EVIDENCE-BASED TREATMENT FOR FIBROMYALGIA

SYNDROME IN ADULTS

By

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A dissertation/thesis submitted in partial fulfillment of
The requirements for the degree of

MASTERS OF NURSING

WASHINGTON STATE UNIVERSITY – SPOKANE, WA

College of Nursing

NOVEMBER, 2012
To the Faculty of Washington State University:

The members of the Committee appointed to examine the dissertation/thesis of OLGA OWENS find it satisfactory and recommend that it be accepted.

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Fibromyalgia syndrome (FMS) is a painful disorder affecting 1 to 5 percent of the United States population, mostly women (Weir et al., 2006). FMS decreases physical and cognitive functionality. The American College of Rheumatology (ACR) FMS classification criteria published in 1990 have been used to identify patients with FMS. The FMS classification criteria include chronic widespread pain present for more than 3 months and specified tender point areas. At least 11 of 18 total tender points must be present upon digital palpation with applied pressure of 4 kg (Dunphy et al., 2011). Wolfe et al., (2010) proposed a diagnostic criteria that does not depend on counting tender points and which measures the symptom severity score (SSS) in the disorder. This consists of measuring severity of fatigue, sleep disruption, cognitive symptoms; and the widespread pain index (WPI), which measures pain lasting three months or more in 11 out of 19 areas of the body. Etiology of the syndrome is not clear; multiple possible causes of the disorder have been proposed such as physical and psychosocial stressors, abnormal functioning of the neuroendocrine and autonomic systems, and a genetic component. Treatment for FMS remains controversial and mainly focused on the primary complaint, generalized pain; however, many other symptoms remain untreated or are exacerbated, sustaining a disturbed cognitive and
physical functionality that results in a decreased quality of life. The purpose of this manuscript is to review the pathophysiology of the syndrome, diagnostic criteria, and pharmacological and non-pharmacological treatments for FMS symptoms that greatly impact patients’ lives.

**Keywords:** Fibromyalgia syndrome treatment, diagnosis, cognitive behavioral treatment, exercise, quality of life, evidence-based treatment.
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Evidence-Based Treatment for Fibromyalgia in Adults

Criteria for diagnosis of fibromyalgia syndrome (FMS) have been established in 1990 by the American College of Rheumatology (ACR). This complex syndrome consists of a combination of symptoms, the most prominent of which is chronic generalized pain in non-articular musculoskeletal sites. Other common symptoms include fatigue, sleep disturbance, mood disturbances, and cognitive dysfunction resulting in decreased ability to carry out activities of daily living (ADLs) and decreased productivity at work or school (Anнеманс, Le Lay, & Taïeb, 2009). Other somatic symptoms may include numbness, dizziness, nausea, irritable bowel syndrome, muscle weakness, headache, and abdominal pain. The etiology of FMS is unclear, but factors that contribute to the pathophysiology include physical and psychosocial stressors, abnormal function of the neuroendocrine and autonomic systems, and a genetic component (Bradley, 2009).

The prevalence of FMS is estimated to be 1 to 5 percent in the United States (Weir et al., 2006). Women are seven times more likely to be affected by FMS than men. Most patients with FMS are between 30 and 50 years of age, and some studies have shown the childbearing years to be the peak age at which women are affected by FMS (Weir et al., 2006). According to Dunphy, Winland-Brown, Porter & Thomas (2011), “seventy percent of individuals diagnosed with FMS self-identify as disabled, and 16 percent receive Social Security benefits.” A cross-sectional observational study of 203 FMS patients found that at least 50 percent of the subjects experienced a disruption in their employment status: approximately 10 percent had a reduced work schedule, 21 percent were considered disabled, and 19 percent were unemployed or had retired early. Those who were employed reported missing as many as 39 days of work per year due to FMS complications (Schaefer et al., 2011). Bennett et al., (2007) conducted an Internet
survey involving 2,596 American patients with FMS, of whom 97 percent reported difficulty with recreational activities and 93 percent with heavy household duties.

Patients with FMS consult between three to six healthcare providers on average, prior to being diagnosed (Bennett, Jones, Turk, Russell & Matallana, 2007). During the investigative stage of the disease, which may take years, the utilization of medical resources and other costs accumulate for these patients. Direct medical costs amount to approximately $10,199 per year and indirect costs $2,913 per patient, per year (White et al., 2008). FMS patients commonly first see their primary healthcare providers seeking a diagnosis and presenting with obscure complaints such as fatigue, dizziness, numbness, pain in multiple locations and cognitive problems, including poor memory and the inability to think clearly. Due to the condition’s confusing and complex presentation and unremarkable diagnostic test results, the confirmed diagnosis may not be made for years.

Pathophysiology

The etiology of FMS is not clear, and multiple factors may contribute to its pathophysiology. Physical stress, (e.g., repetitive motions at labor, heavy lifting, and other manual work) has been associated with the development of generalized musculoskeletal pain. In addition, emotional stress in the workplace and lack of social support by coworkers tends to increase the risk of developing generalized musculoskeletal pain. First-degree relatives of patients with FMS have a higher likelihood of meeting the diagnostic criteria. Low serum levels of serotonin are found in those suffering from FMS, as well as in their siblings. Serotonin and norepinephrine are key neurotransmitters in endogenous pain inhibitory pathways. “There is increasing evidence that fibromyalgia is characterized by an augmentation of sensory input that
is mediated by central nervous system events similar to those associated with neuropathic pain conditions” (Bradley, 2009).

Physiologic abnormalities, such as an abnormally functioning hypothalamic-pituitary-adrenal (HPA) axis, are associated with the inability to suppress cortisol, which results in elevated cortisol levels in fibromyalgia patients. Increased cortisol levels are associated with pain upon awakening and one hour after waking (McBeth et al., 2005). Low cortisol levels have also been observed in FMS patients (Dunphy et al., 2011).

