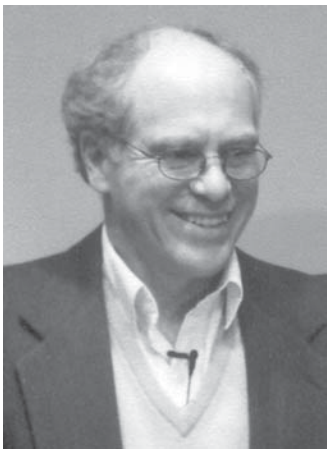


2010 Fibromyalgia Pathophysiology & Treatment

A GUIDE FOR PATIENTS & PHYSICIANS

By Russell Rothenberg, M.D.

Fibromyalgia remains an enigma to many physicians despite its high prevalence in the U.S. population. Why do people chronically hurt all over, feel fatigued, and wake up feeling non-rested despite getting 6-8 hours of sleep? Why do these symptoms often appear to coexist with painful bowel, bladder, and jaw (TMJ) symptoms, as well as symptoms of anxiety and cognitive impairment? The term fibromyalgia (FM) was defined in 1990 by the American College of Rheumatology (ACR). Since then, the National Institutes of Health and other institutions have dramatically increased their funding for FM research, and there have been significant increases in published articles on fibromyalgia and medical conferences that include FM research and treatment in the curriculum.

The major purpose of this article is to provide information that patients can take to their doctors to help them make an accurate diagnosis of fibromyalgia earlier and provide more effective treatment. With the FDA-approved drugs for FM as well as other treatments shown to be effective for FM in scientific studies, doctors can help most FM patients. This article can also be used to provide objective scientific evidence for doctors who still are uncertain whether fibromyalgia is a real medical entity. I've treated over 8,000 patients with FM and hope my experience can help patients and doctors. Since my first article on this subject published in 2007 in *Fibromyalgia Frontiers*, there have been significant advances in research and treatment.

Fibromyalgia is not a new medical problem, it is just better understood. It used to be called different names: "neurasthenia" and "muscular rheumatism" from the mid-1800's until Dr. Gowers created the term "fibrositis" in 1904. In 1978, Drs. Smythe and Moldofsky published the first scientific research on the associated sleep pathology and the peripheral and central nervous system (CNS) pain sensitization that are important parts of the pathophysiology of FM.[1] It was renamed fibromyalgia syndrome in 1990 with the publication of official diagnostic criteria by the ACR.[2] Only recently have we learned that FM is predominately caused by abnormalities in CNS pain sensitization and abnormal levels of neurotransmitters and pain processing in the pain centers of the brain and spinal cord.

FM is a relatively common illness estimated to affect 4-10 million Americans. Demographic studies show that it has a prevalence in the U.S. of 3 ½ % of all women and ½ % of all men over the age of 18 years. These figures are similar to the prevalence of FM in other countries. It has been estimated that 10-20% of patients in a rheumatologist's practice have FM.[3,4]

There is a strong association between fibromyalgia and many of the diseases rheumatologists treat (rheumatoid arthritis, osteoarthritis, Sjögren's syndrome, and systemic lupus) as well as certain infections (hepatitis C and Lyme disease). There is also a primary form of FM which appears to have a genetic basis that can affect multiple members of certain families.

Despite all of the recent advances in the understanding of FM, the problem many patients still experience is a long delay between the onset of their symptoms and their diagnosis of FM. Since patients often have multiple symptoms, and there are no objective lab tests or imaging studies that are

commercially available to make the diagnosis, they often face years of multiple medical evaluations, multiple specialists, a lot of frustration and suffering, and no answers. It would benefit the FM patient if more primary care doctors considered fibromyalgia in their differential diagnosis when a patient presents with chronic pain and fatigue.

FM is not an easy diagnosis to make. A careful history and complete physical examination are necessary to make the diagnosis. It is essential for a doctor to do an adequate medical evaluation to "rule out" other diseases that can mimic FM such as hypothyroidism and rheumatic disease. There are also numerous co-morbid conditions that can be the first symptoms to appear in FM patients including irritable bowel syndrome, interstitial cystitis, vulvodynia, temporomandibular joint syndrome, chronic fatigue syndrome, hyper-extensible joints/Ehlers Danlos Syndrome, non-restorative sleep disturbances, and neurally mediated hypotension. When the diagnosis of a patient with chronic musculoskeletal pain and fatigue is unclear, rheumatologists are available for consultation.

