

Non-pharmacological therapy and complementary and alternative medicine in fibromyalgia

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ABSTRACT

Fibromyalgia is a chronic painful syndrome that affects up to 5% of the world population. It is associated with sleep and mood disorders, fatigue, and functional disability. Its pathogenesis involves a disorder of the central modulation of pain, impairment of the descending inhibitory system, and hyperactivity of substance P. Because of the extensive symptomatology of patients with fibromyalgia and its multifactorial pathogenesis, its ideal treatment requires a multidisciplinary approach including the association of pharmacological and non-pharmacological therapies. The pharmacological therapy currently recommended for the syndrome includes antidepressants, calcium-channel modulators, muscle relaxants, and analgesics. In most cases, the non-pharmacological treatment consists of patient education, supervised aerobic physical activity, and cognitive-behavioral therapy. However, many patients do not respond satisfactorily, or have side effects associated with the long-term use of drugs, in addition to reporting difficulties in adhering to a therapy based on exercises and physical medicine. Thus, physicians and patients are increasingly interested in an alternative and complementary therapy for fibromyalgia. This review approaches the different therapeutic modalities used in fibromyalgia, emphasizing the evidence of non-pharmacological therapy and use of alternative and complementary medicine for these patients.

Keywords: fibromyalgia, complementary therapies, phytotherapy

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INTRODUCTION

According to the International Association for the Study of Pain (IASP), pain can be defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.¹ It is also defined as an unpleasant sensation that alerts the individual to a harmful or potentially harmful action to the organism by either an external agent or an internal morbid process.²

In painful cases of chronic evolution, with no evident structural pathology, pain loses its alarm function and becomes the fundamental nucleus of the problem. This has important emotional, cognitive, and labor repercussions, which can affect the patient's personal life and social and household activities.²

Fibromyalgia is an example of rheumatologic disease that evolves with chronic pain and represents the most common

cause of chronic and diffuse pain in the population of the United States of America.³ Although its pathogenesis has not been totally clarified, several authors consider it either a disorder of the central modulation of pain or an altered central nervous system processing in response to a nociceptive stimulus.⁴⁻⁸ Recent evidence has suggested the participation of environmental factors acting on genetically predisposed individuals developing these disease.⁹ The investigation on the involvement of autonomic nervous system and hypothalamus-pituitary-adrenal axis has also suggested that these systems of response to stress play a role in fibromyalgia susceptibility or in the expression of its symptoms.⁸

Because fibromyalgia is a chronic painful syndrome, it has a significant negative impact on patients' quality of life.¹⁰⁻¹⁵ Furthermore, due to its varied symptomatology and the multifactorial nature of its pathogenesis, treatment of

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fibromyalgia requires a multidisciplinary approach and should include changes in life style, non-pharmacological treatment, and pharmacological interventions aiming at pain relief, and improvement in sleep quality and mood disorders.¹⁶

The pharmacological therapy currently recommended for fibromyalgia includes antidepressants, calcium-channel modulators, muscle relaxants, and analgesics. However, many patients fail to respond satisfactorily or have side effects associated with these drugs long-term use. However, patients have difficulty in adhering to a non-pharmacological therapy based only on exercises and physical medicine. Therefore, patients are highly interested in an alternative and complementary therapy, and physicians have been routinely questioned about complementary or adjuvant forms of treatment.¹⁶

This study reviews the different therapeutic modalities used in fibromyalgia, emphasizing the evidence of the non-pharmacological treatment efficacy and the promising responses of alternative and complementary medicine in literature. Thus, a literature review was carried out in MEDLINE and LILACS databases in the following sites: www.ncbi.nlm.nih.gov/pubmed and www.bireme.br. The following terms related to fibromyalgia were used: diagnosis and treatment, pharmacological and non-pharmacological therapy, alternative and complementary medicine, and phytotherapy. Clinical, randomized, and placebo-controlled studies carried out with fibromyalgia patients were preferentially selected, in addition to systematic reviews and classical articles about its pathogenesis and therapeutics, published in English or Portuguese in the last decade.

PHARMACOLOGICAL TREATMENT

The pharmacological treatment of fibromyalgia is performed individually, and may consist of antidepressants, calcium-channel modulators, muscle relaxants and/or analgesics. The meta-analysis by Garcia-Campayo *et al.*,¹⁷ about the efficacy of treatments used for fibromyalgia, identified 594 articles in literature and included only 33 clinical trials, 11 of which using antidepressants and 21 using other drugs. Amitriptyline was tested in seven assays, and duloxetine in two assays.

