EDITOR'S PICK

In this specially selected article, Fleming gives a fascinating insight into the controversial field of fibromyalgia and polysymptomatic distress disorders. These conditions present with a diverse array of symptoms posing diagnostic challenges which many clinicians will face at some point in their career. The unifying central sensitisation theory discussed provides solace for patients and physicians alike, potentially elucidating the pathophysiology of the disorders and their medically unexplained symptoms. The author goes on to provide useful diagnostic and management strategies which have the potential to raise the standard of care in these common, yet poorly understood, conditions.

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CLINICAL MANAGEMENT OF FIBROMYALGIA AND THE CONTINUUM OF POLYSYMPTOMATIC DISTRESS DISORDERS

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ABSTRACT

The evaluation of patients with fibromyalgia (FM) and other functional somatic syndromes can appear intimidating, but a high index of suspicion and a more systematic approach can improve provider efficiency, reduce frustration, and improve the care experience. FM is a dimensional rather than a categorical disorder, reflecting a continuous spectrum of physical symptoms; it is formally diagnosed after reaching a critical mass of widespread pain and symptom severity. Central sensitisation is a maladaptive neuroplastic response in the higher brain neural pain network that accounts for FM symptoms. Rheumatologists are a scarce medical resource, so their involvement in FM can be considered along 'focussed factory' or 'solution shop' approaches. Multimodal FM treatments should include pharmacologic and nonpharmacologic therapies including cognitive therapies, graded exercise, and stress management.

Keywords: Central sensitisation (CS), fibromyalgia (FM), polysymptomatic distress (PSD), systems approach.

BACKGROUND

Physicians are frequently faced with patients bearing symptoms that lack the confirmatory or exclusionary tests found in categorical disorders such as hip fracture or myocardial infarction. When individuals present with chronic widespread pain, they often have other medically unexplained symptoms (MUS), referring to symptoms that have little or no apparent basis in organic disease. The reported burden of symptoms is out of proportion with what is expected by examination and testing. While some symptoms may be nonspecific and ambiguous, other MUS present along a continuum of organ or system-specific features and may meet diagnostic classifications for fibromyalgia

(FM), chronic fatigue syndrome (CFS), chronic pelvic pain, chronic abdominal pain, irritable bowel syndrome (IBS), or chronic dizziness. Notably, the prior diagnosis of somatisation has been reclassified as 'somatic symptom disorder,' now referring more to the distress of bodily symptoms (i.e. health anxiety) than to their organicity.[1]

Physicians encountering MUS may develop a 'negative empathy' toward patients, which interferes with the consultation.[2] This unwarranted antipathy can be traced to a myriad of symptoms without explanation, high patient expectations, lengthy visits, and heavy practice demands. Very often, this results in unmet expectations and dissatisfaction with the services provided, however extensive.[3] The difficulty in providing help to these patients may foster negative feelings (counter-transference), stigmatisation, and isolation, to which system constraints and physician attributes are often contributory.[4] For clinical staff, such encounters can result in emotional frustration and burn-out. By recognising the risks for unprofessional behaviour and changing strategies, one can improve the therapeutic alliance and repair the clinical encounter. In this article, we review the shared pathology of patients with MUS and offer a systematic approach to increase provider efficiency, streamline testing, and improve the care experience.

DIAGNOSTIC CONTROVERSY

The symptoms accompanying the primary musculoskeletal complaints in FM overlap considerably with other disorders, such as CFS, IBS, chronic pelvic pain, chronic daily headache, interstitial cystitis, temporomandibular disorder (TMD), and other unexplained symptoms.[5-7] Indeed, the 2010 American College of Rheumatology (ACR) Diagnostic Criteria for Fibromyalgia includes chronic widespread pain, but replaced the 1990 tender point requirement with a Symptom Severity Scale (SSS). This scale includes fatigue, unrefreshed sleep, cognitive complaints, and multiple somatic symptoms. The working diagnoses in patients with MUS can depend on the patient's cardinal complaint, organ system clusters, diagnostic bias, and clinician subspecialty.[8] Patients with one diagnostic category are frequently diagnosed with other functional syndromes.[9] Historically, patients with MUS have been diagnosed with hysteria, functional nervous disorder, traumatic neurosis, psychosomatic disorder, hypochondriasis, somatisation, somatoform disorder, and functional somatic symptoms.[2,10] The favoured terminology depends on the prevailing medical, cultural, legal, and employment environment, with a bias toward Cartesian dualism. However, patients often reject diagnoses suggesting psychological origins.[10]

