A Guide to understanding Fibromyalgia research for patients

By Bailey Farstad

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Introduction

Like you, I have been diagnosed with Fibromyalgia (and also Chronic Fatigue Syndrom, but that will not be discussed just yet). After 6 long years of being terribly sick and very often bedridden I was finally given a diagnosis to my condition at the Cleveland Clinic, OH, USA. My doctor explained a bit about FM and CFS/ME and began a treatment program. Upon arriving back home in Norway I wanted to find out everything there is to know about FM and CFS/ME. I started my internet search with using Google, as most of us do, and came across a sea of websites most of which had contradicting information on what FM and CFS/ME is and how it should be treated. Even my doctors are at odds with each other on how to treat my illness. I found this all very stressful and very frustrating and decided to do my own investigation into FM and CFS/ME by only reading research journals published by the leading scientific experts in FM and CFS/ME. As we all know the main stream media doesn't always tell us the whole truth and is often very biased when it comes to information. Most sites dedicated to FM or CFS/ME have chosen one particular way that they believe both syndromes should be treated and have ignored all other information/research. I quite frankly had enough of all of this one-sidedness and decided to launch my own investigation into my condition and I would like to share that information with you all.

Reading scientific journals is not easy, especially if you do not have a science background. There are a lot of big words, scary calculations, graphs, charts, images and empirical data to get through and doing all this with our 'Fibro Fog' can be most daunting. The main reason I am writing this paper now is to help all of my fellow sickies out there to learn what I have learned, without needing a dictionary beside you to understand what all of this science means. My goal is to

explain the research found within this paper in simple and concise terms for the average FM or CFS/ME patient to be able to understand. I am not writing this paper to tell you all about some ground breaking amazing new technology that will cure us. Of course I found no such thing. Like me, I am sure you have a million questions about what is going on in our body and want to know WHY we are sick. I will warn you now that there isn't one answer, we all wish there was, but there isn't one… yet.

Before I got sick I was doing my masters in physics. I had worked as a research scientist for four years investigating fancy lasers, microscopes and even playing with superconductors. I have published a lot of papers myself. As a side interest I also took classes in biophysics and physiology for physicist, which gives me a good background for understanding most of information presented in the papers listed below (I of course did need some friendly help from Wikipedia from time to time). Using my science background I decided to set off and launch my own investigation into the latest research into FM. In this paper you will find a nonbiased account of the latest FM research with a description in easy to understand terms of what the research means. The only agenda I have in writing this is to share information with my fellow FM and CFS/ME patients.

What is Fibromyalgia?

Fibomyalgia means pain in the muscles, ligaments, and tendons, although most patients with FMS have other types of pain and discomfort too. Most patients with Fibromyalgia complain of hurting all over or "from head to toe". The neck and back, hips and shoulders are typically prominent complaints. They will also complain of burning sensations, numbness, dry eyes, dry mouth, temperature sensitivity and feeling cold, headache or migraines,

fatigue, poor sleep, dizziness, abdominal and bladder problems, chest pain, sensitivities to medications, restless legs, problems with their jaw including TMJ, and difficulties with mood, and memory.

Pain: Pain is usually the most prominent complaint in patients with FMS. Their whole body can hurt although the spine, neck, shoulder hips and knees tend to be the most prominent areas involved. The pains can come and go, or move around making it very difficult for the patient or doctor to understand what is going on. Patients can also have tingling, burning types of symptoms in their hands and feet or other parts of their bodies. Typical medicines used for pain such as over the counter anti- inflammatories usually do not provide significant relief. Even strong narcotic type medications at times provide little in the way of pain relief.

Fatigue: Most FMS sufferers have complaints of fatigue although in some patients it can be mild and others it can be disabling. This can be "brain fatigue" where there is difficulty with mental processes such as memory, attention, concentration, and multitasking, which is commonly referred to as "fibro fog". The fatigue will typically manifest as the feeling of having no energy or being unable to work, exercise, or sometimes even move. Many patients will meet the Center for Disease Control (CDC) criteria for Chronic Fatigue Syndrome (CFS).

Sleep: The majority of patients with FMS have non-refreshing or non-restorative sleep which means that when they wake up they feel they haven't slept at all. They will also complain of not getting deep sleep. Sleep studies reveal that even if they do get into deep sleep, called delta or slow wave sleep, that their brain waves appear as if they are still awake, or alpha wave intrusion. This Alpha/Delta Sleep pattern was first described by Dr. Harvey Moldofsky in 1975. Now that there are experimental medications which can improve this phenomenon, his research has become much more relevant. Obstructive Sleep Apnea, Restless Legs Syndrome (RLS) and Periodic Limb Movement Disorder (PLMD) are also frequently

seen in FMS, and can be identified by sleep studies and are amenable to treatment.

Irritable Bowel Syndrome: Anywhere from 40% to 70% of patients with FMS will meet the criteria for Irritable Bowel Syndrome (IBS). Symptoms can include constipation, diarrhea, abdominal pain, gas, nausea, and bloating.

Irritable Bladder: Many patients with FMS will also complain of difficulty with frequent need to urinate, or sense of urgency, and even in some cases urinary incontinence. Sometimes patients are also given a diagnosis of interstitial cystitis.

Tension Headache and Migraine: Over 50% of FMS patients suffer with recurrent headaches that can have the characteristics of tension headaches or of migraine headaches or both. Headache and their treatment can be a difficult aspect of treating patients with FMS.

