressed mood and quality of life. Cognitive-behavioral therapy has been shown to improve depressed mood and to help the patient to cope with the pain, although it lacks direct efficacy on pain, fatigue and sleep disturbances. Multimodal treatment, combining pharmacologic and one or more non-pharmacologic alternatives, is considered to be the best approach to treat patients with fibromyalgia.

Keywords: fibromyalgia; pharmacologic treatment; exercise; education; psychotherapy; multimodal treatment.

Received: March 14, 2013; **Accepted:** May 10, 2013; **Published:** August 10, 2013

Introduction

The first description of the fibromyalgia probably goes back to the 18th century when the expression "muscular rheumatism" was applied to painful but nondeforming musculoskeletal disorders to be distinguished from articular rheumatism. At the beginning of the 20th century Sir William Gowers used the term "fibrositis" and already mentioned that spontaneous pain was frequently associated to sleep disturbances and fatigue, among others [1]. The term "fibromyalgia" was initially proposed by Yunus in 1981 in the first controlled study that described the clinical characteristics of patients with fibrositis as compared with healthy matched controls [2].

However, it was not until 1990 that the first diagnostic criteria for fibromyalgia were proposed by the American College of Rheumatology (ACR) [3]. Although the authors of the study acknowledged the existence of symptoms such as fatigue, morning stiffness,

sleep disturbances and other frequently associated symptomatology, they did not find that the diagnostic accuracy were improved by considering them, and the criteria for the diagnosis of fibromyalgia were solely established in relation to pain. To be diagnosed of fibromyalgia a patient should have experienced widespread pain during at least three months and to experience tenderness in a minimum of eleven of eighteen specific tender points. A new set of diagnostic criteria was proposed, also by the ACR, in 2010 [4]. It substitutes the tender point evaluation by a Widespread Pain Index (WPI) and adds a Symptom Severity Scale (SS) that quantifies fatigue, waking unrefreshed, and cognitive symptoms and also takes in account the presence of other somatic symptoms. To date both kind of diagnostic criteria coexist.

The cardinal symptom that defines fibromyalgia is chronic generalized musculoskeletal pain without an underlying cause. However, although pain is a prominent feature of the fibromyalgia syndrome, other disabling symptoms coexist with it. Sleep disturbances and chronic fatigue are present in almost all patients with fibromyalgia; many patients also report cognitive difficulties, mood disturbances, stiffness, balance problems and hypersensitivity to environmental stimuli [5]. In addition, patients with fibromyalgia frequently suffer from a wide array of associated medical and psychiatric conditions which strongly contribute to a diminished quality of life [6].

Pain in fibromyalgia is not associated with inflammation nor is of neuropathic origin even if referred pain, hyperalgesia, and even allodynia are not uncommon. Currently, fibromyalgia is considered as a central sensitization syndrome, and it is acknowledged that there is an abnormal pain processing [7]. Although the precise mechanisms underlying fibromyalgia pathophysiology are still not completely understood, it is known that both genetic and environmental factors are involved in the development of the disease.

Fibromyalgia, both due to the fact that it is a multisymptomatic disease as for its frequent comorbidity, is associated to increased healthcare costs in relation to patients experiencing other diseases [8-10]. Patients' quality of life is low; although this has been related more with the psychological distress associated to the disease than to the limitations of their physical function [11-12], a recent study found that the intensity of pain, along with anxiety and depression symptoms were the most relevant explanatory variables associated with the impact of fibromyalgia on the quality of life of the patients [13].

Such a complex disease is not easy to treat and, in fact, not a single therapeutic modality has shown to be fully effective to improve the disease. The objective of the present article is to review the different therapeutic options available for the treatment of patients with fibromyalgia.

