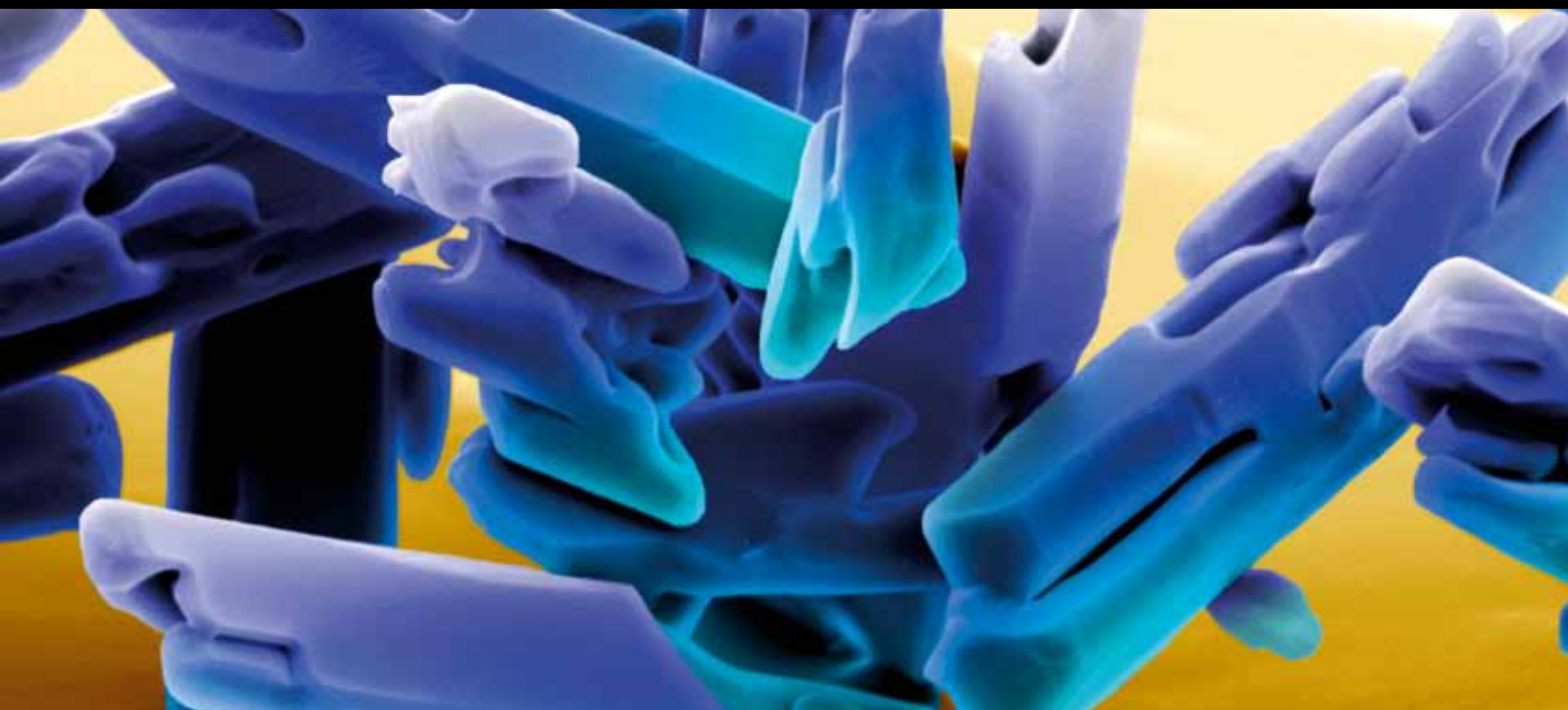


FIBROMYALGIA AS A DISORDER RELATED TO DISTRESS AND its THERAPEUTIC IMPLICATIONS

GUEST EDITORS: PETRA SCHWEINHARDT, MARY-ANN FITZCHARLES,
CHAD BOOMERSHINE, CHARLES VIERCK, AND MUHAMMAD B. YUNUS





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Editorial

Fibromyalgia as a Disorder Related to Distress and its Therapeutic Implications

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The concept of fibromyalgia has considerably evolved over the past two decades and now incorporates symptoms beyond pain, such as affective disturbances and fatigue [1]. This evolution of the clinical understanding of fibromyalgia, together with neurophysiological research showing abnormalities in central pain processing, has helped to establish the implication of the central nervous system (CNS) in fibromyalgia. The CNS, or more specifically the brain, is key when the organism is not (or no longer) capable to mount adaptive responses to stressors, that is, physical or emotional stimuli that threaten homeostasis. As a consequence stress turns into distress and homeostasis of the organism is no longer maintained.

This special issue is centered on incorporating the concept of (dis-)stress into our understanding of fibromyalgia. A wide range of topics is covered, from clinical presentation to pathophysiology to treatment approaches, unified by the attempt to explore how stressors, together with individual vulnerability, impact on fibromyalgia. The paper by M. A. Fitzcharles and M. B. Yunus explains the clinical concept of fibromyalgia, demonstrating what fibromyalgia is from a clinical standpoint and what it is not. A call for standardization of assessment methods in the diagnosis of fibromyalgia and symptom severity as well as treatment outcomes is made by C. S. Boomershine, who provides a comprehensive evaluation of currently available tools. This paper might well serve as a starting point for discussions within groups like Outcome Measures in Rheumatology (OMERACT) with the goal of providing

standardized assessment tools, which would clearly improve comparison of study results. The contribution by M. B. Yunus deals with the prevalence of fibromyalgia in other chronic pain conditions. On one hand, the overlap with other so-called functional pain syndromes is considered; on the other hand, the prevalence of fibromyalgia in diseases with clear (structural) organic cause is discussed. This approach is useful because it demonstrates that peripheral inflammatory and nociceptive events may trigger fibromyalgia symptoms in some patients while such events might be completely absent in patients presenting without any other organic disease. Then, Gracely et al. review commonalities and differences of fibromyalgia and depression. This is important for at least two reasons. First, depression is a frequent comorbidity of fibromyalgia. Second, fibromyalgia symptoms are regarded by some clinicians and/or researchers as a manifestation of a depressive disorder. The authors of this paper come to the interesting conclusion that although, in general, fibromyalgia may be more appropriately grouped with other functional pain disorders, certain subgroups of fibromyalgia patients with high level of psychological distress could be additionally or solely grouped with affective spectrum disorders.

The paper by L. A. Low and P. Schweinhardt investigates how different stressors early in life, including pain itself as well as psychological trauma, contribute to increased vulnerability of stress and pain systems to further insult later in life. This is potentially important because it might explain pathophysiological changes observed in adult fibromyalgia patients. The following four contributions are concerned

in detail with the pathophysiological alterations that might underlie the numerous symptoms of fibromyalgia. Ceko et al. carefully describe the experimental evidence for altered sensory processing that has been obtained in research settings. The authors discuss increased sensitivity to nociceptive stimulation, potentially altered endogenous pain modulation as well as increased sensitivity in response to other unpleasant sensory stimuli, which once more is indicative of a CNS disturbance rather than peripheral tissue abnormalities. Accordingly, they discuss neurobiological changes that might underlie fibromyalgia symptoms. S. Becker and P. Schweinhardt discuss in depth the possibility that dysfunctional neurotransmitter systems might be responsible for fibromyalgia symptoms. At first glance, this notion might seem at odds with the view that alterations in stress systems underlie fibromyalgia. However, the authors carefully explain how various symptoms of fibromyalgia could be explained by dysfunctional neurotransmitter systems and how alterations in the hypothalamic-pituitary-adrenal (HPA) stress system fit into this model. The paper by M. Martinez-Lavin is concerned with the important role of the body's second stress system in fibromyalgia. The paper illustrates how dysregulation of the sympathetic nervous system could be key in converting distress into pain. Light et al. review genetic polymorphisms that have been implicated in conveying susceptibility for fibromyalgia. In addition, they provide novel and existing data showing differential alterations of gene expression profiles in fibromyalgia and fibromyalgia comorbid with chronic fatigue syndrome. These results emphasize the importance of carefully subgrouping fibromyalgia patients. Furthermore, the genes identified include genes pertaining to the adrenergic system, to exercise-responsive metabolite sensing ion channels, and to sensory receptors possibly responding to muscle fatigue. Thereby they provide further evidence how autonomic dysregulation and vasoconstriction could be turned into ischemic muscle pain and fatigue.

Treatment for fibromyalgia presently consists of a multimodal approach combining pharmacological and non-pharmacological interventions. Two papers in this special issue directly address the important topic of treatment, incorporating current information on pathophysiology in the choice of treatment. The first one by C. J. Vierck is built on the hypothesis that pain in fibromyalgia might be partly caused by insufficient perfusion of skeletal muscles, as mentioned in the preceding paragraph. The author focuses on physical exercise as a first-line treatment for fibromyalgia with the rationale that exercise can attenuate consequences of stress in the periphery, that is, vasoconstriction and resulting ischemic pain, as well as in the CNS. In the CNS, exercise could interrupt the reciprocal interactions between stress and systems that control autonomic regulation, mood, sleep, and possibly pain sensitivity. The paper by R. L. Woolfolk et al. in the special issue addresses a therapeutic intervention that directly targets the CNS. They report on using an individually administered form of cognitive behavioral therapy (CBT) with an emphasis on achieving competence in

relaxation methods and improving patients' emotional self-awareness. The results of this form of CBT are impressive—almost two thirds of patients in the treatment group show 30% pain reduction compared to 5% in the control group that received treatment as usual. This is an encouraging start and justifies future studies focusing on determining which aspect of the individualized affective CBT drove those good treatment results by using more sophisticated control groups.

The reader will appreciate some divergence between the different contributions to this special issue. For example, central sensitization has been classically regarded as a spinal process resulting from prolonged and/or high intensity afferent barrage related to peripheral injury. Then, some authors started to use the term relatively loosely by using it for any suspected CNS amplification of nociceptive processing. Recently, psychological stress has been shown to indeed modulate spinal glutamatergic neurotransmission, albeit possibly with different mechanisms than classical central sensitization [2]. These examples indicate that disturbance of homeostasis by different types of stressors, such as peripheral injury or psychological stress, might result in pain augmentation via different mechanisms. It remains to be determined whether there is a final common pathway of how different types of stressors that exceed the adaptive capacity of an individual lead to fibromyalgia. Although many questions regarding fibromyalgia are still unsolved, we have already come a long way. New diagnostic criteria have been developed and new etiological frameworks incorporating vulnerability to stress have been proposed. Research has greatly advanced our understanding of physiological alterations associated with fibromyalgia, including changes of the autonomic system and the CNS. Finally, nonpharmacological treatment approaches have been suggested based on the improved understanding of this challenging condition. Advancing our understanding of the mechanisms responsible for converting distress into pain and other symptoms of fibromyalgia further will likely have important implications for the development of new therapeutic perspectives.

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Review Article

Fibromyalgia and Depression

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Fibromyalgia and depression might represent two manifestations of affective spectrum disorder. They share similar pathophysiology and are largely targeted by the same drugs with dual action on serotonergic and noradrenergic systems. Here, we review evidence for genetic and environmental factors that predispose, precipitate, and perpetuate fibromyalgia and depression and include laboratory findings on the role of depression in fibromyalgia. Further, we comment on several aspects of fibromyalgia which support the development of reactive depression, substantially more so than in other chronic pain syndromes. However, while sharing many features with depression, fibromyalgia is associated with somatic comorbidities and absolutely defined by fluctuating spontaneous widespread pain. Fibromyalgia may, therefore, be more appropriately grouped together with other functional pain disorders, while psychologically distressed subgroups grouped additionally or solely with affective spectrum disorders.

1. Introduction

The primary and debilitating symptom of fibromyalgia (FM) is widespread spontaneous pain. The ACR 1990 criteria also included a demonstration of tenderness. Recently revised diagnostic criteria have delegated the symptom of tenderness to a list of frequent symptoms that include fatigue, lack of refreshing sleep, cognitive impairments, abdominal discomfort, and headache [1]. This list also includes depression, which is prominent in fibromyalgia with a lifetime prevalence of about 90% for depressive symptoms and 62–86% for major depressive disorder (MDD) [2–5]. At any point in time, the best estimate of cooccurrence of depressive symptoms in FM is 40% [6]. The high occurrence of depression in FM has led to consideration of common pathophysiologic mechanisms and to the possible classification of fibromyalgia as one of the family of affective spectrum disorders that include many psychiatric conditions such as MDD, generalized anxiety disorder and

posttraumatic stress disorder, and somatic conditions such as irritable bowel syndrome and migraine [3, 7, 8].

