Assessing patients with fibromyalgia from a rheumatologist’s perspective: a three-step methodology for differential diagnosis

Fibromyalgia (FM) is a topical and controversial disorder of intriguing complexity with beguiling therapeutic challenges. Its pathophysiology remains elusive and for many clinicians, assessing patients with FM is disheartening. This review attempts to demystify the FM presentation and outline a pragmatic three-step process to redirect analysis of FM signs and symptoms. Understanding the impact of sleep quality on central sensitization and patient presentation is essential. Furthermore, the impact of autonomic dysregulation on sleep quality and its prominence in the multilayered FM clinical presentation will be discussed. Finally discussed is how initial segregation of sleep and autonomic regulatory concerns yield a practical, integrative framework for ultimately analyzing other comorbidities.

KEYWORDS: central sensitization, cervical myelopathy, dysautonomia, fibromyalgia, pain

Since the publication of the American College of Rheumatology classification criteria for fibromyalgia (FM) [1], accurate diagnosis has not necessarily been the most challenging problem for clinicians addressing this common condition. The 1990 FM classification criteria are reasonably presented and have a high sensitivity (88.4%) and specificity (81.1%), similar to the diagnostic criteria for rheumatoid and juvenile idiopathic arthritis [2], yet these are superior to other diagnostic criteria used by clinicians to identify many other maladies such as systemic lupus erythematosus [3] and axial involvement of psoriatic arthritis [4]. Reproducible hyperalgesia being present at no fewer than 11 of 18 specific tender-point sites accompanied by a complaint of widespread pain and allodynia for a period of over 3 months is required for diagnosis. FM prevalence has been reported as 4.7% in Europe [5] and 2.5% in the USA [6]. Its prominence as an important medical condition is unquestioned, but opinions vary as to its veracity as a single entity and confusion abounds owing to its varied clinical and historical presentations [7].

While some patients describe onset after illness, surgery or trauma, others site no such antecedent events. While some patients emphasize pain and allodynia, others note a chief complaint of fatigue or cognitive dysfunction [8]. How is an ‘in the trenches’ clinician able to reconcile such a confusing and seemingly random constellation of symptoms from consecutive clinic patients who are all thought to have one specific disorder? This review attempts to explore the essence of FM as a clinical concern and provide a pragmatic three-step evaluation approach to address FM differential diagnosis.

The essence of FM

In the absence of definitive studies and universally accepted recommendations, each clinician has developed their own perspective on FM. This review simply provides another perspective with an expanded explanation. For those convinced that FM is not real, a significant portion of the recent medical literature has been overlooked. Notwithstanding – that is not to say that misgivings and the validation of a sense of uncertainty regarding the diagnosis of FM is unwarranted. Skilled clinicians have many reasons to admit trepidation regarding the clarity of FM as a specific diagnosis. Given the wide range of accompanying disorders treated by both specialists and primary-care clinicians, FM presentation can be confusing indeed.

At the heart of this discussion is the essence of FM. With the US FDA having recently approved three drugs for the treatment of FM [9] (pregabalin, duloxetine and milnacipran), opinions of what FM is and why one concept or treatment option should deserve greater consideration than another are proliferating. However, pivotal studies by Moldofsky et al. [10,11] and Lentz et al. [12] may be particularly compelling since they suggest a method for actually causing FM in normal asymptomatic controls.

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In 1976, Moldofsky used an abrupt 90 db auditory stimulus to disrupt and obliterate deep, stage 3–4 sleep (N3) in college students for 4 consecutive nights, resulting in advancing fatigue and widespread pain with allodynia, characteristic of FM. All symptoms resolved following normal, restorative sleep for 2 nights. A similar experiment eliminating rapid eye movement (REM) sleep did not lead to the development of these symptoms, nor did the disruption of deep sleep in athletic individuals (over at least 4 nights). Older et al. repeated the study, but did not observe widespread pain or allodynia. Interestingly, music was employed as the arousal [13]. Lentz et al. repeated the Moldofsky protocol in middle-aged women and confirmed the original findings [12].

