Fibromyalgia:
A Journey from Rheumatism to Post-Covid Syndrome

Thesis Paper for Physical Medicine and Rehabilitation PhD Program

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Fibromyalgia: What is its aetiology and does Post-Covid Syndrome have a similar causation.

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Purpose: This paper explores the history and evolution Fibromyalgia Syndrome (FMS) while reviewing proposed aetiologies and pathogenesis. We will postulate the most likely cause or set of causes for FMS and compare these to the rapidly emerging hypotheses on Post Covid-19´ syndrome. As most journey do, we will begin at the beginning and discuss what FMS is and how it began.

FMS: Intro.

Fibromyalgia syndrome (FMS) is a chronic condition characterised by generalized body pain, fatigue, and sleep disturbance. To date, despite advancements in science, medicine, and an abundance of research on Fibromyalgia, the aetiology is unknown with both diverse and divergent speculations. Proposed causes have included genetic, traumatic / inflammatory, immunologic, neurologic, psychologic, gastrointestinal, and sleep pathologies.[1] The pathophysiology of the disease is also not clearly understood, although abnormality in pain processing at various levels (peripheral and central), sleep impairment, dysregulation of the hypothalamo–pituitary–adrenal axis, and abnormalities of the autonomic nervous system have been identified as contributory factors.

This paper delves into several topics concerning FMS and takes the reader on a journey from when Fibromyalgia was first described as Rheumatism through many of its proposed aetiologies and pathogenesis to finally a brief glimpse into Covid-19´s post virus syndrome and the similarities it has to Fibromyalgia. As most journey do, we will begin at the beginning and discuss what FMS is and how it began.

FMS: What is it?

Fibromyalgia is a chronic, long-term illness characterized by widespread intermittent musculoskeletal pain accompanied by fatigue and sleep issues. It is the second most common multisystem rheumatologic pain disorder, after osteoarthritis.[2]
As stated, there is no known accepted cause or pathogenesis, although certain factors such as stress and genetics may be predisposing factors.

Is Fibromyalgia a disease, syndrome, or disorder?

A **syndrome** is a recognizable complex of symptoms and physical findings which indicate a specific condition for which a direct cause is not necessarily understood. For example, we refer to the infamous “viral syndrome” as such because of the uncertainty regarding the legion of viral agents that is causing the illness. Once medical science identifies a causative agent or process with a fairly high degree of certainty, we may then refer to the process as a **disease**, and not a syndrome.[3]

In 1994, International Classification of Diseases (ICD-10) listed FM under “diseases of the musculoskeletal system and connective tissue.” [3] However, if a defined etiology and pathophysiology are required for the definition of a disease, then FM is not a disease but does meet the criteria of a syndrome.

A disorder, according to healthwriterhub.com, is the disruption to the normal or regular functions in the body or a part of the body. For example, a disorder resulting from cardiovascular disease is an arrhythmia or irregular heartbeat. An arrhythmia is not a disease itself – it's an abnormal heartbeat that occurs because of having cardiovascular disease. In this context, FM is a chronic pain disorder resulting from a disease of unknown cause aka a syndrome.

A **disease** is a pathophysiological response to internal or external factors.
A **disorder** is a disruption to regular bodily structure and function.
A **syndrome** is a collection of signs and symptoms associated with a specific health-related **cause.**

FMS: History. (Arthritis Natural Research Foundation [4])

European literature contains descriptions of musculoskeletal pain dating back to the 16th century. By the 18th century physicians began to distinguish articular rheumatism with deforming features from non-deforming painful soft tissue musculoskeletal disorders - referred to as muscular rheumatism. In 1841 by Valleix, a French paediatrician, put forward the idea of trigger points causing referred pain. He suggested that muscular rheumatism was in fact a form of neuralgia. Other suggestions at the time included functional changes to the muscles themselves (Inman 1858) causing muscular spasms or according to Cornelius (1903) the pain was a result of hyperactivity of nerve endings.

The German/Scandinavian physicians assumed that there was an exudative proliferative process occurring within the muscles themselves rather than in the connective tissues. In the late 1800s, Beard, an American neurologist, referred to a condition that included widespread pain, fatigue and psychological disturbances. He called this condition neurasthenia/myelasthenia.

At the turn of the century, British neurologist Sir William Gowers introduced the term "fibrositis", which was used for the next 72 years. Symptoms included spontaneous pain and asymptomatic sensitivity to mechanical compression, fatigue, sleep disturbances, and aggravation of symptoms by exposure to acute and chronic cold and muscular overstrain. In 1909, Sir William Osler, put forward that muscular rheumatism involved "neuralgia of the sensory nerves of the muscles." Ambiguity of physical manifestations, inconsistency of histological changes and a lack of specific diagnostic tests hindered a wide recognition of fibrositis by North American physicians.

During World War 2, a high occurrence of Fibrositis among soldiers drew attention to the condition. The absence of inflammation or degeneration, as well as the association with depression and stress, led Boland and Corr (1943) to label the condition as "psychogenic rheumatism".

Hugh Smyth, a Canadian physician, laid the foundation of modern FMS in 1972 by describing widespread pain and tender points. This was the first time FMS was designated exclusively as a generalized pain syndrome incorporating fatigue, lack of sleep, morning stiffness, emotional distress, multiple tender points and factors that either relieved or aggravated the condition.

Smythe provided a working set of diagnostic criteria based on his anecdotal observations. He specified sites of tender points which were used in the 1990 American College of Rheumatology (ACR) criteria.