The autonomic nervous system (ANS) is also thought to be associated with heightened pain levels, an abnormal heart rate, and disturbances in systemic blood pressure. These all contribute to sleep disturbances and fatigue. Sleep disturbances such as early-morning awakening, insomnia, and non-restorative sleep are frequent complaints of fibromyalgia patients. Interruptions in the alpha wave during delta-wave sleep are associated with reduced production of hormones responsible for muscle repair, thus contributing to inhibited repair of daily muscle microtrauma. Inhibited muscle repair is thought to prolong the transmission of pain stimuli to the central nervous system. Generalized pain can result in low quality of sleep and continuous sleep disturbances are correlated with generalized musculoskeletal pain (Davies et al., 2008).

**Diagnostic Criteria**

In 1990, the American College of Rheumatology (ACR) developed criteria for the diagnosis of FMS. A total of 18 trigger points have been identified, at 9 bilateral sites on the body. Pain is elicited by applied pressure of 4 kg during digital palpation. Patients must experience pain upon palpation of at least 11 out of the 18 sites (Dunphy et al., 2011). The pain must be present for more than 3 months and should not be associated with swelling or tenderness in joints (Appendix A). Most patients exhibit normal range of motion and strength. In 2010, a
new symptom-based criterion for the diagnosis of fibromyalgia was proposed by Wolfe et al., (2010). The new criteria address a myriad of symptoms and their severity, but do not rely on palpation of the tender points. The widespread-pain index (WPI) identifies 19 painful body areas, seven or more painful areas of the body out of the 19 must score 5 or higher on the symptom severity scale, or 3 to 6 painful areas must score 9 or higher on the symptom severity scale. Pain must be present for three months or more, and the patient should not have any other disorder that could be the cause of the chronic pain (See Appendix B).

Diagnostic laboratory and imaging studies are usually normal unless comorbid conditions are present. Laboratory tests such as complete blood count, erythrocyte sedimentation rate, creatinine phosphokinase, antinuclear antibody, rheumatoid factors, thyroid-stimulating hormone, T3 resin uptake, and T4 may need to be ordered to rule out other health conditions (Dunphy et al., 2011).

The Fibromyalgia Impact Questionnaire (FIQ) is a tool designed to measure daily impact on a patient’s life and the progress of treatment. The tool is scored from 0 to 100, with a higher score indicating a more negative impact. The Revised Fibromyalgia Impact Questionnaire (FIQR) ranges from 0-10 for all questions and is similar to the original FIQ, thus older scores may be compared at follow up. This updated questionnaire includes questions about somatic symptoms that affect quality of life and questions related to functionality. The form should be filled out by the patient when diagnosis is first made, so that treatment effectiveness can be evaluated (Appendix C).

**Assessment of FMS**

A focused patient history and physical exam are necessary to rule out all other causes that may mimic FMS symptoms (Arnold et al, 2011). A thorough review of a patient’s current
medications should be made as some medications may cause unexplained generalized pain. Chronic use of opioids may cause hyperalgesia (Mystakidou et al., 2011). High doses of statin medication may cause muscle pain, tenderness, and/or weakness. Some diuretics may cause muscle pain or cramps. Sleep problems result in generalized musculoskeletal pain (Mystakidou et al., 2011). Medications that interrupt sleep cycles should be reviewed. Health conditions that result in electrolyte imbalances may result in muscle pain or cramps. Health disorders such as hypothyroidism, rheumatoid arthritis, polymyalgia rheumatica, systemic lupus erythematosus, acquired immune disease, and polymyositis may also mimic various symptoms of FMS (Dunphy et al., 2011).

Risk factors for FMS such as past physical trauma, emotional stress, and a familial predisposition may be revealed when patient history is gathered. Physical exam of the joints should be done to assess for range of motion, tenderness, swelling, and crepitus to assist in the deferential diagnosis. Palpation of tender points is recommended by the ACR (1990) FMS diagnostic criteria. Eleven out of 18 tender points must be present. Physical exam should be done to rule out other pain producing conditions such as rheumatoid arthritis, osteoarthritis, adhesive capsulitis, tendonitis and connective tissue disease (Arnold et al., 2011).

Statement of Purpose

FMS is a combination of symptoms, but the etiology is unclear. Treatment remains symptomatic, particularly for chronic generalized pain, the chief complaint. Analgesics are the treatment of choice for many providers; however, many other symptoms remain untreated or are exacerbated. The treatment is controversial due to the unclear etiology of the FMS. Research directed toward establishing the most effective evidence-based treatment for FMS has yielded promising results. Specifically, certain pharmacological and non-pharmacological modalities
have shown optimistic results. The purpose of this literature review is to identify treatment modalities that produce effective pain management and improved function, thus resulting in improved quality-of-life for individuals with FMS.

**Literature Review**

To obtain literature pertinent to FMS, various search engines including the Cumulative Index to Nursing and Allied Health Literature (CINAHL), PubMed, and Medscape were employed. The keywords and MeSH terms searched included fibromyalgia, fibromyalgia etiology, fibromyalgia treatment, non-pharmacological treatments, and evidence-based. Thirty-five articles were reviewed, and the most relevant, current peer-reviewed articles written in English were selected for this literature review, with the most applicable articles summarized in order to present the most recent data. Ten articles were chosen for topics on non-pharmacologic treatments, four articles on cognitive behavioral therapy, three on exercise, and three on hydrotherapy. Eleven current articles on pharmacological treatments were chosen – one article on Duloxetine, one article on Milnacipran, two articles on Cyclobenzaprine, two articles on Pregabalin, two articles on Gabapentin, and one article on Sodium Oxybate. Articles older than five years containing information on pharmacological studies were excluded. All other current articles were selected for introduction and description of FMS.

**Quality of Life**

The combination of symptoms of FMS negatively impact individuals’ quality of life. The etiology is unclear. Effective management of symptoms is the only proper treatment; otherwise patients experience a vicious cycle with FMS. Sleep disturbance is associated with pain, fatigue, and cognitive and physical dysfunction resulting in decreased work and/or school performance. Chronic pain affects sleep and physical function resulting in psychological issues (Mystakidou et
al., 2011). In the following sections, effective evidence-based pharmacological and non-pharmacological treatments available today are reviewed which have been shown to effectively treat pain, improve functionality, and overall improve the health-related quality-of-life in patients with FMS. Individuals with FMS experience a variety of symptoms or a combination of symptoms which vary in severity and duration. Each patient has various comorbid health conditions resulting in individualized needs. Individuals will have different preferences for activity type which will affect decision making in treatment planning.