There is compelling evidence to link fibromyalgia and depression. They cooccur, they share similar pathophysiology, and the pharmacological treatment of each includes (but is not limited to) the same dual serotonergic and noradrenergic agonists such as amitriptyline, duloxetine, and milnacipran. These similarities support the concept that depression and FM are “differential symptom presentations of a single underlying condition” [9–11].

2. Pathophysiology of Fibromyalgia and Depression: Predisposing, Precipitating, and Perpetuating Factors

The underlying processes of both depression and FM can be characterized by the lifetime course in an individual person. These processes can be organized by the three

“P”s of predisposing, precipitating, and perpetuating factors. Considerable evidence suggests that genetic and environmental factors *predispose* individuals to develop depression or FM. Indeed, a fundamental property of the multiple genetic associations with depression is not that these genes cause depression but rather that they increase the risk of developing depression in response to a precipitating event [9]. The considerable evidence for increased vulnerability to depression includes genes involved in the function of serotonin, catecholamines, monoamines, CRE, glutamate, and brain-derived neurotrophic factor [9, 12–16]. The evidence suggests that these genes result in an intermediate phenotype that increases the general risk of a psychiatric disorder precipitated by an environmental stressor or other triggering event [9, 13]. A similar concept has been proposed for FM in which both genetic factors and environmental events predispose individuals to develop FM in response to a subsequent precipitating event. Genetic factors in FM are implicated by familial prevalence [6, 8, 17, 18]. Converging evidence suggests that a polymorphism in the serotonin transporter (5-HTT) gene, implicated in MDD, may also be implicated in FM [19, 20]. This genetic influence, the established influence of environment, and gene/environmental interactions may all predispose individuals to develop FM and depression. Many of the precipitating events described below, such as physical trauma or sexual abuse, also likely contribute to a predisposed state.

Raphael et al. [18] have provided elegant evidence for the separate and joint predisposition to develop FM and MDD. In a community-based sample, they recruited individuals with both, either, or no MDD and FM, essentially filling 4 cells of a 2×2 table of FM presence (y/n) for one dimension and MDD presence (y/n) for the other dimension. These four cells defined subject categories, and the data of interest were collected from all available adult first-degree relatives of these subjects. Unlike previous studies that used reports of the primary subjects for data on relatives, this study actually interviewed the relatives. The results support a familial aggregation of FM and MDD. In comparison to a baseline rate of MDD of 28.7% in relatives of subjects without either MDD or FM, the rate of MDD in relatives was 39.0% in subjects with MDD and 37.3% in subjects with FM. Having both FM and MDD increased the rate of MDD in relatives to 45.5%. Expressed as odds ratios (ORs) in comparison to the groups that did not have either MDD or FM, the FM and MDD were similar with ORs of 1.47 and 1.56, and the combination of both FM and MDD increased the ORs of family MDD to 2.02.

The results of Raphael et al. [18] were interpreted as support for FM as a depression spectrum disorder. Interestingly, the linkage for FM and MDD was not found for FM and any mood disorder excluding MDD. These results suggest a familial, likely genetic, linkage in the predisposition for acquiring FM and MDD and also suggest that depressive symptoms without MDD can be in reaction to the presence of FM and not due to a linked common mechanism.

Once predisposed to develop FM or depression, these syndromes can be *precipitated* by events ranging from injury to psychosocial stressors [21, 22]. Cited physical

examples include physical trauma, illness, infections such as HIV, surgery, and autoimmune disease and motor vehicle accidents [7, 23]. Psychosocial stressors range from catastrophic events such as war to sexual abuse and other forms of emotional stress and trauma [7, 23]. Physical and psychosocial workplace events can also trigger these syndromes. Harkness et al. [24] documented precipitating physical workplace, events such as heavy lifting and repetitive motion, and psychosocial factors such as monotonous work and low social support.

Once triggered, both depression and FM involve a number of similar physiological mechanisms that likely perpetuate these disorders. It is well known that the acute response to stress, mobilizing the organism to deal with potentially life-threatening events, is beneficial if it remains acute. If abnormally prolonged, the disruption of normal bodily processes can lead to a number of disease states. The acute stress response, detailed in numerous reports, involves activation of the hypothalamic-pituitary-adrenal (HPA) axis which is coupled to the autonomic and limbic systems. Activation of the HPA system involves a chain of events. Corticotrophin-releasing hormone (CRH) is secreted by the hypothalamus, which results in pituitary secretion of ACTH. This CRH effect is synergistically augmented by hypothalamic secretion of arginine vasopressin (AVP). Increased ACTH in turn stimulates adrenal secretion of cortisol. Cortisol is a potent glucocorticoid that activates cytoplasmic receptors throughout the body to ultimately mobilize action and inhibit vegetative processes such as reproduction and growth. The glucocorticoids also provide negative feedback regulation of the HPA axis via multiple pathways acting on the hypothalamus and pituitary. These effects of the HPA axis activation are integrated with the locus ceruleus-norepinephrine system (LCNE) that activates brain systems involved in affect and anticipation, precipitation, propagation and termination of stress-related activity and activation of pain [25].

The pathophysiology of both stress-induced depression and fibromyalgia has been described in terms of the deleterious consequences of an acute stress response that persists far beyond a normal duration, failing to “reset” after the stressor is removed or terminated. The results have been characterized by the effects on cortisol secretion, which interact with neurotransmitter systems and regulation of fatigue, affect, and pain, linking fibromyalgia and the subsets of depression described below.

3. Reactive, Melancholic, and Atypical Depression

The term “depression” is used nonspecifically in the fibromyalgia literature similar to the nonspecific use of pain in the depression literature. The literature distinguishes between depressive symptoms, which can be evaluated by depression questionnaire instruments, and MDD, a diagnosis determined by an appropriately experienced clinician. Depression in fibromyalgia is not a unitary phenomenon. Depression can simply be a reaction to suffering from pain,

compounded by the multiple comorbidities of fibromyalgia. In a broader sense, having any type of pain or just having a medical condition can lead to appropriate reactive depression. Depression may also take the form of a MDD that is physiologically linked to the mechanisms that perpetuate FM. In this case depression and FM might be considered to be parallel processes that share one or more predisposing, precipitating, and perpetuating features. These scenarios need not be mutually exclusive; depression and FM could be linked at numerous physiological and psychological levels that vary over the progression of the disorders.

This complexity is compounded by heterogeneity in both FM and depression. Several studies have identified FM subgroups [26–31], finding major groups without psychological involvement and groups with considerable psychological distress. These subgroups respond differently to pharmacological treatments, for example, 5-HT₃ receptor antagonists have been shown to be effective in patients without psychological distress and ineffective in patients with psychological distress [30]. The features of these subgroups and this differential response to treatment suggest that at least a subset of fibromyalgia patients may share features of an affective spectrum disorder.

Similar to fibromyalgia, diagnostic criteria distinguish three subtypes of MDD. The subtypes of melancholic and atypical depression characterize 60% of all MDD and are considered to be the prevalent types in FM [32, 33]. The third subtype is MDD with psychotic features. A recent study distinguished between melancholic and atypical depression in 76 fibromyalgia patients and observed that 40 met the criteria for atypical depression and 27 met the criteria for melancholic depression [32]. This distinction was not associated with differences in FM characteristics save for greater severity of depression in the melancholic depression group.

4. Maturation of FM and Depression: From Hypercortisolism and Melancholic Depression to Hypocortisolism and Atypical Depression

The presence of melancholic and atypical depression in FM may represent a disease progression that also explains variable findings of HPA axis function in FM. These subtypes of MDD are associated with different alterations of HPA axis function; melancholic depression is associated with augmented cortisol (hypercortisolism) response while atypical depression is associated with a blunted secretion of cortisol (hypocortisolism). Gold et al. [33] have proposed a progression in fibromyalgia in which the early stage is associated with hypercortisolism incorporated with a prolonged normal stress response and the greater depression severity of melancholic depression. Over time, this augmented cortisol response is blunted to below normal levels, leading to hypocortisolism and the clinical features of atypical depression. This progression to ultimately atypical depression and the preponderance of women in both FM and atypical depression may lead to the finding of increased

frequency of atypical depression in FM [32] and present implications for treatments targeted to the stages in this progression.

5. Scenarios of Linked FM and Depression

A physiological progression in FM and a transition from a melancholic to an atypical depression suggest one of several possible links between FM and depression. Aguglia et al. [2] consider three possibilities. The first is the reactive case in which the presence of a chronic painful and disabling disorder is a depressing event. The authors reject this hypothesis because the incidence of depression in FM [3, 34] is considerably higher than that in other comparable pain conditions or diseases. We offer counter arguments below.

Aguglia et al.'s [2] second possibility is that FM reflects a subthreshold depression, an idea that they reject since many FM patients are not depressed and do not become depressed.

Aguglia et al.'s [2] third possibility is that FM and depression can be conceptualized as disorders with multiple peripheral and central manifestations that might belong to the same affective spectrum [8]. The proposed underlying mechanisms that perpetuate this spectrum include the mechanisms discussed above: alteration in HPA axis function, altered serotonergic and noradrenergic function, and altered function of systems that involve substance P, neurosteroids, and cytokines.

6. Laboratory Evidence for the Role of Depression in FM

A study by Bartley et al. [35] explored the association of mood and fibromyalgia by examining the effect of FM on affective processing. Both FM patients and healthy controls, 17 per group, viewed pleasant, neutral, and unpleasant images and rated the pleasantness/unpleasantness and arousal evoked by the pictures. A number of physiological variables were recorded, and two-thirds of the pictures were accompanied by white noise stimuli to induce eye blinks. In comparison to controls, FM patients showed greater negative ratings, arousal, and EMG responses to the negative unpleasant images but no differences in responses to the pleasant images. These results, found also for olfactory stimuli [36], suggest that the mechanisms that modulate mood in FM do not result in an anhedonia, that is, a diminished ability to experience pleasure, but rather increase the unpleasantness of unpleasant material.

A number of laboratory studies have explored the interaction of depression and evoked pain sensitivity in fibromyalgia. Several have examined sensitivity to electrical stimuli at the spinal level. In an extension of previous findings of enhanced nociceptive flexion reflex (NFR) in fibromyalgia [37, 38], Ang et al. [39] explored the role of depression in the NFR in 32 women with FM. The Patient Health Questionnaire 8-item Depression Scale (PHQ-8) was used to divide subjects into depressed (score > 9) and nondepressed groups. An inverse association between the NFR threshold and ratings of current pain was observed in

the nondepressed group (-3.9 mA change in NFR threshold per unit of current pain) but not in the depressed group (0.07 mA change in NFR threshold per unit of current pain). These results suggest that the presence of depression disrupted the positive relationship between ratings of current pain and NFR sensitivity in FM.

Neuroimaging studies have examined the influence of depression on supraspinal responses to painful pressure stimulation. Giesecke et al. [40] used the fMRI BOLD method to evaluate cerebral responses evoked by painful pressure applied to the thumb in 30 patients with FM. Depression was assessed by the Center for Epidemiological Studies Depression Scale (CES-D) and the Composite International Diagnostic Interview (CIDI). Two analyses were performed on the data. In the first correlational analysis, the brain activity evoked by a subjectively similar pressure stimulus was computed for each subject for each voxel of the brain. For each of the 30 subject scores at each voxel, a linear regression was performed between each patient's pain-evoked fMRI activity and each patient's depression score on the CES-D. This resulted in a scatter plot in which each point is a person, defined by their depression score and the pain-evoked activity at that brain location. Correcting appropriately for multiple comparisons, there were significant associations in bilateral amygdala and in contralateral insula. In the second, intra-group, analysis, 7 FM patients diagnosed with MDD were matched to 7 FM patients without MDD and to 7 healthy control subjects. Equally painful stimuli, evoked by significantly less pressure in the FM groups, revealed activations in the pain matrix observed in the full group analysis above and in previous studies of painful thumb pressure pain. In addition, in the MDD group, these stimuli evoked activations in bilateral amygdala and contralateral insula, regions implicated in affective processing. The results suggest that the presence of depression had no effect on the sensory-discriminative processing of pain stimulation and had a selective effect on brain regions that process the affective-motivational dimension of pain.