Multiple Chemical Sensitivity: Studies have shown that a subset of patients with FMS are sensitive to odors and noises and can also be very intolerant of many medications due to the fact that they "get every side effect". This has been referred to as Multiple Chemical Sensitivity (MCS).

Primary Dysmennorhea: Painful and irregular periods can be experienced with many female patients with FMS. This has lead to increase use of birth control pill to help control the symptoms. Some patients undergo hysterectomy and have their ovaries removed which leaves patients without any ovarian hormones at all making hormonal balance more challenging.

Temporomandibular Joint Dysfunction: Many FMS patients have tremendous jaw and face pain. This has also been described as TMJ syndrome although the tempormandibular joint is not always affected.

Myofascial Pain Syndrome: The majority of patients have pain in the muscles, joints, tendons, and ligaments. Morning stiffness is commonly reported in FMS patients.

What causes Fibromyalgia?

The ultimate cause of FMS is still a mystery, but there is a lot that is now known about this condition...

GENETICS: A family history is seen in one third of patients. Research is looking at the COMT gene which plays a role in serotonin regulation, the autonomic system, and pain control.

NEUROCHEMISTRY(Brain function): The best documented abnormality in FMS is low serotonin levels in the spinal fluid which could impair the nervous system ability to control pain. Substance P is a neuromodulator that induces pain and studies have shown that this chemical is elevated three fold in patients with FMS. This concept is referred to neurologically as central pain augmentation or central pain amplification. It is important to understand that the pain in FMS is not caused by inflammation on the tissue level, but rather pain amplification within the neurological system itself.

HORMONES: Abnormalities have been shown in growth hormone (GH), thyroid hormones, cortisol and corticotropin releasing hormone (CRH), as well as gonadotropes including estrogen and testosterone. Early childhood trauma or turbulence, whiplash injuries, extremely stressful events, and even infections have been associated with the developement of FMS.

SLEEP: Deep sleep or slow wave sleep is responsible for tissue repair, immune system regulation, hormonal and neurochemical regulation. Disturbed deep sleep (Alpha-Delta Sleep), which is seen in the majority of patients, is associated with many of the neurochemical and hormonal problems in FMS and is consequently a major focus in

current research and treatment. Other types of sleep problems are frequently seen in patients with FMS including Non-Restorative Sleep, Insomnia, Fatigue, Restless Legs, Sleep Apnea, and Upper Airway Resistance.

Environment: Triggers that may be involved in the development of fibromyalgia include mechanical/physical trauma or injury and psychosocial stressors. Commonly reported physical traumas include acute illness, physical injury, surgery, and motor vehicle accidents. Commonly reported psychosocial triggers include chronic stress, emotional trauma and emotional physical or sexual abuse. The effect of mental stressors may be especially important because in addition to the onset of chronic wide spread pain, these mental stressors may also contribute to enhanced pain responses via involvement of neuroendocrine system (neurotransmitters released by nerve cells).

Genetic Aspects of Fibromyalgia

Many genetic studies subscribe to the theory that FM is a neurological disorder and environmental factors may trigger the onset of the disorder. There are many cases of family members all developing FM at different stages in development (meaning different ages); suggesting there is a heritable disorder. The research suggests that having a family history of a low pain threshold and history of mental illness or instability, such as depression, may be related to the development of Fibromyalgia. Researchers in Sweden evaluated pain data from the Swedish Twin Registry that had been collected on 15,950 twin pairs at least 42 years of age. In general, genetics and a shared environment each explained about half of

the variation in the occurrence of chronic widespread pain, suggesting a modest genetic influence.

Studies have identified a variety of possible candidate genes linked to FM (such as those encoding HLA DR4 antigen, serotonin transporter, catecholo-O-methyltransferase, D2 and D4 Dopamine receptors on chromosome 11 and substance P receptor (NK1)). Although the results were not overwhelming or conclusive, they were significant. Finding alterations in the serotonin and dopamine neurotransmitters is important because together they control the following functions in the brain: regulation of mood, appetite, pain, sleep and cognitive functions including memory and learning; behavior and cognition, voluntary movement, motivation, punishment and reward, inhibition of prolactin production (involved in lactation and sexual gratification), sleep, mood, attention, working memory and learning, respectively. All of which are areas that FM patients have difficulty with on a daily basis.

Serotonin levels are also naturally lower in women versus men, which may explain the predominance of women developing FM over men, and it has been found to play an important role in sleep regulation which may explain why FM patients have disrupted sleep.

Brain Function in Fibromyalgia patients

With improved technologies in imaging machines, scientists are able to view how the brain function of fibromyalgia patients differ from that of normal patients.

In the study, "**Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity**," researchers found that the resting brain activity of a fibromyalgia patient reveals that even without external stimulus, the patient's brain is still receiving pain signals. The can also see that the connections in the brain that are known to process evoked pain show greater connectivity than in the brains of healthy subjects. The significance of this study is that where most studies show that FM patients feel pain stronger than healthy patients do, FM patients continue to feel pain even when no one is applying a painful stimulus.