Deep sleep is required for muscle rehabilitation, growth hormone production, reduction of fatigue and improved cognition [14,15]. The concept of central sensitization attributed to FM has only recently been directly linked to deep sleep deficit, but examples of torture suggest that amplified pain may be a predictable consequence of sleep deprivation [16]. Thalamic and other theories supporting the mechanism behind this change in pain perception are still developing [17–19]. However, functional MRI brain studies clearly demonstrate a significant alteration in the brain region controlling pain perception, with a shift towards enhanced pain in patients with FM compared with normal controls (Figure 1) [20].

Arguably, the nature of the arousal used to deplete subjects of deep, stage 3–4 sleep may also play a significant role, given results from the Older study [13]. Generally, it is likely that an autonomic arousal that wakes an individual, or is short of waking, elevates the level of sleep from stage 3–4 to lighter stage 1–2 sleep. The computer-generated auditory arousal employed by Moldofsky and Lentz may have had additional causal implications compared with the possibly less startling musical arousal used in the Older study. A startling arousal, possibly more autonomically arousing, combined with effective deep sleep deprivation may be applicable to FM.

In turn, it is known that autonomic dysregulation is a hallmark of FM [21–23], leading to many associated dysautonomic symptoms such as irritable bowel syndrome (IBS), irritable bladder, hyperacidity, irregular thermoregulation, palpitations, bruxism and restless legs syndrome (RLS) (Box 1) [24,25]. In patients with FM, sympathetic arousal is inappropriately elevated at night when they should be acquiring stage 3–4 sleep (Figure 2) [26]. FM patients not only have excessive autonomic arousal, but they also have ineffective autonomic response to stressors, possibly owing to a ceiling effect [27]. Once overactivated, the autonomic response is already overextended and consequently, is less responsive to new events.

These autonomic concerns are important, not only as an explanation of how a diffuse pain state such as FM could be associated with so many dysautonomic features, but also with regard to how the deep sleep deprivation model of its pathogenesis may be reconciled. Autonomic dysregulation may be the fundamental protagonist for the initiation and perpetuation of FM deep sleep deprivation.

Inversely, appropriate reduction in ‘fight-or-flight’ activity (sympathetic activity) in normal controls may account for how the asymptomatic individual achieves deep restorative sleep while patients with FM do not. Therefore, consistent with the Moldofsky and Lentz model, the FM patient pays a predictable price for reduced restorative sleep, resulting in amplified pain, lack of normal growth hormone levels, reduced muscular repair maintenance, cognitive deficits and fatigue.

Navigating the varied presentation of FM
How can individual patients present with symptoms that vary from day to day, and why is symptom intensity so variable among different

Box 1. Clinical fibromyalgia features that are attributable to, or influenced by, the autonomic nervous system.

**Cardiovascular**
- Palpitations
- Orthostatic hypotension
- Tachycardia
- Flushing
- Dizziness
- Raynaud’s phenomenon

**Gastrointestinal**
- Irritable bowel syndrome
- Dyspepsia

**Genitourinary system**
- Irritable bladder
- Interstitial cystitis

**Endocrine system**
- Hypoglycemia
- Hormonal dysregulation

**CNS**
- Sleep-stage architecture
- Nightmares
- Restless legs syndrome
- Thermoregulation
- Mood disturbance
- Anxiety and bipolar disorder
- Post-traumatic stress disorder
patients with FM? These very reasonable questions justify a large proportion of clinician skepticism regarding FM. Pneumonia, myocardial infarction, hypothyroidism, seizure disorder and cancer symptoms vary, but not in the seemingly inexplicable way that FM symptoms may vary, either in an individual patient over time or among a group of patients with FM. Superior diagnostic testing certainly increases clinician confidence when dealing with these other disorders, regardless of their varied presentations. Nevertheless, FM criteria are also reliable and applicable. So, what is the missing issue? It may result from an overly concrete concept of FM. Fibromyalgia is not akin to being pregnant. It is not an issue of ‘to be or not to be’. It is best considered as a process or continuum with sufficient autonomic arousal and stage 3–4 sleep.