Scientific Findings That Support Fibromyalgia As A Medical Entity

Tender Point Exam & Pain Threshold Studies

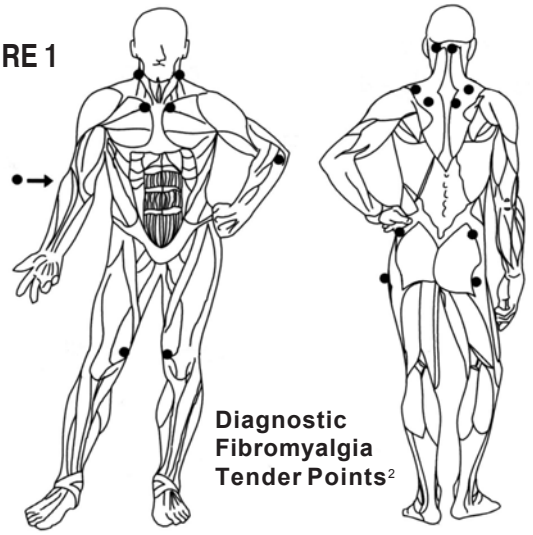
The ACR definition of fibromyalgia includes the identification of at least 11 of a possible 18 anatomically specific tender points (See Figure 1) and requires the history of widespread pain being present for at least three months. These tender points can be assessed by pressing on specific locations of the body with a pressure of 4 kg/m2 (enough pressure to blanch the skin under the thumb nail). Pressing on these painful points can cause a very painful response, and the doctor should press gently initially and stop when it hurts. The tender point exam is a good diagnostic test (88.4% sensitive and 81.1% specific to FM),[5] but tender points are not the only tender areas FM patients have. They also have generalized increased pain to normal touch all over the body (allodynia). It is very upsetting not to want to be touched or hugged by your loved ones, but that is what FM patients experience.

Research doctors have shown in studies that the tender point exam is reproducible in FM patients. Dr. Bradley has demonstrated that lower pain threshold responses to thermal stimuli consistently are present in FM patients compared to normal controls, and this scientific finding has been reproduced by Dr. Geisser.[6] Drs. Gracely and Clauw have demonstrated with functional brain MRI's that a FM patient's response to painful stimuli consistently activates the areas of the brain associated with pain recognition at lower pain thresholds than in normal controls.[7]

Sleep Studies

Fatigue is an important FM symptom, and it is often multi-modal in cause. Chronic pain, non-restorative

FIGURE 1



Diagnostic Fibromyalgia Tender Points[2]

- **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 trochaneric prominence.
- **KNEE:** bilateral, at the medial fat pad proximal to the joint line.

sleep disturbances, autonomic nervous system dysfunction, chronic anxiety and depression, exercise deconditioning, sedative effects of prescribed medications, and poor management of available energy can cause patients to be fatigued. While sleep medications such as zolpidem (Ambien) that induce sleep while preserving normal sleep architecture are effective in treating the fatigue of fibromyalgia, they are not effective in treating FM pain for most patients.

The sleep abnormalities in FM are reproducible in overnight sleep studies (this test may be ordered but is not necessary for the diagnosis of FM). One sees alpha wave intrusion in delta sleep and a decrease in stage 3 and 4 sleep in many FM patients (though these findings may not be present in treated patients). These findings appear to be responsible for the non-restorative sleep and daytime somnolence often described by those with fibromyalgia, and they can also be seen in patients with rheumatoid arthritis, osteoarthritis, and Sjögren's syndrome as well as other illnesses.[8]