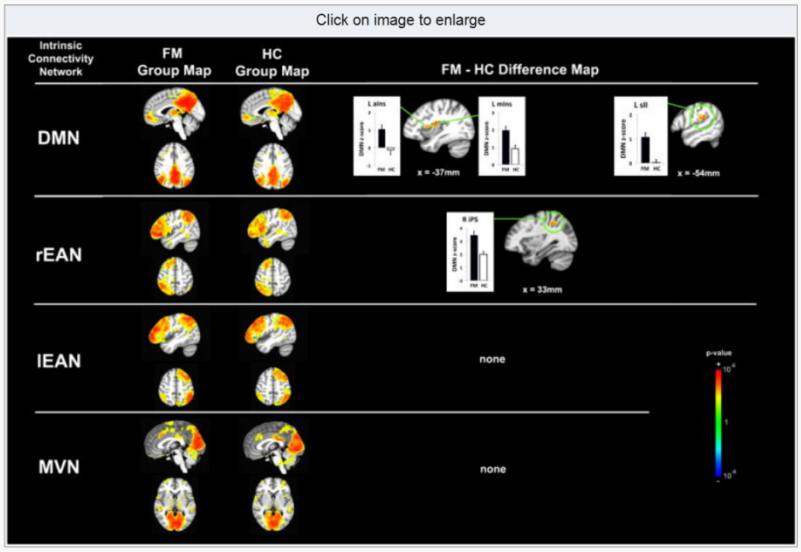


Figure 1

ICN Group and Difference Maps. Group maps for HC and FM demonstrate the expected anatomical scope of the canonical DMN, EAN, and MVN for both groups, with the EAN split into a right and left lateralized network. Difference maps contrasting FM versus HC demonstrated that FM patients had greater intrinsic DMN connectivity to several brain regions outside the DMN but known to process evoked pain (insula). FM also demonstrated greater rEAN connectivity within this ICN (iPS). n.b. SII = secondary somatosensory cortex, iPS = intraparietal sulcus.

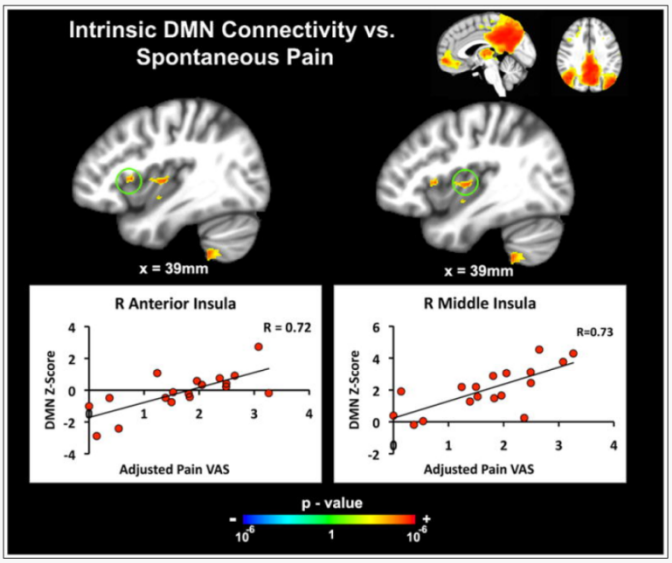


Figure 2

Covariation between DMN connectivity and age-adjusted spontaneous pain. Greater spontaneous pain intensity correlated with linearly increasing intrinsic DMN connectivity to the right middle and anterior insula.