An additional study in this laboratory used a correlational analysis to assess the influence of catastrophizing, a putatively depression-driven cognitive style of attaching overly negative interpretations to events [41, 42]. Since some argue that this style is a variant of depression [43, 44], the analysis controlled for depression, identifying brain regions of evoked pain activity associated with a measure of catastrophizing (Coping Strategies Questionnaire). [43] Applying an analysis strategy described above for Giesecke et al. [40], the analysis both identified brain regions, in which activation by painful thumb pressure was associated with catastrophizing, and regions in which activation in response to painful pressure was significantly different in groups with low or high catastrophizing scores divided by a median split. The results identified several brain regions in which pain evoked by pressure to the thumb was associated with catastrophizing over a sample of 29 FM patients. These regions include contralateral anterior cingulate cortex, medial frontal gyrus, lentiform and ipsilateral middle frontal gyrus, secondary somatosensory cortex, claustrum, and cerebellum. These regions did not overlap with the brain regions (amygdala and

insula) associated with depression in the study by Giesecke et al. [40], likely because the analysis controlled for the effect of depression [41]. Significantly greater activations in high versus low catastrophizing groups were observed in contralateral medial frontal gyrus and inferior parietal lobule, and in ipsilateral medial frontal gyrus, superior frontal gyrus, secondary somatosensory cortex, and anterior cingulate cortex. One region, ipsilateral inferior parietal lobule, showed significantly greater activation in the low catastrophizing group. Both analyses found effects in contralateral medial frontal gyrus and in ipsilateral secondary somatosensory cortex. These combined results suggest that catastrophizing is uniquely associated with brain regions involved in attention to pain and pain affective processing.

In another fMRI study in FM patients, depression and catastrophizing were not associated with the effects of pressure stimulation in any brain region. [45]. However, this study used randomly delivered stimuli of much shorter duration, which might have served to maximize the sensory saliency, and minimize the unpleasantness, of the stimulus-evoked sensations.

7. Treatment Evidence from Clinical Trials

Depression and FM also appear to be linked because drugs with dual serotonergic and noradrenergic action are used to treat both conditions. The two prime examples are the noradrenergic, serotonergic reuptake inhibitors (NSRIs) duloxetine and milnacipran, antidepressants approved recently in the US for treatment of FM. These agents mimic the dual action of amitriptyline, a tricyclic antidepressant which has long been used to treat chronic pain, including FM. One significant advantage is that these recent agents have a superior adverse-effect profile since they do not possess the well-known anticholinergic effects of amitriptyline.

Classic analgesic studies of amitriptyline suggest that the pain-relieving mechanism is independent of the antidepressant effects. Pain relief is accomplished at a much smaller dose (25 mg) than those used for depression (100–150 mg), and analgesic effects are observed after one week of treatment while antidepressant effects were usually observed after three weeks of treatment. In addition, the pain-relieving effects are independent of the effects on depression and are observed in both depressed and nondepressed patients [46, 47]. The recent trials of duloxetine and milnacipran also provide evidence for a pain-relieving action of dual serotonergic and noradrenergic agonists, that is, independent of depression [48–51]. A recent secondary analysis of 4 clinical trials of duloxetine in fibromyalgia explored treatment effects in patients who were comorbid with MDD. This analysis demonstrated the relative independence of MDD and fibromyalgia in that the baseline level of one did not affect the treatment efficacy of the other [4]. A path analysis also found predominant direct effects of treatment on mood and pain. These results suggest that the effects of the NSRI duloxetine on pain and MDD were mediated by independent mechanisms. However, the path analyses also showed indirect effects in which improved mood resulted in improved pain and improved pain resulted in improved mood. In the case of

pain with unpleasantness and affective dimensions, the indirect effects of mood are reasonable and practically expected. Similarly, relieved pain can be expected to improve mood.

These indirect effects may reflect the influence of reactive depression elements in FM. Aguglia et al. [2] reject this scenario above because FM has a higher incidence of depression than similarly severe pain conditions or diseases. However, we feel that this issue deserves close scrutiny. Although comparative diseases (such as rheumatoid arthritis) may be comparable on severity, they may not be comparable on other disease features that more powerfully drive reactive depression. There are several aspects of FM that would fuel an augmented reactive depression in comparison to many other pain or medical syndromes. The pain is widespread, including by definition all four body quadrants and the axial skeleton. Pain extent is likely associated with the incidence and severity of depression. Manchikanti et al. [52] have shown that the incidence of MDD was 4% in a control group, 20% in a group with chronic pain in region of the body, and 32% in patients experiencing pain in more than one body region. This type effect might be assumed to be the highest in FM, in which the whole body pain encompassing 5 major regions would place it high on the function relating MDD to a number of body sites.

In addition to the extent, FM is characterized by significant spontaneous pain. In contrast, many pain conditions are characterized less by spontaneous pain and more by movement-evoked pain. The inability to alleviate pain by quiescence or postural adjustment may contribute to depression. Similarly, the extensive spontaneous pain of FM is accompanied by a large number of symptoms and comorbidities that likely contribute to the probability of reactive depression.

Furthermore, unlike other conditions such as rheumatoid arthritis or pain conditions with physical correlates, patients with fibromyalgia suffer symptoms with minimal objective signs. Many in the medical field still deny the very existence of FM, relegating it to general somatization or other psychiatric processes. Patients feel that they are not believed and must fight for acceptance. This lack of credible objective evidence for diagnosis or underlying mechanism likely explain the enthusiastic embrace of recent findings such as altered concentrations of substance P in CSF [53–56] and evidence of altered CNS processing at spinal [37, 38] and supraspinal [37, 38, 40, 48, 53–77] levels. It also is a very reasonable explanation for increased frequency and severity of reactive depression in FM.

Finally, in concert with the lack of objective signs, patients with fibromyalgia live with increased uncertainty of what they have and their prospects for the future. Since many features of depression are future-oriented (despair, hopelessness), this uncertainty is likely linked to depression.

8. Summary

In summary, depression and FM share both common features and differences at multiple physiological and psychological levels. Clear evidence indicates a mutual predisposition; for example, biologically based MDD is predicted

nearly equally by the presence of familial MDD or FM. This mutual predisposition is likely due to a combination of genetic and environmental factors [12, 19, 78–82]. These predisposed individuals are particularly vulnerable to a precipitating event that triggers FM or MDD. An injury, motor vehicle accident, illness, or psychosocial stressor can activate a cascade of events with potent, persistent consequences. There is considerable support for the hypothesis that these precipitating events trigger an appropriate acute stress response, including increased CRH, AVP, ACTH, and cortisol. The initial elevations in cortisol are associated with a melancholic depression, and a gradual shift to hypocortisol levels coincides with a shift from melancholic depressive disorder to atypical depression disorder. FM has been characterized by both lowered and elevated wakening cortisol levels and associated with both melancholic and atypical depression [81, 83, 84]. The HPA axis system is complex with multiple regulating feedback loops. Although predisposed by similar mechanisms, FM and MDD may be mediated by distinctly different alterations of HPA function. For example, depressed mood may be due to internal dysregulation of the HPA system while the persistent pain of FM may be due to known cytokine-mediated HPA activation [85–87]. Similarly, involvement of systems mediated by serotonin and norepinephrine may be common to both FM and depression, yet the differential effects of NSRI and tricyclic treatments suggest at least distinct differences in the functioning of these systems in these two disorders.

FM and depression are clearly intertwined at the experiential and measurement level. An examination of depression questionnaires reveals numerous somatic items that would be endorsed by a person suffering from chronic pain. Depression hurts or at least provokes responses similar to hurt; for example, “I do not feel as well as I used to,” “I ache all over.” Conversely, to have pain is depressing, and the behavioral consequences of reduced activity and social isolation compound negative mood. FM is not fully endorsed by all clinicians and is mediated by unknown mechanisms with unknown prognosis. The patient’s current state is unknown and uncertain, and the future more so. A persistent, intractable pain syndrome fuels helplessness and despair. The interactions can become cyclical and self-perpetuating. When treatments such as exercise or cognitive behavioral methods are shown to be effective, depression can rob the initiative and the ability to comply with such treatments.

FM has been included in the family of affective spectrum disorders (ASDs) that include other physical conditions such as migraine and irritable bowel syndrome and numerous psychiatric disorders such as attention-deficit/hyperactivity disorder, bulimia nervosa, dysthymic disorder, generalized anxiety disorder, major depressive disorder (MDD), obsessive compulsive disorder, panic disorder, posttraumatic stress disorder, premenstrual dysphoric disorder, and social phobia [3, 7, 8]. While sharing features such as predisposition to develop psychiatric conditions such as MDD, FM also is associated with a number of somatic comorbid conditions. With the predominant symptom of widespread pain, FM may be grouped also with other functional pain disorders such

as temporomandibular pain disorders, Gulf War syndrome, and vulvodynia as well as irritable bowel syndrome and migraine. All of these may be expected to have some effects on common physiological systems such as dysregulation of the HPA axis, autonomic functions, and of systems regulating serotonin and norepinephrine. This commonality may reflect both the widespread role of these systems in health and disease and the limited repertoire of physiological responses to multiple sources of pathophysiology. Disparate mechanisms may result in similar symptoms, representing components of a stereotypic stress response as described by Selye [88]. The independence of treatment effects suggests that depression and FM are mediated by largely independent mechanisms with mutual modulation of specific symptoms. The widespread pain that characterizes FM suggests association with a family of somatic disorders, while psychologically distressed subgroups, requiring different treatment, may represent the additional or sole association with a family of affective spectrum disorders.

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Review Article

The Prevalence of Fibromyalgia in Other Chronic Pain Conditions

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Central sensitivity syndromes (CSS) include fibromyalgia syndrome (FMS), irritable bowel syndrome, temporomandibular disorder, restless legs syndrome, chronic fatigue syndrome, and other similar chronic painful conditions that are based on central sensitization (CS). CSS are mutually associated. In this paper, prevalence of FMS among other members of CSS has been described. An important recent recognition is an increased prevalence of FMS in other chronic pain conditions with structural pathology, for example, rheumatoid arthritis, systemic lupus, ankylosing spondylitis, osteoarthritis, diabetes mellitus, and inflammatory bowel disease. Diagnosis and proper management of FMS among these diseases are of crucial importance so that unwarranted use of such medications as corticosteroids can be avoided, since FMS often occurs when RA or SLE is relatively mild.

1. Introduction: Historical Overview and the Importance of Nomenclatures

The fact that fibromyalgia syndrome (FMS) is associated with several similar conditions without structural pathology was first reported in a controlled study in 1981 [1], following which a conceptual model was proposed with a Venn diagram, showing the mutual overlaps in these syndromes [2]. Since then, a large number of studies have confirmed these associations, compared with both healthy controls as well as diseases with structural (the so-called “organic”) pathology (DWSP) [3, 4]. (Although there are structural changes, e.g., decreased hippocampus and gray matter volume in some CSS conditions, these changes seem to result from prolonged central sensitization (CS) and will be discussed at the end.) These overlapping conditions are collectively known as central sensitivity syndromes (CSS) [5–8], since CS is the common binding glue between them. The term CSS was first coined in 2000 [5] and has been reviewed [5–8]. We [6] and others [9] have described mutual associations among the CSS conditions.

In contrast to association of FMS with other CSS members, association of FMS with DWSP was reported somewhat later [10] and more frequently only in recent years. Wolfe and

Cathey were the first to recognize the association of FMS with rheumatoid arthritis (RA) [10]. Although they were called “secondary fibrositis,” these were cases of concomitant FMS with typical symptoms and multiple tender points (TP) in association with RA. The diagnosis of FMS in the pre-1990 ACR criteria era was made on the characteristic symptoms of FMS as well as many tender points [10].

