Review Article

Treatment Recommendations for Fibromyalgia

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ABSTRACT

Fibromyalgia (FM) is a chronic condition that includes persistent widespread pain, fatigue, insomnia, non-restorative sleep, stiffness, cognitive disturbances, anxiety, and depressed mood. The disorder produces negative impacts on physical and social functioning, health related quality-of-life, emotional health and wellbeing, personal relationships, and the ability to complete daily work/life activities. It is considered to be a central sensitivity syndrome and a member of several overlapping conditions that produce diffuse pain such as chronic fatigue syndrome, irritable bowel syndrome, tension headache, myofascial pain syndrome, and restless legs syndrome. In order to address the illness and its related comorbidities, successful treatment plans are multidisciplinary, patient centered, individualized and multifaceted. Plans must be comprehensive and include disease education for patient and family members, lifestyle changes, aerobic exercise, dietary consults for weight reduction, sleep hygiene, strength training, cognitive behavioral therapy, pharmacotherapy, and perhaps complementary and alternative medicine-based therapies. There is good evidence to support the use of exercise to improve functioning and reduce symptoms. Amitriptyline, pregabalin, duloxetine, milnacipran, tramadol, and cyclobenzaprine have the best evidence for efficacy in reducing the symptoms and treating comorbidities. Some data exists supporting the use of acupuncture, mind-body interventions such mindfulness-based stress reduction, acceptance and commitment therapy, hypnosis, and biofeedback. Insufficient research is available for non-steroidal anti-inflammatories agents, acetaminophen and gabapentin. All other opioids, benzodiazepines, atypical psychotics and sedative hypnotics have no proven efficacy and are not a part of current FM treatment guidelines.

Keywords: Fibromyalgia, exercise, cognitive behavior therapy, multidisciplinary, complementary alternative medicine, pharmacotherapy

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INTRODUCTION

Fibromyalgia (FM) is diagnosed primarily in females (80%), mean age 49 years, and affects 2-8% of the worldwide population [1-3]. It is characterized by chronic widespread pain lasting for more than 3 months, fatigue, insomnia, non-restorative sleep, stiffness, cognitive disturbances, anxiety, and depressed mood [1,4]. The disorder greatly impacts work/life causing significant detriments in mental and physical functioning, work productivity, career advancement and longevity, personal relationships, activities of daily living (ADLs), and health-related quality-of-life (HRQOL) [5-8].

FM is classified as either primary, where there is no underlying medical condition as a causative factor or, concomitant with other medical conditions that may contribute to pain and/or fatigue such as rheumatoid arthritis, systemic lupus erythematosus, or hypothyroidism [9]. However, no specific disease-related variances between primary and concomitant FM have been found and, a third possible category of post-traumatic FM has also been discussed [10].

FM is considered a simple neurosensory disorder in which the central nervous system has difficulties in processing pain [11,12]. The etiology of FM has evolved to where it is now considered a central sensitivity syndrome and a member of several overlapping conditions that produce diffuse pain such as chronic fatigue syndrome, irritable bowel syndrome, tension headache, myofascial pain syndrome, restless legs syndrome, functional dyspepsia, bladder pain syndrome or interstitial cystitis, posttraumatic stress disorder, and Golf War Syndrome [13,14]. FM may also occur

concomitantly with systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, and chronic hepatitis C infection making it important for clinicians to identify which is the primary and secondary disorder when formulating a treatment plan [10].

Treatment goals should focus on pain amelioration, improved physical and cognitive functioning, and enhanced quality-of-life [15,16]. Patient care plans should be multidisciplinary, patient centered, and individualized [15]. Clinical practice is multifaceted and utilizes cognitive behavioral therapy (CBT), pharmacotherapy, lifestyle changes, physical activity, and complementary and alternative medicine (CAM) [10]. This mini-review will focus on the current effective treatment choices available.