**Effective Pain Management**

**Non-pharmacological Treatments.**

Non-pharmacological interventions such as cognitive-behavioral therapy, exercise and hydrotherapy prove beneficial in managing pain and improving other symptoms of FMS. Such interventions may be introduced into a treatment plan initially upon diagnosis of FMS as a complementary therapy to pharmacological therapy in order to optimize patients’ health and quality of life. A patient’s physical and psychological readiness will determine when these interventions are to be integrated into their treatment plan. Symptoms such as intense generalized pain and pain at tender points may need to be controlled with pharmacological agents before a patient is ready and willing to participate in physical activity or other intervention.

* Cognitive behavioral therapy. Woolfolk, Allen, and Apter (2011), conducted a randomized controlled trial with an additive design to assess the effectiveness of an individually administered form of affective-cognitive behavioral treatment (ACBT) for FMS. Seventy-six participants with FMS were divided into two groups: (Group 1) experimental affective-cognitive behavioral therapy plus treatment-as-usual (TAU) and (Group 2) TAU. The ACBT focused on “relaxation training, activity regulation, facilitation of emotional awareness, cognitive
Restructuring and training in interpersonal communication.” It was intended to elicit and explore affect with “patients who cannot or do not willingly access or experience emotion (Woolfolk et al., 2011). The ACBT was used to investigate its effect on pain intensity and to improve other symptoms of FMS. At the end of the experimental trial and at a nine-month follow-up the results indicated that the FMS patients in the experimental group had significantly decreased pain severity, and also showed 30 percent improvement in pain severity on the visual analogue scale (VAS). The limitation of this study is the omission of a group of FMS participants receiving only ACBT without TAU to compare the efficacy of ACBT alone. Even so, the results of this study indicate that ACBT provides an effective modality for pain management and an excellent supplement to TAU.

Junquist et al, (2010) conducted a randomized, parallel-group, single blind trial of cognitive behavioral therapy for insomnia (CBT-I) to test whether improved sleep decreases pain in patients with chronic pain. Patients followed an 8-week regimen that included 4 components related to sleep: sleep restriction therapy, stimulus control instructions, sleep hygiene instructions, and cognitive therapy. Treatment produced decreases in pain; however, results were statistically insignificant according to the pain severity scale of the multidimensional pain inventory (MPI). The limitation of this study is its small 28 subject sample; however, improvements were reported and results may differ in a larger sample.

**Hydrotherapy.** Studies using balneotherapy, a treatment using warm mineral water baths from natural springs have shown to be beneficial for decreasing pain and fatigue in FMS patients. In a systematic review of the therapeutic effect of balneotherapy on chronic pain (Falagas, Zarkadoulia, & Rafailidis, 2009), results showed decrease in pain level, morning stiffness, number of tender points, and consumption of analgesics. Improvements lasted from
three weeks to six months post-intervention termination. A systematic review of randomized control trials (RCT’s) conducted outside of the United States was done to determine the effectiveness of hydrotherapy for FMS (Langhorst, Musical, Klose, & Hauser 2009) and improvements in pain scores and health-related quality-of-life were reported. Limitations of the RCTs reviewed include small sample sizes and the exclusion criteria.

**Exercise.** Hooten, Qu, Townsend, and Judd, (2012) conducted a randomized equivalence study comparing the effects of aerobic exercise and strength exercises for FMS patients. Patients were divided into aerobic and strength training groups. In the aerobic group participants used a stationary bicycle for 10 minutes daily the first week, gradually increasing the time to 30 minutes by week three. The strength training involved the primary muscle groups of the upper body and lower body, alternated daily. The aerobic and strength exercises produced equally significant improvements in pain intensity. The limitations of this study include: all patients were referred for pain rehabilitation, participants were of white ethnicity and were able to afford to participate in the 3-week outpatient program, and all participants received CBT sessions and relaxation techniques, which may have influenced the results. These results cannot be generalized to all with FMS.

Altan, Bingol, Aykac, Koc, and Yurtkuran, (2003), investigated the effects of pool-based exercise on patients with FMS. In a 12-week study 50 women were randomized into two groups. Participants in group one performed aerobic exercise 35 minutes per session three times a week. The second group received passive 35-minute sessions of balneotherapy three times a week in the same pool. Participants in the balneotherapy-only group were instructed not to perform any type of exercises. At the end, both groups had decrease in pain intensity and the number of tender points. However, long-lasting positive effects on fitness, wellbeing, and other FMS
symptoms were produced only in the aerobic exercise group. The strengths of the study included having a control group and comparison with another popular therapeutic modality for FMS, while the limitations were that it included women only and had a small sample size.

**Pharmacological Treatments.**

Research has demonstrated Serotonin Norepinephrine Reuptake Inhibitors, GABA analogues, and Sodium Oxybate to be effective in pain management in FMS patients. Initiation of therapy with any pharmacological agent will depend on the individual’s symptoms, symptom severity, health conditions, and willingness to tolerate side effects. Pain may need to be controlled with pharmacological agents before any non-pharmacological interventions are initiated.

**Duloxetine.** Duloxetine is a serotonin norepinephrine reuptake inhibitor (SNRI) and one of the FDA approved pharmacotherapies for FMS. Chappell et al., (2009) conducted a 60-week study, with an eight-week open label period and a final two-week taper period. It was a double-blind, randomized study of 307 FMS patients. Participants in two groups each received 30 mg of duloxetine for one week, then 60 mg for 7 weeks. Next, they were randomized into two groups to receive either 60 mg or 120 mg daily. At the end of the study 61 percent of patients on 60 mg per day and 57 percent on 120 mg per day had reductions of greater than 50 percent in Brief Pain Inventory (BPI) average pain scores. A significant reduction in the number of tender points and intensity of pain at tender point in the 60 mg per day group was observed. The therapeutic effect of medication persisted till the end of the study. The strength of this study is its duration. The limitations of the study may be the exclusion of individuals who were medically or psychiatrically unstable or who suffered from other chronic musculoskeletal disorders, which are
frequently seen in patients with FMS. The results might not be generalized to FMS patients with some of the comorbid health conditions excluded in this study.