In that same year, Hauser *et al.*¹⁸ published a meta-analysis, whose objective was to determine the efficacy of antidepressants in fibromyalgia. The authors assessed studies on the pharmacological therapy for fibromyalgia between 1966 and August 2008 (MEDLINE and PsycINFO), and between 1980 and August 2008 (Scopus and Cochrane Library). Of the 337 clinical assays selected, only 18 met the criteria required by the study (to meet the American College of Rheumatology

criteria for fibromyalgia, and to be clinical, randomized and placebo-controlled trials, or to use any type of antidepressant drug), and were included. The efficacy of antidepressants for reducing pain, and sleep and mood disorders, and for improving the patient's overall condition was strongly evidenced. According to these authors, the most significant results in the treatment of the syndrome were obtained with the use of amitriptyline hydrochloride and duloxetine hydrochloride for pain and sleep. In the case of amitriptyline, there are many studies with favorable responses, and, in the case of duloxetine, there have been a large number of patients already assessed in placebo-controlled and randomized studies.

In addition to amitriptyline¹⁸ and duloxetine,¹⁹ other antidepressants, such as fluoxetine²⁰ and milnacipran,^{21,22} and several other drugs, such as ciclobenzaprine,^{23,24} gabapentin,²⁵ pregabalin,^{26,27} and tramadol,^{28,29} have been tested in controlled studies and have shown promising responses in relieving fibromyalgia symptoms. Although all the above-cited drugs have been studied and have been part of these patients' pharmacological therapy, currently, duloxetine and pregabalin are the only drugs approved by the Food and Drug Administration (FDA) for treating fibromyalgia.

Table 1 describes the main drugs used in the pharmacological treatment for fibromyalgia, in addition to new forms of therapy consisting of agonists and/or antagonists of receptors associated with chronic pain and fibromyalgia.

NON-PHARMACOLOGICAL TREATMENT

The non-pharmacological treatment of fibromyalgia consists, in most cases, of patient's education, supervised aerobic physical activity, and cognitive-behavioral therapy.^{41,42}

Physical exercises

Stimulating the practice of physical activity in patients with fibromyalgia aims to improve or maintain the patient's physical fitness; provide emotional well-being; improve the symptoms of fibromyalgia; and improve health and overall well-being. Domestic chores, such as walking from home to work, cleaning the house, and removing leaves from the sidewalk among other tasks, are considered productive ways to add physical activity to patient's daily routine. Physical activity of moderate intensity, such as walking, dancing, and stationary biking, is the aerobic activity that can be considered for the physical therapy of such patients.⁴³

Physical exercise programs, mainly aerobic exercises,^{44,45} with neither load nor high impact on the musculoskeletal system, such as dancing, swimming, and water aerobics, greatly

Table 1
Current pharmacological therapy and therapeutic perspectives in fibromyalgia

Drugs and dose (oral route)	Mechanisms of action	Authors
Amitriptyline hydrochloride (25-50 mg/day)	Non-selective inhibition of monoamine uptake - competition for the binding site of the transport protein and antagonism of the NMDA* receptor	Carette <i>et al.</i> , ²⁴ Ginsberg <i>et al.</i> , ³⁰ Goldenberg <i>et al.</i> , ³¹ Hannonen <i>et al.</i> ³²
Fluoxetine hydrochloride (20-80 mg/day)	Selective inhibition of the 5-HT** uptake and of the Na ⁺ -K ⁺ -dependent transporter, adenosine triphosphatase	Arnold <i>et al.</i> , ²⁰ Ozerbil <i>et al.</i> ³³
Duloxetine [§] (60-120 mg/day)	Effective inhibition of the 5-HT and noradrenaline uptake	Arnold, ¹⁹ Arnold <i>et al.</i> ³⁴
Milnacipran (100-200 mg/day)	Effective inhibition of the 5-HT and noradrenaline uptake, and mild inhibition of the NMDA receptor	Gendreau <i>et al.</i> , ²¹ Mease <i>et al.</i> ²²
Cyclobenzaprine hydrochloride (10-30 mg/day)	Decreased activity of the efferent motor neuron (suggested)	Bennet <i>et al.</i> , ²³ Carette <i>et al.</i> ²⁴
Gabapentin (900-2000 mg/day)	Interaction and modulation of the alpha-2-delta ($\alpha_2\Delta$) subunit of voltage-gated Ca ²⁺ channels	Arnold <i>et al.</i> ²⁵
Pregabalin [§] (300-450 mg/day)	Interaction and modulation of the $\alpha_2\Delta$ subunit of voltage-gated Ca ²⁺ channels	Arnold <i>et al.</i> , ²⁶ Mease <i>et al.</i> ²⁷
Tramadol (50-200 mg/day)	Agonist of the μ -opioid receptor and inhibition of the 5-HT and noradrenaline uptake	Russel <i>et al.</i> , ²⁸ Bennet <i>et al.</i> ²⁹
Tropisetron (5-10 mg/day)	Antagonist of the 5-HT ₃ receptor	Haus <i>et al.</i> , ³⁵ Stratz <i>et al.</i> , ³⁶ Haus <i>et al.</i> ³⁷
Dextromethorphan (50-200 mg/day)	Antagonist of the NMDA receptors	Price and Staud, ³⁸ Staud ³⁹
Pramipexole (4.5 mg/day)	Dopaminergic agonist of the D3 dopaminergic receptor	Holman and Myers ⁴⁰