What’s in a name? Asked Shakespeare rhetorically in *Romeo and Juliet*. My own answer is “A lot.” A name should be meaningful, tell the gist of the topic, and must not distort the underlying truth, recognizing that scientific truth is not carved in rock and does change over time. In this discourse, I shall use the terms syndrome, illness, condition, and disease synonymously. Further, since the term fibromyalgia implies nothing more than pain as has been discussed by Fitzcharles and Yunus in this issue of the journal, I prefer the term “fibromyalgia syndrome” since FMS is so much more than pain with a large number of other distressing symptoms.

Elsewhere, I have argued that differentiation between illness and disease is artificial and contrary to patient interest and hampers proper management of CSS conditions, since anything that is not currently viewed as a disease (i.e., does not have structural pathology, e.g., inflammation, degeneration, or neoplasm) is viewed as predominantly

or exclusively psychological and benign and is not taken seriously by the health care providers, accentuating the suffering of the patients [7]. In an irresponsible way, this untruthful “dogma” is passed down from the professor or the attending to the students, and the victims are our patients.

I have also rationalized that the use of the term “organic” for DWSP is irrational, since organs are involved in both CSS and DWSP—functional changes in the former and structural in the latter [7]. In the same context, the use of the nosology “functional” for CSS is antithetical, since the neurochemical-endocrine status of organs involved in CSS is dysfunctional!

Such nomenclatures as “medically unexplained symptoms” or MUS and “somatization disorder” (SD) are equally fallacious and detrimental to scientific progress, and statements of bias. Such a bias impedes empathetic and proper patient care. By DSM IV-TR definition, in SD “laboratory tests are remarkable for the absence of findings to support subjective symptoms.” This is obviously not true of CSS diseases as has been adequately discussed [7]. CSS are medical conditions based on objective pathology of neurochemistry and neuroimaging that explain many symptoms of CSS diseases [7]. So, terms like MUS seem to sprout in a fertile mind of bias. The problem is that MUS represents illness and illness is a second class citizen in the land of medicine.

2. Materials and Methods: Process of Locating Articles for This Review and the Author’s Own Views

Several sources of literature search were employed: PubMed, Science Citation Index—ISI Web of Knowledge and CINAHL Plus. A large number of key words were used, including fibromyalgia, fibromyalgia syndrome, functional syndromes, somatic syndromes, medically unexplained symptoms, CS, central sensitivity syndromes, overlapping conditions, chronic pain, individual members of central sensitivity syndromes (e.g., irritable bowel syndrome, headaches, migraine, temporomandibular disorder, myofascial pain syndrome, restless legs syndrome, vulvodynia, and interstitial cystitis), chronic back pain, chronic neck pain, chronic pelvic pain, and chronic disease, as well as a number of chronic pain conditions with structural pathology (e.g., RA, systemic lupus erythematosus, osteoarthritis, ankylosing spondylitis, diabetes mellitus, ulcerative colitis, Crohn’s disease, endometriosis, carpal tunnel syndrome, and neuritis). Additionally, all references of a given article were searched for an additional source. Finally, this paper adds my own ideas.

3. FMS in CSS Diseases: Associations Are Bidirectional

CSS conditions include FMS, irritable bowel syndrome (IBS), functional dyspepsia, chronic fatigue syndrome (CFS), myogenic temporomandibular disorder (TMD), tension-type headache, migraine, regional pain syndromes (myofascial pain syndrome and neck and back pain without structural pathology), restless legs syndrome, interstitial cystitis, multiple chemical sensitivity, posttraumatic stress

disorder (PTSD), Gulf War syndrome, and vulvodynia [6–9]. Undoubtedly, the number will grow by the Yunus criteria for CSS [6]. Although the literature is ripe with reports of increased prevalence of various members of CSS in FMS (too many to provide references), reports on their bidirectional interrelationships are relatively few [6, 9]. Thus, while prevalence of irritable bowel syndrome (IBS) in FMS is increased compared with controls [1, 3–9], same is also true for FMS in a population of IBS and other CSS members, such as (TMD) (see below).

Studies of the occurrence of FMS in other CSS conditions are generally limited at this time (compared with prevalence of CSS in FMS). Number of studies is indicated by the number of references (Table 1). Increased prevalence of FMS, either by the use of a healthy control group or by consideration of the prevalence of FMS in the general population, has been reported in IBS [9, 11–14], TMD [9, 15–19], headaches [9, 20–23] (including tension-type headache, migraine, and a mixed group of TTH and migraine), interstitial cystitis [9, 24–27], chronic fatigue syndrome [9, 28, 29], vulvodynia/vulvar vestibular syndrome [30, 31], and Gulf War syndrome [32–34].

Sixty-seven percent of patients who present with “idiopathic” chronic low back pain were found to have FMS [9]. Patients presenting with chronic low back or neck pain demonstrate evidence of CS [6, 8, 9], and these patients often develop widespread pain and fibromyalgia at a later time [6, 35].

MPS and FMS are overlapping syndromes [6]. There is strong evidence for CS in MPS, including decreased pain threshold by various nociceptive stimuli at sites remote from painful area, accentuated spinal nociceptive flexion reflex [6], and augmented cortical activation by functional magnetic resonance imaging (fMRI) [6, 36].

Most cases of FMS begin with regional pain similar to MPS. Trigger points (TrP), in addition to tender points (TP), are also present in FMS [37]. It has been suggested that a continuous input from a TrP leads to, and maintain, CS both in MPS and FMS [37]. The cause of TrP is speculative but include local trauma (including fall, motor vehicle accident, overuse, and repetitive use), spinal stress (e.g., scoliosis or poor posture), and perhaps systemic factors, for example, mental stress. TrP are likely sustained by CS [36].

4. FMS in Chronic Painful Diseases with Structural Pathology: An Expansion of the Fibromyalgia Territory

As early as 1983, Wolfe and Cathey recognized the concomitant occurrence of FMS among RA patients. It was an astute observation since many features of FMS, for example, pain at multiple sites (including bursal and tendon areas), fatigue, a feeling of malaise and tenderness at multiple spots, including joint areas, may also be present in RA itself. What was not definitely known at that time is whether RA patients were also tender in muscles and other sites of typical tender points. As it turned out, multiple TPs are a unique feature of FMS,

TABLE 1: Prevalence of fibromyalgia syndrome (FMS) in other central sensitivity syndromes (CSS) conditions.

CSS condition*	% prevalence of FMS (mean)	% prevalence of FMS (range)	Reference no.
Irritable bowel syndrome	40.7	20.0–65.0	[9, 11–14]
Temporomandibular disorder	23.7	13.0–52.0	[9, 15–19]
Headaches (all)	26.3	10.0–40.0	[9, 20–23]
Tension-type headache	29.7	23.0–36.4	[9, 23]
Migraine	16.0	10.0–22.0	[21, 22]
Mixed [†]	38.2	36.4–40.0	[20, 23]
Interstitial cystitis	15.4	12.0–22.4	[9, 24–27]
Chronic fatigue syndrome	55.2	15.6–80	[9, 28, 29]
Vulvar vestibular syndrome	23.4	15.6–31.2	[30, 31]
Gulf War syndrome	17.6	2.0–33.8	[32–34]

* Prevalence of FMS in other CSS conditions with a single study has been discussed in the text.

[†]Mixture of tension-type headache and migraine.

although they are present to a lesser extent in other members of CSS as a manifestation of CS [6].

It was not until 1990s when the presence of FMS in many chronic diseases with structural pathology was generally recognized among the researchers. Now, it is known that FMS is significantly associated with RA [10, 38–41], systemic lupus (SLE) [42–48], ankylosing spondylitis (AS) [49, 50], osteoarthritis (OA) [51], diabetes mellitus [52, 53], endometriosis [54], hypothyroidism [55], and inflammatory bowel disease [56, 57] (Table 2).

CS alone (without FM) has been reported in juvenile chronic arthritis [59], OA [60–65], endometriosis [66], carpal tunnel syndrome [67–69], chronic pancreatitis [70, 71], and Parkinson's disease [72–74]. It is likely that CS is the harbinger of future development of FMS, as may be demonstrated in future studies. It is as if “fibro, fibro everywhere and not a place for the (rational) eyes to hide.” An interesting question is, and data have not emerged yet to answer it, are other members of the CSS family, such as IBS and myogenic TMD also associated with these chronic diseases with structural pathology?

FMS has been reported also in Sjogren's syndrome, hepatitis C, HIV, and other infections, for example, Lyme disease. True to the title of this essay, however, only those diseases that usually cause pain have been described in this paper.

5. Critical Evaluation of the Studies: Imperfect but the Associations Are Real

A number of studies, both in the category of FMS in CSS and FMS in DWSP, are less than satisfactory because of small numbers, unspecified or nonstandard criteria used (both for FMS and the associated diseases), an absence of, or the use of inappropriate controls as well as inappropriate statistics, for example, a failure to adjust for multiple comparisons. Lack of blindness, a critical procedure to avoid bias, was universal, as is the case with most published studies in any disease.

However, reported prevalence rates of FMS in general were much higher than that in the general population. Since the results of all the studies converge in the same direction,

that is, increased prevalence of FMS compared with study or population controls, it seems proper to conclude that true associations of FMS with the diseases discussed exist.

6. Pathophysiological Mechanisms of Disease Associations with FMS: Central Sensitization Is Central

6.1. CS and CSS Conditions. Central and common to CSS diseases are CS. The pathophysiology of CS has been discussed elsewhere [6, 8, 75] and is beyond the scope of this essay. To be sure, the mechanisms involved in CS are multiple and complex [75]. Some of these mechanisms involve temporal summation (windup), long-term potentiation (LTP), heterosynaptic potentiation, a dysfunctional descending pain inhibition, and an activation of the descending facilitatory pathway [75]. It is also evident that input in one set of nociceptive fibers amplifies subsequent response to other nonstimulated nociceptive or nonnociceptive fibers (heterosynaptic potentiation). Such phenomena explain diffuse distribution of pain as well as allodynia.

After many years of research in animal models, human volunteers, and chronic pain conditions, several facts have emerged. While a noxious stimulus at some point in the past might have initiated increased neuronal sensitivity, no further nociceptive stimulus is necessary to perpetuate and sustain a state of hyperalgesia or allodynia. That sustained pain is no longer nociceptive in nature, provoking some physicians to take recourse to such derogatory lexicons as neurotics, malingerers, somatizers, and “medically unexplained symptoms” (read “your symptoms are all in your head”). In other cases, following the adequate initial nociceptive input, only a very low level of nociceptive stimulus was needed to maintain the CS [75].

With regards to tender points, it is often stated that they are subjective (thus there is an issue of secondary gain here), but CS may be elicited by stimuli that do not require patient's subjective response and are thus purely objective. Such an objective “test” is nociceptive spinal flexion reflex that has been demonstrated in several CSS conditions [6]. Using ascending and random paradigms, it has been demonstrated

TABLE 2: Prevalence of fibromyalgia syndrome (FMS) in chronic painful diseases with structural (organic) pathology (DWSP)

Chronic DWSP	% prevalence of FMS (mean)	% prevalence of FMS (range)	Reference no.
Rheumatoid arthritis	15.4	12.2–19.8	[10, 38–41]
SLE	16.2	5.0–25.3	[42–48, 58]
Ankylosing spondylitis*	30.4	10.8–50.0	[49, 50]
Osteoarthritis	11.0	—	[51]
Diabetes mellitus*	17.5	17.0–18.0	[52, 53]
Endometriosis	5.9	—	[54]
Hypothyroidism	34.0	—	[55]
Crohn's disease	26.0	3.0–49.0	[56, 57]
Ulcerative colitis	11.4	3.7–49.0	[56, 57]

SLE: systemic lupus erythematosus.

*Female patients only.

that response bias does not play a major role in pain report during CS testing in human pain laboratory [76]. Other objective findings are brain abnormalities by neuroimaging techniques and measurements of several neurotransmitters, for example, substance P, serotonin and its metabolites, and nerve growth factor [7].

There is evidence that CS is causal and not just an effect of chronicity among CSS members [6]. Asymptomatic individuals displaying CS in conjunction with genetic factors develop a CSS condition when followed up for a few years (see [6] for specific studies). Further, several centrally acting medications efficacious in FMS decrease CS [6].