In 1975, Moldofsky carried out the first sleep ECG study, demonstrating the role of sleep in FMS. Smyth and Moldofsky asserted that "the existence of exaggerated tenderness at anatomically reproducible locations is central to acceptance and recognition of the syndrome." In 1976, Dr P.K. Hench was the first to use the modern term Fibromyalgia.

Mohammed Yunus conducted a study including a cohort of FMS patients matched with healthy control subjects. This study confirmed that the symptoms characteristic of FMS were significantly more common as well as more severe in FMS patients. Additional symptoms, including swelling of tissues, paresthesia, headaches and irritable bowel syndrome were also shown to be considerably increased in FMS patients.

FMS: Symptomatology.

Widespread muscle and joint pain along with fatigue and sleep problems are the defining symptoms of Fibromyalgia.

Pain and stiffness can occur in muscles and joints throughout the body. Commonly impacted areas include the spine, torso, and pelvic / shoulders girdles. Mid-Scapula and Cervicothoracic pain are often reported. Pain may be either a general soreness or a gnawing ache, and stiffness is often worst in the morning. Numerous "tender points," specific areas that are painful to touch, are also present in patients suffering from FMS. The allodynia felt at these tender points was previously pathognomonic for FMS.

Most people with Fibromyalgia feel abnormally tired, even though they may have slept well. However, fatigue is most likely linked to insomnia and various other sleep issues frequently seen with FMS.

FMS affects people differently. Most common symptoms include (CDC[5])

- Pain and stiffness all over the body
- Fatigue and tiredness
- Depression and anxiety
- Sleep problems
- Problems with thinking, memory, and concentration
- Headaches, including Migraines

Other symptoms may include: (CDC[5])

- Pain in the face or jaw, including TMJ.
- Digestive problems, such as abdominal pain, bloating, constipation, GERD and IBS.
- Tingling or numbness in hands and feet.

Fibromyalgia flare-ups / increase in symptom presentations and or severity can be caused by a variety of everyday factors including: (CDC[5])

- Changes in daily routines.
- Dietary changes or a poor diet
- Hormone fluctuations.
- Lack of sleep.
- Stressors such as work-related, illness, emotional stress.
- Treatment changes.
- Change in sleep patterns (for example, shift work).
- Weather or temperature changes.

FMS: Epidemiology.

According to ACR (American College of Rheumatology, Fibromyalgia is most common in women (80-90% [32]), though it can occur in men. It most often starts in middle adulthood but can occur in children and in old age. Up to 20% of patients who suffer from other chronic rheumatic diseases such as osteoarthritis, lupus, rheumatoid arthritis, ankylosing spondylitis and sarcoidosis also suffer from FMS. FMS is also a genetic predisposition. If a parent or sibling has FMS, there is a higher likelihood of diagnosis.

Estimated prevalence rates for FMS are 0.5% to 5.8% in North America and Europe.[6]

The Canadian Guideline for FMS[10] reports that:

- Chronic widespread pain remains the core symptom of Fibromyalgia, reported as diffuse, fluctuating and with neuropathic features among some patients.
- Fatigue is present in more than 90% of patients with Fibromyalgia.
- Abnormal sleep with prolonged sleep latency, sleep disturbance and fragmented sleep occurs in up to 75% of patients.
- Cognitive dysfunction is associated with pain disorders and includes poor working memory, free recall and verbal fluency, and spatial memory alterations.
- Mood disorder, including depression, anxiety, or both, is present in up to 75% of patients with Fibromyalgia.

FMS: why women?

The differences in gender ratios between clinical and epidemiological studies might be explained by:
1. Tender points are more frequently reported by women than by men in the general population.[7]
2. In Western countries, women consult the health care system more frequently than men in cases of somatic and psychological symptoms.[8]
3. As FM is regarded to be a "disease of women," physicians may neglect to consider this diagnosis when a man presents with chronic widespread pain, and/or a man may wish to avoid the stigma of a diagnosis of a predominantly female condition. [9]

FMS: Diagnosis.

The diagnosis of FMS requires a history of a cluster of symptoms that define the disorder according to expert consensus and clinical studies. The diagnosis of FM is made if the symptoms reported by the patient meet predefined criteria and if other somatic diseases sufficiently explaining the symptoms are excluded.

Fibromyalgia was initially defined by the American College of Rheumatology (ACR) in 1990, as chronic widespread pain identified in all 4 quadrants of the body and axial for at least 3 months and “tenderness” in at least 11 of 18 defined specific locations, “tender points.” (Figure 1.)

In the current revision of the (ACR) provisional criteria, tender points have been eliminated. The most important diagnostic variables were Widespread Pain Index (WPI) (Figure 2) and categorical scales for cognitive symptoms, unrefreshed sleep, fatigue, and a number of somatic symptoms 3 months or greater and not caused by another disorder that would explain the pain. The categorical scales were summed to create a Symptom Severity Scale (SS). (Figure 3.)