Genetic Studies

There is a growing body of scientific evidence which suggests that a subset of FM patients have genetic factors that predispose them to develop FM. Dr. Arnold and colleagues showed that the first-degree relatives of FM patients had an eight-fold greater risk of developing FM than did the general population.[9] These patients tend to have primary FM which has usually been present since the teenage years, though the symptoms may not be clinically apparent until the patient is exposed to significant physical or emotional stressors. Secondary FM is usually secondary to an overwhelming infection, injury, or a significant pain-generating problem that causes increased CNS pain called central sensitization. Genetic abnormalities in the serotonin transporter promoter gene have been noted in FM.[10] Patients with adequate serotonin transporter promoter genes seem to be less susceptible to the adverse effects of chronic stress and depressive events. Another gene, catecholamine-0- methyltransferase (COMT) has been shown to be associated with pain regulation and myofascial pain of the jaw, and there is an increased association of COMT deficiency in FM patients.[11]

Myofascial Pain

Myofascial pain is a big problem for many FM patients. Patients with this condition get palpable "knots" in their muscles and soft tissues that cause significant pain which at first glance may be mistaken for painful muscle spasms. I have had patients misdiagnosed as having fibrocystic breast disease who really had tender myofascial nodules in their breast tissue that could be eliminated with massage therapy techniques! I've seen orthopedic surgeons want to operate on moderately severe osteoarthritis of the knee when the real problem was severe myofascial pain around the knee that responded to medication and physical therapy.

Doctors of physical medicine and rehabilitation often describe myofascial pain as originating in painful tissue which contains nodules associated with "trigger points" (not to be confused with the diagnostic "tender points" of fibromyalgia!) which are palpable, tense, or taut bands of muscle and surrounding tissue. These trigger points are often so painful that the patient is very uncomfortable. There can also be "latent trigger points" that the patient doesn't report as tender, but can be very painful upon examination. Trigger points are typically associated with a referred pain pattern, sometimes at distant sites from the primary pain source, (See Figure 2) and are responsible for musculoskeletal stiffness, weakness, and limitation of motion.

Scientific evidence has demonstrated that painful myofascial tissue has increased levels of the pain neurotransmitters Substance P and glutamate as well as other mediators of pain and inflammation.[12,13] Dr. Jay Shah at the NIH is involved in much of the recent investigations into the pathophysiology of these palpable, hyperirritable nodules that cause myofascial pain.[13] There appears to be an association between myofascial pain and low levels of Vitamin B12 and D as well as iron deficiency, and these common deficiencies should be treated if present in FM patients.

Autonomic Nervous System Abnormalities

There is research that suggests that autonomic nervous system dysfunction, which includes increased sympathetic tone, is an important factor in the pathophysiology of FM as well.[14] FM