The relative role of peripheral and central factors and ascending and descending pathways in fibromyalgia and other CSS diseases are not known at this time. In FMS, drugs acting on both ascending pathway (pregabalin) and descending pathway (e.g., duloxetine and milnacipran) are equally effective in general. In an editorial that evaluates several controlled studies, Martin Ingar states that descending pain control plays an important role in FMS [77]. It has been asserted that peripheral nociception is essential for CS in FMS [78]. In support of this view, the author cites a number of studies showing muscle abnormalities in FMS. Unfortunately, these studies did not include controls matched for aerobic fitness employing VO₂max, nor were they blinded. Bennett and his colleagues showed that 80% of the FMS patients were not physically fit as assessed by maximal oxygen uptake (VO₂max) [79]. The authors emphasized the need for using sedentary controls in FMS muscle studies.

Using appropriately matched sedentary controls using VO₂max, Simms et al. showed that energy metabolism in trapezius and tibialis anterior muscles of FMS patients, including intracellular pH, was normal when compared with controls [80]. In our initial uncontrolled muscle biopsy study, mitochondrial and other changes were found [81]. However, in our subsequent activity-controlled (indirectly sedentary controlled) and blinded study, no abnormalities in the trapezius muscle were noted in FMS as compared with the controls [82] (this is the only blinded muscle biopsy study in the literature to my knowledge).

However, contribution of peripheral input (versus pathology) in FMS has been demonstrated [83]. Staud et al.

showed that lidocaine injection in the trapezius muscle increased pressure pain threshold locally in both FMS patients and controls, but placebo injection did not. In addition, heat hyperalgesia of FMS patients in remote site (forearm) was also decreased, suggesting the role of peripheral input in heat hyperalgesia at a remote site (CS) [83]. However, clinical pain rating was not affected and the nature of such nociceptive locus in the muscle (e.g., inflammation and ischemia) is not clear, nor is it known if hyperalgesia from other forms of stimuli is maintained by peripheral nociception.

In a recent placebo-controlled study [84], Affaitati et al. have shown that injection of a TrP with local anesthetic deep in the muscle tissue (the placebo group received injections near the trigger points, presumably in superficial tissue) produced a decrease in number as well as pain intensity in TrP with an increase in pain pressure threshold both in TrP and nonpainful sites.

In the same study [84], the investigators applied hydroelectrophoresis to a FMS group having a painful joint or an area of rotator cuff partial tear using diclofenac and betamethasone in agarose gel in a tube as well as electrodes that were connected to a computerized current stimulator. The placebo group received a gel without active ingredients. The active treatment group reduced their FMS pain as well as number of TP, and the pressure pain threshold in nonpainful areas also increased. The placebo group did not demonstrate such improvement. This study also suggests that peripheral input contributes to CS. Interestingly, generalized hyperalgesia significantly improved in women with endometriosis following hysterectomy [66].

From the above discussion, it is clear that peripheral input is necessary in at least some patients. Visceral afferent input [75] may be operative in IBS [85], interstitial cystitis, and chronic pelvic pain. These patients also demonstrate somatic sensitization. Since no definite nociceptive pathology has been convincingly demonstrated in the peripheral tissue, is it possible that CS itself contributes to peripheral input in a vicious cycle? It is relatively easy to conceptualize the role of initial peripheral inflammation in cases of significant trauma incidents, for example, motor vehicle accident (MVA) and falls. In a “hit and run” phenomenon, the initial inflammation triggers CS and is maintained with

little or no further peripheral input as is well accepted from experimental models [75].

From other experimental examples, it seems that peripheral input may not be necessary at all [75]. Such apparently “innate” CS may be due to genetics, early adverse childhood experience, prenatal stress, chemical exposure (as in multiple chemical sensitivity), dopamine deficiency (as in restless legs syndrome and Parkinson’s disease), other neurotransmitter or endocrine abnormalities, past trauma as mentioned above (MVA, falls), severe and continuous sleep deprivation, and psychological trauma or stress. Other factors, for example, infection, autonomic nervous system dysfunction, inflammatory cytokines, and CNS microglia and astrocytes may contribute to CS of CSS conditions. The issue of relative role of peripheral and central factors in CS must be regarded unresolved at this time. Our best guess is that both are necessary and the relative contribution will vary from individual to individual, partly determined by genetic predisposition.

It is interesting to speculate that there are subgroups of CS. Some may result from obvious peripheral source (such as trauma, local inflammation, neuritis, or arthritis), and others are independent of such peripheral input because of genetics, sleep deprivation, or psychological distress. Moreover, some may predominantly result from reduced descending inhibition, others from descending facilitation, and yet others from cortical or limbic activation. Future research may determine that certain drugs work predominantly in one pathway but not the others. It is entirely possible that all of the neural pathways are involved in a given individual, likely in an interacting way.

6.2. FMS in Chronic Painful Diseases with Structural Pathology. An obvious source of nociception is present in RA, OA, AS, SLE (associated with arthritis), endometriosis, and inflammatory bowel disease. Pain often causes poor sleep that in turn may contribute to CS. Neuritis may contribute to CS and subsequent FMS in diabetes mellitus. The mechanism of CS in hypothyroidism [55] is not obvious. However, this is a single study and needs further confirmation. RA patients with concomitant FMS have worse disease activity with joint swelling and tenderness [40, 41] and greater psychosocial distress [41]. There were no significant differences in SLE activity between SLE patients with or without FMS. FMS features, for example, fatigue and poor sleep, were more common in the SLE plus FMS group. Whether inflammation, cytokines, genetics, or endocrine factors are contributory is unknown. Concomitant presence of FMS in the above diseases has universally shown greater disability in all studies that addressed the function and overall symptom severity.

Patients with OA plus FMS had greater sleep difficulties (70%) that correlated with fatigue [51]. Those with sleep problems had more severe OA, and depression was also common. It has been suggested that repeated acute inflammation in chronic pancreatitis leads to sensitization of peripheral pancreatic nerves that subsequently lead to central neuroplasticity [86]. In Parkinson’s disease, CS has been explained on the basis of somatosensory function of the basal ganglia. The role of D2 receptors in pain processing and

a deficiency of dopaminergic inhibition have been suggested [72].

6.3. Brain Changes in Chronic Pain. Until recently, central sensitization was attributed to an abnormal function of the nociceptive/antinociceptive neurons at different levels of neuroaxis leaving the brain structure intact. The advent of magnetic resonance imaging has demonstrated that not only there is a functional reorganization of the cerebral cortex in chronic pain, for example, FMS, IBS, and chronic back pain, but also there is actual anatomic decrease in the gray matter of various regions of the brain. This imaging technique is called MR morphometry. Although areas involved vary depending on the type of chronic pain, a general picture has emerged to involve the cingulate cortex, the orbitofrontal cortex, the insula, and the dorsal pons, representing a common “brain signature” [87]. The anterior cingulate cortex (ACC) plays a particularly important role in pain modulation and analgesia. ACC interacts with orbitofrontal cortex, PAG, and the amygdala. Together, it plays a crucial role in endogenous pain control. An anatomic shrinkage thus may contribute to enhanced sensitivity in chronic pain.

In FMS, a reduction in gray matter has been demonstrated in left parahippocampal gyrus, cingulate gyrus, insula, and medial frontal cortex. A decrease in gray matter involves simple reduction of cell size or atrophy of the neurons or the glia and does not necessarily imply neuronal destruction. Thus, with proper treatment of chronic pain, the gray matter may regain its original size [87]. An important question is whether continued and prolonged chronic pain will lead to irreversible degeneration. A crucial issue is whether the morphometric changes with atrophy of the gray matter are the cause or consequence of chronic pain. It seems that the changes result from ongoing CS. If so, centrally acting medications that diminish CS may retard or even reverse the gray matter change.

7. Significance of Disease Associations with FMS: Implication for Science and Patient Care

The concept of mutual association of the CSS has helped to better diagnose these conditions without extensive and unnecessary investigations. Recognition of an objective pathophysiological basis has contributed to a better understanding and treatment as well as physician acceptance of these common problems that cause much distress to our patients. Thus, it has helped us to understand why nonsteroidal anti-inflammatory drugs that act peripherally are not efficacious in FMS and why centrally acting medications as well as nonpharmacologic approach, for example, cognitive behavioral therapy (that act centrally), should be the appropriate management approach. Since total disease burden with functional impairment is greater in those with many associated conditions, a practicing physician should treat all these conditions for optimal results.

Since pathophysiologically the CSS disorders are similar, discovery of a certain mechanism and effective medication

in one disease may be applied to others. In developing new therapy, the effect of a new medication on CS may be investigated before undertaking expensive clinical trials.

The most important implication of concomitant FMS in chronic diseases with structural pathology is its recognition for optimal management. For example, when FMS symptoms (e.g., increased pain and fatigue) with multiple tender points are present in RA or SLE, they should not be automatically attributed to increased activity of these diseases and one should not prescribe higher doses of a biologic agent or corticosteroids without proper TP examination and laboratory evaluation. Appropriate attention should be directed to the management of FMS with centrally acting medications, cognitive behavioral therapy, and management of sleep problems. A patient with severe pain in OA will require both peripherally acting analgesics as well as those that act centrally, such as cyclobenzaprine, pregabalin, duloxetine, and milnacipran.

8. Summary: A Few Words to Store and Ponder

CSS diseases are based on a neurochemical pathology, and they are not psychological or psychiatric illnesses. Associated psychosocial issues, as may be present in any chronic disease, including RA or SLE or cancer should be addressed. CSS conditions are mutually associated, and a particular patient may have several of them. Multiple symptoms in these patients have a demonstrable pathophysiological basis and do not represent somatization. It is most important that FMS is suspected in all chronic diseases with structural pathology, for example, RA, SLE, OA, and AS, so that proper diagnosis and management can be undertaken.

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Review Article

The Clinical Concept of Fibromyalgia as a Changing Paradigm in the Past 20 Years

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Fibromyalgia (FMS) is a valid clinical condition that affects 2%–4% of the population with a pivot symptom of widespread body pain. The cause and cure of FMS are as yet unknown. The concept of FMS has evolved over the past two decades to incorporate symptoms beyond pain as contributing to the global spectrum of suffering. FMS is now recognized to be grounded in the neurological domain with evidence of dysregulation of pain processing. Appreciation of the neurophysiologic mechanisms operative in FMS has contributed to rational treatment recommendations, although a “gold standard treatment” does not currently exist. Ideal treatments for FMS patients should be individualized with emphasis on active patient participation, good health practices, and multimodal intervention, incorporating nonpharmacologic and pharmacologic treatments. Predictors of outcome, which is favourable in over 50% of patients, are unknown, but those with better outcome do more physical activity and use fewer medications.

1. Introduction

1.1. The Coming of Age after 20 Years. Fibromyalgia (FMS) is a condition characterized by the pivot symptom of pain throughout the body, and with abnormality centered in the nervous system [1]. Over the past 20 years, knowledge regarding both the clinical as well as the neurophysiological basis for this condition has accumulated. FMS affects 2%–4% of populations worldwide and is a cause of considerable suffering and functional impairment [2]. The clinical concept of FMS was initially described by Yunus and colleagues and crystallized by the publication of the 1990 American College of Rheumatology (ACR) criteria for the classification of FMS [3, 4].

An evolution of the clinical understanding of FMS over the last two decades has emphasised the importance of symptoms beyond pain which form an integral part of this condition and contribute to global suffering. In this context, it

became necessary for the criteria for a diagnosis of FMS to be reevaluated. The coming of age of FMS was heralded by the publication of updated criteria for the diagnosis of FMS, taking into consideration additional symptoms that are present to a variable degree in individual patients [5]. In addition, the new concept of FMS recognizes that symptoms are not an all-or-none phenomenon, but can be expressed with varying severity with periods of waxing and waning [6].

Neurophysiological studies have contributed to the acceptance of FMS as a valid condition. Demonstration of objective changes in the research setting has given clinicians the confidence to acknowledge a condition that presents with only subjective complaint and no objective clinical findings [1]. Dysregulation of pain processing has been demonstrated at various levels in the nervous system, but we still lack an objective test in the clinical setting to confirm a diagnosis or gauge response to treatments [1, 7]. However, this is no different than other well-recognized conditions, for example,

irritable bowel syndrome (IBS), migraine, and depression. It is undeniable that depression is a serious condition and yet it lacks an objective test.

