**Background:**

Presentation & Epidemiology - Fibromyalgia (FM) & Chronic Fatigue Syndrome (CFS) is a common Neuro-Musculoskeletal (MSK) condition affecting 2-4% of the population with a F > M incidence ratio of 9:1 & involving widespread aches & pains, fatigue, characteristic tender if not trigger points, alldynia, & other symptoms ranging from TMJ syndrome, to muscle spasms, neuritic pains with paresthesias, to sleep disturbances with non-restoreative sleep, & cognitive dysfunction known as "brain fog". It is associated with depression & psychiatric co-morbidities & multi-system involvement such as Irritable Bowel Syndrome (IBS). Typically, symptoms wax & wane fueled by stress and/or illness. Clinicians are frequently confronted establishing a diagnosis of FM/CFS when evaluating patient’s with chronic disabling widespread symptoms (~15% of MSK). Diagnosis of FM/CFS is a common diagnostic dilemma in rheumatology, neurology, psychiatry, & internal medicine. It is critical to avoid misclassification of a distinct disease entity under the rubric of ‘FM & CFS’ & thus through H & P supported by labs &/or radiology is required.

**Differential Diagnosis:** Diseases that mimic FM & CFS -

- **Rheumatic Diseases**: Rheumatoid arthritis (RA), SLE, Spondyloarthopathies- Ankylosing spondylitis (AS), Reiter’s Syndrome, Enteropathic Arthritis, e.g., Arthritis associated with Inflammatory Bowel Disease (IBD), Psoriatic Arthritis, Scleroderma, Sjogren’s Syndrome, Polymyalgia Rheumatic (PMR), & ‘Overlap Syndromes’, can mimic FM & CFS. RA may be confused with FM in the early stages given diffuse arthralgia, stiffness, female predominance & age of onset. Careful history, serial exams & judicious labs is key, including ESR, CRP, Anticyclic citrullinated peptide Ab. Note: ~15% of RA pts have concomitant or secondary FM. SLE can also have similarities in that both disorders have fatigue, arthralgia, myalgia, & F >> M population. ~95% have a +ANA, but ~9% of FM patients have a weakly +ANA as well. Features such as nephropathy, hematopoietic & skin changes, point towards SLE. Note: ~10% of SLE pts can have FM. PMR is a common inflammatory condition confused with FM esp. in aging women presenting with myalgia, proximal weakness & arthralgia. Differentiating features: Age >50, ↑↑ ESR, association with Giant Cell arteritis (headache & jaw pain). Repeat opt pain due to dural & meningeal irritation. Spondyloarthopathies usually involve axial >appendicular joints, LE=UE joints, M > F ratio 3:1. Insidious onset of fatigue, generalized weakness & tender points may suggest FM. Clues include morning stiffness that improves with exercise rather than rest, restricted spinal mobility, insertion tendinopathy (enthesisopathy) at heels, ribs, scapulae, hips; uveitis (AS, Reiter’s), skin (Psoriatic) lesions, HLAB27 association & sarcoiditisis on imaging. FM patients can have coexistent Irritable Bowel Syndrome & thus can be confused with early Enteropathic arthritis associated with Inflammatory Bowel Disease (IBD), Enteric infections & Celiac Disease. The incidence of joint involvement in IBD can be 5-15%, involving both spine & peripheral joints. An acute or chronic relapsing arthritis may occur closely following the clinical course of bowel involvement more so in UC than Crohn’s. Asymptomatic nondestructive oligoarthritis starting weeks after a bout of gastroenteritis in otherwise healthy individuals should raise suspicion of Reactive Arthritis secondary to Gram- enteric bacterial infections (Campylobacter, Salmonella, Shigella). Gluten enteropathy (Celiac Disease) presents with joint symptoms in 25% of pts. Celiac disease Abs & endoscopic endomyosal biopsy is often diagnostic.