**Milnacipran.** A double-blind, placebo-controlled trial of 1,025 patients with FMS was conducted by Arnold, Gendreau, Palmer, Gendreau, and Wang (2010). Treatment with milnacipran, a SNRI, produced greater than 30 percent improvement in pain within the second week of dose increase and until the end of the 12-week trial versus those treated with placebo. The strength of this study is that it is a large double-blind, placebo-controlled study with a focus on safety and therapeutic effectiveness for symptoms of FMS. However, several limitations are present including the short-term duration of treatment with milnacipran and unknown long-term efficacy. Individuals with current major depressive episodes, other forms of psychopathology, and comorbid pain disorders were not included, which makes the results not generalizable to all FMS patients.

**Pregabalin.** Arnold et al., (2008) conducted a 14-week, randomized, double-blind, placebo-controlled monotherapy study of pregabalin in 3 doses: 300 mg, 450 mg and 600 mg per day. Pregabalin may provide as much as 50 percent pain relief. Improvements in patient global impression of change (PGIC) were 40 percent for patients taking pregabalin in all three groups. It was shown that pregabalin is more efficacious at 450 mg per day than 300 mg per day. While no significant improvements were seen at 600 mg per day, fewer adverse effects were experienced at 450 mg per day. The strength of this study is that it investigated the effectiveness of the same medication in different doses to identify the safest dose with the most benefits. Individuals on disability and those with other comorbid health conditions were excluded from the study, making results not generalizable to patients with severe FMS.
**Gabapentin.** Gabapentin, a recent FDA approved treatment for FMS. Structurally similar to Pregabalin; it is eliminated through the kidneys, as well, and may have similar side effects. A study by Arnold et al., (2007) has shown that gabapentin, at doses as high as 1,200 to 2,400 mg per day, are safe and effective for treatment of FMS. A systemic review of gabapentin results showed significant improvements in pain and pain severity scores and other FMS symptoms. However, majority of the studies on gabapentin used small sample sizes (Tzellos et al., 2010).

**Sodium Oxybate.** In a 14-week, double-blind, placebo-controlled study, 548 patients with FMS were randomized into three groups (Russell et al., 2011). One group received placebo and two treatment groups were administered 4.5 mg and 6 mg of Sodium Oxybate, respectively. Significant improvements in the pain scores and intensities of pain in tender points were achieved within the first week of the study. The strength of this study is that it was a double-blind, placebo-controlled study of 548 patients randomized into three groups, studying two different doses and a placebo. The limitation of this study may be its exclusion of FMS patients with major depressive disorder and generalized anxiety disorder, making results not generalizable to all individuals suffering from FMS.

**Improved Function**

**Non-pharmacological Treatments.**

Research shows that approximately 73 percent of patients with FMS experience sleep disturbances (Davies et al, 2008). Sleep disturbance in FMS contributes to physical and mental fatigue, low functionality, altered mood and a decreased quality of life. Non-pharmacological interventions such as CBT are intended to help patients modify behaviors and thought processes which may cause or exacerbate symptom of FMS. Physical exercise improves strength, muscle tone, general health, and functionality and quality of life. Hydrotherapy in a form of
balneotherapy has positive effects on joint mobility, muscle tone and pain intensity. Before recommending any physical exercises, a patient’s physical fitness level and preference for type of exercise and intervention must be considered as these factors may influence adherence.

**Cognitive behavioral therapy.** Miro et al., (2011) compared the effects of cognitive behavioral therapy (CBT) for insomnia and sleep hygiene (SH) program in a randomized, controlled pilot trial. The individuals in the CBT group received education on FMS and the relationship between sleep and FMS. Education was provided on the subjects of sleep stages, sleep hygiene, relaxation training, cognitive therapy related to insomnia and insomnia relapse prevention tactics. The SH group received education only on SH. Eighty-five percent of the FMS participants in the CBT group had improvement in sleep quality compared to 55 percent of those in the SH group (Miro et al., 2011). In addition, clinically significant improvements in daily functioning were reported in the CBT group. The limitation of this study was the recruitment of women only, so the results may not be generalizable to both genders.

Woolfolk, Allen, and Apter (2011) also observed improved physical function and self-efficacy at the end of the individual affective cognitive behavioral therapy study.

**Exercise.** Sanudo, Carrasco, deHoyo and McVeigh (2012) conducted a study to evaluate the immediate effects of exercise training on physical function and the impact of repeated delivery of the exercise program after a period of de-training in women with FMS. Twenty-one women were randomly assigned to the exercise group (EG) and 20 to the control group (CG). Participates in the EG exercised two times a week for 45 to 60 minutes per session. Each session included 10 minutes of slow walking for warm up, 10 to 15 minutes of aerobic exercises, 15 to 20 minutes of muscle strengthening, and 10 minutes of flexibility exercises. The exercise group experienced significant improvements on the FIQ after six months of training. At the end of the
six month study, participants were instructed to stop all exercises for six months and then resume exercise for another six months. Participants continued such cycle of training and detraining for a duration of 30 months. Follow-ups were conducted at 18, 24, and 30 months to evaluate the duration of the positive effects. Improvements on the FIQ were maintained throughout the 30-month follow-up, and when compared to scores recorded at end of the exercise program, only a 2 point drop in scores was seen. The strength of this study is its examination of the effects of exercise and the duration of those effects on the physical functionality and quality of life for 30 months. The limitation of this study is its small sample size.

In a systemic literature review conducted by Busch, Barber, Overend, Peloso, and Schachter (2008) aerobic-only exercise provided significant improvements in physical functioning comparing to all other forms of exercise. Flexibility-only exercises have produced good results and may be implemented for FMS patients with stiffness. Also, supervised exercise programs show highest adherence. Exercise regimens that begin at low intensity and gradually increase the self-efficacy in patients.