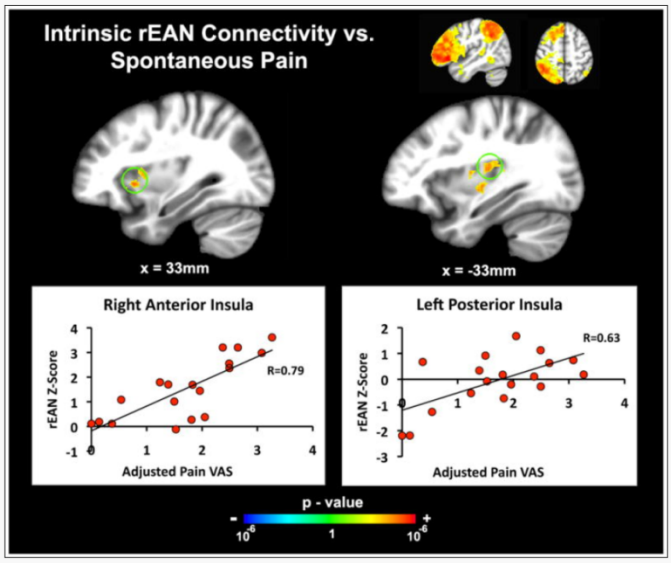
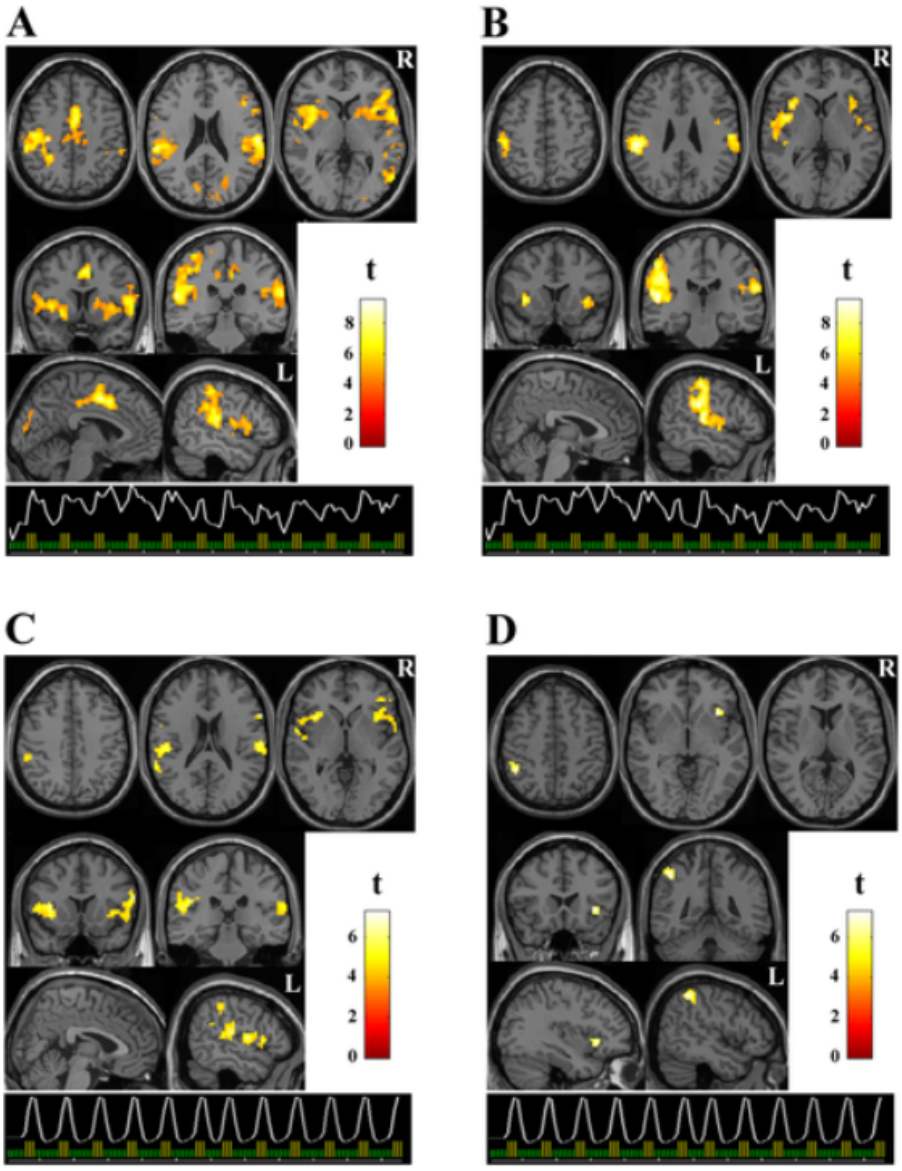


Figure 3

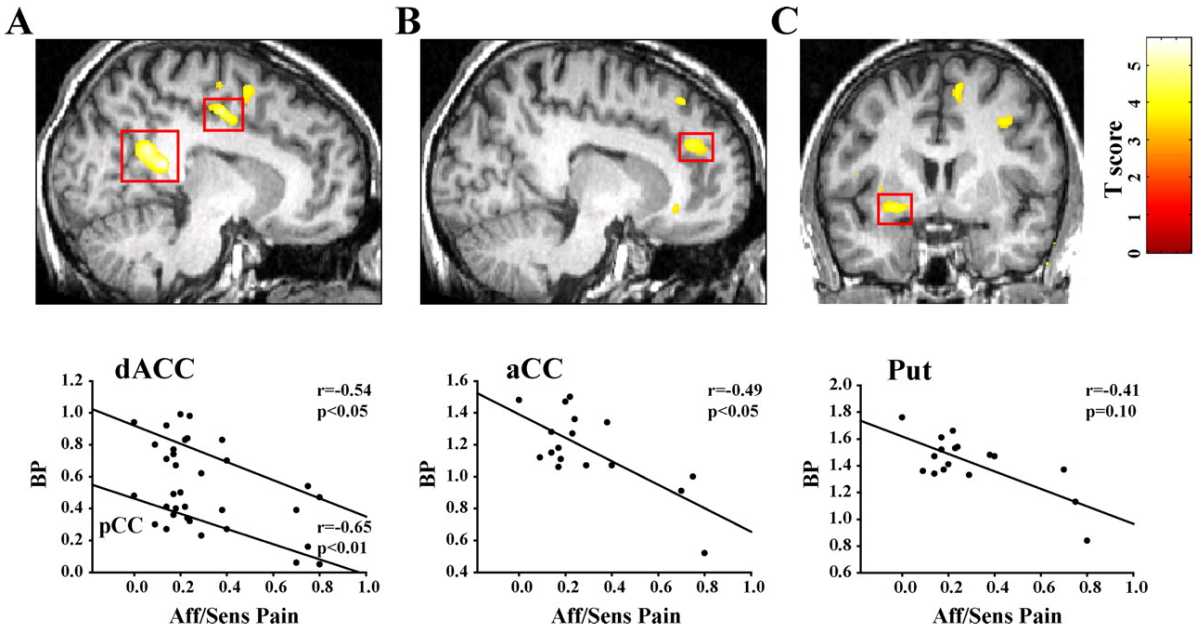
Covariation between rEAN connectivity and age-adjusted spontaneous pain. Greater spontaneous pain intensity correlated with linearly increasing intrinsic rEAN connectivity to the right anterior insula and left posterior insula.

In this next study, patients were given a pressure stimulus using a controlled hydraulic device on their thumbnail and their brain activity was mapped.