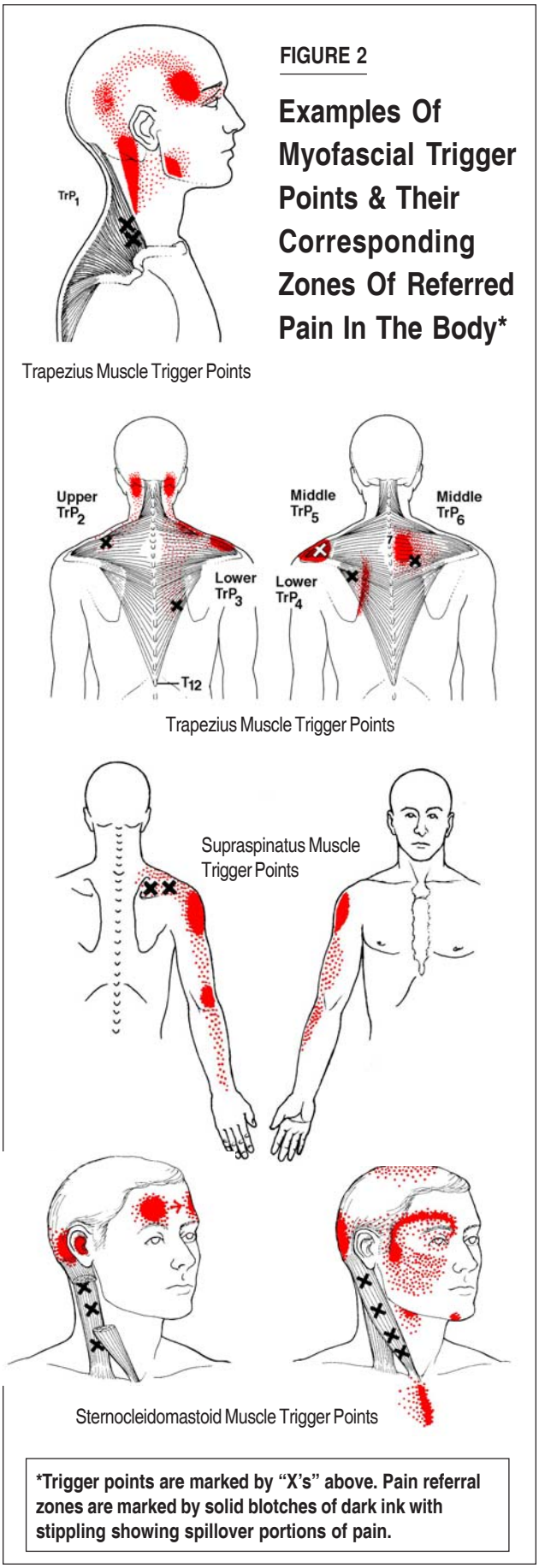


FIGURE 2

Examples Of Myofascial Trigger Points & Their Corresponding Zones Of Referred Pain In The Body*

***Trigger points are marked by "X's" above. Pain referral zones are marked by solid blotches of dark ink with stippling showing spillover portions of pain.**

patients commonly have autonomic nervous system abnormalities that make them vulnerable to coexistent conditions such as neurally-mediated hypotension/reduced heart rate variability, irritable bowel and bladder syndromes, and vascular headaches. Autonomic dysfunction may be partially due to neuroendocrine abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis found in FM. Documented abnormalities include low AM cortisol and 24-hour urinary cortisol levels, inappropriately high levels of adrenocortical trophic hormones (ACTH), and failure to suppress ACTH with dexamethasone. The physician needs to be aware of the need to treat neurally-mediated hypotension in FM patients with adequate salt and fluids as well as explaining the need for conservation of energy. If the hypotension is more severe, cardiac consultation for tilt table testing can be requested.

Central Sensitization, CNS "Windup" & Hyperalgesia

The central nervous system is the major source of pain in FM, and treatment of CNS pain is essential. FM patients get a phenomenon called central sensitization, the amplification of CNS pain transmission and processing, that causes hyperalgesia (increased sensitivity to pain) and allodynia (painful perception of normal situations). We now understand that increased afferent pain pathways in the CNS are associated with elevated levels of the neurotransmitters Substance P and glutamate. There is also a reduction of pain modulating neurotransmitters (serotonin and norepinephrine) in the descending CNS pain pathways that normally dampen pain transmission. These abnormal changes occur in the dorsal horn of the spinal cord and contribute to the hyperalgesic state. Functional brain MRI studies show increased pain processing activity in the brain in response to noxious stimuli in FM, confirming central sensitization.

Drs. Price and Staud have demonstrated that with increasing nociceptive inputs, there is an increased temporal summation of CNS pain discharges or "windup."[15] This increased activity of the nociceptive neurons in the spinal cord involves increased NMDA receptor activity and neural plasticity of nociceptive spinal cord pathways, and it is an important factor in

central sensitization. The pain in FM is not due to inflammation, and traditional pain medications such as non-steroidal anti-inflammatory drugs (NSAID's) or corticosteroids which treat pain and inflammation are not effective in treating FM pain.[16]

Treatment of Fibromyalgia By The Patient's Primary Care Doctor

I've listed below some of the most commonly prescribed treatments for FM. I've tried to emphasize the FDA- approved drugs and other evidence-based, successful therapies. No one therapy is successful for all FM patients. It is very important for physicians to see patients on a regular basis and carefully determine which therapies are most successful for each particular patient. Since patients often have multiple symptoms, it is important to treat FM holistically rather than treat each symptom separately with a polypharmacy approach. However, since no one drug in clinical trials appears to successfully treat FM in more than 50% of cases, multiple drug therapy is necessary for many FM patients.