Pharmacologic Therapy

The current clinical practice in fibromyalgia is limited by the complex nature of the disease. This is reflected by the lack of a single agent able to control all the symptoms of the disease and in the limited number of available pharmacotherapies that are approved by the drug regulatory authorities for the treatment of fibromyalgia. While only three drugs have been approved by the US Food and Drug Administration (FDA), pregabalin in 2007, duloxetine in 2008, and milnacipran in 2009, the European Medicines Agency (EMA) has not granted the approval for any drug so far. The currently available therapeutic options for the treatment of fibromyalgia are discussed below.

Antidepressants

Besides their role in the management of depression and anxiety disorders, antidepressants are effective in the treatment of chronic pain modifying both the central and peripheral sites involved in pain transmission and perception (**Table 1**) [14, 15]. Several clinical studies have investigated the efficacy of the various antidepressant classes in the treatment of fibromyalgia, including tricyclic antidepressants (TCA), serotonin and norepinephrine reuptake inhibitors (SNRI), and selective serotonin reuptake inhibitors (SSRI) (**Table 2**).

Tricyclic Antidepressants

Tricyclic antidepressants (TCA) are one of the oldest antidepressant classes. Their clinical use has not been restricted to depression, as they are widely used in different chronic pain conditions including neuropathic pain, headache, low back pain and fibromyalgia [15]. In a recent meta-analysis that evaluated the efficacy and

safety of antidepressants in the treatment of fibromyalgia, either TCAs, SSRIs, and SNRIs were associated with significant improvement at the level of pain, sleep, fatigue, depression and health-related quality of life; however the TCAs had the largest effect sizes in improving pain and sleep disturbances as compared to the other classes [16-17]. In another meta-analysis comparing amitriptyline with duloxetine and milnacipran, it was found that amitriptyline was superior in reducing pain, sleep disturbances, fatigue and health-related quality of life; however, and due to the methodological limitations of the trials (small number of patients and short-termed studies), the authors concluded that amitriptyline could not be regarded as the gold-standard in the treatment of fibromyalgia [18]. This fact confirms the need for well-designed, long-term clinical trials able to evaluate the actual efficacy of amitriptyline in fibromyalgia. The doses of TCAs showing efficacy in fibromyalgia are lower than those recommended for the treatment of major depressive disorder, which is not the case for other antidepressant classes; this is probably due to their multiple mechanisms of action, both at central and peripheral sites, involved in their capacity to counteract pain-generating mechanisms [15].

Table 1. Pharmacologic actions of antidepressants in relation with persistent pain signaling*

Mechanism of Action	Site of action	TCA	SNRI	SRI
Reuptake inhibition of Monoamine	Serotonin	+	+	+
	Noradrenaline	+	+	–
Receptor Antagonism	α-Adrenergic	+	–	–
	NMDA	+	(+) milnacipran	–
Blocker or activator of ion channels	Sodium channel blocker	+	(+) venlafaxine – duloxetine	(+) fluoxetine
	Calcium channel blocker	+	?	(+) citalopram fluoxetine
	Potassium channel activator	+	?	–
$GABA_B$ receptor	Increase of receptor function	+ amitriptyline desipramine	?	+ fluoxetine
Opioid receptor binding/opioid-mediated effect	μ- and δ-Opioid receptor	(+)	(+) venlafaxine	(+) paroxetine

Abbreviations: SNRI= serotonin and norepinephrine reuptake inhibitor; SRI= selective serotonin reuptake inhibitor; TCA= tricyclic antidepressant; + indicates mechanism of action documented *in vitro* and/or *in vivo*; (+) indicates mechanism of action documented *in vitro* and/or *in vivo* at high concentration; – indicates no known mechanism of action; ? indicates not investigated/not known

*: Adapted from reference [15]

Table 2. Effect sizes of the different classes of antidepressants on different fibromyalgia symptoms*