Figure 1. Stimuli and responses during pain scans. Common regions of activation in patients (red) and in the subjective pain control condition (green), in which the effects of pressure applied to the left thumb sufficient to evoke a pain rating of 11 (moderate) are compared with the effects of innocuous pressure. Significant increases in the fMRI signal (arrows) resulting from increases in regional cerebral blood flow are shown in standard space superimposed on an anatomic image of a standard brain. Images are in radiologic view, with the right brain shown on the left. Overlapping activations are shown in yellow. The similar pain intensities, produced by significantly less pressure in patients, resulted in overlapping or adjacent activations in the contralateral primary SI, IPL, SII, STG, insula and putamen, and in the ipsilateral cerebellum. The fMRI signal was significantly decreased in a common region in the ipsilateral SI. Compared with stimulation with innocuous pressure, stimulation of healthy controls by the pressure levels used in the patients evoked significantly less pain and two regions of significant increases in regional cerebral blood flow, in the ipsilateral superior temporal gyrus and precentral gyrus (not shown). Neither of these regions coincided with regions of activation in the patient group. The graph demonstrates mean pain rating plotted against stimulus intensity for the experimental conditions. In the fibromyalgia condition, a relatively low stimulus pressure (2.4 kg/cm²) produced a high pain level (mean ± SD: 11.30 ± 0.90). In the stimulus pressure control condition, administration of a similar stimulus pressure (2.33 kg/cm²) to control subjects produced a very low level of rated pain (mean ± SD: 3.05 ± 0.85). In the subjective pain control condition, administration of significantly greater stimulus pressures to the control subjects (4.16 kg/cm²) produced levels of pain (mean ± SD: 11.95 ± 0.94) similar to those produced in patients by lower stimulus pressures. fMRI: Functional MRI; IPL: Inferior parietal lobule; SD: Standard deviation; SI: Somatosensory cortex; SII: Secondary somatosensory cortex; STG: Superior temporal gyrus. Reproduced with permission from [20].
deficit to produce widespread allodynia and hyperalgesia at at least 1 of 18 tender points for at least 3 months [28]. The degree of pain, fatigue, allodynia and autonomic features relate to the intensity and severity of the FM process present at a specific clinician–patient encounter. Each patient reflects their autonomic nervous system (ANS) and sleep-stage architecture individually based on lifestyle, personal circumstances, general health and any other concern that may impact autonomic arousal and sleep quality/depth. Focusing on the sleep history first, with the autonomic issues as a close second, makes the presentation of FM less formidable and confusing.

Moldofsky caused allodynia following 4 consecutive nights of stage 3–4 sleep deprivation [11]. What he caused after just 1 or 2 nights is unknown or unreported. It was demonstrated that 2 nights of uninterrupted sleep were required for recovery. How much recovery took place after just 1 night?

In terms of a conceptual framework, hypertension (HTN) is a reasonable analogy in that normal, borderline, mild, high and malignant HTN are all features of a similar process. Each stage presents to the clinician differently and requires a differential response and level of concern. Similarly, FM is more meaningful if one envisions it as a spectral process as promoted by Wolfe and Michaud [28]. At its most intense, patients are miserable. At its milder stages, patients probably attribute subtle fatigue, modest muscular tension and slightly reduced cognition to whatever society attributes such issues to at the time. Currently, such symptoms are often rationalized to be the result of a hectic, busy lifestyle, obligations or stress, while they may actually be a consequence of the early stages of altered sleep-stage architecture. In an attempt to discredit the validity of FM, Hadler controversially described it as ‘the syndrome of out of sorts’ [29]. Ironically, this conjecture may prove more supportive of FM as a continuum process than the author originally envisioned.

**Step one: assessing all signs & symptoms through the lens of sleep quality**

After reorganizing FM as a process rather than a firm diagnosis (except as the end point of that process), its variability seems somewhat more reasonable. FM patients need to share details about their sleep, remembering that each night is not identical. Sleep questionnaires, such as the Jenkins scale [26,30], are informative, as is the most common tool used for FM regulatory approval – the Fibromyalgia Impact Questionnaire (FIQ) [31], which asks patients to describe their pain, fatigue and sleep status and so on, averaged over a week or a month. Poorer, less restorative sleep should correlate with greater symptom intensity, particularly pain, fatigue, mood and dyscognition.

Notation in medical records describing either a ‘good day’ or a ‘bad day’ with a sleep quality assessment may convey greater meaning to a subsequent reviewer considering the physical examination findings. In addition, beyond sleep, medication use often leads to variable presentation. The presence of tender points may be a reflection of the end point of the FM process, but earlier stages are still relevant. Addressing the FM process to reduce fatigue and dyscognition remains important, even if tender points are not prominent. It would be unethical to either withdraw therapy or to delay treatment to confirm that worsening sleep correlates with overt FM and tender points when so many other features of the FM process are present.