RECONCEPTUALISING FIBROMYALGIA

The stakes are high. Annually, FM patients average 5.5 million outpatient visits, direct healthcare costs reach $9,000, and indirect costs (absenteeism, disability, unemployment, early retirement) approach $30,000.[11,12] The functional syndromes share diagnostic overlap because they are consanguine dimensional disorders rather than categorical diseases with discrete pathologic causes, reflecting a continuous spectrum of sensitivity to physical symptoms which are formally diagnosed after reaching a critical mass.[13] Patients frequently have a myriad of complaints unexplained by physiological or structural pathology, but often have recognisable symptom clusters (FM, IBS, chronic pelvic pain). A polysymptomatic distress (PSD) score can be calculated by taking the sum of the two scores from the 2010 ACR FM diagnostic criteria, namely the Widespread Pain Index (WPI) and the SSS.[14,15] Patients meeting the 2010 ACR FM criteria will have a PSD score of ≥12 (WPI ≥3). The PSD score represents a measure of 'fibromyalgianess'.[13]

For patients with PSD, the physician must provide a plausible explanation for their symptoms beyond listing negative findings, or the residual uncertainty reduces clinical trust. The neurophysiological process called central sensitisation (CS), may fill that explanatory gap. CS is currently felt to be a centralised pain state reflecting a progressive process whereby the central nervous system (CNS) amplifies pain and other stimuli across many organ systems.[16] In this model, it is postulated that there are peripheral and central components to the abnormal sensory processing, a neuroplastic maladaptation effecting spinal sensitisation, and a disproportionately augmented response in the higher brain pain network. Cellular processes alter nociceptive neuronal function, and repeated nociception induces an increased response termed sensitisation. CNS glial cells release proinflammatory cytokines, which help initiate and maintain central sensitivity and chronic pain. These immunologic processes undermine the usual dichotomy of inflammatory versus non-inflammatory pain in FM versus rheumatologic disorders.

Table 1: Features of central sensitisation.[10,21-40]

- Increased neural membrane excitability
- Facilitation of neural synaptic strength
- Decreased inhibitory transmission
- Affected neurons display spontaneous activity, reduced activation threshold, enlarged receptive fields
- Neuronal memory
- Elevated serum neuropeptides: substance P, corticotropin-releasing hormone, haemokinin-1
- Elevated serum and cerebrospinal fluid inflammatory cytokines
- Activation of spinal cord glial cells
- Dorsal horn sensitisation
- Spinal sensitisation: enhanced temporal summation
- Increased sensitivity for future stimulation
- Non-painful stimuli activate nociceptive specific dorsal horn cells
- Heightened activity in ascending pathways
- Reduced descending inhibitory pathway response
- Increased/no change in descending facilitatory pathway response
- Reduced efficiency of conditioned pain modulation, psychophysical responses
- Autonomic dysregulation (lower baseline parasympathetic activity, elevated baseline sympathetic activity or predominance, reduced heart rate variability, orthostatic hypotension/tachycardia
- Hypothalamic–pituitary axis dysregulation: impaired cortisol reductions during sleep, low cortisol response to stress, defects in growth hormone and insulin-like growth factor–paracrine axis
- Increased growth hormone, decreased cortisol after exercise intervention in fibromyalgia
- Hyper-responsive central neural network (sensory and discriminative, affective and motivational, cognitive and evaluative), amplifying pain perception
- Cognitive–emotional amplification and extension of pain (catastrophising, fear of movement)
- Altered regional cerebral blood flow (pain, cognition)
- Spinal and supraspinal mechanisms treat all sensory input as salient
- Lowered thresholds for stimulus tolerance
- Amplification of painful stimuli (hyperalgaesia); regional/widespread
- Amplification of nonpainful stimuli (allodynia)
- Visceral hypersensitivity
- Insomnia: disrupted, fragmented, nonrestorative sleep
- Lower sleep efficiency (more Stage N1, poor sleep continuity)
- Dermatographia, livedo reticularis