Figure 1

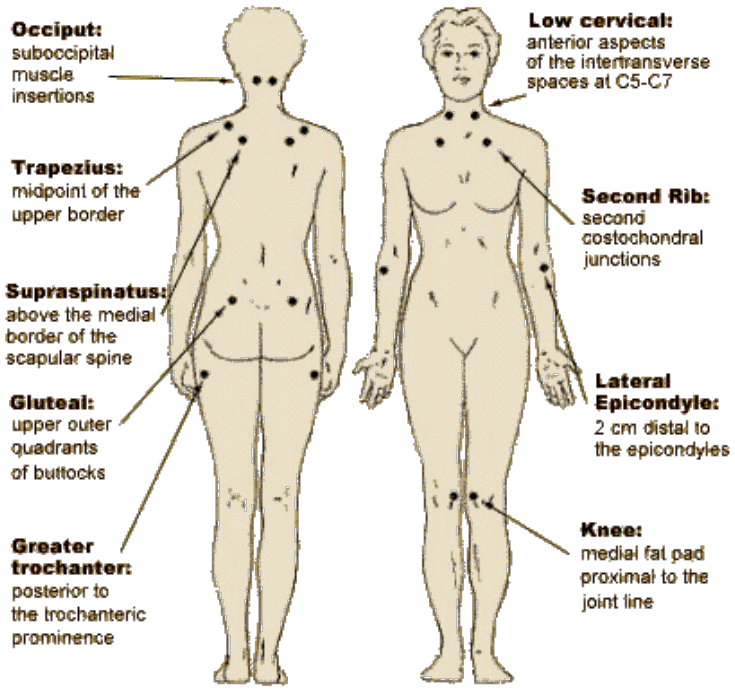
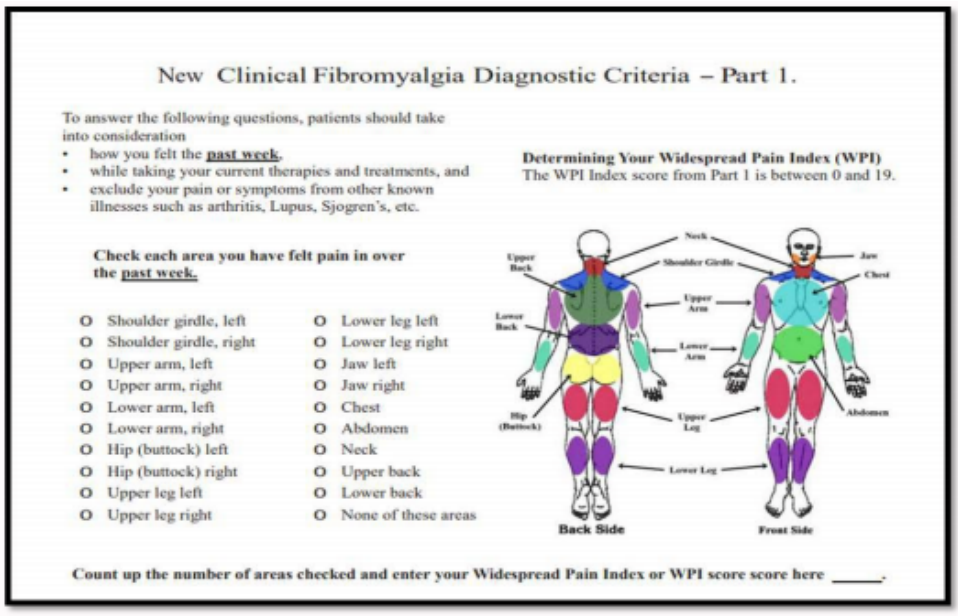


Figure 2



New Clinical Fibromyalgia Diagnostic Criteria – Part 1.

To answer the following questions, patients should take into consideration

- how you felt the **past week**.
- while taking your current therapies and treatments, and
- exclude your pain or symptoms from other known illnesses such as arthritis, Lupus, Sjogren's, etc.

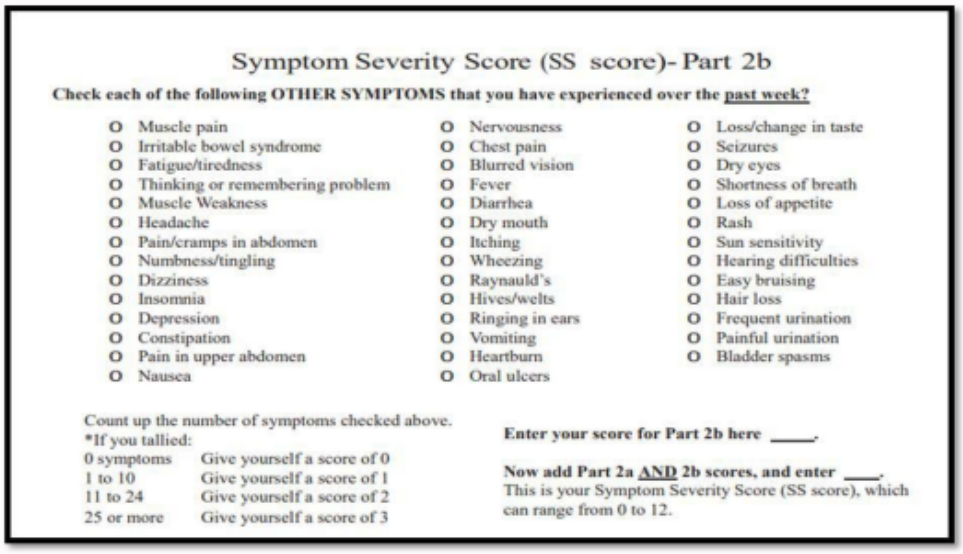
Determining Your Widespread Pain Index (WPI)
The WPI Index score from Part 1 is between 0 and 19.

Check each area you have felt pain in over the past week.

- O Shoulder girdle, left
- O Shoulder girdle, right
- O Upper arm, left
- O Upper arm, right
- O Lower arm, left
- O Lower arm, right
- O Hip (buttock) left
- O Hip (buttock) right
- O Upper leg left
- O Upper leg right
- O Lower leg left
- O Lower leg right
- O Jaw left
- O Jaw right
- O Chest
- O Abdomen
- O Neck
- O Upper back
- O Lower back
- O None of these areas

Count up the number of areas checked and enter your Widespread Pain Index or WPI score score here _____.