Many FM patients have problems with multiple chemical sensitivities. Part of the problem could be due to how they metabolize or eliminate certain medications. I often tell patients if they could tolerate the full dose of a prescribed drug their FM problems would be much less severe. Another problem is that the FDA-approved FM drugs were tested as monotherapies, meaning that patients were not allowed to take other FM medications during the clinical trials. Patients on more than one medication can experience drug-drug interactions which require them to use a lower dose of medication due to increased side effects on the full dose. Some drugs have generic alternatives that may be absorbed differently than the brand name drug. These problems can often cause FM patients to have difficulty taking standard doses of medication due to intolerable side effects. It is not uncommon for FM patients to need to start at lower than standard doses of medications.

Medical Management For Fibromyalgia

In addition to a tender points exam and an assessment of the patient's myofascial pain, range of motion, posture, and gait, what other diagnostic criteria should the physician use to assess the status of the FM patient? First, it is important for the physician to see the patient often until his or her symptoms stabilize and to have the patient keep a pain and activity diary. By asking on a regular basis about his or her functional status (activities of daily living, exercise, and work) and recording the patient's subjective pain score (0-10), the physician will have a better idea of how the patient is doing.

Important non-pain symptoms associated with FM usually include chronic fatigue, non-restorative sleep disturbances and daytime somnolence, neurally-mediated hypotension, cognitive dysfunction, irritable bowel syndrome, increased anxiety, and reactive depression (which is distinguished from major depressive disorder). In my clinical experience as a rheumatologist who has treated FM patients for over 25 years, successful treatment of these other co-morbid FM problems is essential to a good clinical outcome.

It is also important to identify the patient's pain generators. These pain generators can come from co-existing osteoarthritis, rheumatoid arthritis, systemic lupus, myofascial pain, or other mechanical problems such as degenerative disc disease or spinal stenosis. Adequate control of these additional sources of pain, if present, is an important therapeutic challenge.

When a FM patient has a pain flare, it usually involves a CNS windup and central sensitization. In my experience, it is essential to aggressively treat this type of pain before it causes a chronic escalation of the patient's pain syndrome. It also gives the patient a sense of control and avoids unnecessary emergency room visits. I encourage my patients to have adequate pain medication at home for the short-term treatment of this type of emergency, breakthrough pain.

PHARMACOLOGY FOR FIBROMYALGIA

1. ANTIDEPRESSANTS

These drugs block the biogenic amines that are abnormal in the CNS in FM.

a. Tricyclic Antidepressant Drugs (TCA): Bedtime doses of low-dose amitriptyline (Elavil) and doxepin (Sinequan) have been effective in FM.

b. Selective Serotonin Reuptake Inhibitors (SSRI): Only 40-80 mg. of fluoxetine (Prozac) has been shown to be effective in small FM studies. The other SSRI's are effective in treating anxiety and depression, but not effective treating pain in FM studies.

c. Serotonin-Norepinephrine Reuptake Inhibitors (SNRI): Duloxetine (Cymbalta) and milnacipran (Savella) are now FDA-approved for the management of fibromyalgia. Cymbalta is also approved for the treatment of diabetic neuropathic pain, generalized anxiety disorder, and major depressive disorder. Savella has a higher concentration of norepinephrine than Cymbalta and may be more effective in the treatment of FM fatigue. In clinical trials, both drugs appear to be very effective in 30% of FM patients and partially effective in 50% of FM patients.

2. ANTI-EPILEPTIC

(Calcium Channel Inhibitor Drugs) These drugs block the release of neurotransmitters Substance P and Glutamate in hyper-excited nerve fibers.

a. Pregabalin (Lyrica) is now FDA-approved for the management of fibromyalgia. It is also approved for the treatment of shingles and diabetic neuropathic pain. In clinical trials, it appears to be very effective in 30% of FM patients and partially effective in 50% of FM patients.

b. Gabapentin (Neurontin) is commonly used in the treatment of FM and neuropathic pain. It is FDA-indicated for shingles neuropathic pain and was shown to be effective for the treatment of FM in one clinical trial funded by the National Institutes of Health.

