

## DRUG AND NON-DRUG TREATMENT OPTIONS OF FIBROMYALGIA

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## ABSTRACT

There is no clear specific pathophysiological therapeutic target of fibromyalgia (FM) management. The management of this complex condition has thus perplexed the medical community for many years, and several national and international guidelines have aimed to address this complexity. Pain relieving pharmaceutical medications are generally connected with an assortment of unfriendly reactions, for example, constipation, urinary retention, nausea, sedation, respiratory depression, myoclonus, delirium, sexual dysfunction, and hyperalgesia. The challenge of achieving adequate pain control without adverse side effects further compounds the problem and provides rationale for seeking complementary medicine and non-medicine alternatives.

**Keywords:** fibromyalgia; chronic noncancer pain; neurofeedback; cognitive behavioral therapy; acceptance and commitment therapy; inflammatory arthritis

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**Figure 1: Perspectives on Living with Fibromyalgia [1].** Perceptions of people living with chronic illness change over time, contributing to health-related stress that necessitates coping skills. Self-efficacy operates as an important cognitive factor in the control of symptoms such as pain, with self-efficacy beliefs helping to explain many of the behaviors and disabilities of those with persistent symptoms.

Fibromyalgia (FM) is an idiopathic chronic condition that causes widespread musculoskeletal pain, hyperalgesia and allodynia, affecting 2.10% (a total of 4% female and 2-5% male) of the world's population, 2.3% of the European population, 2.4% of the Spanish population [2,3]. In France, work productivity loss contributed almost 90% of the total costs incurred by patients with FM, with an economic cost of 13000 million euros annually which is around \$100 billion in US [2], [4,5]. Work disability was found to be 35% in US and Australia and 30% reported in Canada due to FM [6]. FM is more common in women compared to men, with a ratio of 2:1 [7] or 3:1 [8], although other studies say 85%-90% FM patients are middle aged women [9,10]. 30-50% of FM patients have anxiety and/or depression at the time of diagnosis [11], while patients have a lifetime history of depression (50-75%) [12] and depressive disorders (13%-63.8%) [13]. Chronic tension type headache was endorsed by 50-80% of treatment-seeking FM patients [7], [14]. FM is also common in 10-30% of patients with primary rheumatic diseases [15,16]. Rheumatic fever, neck pain, constipation, diarrhea, fatigue and notably insulin resistance are the most predictive symptoms of having future FM [4], [17-20]. A nearly 75% FM patients have comorbidity issues of pain-non-pain symptoms, psychological distress, social security and work disability [21]. FM patients incur direct costs approximately equal to RA patients, but visit more emergency physicians, physicians, and physical therapists [22]. Duloxetine, amitriptyline and pregabalin are among the most widely used medications with higher efficacy reported with duloxetine [23-26]. As the medical management of FM is often only partially successful, health professionals need to give patients sustained support to become expert, active self-managers [27,28]. Emerging data suggests that a common feature associated with treatment failure is pain arising from dysfunctions within the brain and spinal cord [29]. Also, long-term safety of conventional drugs is unknown [30]. NSAIDs are widely used in FM, despite being considered not to be effective [31,32]. Also, opioid users showed less improvement in pain-related interference with daily living, functioning, depression, and insomnia [33]. Evidence for effectiveness of cannabinoids in chronic noncancer pain (CNCP) is also limited [34] and but not in FM [35, 36], although strong monitoring is mandatory. Cytokines/chemokines, lipid mediators, oxidative stress and several plasma-derived factors underlie the inflammatory state in FM [37]. Adding palmitoylethanolamide (PEA) to initial duloxetine + pregabalin therapy improved the outcome of FM [38]. Schweiger et.al, 2019 demonstrated ultra-micronized PEA treatment was well-tolerated among FM patients with GI symptoms (diarrhea, dyspepsia, bloating, constipation, vomiting) reported in nearly 14% patients [39]. Herbal medicine includes over 2000 different medicinal substances with 80-100 commonly used for the treatment of FM [40]. Studies show that 70% FM patients tried nutritional supplements to control FM symptoms, although none of them found to be consistently effective [41]. Transient, burning and pricking, skin irritation, dizziness, nausea, dry mouth, drowsiness, constipation and insomnia were some of the side effects associated with herbal medicines [42]. A nearly 70% German FM patients used thermal baths,