Even with objective scientific support of abnormality, some scepticism still exists regarding the validity of subjective complaints requiring complete reliance on the practice of the art of medicine [8]. The controversy regarding the existence of this syndrome should now be put to rest. Efforts should be directed towards better understanding of the neurophysiological abnormalities, improved clinical recognition of patients, and translation of mechanistic studies into optimizing treatments. In this paper, we will present current concepts of FMS, which can be applied to the rational management of these patients. This paper will address current concepts and challenges pertaining to the clinical understanding of FMS.

2. Methods

This paper is based on a review of the literature achieved by a comprehensive literature search using MEDLINE, CINAHL, Cochrane, PUBMED, EMBASE, Cochrane Library, and PsycINFO. MEDLINE is widely used as a premier source for biographic coverage of the literature and the CINAHL for nursing literature. In addition to the formal search, a manual search from the references cited by original studies and reviews was also used where indicated.

2.1. The Clinical Challenge Remains. Clinicians are traditionally skeptical of any condition wherein there is disconnection between complaint and physical examination findings. This was first evident with the construct of phantom limb syndrome, now accepted as a real phenomenon and cause of pain in the absence of anatomical tissue in the periphery [9]. Beginning in the 1980's, there were emerging reports that body pain, in the absence of tissue damage, could be present [3, 10, 11]. These patients were mostly referred to rheumatologists in order to rule out some connective tissue disease. The notion that FMS is indeed a true entity follows publication of neurophysiological studies attesting to objective findings in a clinical condition that was often perceived to be nebulous.

Beginning with their landmark study in 1981, Yunus and coworkers have championed the recognition of this condition over the past three decades [3]. In this paper, the authors emphasized that FMS is more than pain, adding many other symptoms or associated conditions, for example, fatigue, stiffness (which is a prominent symptom in some patients), poor sleep, morning fatigue, tension-type headache, migraine, IBS, subjective swelling (which often leads to a misdiagnosis of rheumatoid arthritis), subjective numbness, anxiety, stress and depression, as well as modulating factors of pain and stiffness [3].

There have been physicians who have disputed the validity of a condition presenting with subjective complaints and associated with considerable functional impairment, without objective clinical findings. Some have even suggested that FMS was mostly a manifestation of depression [12, 13].

However, depression and FMS are biologically two different diseases, including an absence of central sensitization in depression by almost all stimuli [14, 15].

The clinical challenge of this condition remains as there is still no objective clinical finding or test to confirm the diagnosis, or gauge severity of symptoms. Physicians are required to assess this syndrome on the basis of subjective report only. This has fostered a sense of clinical uncertainty leading physicians to often consider a diagnosis of FMS only when other possible diagnoses have been excluded [16]. This insecurity by health care professionals may be a factor leading to frequent use of unnecessary investigations and can contribute to excessive medicalization of patients. It has been clearly documented that a definite diagnosis of FMS leads to reduced health care use and also better global patient health [17, 18].

2.2. Fibromyalgia Is More Than Just Pain. Initially, FMS was considered to be a condition of pain, and this concept was reinforced by the 1990 ACR criteria which only included features of pain and localized body tenderness [4]. The understanding of FMS today acknowledges that patients with FMS will have a symptom complex characterized by more than just pain with other complaints present with variable intensity [19]. Besides those mentioned above, that is, fatigue, sleep disturbance, cognitive changes, and mood disorder, other symptoms or associated conditions include restless legs syndrome, periodic limb movements in sleep, temporomandibular disorder (TMD), multiple chemical sensitivity, and interstitial cystitis [20, 21]. Each of these symptoms plays a variable role in the presentation of an individual patient and all contribute to a greater or lesser degree towards the overall effect of impaired quality of life and reduced functional activity.

The typical patient is female in her 40's or 50's with a few years of ill-defined musculoskeletal pain [22]. Onset of symptoms is usually gradual, but occasionally there may be a sudden onset following an identifiable event, such as a medical illness, a mentally stressful incident or physical trauma. Only 5–7% of the FMS patients are males. The clinical characteristics of FMS among men are similar to those in women, except that men have fewer symptoms, fewer pain sites, less frequent fatigue and IBS, and fewer tender points [23].

Pain is described as being diffuse, deep, and continuous often with periods of exacerbation. Pain symptoms may be modulated by various factors including psychological stress, excessive physical activity, fatigue, or changes in the weather [24]. Some patients also report a superficial burning quality to pain with increased sensitivity to painful stimuli—termed hyperalgesia, and may also have features of allodynia or pain following an innocuous stimulation such as touch [25]. Pain quality or unpleasantness is an equally important component of the pain experience, but is not commonly measured either in clinical practice or even in the study setting of patients with FMS.

Multiple symptoms contribute to the burden of suffering and are increasingly recognized as important from

the patient perspective and require attention for achieving optimal patient care [5, 19, 26]. Nonrestorative sleep is associated with widespread pain [27]. Many components of sleep have been measured as abnormal in FMS patients including sleep latency, sleep disturbance, and impaired daytime functioning [28]. Poor quality and duration of sleep has been shown to have a negative impact upon fatigue and affect [29]. Other sleep disorders such as restless leg syndrome or sleep apnoea may also occur in patients with FMS.

FMS patients can experience important cognitive dysfunction, which associates with pain, but not current depression or anxiety, and includes poor working memory, spatial memory alterations, free recall, and verbal fluency [30–32]. Cognitive symptoms are present in FMS even after adjusting data for age, medications, education, and depression [31]. Cognitive changes were however no different when compared to other pain patients, suggesting that pain per se may affect cognition [33]. Although most patients experience associated symptoms in varying degree, it is not required that these be present for a diagnosis of FMS.

Patients with FMS are heterogeneous and attempts have been made to group patients into categories to help direct treatments and predict outcome [25, 34, 35]. Subgrouping of patients with FMS according to psychological distress, depression in particular, has been most commonly reported, but longitudinal studies using subgroups to direct treatment and predict outcome are still required. In a recent analysis of over 3000 patients in various clinic settings in Germany, patients could be subgrouped into 5 categories depending upon pain characteristics and associated comorbidity of depression [25]. It is however still premature to attempt to categorize patients in the clinical setting, other than to pay particular attention to psychological status.

FMS may accompany other medical, neurological, or rheumatologic illnesses as a comorbid condition [36]. Conditions that have been associated with FMS include amongst others various rheumatologic conditions such as systemic lupus erythematosus and rheumatoid arthritis as well as neurologic disorders such as multiple sclerosis and postpolio syndrome [36, 37]. It is important to appreciate that FMS can coexist with these conditions in order to direct treatment appropriately. For example, a continuous complaint of pain due to FMS in a patient with rheumatoid arthritis would be incorrectly treated by increasing treatments with disease modifying agents, rather than addressing the symptoms associated with FMS.

2.3. The Conundrum of Criteria for Diagnosis of Fibromyalgia. Criteria for the classification of FMS were established almost two decades ago and take into account only the symptom of pain [4]. Although the cardinal symptom of FMS remains pain, symptoms of fatigue, sleep disturbance, cognitive changes, mood disorder, and other somatic symptoms contribute to the complexity of this syndrome [19].

The original 1990 criteria for classification of FMS pose at least 2 important practical problems [4]. Firstly, they were

developed specifically for the purpose of identifying patients for further research in this condition, and secondly, they addressed only the complaint of pain by means of a report of pain and examination of tender points. These criteria were often erroneously used to validate a diagnosis in individual patients in the clinical setting and did not take into account any other concomitant symptoms or severity of symptoms.

According to the 1990 criteria for a classification of FMS, in addition to widespread body pain, tender points were required to be present in at least 11/18 designated areas [4]. Tender points are located at soft tissue sites and reflect a reduction in pain threshold without underlying tissue pathology. Tender points have elicited considerable debate and their true value has been questioned. Tender point examination is a subjective test, open to individual interpretation and reflects an overall reduction in pain threshold, rather than a pathological process at the soft tissue site [38]. They may be present in normal individuals and can increase with age. Reliability is variable, ranging from good to poor [39, 40]. The association of pain report and tender point count is however poorly correlated, suggesting that these measurements represent different parameters of pain experience in FMS [41].

The correct examination method for tender points is also debatable. Methods that have been used include digital palpation, myalgic scoring, or dolorimetry [42]. Although digital examination is the most commonly used method of assessment, it is often not used by physicians caring for FMS patients [5]. There is also report of poor concurrent validity when tender points were examined digitally or by dolorimetry [43]. A person's current psychological state has been shown to influence measurement of tender points suggesting an association with distress rather than an accurate indicator of pain [44]. It has even been suggested that the examination of a few selected points may be sufficient to identify FMS [45]. It is also argued that tender points can be faked, and that they truly bear no consequence to the composite of suffering of FMS.

Taking into account the presence of symptoms other than pain and the questions posed by tender points, new criteria for a diagnosis of FMS have recently been published [5]. These new criteria, which may be viewed as complementary to the 1990 criteria, with the elimination of the tender point examination, perform well in identification of patients with a previous diagnosis of FMS [5]. The new criteria therefore have included other symptom domains and made them an essential part of the criteria set. However, elimination of tender points also decreases specificity. Thus, unlike the 1990 ACR criteria, the new 2010 criteria require exclusion of other conditions causing pain. Further, these criteria have not been validated in primary care setting. A recent German working group has concluded that FMS not only can be diagnosed for clinical purposes on the basis of symptoms without a tender point examination, but may also be established using the old 1990 ACR criteria [46]. Therefore, wisdom suggests that a clinical diagnosis of FMS today should not

be dependent solely upon a subjective count of tender points, but physicians may continue to use them for the present time in order to help solidify a diagnosis, as well as diagnosis of concomitant diseases, including depression [44, 47].

2.4. Fibromyalgia Is No Longer a Diagnosis of Exclusion. As early as 1989, Yunus has advocated that a diagnosis of FMS should not be made by exclusion, but rather by positive assessment of a constellation of symptoms [48]. Additionally, this clinical diagnosis should be made in the primary care setting without need for excessive and costly investigation or repeated specialist referral [16]. A detailed medical history and good physical examination can be used to exclude other rheumatologic conditions [8, 49].

Primary care physicians will be the first to evaluate and manage patients with a complaint of body pain due to FMS [16, 50, 51]. Family physicians are likely best suited for the care of these patients in view of the multiplicity of complaints and need for therapies that span many categories [16]. It is also questionable whether there is truly a need for the diagnosis to be confirmed by a medical specialist such as a rheumatologist. The value of specialist opinion should be for the patient in whom some other condition requires exclusion, rather than to confirm the diagnosis of FMS.

The clinical presentation of FMS can however be quite diverse with some areas of the body more painful than others, fluctuations in intensity of pain and variable intensity of other associated symptoms. Patients also differ considerably in terms of severity of functional impairment [52, 53]. This awareness of differences in presentation and heterogeneity of FMS is increasingly appreciated and is helpful to the clinician.

It is also time to dispel the fallacy that FMS is a primary psychogenic condition. As mentioned earlier, depression and FMS are biologically different conditions and depression is present in any chronic diseases, including those with organic pathology, such as cancer and coronary artery diseases. There is no question that the psyche and the body are tightly linked. Illness, particularly prolonged and poorly recognized, fosters mood disturbance. Conversely, mood disorder is associated with reduced motivation to be physically active, resulting in muscle deconditioning and subsequent pain complaint. FMS patients have a greater prevalence of lifetime as well as current mood disorder compared to other populations, but this should not be viewed as causative in each and every patient. It is possible that a vulnerable psychological status may predispose an individual to onset of a pain process, particularly if triggered by some event [54–56].

A clinical evaluation can be used to exclude most other conditions that could masquerade as FMS [49, 57]. Some common medical conditions that should not be missed in a patient presenting with chronic widespread pain include hypothyroidism, statin-induced myopathy, and polymyalgia rheumatica, especially in the older patient. These are familiar to primary care physicians and should not cause confusion. Of greater concern is that a diffuse pain syndrome may either herald or mask a treatable rheumatologic condition such as

rheumatoid arthritis, systemic lupus erythematosus, or a neurological illness such as multiple sclerosis, although this has only rarely been recorded in a few prospective studies.

3. What Causes Fibromyalgia?

Although the exact cause of FMS is unknown, abnormalities of nervous system pain processing can plausibly explain the persistence of pain in the absence of tissue damage [58]. The reason for this dysregulation is likely dependent upon a number of interacting factors, which include genetic predisposition, neurophysiological changes, and abnormal stress response. As following articles in this publication will elaborate further on pathogenesis, we will provide only a brief overview.