Outcome	Effect Size (95% CI)**		
	TCA	SSRI	SNRI
Pain	-1.64 (-2.57 to -0.71)	-0.39 (-0.77 to -0.01)	-0.36 (-0.46 to -0.25)
Fatigue	-1.12 (-1.87 to -0.38)	-0.17 (-0.47 to 0.12)	-0.08 (-0.20 to 0.05)
Sleep	-1.84 (-2.62 to -1.06)	-0.23 (-0.56 to 0.10)	-0.31 (-0.47 to -0.14)
Depressed mood	-0.60 (-4.53 to 3.33)	-0.37 (-0.66 to -0.07)	-0.26 (-0.42 to -0.10)
HRQOL	-0.31 (-0.60 to -0.01)	-0.41 (-0.78 to -0.05)	-0.31 (-0.44 to -0.17)

Abbreviations: CI= Confidence Interval; TCA= Tricyclic antidepressant; SSRI= Selective serotonin reuptake inhibitor; SNRI= Selective serotonin norepinephrine reuptake inhibitor; HRQOL= Health-related quality of life.

*: Adapted from reference [17]. **: Small = 0.2-0.49; Medium = 0.5-0.79; Large ≥0.8

Selective Serotonin Norepinephrine Reuptake Inhibitors

To date, the three SNRIs that have been tried in the treatment of fibromyalgia are venlafaxine, duloxetine and milnacipran. The latter blocks with similar affinity the reuptake of serotonin and noradrenaline whereas duloxetine shows a 10-fold selectivity and venlafaxine a 30-fold selectivity for serotonin [19]. In spite of the fact that venlafaxine was the first SNRI to be studied in fibromyalgia, it has not been extensively investigated in this indication as it has been shown to be effective in alleviating pain and depressive symptoms only in two small uncontrolled trials [20-21]. Duloxetine 60-120 mg/day and milnacipran 100-200 mg/day have been shown to significantly reduce pain and depressive symptoms and to improve quality of life; while duloxetine therapy lead to significant improvement in sleep disturbances, it had non-significant effect on fatigue that was, on the other hand, significantly improved by milnacipran [18, 22]. Duloxetine has been shown to reduce pain and other symptoms of fibromyalgia both in patients with or without major depressive disorder [23]. In contrast to the short-term studies investigating the effect of TCAs in fibromyalgia, duloxetine and milnacipran have been studied in 1-year follow-up studies, where their efficacy has been shown to be preserved over the entire period for both antidepressants with a good tolerability and safety profile [24-25].

Other Antidepressants

Selective serotonin reuptake inhibitors are not as effective as the other antidepressants in the treatment of fibromyalgia. In the meta-analysis performed by Häuser and coworkers [16] although the effects of SSRIs on pain, sleep, fatigue depression and quality of life were statistically significant, their effects sizes were found to be small or non-substantial. The same reason promoting the tolerability of SSRIs in clinical practice might be the factor leading to their inferiority in the management of chronic pain conditions, as their selectivity to inhibit one monoamine system makes them less efficacious in treating chronic pain conditions as compared to TCAs [26]. However and following the concept of individualized patient care, SSRIs could be beneficial in fibromyalgia patients presenting concurrent depressive symptoms and they remain to be the drugs of choice in patients who are not able to tolerate other antidepressants.

Trazodone, an old second generation antidepressant with significant sedative activity, is frequently used, in an off-label basis, in the treatment of insomnia in many countries. Trazodone was recommended by the Ameri-

can Pain Society for use in patients with fibromyalgia with prominent sleep disturbances. A small two-month double-blind controlled crossover study, only published in an abstract form, found that trazodone use in fibromyalgia was associated with improvements in sleep disturbances, but had not any significant effect on psychological profile and clinical symptoms [27]. Later, two uncontrolled studies have been published. The first of them found that trazodone, in a flexible dose up to 300 mg/daily, improved sleep quality, anxiety and depression but had no effect on pain [28]. The second one found that the addition of pregabalin to trazodone treatment potentiated the antidepressant efficacy and improved pain, with the combination of the two drugs being well tolerated [29].