**Hydrotherapy.** Gusi, Tomas-Carus, Hakkinen, Hakkinen, and Ortega-Alonso (2006), conducted a study in which thirty-four women were randomly assigned to an exercise group and to a control group to test the short and long-term effectiveness of a combination of physical exercises. The study investigated the effectiveness of aerobic, strengthening, and proprioceptive exercises in a warm waist-high pool. The study lasted 12 weeks with exercise done 3 times a week for one hour. Increased muscle strength was achieved without exacerbating pain, and higher physical independence in activities of daily living was observed. Health-related quality-of-life improved by 93 percent in the exercise group. After the 12-week training period exercise was terminated and a 12-week de-training period began during which no exercise was
performed. Pre-training physical condition levels and FMS symptoms returned close to baseline; however, the perception of improved health-related quality-of-life remained. The strength of this study is its testing of the effects of balneotherapy combined with exercise. The limitation of this study is its small sample size.

Results of a meta-analysis of multiple RCTs on hydrotherapy conducted by Falagas, Zarkadoula, and Rafailidis (2009) showed statistically significant improvements in the FIQ.

**Pharmacological Treatments.**

**Milnacipran.** Milnacipran has produced significant improvements in the FIQ scores and patient global impression of change (PGIC) score. Improvements in fatigue, physical functioning and depressive symptoms have been reported as well (Arnold, Gendreau, Palmer, Gendreau, & Wang, 2010).

**Cyclobenzaprine.** In an 8-week, double-blind, placebo-controlled, dose escalating study Moldofsky, Harris, Archambault, Kwong, and Lederman (2011) observed improvements in musculoskeletal pain, tenderness at trigger points, sleep, fatigue, and patients’ moods at a dose of 1-4 mg of cyclobenzaprine when administered at bedtime. Patient taking low doses at nighttime report fewer and less intense adverse-effects the following morning. The strength of this study is its report on the use of a polysomnograph in a sleep laboratory to evaluate effectiveness of cyclobenzaprine. The limitation of this study is the small sample of 37 subjects. Results may be very different in a larger sample.

**Pregabalin.** Participants in a study by Arnold et al. (2008) were randomized into three groups taking three different doses of Pregabalin (300 mg, 450 mg, and 600 mg per day). All had significant improvements in sleep and PGIC and FIQ total scores at doses of 450 mg per day and 600 mg per day.
**Sodium oxybate.** Russell et al. (2011) conducted a 14-week, double-blind, placebo-controlled study randomizing 548 patients with FMS into three groups to study the effectiveness of Sodium Oxybate on sleep quality. Sodium Oxybate is a central nervous system depressant, and being an agonist of GHB-specific and GABA receptor it reduces the frequency of awakenings per night as it reduces the alpha interruptions in non-rapid eye movement and increases slow-wave sleep (Russell et al., 2011). Two treatment groups were administered 4.5 mg and 6 mg of Sodium Oxybate, respectively. A reduction in sleep disturbance and an improvement in fatigue scores were achieved within the first week of therapy and maintained until the end of the study. An improvement of greater than 30 percent was seen on the FIQ. Functionality and health related quality of life scores significantly improved in the Sodium Oxybate groups. The strength of this study is that it is a double-blind, placebo-controlled study of 548 patients with FMS. The limitation of this study may be the exclusion of FMS patients who have major depressive disorder and generalized anxiety disorder, so the results may not be generalizable to all individuals suffering from FMS.

**Discussion**

This literature review has been completed to identify the most effective symptom management modalities that result in improved quality of life in patients with FMS. Currently, there is no gold standard for treatment of the combination of symptoms of FMS because the etiology is unknown. Treatment remains symptomatic, especially for chronic pain. Analgesics are the treatment of choice for many providers. Fitzcharles, Ste-Marie, Gamsa, Ware, and Shir (2011) conducted a chart review of FMS patients to evaluate the prescription frequency of opioid medication for treatment of the syndrome. Of the 457 patients with FMS reviewed, 32 percent used opioids; 105 patients used “strong opioids,” such as hydromorphone, oxycodone,
meperidine, fentanyl patches or morphine; and 39 used “weak opioids,” such as codeine and tramadol.

This literature review has shown opioids are not an effective treatment for FMS. They may contribute to increased pain sensitivity and decreased functionality. Opioids can be counterproductive as their adverse effects are similar to the symptoms of FMS. Chronic opioid use also frequently results in opioid-induced REM sleep loss which is crucial for restorative sleep. Chronic REM sleep loss results in hyperalgesia and fatigue. Research has shown that in healthy individuals even a single dose of oral opioid medications may considerably disturb sleep architecture, resulting in opioid-related fatigue (Mystakidou et al., 2011). Chronic sleep disturbances, such as non-restorative sleep, have been associated with chronic widespread pain.

This literature review revealed effective pharmacological and non-pharmacological treatment modalities for pain management and improvement of functionality. Sleep disturbance is a common symptom in FMS patients leading to a significant interruption in daily functioning because of physical and mental fatigue due to sleep deprivation. Decreased physical and mental functioning is associated with decreased quality-of-life. Junquist et al. (2010) observed decreased intensity of chronic pain in patients who underwent cognitive behavioral therapy for insomnia. In a study by Miro et al. (2011) improvements in sleep were achieved and significant improvements in daily functioning were observed. Exercise has been shown to be beneficial in improving many symptoms of FMS. In a systemic literature review conducted by Busch, Barber, Overend, Pelosi, and Schachter (2008) aerobic-only exercise provided significant decrease in pain and improvements in physical functioning compared to all other forms of exercise. Flexibility-only exercises have produced good results and may be implemented for FMS patients with stiffness.
Also, supervised exercise programs show highest adherence. Exercise regimens that begin at low intensity and gradually increase heighten self-efficacy in patients.

The SNRIs antidepressants inhibit the reuptake of serotonin and norepinephrine at receptor sites, resulting in central and peripheral anticholinergic effects. Research suggests that pain and other symptoms of FMS are reduced by increasing and correcting the functional deficit of norepinephrine and serotonin neurotransmitters (Arnold et al., 2010). The SNRIs significantly decrease the level of pain as shown by various studies. Duloxetine is effective for generalized pain and pain at the tender points at doses ranging from 60 to 120 mg per day. Also, improvements in physical functioning have been observed. This pharmaceutical agent may be considered as the initial treatment for relief of generalized musculoskeletal pain and pain at the tender points. The persistent therapeutic effects of Duloxetine suggest its use for long-term therapy. However, patients with mild to moderate renal impairments must be started at lower doses with the dose gradually increased. Individuals who consume alcohol on a regular basis or who have hepatic impairments are at increased risk for hepatic complications. Abrupt discontinuation of the medication may cause withdrawal presenting as headaches, dizziness, nightmares, irritability, paresthesia, nausea, and vomiting and may result in an abstinence syndrome (Chappell et al., 2009).