Figure 3



Symptom Severity Score (SS score)- Part 2b

Check each of the following OTHER SYMPTOMS that you have experienced over the past week?

- O Muscle pain
- O Irritable bowel syndrome
- O Fatigue/tiredness
- O Thinking or remembering problem
- O Muscle Weakness
- O Headache
- O Pain/cramps in abdomen
- O Numbness/tingling
- O Dizziness
- O Insomnia
- O Depression
- O Constipation
- O Pain in upper abdomen
- O Nausea
- O Nervousness
- O Chest pain
- O Blurred vision
- O Fever
- O Diarrhea
- O Dry mouth
- O Itching
- O Wheezing
- O Raynauld's
- O Hives/welts
- O Ringing in ears
- O Vomiting
- O Heartburn
- O Oral ulcers
- O Loss/change in taste
- O Seizures
- O Dry eyes
- O Shortness of breath
- O Loss of appetite
- O Rash
- O Sun sensitivity
- O Hearing difficulties
- O Easy bruising
- O Hair loss
- O Frequent urination
- O Painful urination
- O Bladder spasms

Count up the number of symptoms checked above.
*If you tallied:

0 symptoms	Give yourself a score of 0
1 to 10	Give yourself a score of 1
11 to 24	Give yourself a score of 2
25 or more	Give yourself a score of 3

Enter your score for Part 2b here _____.

Now add Part 2a AND 2b scores, and enter ____.
This is your Symptom Severity Score (SS score), which can range from 0 to 12.

New proposed diagnostic criteria for FMS:

Wolf et al (2010) combined the WPI and the SS scale to recommend new diagnostic criteria for Fibromyalgia: (WPI > or =7 AND SS > or =5) OR (WPI 3-6 AND SS > or =9).[26]

Boomershine et al, [25] conducted comprehensive evaluation of the standardized assessment tools for diagnosing FMS and assessing the severity of symptomatology. Their findings are summarized in figure 4 below.

Recommended assessments for fibromyalgia diagnosis and core symptom domains.

Symptom domain	Assessment
Diagnosis	1990 ACR fibromyalgia classification criteria utilizing the MTPS
Pain intensity	NRS from question 5 of the BPI
Physical functioning	FIQR physical functioning subscale
Overall/Global improvement	PGIC and FIQR global score
Depression	HADS-D
Cognitive dysfunction	MASQ
Fatigue	FSS
Multidimensional function/health-related quality of life	FIQR
Sleep disturbance	JSS
Tenderness	MTPS-FIS

ACR: american college of rheumatology, BPI: brief pain inventory, FIQR: revised fibromyalgia impact questionnaire, FIS: fibromyalgia intensity score, FSS: fatigue severity scale, HADS-D: depression subscale of hospital anxiety and depression scale, JSS: jenkins sleep scale, MASQ: multiple abilities self-report questionnaire, MTPS: manual tender point survey, NRS: numeric rating scale, PGIC: patient global impression of change.

Figure 4

According to the Canadian Fibromyalgia Guidelines: [10]

1. The diagnosis of FMS is made based on a composite of symptoms, centred on chronic widespread pain and absence of physical findings that would indicate another condition.
2. Clinical evaluation should include a history of physical and mental health, with attention to the patient's psychosocial context, because these factors may influence the expression of fibromyalgia.
3. A physical examination is required for all patients, and findings may be completely within normal limits.
4. Examination for tender points is not required to confirm the diagnosis.
5. Only limited laboratory testing should be conducted for most patients.

Laboratory Testing:

Lab tests of FMS may contain information for both diagnosis and disease progression however as FMS is a diagnosis of exclusion, most of the Lab testing are more helpful in this capacity. Some of the tests that can be applied to a patient who has a suspicion or diagnosis of Fibromyalgia include the following [27]:

1. Kidney and liver function tests
2. Calcium / Phosphate Levels
3. Creatine phosphokinase level
4. Erythrocyte Sedimentation Rate
5. C-reactive Protein
6. Vitamin D
7. Antinuclear Antibody (ANA)
8. HLA-B27

FMS. 4 Classification.

Davis et al [20] describe FMS as a continuum spectrum and identified 4 possible classes of the disease:

Class 1: was represented by a mostly regional FM within the contest of the widespread pain.

Class 2: was characterised by a greater severity of pain, a broader involvement of body regions and several associated symptoms. These two classes represented the most prevalent in the study population, and their clinical phenotype overlaps with the one identified by the diagnostic criteria.

Class 3: was characterised by an increase in the level of pain compared to the previous classes, a strict association with sleep disorders and to the possibility of chemical sensitivity.

Class 4: highest severity - which represented the "secondary FM" to other diseases such as multiple sclerosis and lupus, which had a high prevalence in this class.

They suggest that FM represents a disease continuum in which the centralised pain becomes more centralised as the disease progresses.[20]

FMS: Complications and Associations.

The CDC[4] states that if you have FMS, you will have a lower quality of life, are 2x as likely to be hospitalized as someone without Fibromyalgia and are 3x more likely to have major depression. FMS patients have higher death rates from suicide and injuries and higher rates of other rheumatic conditions - osteoarthritis, rheumatoid arthritis, systemic lupus erythematosus, and ankylosing spondylitis.