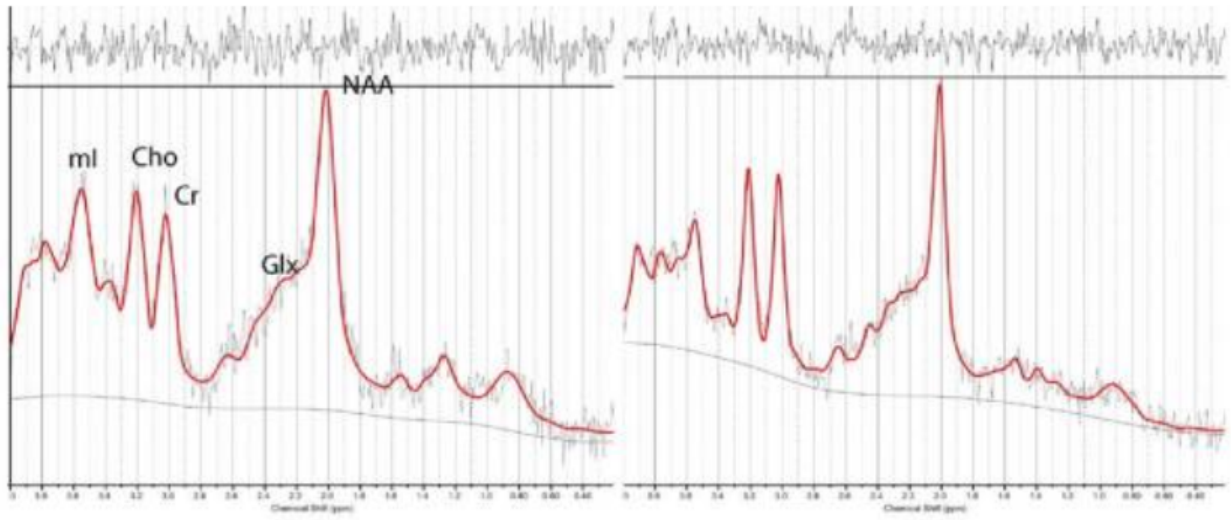


The above picture is the brain response to 4 kg/cm^2 of pressure applied on the right thumb. Picture **A** depicts fibromyalgia patients and picture **B** that of healthy patients. Picture **C** depicts the brain activity of fibromyalgia patients after the stimulus is gone and **D** that of healthy patients after the stimulus is removed **[(2009) Mapping Brain Response to Pain in Fibromyalgia Patients Using Temporal Analysis of fMRI]**

In this next study, researches use a positron emission tomography (PET) scan to investigate the pain receptors in FM patients. They found that FM patients have a disregulation of the neurotransmitter system. This agrees with other research showing a low value of serotonin in cerebral spinal fluid in FM patients.



The occurrence of central neurobiological factors in fibromyalgia is becoming increasingly observed. These next researches use a brain imaging tool called proton magnetic resonance spectroscopy, which can asses the concentration of specific metabolites in the human brain, and looked for altered levels of brain neurotransmitters in individuals with FM. This imaging technique has been mostly used to study such brain disorders as depression, Alzheimer's disease and epilepsy. This new imagining technology is particularly important and insightful as its method allows for the detection of the brain's major excitatory and inhibitory neurotransmitters, glutamate (Glu) and gamma amino-butyric acid (GABA), respectively.



The above picture shows the left hippocampus spectrum for a control patient (**a**) and a patient with fibromyalgia (**b**). For the patient with FM, a decrease in the myoinositoal peak amplitude and in the relation to creatine was noted.

Imaging techniques, such as the ones listed above, are evidence that the chronic central pain in Fibromyalgia may stems from altered brain neurotransmitter levels. The elevated levels of Glu shown in the functional magnetic resonance imaging studies of FM may be the cause of neuronal hyper-excitability (meaning one of the neurotransmitters is creating the pain stimulus).

Fibromyalgia and Sleep

Fatigue is a debilitating symptom of Fibromyalgia and is seen in up to 80% of patients with FM. Not only is the fatigue physical, but it encompasses the mental fatigue and impaired concentration or fuzziness commonly referred to as "FibroFog." Recent studies suggest that the fatigue and difficulty in sleeping stems from a sleep

abnormality characterized by alpha wave intrusions during the deep sleep cycle (delta wave). A person's brain is constantly active and an EEG machine can measure that activity (the figures are shown below). Brain activity is measured in waves and the type of brain wave that is emitted usually describes the type of activity a person is participating in. When we are wide-awake, the average brain will emit Alpha waves. When the average person is in deep sleep, we expect to see delta wave (slow wave) sleep. For researches to see Alpha waves emitting from a person who is in deep sleep, this suggests that the patient's brain is suddenly 'turning on' and becoming active, as if that patient were wide-awake. The repercussions of this are that REM is not obtained and the patient does not get any restorative sleep, which can lead to the fatigue, pain intensity and hormonal dysregulation that FM patients suffer.