Over time, perceptions become uncoupled from the intensity, duration, or even the presence of noxious peripheral stimuli. Hypersensitivity amplifies and distorts sensations elicited by innocuous stimuli and normal body sensations; more pain-related activity ascends, unimpeded by descending pain inhibition. This produces a disparity between stimulus and perception, reduced sensory tolerance, increased pain sensitivity, widespread hyperalgesia experienced clinically as pain, and other somatic complaints (Table 1).[9,16-20]

A UNIFYING DIAGNOSIS

CS-produced symptoms occur along a continuum, and frequently overlap. Indeed, somatic functional disorders often share diagnostic criteria and core symptoms.[13] Patients are frequently diagnosed with more than one such disorder, whether initially or progressively over time.[5,14] However, there is a heterogeneity of symptom expression; diagnoses occur in clinical clusters, and sensitivity to stimuli is not uniform across functional syndromes.[6,8]

Patients who meet 2010 ACR FM criteria have a PSD score of ≥12, but there is a bell curve distribution of symptom severity and the cut-off for FM diagnosis is designated as the extreme end of that spectrum.[10,13] There are similar distributions of severity in IBS,[41] TMD,[42] burning mouth syndrome,[43] and postural orthostatic tachycardia syndrome.[44]

Patients with functional syndromes frequently report multiple medication allergies or intolerances. These are often non-allergic hypersensitivity reactions to several classes of chemically unrelated agents.[45] The mechanism is unclear, but CS-mediated visceral and sensory hypersensitivity seems likely. One should consider the presence of multiple drug, food, and environmental intolerances as indicative of CS.[46,47]

Regardless of whether it is known as MUS, functional somatic syndrome, PSD,[13] or bodily distress syndrome,[48] CS serves as an organising principle by being descriptive and avoiding psychological or tautological terminology.

The current hypothesis is that the continuum of CS appears to be the common process linking these disorders, and may be a heritable 'vulnerability phenotype' for developing FM and related syndromes.[9] CS offers a feasible explanatory neurophysiologic model that is readily understood by patients, providing a useful cognitive anchor for future management. This explanation has proven helpful in our clinic by fostering patients to move from a diagnostic mindset (i.e. requesting more tests and consultations) to rehabilitative and recovery approaches. Whether considered as one disorder or many, differentiation remains useful, whilst remaining aware of diagnostic overlap, the continuum of symptoms, and the maladaptive neuroplastic process of CS. Despite this proposed clinical utility, CS remains theoretical, and the science must be consistently updated for patients so that it does not become a Kiplingesque 'Just So' story, which would harm the therapeutic relationship.

A SYSTEMS APPROACH

Focussed Factory Versus Solution Shop

Rheumatologists are a scarce medical resource. A workforce study projected a deficit of 2,600 adult rheumatologists by the year 2025. As of 2010, regional shortages of rheumatologists were already identified, with limited access for cities with populations of <50,000. Some regions with populations of >200,000 had no practicing rheumatologists.[49,50] As a result, rheumatology practices must clarify their service lines. Some rheumatologists prefer to be 'focussed factories', limited to specialty care (e.g. lupus, rheumatoid arthritis [RA], mixed connective tissue disease). Others may prefer to take all comers, the 'solution shop' approach.[51] Alternatively, a focussed factory specific to FM could be considered.

Notably, many physicians report being uncomfortable diagnosing FM. In one study, 53% of doctors found FM somewhat or very difficult to diagnose, citing inadequate training or knowledge.[52] Nonspecialists rarely or improperly use ACR FM criteria, and delayed or misdiagnosis is frequent.[53] As a result, referrals for FM diagnosis are likely to persist. Notably, FM affects 12–17% of RA patients, and FM pain maybe misinterpreted as active disease in RA (i.e. 'fibromyalgic RA').[54] Systemic lupus erythematosus (SLE) autoantibodies lead to chronic pain, arthralgia, morning stiffness, fatigue, and damage to the renal and CNSs. SLE can be difficult to differentiate from FM due to provider inexperience, higher FM prevalence (10-fold greater than SLE), and early symptoms that do not meet SLE diagnostic criteria.[55] The differentiation between SLE and FM among subjects that are antinuclear antibody positive is beyond the scope of this article, but FM affects 13–33% of patients with SLE, and is more likely to develop in the later stages of the disease. FM is also found in systemic sclerosis and Sjögren's syndrome.[18,56,57]