Understanding this concept is germane to the evaluation and eventual differential diagnosis in the setting of FM. Again, other diagnostic challenges provide an analogy. Confidence in
the presence of new HTN or diabetes mellitus (DM) may require more than one abnormal blood pressure reading or blood glucose level to be observed at a single clinical encounter. The pattern and persistence of the hypertensive or diabetic process is required. Certainly, the more intense the process presents, the more readily the clinician will confidently identify HTN or diabetes. Thankfully, extensive research has identified the minimum thresholds for diagnostic confidence for early HTN and DM. By contrast, FM has been validated and classified only at the end point of its process when the signs and symptoms are most severe.

Short of a formal polysomnogram (PSG), patients can readily share details about their sleep quality. Nonrefreshing sleep (regardless of duration), abnormal sleep latency or frequent waking raises concern for the FM concept and its consequences. Analysis of clinical signs and symptoms can be adjusted when patients note increasingly poor sleep quality [32]. Beyond an expectation of increased fatigue and dyscognition, all sensations are amplified [33]. To clinicians, such an analysis of disproportionate intensity of expected symptoms can be equally as challenging as evaluating completely unexpected symptoms. Reconsidering the symptoms in the context of how sleep deprivation affects their intensity is the first step in reorganizing an analysis for a differential diagnosis of FM. Poor, unrefreshing sleep leads to the distortion of signs and symptoms and requires clinicians to reconsider patient presentation. Symptom intensity is indirectly proportionate to sleep quality.

**Step two: identify all autonomically-mediated symptoms**

After restructuring the patient presentation in the context of how sleep quality affects the intensity of their perceptions and reports, comprehensive diagnosis remains challenging owing to a plethora of autonomically-associated problems that commonly accompany FM. To reveal other important comorbidities, identifying autonomc concerns should precede evaluation of other diseases and disorders. Eventually, assessment of autonomic status by heart rate variability (HRV) analysis may prove useful when it is more widely available. However, currently, obtaining an inventory of dysautonomic features is helpful (Box 1) in addition to interpreting the painful processes in the context of sleep deprivation [34]. Only then may the final unexplained features of their presentation be more evident and assailable (Figure 3).

Interestingly, the presence of sleep deprivation and its consequences (amplification of sensations) also distorts the FM presentation of dysautonomia. Furthermore, clinical dysautonomic features complicate the interpretation of patient complaints related to pain perception, fatigue and other sleep effects. This cyclical relationship remains problematic for most clinicians. Sleep deprivation amplifies all perception, including the perception of dysautonomic phenomena (IBS, dyspepsia, irritable bladder, thermoregulation, palpitations and unexplained chest pains). Nevertheless, initially recognizing each of these two factors (sleep effects and dysautonomia) can yield what remains for differential diagnosis.

**Step three: after poor sleep & dysautonomia, what remains unexplained?**

Patients with FM can have any other disorder seen in patients without FM, but their interpretation differs. FM is not a diagnosis of exclusion. Symptoms from orthopedic, neurological and other painful disorders may be amplified and allow earlier identification, but this is not usually the case. The overwhelming nature of FM and its cardinal feature of widespread allodynia and hyperpathia more often confuse or mask other types of pain. Both clinicians and patients may too often attribute non-FM symptoms to FM.

Allodynia can also make physical assessment more difficult. Identification of tenderness associated with orthopedic injuries, strains, bursitis and tendinitis can be problematic. The medial knee tender point in FM is virtually indistinguishable from pes anserine bursitis, as is greater trochanteric bursitis, located near the outer hip FM tender point. However, assessment with movement is often very helpful and more interpretable. To evaluate comorbid pain in a patient with FM, isolation and identification of the comorbidity without palpation is often essential.