- **Primary Muscle Diseases/NMJ Disorders**: Inflammatory Myopathies: Poly/Dermatomyositis(PM/DM), Inclusion Body Myositis (IBM), Limb-Girdle & Myotonic Dystrophy, Metabolic Myopathies (McArdle’s), Neuromuscular Junction (NMJ) Disorders-Myasthenia gravis (MG) & Lambert-Eaton Syndrome (LEMS) uniformly present with proximal & distal weakness, fatigue with or without pain. PM/DM commonly presents sub-acute with proximal muscle weakness, fatigue & myalgias. It has a bimodal age distribution (5 -14 & 45-65); Incidence 0.2-0.9/100 K. DM associated with erythematous rash on face & limbs raises concern for underlying malignancy. Diagnosis is supported by ↑CPK, + EMG & muscle biopsy for myositis/myopathy. 20% PM/DM have ‘Overlap Syndromes’ with other Connective Tissue disorders- Scleroderma, Sjogren’s, SLE & RA. Inclusion Body Myositis/IBM is a distinct entity 1° affecting adults > 50 presenting insidiously with weakness, fatigue LE=UE (quadriceps esp. involved), ↑CPK, & myopathic EMG. Muscle biopsy shows intranuclear/intracytoplasmic inclusion filaments by EM. NMJ disorders as MG (F > M; 7:3) & LEMS presents with insidious onset fatigue & weakness. McArdle’s Disease is a rare condition due to Myophosphorylase deficiency having features of poor exercise tolerance, cramps, fatigue, ↑CPK, abnormal repetitive NCS & + ischemic forearm test for blood lactate.

- **Infectious Etiologies**- Lyme Disease, HIV, Parasitic, Viral, i.e. Parvovirus B19, Bacterial (Whipple’s), Hep. B & C. In Lyme Disease, > 50% have MSK symptoms in all disease stages with features of migratory polyarthalgias, myalgias & neuropathies in association with CFS. Careful history & serologic tests helps in isolating this viral infection. HIV is associated with a myriad of MSK presentations to include: Myalgias (33% prevalence), HIV associated PM is a presenting symptom in some- Incidence 2.2/1000 in one large series, rarely with rhabdomyolysis. 11% of HIV pts. have concomitant FM/CFS. After Epstein-Barr virus related Mononucleosis & Parvovirus B-19 infection associated with an initial bout of acute polyarthritis, a minority of pts. may experience chronic relapsing arthralgias, morning fatigue & stiffness due to recurrent synovitis. Chronic relapsing debilitating arthralgias may also be a long term sequela of mosquito borne α-virus infections in travelers to Africa, Asia and Oceania- Chikungunya & Ross River Virus. Hepatitis B & C viremia can present with malaise, myalgia & arthralgias without fever or jaundice in an extended prodromal phase of the illness.

- **Endocrine Disorders**- Thyrotokisosis, Hypothyroidism (Myxedema), Cushing’s, GH Deficiency may all mimic FM/CFS.

- **Miscellaneous**- Drug induced Myopathy (Zidovudine, Statins, Corticosteroids, Interferon), Vasculitis, Sarcoidosis, Vit. D deficiency, Light chain Amyloidosis, can also mimic FM/CFS. The later can present insidiously in middle to older age with fatigue, weakness, myalgia, arthralgias, neuropathy (ranging from CTS to mononeuritis multiplex) & multisystem organ involvement. Timely immunofixation electrophoresis helps with diagnosis. Sarcoidosis can be confusing to the clinician as there is no specific test, but early on, can present with features similar to FM/CFS. Recognizing the total clinical picture is helpful. Elevated serum or CSF ACE can be useful.

**Conclusion**- There are many conditions presenting with a common theme of fatigue, generalized weakness, & focal or diffuse MSK pain early in the course of the illness, although over time & sometimes steadily, the presentation transitions into more distinct entities that are not 1° FM &/or CFS. One must maintain a high index of suspicion for alternative diagnoses before concluding FM/CFS. Careful history, thorough physical examination & judicious use of labs & imaging studies is paramount.

‘FM/CFS’ remains difficult to manage, but there are newer treatment options with + response in many. This includes FDA approval for TCA & mixed agents such as Cymbalta/Duloxetine & AED such as Lyrica/Pregabalin.