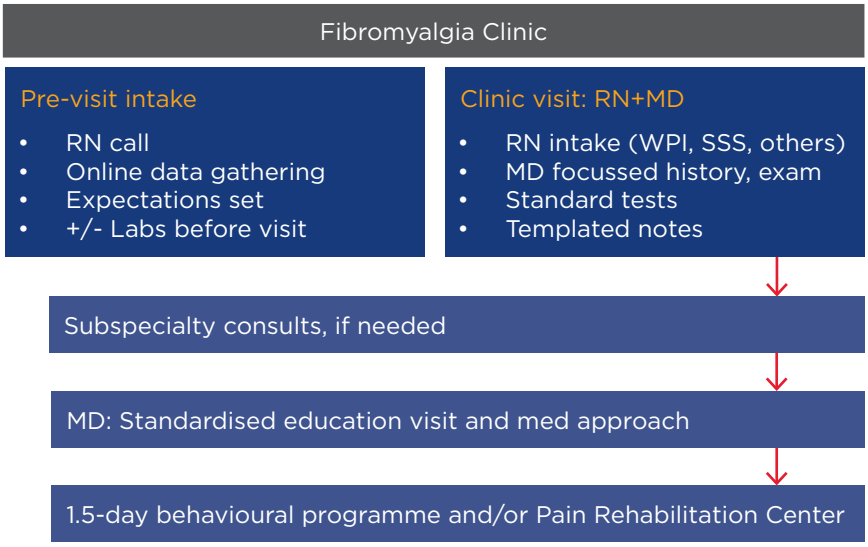

Figure 1: Mayo Clinic Fibromyalgia and Chronic Fatigue Clinic standardised assessment.
(Mayo Foundation©).
RN: registered nurse; MD: medical doctor; WPI: Widespread Pain Index; SSS: Symptom Severity Scale.

Consequently, patients with organic rheumatologic disease may have or develop CS pain and PSD disorders such as FM. The correct interpretation of the FM symptoms is crucial in avoiding overtreatment because concomitant FM can simulate flares of pain in rheumatologic disorders.

RECOMMENDATIONS

Filtering

Excluding patients with MUS requires gathering data to reduce the likelihood of the prospective patient having a functional somatic disorder.

- Screening laboratory tests can be a useful filter, restricting consultations to patients with abnormal rheumatologic serologies or inflammatory markers. Cut-off levels may risk missing false negatives, which should prompt repeated requests for consultation. False positives would not be discovered without more extensive pre-consultation testing
- Requiring written referrals can provide a filter, especially in closed networks. However, this can be labour intensive, and can risk false positives and false negatives
- Patient narratives regarding the clinical question can help determine whether to offer a rheumatology appointment. Queries can be limited to a few written paragraphs and be provided online. Automated scripts could flag keywords and phrases for review
- High PSD values are correlated with FM and functional disorders. An arbitrary PSD cut-off score of >12 would reduce (but not eliminate) the most severe cases. Cut-offs may be modified by regional experience and clinical volume
- Given the significant overlap among functional syndromes, screening for their presence may similarly predict the likelihood of CS[7]
- Current narcotic use can also be discriminative
- Precautions:
  i) Patients with RA and degenerative joint disease often have varying degrees of FM. Patients would still require management of their 'fibromyalgianess', but earlier attention may forestall progression
  ii) To avoid exclusion, patients may under report or misrepresent symptoms and prior diagnoses. This can limit the utility of PSD screening, but patients who do so risk a negative clinic experience. This can be made explicit (and acknowledged) when completing these forms
  iii) In regions with limited access to rheumatologists or FM/chronic pain treatment programs, filtering patients may leave them without adequate care

Rheumatologists using the solution shop or mixed approach must integrate FM into the practice, including the continuum of PSD, but an alternative system of care delivery is useful. The Mayo Clinic Fibromyalgia and Chronic Fatigue Clinic employs a standardised assessment of FM patients (Figure 1). This applies a focussed factory approach, dividing labour to reduce the workload and improve staff retention.