Anti-epileptics

To use the term antiepileptics is probably misleading since only one class of antiepileptic drugs, those of calcium channel modulators, has been shown to be useful in the management of fibromyalgia. Pregabalin and gabapentin play a critical role in pain perception through the modulation of α2δ voltage-gated calcium channel that leads to the inhibition of the synaptic release of glutamate, substance P and other neurotransmitters mediating pain response [30]. They are widely used in several chronic pain conditions both in Europe and in the United States. Pregabalin is FDA-approved for the treatment of diabetic peripheral neuropathy, postherpetic neuralgia, neuropathic pain due to spinal cord injury and fibromyalgia, and EMA-approved for peripheral and central neuropathic pain, whereas gabapentin is FDA-approved only for the treatment of postherpetic neuralgia and EMA-approved for the treatment of peripheral neuropathic pain. Pregabalin shows better pharmacokinetic and pharmacodynamic profiles [31] making it preferable to gabapentin (studied in only one small 12 week randomized clinical trial) that could be considered in patients who are responsive but cannot tolerate pregabalin. Their use in fibromyalgia is supported by two recent meta-analyses [32-33]. Both drugs have been found to reduce pain and to improve sleep and health-related quality of life; however, they showed non-substantial effect on fatigue and anxiety and lacked effect on depression with adverse events that included dizziness, somnolence, dry mouth, weight gain and peripheral edema. The evidence for pregabalin efficacy is stronger than the one for gabapentin.

Analgesics

Non-steroidal Anti-inflammatory Drugs

Although pain is the cardinal symptom of fibromyalgia, NSAIDs do not contribute significantly to its management, which is not surprising given the non-inflammatory nature of the disease. Although the evidence concerning their effectiveness in the treatment of fibromyalgia is limited, controlled trials have shown little or no efficacy either when administered alone or combined with other drugs such as amitriptyiline or benzodiazepines [34-37]. However, they are still widely used, although they are not perceived among the most effective medications [38].

Opioids

Clinical trials evaluating the efficacy of opioids are limited to a very small double-blind trial of intravenous morphine showing no efficacy and low tolerability. However, despite the fact that there is no convincing evidence of efficacy, opioids are frequently prescribed for the treatment of pain in fibromyalgia in many countries [39]. An uncontrolled study, published only in abstract form, did not find evidence of pain improvement during a four-year follow-up of fibromyalgia patients treated with opioids but found that, after two years of treatment, depression increased [40]. The use of opioids in fibromyalgia is also problematic due to their side-effect profile; in addition to the risk of dependence, there is also of concern the constipation, considering that this is a very common symptom reported by patients with fibromyalgia whose comorbidity with irritable bowel syndrome is high; likewise, opioids sedation and mental clouding may worsen the cognitive dysfunction experienced by many patients [39].

Other Analgesics

Tramadol is a drug that acts both as agonist on μ opioid receptors and as inhibitor of serotonin and noradrenaline reuptake. It has been shown to be effective in the management of pain in fibromyalgia both as monotherapy [41] and combined with paracetamol [42]. The use tramadol or tramadol-paracetamol combination for the

treatment of pain should be better reserved for "as needed" medication, for periods of fibromyalgia flare-ups, rather than for chronic use.

Tapentadol, a centrally-acting analgesic, is structurally related to tramadol; it has higher affinity than tramadol for μ receptors and inhibits the reuptake of noradrenaline but not of serotonin [43]. It has shown to be effective in different types of chronic non-cancer pain with better tolerability than pure μ-opioid receptor agonists [44]. Although it seems a promising drug for the treatment of pain in fibromyalgia, its potential role in this indication awaits further investigation.