FMS is also associated with various other disorders and syndromes including but not limited to the following:

Sleep disorders.
Bigatti found that 90% of patients with FMS complain about sleep problems such as difficulty falling asleep, difficulty falling back to sleep after waking up during nocturnal sleep, and unrefreshing sleep. He suggests that sleep problems play a critical role in exacerbating FMS symptoms and predict subsequent pain in FMS patients.[21]
Several studies conducted by (Lentz et al., 1999[22]; Moldofsky et al., 1975 [23]; Moldofsky & Scarisbrick, 1976 [24]) looked at normal healthy control groups and deprived them of normal sleep periods or disrupted their normal patterns of sleep. All reported increases in musculoskeletal pain and/or decreases in pain threshold after a period of sleep disruption or deprivation. Moldofsky's group found that the stage 4 sleep deprived group also showed a significant increase in muscle tenderness between the baseline and deprivation conditions and an altered pattern of overnight change in muscle tenderness in response to deprivation.

These data indicate that partial sleep deprivation can produce the hallmark symptoms of FMS – namely, musculoskeletal achiness, marked daytime fatigue, and cognitive problems.
Thyroid dysfunction: The CDC[4] that people with Thyroid dysfunction (hypothyroidism) are 30-40% (or higher with newer diagnostic criteria for FMS) more likely to have FMS.

TMJ Syndrome.
The National Institutes of Health (NIH) concluded that nearly 70% of FMS patients experienced facial pain near the TMJs while 35% of the study's participants reported TMJ disorder symptoms such as difficulty opening the mouth and discomfort when eating. The NIH concluded that patients diagnosed with fibromyalgia should also be tested for TMJ disorder.

Irritable Bowel Syndrome.
IBS including altered intestinal motility, visceral hypersensitivity, altered compliance of the gut wall, or any combination of these conditions, is 1.54 more times likely in FMS suffers.[38]

Migraines.
20-36% of patients with migraine also have FMS. Similarly, the frequency of migraine in patients with FM ranges from 45-80%, suggesting that migraine is common in patients with FMS. Penn and Chuang´s were the first to reveal a population-based bidirectional association between onset of FM and that of migraine in patients with migraine and those with FM, respectively.[29]

Lyme Disease.
There is a well-established connection between Lyme disease (caused by Borrelia burgdorferi) and Fibromyalgia. Many patients who have been treated for Lyme, experience unusually high frequency of Fibromyalgia, triggering some to question whether FMS is a non-diagnosed post Lyme Disease Syndrome. Lyme disease may trigger FMS, but antibiotics do not seem to be effective in the treatment of the Fibromyalgia.[30]

FMS: Current Treatments.

Medical sciences may be close to understanding the aetiology of FMS, unfortunately a cure is much further away. The goal of treatment is therefore focused on improving symptoms and optimizing function. However, symptom-based management must consider the heterogeneous nature of Fibromyalgia and the patients suffering from it.[22] The ideal strategy will combine nonpharmacologic and pharmacologic treatments in a multimodal individualized approach.

Management should be directed at the most troublesome symptoms. Patients must be encouraged to be active participants in their health care management, because self-efficacy and adherence to treatment predict improved positive outcomes. The belief that only external factors can influence health, and personality traits such as neuroticism and catastrophizing; predict negative outcomes.[10]

The Canadian Guidelines[10] summarize FMS treatment as such:

1. **General concepts:**

- No single treatment outperforms others, so a multimodal approach is best.
- The outcome goal is symptom control and improved function.
- Patient engagement improves adherence, and treatment failure is associated with passivity, uncontrolled mood disorder, catastrophizing and secondary gain.

2. **Nonpharmacologic treatment:**

- It is essential that nonpharmacologic therapies be incorporated in a treatment plan.
- Coping skills, self-efficacy and patient education form the foundation of self-management.
- Regular exercise should be encouraged for all patients, even though the evidence is currently limited.
- There is insufficient evidence for recommendation of complementary and alternative medicine treatments.

3. **Pharmacologic treatment:**

- Symptom-based management should address individual symptoms of pain, sleep, mood and fatigue, but effects may be modest.
- A “start low, go slow” approach is recommended when starting pharmacologic therapy.
- Drugs with different mechanisms of action may be combined to improve efficacy.
- Throughout treatment, the efficacy and adverse-effect profile should be monitored.

Other treatment options (with varying levels of evidence to support) for FMS include following: [31] Chiropractic, [32] Vagus Nerve Stimulation, [33, 34] Tai chi, yoga, mediation & Biofeedback, [35] Transcranial magnetic stimulation (TMS), [36] Vitamin D [37] and Acupuncture [38]

FMS: Categorizations & Proposed Aetiologies.

As mentioned previously, there has been a myriad of proposed aetiologies as medical sciences continue to better understand and categorize FMS. We will review and discuss what are the most probable candidates. These first 4 topics discussed are medicine´s attempt to categorize FMS and the latter are more plausible causes.

1. Fibromyalgia is a pain disease.

Chronic primary widespread pain, in one or more anatomic regions that persists or recurs for longer than 3 months and is associated with significant emotional distress or significant interference with activities of daily life and participation in social roles and that cannot be better explained by another chronic pain condition.[12]

The new diagnostic criteria for FMS give unrefreshed sleep and fatigue a nearly equal weight for diagnosis and even include depression as a minor symptom,[13] therefore labelling FMS as a mere but noteworthy pain syndrome does not do it justice and is more of a descriptor of the overall outcome of the disorder.