35.2% use alternative interventions such as homeopathy, dietary supplements, and 18.4% use meditative exercises such as yoga or Tai chi [43]. Research has suggested that traditional Eastern practices such as tai chi, qigong and yoga can relieve FM symptoms, the same practices found to be effective adjunct for Anxiety, MDD and insomnia management [44-47]. Low FODMAP was found to be effective in QOL, quality of sleep, anxiety and depression and inflammatory biomarkers in FM patients [48-53]. In general, exercise and psychoeducational approaches have the greatest evidence of efficacy among non-pharmacological therapies, but they need to be tailored to the individual [54]. Electroencephalography biofeedback (EMG-BFB) or Neurofeedback might reduce pain intensity; improve attention and QoL more successfully than other psychological or multicomponent programs [55-57]. Cognitive behavioral therapy (CBT) interventions may slow or reverse cortical gray matter atrophy, reduces circulating proinflammatory cytokines (IL-6, IL-8, and TNF- $\alpha$  level) of fibromyalgia patients, pain symptoms and pain perceptions, helps FM patient having fear of pain, anxiety, depression and insomnia [58-62]. CBT and specialized neuromuscular exercise intervention offer stronger treatment benefits than CBT alone in juvenile FM [63]. Significant differences regarding trait anxiety, sleep quality, and tenderness at some points along with alleviation of pain intensity, fatigue and depression reported with audio-recorded guided imagery (one component of CBT) relaxation on people with FM [64-67]. Fear of pain leads to depression, social isolation, disability or reduced participation in daily life activities [68]. Fear avoidance beliefs alleviates inactivity/disability [69,70], a 20-30% improvement in pain disability reported by Palstam et.al, 2016 [71]. The goal within acceptance and commitment therapy (ACT) is to reduce the dominance of pain in person's life through increased psychological flexibility [72]. A significant change in psychological inflexibility, self-efficiency, pain-related functioning, FM impact (due to improved pain acceptance) reported with ACT [73-75]. However, ACT was not more effective than the "active" comparison conditions (eg, CBT) in chronic pain management [76]. Exercise is effective for the management of fibromyalgia syndrome for up to 6 months. individualized resistance exercise was followed by changes in IGF-1 and leptin, reduced pain, fatigue and improved muscular strength [8], [77-79], however, poor concordance to exercise interventions and adherence reported by Álvarez-Gallardo et.al, 2019 [80]. So, the therapeutic validity of exercise intervention programs in fibromyalgia is low. Mixed exercise probably improves HRQoL, physical function, and fatigue [81]. Aerobic exercise may slightly decrease pain intensity, may slightly improve physical function, and may lead to little difference in fatigue and stiffness [82]. Whole body vibration (WBV) to exercise protocol positively affects on pain intensity [83-85]. Although, Dong et.al, 2019 reported no significant relieve from chronic musculoskeletal pain compared with the traditional treatment [86]. Acupuncture therapy is an effective and safe treatment for patients with FM, it was more effective in relieving pain in both the short and long term compared with conventional medication [87-89]. Changes in serum serotonin and SP levels may be a