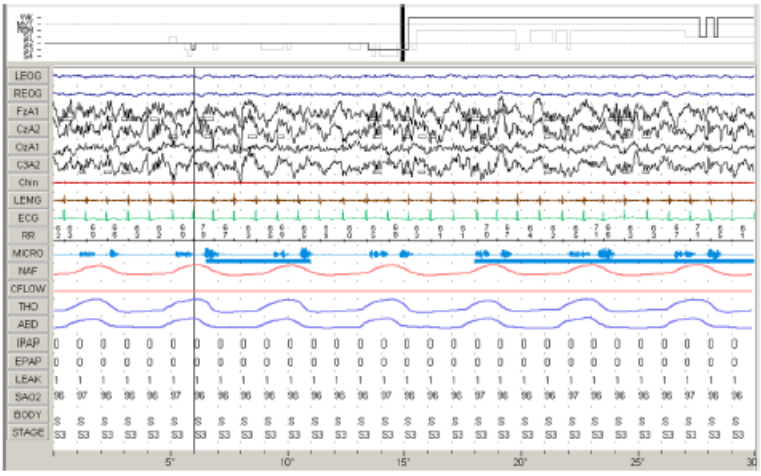


Fig. 1: Polysomnogram demonstrating Alpha Event Quantitation during a 30 second epoch.

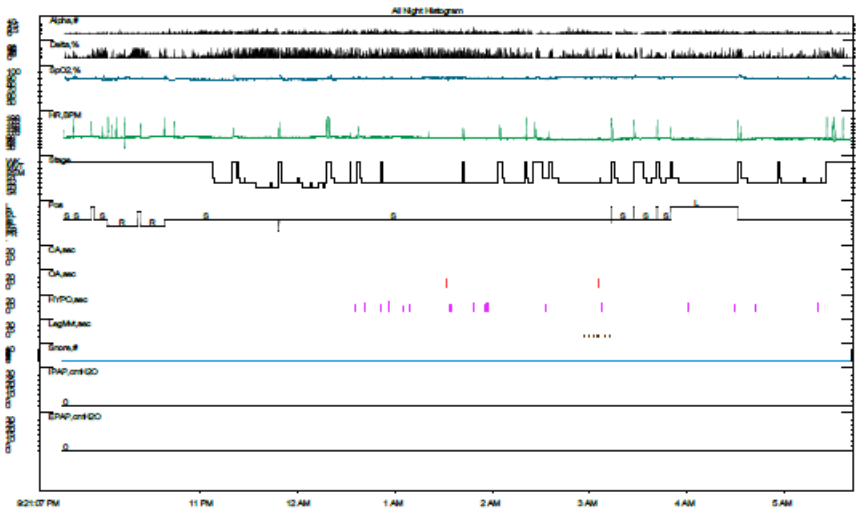


Fig. 3: Hypnogram demonstrating typical FMS patient with “Alpha/Delta” revealed by qEEG

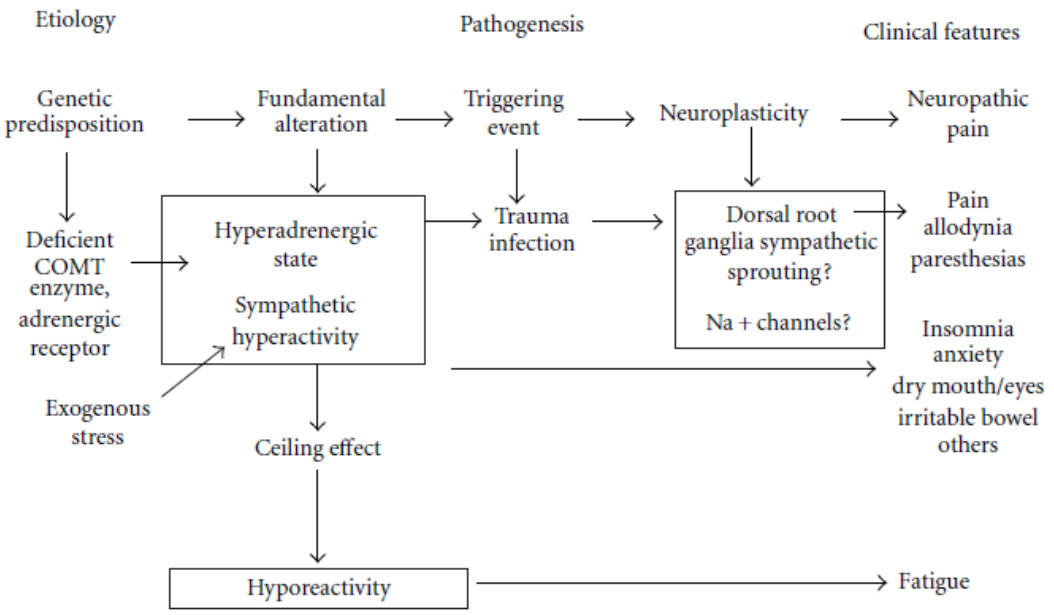
Fibromyalgia and the Sympathetic Nervous system

The sympathetic nervous system (SNS) is one of the three parts of the autonomic nervous system. Its general action is to mobilize the body’s fight or flight response, besides the constant job of maintaining homeostasis. When we feel the fight or flight response, our body undergoes stress. Regardless of whether it is physical or mental stress, our sympathetic nervous system kicks in and in Fibromyalgia patients, this kick may be the cause of FM development.

Researchers have begun to investigate the sympathetic nervous system dysfunction in patients suffering from FM. It is clear that several sympathetic abnormalities in FM patients occur, which lead researchers to consider it to be a neuropathic pain syndrome. Meaning we can view it as a failed attempt of our body trying to

kick in the fight or flight response as we deal with major stress in our lives. Previously mentioned genetic studies support the concept of FM as a sympathetically maintained pain syndrome. I'd like to note that the genetic studies also show a gene polymorphism (abnormality/change) associated with defective adrenergic receptors. If you put these two theories together then it suggests that FM is a genetically predisposed disease where distress is transformed into pain through our sympathetic nervous system. Meaning many people can carry the gene that would trigger FM, but if they never experience the stress needed trigger the dysfunctional sympathetic stress response, they won't develop FM.