3. OPIOIDS

a. Tramadol (Ultram), Tramadol with Acetaminophen (Ultracet), and Tramadol Extended Release (Ultram ER): are weak opioids, but they are not considered controlled substances as determined by the U.S. Drug Enforcement Agency (DEA). They also have TCA effects and are FDA-approved for the treatment of moderate to severe pain. Clinical trials show them to be effective in the treatment of FM pain. My experience is that Ultracet is more effective than Ultram with fewer adverse effects, and Ultram ER offers the important benefit of 24-hour pain control without breakthrough pain when the short acting drug wears off in 6-8 hours.

b. Long-Acting Opioids: Fentanyl patch and time-release morphine have been shown to be effective for long-term use in chronic low back pain and osteoarthritis pain, but their use should be limited to only the most severe chronic pain patients due to concerns about addictive potential and adverse effects. The EULAR (European League Against Rheumatism) evidenced-based guidelines do not recommend these drugs for the treatment of FM pain.[17]

c. Short-Acting Opioids: Hydrocodone and oxycodone, in combination with acetaminophen or ibuprofen, are excellent short-acting analgesics for acute peripheral and CNS pain. They should not be used for chronic pain except in rare instances due to concerns about addictive potential and adverse effects, including the potential for withdrawal-related symptoms of increased pain.

4. MUSCLE RELAXANTS

Muscle relaxants are commonly used both chronically and for acute pain flares in FM. Cyclobenzaprine (Flexeril) is effective in FM due to its tricyclic antidepressant and muscle relaxant properties, and it is often used to help with sleep. There is now a 24-hour time release form of cyclobenzaprine, Amrix, which usually causes less sedation than cyclobenzaprine if used during the day.

5. SEDATIVE HYPNOTICS

a. Non-Benzodiazepines: Zolpidem (Ambien) has been shown to improve FM sleep disturbances and fatigue.

b. Benzodiazepines: Alprazolam (Xanax) has been shown to be effective in FM.

NON-PHARMACOLOGIC TREATMENT FOR FIBROMYALGIA

1. EDUCATION:

When a FM diagnosis is made, and the condition is properly explained to the patient and family, the intensity of symptoms will often be reduced by one-third due to reduction in patient anxiety which contributes to abnormal pain processing. An essential goal of FM treatment is to empower the patient to understand his or her illness and learn how to best manage the disease.

2. PHYSICAL THERAPY:

Proper posture, balance, muscle tone, and physical conditioning are important needs to correct in many FM patients, much more so than for their non-fibromyalgia friends with similar poor posture, muscle tone, and physical conditioning. It is often necessary to prescribe physical therapy with a therapist skilled in FM, myofascial release, and neuromuscular re-education before the patient can successfully progress to an appropriate exercise program.

3. EXERCISE:

Low impact, aerobic exercise is an important treatment for almost all FM patients to improve their pain (by increasing endorphins in the CNS), mood, physical conditioning, and functional status. It is important to combine exercise with adequate stretching as well as energy conservation to prevent injury or FM flare. I find core and Pilates exercises as well as warm water aquatic exercises (when possible) to be very effective for most of my FM patients.

4. COGNITIVE BEHAVIORAL THERAPY & BEHAVIORAL MODIFICATION THERAPY:

These are being used in FM with increasing frequency and success. Proper conservation of your available energy and development of coping skills to reduce anxiety over dealing with chronic pain are important goals in the management of FM.

5. ACUPUNCTURE

This discipline has been shown to be an effective FM treatment in small clinical studies. It should be considered a supplemental therapy for FM patients and can be very beneficial in selected patients.

Important Note: Before attempting any new form of medication or treatment, be sure to check with your physician.

Conclusion

As my experience treating FM patients grows, and the science regarding the disease and treatment options increases, I find myself becoming more and more optimistic about good patient outcomes. Most FM patients have symptoms that do not worsen over time, and many patients improve to a level of pain they can tolerate and be functional. The mainstay of treatment is the use of evidence-based treatments which include patients' active participation to fine tune their treatment plans to their particular needs, as part of the medical team. This formula ensures a successful and positive relationship for both doctor and patient.

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