**FM mimics**

Classic mimics of FM are not very common. Widespread allodynia and hyperpathia are not easily caused by other disorders, while widespread pain (not intensified by palpation) can be. Widespread allodynia with fragmented, nonrefreshing sleep is often associated with FM, but it may not always be specific to FM patients. Endocrine disorders (hypothyroidism) can mimic some FM features, including fatigue,
sleep disturbance, autonomic derangement (temperature, gastrointestinal and cardiac), sleep quality, mood and musculoskeletal aching. Inflammatory rheumatic diseases may mimic some features of FM, but synovitis, nephritis, vasculitic rash, anemia, leucopenia, thrombocytopenia and pneumonitis are not features of FM. Generalized stiffness is common in FM patients, but axial stiffness can be associated with ankylosing spondylitis (AS). However, this may be better categorized as a comorbidity rather than as a mimic. AS stiffness often improves with exercise while FM stiffness and pain usually intensifies with activity. Chronic fatigue syndrome (CFS) encompasses some features of pain and has considerable FM overlap with fatigue and dyscognition, but pharyngitis, mild fever and infectious symptoms are inconsistent with FM symptoms and allodynia is inconsistent with CFS features. Chronic infections, particularly hepatitis C, can be commonly found in conjunction with FM, but also lack widespread allodynia.

Figure 3. Three-step analysis of a fibromyalgia patient with varied symptoms. First, assess all symptoms and complaints (VAS pain score noted) and reconcile pain by sleep quality deficit (9/10 poor sleep amplifies pain). Consequently, reconsider 10/10 shoulder pain with 9/10 poor sleep, as what shoulder pain may have been, present in a patient with more normal sleep (pain estimate of 10 reduced to 7). Second, identify autonomically-mediated symptoms and segregate for analysis and treatment. Third, identify what remains for traditional differential diagnosis.

**FM & comorbidities**

As opposed to mimics, comorbidities are much more likely to occur in patients with FM. A new intriguing possibility is the development of positional cervical spinal cord compression (PC3), which was identified in 71% of a recent cohort with FM and in 85% with chronic widespread pain (without FM allodynia) using a flexion–extension cervical spine MRI protocol. Usually, compression of the cervical spinal cord is due to disc and ligamentum flavum displacement, leading to compression of the cord in an extended position. Only 21% of positive cases of cord compression were seen on a typical neutral cervical spine MRI protocol. A controlled study is currently underway.

Intermittent abutment of the cervical spinal cord is a potent autonomic arousal in animal models. It is also postulated to be a source of widespread referred pain. Surgical reduction of cervical spinal cord compression and also, the Chiari malformation in patients...
who also have FM, has led to the occurrence of reduced FM symptoms. Hypothetically, this surgical reduction of the cord irritation from compression may improve autonomic regulation and restore normal sleep stage architecture [41]. Hence, FM symptoms improve.

Alternatively, surgical reduction of cord compression could result in an improvement in pain scores through a referred pain or a spinal cord mechanism related to descending inhibition. Additional research is required to elucidate this spinal cord–FM interaction, but altered descending inhibition of pain pathways through the cervical cord is already a major topic of discussion [42,43]. Furthermore, this rationale is thought to explain the beneficial effect of two of the three FDA-approved medications for FM (duloxetine and milnacipran). A third medication approved for treatment of FM in the USA — pregabalin — was also approved by the European Medicines Agency (EMEA) for the treatment of cervical spinal cord patients in Europe. One may wonder if these medications actually treat pain, sleep or the dysautonomic issues inherent in FM, or whether they simply address a common cervical spinal cord comorbidity. Since none of these pharmaceutical trials screened for comorbid spinal cord compression, this concern remains conjectural.

Other sleep disorders can also coexist with FM and affect presentation and treatment outcome. Obstructive sleep apnea can be seen in patients with FM [44], but regrettably, traditional risk factors, such as snoring, BMI, the Epworth scale and Berlin scale, do not adequately screen most patients. Narcolepsy has been reported in patients with FM [45], and interestingly, one of the FDA-approved treatments — sodium oxybate — is currently in clinical trials to compete for an eventual FDA treatment indication for FM [46]. Sodium oxybate does not affect the spinal cord but acts to convert stage 2 sleep into stage 4 sleep, favoring the Moldofsky/Lentz FM model.

Finally, genetic factors and social situations also play a role in FM presentation. Some patients have poor sleep hygiene and require counseling regarding proper sleep habits [47]. Many patients with FM have innate activation of autonomic arousal. Benign joint hypermobility (BJH) is common, ranging in prevalence from 6% in Caucasians [48,49] to 57% in Yoruba Africans [50]. Autonomic dysregulation is an extra-articular feature of BJH [51], and not surprisingly, BJH has been associated with FM [52,53]. BJH is also associated with anxiety disorder, bipolar disorder and post-traumatic stress disorder [54]. BJH is also commonly associated with pes planus, plantar fasciitis, chondromalacia patellae, persistent ligamentous injuries of the ankle and spine, palpitations and unexplained chest pain.