Theoretical etiopathogenetic mechanisms in Fibromyalgia by Dr. Manuel Martinez June 2011



Treatment Options for Fibromyalgia

Because Fibromyalgia is such a multisystem disease, finding one cure all tablet or procedure is impossible at this time. The understanding of the effects and functions of the disease have come a long way in the last 10 years, and doctors are hopeful that with more research and understanding, there may one day be a cure or prevention. Until that beautiful day comes, we have to tailor our management of FM to our individual symptoms, biology and lifestyle.

Optimal treatment of an FM patient requires that the physician really listen each specific patient and tailors the treatment plan to the individual and the presenting symptoms. It cannot be stressed enough that FM is a multisystem disease comprised of a range of symptoms and features and no two FM patients experience the exact same symptoms. To properly treat an FM patient and improve their quality of life a multidisciplinary approach tailored to the individual's ability and symptoms is necessary. Such an approach will include both pharmacological (medication) and non-pharmacological (physical and or psychological therapies). When choosing among available medications, it is helpful to consider the most troubling symptoms of the patients. If depression and poor sleep are significant concerns, a sedating antidepressant may address both symptoms, and thus not over medicating the patient – which can result from treating each symptom with different medications.

FM patients also need to understand, and this should be stressed by their doctor, that medications may reduce some of their symptoms, but they are likely to be far more effective if taken in conjunction with exercise, stretching and stress management techniques.

Meaning, do not expect to go to your doctor and get a pill to feel better and neglect taking an active role in your own recovery.

Non-pharmacological therapies that have been found to be effective in FM patients include: heated pool treatment with or without exercise, mild aerobic exercise and strength training, cognitive behavioral therapy (CBT), acupuncture, massage and meditation or other mental relaxation techniques. FM is well established as a stress related disorder and performing physical activity is known to help reduce stress in individuals. Therefore, reducing stress in an FM patient will also reduce the amount of pain the individual experiences. It is highly recommended that any exercise program proposed to an FM patient be started gradually, as to not cause the patient more pain that before they started physical treatment. During pain flares, which may occur after physical exertion, programs should be modified but not stopped. For me, personally, my doctor asked me to start with 5 min of 'doing something out of your routine' every other day. After 6 months, I can now take hour long walks every other day, which is a tremendous improvement.

Cognitive behavioral therapy has been shown to have benefits in some fibromyalgia patients. Patients who received both CBT and medication over a 5 year period showed continual improvement versus those who only received CBT, which had a 60% rate of having the same or worse symptoms of FM than when they started CBT 5 years prior. It has also been shown, and this is very important for doctors to note, that those FM patients that improve the most with CBT are those who have a tendency to 'catastrophise' their situation or show signs of depression and hysteria. Patients who are well educated in their condition and have a positive attitude toward their situation had little to no change in their FM symptoms. I think CBT and its usefulness with patients is analogous to people who have

traumatically become paralyzed versus those who were born with a disabling condition. When a person experiences such trauma as to lose the use of their legs (for example), they will certainly become depressed with the situation and have a hard time coping with losing the lifestyle they knew. It's understandable that seeking physiological treatment to deal with such a tragedy will help them with their outlook on life and to find a way to make a new life for themselvs. People who become sick with FM loose the life that they knew. They become isolated and their pain is debilitating and even mundane household choirs become impossible. Talking with a therapist and learning to see the positive in their lives and learn better ways to cope with pain will of course help these patients to have a better quality of life.

Science has proven that FM patients have a neuro-chemical disease that involves pain processing in the brain and neurotransmitters of pain signals. It is therefore logical that introducing medication that will help modify these pain signals and processing dysfunction will reduce the amount of pain FM patients experience and that will greatly improve their quality of life. Pain reduction in FM patients also enables them to become more active and follow the other non-pharmacological guidelines recommended. Antidepressants such as amitriptyline, fluoxetine, duloxetine, milnacipran, moclobemide and pirlindole, have been shown to reduce pain and often improve function in FM sufferers.

Table 4. Medications Used in Fibromyalgia Treatment

Drug	Recommended Dose	Comments
Antiepileptic medications		
Gabapentin	100-600 mg daily; maximum dose: 1,800 mg daily	Titrate slowly; may cause sedation or dizziness; dose adjustment for renal failure
Pregabalin (Lyrica, Pfizer)	300-450 mg daily; maximum dose: 600 mg	FDA-approved for fibromyalgia; maximum dose is for the indication PHN
TCAs		
Amitriptyline	10-50 mg at bedtime	May cause sedation and confusion
Nortriptyline	10-50 mg at bedtime	Avoid using in patients with narrow-angle glaucoma. Baseline echocardiography recommended to evaluate Q-T prolongation; if present, avoid use.
SSRIs		
Citalopram	20-40 mg daily	—
Fluoxetine	20-80 mg daily	Patient tolerability of SSRIs is superior to that of TCAs.
SNRIs		
Duloxetine (Cymbalta, Lilly)	30-60 mg daily	FDA-approved for fibromyalgia; avoid using in patients with liver disease or narrow-angle glaucoma.
Milnacipran (Savella, Forest Laboratories)	100-200 mg daily (divided doses)	FDA-approved for fibromyalgia; avoid using in patients with liver disease or narrow-angle glaucoma.
Venlafaxine	75-100 mg daily[a]	Avoid using in patients with uncontrolled hypertension.
Analgesics		
Tramadol	50-100 mg every 6 hours as needed	May cause sedation and confusion. Avoid using in patients with seizures. May cause serotonin syndrome in combination with SSRIs or other antidepressants. Dose adjustment for renal failure
Muscle relaxants		
Cyclobenzaprine	5-10 mg nightly	Likely to cause sedation; side effects similar to TCAs