Milnacipran, a SNRI, binds primarily to norepinephrine transporter sites and less to the serotonin receptor sites. It is effective for pain management in FMS. Improvements in pain scores at doses of 100-200 mg per day have been achieved (Arnold et al., 2010). Initial doses of Milnacipran for FMS are 12.5 mg on the first day with gradual titration to the maintenance dose of 100 mg per day (50 mg two times a day) or to 200 mg depending on the patient’s response and renal and hepatic function (Chwieduck & McCormack, 2010). The onset of effects is seen within
two weeks of therapy; however, long-term efficacy is unclear. Future research needs to be conducted to study the persistence of therapeutic effect in long-term use. The hepatic metabolism of the drug is minimal; however, for those with hepatic impairments, careful dosing is necessary. Elimination is mainly renal; thus, individuals with renal insufficiency are started at decreased doses. Nausea was the most common adverse effect, though in most cases it resolved within 3 weeks of initiation of the therapy (Arnold et al., 2010). Its use is contraindicated during monoamine oxidase inhibitor (MAOI) therapy, and either class of drug must be taken at least two weeks after discontinuation of the other. As with other SNRIs or SSRIs, serotonin syndrome may occur, especially with polypharmacy of similar class.

Pregabalin and Gabapentin are very similar in structure and effectiveness. Both produce generalized pain relief. Study results demonstrate with Pregabalin as much as 50 percent generalized pain relief is achieved, but no effect on pain at the tender points (Tzello et al., 2010). Pregabalin is effective for FMS symptoms at 450 mg per day with minimal adverse effects. Pregabalin and Gabapentin have also demonstrated to be efficacious for sleep disturbances (Tzello et al., 2010). Patients with less severe pain intensity but with significant sleep disturbances may be prescribed these medications. Effects of Gabapentin on FMS have been studied in small sample sizes; therefore, considering other agents prior to this one may be best for optimal outcome. Common adverse effects are somnolence, dizziness, dry mouth, and weight gain. The FDA warns consumers of possible peripheral edema with Pregabalin. Renal impairment must direct the dosage of Pregabalin as its elimination is via the renal system (Straube, Derry, Moore, & McQuay, 2010).

Cyclobenzaprine is a muscle relaxant used “off-label” for treatment of FMS as it has been shown to improve some symptoms of FMS. Cyclobenzaprine is thought to block the
norepinephrine and serotonin reuptake and thus provides central and peripheral anticholinergic effects. Studies have shown that Cyclobenzaprine in high-doses improves pain scores, sleep, and quality of life when compared to patients’ baselines (Tofferi, Jackson, & O’Malley, 2004). In small doses (1-4 mg) it is effective for musculoskeletal pain, tenderness at trigger points, and sleep when taken at bedtime (Moldofsky et al., 2011).

Sodium Oxybate is an endogenous metabolite of GABA which regulates noradrenergic, serotonergic, dopaminergic, cholinergic and glutamnergic neuron activity and also promotes secretion of growth hormone (Russell et al., 2011). It assists in increasing slow-wave sleep, the deep sleep, and reduces nocturnal awakenings after sleep onset. Research shows that when taken at bedtime Sodium Oxybate is effective in improving sleep and thus results in decreased fatigue, increased functionality, all of which contribute to improvements in health-related quality of life. The most common side effect is headache reported by 23.1 percent of participants in the group taking the 6 mg dose and 14.8 percent in the group taking the 4.5 mg dose. Nausea, dizziness, vomiting, and diarrhea are other common adverse-effects mentioned in the treatment groups. Patients with hepatic impairments must be prescribed half the therapeutic dose. It should not be taken with any other central nervous system depressants and is not appropriate for patients with respiratory function issues. Caution should be used as the drug is excreted primarily via the lungs (Russell et al., 2011).

Cyclobenzaprine and Sodium Oxybate are central nervous system depressants and therefore are not to be taken together. Cyclobenzaprine has shown to be effective in small doses (1-4 mg at bedtime) for relief of pain at the tender points, and improved sleep, fatigue, and mood with few side effects. Sodium Oxybate is very effective in reducing nighttime awakening and improving sleep quality that results in decreased fatigue, intensity of generalized pain, and pain
at the tender points. The onset of effects is within one week of initiation of Sodium Oxybate. Both agents have been studied to investigate their effectiveness on FMS symptoms, but a larger sample size was studied for Sodium Oxybate. Selection of these agents will depend on patient’s symptoms and their severity; comorbid health conditions and other factors must be considered before prescribing.

Best treatment outcomes may be achieved when a combination of pharmacological and non-pharmacological treatment modalities is adhered to for maintenance of symptoms and improved health-related quality of life. Some studies in this review have shown better results when a combination of non-pharmacological interventions are implemented concurrently. Also, in studies comparing a TAU group to a combination group (non-pharmacological treatment with TAU) better results were achieved in the combination group.

**Implications for Practice**

Primary care providers are often the first to encounter a patient with a variety of FMS symptoms. A FMS diagnosis requires a focused history and physical assessment along with the implementation of appropriate fibromyalgia diagnostic tools. Effective diagnosis may be a time-consuming process, but it is necessary as FMS decreases a patients’ quality-of-life and results in an economic burden to patient and society. When diagnosed correctly, both the healthcare provider and the patient can work as a team to tailor a patient-specific treatment program for improved patient health and health-related quality of life. Upon diagnosis of FMS, education about the disorder should be provided so that the patient will understand the condition and learn effective strategies to control the symptoms independently with multiple treatment modalities. While considering evidence-based treatment modalities, all contextual factors of a patient’s life should be considered as many factors individually influence overall behavioral outcomes. To
enhance health-promoting behavior, collaboration between the healthcare provider and the patient is required for choosing the treatment for the individual.