Identifying comorbidities associated with FM is important in addressing all patient concerns, but they may also influence the response to treatment options. Analgesics, including narcotic analgesics, are commonly used to treat FM, but comorbid obstructive sleep apnoea (OSA) may be adversely affected by a medication capable of respiratory suppression. Methods to reduce autonomic arousal may be considerably inhibited by the presence of potent autonomic arousals, such as OSA and PC3 [55]. Attempts to restore sleep quality may be considerably hindered if inappropriate social circumstances prevent a safe restorative environment. A history of serious mental or physical abuse is not uncommon among patients with FM [56]. In general, there may be a variety of independent pain sources (pain generators) capable of activating sufficient autonomic arousal to deplete stage 3–4 sleep requiring initial attention if the FM is essentially a secondary, reactive process.

**Figure 4. Positional cervical spinal cord compression in a patient with fibromyalgia.** C5–6 disc and ligamentum flavum distortion compression of the cervical spinal cord are only in the extended sagittal view (arrow).
When considering FM differential diagnosis, recommended testing for patients with FM is incomplete and poorly validated. Basic assessments beyond a careful history evaluation (including sleep history) and physical examination measuring creatinine phosphokinase, complete blood count, aspartate aminotransferase, alanine aminotransferase, creatinine and erythrocyte sedimentation rate are reasonable. For older patients, including a quantitative measure of C-reactive protein to validate the erythrocyte sedimentation rate and conducting a serum protein electrophoresis (SPEP) to consider benign gammapathy and multiple myeloma are appropriate. Serum iron and magnesium levels affect autonomic regulation, but evidence suffers from a lack of controlled studies and adequate sensitivity, respectively. Studies in patients with FM report mixed results regarding vitamin D, but regionally, it is reasonable to test 1, 25 vitamin D levels \([57–61]\) as well as thyroid-stimulating hormone, testosterone \([62]\) and dehydroepiandrosterone sulfate \([63]\). Imaging and polysomnography are expensive yet very helpful for documenting PC3 as well as lack of stage 3–4 sleep and OSA. Regrettably, many sleep laboratories are not interested in FM and the flexion–extension C-spine MRI is not yet routinely available.

**Conclusion**

Instead of considering FM as many different yet related forms of central sensitivity, one may consider FM as the predictable end point of autonomic fragmentation of deep sleep, and sort through the dysautonnia to focus on comorbidities. Understanding these physiological concepts, including the influence of sleep-stage architecture and autonomic tone on patient presentation, is integral to understanding health status and is an impetus for the trust that patients bestow upon their clinicians. Assessing patient concerns in the context of how well they slept and exploring the autonomic influences on symptomatology is a collaborative process between patient and clinician. Both can analyze symptoms within an autonomic framework to gain an understanding of how symptom amplification relates to sleep quality and thereby, avoid inaccurate conclusions and aberrant assumptions. However, ultimately, it is incumbent of clinicians to first gain a comfort level owing to the misleading features of sleep quality-related, sensory amplification, to weed out autonomic symptomatology and then to focus on the remaining signs and symptoms to consider a differential diagnosis in a patient with FM.

**Future perspective**

History repeatedly teaches us that complex and, often insurmountable, problems often appear elegantly simplistic and rationally based in retrospect. There is no doubt that FM will eventually be considered similarly.

In Europe, clinicians are already beginning to consider the ANS as a pivotal control point related to many different disease processes. Although not envisioned as the ‘cause’ of most medical disorders, clinicians are beginning to appreciate the role of the ANS as a chief regulator (with the endocrine system) of homeostasis and as a conduit for expression of many disease processes. Autonomic compensation (and lack of compensation) of pulmonary, cardiovascular and gastrointestinal diseases have been well studied. Many clinical symptoms are related to autonomic vascular or motility responses for both the underlying disease and the therapeutic intervention. Recognition and appropriate manipulation of these autonomic processes may significantly impact disease expression, treatment response and possibly, even disease initiation.