DIAGNOSIS AND ASSESSING SEVERITY

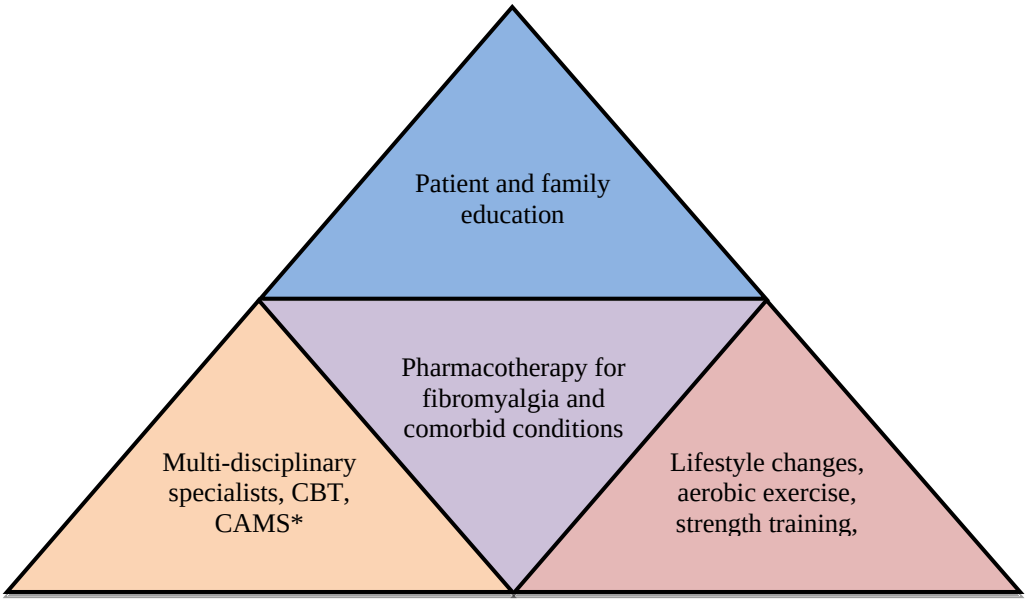
Despite the revised diagnostic criteria for FM from the American college of rheumatology (ACR), there remains no specific biomarker or "gold standard" to confirm a clinical diagnosis. FM may well be the diagnosis of exclusion when all other potential causes of presenting symptoms have been ruled out [10]. Currently, the diagnosis is made based on persistent symptomatology for 3 months or longer including fatigue, stiffness, non-refreshing sleep, cognitive difficulties ("fibromyalgia fog" or "fibro-fog"), mood changes, psychological distress, paresthesia, chronic widespread pain (CWP) involving bilateral tenderness/pain above and below the waist inclusive of the axial skeletal spine, and other unexplained complaints such as loss of the ability to care for oneself, depression and/or anxiety [10]. FM patients are at their best between the hours of 10 a.m. and 2 p.m. and are "worst" in the morning, late afternoon, and evenings [17]. Spring and summer months are times of reduced symptoms and improved functioning whereas the months of November and March tend to bring on increased pain and suffering, reduced energy, and depressed mood [17].

Historically FM has been diagnosed by the presence of CWP for ≥ 3 months in at least 11 out of 18 identified tender points (TPs) via digital palpitation using about 4 kg of force [4]. Now that FM is considered to be a central sensitivity syndrome often involving several comorbidities, TP evaluation as a primary diagnostic tool is being replaced with criteria focused on addressing the wide range of patient symptoms [18,19]. The 2010 American College of Rheumatology (ACR) guidelines have replaced the traditional TP examination with the Fibromyalgia Survey Questionnaire, a patient self-report instrument to assess numerically the widespread pain index (WPI) and symptom severity (SS) scores [4,19]. A positive diagnosis of FM occurs when: WPI ≥7 and SS ≥5 or WPI 3-6 and SS ≥9 (4). The ACR criteria was further modified in 2011 with the elimination of the somatic symptoms estimation and expansion of the WPI to a new 0-31 FM symptom scale (FSS) that included 19 pain locations, 6 self-reported symptoms (e.g. fatigue, headache, sleeping difficulties, reduced cognition, depression, and abdominal pain), and FSS scores of ≥ 13 [19].

Severity of illness, effects on HRQOL, and response to therapy can be evaluated using of the revised fibromyalgia impact questionnaire (FIQR) [20-22]. The FIQR has good psychometric attributes, can be done online in less than 2 minutes, and is easily scored. The FIQR encompasses 21 questions (0-10 scoring on each) that evaluate the patient's ability to complete ADLs and accomplish planned tasks, as well as, severity of pain, energy level, stiffness, point tenderness, balance, environmental sensitivity, anxiety, depression, cognitive disturbance and changes in sleep quality over the previous 7 days [22]. Improvements in disease severity are clinically and statistical significant when patients achieve a 14% or better improvement in their FIQR scores [22].