3.1. Genetic Factors. The evidence for genetic predisposition stems from studies showing familial aggregation of FMS [59, 60]. The odds ratio for a diagnosis of FMS was reported as 8.5 for a patient with a first-degree relative with FMS compared to having a relative with rheumatoid arthritis [60]. Familial aggregation should be a clue for some genetic contribution, but does not concretely prove a genetic link, as factors such as environment or a triggering event need to be taken into consideration. Candidate genes implicated in FMS include those controlling serotonin mechanisms, dopamine receptors, as well as metabolism of catecholamines [7, 61].

3.2. A Vulnerable Psychosocial Setting. Psychologic and stress-related factors are the second area of consideration regarding pathogenesis of FMS. Up to 40% of patients' report the onset of symptoms preceded by some triggering event, which might be either psychological or physical [62]. An abnormal physiological response to a stress mechanism could explain this phenomenon [54–56]. Impairment of the stress response, as measured by hypothalamo-pituitary-adrenal (HPA) axis response, was identified prior to the onset of chronic widespread pain in a prospective population-based study in England [63]. Psychological factors therefore play an important role in neurophysiological responses and have even been shown to affect changes at the spinal level [64].

Although FMS patients have a greater lifetime frequency of depression [65], depression per se appears not to be a direct causative factor in the pathogenesis of FMS [66]. Psychological symptoms, of which depression and anxiety are the most common, are however present in between 30 and 80% of FMS patients and contribute to poor global health [66].

3.3. Neurophysiological Changes. The concept of a neurological versus a purely somatoform disorder to explain the pathogenesis of FMS continues to stimulate debate [1, 67]. There is however convincing documentation of changes at various levels of the nervous system supporting an abnormality that is primarily neurogenic and will be further elaborated in ensuing articles in this supplement. A recent development in the pathophysiology of FMS is that it is

characterized by central sensitization (CS), well documented in the laboratory setting [20, 21, 68]. CS also binds FMS to other similar syndromes, for example, IBS and TMD, collectively known as central sensitivity syndromes [20, 21].

Chronic pain, as occurs in FMS, may be perpetuated by numerous interacting mechanisms, including increased excitation or reduced inhibition [58, 69]. Neurophysiologic studies have demonstrated evidence of dysfunctional central pain mechanisms including spinal hyperexcitability [68, 70], changes in thalamic and cortical pain matrix, as well as a grey matter volume [71, 72], and impaired function of normal descending inhibitory mechanisms [73, 74]. In simple terms, there is evidence for excessive pain-related neuronal activity at multiple levels of the central nervous system, structural, and functional changes in the brain by imaging studies and impaired function of normal descending inhibitory mechanisms.

4. Treatment Challenges

Treatments will be fully addressed in another article of this supplement. We will however provide a brief introduction by emphasizing new concepts that apply to management of FMS. Firstly, the concept of symptom-based treatments is logical and will allow a focussed starting point for a physician. Secondly, in the setting of no single “gold standard” treatment, a multimodal approach which includes both non-pharmacologic and pharmacologic treatments is rational [75–77]. In this regard, patient education with emphasis on an active role of the patients is critical. A patient-centred approach with individualization of management is very important.

Finally, as patients with FMS commonly report sensitivity to medications, clinical experience suggests that low doses of medications can be used, with gradual increase in dose depending upon efficacy and tolerability. It is the authors’ experience that doses of medications used in real life clinical practices are often much lower than those reported in industry-controlled studies. It is also notable that many of the adverse effects of medications present symptoms similar to those experienced by patients with FMS. Therefore, any patient being treated with a medication should be carefully evaluated for both efficacy as well as side effects, and medications should be discontinued unless there is evidence for definite benefit. In addition, combinations of medications are also more commonly used in practice, although there is limited evidence to support this practice from randomised clinical trials.

A key principle to management of patients with FMS is to encourage a shift of locus of control towards the patient and to ensure that the patient is an active rather than a passive participant in management. Understanding and support should form the cornerstone of care for these patients, with treatment strategies directed towards psychological status and physical symptoms within the context of family and society. Most patients will eventually with time find some treatment modality which will at least somewhat modulate, but

not cure symptoms, improve health status globally and improve function.

Evidence-based treatment guidelines include those developed by the American Pain Society (APS) in 2005 and the European League Against Rheumatism (EULAR) in 2008 [49, 78]. Recent reviews of treatment options state that there is good to moderate evidence for efficacy of over 20 treatment interventions in FMS, highlighting the uncertainty in management of these patients [79]. Approval of several drugs by the FDA in recent years, for example, pregabalin, duloxetine, and milnacipran, has been of great help in alleviating symptoms. Other medications may also be used [77].

Nonpharmacologic treatments are an important component of management and recommended in both sets of guidelines. These might include a tailored exercise program, water therapy, physiotherapy, relaxation, cognitive behavioural training, and psychological support [80].

5. Outcome Is Not Universally Bleak

Factors that can help predict the outcome for patients with FMS are as yet not fully understood, but patients that do well are more likely to be engaged in physical activity and use less medication. Realistic outcome goals should be emphasized. Reduction of symptoms should be translated into improved functional status. When a patient reports improvement in symptoms without a parallel functional change, the physician should question first the true efficacy of the treatment, secondly the side effect profile which might be contributing to poor effect on function, and finally patient motivation to achieve an improved health status.

A study of outcome done by postal questionnaire in the USA suggested continued pain and disability, with little change over time [52, 53]. However, publications from Australia, Mexico, and Canada have reported a more favourable outcome [81–83]. In a Canadian prospective study of FMS patients, almost 50% reported a clinically meaningful improvement in overall status of FMS over a 3-year observation period [83]. This improvement in outcome is further supported by the findings that 65% of subjects improved over a 2-year period in a community-based study in England [84]. Good long-term prospective studies are still lacking and many questions regarding prognosis and outcome remain unresolved.

6. Conclusion

There is accumulating and ample evidence in the scientific literature to support the existence of FM as an entity and as a diagnosable condition by its own characteristic features, even in the absence of an objective clinical test. There has been a substantial progress in an understanding of the pathophysiology of FMS in the past 20 years. Now it is known that it is a neurobiological disease. The mechanisms predominantly involve central sensitization, contributed by genetics, endocrine factors, poor sleep, psychosocial and physical stress, and physical trauma.

The initial clinical challenge is to correctly diagnose FMS on the basis of patient report and in the absence of an objective clinical test to confirm diagnosis or gauge severity of symptoms. Therefore, the accurate recognition of FMS and assessment of response to treatments still require the time-honoured art of clinical medicine [85]. There is currently no cure for FMS, and no single treatment is universally effective for control of pain and the associated features of this condition. Even in the absence of complete understanding of cause and pathogenesis, treatments can be directed to alleviate symptoms with the goal to improve functional status. Global outcome with attention to overall well-being represents a more realistic outcome measure that is both clinically applicable and pertinent to the patient. The translation of the knowledge of the pathogenesis of FM has however greatly facilitated introduction of treatment options, including use of pharmacological agents, that are finally beginning to show promise for the management of this illness.

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Review Article

Neurobiology Underlying Fibromyalgia Symptoms

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Fibromyalgia is characterized by chronic widespread pain, clinical symptoms that include cognitive and sleep disturbances, and other abnormalities such as increased sensitivity to painful stimuli, increased sensitivity to multiple sensory modalities, and altered pain modulatory mechanisms. Here we relate experimental findings of fibromyalgia symptoms to anatomical and functional brain changes. Neuroimaging studies show augmented sensory processing in pain-related areas, which, together with gray matter decreases and neurochemical abnormalities in areas related to pain modulation, supports the psychophysical evidence of altered pain perception and inhibition. Gray matter decreases in areas related to emotional decision making and working memory suggest that cognitive disturbances could be related to brain alterations. Altered levels of neurotransmitters involved in sleep regulation link disordered sleep to neurochemical abnormalities. Thus, current evidence supports the view that at least some fibromyalgia symptoms are associated with brain dysfunctions or alterations, giving the long-held “it is all in your head” view of the disorder a new meaning.

1. Introduction

In order to examine the neurobiology underlying the symptoms of fibromyalgia, we must first determine what those symptoms are. Until recently, fibromyalgia (FM) was diagnosed based on the ARC1990 criteria [1], which were widespread pain in combination with tenderness at 11 or more of 18 specific tender point sites. The provisional ACR 2010 FM diagnostic criteria [2], suggested as an alternative method of diagnosing FM, do not require the presence of tenderness, but rather include a list of several other symptoms, including fatigue, unrefreshing sleep, and cognitive symptoms, as well as a mix of some other symptoms that could include headache, depression, and lower abdominal pain/cramping. The hallmark symptom is still widespread pain, and a diagnosis of fibromyalgia requires this symptom. However, a patient must also have some of the other symptoms that are common among FM patients in order to reach

a composite score that would lead to a diagnosis of FM. In addition to clinical symptoms that make up the diagnosis of FM, experimental studies have identified a number of other abnormalities in FM patients, including increased sensitivity to multiple types of painful stimuli, increased sensitivity to other sensory modalities, and alterations in pain modulatory mechanisms. Further, neuroimaging studies have found functional, anatomical, and neurochemical differences in the brains of FM patients compared to healthy control subjects. Most of the clinical symptoms associated with FM have not been systematically studied in the experimental setting, but there are a number of studies that have provided an objective evaluation of the altered cognitive functioning and sleep disturbances reported in FM patients. Thus, this paper will focus on the experimental evidence related to FM symptoms and connect these perceptual and cognitive signs to abnormalities observed in the brains of FM patients.

1.1. Altered Pain Perception in FM Patients. The hallmark symptom of FM is widespread ongoing musculoskeletal pain. In addition, FM patients have been distinguished from other patients with widespread pain syndromes primarily by the presence of tenderness that has been assessed clinically by finding pain evoked by 4 kg manual pressure in at least 11 of 18 defined tender points. This tender point concept was not based on an understanding of the underlying pathophysiology, but rather on empirical observation. Thus, although the ARC-90 diagnostic criteria provided an important uniform tool for defining the FM syndrome, they did not validate the tender point concept, due to the circular evidence on which the criteria were based [3]. In fact, much evidence indicates that tender points are just sites normally more sensitive to pressure pain in all individuals [4–7] and that FM patients have an increased pressure sensitivity at non-tender-point sites as well [8]. Accumulating evidence now shows that FM patients have increased sensitivity to many types of painful stimulation, including pressure at non-tender-point sites [9], heat and cold pain [6, 10–14], electrical stimulation [6], and intramuscular hypertonic saline injection [15]. Despite the plethora of evidence for hypersensitivity to painful stimuli, there is less evidence that FM patients are more sensitive to innocuous somatosensory stimuli. Detection thresholds for tactile and electrical stimuli are not altered in FM [6, 12, 13], but Hollins et al. [16] found that FM patients rated innocuous pressure as more intense than did healthy controls, although the effects in the innocuous range were weaker than in the noxious range. The evidence for changes in cool or warm detection also is mixed, with most investigators finding no differences between FM and controls for heat [6, 10] or cold [10, 12], whereas one study found FM patients to have reduced heat detection thresholds [12], and one study found patients to have reduced cold detection thresholds [6]. Thus, it appears that the altered sensitivity within the somatosensory system is more profound in the noxious range than in the innocuous range.

1.2. Evidence for Generalized Hypersensitivity to Unpleasant Stimuli. The hypersensitivity of FM patients to painful stimuli has led some investigators to propose that fibromyalgia involves a hypervigilance to pain and pain-associated information [17–19]. However, there is now evidence that the hypersensitivity to unpleasant stimuli extends beyond the somatosensory system, which has led to the hypothesis that there is a generalized hypervigilance for sensory stimuli in FM [16, 20, 21]. A few studies have examined the sensitivity of FM patients in modalities other than pain and found perceptual amplification. FM patients have been shown to have decreased tolerance of unpleasant noise [20] and increased sensitivity to loud unpleasant auditory stimuli that parallels their increased pressure pain sensitivity [22]. Similarly, FM patients perceive unpleasant olfactory stimuli to be more intense and more unpleasant than do matched control subjects [23]. On the other hand, when pleasant odors were tested, FM patients and controls perceived the odors as equally intense, consistent with another evidence that the hypersensitivity across perceptual modalities may be

confined to stimuli in the unpleasant range [24]. Nevertheless, for pleasant odors, although FM patients did not rate them as more intense, they did evaluate the pleasant odors as less pleasant than did control subjects. Further, a range of auditory stimuli were rated as more intense by FM patients than by controls, and auditory stimuli rated as mildly pleasant by healthy subjects were rated as somewhat unpleasant by FM patients [16]. The finding of hypersensitivity in multiple modalities of stimulation, particularly for unpleasant stimuli, suggests that the evoked pain sensitivity of FM may be related to an altered hedonic appreciation for sensory stimuli, rather than to peripheral tissue abnormalities.