2. Fibromyalgia is a masked depression.

Some believe that FMS is a masked depression or an affective spectrum disorder.[14] The lifetime prevalence of depressive disorders in FMS patients ranges between 40-80%, depending on the criteria used.[15] Not every patient with FMS has depression and not every patient with depressive disorder reports chronic widespread pain. The association of FMS and depressive disorders can be better explained by symptom overlap and shared biological and psychological mechanisms.

The German FMS guidelines clearly state that FMS and depression are not interchangeable, therefore depression is also a likely consequence of the syndrome and not a cause.[16]

3. Fibromyalgia is a persistent somatoform pain disorder.

The absence of a defined aetiology and pathogenesis and the association of FMS symptoms with psychosocial stress prompted the belief that FMS was “persistent somatoform pain disorder.” 60% to 80% of FMS patients meet the diagnostic criterion of either the onset or aggravation of FMS symptoms by psychosocial stress and emotional conflicts.[17]
Again, the German FMS guideline states that FM and persistent somatoform pain disorder are not interchangeable. [16]

4. Fibromyalgia is a somatic symptom disorder (SSD).

The American Psychiatric Association have recently substituted the category “pain disorder” with SSD. The diagnosis of SSD may be made when there are persistent (> 6 months) somatic symptoms that are distressing and/or significantly disruptive of daily life and are accompanied by excessive and disproportionate symptom-related thoughts, feelings, and behaviors.[18] Arguments

can be made that FMS fits this new categorization, but again it does not fully account for all of complexity and multisystem aspects of FMS.

5. Fibromyalgia is a post viral infection syndrome.

The Epstein-Barr virus, influenza viruses, and hepatitis B and C have all been implicated in the development of FMS. Dr. Bruce Solitar, clinical associate professor of medicine at NYU Medical Center/Hospital for Joint Diseases in New York believes it is possible that viral particles attach to glial cells in the brain and affect neurotransmission thereby influencing the pain response. This points more to causality rather than categorization for FMS but could perhaps be more effective in prevention and treatment of FMS. Although it has been postulated that FMS could be a post viral infection, most FMS suffers do not recall a specific precipitating viral illness in proportion to their current symptomatology. In other words, the impact of the initial viral infection was far less than the sequela it caused. This is an important note we will revisit in the Covid section of our journey.

6. Fibromyalgia is Genetic Problem.

Genome-wide association studies investigating genes potentially involved in Fibromyalgia pathogenesis suggest that genetic factors are possibly responsible for up to 50% of the disease susceptibility. [40] FMS is characterized by altered DNA patterns, in genes involved in stress response, DNA repair, autonomic system response, and subcortical neuronal abnormalities. MicroRNAs differences were also found in multiple tissues, indicating the involvement of distinct processes in Fibromyalgia pathogenesis.[40] Again, pointing more to a potential causation of FMS and perhaps more to the likely multifactorial causality of FMS.

7. It is a Microbiome & Gut Health problem.

The composition of the gut bacterial community is altered in individuals with FMS. Approximately 20 different species of bacteria were found in either greater or lesser quantities in the microbiomes of FMS patients. Some of these species have established metabolic activity which could have pertinence in the expression of FM symptoms. The putative mechanisms which could allow these bacterial species to affect pain, fatigue, mood, and other symptoms include the entry of short-chain-fatty-acids, bile acids, neurotransmitters, and bacterial antigens into the host circulation.[28]

Dr. Amir Minerbi of the Alan Edwards Pain Management Unit at the McGill University Health Centre (MUHC) stated, “We used a range of techniques, including Artificial Intelligence, to confirm that the changes we saw in the microbiomes of Fibromyalgia patients were not caused by factors such as diet, medication, physical activity, age, and so on, which are known to affect the microbiome.” [28] Research on the microbiome and its link to immunology and now even to neurophysiology is rampant but still in its infancy. As more is discovered in the fascinating field, we will uncover links to endless unknown pathological processes.

8. Fibromyalgia is Neurological problem.

Which leads us to the last category and most promising theory regarding FMS, that it is a complex neurological problem. It is a syndrome of abnormal central pain processing and increased central sensitivity caused by neurobiological changes that cause dysregulation of mechanisms that normally regulate pain sensation. It is therefore considered one of the most common central sensitivity syndromes (CSS).

Central sensitization (CS) refers to the amplification of the signaling of neurons within the central nociceptive pathway secondary to increased release of excitatory neurotransmitters, enhanced synaptic sensitivity and decreased inhibition. This clinically manifests as mechanical hypersensitivity, allodynia and hyperalgesia. CS pain represents the augmentation of a broad spectrum of noxious sensory experiences in a pathologic excitatory feedback loop.[19]

The Canadian guidelines[10] describes several neurological pathologies associated with but not unique to, FMS, including central sensitization at the level of the dorsal horn, peripheral sensitization at the primary somatosensory neuron, changes in the thalamus and brain gray matter, and impairment of the natural pain inhibition mediated via descending pathways from the brainstem to the dorsal horn of the spinal cord (diffuse noxious inhibitory control). [10]

In Häuser & Fitzcharles[12] paper regarding FMS, they state that the best-established pathophysiological features of FMS are those of central sensitization, with increased functional connectivity to pronociceptive brain regions and decreased connectivity to antinociceptive regions and accompanying changes in CNS neurotransmitters. They also noted changes in the size and shape of brain regions.[12]

So, what is the most probable cause of FMS?

In my opinion, as many before me have postulated it is multifactorial. I believe there is a genetic predisposition that is triggered by a dysfunctional immune system (a compromised gut microbiome and unresolved viral assault) resulting in a central sensitization and neural adaptation.