Pre-Visit Work

External records

- Performed by patient
- Limit material to past 2 years, maximum 50 pages
- Do not mail; records will not be reviewed prior to visit
- Discard blank/illegible/non-medical notes and duplicates
- Put in chronological order
- If not done in time for the visit, records may not be reviewed
- Failure to complete these tasks may result in delays, rescheduling, or limited record review
- If available, have non-physician personnel confirm compliance; separate laboratory, procedures, and image reports

Medications

- Prior medications, narcotics, psychoactive medications for rheumatologic diagnosis (start/stop dates, compliance, side effects, degree of benefit, reason for discontinuation)
- Supplements
- Self-reported allergies and intolerances

Prescheduling

- To complete the clinician assessment efficiently, desired laboratory tests are best done prior to the visit
- If the patient wants other PSD complaints evaluated, the practice must decide whether to:
  a) Make recommendations to be completed elsewhere
  b) Complete the tests at this episode of care, thus requiring prescheduled tests and consultations. This should be focussed on the most concerning or worrisome complaints

The fibromyalgia/polysymptomatic distress visit

In order to manage expectations, the time available (both prior to and at the visit) must be made explicit. Focus on the current symptoms of concern and reduce time spent discussing a medicalised history, which is often obfuscated rather than clarified by these data. Rheumatologists will narrow the inquiry to the cardinal symptoms, but remain alert to symptoms that might pose significant risks.

After sufficient review, past treatment options should be explored, including medications and surgeries. These data could be gathered online (pre-visit), by questionnaire, or by medical assistants. It is important to note whether or not the intervention changed the symptoms (range 0–100% better; or got worse). CS syndromes are often characterised by brief intervals of improvement, perhaps a few weeks or months, followed by recurrence (placebo effect).

SPECIAL ISSUES IN POLYSYMPTOMATIC DISTRESS

Comorbid Psychiatric Disorders

Individuals presenting with PSD often have accompanying psychiatric disorders associated with a range of coping and self-regulation deficits that increase the sensitivity to stress. Anxiety, depression, personality disorders, and self-critical perfectionism have been correlated with various chronic pain and functional somatic syndromes.[58-60] However, not all patients with PSD have diagnosable psychiatric disorders. In one study of patients with functional somatic syndromes, depression was absent in as many as two-thirds, and no anxiety was found in upwards of 72%.[48] Many patients assert that depression arose because of their symptoms. Avoid narrowing the interview to psychiatric dysfunctions, especially early on, as this may disrupt the discussion ("You think it's all in my head").

Traumatic Events

FM and other PSD syndromes tend to have a female predominance and are closely associated with significant stressors such as physical or sexual abuse, catastrophic events (war, natural disasters), infections, and peripheral pain triggers.[61,62] The association between abuse/trauma and CS, and the subsequent development of chronic pain/PSD functional disorders is important. However, the rheumatologist should avoid focussing on trauma, except briefly in the context of discussing CS, where alluding to the connection is sufficient. One can point the direction without requiring the patient to acknowledge or divulge such a history. Previously unaddressed or ongoing/current abuse warrant further referral.

Despite the relationship between trauma history and CS, the evidence for a direct causal association between specific traumas and FM is controversial, perhaps even 'weak to nonexistent'.[63] Lawsuits and disability claims may be seeking a level of certainty from healthcare providers regarding 'direct causation' that cannot be provided. The temporal association to a single trauma (e.g. car accident) is often uncertain or remote, premorbid CS complaints are frequent, and symptoms are often in excess of identifiable physical pathology. Traumatic events may represent a tipping point rather than the discrete onset of CS. Being a dimensional rather than categorical disorder, CS origins are multifactorial, influenced by the complex interplay of genetics, biological factors, the environment, events, and psychosocial responses progressing along multiple causal paths (Table 2). The ways in which the courts, insurance, and employment realms manage this complexity is beyond the scope of this article, but assigning causation to specific traumatic events or psychiatric disorders is often inconsistent with the current medical evidence.