Self-efficacy is enhanced when providers assist FMS patients in setting their own goals and thus ensuring greater adherence to health promoting lifestyles. Patients tend to know their situations better and are often able to evaluate what is realistic for their treatment initially. Exploration of the patient’s perceptions regarding the proposed treatment facilitates the treatment process. The individual’s perception of benefits and barriers to treatment will influence adherence to therapy and behavioral outcomes. A healthcare provider should present patients with both pharmacologic and non-pharmacologic treatment options and make appropriate referrals to optimize patient health.

Treatments should be individualized as patients with FMS experience different symptoms and other factors that direct treatment. Pharmacological treatment options may be initiated before the non-pharmacological, especially for patients with pain. Patients may not be willing or able to participate in any exercise activities until pain is controlled or at a tolerable level. Medication dosing depends on a patient’s general health and tolerance of treatment. Adherence will depend on the willingness of the patient to tolerate adverse effects and the intensity of non-pharmacologic treatments. Appropriate non-pharmacological treatment options should be discussed with the patient. The patient’s symptoms, symptom severity, perceptions, life situations, and comorbid health conditions must be considered before recommendations are made for any specific treatment intervention. Non-pharmacological interventions such as CBT must be pertinent to symptoms experienced by the patient. Primary care nurse practitioners need to educate FMS patients about the risks and benefits of all treatment modalities. At follow-up
appointments, the effectiveness of all implemented interventions needs to be evaluated to assure the patient-specific treatment plan is improving the patient’s health and quality of life.

Pharmacologic and non-pharmacologic treatment may be initiated concurrently, but the treatment plan will depend on the individual with FMS. The healthcare provider must also address any comorbid conditions by referring the patient to specialists. As FMS is a chronic condition, symptoms may decrease in intensity or may increase. For health maintenance and symptom control daily effort should be emphasized.

**Conclusion and Recommendations for Future Research**

FMS is a chronic condition affecting 1 to 5 percent of the population in the United States, primarily women (Weir et al., 2006). The syndrome significantly decreases a patient’s quality-of-life and results in a financial burden to the individual and society. Appropriately utilized diagnostic criteria and a thorough physical assessment and patient history are crucial for the diagnosis of fibromyalgia syndrome. The role of the primary care provider is to collaborate with the patient to create an individualized treatment plan based on the patient’s symptoms, symptom severity, comorbid health conditions, preferences, perceptions, and capabilities after appropriate education on treatment options is provided. This literature review identifies evidence-based treatments currently available for effective symptom management of this complex disorder of an unknown etiology. Pharmacological and non-pharmacological treatments have been shown to produce significant improvements in FMS symptoms. However, more research investigating long-term efficacy of many pharmacological agents for this chronic syndrome is needed and most of the non-pharmacological intervention results need to be replicated in larger sample sizes.
References


preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity.

*Arthritis Care & Research.*, 62, 600-10.


ACR 1990 Criteria for the Classification of FMS


   Definition. Pain is considered widespread when all of the following are present: pain in the left side of the body, pain in the right side of the body, pain above the waist, and pain below the waist. In addition, axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back) must be present. In this definition, shoulder and buttock pain is considered as pain for each involved side. "Low back" pain is considered lower segment pain.

2. Pain in 11 of 18 tender point sites on digital palpation.

   Definition. Pain, on digital palpation, must be present in at least 11 of the following 18 sites:
   Occiput: Bilateral, at the suboccipital muscle insertions.
   Low cervical: bilateral, at the anterior aspects of the intertransverse spaces at C5-C7.
   Trapezius: bilateral, at the midpoint of the upper border.
   Supraspinatus: bilateral, at origins, above the scapula spine near the medial border.
   Second rib: bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces.
   Lateral epicondyle: bilateral, 2 cm distal to the epicondyles.
   Gluteal: bilateral, in upper outer quadrants of buttocks in anterior fold of muscle.
   Greater trochanter: bilateral, posterior to the trochanteric prominence.
   Knee: bilateral, at the medial fat pad proximal to the joint line.

   Digital palpation should be performed with an approximate force of 4 kg. For a tender point to be considered "positive" the subject must state that the palpation was painful. "Tender is not to be considered "painful."

* For classification purposes, patients will be said to have fibromyalgia if both criteria are satisfied. Widespread pain must have been present for at least 3 months. The presence of a second clinical disorder does not exclude the diagnosis of fibromyalgia.

Appendix B

Clinical Diagnostic and Severity Criteria for Fibromyalgia: Widespread Pain Index (WPI) and Symptom Severity (SS) Scale

WPI (0-19) Directions: Note the number of areas where patient has had pain during the past week. In how many areas has the patient had pain?

<table>
<thead>
<tr>
<th>Shoulder girdle, left</th>
<th>Lower arm, right</th>
<th>Lower leg, left</th>
<th>Abdomen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulder girdle, right</td>
<td>Hip (buttock), left</td>
<td>Lower leg, right</td>
<td>Neck</td>
</tr>
<tr>
<td>Upper arm, left</td>
<td>Hip (buttock), right</td>
<td>Jaw, left</td>
<td>Upper back</td>
</tr>
<tr>
<td>Upper arm, right</td>
<td>Upper leg, left</td>
<td>Jaw, right</td>
<td>Lower back</td>
</tr>
<tr>
<td>Lower arm, left</td>
<td>Upper leg, right</td>
<td>Chest</td>
<td></td>
</tr>
</tbody>
</table>

SS scale score (0-12) = Symptom severity + Extent of Somatic Symptoms

Using a scale of 0-3, indicate the patient’s level of symptom severity over the past week in each of the 3 symptom categories. Choose only 1 level of severity for each category.

<table>
<thead>
<tr>
<th>Fatigue</th>
<th>Waking unrefreshed</th>
<th>Cognitive symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = No problem</td>
<td>0 = No problem</td>
<td>0 = No problem</td>
</tr>
<tr>
<td>1 = Slight or mild problems; generally mild or intermittent</td>
<td>1 = slight or mild problems; generally mild or intermittent</td>
<td>1 = slight or mild problems; generally mild or intermittent</td>
</tr>
<tr>
<td>2 = Moderate; considerable problems; often present and/or at a moderate level</td>
<td>2 = Moderate; considerable problems; often present and/or at a moderate level</td>
<td>2 = Moderate; considerable problems; often present and/or at a moderate level</td>
</tr>
<tr>
<td>3 = Severe; pervasive, continuous, life-disturbing problems</td>
<td>3 = Severe; pervasive, continuous, life-disturbing problems</td>
<td>3 = Severe; pervasive, continuous, life-disturbing problems</td>
</tr>
</tbody>
</table>

Symptom Severity Scale (other somatic symptoms)

Using the symptoms list, determine the extent of other somatic symptoms the patient may have experienced over the past week.