This ends our review and discussion of FMS, we will now continue our journey with an introduction to Covid-19 and its post infection syndrome, concluding with a comparison of the two.

Post-Covid Syndrome – any connection to FMS?

Does Post-Covid Syndrome (PCS), otherwise known as Long Haul Syndrome, have any connection to Fibromyalgia which may, as we have discussed earlier, be a post-viral syndrome as well? Let´s begin this discussion by examining what Covid and Post-Covid Syndrome are.

What is Covid?

The COVID-19 pandemic is currently a serious global public health concern. This disease is caused by a novel coronavirus (SARS-CoV-2) which was first discovered in Wuhan, China in 2019 and spread in epidemic proportions throughout the world.

Symptoms include fever, cough, encephalitis, myalgia, fatigue, muscle weakness, arthralgia, anosmia, and impairment in other bodily functions in the acute phase. In 17% to 67% of cases, COVID-19 patients will develop acute respiratory distress syndrome (ARDS) and critical illness. Covid not only impacts the respiratory system, but it can also affect the central nervous system, cardiovascular system, musculoskeletal system, and gastrointestinal system.[41]

What is Post-Covid Syndrome?

Maltezou et al[41] describe post-COVID syndrome as a new clinical entity in the context of SARS-CoV-2 infection. Symptoms persisting for more than three weeks after the diagnosis of COVID-19 characterize the post-COVID syndrome. Its incidence ranges from 10% to 35%, however, rates as high as 85% have been reported among patients with a history of hospitalization. Currently, there is no consensus on the classification of post-COVID syndrome.[42]

The pathogenesis of post-COVID syndrome is multifactorial and more than one mechanism may be implicated in several clinical manifestations. Prolonged inflammation has a key role in its pathogenesis and may account for some neurological complications, cognitive dysfunction, and several other symptoms. Other pathogenetic mechanisms that are implicated in post-COVID syndrome include immune-mediated vascular dysfunction, thromboembolism, and nervous system dysfunction. [42]

The NIH termed the syndrome, post-acute sequelae of SARS-CoV-2 infection (PASC). It is like post-ICU syndrome in critically ill patients, however PASC symptoms may occur even in the absence of ICU admission. Diagnostic Criteria for PASC are included in Figure 5 on the following page. [35]

The Mayo Clinic multidisciplinary COVID-19 Activity Rehabilitation Program (CARP) program Post- Covid / PASC found that patients presented with diverse and complicated symptoms including respiratory (23%) and mental health, including depression and/or anxiety (34%.) The majority (75%) had not been hospitalized for COVID-19 / PASC.[43]

Common presenting symptoms were fatigue (80%), respiratory complaints (59%), and neurologic complaints (59%) followed by subjective cognitive impairment, sleep disturbance,

and mental health symptoms. More than one-third of the patients (34%) reported difficulties with performing basic activities of daily living. Only 1/3 patients had returned to unrestricted work duty at the time of the analysis. For most patients, laboratory and imaging studies were normal or non-diagnostic despite debilitating symptoms.[43]

Most of the patients did not have COVID-19 / PASC related symptoms that were severe enough to require hospitalization, were younger than 65 years, and were more likely to be female, and most had no pre-existing comorbidities before severe acute respiratory syndrome coronavirus infection. Symptoms including mood disorders, fatigue, and perceived cognitive impairment resulted in severe negative impacts on resumption of functional and occupational activities in patients experiencing prolonged effects.[43]

Commonalities.