*NMDA: N-methyl-D-aspartate; **5-HT: 5-hydroxytryptamine. §Approved by the FDA for the treatment of fibromyalgia.

reduce the impact of fibromyalgia symptoms on patients' lives. Low-intensity exercises or those in which the patient can identify the limit of his/her exertion and pain seem to be the most effective. Physical activity exerts an analgesic effect by stimulating the release of endorphins, acting as an antidepressant and providing an overall well-being and self-control sensation.⁴⁶⁻⁴⁸

Individuals with fibromyalgia, mainly those initiating the practice of physical exercises, should undergo a mild-to-moderate intensity exercise program for at least four weeks, and they can continue indefinitely to exercise at moderate intensity, as long as their activity level generates neither discomfort nor excessive pain. In such situations, the reduction in intensity and duration of exercises, in addition to increasing the day interval between exercises, can resolve or relieve the discomfort.⁴³

According to Valim,⁴⁹ although exercise should be practiced indefinitely, the benefit appears only between the eighth and tenth weeks after beginning the program, and continues to increase up to the twentieth week, but some patients may feel worse and experience more pain initially. According to

the author, there is strong evidence that the supervised aerobic exercise reduces pain, the number of tender points, depression, anxiety, and improves the quality of life in addition to other psychological aspects.

An exercise program usually comprises warm up, physical activity, and relaxation, followed by stretching before and after exercising. Warm up is important in individuals with fibromyalgia because it can help to reduce the stiffness associated with the disease, and, for many patients, the warm up itself promotes fitness for performing other aerobic activities. Physical activities are usually performed gradually, followed by endurance training, and tailored to each patient's needs. Flexibility exercises and mild or recreational activities, mainly when performed in group, or even reading, listening to music, yoga, and other forms of relaxation have also been associated with improvement in some patients.^{43,50,51}

In the clinical assay by Munguía-Izquierdo and Legaz-Arrese,⁵² physical exercise in warm water, three times a week for 16 weeks, was effective in reducing the pain and intensity of fibromyalgia. Additionally, adult women who had not

undergone physical exercises previously and who had important painful symptomatology at the beginning of the study had their cognitive function improved.

Cognitive-behavioral therapy

In patients with important physical limitation due to pain or difficulty to exercise, or even with mood disorders, psychological and/or psychiatric intervention is required. Cognitive-behavioral therapies,^{53,54} especially when combined with aerobic exercises, stretching, and family education, have provided excellent results.^{48,52}

A randomized and controlled study of 60 patients has assessed the efficacy of cognitive-behavioral therapy in patients with fibromyalgia.⁵⁵ All patients received amitriptyline 25 mg/day, but only half of them underwent cognitive-behavioral therapy. The results showed that cognitive-behavioral therapy was effective when used in association with pharmacotherapy.⁵⁵

ALTERNATIVE AND COMPLEMENTARY MEDICINE

In recent years, alternative and complementary medicine has been requested by the population, especially by individuals with fibromyalgia, for whom the isolated conventional therapy has shown limited benefits, requiring multidisciplinary treatment.⁵⁶

In 1997, a study was carried out via telephone interviews in the USA with 2,055 individuals, 42% of whom reported the use of some type of alternative and/or complementary medicine in the previous year as follows: medicinal herbs, polyvitamins, massages, self-support groups, homemade formulations, religiousness, and homeopathy, for both preventing and treating specific diseases.⁵⁶ In that same year, Nicassio *et al.*,⁵⁷ studying 111 patients with fibromyalgia, assessed the frequency at which they sought alternative and complementary medicine and the factors involved. The authors concluded that, in this group of patients, pain intensity and disability were the main factors leading patients with fibromyalgia to seek such therapy.