Muscle pain, depression, itching, dry eyes, irritable bowel syndrome, constipation, wheezing, shortness of breath, fatigue/tiredness, pain in upper abdomen, Raynaud’s, loss of appetite, thinking or memory problem, nausea, hives/welts, rash, muscle weakness, nervousness, ringing in ears, sun sensitivity, headache, chest pain, vomiting, hearing difficulties, pain/cramps in abdomen, blurred vision, heartburn, easy bruising, numbness/tingling, fever, oral ulcers, hair loss, dizziness, diarrhea, loss/change in taste, frequent urination, insomnia, dry mouth, seizures, bladder spasms.

Determine the quantity of somatic symptoms using the following scale.

| 0 = No symptoms | 1 = Few symptoms | 2 = A moderate number of symptoms | 3 = A great deal of symptoms |

Criteria: Fibromyalgia criteria is met when a patient meets the 3 conditions:

WPI ≥7 and SS scale score ≥5 or WPI 3-6 and SS scale score ≥9.

Symptoms have been present at a similar level for at least 3 months.

The patient does not have a disorder that would otherwise explain the pain.

Appendix C

The Revised Fibromyalgia Impact Questionnaire

Domain 1 directions: For each of the following nine questions, check one box that best indicates how much your fibromyalgia made it difficult to do each of the following activities over the past 7 days.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Difficulty Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brush your hair</td>
<td>No difficulty ○ ○ ○ ○ ○ ○ ○ ○ ○ Very difficult</td>
</tr>
<tr>
<td>Walk continuously for 20 minutes</td>
<td>No difficulty ○ ○ ○ ○ ○ ○ ○ ○ ○ Very difficult</td>
</tr>
<tr>
<td>Prepare a homemade meal</td>
<td>No difficulty ○ ○ ○ ○ ○ ○ ○ ○ ○ Very difficult</td>
</tr>
<tr>
<td>Vacuum, scrub, or sweep floors</td>
<td>No difficulty ○ ○ ○ ○ ○ ○ ○ ○ ○ Very difficult</td>
</tr>
<tr>
<td>Lift and carry a bag full of groceries</td>
<td>No difficulty ○ ○ ○ ○ ○ ○ ○ ○ ○ Very difficult</td>
</tr>
<tr>
<td>Climb one flight of stairs</td>
<td>No difficulty ○ ○ ○ ○ ○ ○ ○ ○ ○ Very difficult</td>
</tr>
<tr>
<td>Change bed sheets</td>
<td>No difficulty ○ ○ ○ ○ ○ ○ ○ ○ ○ Very difficult</td>
</tr>
<tr>
<td>Sit in a chair for 45 minutes</td>
<td>No difficulty ○ ○ ○ ○ ○ ○ ○ ○ ○ Very difficult</td>
</tr>
<tr>
<td>Go shopping for groceries</td>
<td>No difficulty ○ ○ ○ ○ ○ ○ ○ ○ ○ Very difficult</td>
</tr>
</tbody>
</table>

Domain 2 directions: For each of the following two questions, check one box that best describes the overall impact of your fibromyalgia over the past 7 days.

| Question                                          | Difficulty Options      |
|                                                  |                           |
| Fibromyalgia prevented me from accomplishing goals for the week | Never ○ ○ ○ ○ ○ ○ ○ ○ ○ Always |
| I was completely overwhelmed by my fibromyalgia symptoms          | Never ○ ○ ○ ○ ○ ○ ○ ○ ○ Always |

Domain 3 directions: For each of the following 10 questions, check the one box that best indicates the intensity of your fibromyalgia symptoms.

<table>
<thead>
<tr>
<th>Question</th>
<th>Intensity Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Please rate your level of pain</td>
<td>No pain ○ ○ ○ ○ ○ ○ ○ ○ ○ Unbearable pain</td>
</tr>
<tr>
<td>Please rate your level of energy</td>
<td>Lots of energy ○ ○ ○ ○ ○ ○ ○ No energy</td>
</tr>
<tr>
<td>Please rate your level of stiffness</td>
<td>No stiffness ○ ○ ○ ○ ○ ○ ○ Severe stiffness</td>
</tr>
<tr>
<td>Please rate the quality of your sleep</td>
<td>Awoke rested ○ ○ ○ ○ ○ ○ ○ Awoke very tired</td>
</tr>
<tr>
<td>Please rate your level of depression</td>
<td>No depression ○ ○ ○ ○ ○ ○ ○ Very depressed</td>
</tr>
<tr>
<td>Please rate your level of memory problems</td>
<td>Good Memory ○ ○ ○ ○ ○ ○ ○ Very poor memory</td>
</tr>
<tr>
<td>Please rate your level of anxiety</td>
<td>Not anxious ○ ○ ○ ○ ○ ○ ○ Very anxious</td>
</tr>
<tr>
<td>Please rate your level of tenderness to touch</td>
<td>No tenderness ○ ○ ○ ○ ○ ○ ○ Very tender</td>
</tr>
<tr>
<td>Please rate your level of balance problems</td>
<td>No imbalance ○ ○ ○ ○ ○ ○ ○ Severe imbalance</td>
</tr>
<tr>
<td>Please rate your level of sensitivity to loud noises, bright lights, odors, and cold</td>
<td>No sensitivity ○ ○ ○ ○ ○ ○ ○ Extreme sensitivity</td>
</tr>
</tbody>
</table>

Scoring: Step 1. Sum the scores for each of the three domains (function, overall, and symptoms). Step 2. Divide domain 1 score by three, divide domain 2 score by one (that is, it is unchanged), and divide domain score 3 by two. Step 3. Add the three resulting domain scores to obtain the total Revised Fibromyalgia Impact Questionnaire score.