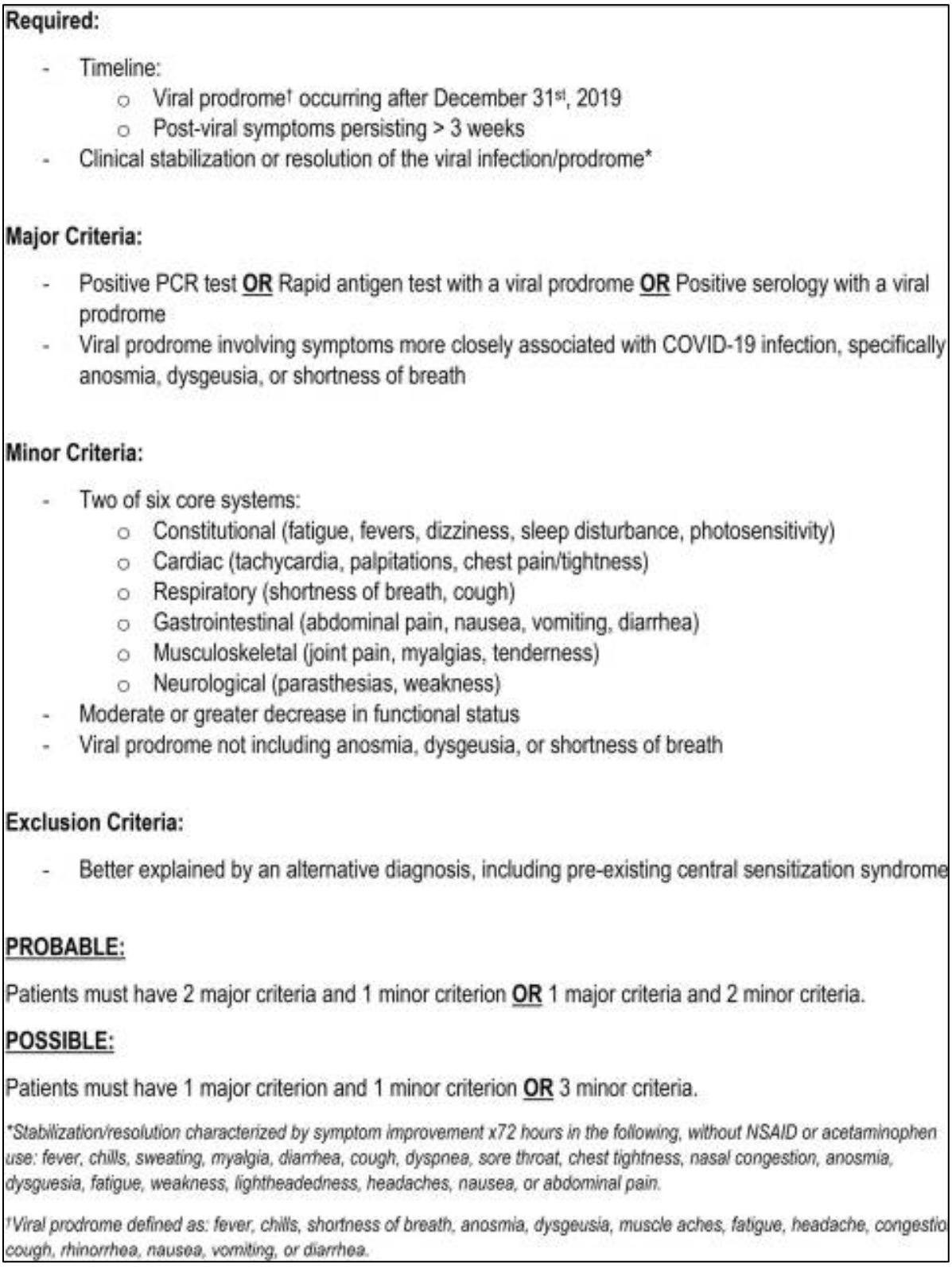
- Post-viral cause
- Sequelae far outweighed the initial viral infection
- Impacts women more than men
- Fatigue
- Pain & other neurological symptoms like headaches and migraines
- Difficulty concentrating or focusing
- Difficulty sleeping
- Exercise intolerance
- Depression
- Anxiety
- Mood Disorders
- Normal Lab results

The above symptoms are notably consistent with other post-infectious syndromes and central sensitization syndromes (CSS) such as FMS and Chronic Fatigue Syndrome (CFS). As more info becomes available regarding PASC, it is manifesting more congruent with the latter. FMS and CFS are very analogous with the degree of fatigue associated being the greatest differentiation between them.

Fatigue is also one of the core symptoms in central sensitisation disorders, leading to the hypothesis that central sensitisation might be the underlying common etiology in chronic pain patients and PASC patients. [42] In fact, Harvard Health reported that Dr. Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, has speculated that PASC likely is very similar to Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS).

ME/CFS can also be triggered by other infectious illnesses — such as mononucleosis, Lyme disease, or severe acute respiratory syndrome (SARS), another coronavirus disease.

Fig 5



Required:

- Timeline:
  - Viral prodrome† occurring after December 31st, 2019
  - Post-viral symptoms persisting > 3 weeks
- Clinical stabilization or resolution of the viral infection/prodrome*

Major Criteria:

- Positive PCR test **OR** Rapid antigen test with a viral prodrome **OR** Positive serology with a viral prodrome
- Viral prodrome involving symptoms more closely associated with COVID-19 infection, specifically anosmia, dysgeusia, or shortness of breath

Minor Criteria:

- Two of six core systems:
  - Constitutional (fatigue, fevers, dizziness, sleep disturbance, photosensitivity)
  - Cardiac (tachycardia, palpitations, chest pain/tightness)
  - Respiratory (shortness of breath, cough)
  - Gastrointestinal (abdominal pain, nausea, vomiting, diarrhea)
  - Musculoskeletal (joint pain, myalgias, tenderness)
  - Neurological (parasthesias, weakness)
- Moderate or greater decrease in functional status
- Viral prodrome not including anosmia, dysgeusia, or shortness of breath

Exclusion Criteria:

- Better explained by an alternative diagnosis, including pre-existing central sensitization syndrome

PROBABLE:

Patients must have 2 major criteria and 1 minor criterion **OR** 1 major criteria and 2 minor criteria.

POSSIBLE:

Patients must have 1 major criterion and 1 minor criterion **OR** 3 minor criteria.

**Stabilization/resolution characterized by symptom improvement x72 hours in the following, without NSAID or acetaminophen use: fever, chills, sweating, myalgia, diarrhea, cough, dyspnea, sore throat, chest tightness, nasal congestion, anosmia, dysguesia, fatigue, weakness, lightheadedness, headaches, nausea, or abdominal pain.*

†Viral prodrome defined as: fever, chills, shortness of breath, anosmia, dysgeusia, muscle aches, fatigue, headache, congestio cough, rhinorrhea, nausea, vomiting, or diarrhea.

Figure 5 Oronsky, B., Larson, C et al 2021. A Review of Persistent Post-COVID Syndrome (PPCS). Clinical Reviews in Allergy and Immunology.

Conclusion.

This concludes our journey. What is abundantly clear throughout time and literature is that more research is needed to fully understand FMS. The ideologies that genetics and immunology (gut health and post viral responses), are involved in causality are quite strong and will continue to evolve as with advancements in those fields. The more recent developments and higher understanding of central sensitization will also continue to aid in our overall understanding of FMS.

As more time passes, we will also develop new and stronger understandings of PASC and with it having more current and worldly implications, perhaps it will help to unlock the mystery of FMS.

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