TREATMENT PLAN

Care for FM should be multidisciplinary, patient centered, individualized, and multifaceted. Successful treatment plans incorporate disease education for patient and family members, lifestyle changes, aerobic exercise, dietary consults for weight reduction, sleep hygiene, strength training, CBT, pharmacotherapy, and perhaps CAMs to address both the illness and its associated comorbid conditions (**Figure 1**). The best outcomes (e.g. reductions in pain and fatigue, improved mood and HRQOL) occur when patients are actively engaged in their care [23].



*CAMs (complementary and alternative medicines): includes massage therapy, manipulation, acupuncture, biofeedback, aqua-therapy, guided imagery, mindfulness, problem solving, coping strategies, stress reduction)

Figure 1: Fibromyalgia Patient Centered Care Plan.

Exercise

Many FM sufferers experience poor aerobic fitness, strength, and flexibility. Likewise, several FM symptoms (e.g. pain, fatigue, sleep disturbance) are often related to deconditioning [24]. There is good evidence supporting exercise (e.g. water and land aerobics, strength and/or flexibility training) to improve functioning and reduce FM symptoms [25-30]. Patient adherence to an exercise program works best with regimens that are individualized, low-intensity, and low impact [30]. Hauser et al. found that land- or water-based exercises up to moderate intensity (2-3 times weekly for at least 4 weeks) were successful in maintaining patient motivation to continue [31]. It has been noted that high intensity exercise may aggravate pain when compared with low intensity [30]. Flexibility exercises including yoga and Tai Chi have demonstrated primarily positive results even given the limited evidence available for Tai Chi [32-35]. A meta-analysis of meditative movement therapies from 2 randomized controlled trials (RCTs) of 88 fibromyalgia sufferers found that yoga significantly reduced fatigue and improved pain, sleep, depression, and HRQOL [32]. Two RCTs (N=132) found that Tai Chi significantly improved sleep and HRQOL [32]. Research on Qigong however has been limited and the findings are mixed. A meta-analysis by Lauche et al. reported that Qigong improved pain, HRQOL, and sleep quality when compared to usual care controls however these results were not demonstrated in RCTs using active control cohorts [36].

Success in relieving FM symptoms has been demonstrated with resistance and aquatic exercise training [26,28,30,37,38]. A recent RCT reported that resistance exercise showed significant improvements in health status, current pain intensity, pain disability, pain acceptance, and isometric knee-extension and flexion when compared to controls [37]. A Cochrane Database review also supported resistance training for FM sufferers; demonstrating improvements in muscle strength, pain, tenderness and overall functioning [26]. Aquatic exercise has shown significant improvements in FM outcomes (e.g. pain, stiffness, physical functioning, muscle strength) when compared to control groups [38]. Aquatic was equal to land-based exercise in self-reported physical functioning, pain and stiffness, as well as overall functioning [38]. Land-based exercise was significantly better than aquatic for improvements in strength [38]. It is important to note however, that the level of evidence for resistance and aquatic exercise training remains limited as there are only a small number of RCTs completed to date. Moreover, optimal training regimens (e.g. frequency, timing, intensity, progression) have not been formulated. FM patients should be advised to focus on a consistent exercise program that minimizes delayed muscle soreness, not to attempt strength

training during a disease flare, avoid the use of high-intensity power workouts (e.g. high intensity interval training, CrossFit, boot camps, pylometrics), not to over train during times of improved wellness, limit pain-inducing postures by working within natural joint range of motion (do not hyper extend or flex), and link their exercise activity to something enjoyable to help ensure a life-long practice [30].

Education and Psychological

In addition to exercise, education in concert with psychological and behavioral interventions (e.g. CBT, problem solving, coping skills) are important aspects provided in FM treatment guidelines [16,39]. Educational interventions are well proven and groups that include patients, family members, and caregivers appear to be the most effective approach [40,41]. Education can be the cornerstone for illness understanding, coping, self-care, exercise advice, and psychological interventions. CBT is considered a key component in the multidisciplinary approach to assist in the treatment of comorbid mental illness and is helpful in both individual as well as group settings [10,15,42,43]. CBT can improve mood, reduce catastrophizing, pain sensitivity and pain-related anxiety as well as promote fear-free activity and behavioral changes in regards to inner thoughts and feelings [44,45]. Best results for CBT are seen when it is combined with other treatment modalities (e.g. pharmacotherapy, exercise, education, mind-body) [45,46].