Methods to assess disease modulation by autonomic mechanisms as they relate to cardiovascular disease, DM and the metabolic syndrome already abound in the recent medical literature and I expect an even further expansion of our knowledge in the next 5–10 years. Assessment tools, including autonomic evaluation by HRV, have expanded in their usage from initial use to optimize athletic training and astronaut preparation to cardiovascular research. Ultimately, mainstream medicine is likely to use these noninvasive tools routinely since evidence has already been presented that they can predict, not only cardiovascular morbidity risks \([64,65]\), but also mortality from a range of causes, including cancer \([66]\). HRV has also been used in a pilot study to predict anti-TNF treatment outcome in inflammatory arthritis in a 52-week double-blind study \([67]\).

Studying FM leads to improved understanding of many aspects of human physiology, including sleep, pain/sensory perception and the ANS. When the media, government and industry begin to review the mounting evidence of autonomic impact on human disease, I expect to see an explosion of interest in this field and a quantum reduction in human disease burden.
Executive summary

Overwhelming complexity & variability of fibromyalgia presentation often limits effective evaluation
- Sequential dissection of fibromyalgia (FM) presentation yields a three-step methodology to consider pain, then the autonomic nervous system (ANS) and then comorbidities.
- Such a methodology is consistent with FM being hypothesized as being a common final pathway of a continuum related to stage 3–4 sleep deprivation.
- Developing a reliable framework to define comorbidities with FM is essential.

Reconsidering the role of pain amplification and history upon examination is essential
- Pain and other perceptions vary from day to day and from patient to patient based on circumstances, genetics and recent sleep deprivation.
- Analysis of pain and sensation intensity related to degree of recent stage 3–4 sleep deprivation reduces confusion.
- Perception is inversely proportional to stage 3–4 sleep deprivation.
- Stage 3–4 sleep is required for normal restorative functions (growth hormone levels, muscle repair, cognitive and fatigue recovery) and is lacking in FM patients.

Autonomic nervous system features color the fibromyalgia presentation
- As the major human ‘house-keeping’ function, the ANS controls cardiovascular, gastrointestinal, thermoregulatory, immune, sleep, metabolic and restorative functions.
- ANS arousal in FM inadequately responds to new stressors but is also chronically overactive.
- ANS overactivity at night is likely to reduce stage 3–4 sleep leading to the predictable consequences of fatigue, dyscognition and central sensitization (amplified pain etc.).
- Overlap of the dysautonomic protagonist of deep sleep deprivation yields the composite presentation of FM (allodynia, fatigue and dyscognition with autonomic features including palpitations, irritable bowel and bladder, dyspepsia, temperature dysregulation, orthostasis with dizziness, hypoglycemia, insomnia, restless legs, bruxism, nightmares and intensified mood disorders).

Fibromyalgia differential diagnosis & identifying comorbidities
- After reconciling pain intensity with sleep status and cataloging ANS features for treatment, comorbidities can be considered.
- FM mimics are rare but comorbidities are common.
- FM is not a diagnosis of exclusion but can accompany any disorder, including other sleep disorders, pain processes, diseases and injuries.
- FM presentation complexity and intensity increases the risk of ascribing too many symptoms to FM.

Conclusion
- The FM presentation is complex, confusing and variable, but teasing out its components can provide a framework for improved understanding and can lead to an integrative, focused treatment plan.
- First, one should reconcile the intensity of sensations with sleep quality status and then identify all ANS components in the presentation to finally evaluate what remains of concern and is unrelated to FM.
- Remain aware that sleep status affects the intensity of both comorbid and ANS symptomatology and that the ANS also mediates and influences the symptomatology of diseases that may be comorbid with FM.

Bibliography

Papers of special note have been highlighted as:
* of interest
** of considerable interest

- Fundamental paper that all clinicians who treat FM patients should have.
**Pivotal paper discussing the role of sleep abnormality in fibromyalgia (FM).**


- Pivotal paper on the role of sleep abnormality in FM.

- Important confirmation of the Moldofsky results.

- Important negative paper to compare with Moldofsky and Lentz [12] with particular emphasis on their experimental methods.


- Important paper raising concern over a connection between FM and the cervical spinal cord.

- Significant paper on the role of the autonomic nervous system in FM.

- Fundamental paper demonstrating why FM patients experience amplified pain.


- Pivotal paper on the role of sleep in the thalamus.

- Important paper on the role of the autonomic nervous system in fibromyalgia.
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