Other drugs

Cyclobenzaprine

Cyclobenzaprine, licensed as a muscle relaxant, is an old drug structurally similar to TCAs. In a meta-analysis including 5 randomized, placebo-controlled trials, cyclobenzaprine demonstrated effectiveness in improving sleep, and modestly improving pain in the early stages of treatment, but it didn't improve fatigue or tender points [45]. Favorable outcomes of very low dose cyclobenzaprine (1- 4 mg) were achieved in an 8-week, double-blind, placebo-controlled trial, where it was associated with significantly improved pain, tenderness, depressive symptoms, and increased nights of restorative sleep [46].

Sodium Oxybate

Sodium oxybate, the sodium salt of gamma-hydroxybutyrate that gained FDA orphan drug status for the management of cataplexy and daytime sleepiness in patients with narcolepsy, has been shown to be effective for the treatment of fibromyalgia in four large randomized controlled clinical trials; however, it failed to gain the FDA approval for use in fibromyalgia due concerns of potential abuse [47]. In all of these studies, sodium oxybate improved outcomes of pain, fatigue, sleep disturbances, Fibromyalgia Impact Questionnaire scores and the patient global impression of change [48].

Sedative-hypnotics

The suggested role of sedative hypnotics in the management of fibromyalgia arises from the major sleep disturbance that this group of patients experiences. Knowing that a positive association exists between poor sleep and pain and fatigue [49], improvement of sleep symptoms was expected to be associated with better outcomes on pain and other fibromyalgia symptomatology. However, some benzodiazepines, temazepam, alprazolam, and bromazepam, have been tried in the treatment of fibromyalgia with little or no result [36, 37, 50]. Also, the two non-benzodiazepine GABA-A agonists zolpidem and zopiclone, improved sleep but neither pain nor mood disturbances [51-53]. Thus, it seems that the role of these drugs in the management of fibromyalgia is very limited.

Dopamine Agonists

The evidence for a possible role of the D2 dopaminergic agonists in the treatment of fibromyalgia is conflicting. A randomized controlled trial with pramipexole found that the drug improved pain, fatigue and global well-being [54]. However, two additional clinical trials evaluating ropinirole and extended-release ropinirole failed to find any treatment-related benefit [55]. One trial with extended-release pramipexole (NCT00689052) was early terminated and other with rotigotine (NCT00464737), has been completed but not published [56-57].

5-HT3 Antagonists

Several trials with intravenous or oral tropisetron and one with intravenous dolasetron in the treatment of fibromyalgia have been published showing a significant decrease of pain levels. The use of these drugs has been advocated mainly for patients suffering high levels of pain and not showing relevant psychological distress [58].

One Drug or Combination Therapy?

As there is not a drug able to control all the symptoms of the disease, the possibility to administer more than one drug simultaneously seems logical and, in fact, several studies have found that in the routine clinical practice, patients receive a mean of 2-3 concomitant drugs [59-61]. However, and in contrast with the abundance of published monotherapy clinical trials, little information is available concerning the efficacy and

tolerability of drug combinations. Thus, when considering polytherapy, therapeutic decisions must be based on data from monotherapy trials and a sound knowledge of the pharmacological profile of each drug in order to combine drugs that improve different symptoms of the disease while avoiding the overlapping of side effects [62].

Non-pharmacologic Therapy

Several non-pharmacologic treatment options have been shown to be effective as part of the management of fibromyalgia, and they are currently regarded as fundamental components in the treatment plan of fibromyalgia patients.