From February to July 2003, Wahner-Roedler *et al.*⁵⁸ carried out a study to assess the use of alternative and complementary medicine in a tertiary center for treatment of fibromyalgia. Of the 289 participants (263 women and 26 men), 98% reported the use of some type of alternative and complementary therapy, and the most frequently reported were: exercises (48%); treatment through prayers (45%); therapeutic massages (44%); chiropraxis (37%); use of vitamins C (35%) and E (31%), magnesium (29%), complex B (25%), and green tea (24%); and weight loss programs (20%). Moreover, 51% of the patients reported using one or more medicinal herbs or dietary supplements, and 8%

of patients of all ages, mainly those between 18 and 64 years, reported the use of ginseng.

Although non-pharmacological treatments, such as exercises and cognitive-behavioral therapy, are sometimes considered an alternative and complementary form of medicine, the National Institutes of Health (NIH) do not classify them as such. Historically, alternative and complementary medicine has been defined as medical interventions, which are uncommon at medical schools, non-routinely prescribed by clinicians of Western medicine. The NIH classify that type of medical practice into five groups: 1) alternative medicine: Chinese traditional medicine (including acupuncture), naturopathic, ayurvedic or homeopathic medicine; 2) biologically-based therapies, including phytotherapy, dietary supplementation, and individual biological treatment - the latter has not been approved by the FDA; 3) energetic therapies, such as Reiki, therapeutic touch, and magnetic therapy; 4) practices based on body manipulation: chiropraxis, osteopathy, and massages; 5) body-mind interventions, such as meditation, relaxation, biofeedback, and hypnotherapy.⁵⁹

The literature has shown low level of evidence for the above-described alternative and complementary treatments for fibromyalgia, except for acupuncture, some phytotherapeutic agents, nutritional supplements, and massages.^{60,61} According to Ernst,⁶⁰ there is a tendency towards a positive result with homeopathy, but such data are insufficient to indicate its use.

Acupuncture

In alternative medicine, the best results have been obtained by use of acupuncture, whose benefits for patients with fibromyalgia have been mostly reported in studies inadequately controlled and non-double-blind.⁶² However, two controlled clinical studies have supported this evidence. The first, with 70 patients undergoing electroacupuncture, has reported a 70% improvement in several parameters assessed in the active intervention group against 4% in the sham acupuncture group.⁶³ The second study, conducted with 60 patients, has compared traditional acupuncture with sham acupuncture for 16 weeks. In the latter, all patients received 25 mg of amitriptyline at bedtime, and pain and depression measurements differed significantly between both groups, and no improvement was observed in control group.⁶⁴ The following methodological problems have been detected in these two studies: study duration shorter than three months; lack of functional measure assessment in the first study; and lack of tender point assessment in the second study, which added amitriptyline to acupuncture.

In addition to the methodological problems, the use of acupuncture in a chronic disease such as fibromyalgia should

be taken into consideration. Further controlled studies, mainly focusing on type, time and frequency of acupuncture treatment, are required, aiming at consolidating the use of acupuncture in the scientific field.⁶¹

Diet, nutritional supplements and therapeutic herbs (phytotherapy)

Several authors have reported the beneficial effects of food on symptoms of rheumatologic diseases, especially the vegetarian diet.⁶⁵⁻⁶⁷ Bramwell *et al.*⁶⁵ and Kartinen *et al.*⁶⁶ have studied the role of diet in the improvement of patients with fibromyalgia. The first study, assessing 12 patients receiving a mixture of ascorbic acid and broccolis, has reported a reduction in the pain and quality of life parameters. The second study has assessed the efficacy of a strictly vegetarian diet, and concluded that such diet was beneficial, although for a short period of time. Both were open, non-randomized studies, requiring larger and double-blind population groups.

Donaldson, Speight and Loomis⁶⁷ have reported an improvement in several parameters for following-up fibromyalgia (pain, sleep, fatigue, and quality of life) in 19 of 30 patients receiving an exclusively vegetarian diet for seven months. However, this study had limitations regarding its design (non-controlled and open), and all patients maintained the conventional treatment during the study.