Massage, Manipulation, and Acupuncture

No consistent or positive evidence is available to support the use of manipulative therapies including chiropractic and massage for the treatment of fibromyalgia [47]. Research on the use of acupuncture for FM has been mixed but some studies have reported significant effects on pain over the short term [48]. Deare et al. conducted a systematic review of nine trials and found that electro- and manual-acupuncture where not significantly better than sham acupuncture in relieving FM symptoms (e.g. pain, fatigue, sleep disturbance, global well-being) except for stiffness at one month [48]. Moreover, acupuncture's effects last about one month and are not maintained at six month's follow-up indicating that monthly treatments are most likely needed in order to sustain efficacy [48]. Electro-acupuncture may be better than manual acupuncture for pain, fatigue, sleep disturbance, and overall well-being [48]. The National Institutes of Health (NIH) consensus statement concerning acupuncture supports its use in various pain conditions including FM and state that, "acupuncture may be useful as an adjunct treatment or an acceptable alternative or may be included in a comprehensive management program [49,50]." Overall, acupuncture appears to be safe and FM patients may consider using electro-acupuncture with or without exercise and medication. Of important note is that due to acupuncture's stimulation on the endogenous opioids, it may not be as effective in those taking daily doses of opioids on a chronic and regular basis [10].

Mind/Body Interventions

There is some positive evidence that supports the use of mind-body interventions (MBIs) such mindfulness-based stress reduction, acceptance and commitment therapy, hypnosis, and biofeedback for the treatment of FM [39,51,52]. More research is needed however to document the sustainability of MBI treatment outcomes. MBIs are generally well tolerated however, and may be a good choice as an adjunctive therapy to complement the overall patient care plan.

Pharmacotherapy

Common types of medications prescribed for FM include analgesics, tricyclic antidepressants (TCAs), serotonin and norepinephrine reuptake inhibitors (SNRIs), alpha-2 delta ligands, and muscle relaxants [16,53]. The US Food and Drug Administration (FDA) has approved pregabalin, duloxetine, and milnacipran for the treatment of FM. Canada and Japan have approved duloxetine and Japan has also approved pregabalin [16,53]. The European Medicines Agency (EMA) however, has not approved any medications specifically to treat FM and pharmacotherapy outside of the US primarily remains "off label" [54,55]. **Table 1** outlines the characteristics of medications that have been found to be effective for FM [10,53]. Pharmacotherapy should be part of a multi-modal treatment approach, patient specific, and may require a combination of medications in order to maximize effectiveness [16,23].

Table 1: Medication that have been shown to be effective for treatment of fibromyalgia.

Medication	Class	Dosage (mg/day)	Uses	Common adverse effects
Amitriptyline	TCA	10-50	Pain, fatigue, sleep disturbance	Somnolence, weight gain, constipation, dizziness, headache, blurred vision
Cyclobenzaprine	Muscle relaxant	5-30	Muscle relaxation, sleep disturbance	somnolence, dizziness, xerostomia, constipation
Duloxetine[1-3]	SNRI	60-120	Pain, depressed mood, sleep disturbance	nausea, dizziness, dry mouth, hyperhidrosis
Milnacipran[1,4]	SNRI	100-200	Pain, fatigue, cognitive dysfunction	headache, dizziness, nausea, diaphoresis, hypertension, tachycardia, palpitations, hyperhidrosis, constipation
Pregabalin[1,3,4]	$\alpha_2\delta$ ligand	300-600	Pain, sleep disturbance	dizziness, weight gain, drowsiness, peripheral edema
Tramadol	Opioid	100-300	Pain	somnolence, nausea, vomiting, dizziness, constipation, insomnia, pruritus, headache, flushing, xerostomia

[1]Approved for the treatment of fibromyalgia in United States of America;
[2]Approved for treatment of fibromyalgia in Canada;
[3]Approved for treatment of fibromyalgia in Japan;
[4]Approved for treatment of fibromyalgia in Australia

Analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and opioids are prescribed to treat FM pain. Unfortunately there is only limited data available for the use of acetaminophen and NSAIDs in FM [56]. Wolfe et al. surveyed 1799 patients with fibromyalgia, rheumatoid arthritis, and osteoarthritis and found that 60% of patients preferred NSAIDs to acetaminophen and only 14% preferred acetaminophen over NSAIDs [57]. In general, the use opioids (e.g. codeine, hydrocodone, oxycodone, morphine) should be avoided due to the risk of addiction and lack of evidence to support their effectiveness [16,58]. The only opioid to date that has shown effectiveness in reducing FM-related pain is tramadol with or without acetaminophen [59-61]. Tramadol has been found to enhance serotonin release and inhibit epinephrine uptake which may attribute to its analgesic effect versus other opioids [62]. FM patients have diminished ability to respond to pain stimuli that has been attributed to mu-opioid receptor dysfunction and may explain why most opioids, except for tramadol, are not effective in reducing FM pain [10,63,64]. Antidepressants are effective in reducing pain, fatigue, and sleep difficulties as well as improving mood and HRQOL in some FM patients [10,65]. Most importantly, the selection of antidepressant pharmacotherapy should also consider comorbidities (e.g. depression, anxiety and insomnia) and tolerability. The TCA amitriptyline and SNRIs duloxetine and milnacipran have the best evidence and are considered first line pharmacotherapy for FM [65]. Low dose amitriptyline at bedtime is especially useful for those with sleep disturbance, pain, and fatigue [66]. Duloxetine has been shown to be effective at reducing pain, severity of illness, and depression while improving HRQOL and physical functioning [67-69]. Milnacipran has superior analgesic properties compared to SSRIs, improves HRQOL, and relieves pain, fatigue, sleep disturbance, cognitive dysfunction and depression [10,69-72]. Research has shown that the selective serotonin reuptake inhibitors (SSRIs) fluoxetine, citalopram, and paroxetine have limited to no analgesic effectiveness, do not assist with fatigue, and are most useful for treatment of depression and perhaps sleep disorders in FM [10,65,73]. Potential medication-related adverse effects (e.g. SSRI: sexual dysfunction and weight gain, TCA: weight gain, SNRI: hyperhidrosis, hypertension and tachycardia) are important

to consider when prescribing antidepressants [65]. Moreover, patients should be educated about the fact that antidepressants may not completely relieve their FM symptoms [65].

Second generation anticonvulsants pregabalin and gabapentin are prescribed as initial pharmacotherapy for fibromyalgia [74-76]. The best evidence for efficacy however is with pregabalin which modestly but significantly reduces pain, fatigue, anxiety and depression as well as improves HRQOL when compared to placebo [75]. Studies indicate that about 40% of pregabalin patients experience a 30% or greater reduction in pain intensity as compared to 29% of those taking placebo [75]. Due to the paucity of data available, there is no robust evidence at the present time to support the efficacy of gabapentin in the treatment of FM [74,75,77].

The centrally acting muscle relaxant cyclobenzaprine, with a similar chemical structure to amitriptyline, is commonly prescribed in FM [1]. It's use in FM aims at improving musculoskeletal symptoms and providing more restorative sleep [78]. A meta-analysis of 5 RCTs by Tofferi et al. found that when given three times a day, cyclobenzaprine improved global functioning and sleep quality [79]. A RCT conducted in 37 FM patients using very low dose cyclobenzaprine (1-4 mg at bedtime) reported significantly improved pain, tenderness, restorative sleep and mood [80]. Due to cyclobenzaprine's ability to cause somnolence and dizziness, this bedtime dosage regimen may offer a way to limit these adverse effects and improve functionality during daytime hours.

Other medications prescribed to FM patients include benzodiazepines (e.g. alprazolam, clonazepam, temazepam), atypical antipsychotics (e.g. olanzapine, quetiapine, ziprasidone, amisulpride), and sedative-hypnotics (e.g. zolpidem, zopiclone) [10,55,81-85] None of these medications have proven efficacy in FM and are therefore not a part of current treatment guidelines.

CONCLUSIONS AND RECOMMENDATIONS

FM negatively impacts physical and social functioning, HRQOL, emotional health and wellbeing, personal relationships, and the ability to complete daily work/life activities. In order to address the illness and its associated comorbidities, successful treatment plans are multidisciplinary, patient centered, individualized and multifaceted and include disease education for patient and family members, lifestyle changes, aerobic exercise, dietary advice for weight reduction, sleep hygiene, strength training, CBT, pharmacotherapy, and perhaps CAMs. Exercise and education in concert with psychological and behavioral interventions should be included in all patient care plans. Amitriptyline, pregabalin, duloxetine, milnacipran, tramadol, and cyclobenzaprine have the best evidence for efficacy in reducing the symptoms and treating comorbidities. Some data exists supporting acupuncture, mind-body interventions, hypnosis, and biofeedback in FM and these may be useful as adjunctive therapy. To date, there is not sufficient research to support the use of non-steroidal anti-inflammatories agents, acetaminophen and gabapentin. All other opioids with the exception of tramadol, benzodiazepines, atypical psychotics and sedative hypnotics have no proven efficacy and are not a part of current treatment guidelines.

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