Education

Education is viewed as a basic component of a well-designed therapeutic plan in fibromyalgia. This intervention is characterized by an informative role that aims toward increasing patients' awareness about the various aspects of the disease, such as the possible pathogenesis and its correlation with the different symptoms, the role of pharmacologic therapies in fibromyalgia and the extent of the benefit they provide, in addition to the possible lifestyle factors and activities that might alleviate or exacerbate fibromyalgia symptoms. However, clinical trials assessing the role of education in fibromyalgia have evaluated this intervention mostly as an add-on of other non-pharmacologic therapies except in four controlled clinical studies that evaluated the discrete role and benefit of education. Burckhardt, *et al.* [63] compared education alone and education plus physical training with a waiting-list control group and found a significant positive impact on quality of life and self-efficacy for both interventions as compared to the control group. Bosch, *et al.* [64] evaluated the impact of education versus no intervention in two groups of patients with fibromyalgia; they found that the education group improved only in the perception of body pain. Rooks, *et al.* [65] compared education alone with two kinds of exercise programs and the combination of education and exercise; they found all of four groups improved but that the degree of improvement was highest in the combination group. Stuifbergen, *et al.* [66] compared education alone with education plus lifestyle changes and again it was found that both groups improved along the time but that the combined group improved more in physical activity and stress management.

Although the available evidence is limited, the results of these studies support a modest beneficial role of education that also seems to potentiate other non-pharmacologic interventions. Thus, education would be mostly indicated in multimodal therapeutic interventions.

Exercise

The role of exercise has been widely studied for its potential benefits in fibromyalgia. The types of exercise interventions that have been investigated in fibromyalgia include aerobic exercise (land-based and water-based), strength, and flexibility, and different combinations of these, with aerobic exercise being the most investigated intervention. Exercise interventions in fibromyalgia have been generally found to be associated with decreased pain intensity, reduced severity of fibromyalgia symptoms, and improved emotional and mental health [67]. Combined exercise modalities and aerobic exercise are the interventions that have the strongest evidence of benefit in patients with fibromyalgia [68]. A meta-analysis evaluating the effects of the different types of aerobic exercise (land-based and water-based) showed that both types of physical activities significantly improved pain, depressed mood, fatigue, quality of life and physical fitness but had non-significant influence on sleep disturbances [69]. A review aiming to evaluate which kind of physical exercise is best for fibromyalgia found that there were not clear differences in the efficacy of either land-based aerobic exercise, water-based aerobic exercise and muscle strengthening, although water-based exercise and strengthening seemed to be slightly more effective in reducing spontaneous pain and depressive mood [70]. Despite not being frequently reported, adverse effects associated with exercise therapy such as increase in symptoms (pain, stiffness and fatigue) and musculoskeletal problems should be also evaluated and considered [67]. Accordingly, it is recommended to consider individualized plans of exercise therapies that are primarily determined by the patients' preference and accessibility; these plans should cover the specific physi-

cal needs of the patient and ensure adequate compliance in order to avoid attrition that is frequently reported.

Psychotherapy

The most studied psychotherapeutic approach in fibromyalgia is the cognitive behavioral therapy (CBT). CBT combines cognitive and behavioral therapies that are intended to assist patients in building a set of skills to encounter dysfunctional emotions, thoughts and behaviors [71]. Pain catastrophizing represents the characterization of pain as being awful, horrible and unbearable, a feature that suggests psychological vulnerability and constitutes a major contributor to the exaggeration of pain experience and depression [72]. Compared to patients with rheumatoid arthritis, fibromyalgia patients show a significantly more prominent catastrophizing profile, suggesting the need for cognitive therapy and coping skills [73]. In a meta-analysis including 23 studies that evaluated different psychological treatments in patients with fibromyalgia, psychotherapy effectively reduced sleep problems, depression, functional status, and catastrophizing with CBT having the greatest effect size compared to other psychological interventions (relaxation, education, behavioral treatments, mindfulness-based treatments, and eye movement desensitization and reprocessing) [74]. In another meta-analysis including 14 randomized clinical trials specifically investigating the efficacy of CBT in fibromyalgia, CBT was associated with significant decrease in depressive symptoms, self-efficacy pain (i.e. subjects' perceived ability to manage and cope with pain and its emotional and behavioral consequences) and the number of physician visits at follow-up; however, non-significant effects on pain, sleep, fatigue and health-related quality of life were obtained [75]. Therefore, it can be concluded that psychotherapeutic intervention remains an essential component in the treatment of fibromyalgia given the psychological vulnerability of fibromyalgia patients.