TREATMENT

Given the diagnostic overlap of functional disorders, their treatment suggests a similar management overlap. Single modality treatments (medications, physical therapy) for FM have limited benefit. Multimodality treatments (education, physical therapy, cognitive behavioural therapy) are advised and evidence for their positive effects in FM have been reported.[64,65] This can, however, be logistically difficult, and access to multidisciplinary pain centres can be rather limited. Initial FM treatment should include symptom validation, understanding the stress response, the maladaptive nature of CS (especially how it can cause pain and other symptoms of bodily distress), and hope for improvement. The basics of neuroanatomy, the stress response, neuroplasticity, and their relationships to pain and symptom management can be simplified and readily understood by most adults.

Table 2: Mayo Clinic fibromyalgia self-management group programme.

1. Fibromyalgia diagnosis
• Diagnostic criteria • Self-management
2. Stress neurobiology
• Stress response • Autonomic nervous system • Acute versus chronic pain • Central sensitisation • Neuroplasticity
3. Pain cycle
• Symptom-focussed behaviours, somatic hypervigilance • Relationships • Cycle of chronic pain with example, activity when timely • Goal setting
4. Moderation
• Time management • Energy conservation • Graded exercise
5. Grief, spirituality, mood
• Grief and loss • Forgiveness, spirituality • Cognitive behavioural therapy • Behavioural activation • Effective and ineffective interventions • Depression, anxiety • Managing stress
6. Nutrition, sleep, cognition
• Nutrition • Sleep hygiene • Brain fog: improving cognitive performance • Humour • Relaxation • Mindfulness • Paced breathing
7. Additional resources
• Non-pharmacological treatments i) Biofeedback ii) Complementary therapies iii) Creative work iv) Hypnotherapy v) Mind–body techniques vi) Meditative movement (tai chi) • Medications • Opioid-induced hyperalgaesia • Difficult day planning

Finally, the concepts of moderation, graduated exercise, and reduced somatic hypervigilance are employed.

Non-pharmacological therapies can be targeted to pain generators, deconditioning, and loss of function (physical therapy, massage, acupuncture). Cognitive behavioural therapies are key for somatic symptoms and mood disorders. Psychotherapy may be helpful for depression and anxiety. Pharmacological and dietary therapies can be targeted at symptomatic relief of common symptom clusters (e.g. IBS, bladder pain). Management literature on specific functional syndromes and local expertise can be helpful. Central pharmacotherapies for functional syndromes have modest efficacy, with the greatest success from tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, and alpha 2 delta ligands.[66]

Table 3: Central sensitisation: Multifactorial aetiology.

• Genetic influence
• Biologic vulnerability
• Hypersensitivity phenotype
• Hormonal/gender influence
• Infections
• Autonomic dysfunction
• Prolonged pain generators (arthritis, neuropathy)
• Environmental factors
• Prolonged stressors (physiological, psychosocial)
• Mood disturbances
• Cultural factors
• Sleep disorders

Long-term use of narcotics should be avoided due to side effects, tolerance, dependence, opioid induced hyperalgaesia, and increased mortality.[67,68] At our medical centre, patients participate in a 1.5-day multimodality treatment programme for FM which has a significant positive effect. The programme includes an evaluation with a care team for diagnosis/confirmation of FM, followed by FM education and an interactive self-management session. Participants report significant improvements in physical functioning, work status, pain, stiffness, fatigue, anxiety, depression, sleep, and overall well-being (Table 3).[69,70]

CONCLUSION

Functional syndromes arise from a nociceptive disorder with disruptions of pain neurotransmitters, the hypothalamic–pituitary axis, autonomic system, and sleep that produces bodily distress. FM is a dimensional disorder where complaints fall on a continuum of PSD. Although the clinical definitions of functional disorders have symptom overlap, they are based on cardinal complaints and clinical/organ system clusters, and reflect a degree of severity that interferes with normal social roles and employment. Patients often have more than one such diagnosis, and these disorders often complicate other medical illnesses such as RA and even cancer.

FM will continue to involve rheumatologists as some providers remain uncomfortable confirming the diagnosis, especially when tests are not completely normal and there are numerous non-rheumatological symptoms. Subspecialists also have practical experience regarding the amelioration of FM complaints. Nevertheless, there are standard approaches to FM that can be undertaken by non-specialists. Multimodal approaches best include pharmacological and non-pharmacological therapies, e.g. cognitive therapies, graded exercise, and stress management. A systems approach can improve the FM care process.

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