S-adenosyl-L-methionine (SAME) is one of the 25 most commonly used dietary supplements in the USA. It has antidepressant, anti-inflammatory, and analgesic properties. Compared with placebo, SAME, at the oral dose of 800 mg/day for six weeks, provided a significant improvement in duration of morning stiffness, pain at rest, fatigue, and overall disease activity of 44 patients with fibromyalgia. However, it was not well accepted because of the high incidence of side effects. Additionally, its effect on tender points, muscle strength, and mood did not differ from that of the control group.⁶⁸

The following two studies have shown that the herb considered a dietary supplement, *Chorella pyrenoidosa* (unicellular, green algae, rich in proteins, vitamins, and mineral salts), provided relief of some symptoms of fibromyalgia, especially a reduction in the number of tender points: one open study with 18 patients; and a randomized, double-blind, and controlled study with 37 individuals. Both studies have been developed by the same group.^{69,70} Further studies with significant samples and better designs are required, so that those results can be confirmed.

The discipline of rheumatology of the Federal University of São Paulo has carried out a randomized, controlled, double-blind study with *Hypericum perforatum* and

amitriptyline, aiming at assessing the efficacy and tolerability of *H. perforatum* for treatment of patients with fibromyalgia, based on this plant antidepressant properties. The study comprised 79 patients (randomized ratio of 1:1). At the end of 12 weeks of treatment, both groups had improved significantly, according to pain visual analogue scale (VAS) and the Fibromyalgia Impact Questionnaire (FIQ), and no difference was observed between groups. The authors have concluded that *H. perforatum* and amitriptyline were effective for treating patients with fibromyalgia, with no difference between groups.⁷¹

A double-blind, placebo-controlled study has assessed nabilone, a cannabinoid phytochemical that is a selective antagonist of the serotonin (5-HT₃) receptor, in 40 patients with fibromyalgia. The oral use of nabilone at the dosage of 0.5 to 2 mg/day has determined a reduction in pain (pain visual analogue scale) and anxiety, suggesting a probable adjuvant role for this phytochemical in treatment of fibromyalgia.⁷²

The phytochemical *Panax ginseng* C.A. Meyer has been used in oriental medicine for centuries, primarily for treating weakness and fatigue.⁷³ Clinical studies assessing the analgesic effects of *P. ginseng* are scarce in literature. Recently, a clinical, randomized, double-blind, controlled study has compared the effect of *P. ginseng* root extract (100 mg/day) with amitriptyline (25 mg/day) and placebo in 38 women with fibromyalgia for 12 weeks. The following were assessed: pain, fatigue, sleep, and anxiety using VAS; the number of tender points; and the quality of life using FIQ. In this study, *P. ginseng* was able to improve all parameters assessed, but differed from neither placebo nor amitriptyline, and the latter was better than placebo and *P. ginseng* in improving anxiety. Considering the benefits in the parameters assessed, the authors believe that *P. ginseng* may represent, after further studies with larger samples and/or at higher doses, a complementary therapy for patients with fibromyalgia, or even for those who do not respond to or cannot undergo conventional therapy.⁷⁴

According to Kolasinski,⁷⁵ the following aspects should be considered when instructing patients about the use of complementary medicine, especially phytochemicals and dietary supplements: natural medication is not always effective; many commercially available products guarantee neither efficacy nor safety; the amount and quality of active ingredients may vary from product to product and from time to time in the same product; herb-based products are not universally considered medicaments and are subject to contamination; the interaction of natural products with medicaments used by patients can have serious consequences; and, finally, some population groups, such as children, pregnant women, those

trying to get pregnant, and the elderly, should not undergo any complementary medicine treatment without medical supervision.⁷⁵

FINAL CONSIDERATIONS

Alternative and complementary medicine has been requested by the population in recent years, especially by individuals with fibromyalgia, a chronic painful condition of multifactorial etiopathogenesis. There is consensus that the treatment of that syndrome, which has varied symptomatology and affects different groups of patients, requires a multidisciplinary therapy, including the association of pharmacological and non-pharmacological treatments, based on randomized, placebo-controlled clinical trials. The correct use of this association for treating these patients has been increasingly common in medical prescriptions. However, a challenge in the treatment of fibromyalgia is the inclusion of an alternative and

complementary therapy in the daily routine of rheumatologists, when the previously indicated therapy fails, in the presence of side effects, or when the patient refuses to undergo the conventional treatment.

In fact, little is known about the efficacy of alternative and complementary therapies in fibromyalgia and their tolerance. Studies of scientific quality are scarce, and they are always questioned due to the reduced size of their samples, and the lack of both adequate control groups and adequate follow-up. Moreover, even the studies conducted with strict scientific quality, with confirmed safety and efficacy of the therapeutic modalities, are rarely discussed by rheumatologists.

It is worth noting that physicians should become informed about alternative and complementary therapies in fibromyalgia and their evidence for use. They also should talk to their patients and instruct them about these forms of treatment, prescribing them or contraindicating them, thus providing a greater range of therapeutic options in fibromyalgia.

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