Complementary and Alternative Medicine

As there is no cure for fibromyalgia and as the available therapies offer only partial efficacy, patients frequently turn to complementary and alternative medicine (CAM) looking for additional relief [76-77]. CAM is a broad term which encompasses a huge variety of therapies that are not generally considered to be part of the conventional medicine and that patients can use together with it (hence the expression complementary) or in its place (hence the expression alternative). The U.S. National Institutes of Health broadly classifies CAM in the following four categories [78]:

- natural products: such as herbal medicines, vitamins, minerals, dietary supplements and probiotics.

- mind and body medicine: including acupuncture, relaxation techniques, qi gong, tai-chi or hypnotherapy among the most known.

- manipulative and body-based practices: including spinal manipulation and massage therapy among the most frequently used.

- other CAM practices: that include movement therapies, traditional healers practices, energy fields, and whole medical systems.

Many CAM therapies have never been adequately investigated for efficacy and among those that have been studied, there were usually few trials of small sample size. A recent meta-analysis of CAM in the treatment of fibromyalgia found that only balneotherapy had effect sizes indicating that they reduced pain in fibromyalgia [79]. Massage, acupuncture and nutritional supplements showed no clear evidence of efficacy. Finally, manipulative, vibration, magnetic, homeopathy, movement therapy and energy medicine had 3 or less trials and could not be analyzed. Thus, it seems clear that additional studies are needed to evaluate the values of the different CAM therapies in the management of fibromyalgia.

Multi-component Treatment

The complexity of fibromyalgia and its overlapping pathophysiological mechanisms makes difficult to control the broad range of the disease symptoms. All of the pharmacologic and non-pharmacologic options previously mentioned are associated with a limited extent of improvement in fibromyalgia symptomatology, and none of them provides sufficient benefit when pre-

scribed alone. Therefore, it is widely accepted among healthcare professionals that a patient-specific multi-component therapeutic approach including both non-pharmacologic and pharmacologic therapies should be employed to attain optimal clinical outcomes. Given the distinct mode of activity of each type of intervention, it makes sense to combine them for obtaining a maximal benefit of symptomatic improvement. In a meta-analysis including 9 RCTs with 1,119 subjects, it was shown that a multi-component therapy with at least 2 non-pharmacologic therapies (at least 1 educational or other psychological therapy and at least 1 exercise therapy) was associated with strong evidence for reducing pain, fatigue, depressive symptoms, physical fitness and limitations to health-related quality of life [80]. In a recent randomized clinical trial assessing the efficacy of multidisciplinary treatment (conventional pharmacologic treatment, CBT, and physical therapy) versus a control group receiving conventional pharmacologic treatment only in women with low educational level, it was found that improvements in functionality, sleep disturbances, pain intensity, catastrophizing and psychological distress were significantly superior in the multidisciplinary treatment group and that improvements of sleep disturbances, catastrophizing and psychological distress were maintained at 12-month follow-up [81]. The strength of evidence supporting the adaptation of multidisciplinary approach in fibromyalgia is a moderate to strong evidence; however it is not yet known which combinations best provide the optimal benefit in fibromyalgia [82]. Various combination approaches are possible, and the selection of these options relies on the specific patient's needs on the one hand and on the patient's accessibility to the suggested treatment options on the other hand. At least, the combination of pharmacologic therapy and exercise should be mandatory; patients' education and/or CBT should be added whenever possible.

Conclusion

Fibromyalgia is a disabling and difficult to treat condition. Although several drugs and other treatment modalities have been evaluated in randomized clinical trials, only a few of them have shown to provide statistically significant but modest benefit. Therefore, it is widely accepted that patient-centered multi-component approach including both pharmacological and non-pharmacologic therapies is required for optimizing treatment outcomes. In addition, there is a clear need for more research on individual therapies and treatment combinations.

Disclosure

There are no conflicts of interest.

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