PHN, postherpetic neuralgia; **SNRIs,** serotonin-norepinephrine reuptake inhibitors; **SSRIs,** selective serotonin reuptake inhibitors; **TCAs,** tricyclic antidepressants

[a] Doses up to 375 mg daily have been studied by MM Dwight et al (*Psychosomatics* 1998;39[1]:14-17).

The following is a chart suggested by experts to be the most efficient and effective treatment of FM, where the 'First Line' treatments are given simultaneously and then 'Second Line'. Noting patients' responses to pain and additional symtoms will help the physician asses treatment and adjust it accordingly. It is very important that both the FM patient and doctor play an active role and communicate regarding any changes, improvements or otherwise, that the patient experiences. Many doctors recommend that the FM patient keep a journal to keep track of how activity, diet, sleep and medication affect them on a daily basis.

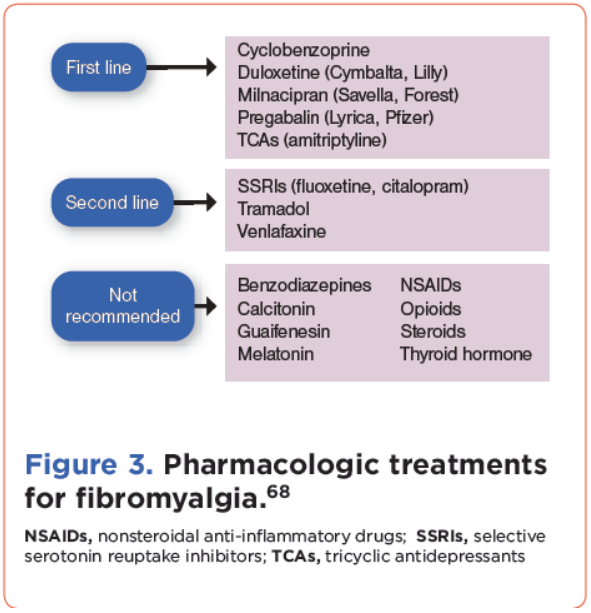


Figure 3. Pharmacologic treatments for fibromyalgia.[68]

NSAIDs, nonsteroidal anti-inflammatory drugs; **SSRIs,** selective serotonin reuptake inhibitors; **TCAs,** tricyclic antidepressants

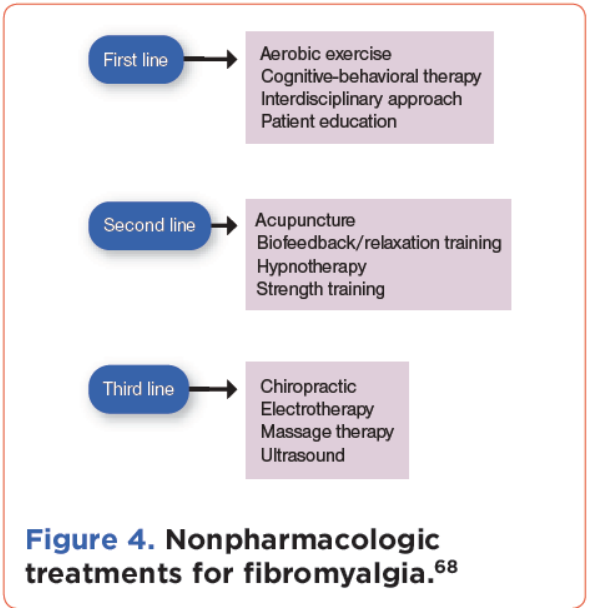


Figure 4. Nonpharmacologic treatments for fibromyalgia.[68]

The last two recommendations for fibromyalgia treatment involve food and nutrition. There are several foods that are known to cause discomfort or increase pain symptoms in FM patients. Research shows that at least half of the people with FMS or ME/CFS get significant relief from symptoms - including pain, fatigue, headaches, bloating and breathing difficulties - by eliminating certain foods. The most common problem foods are corn, wheat, dairy, citrus, sugar, and vegetables in the nightshade family: but it varies from person to person. In addition to diet changes, may doctors also recommend that FM patients introduce B vitamins, especially B-12, into their health regime. B vitamins are essential for energy production, and a few studies show the majority of FM patients are low in B12. Some experts on these illnesses recommend at least 50 mg daily of most B vitamins, and 500 micrograms of B12. Several treatment protocols use B12 injections. Many FM patients are B-12 deficient which leads to nerve dysfunction in the brain (fibro fog/cognitive impairment), the spinal cord (degeneration of the cord), and in the peripheral never (which means damage to the nerve sensors which can cause muscle spasms, weakness, cramping, pain, tingling, numbness, loss of balance among others).

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