valuable explanation for acupuncture mechanisms in FM treatment [90]. People with FM may consider using electro-acupuncture (EA) alone or with exercise and medication [91]. Physiotherapy and acupuncture, both are effective, not found to be more beneficial than the other, longer post-treatment follow-up may help determine the superior treatment option [92]. El-Shewy et.al, 2019 and Atzeni et.al, 2019 reported that Hyperbaric oxygen therapy (HBOT) has been utilized and has recently shown promising effects in the management of FM [93, 94]. HBOT in FM induces changes in cortical excitability and a secondary reduction in pain and muscle fatigue, improved the ability of the central motor command to generate the same effort (MVC) with fewer recruited fibers [95]. Tirelli et.al, 2019 reported significant improvement without side effects with ozone therapy [96]. Mindfulness can be conceptualized as a primarily cognitive practice; in that it involves the purposeful control of attention to foster nonjudgmental awareness of the present moment [97]. Higher mindfulness is associated with less pain interference, lower impact of fibromyalgia, and better psychological health and quality of life in people with FM [98]. Mindfulness meditation may provide an effective complementary treatment when combined with other reliable techniques (exercise, CBT) [99]. An average 12-minute exposure to a therapy dog reduces anxiety in 34% of fibromyalgia patients, together with reductions in pain and improvements in mood [100]. Massage therapy may improve pain, anxiety, depression, and sleep disturbance by complex interplay of both physical and mental modes of action [101,102]. de Oliveira et.al, 2018 reported improved QoL, reduced perceived stress index and pain with massage therapy [103]. Honda et.al, 2018 discussed several physical-agent modalities like low-level laser therapy (LLLT), thermal therapy, electromagnetic field therapy, and transcutaneous electrical nerve stimulation (TENS) for FM management. Thermal therapy and LLLT had a partial effect on pain relief in FM patients [104]. TENS has short-term efficacy in relieving symptoms of fibromyalgia while the stimulator is active [105]. There is no high-quality evidence to support or refute the use of TENS in FM [106]. Exercises combined with TENS might be useful due to quick myalgic pain relief in the treatment of fibromyalgia in everyday practice [107]. Thermal therapy combining sauna therapy and underwater exercise improved the QoL as well as the pain and symptoms of FM [108]. Spa therapy comprises a broad spectrum of therapeutic modalities including hydrotherapy, balneotherapy, physiotherapy, mud-pack therapy, and exercise. It can represent a useful backup to pharmacologic treatment of FM [109]. Adding water therapy to the usual care for FM patients is cost-effective for both healthcare and societal costs [22]. Nascimento et.al, 2015 suggested that cyclodextrin-complexed *Ocimum basilicum* leaves essential oil increases Fos protein expression in the CNS and might be a therapeutic alternative to FM management [110]. Patients severely affected by fibromyalgia can obtain short-term improvements following topical capsaicin 0.075 % treatment three times daily for 6 weeks [111]. Touch therapy, aromatherapy, reflexology, chiropractic and massage therapies and hypnotherapy can be effective in improving QoL in FM patients [112-115]. Clinical trials of

pharmacological and nonpharmacological therapies have shown that improving sleep quality can reduce pain and fatigue in FM [116]. Music acts as a sleep aid, reduces the pain perception and FM-associated sleep disturbances [117,118]. Low to moderate intensity endurance and strength training are strongly recommended in FM patients [119]. Strength training reduces pain, fatigue, number of tender points, depression, and anxiety, with increased functional capacity and QoL [120]. Exercise activates the endogenous opioid and adrenergic systems but does not consistently mitigate pain in FM patients [121]. Roitenberg et.al, 2019 recommended special training for the physiotherapists treating FM to reduce their uncertainty and role ambiguity [122]. Perceptual surfaces are efficacious in treating female patients with FM, similar to physical group exercises, improving physical function and mitigating pain [121]. Clinical interventions such as patient education on central pain management could lead to promising results, but the effectiveness of education in the reduction of the main symptoms is limited [123]. In comparison to inflammatory arthritis (IA), it can seem ill defined with no clear understanding of the pathology and therefore no specific targeted treatment. Treatment should be multidisciplinary and individualized with close attention to the patient's symptoms. A coordinated multidisciplinary team approach including physicians, mid-level practitioners, nursing staff, and where needed, pharmacists and physical therapists will produce the best results.

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## ABBREVIATIONS

Fibromyalgia (FM); Rheumatoid Arthritis (RA) Non-Steroidal Anti-Inflammatory Drugs (NSAIDs); Chronic Noncancer Pain (CNCP); Palmitoylethanolamide (PEA); Fermentable Oligo-, Di-, Mono-saccharides And Polyols (FODMAP); Electroencephalography Biofeedback (EMG-BFB); Cognitive Behavioral Therapy (CBT); Interleukin-6 (IL-6), Tumor Necrosis Factor Alpha (TNF- $\alpha$ ); Acceptance And Commitment Therapy (ACT); Health-Related Quality of Life (HRQoL); Whole Body Vibration (WBV); electro-acupuncture (EA); Hyperbaric Oxygen Therapy (HBOT); Low-Level Laser Therapy (LLLT); Transcutaneous Electrical Nerve Stimulation (TENS)

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