1.3. Other Phenomena Related to Altered Pain Perception. Other types of evidence from experimental pain studies in FM patients support the idea of a centrally mediated up-regulation of nociceptive activity in the CNS. A central pathophysiological process that appears to be disturbed in FM patients is the “windup” of central nociceptive processing of C-fibre input to the spinal cord, resulting in the perceptual phenomenon of temporal summation of pain. Windup of nociceptive activity is dependent on activation of the NMDA receptor complex in the spinal cord by input from C-nociceptors [25, 26]. Some FM patients show increased temporal summation of pain and increased after sensations at the termination of noxious stimulation [27]. These enhanced responses could be related to one or more of several possible factors: (1) an ongoing peripheral source of input from C-nociceptors other than the applied stimulus; (2) sensitized NMDA receptors on central nociceptive neurons; (3) abnormalities in descending modulation; (4) abnormal processing at supraspinal levels. Evidence of increased sensitivity in multiple sensory modalities suggests that ongoing C-nociceptor input cannot alone account for FM symptoms, indicating that there probably also are either sensitized NMDA receptors, abnormalities in modulatory systems in the brain, or abnormal sensory processing at spinal or supraspinal levels. Increased sensitivity has been demonstrated at the spinal level in FM [11]. Staud et al. [28] showed that an NMDA inhibitor reduced temporal summation in both healthy people and FM patients, suggesting that NMDA receptors probably are not sensitized in FM. On the other hand, experimental evidence shows that there are abnormalities in pain modulatory systems in FM patients that could account for altered temporal summation and other putative spinal effects.

1.4. Altered Pain Inhibition in FM Patients. For hundreds of years, clinicians have known that pain inhibits pain, a phenomenon termed “counterirritation.” More recently, a physiological basis of this phenomenon has been identified; the application of noxious stimulation activates an endogenous analgesic system involving supraspinal descending control of dorsal horn nociceptive activity. This system is termed “diffuse noxious inhibitory control” or DNIC and its physiological basis in the spinal cord has been studied extensively in anesthetized animals [29, 30]. Nevertheless, when competing noxious stimuli are presented in conscious humans, other systems that modulate pain, such as distraction, also are

probably in effect, so that care must be taken in inferring that perceptual effects are due to DNIC. Accordingly, a group of interested researchers has suggested that the term “conditioned pain modulation” be used in humans studies to avoid the mechanistic implication [31]. Studies that have examined conditioned pain modulation in FM patients show that conditioning stimuli that produce an analgesic response to experimental pain stimuli in healthy control subjects fail to have an effect on FM patients [13, 32–34]. One of these studies controlled for the effects of distraction and habituation and found a similar lack of conditioned pain modulation in FM patients [33], suggesting the possibility that the DNIC system is in fact impaired in these individuals. Alternatively, DNIC and other descending inhibitory systems could be activated by the widespread pain of FM, and the failure to demonstrate DNIC in FM could represent a ceiling effect in which these activated systems cannot be further engaged by the experimental manipulations [8]. In addition, distraction can have a powerful pain-inhibiting effect [35–39], and some researchers have suggested that FM patients have altered attentional focusing, with a hypervigilance to unpleasant stimuli (see discussion above).

2. Other Symptoms of FM

2.1. Altered Cognitive Function in FM Patients. In addition to pain, many patients with fibromyalgia complain of problems with memory and concentration, often referred to as “fibrofog” [40–43]. This clinical symptom has received a large amount of experimental study, and studies using objective cognitive tests substantiate patients’ subjective reports of cognitive dysfunctions, most commonly related to speed of information processing, attention, and memory [43–56]. The most robust deficits in tests of memory and attention have so far been observed in paradigms involving a prominent distraction from a competing source of information, wherein FM patients are less capable than healthy controls to retain new information when rehearsal is prevented by a distraction [49, 50, 57]. Milder deficits have been observed in memory free of distraction at encoding [43, 44, 48, 49, 51, 58, 59]. FM patients frequently display greater impairments in the ability to actively retrieve past episodic events in the absence of a cue (free recall) than on recognition tests, which serve to evaluate the retrieval of remembered information and are more resistant to the effects of impaired attention and concentration [43, 44, 48, 51]. It has thus been proposed that memory impairments in FM are more highly related to attentional factors that modulate the efficiency of memory functioning than to primary memory processes per se [48, 60, 61]. Thus, the inability to manage distraction seems to be a particular problem in fibromyalgia patients and is reflected in patients’ reports of difficulty concentrating and dealing with complex, rapidly changing environments [61] and by memory tests showing performance decrements in the presence of distraction. Impaired cognitive performance is evident even after controlling for anxiety and depression and the influence of medications that might affect cognitive functioning [43, 50, 52, 58]. Another area of cognitive

functioning that has been shown to be abnormal in FM is that of emotional decision making [62, 63]. A similar deficit has been shown in chronic back pain patients, suggesting that this is not unique to FM [64].

2.2. Sleep Disturbances in FM Patients. Many FM patients complain of unrefreshed sleep. Several laboratory studies using objective measures of sleep physiology such as EEG substantiate these reports by showing disordered sleep architecture in FM patients, including delayed onset to sleep, altered sleep stage dynamics, and reduced slow wave sleep (deep sleep) and rapid-eye movement (REM) sleep [65–68]. The intrusion of EEG frequencies characteristic of wakefulness (alpha waves) in the deep non-REM sleep (delta waves) seems to be a prominent feature of the nonrestorative sleep of FM patients [65, 69–71]. Further, patients with FM often have fragmented sleep resulting from periodic intrusions such as involuntary limb movements (restless legs), sleep apnea, and arousal disturbances [68, 72–74]. Although FM patients tend to report greater disturbances in sleep duration and quality than shown in laboratory studies, and their subjective reports correlate better with the severity of clinical symptoms [75], objectively measured sleep disturbances have been associated with pain and subjective daily sleepiness in several studies [67, 68, 71, 73].

3. Brain Changes That Could Underlie Symptoms

3.1. Neural Basis of Pain Amplification and Altered Pain Modulation. Functional brain imaging studies support psychophysical findings of increased pain perception in FM, in that there is an augmentation of sensory processing throughout pain-related brain regions [9, 76–81]. This is important, since laboratory findings of increased sensitivity could be interpreted as a reporting bias, rather than evidence of increased activation in pain pathways. The functional imaging studies have found that fibromyalgia patients show significantly more activity in response to pressure and thermal stimuli compared to controls in a number of brain regions. Increased activations were observed not only in limbic structures, but also in brain regions involved in sensory-discriminative processing, such as primary and secondary somatosensory cortices, which supports the view that neural responses to afferent signals are amplified in fibromyalgia.

Although the increased pain-evoked brain activations corroborate patients’ reports, the correlation between increased brain activity and increased pain perception does not explain how the afferent signal is amplified. As discussed above, there is psychophysical evidence of dysfunctions in pain modulation as well as pain perception. There is now much evidence that the activation of descending control circuitry is involved in pain modulation and that this circuitry includes parts of prefrontal, cingulate, and insular cortices [23, 36, 37, 82, 83]. A number of anatomical imaging studies in FM patients reveal decreased brain gray matter in these regions [84–90]. Although the cellular basis of decreased gray matter in FM patients is not known, it is possible that due to

neuronal loss, decreased dendritic arborisation, or changes in glial activation, pain inhibitory systems do not work in FM patients as well as in healthy individuals.

Consistent with the idea that pain modulatory systems may be disturbed in fibromyalgia are data showing that some FM patients have abnormalities in neurochemical systems involved in pain control, including the forebrain opioid and dopamine systems. A positron emission tomography (PET) competitive binding study using the D2/D3 receptor antagonist [^{11}C] raclopride showed that striatal dopamine is released in response to painful muscle stimulation in healthy subjects, but not in FM patients [15, 91], which might partially explain the increased sensitivity of FM patients to the painful muscle stimulation. For the opioid system, investigators using PET found that FM patients had decreased binding potentials at rest for the exogenously administered μ -opioid receptor agonist carfentanil in several brain areas, including the ventral striatum, the anterior cingulate cortex, and the amygdala [92]. These areas are implicated in pain and its emotional modulation, and correspondingly, the binding potentials showed a negative relationship with the magnitude of affective pain scores relative to the sensory scores. Although results of this study do not tell us whether levels of endogenous opioids were increased or whether receptor availability was decreased, the findings support the notion that disturbances in the opioidergic system might be related to the increased pain sensitivity in fibromyalgia. For both dopamine and opioids, the ongoing widespread pain of FM could lead to a tonic activation within these systems and thus be a main factor in altering receptor availability and associated responsiveness to externally applied painful stimuli.

3.2. Neural Basis of Cognitive Symptoms. It is well known that cognitive capabilities such as attention and memory functions decline continuously across the adult lifespan [93], which, together with findings of accelerated age-related decline of brain gray matter observed in FM patients [84], suggests that there may be a relationship between gray matter reductions in FM and cognitive deficits in these patients. Two recent studies have linked FM to impaired emotional decision making [62, 63]. Anatomical imaging studies have reported that FM patients have decreased gray matter in the medial prefrontal and insular cortices [84, 85, 89], areas implicated in emotional decision making [94–99]. Together, these data suggest a possible association between gray matter loss and emotional decision making in FM. One study has directly examined the relationship between performance on working memory tasks and gray matter in FM patients and found that an individual's performance was positively correlated with gray matter values in medial frontal and anterior cingulate cortices, thereby providing direct evidence for an association between altered working memory and gray matter morphology in fibromyalgia [51]. Both of these brain regions, together with lateral premotor cortex, lateral prefrontal cortex, frontal poles, and posterior parietal cortex, are areas known to be related to working memory processes [100–105]. In terms of the neurochemical abnormalities

in FM discussed above, dopamine plays an important role for cognitive functioning. Multiple lines of evidence demonstrate the importance of mesocortical and striatal dopaminergic pathways in memory tasks, perceptual speed, and response inhibition (see [106] for review). Thus, there is an overlap between tasks in which fibromyalgia patients perform poorly and tasks that are related to dopamine functioning, suggesting that a dysfunctional dopamine system could contribute to the cognitive symptoms of fibromyalgia.

3.3. Neural Basis of Sleep Disturbances. While many studies have used EEG and related methods to show various aspects of disordered sleep physiology in FM patients, little is known about the neurobiology underlying these disturbances. Several neurotransmitters have been proposed to influence CNS hypersensitivity associated with sleep alterations. For example, inhibition of the CNS serotonin synthesis has been linked to insomnia and increased pain sensitivity [107]. Accordingly, in FM there is evidence for low serum and cerebrospinal fluid serotonin levels [108, 109]. Injecting amounts of substance P into the CNS of rats has been shown to reduce sleep efficiency, increasing latency to onset to sleep and provoking awakenings from sleep [110], and there is evidence for elevated cerebrospinal fluid levels of substance P in FM patients [111, 112].

3.4. What Do the Psychophysical, Cognitive, and Neuroimaging Studies Tell Us about the Neurobiology Underlying FM Symptoms? The wealth of experimental evidence showing that FM patients are hypersensitive to painful stimuli, as well as unpleasant stimuli from other sensory modalities, in conjunction with functional brain imaging data showing increased stimulus-evoked activation throughout nociceptive pathways, shows that the defining symptom of FM—increased pain—is in fact real and not just a response bias of the patients. The finding that perception is increased in multiple modalities speaks against the hypothesis that FM pain is due to an upregulation of peripheral nociceptive processes. Further, psychophysical evidence that descending modulatory systems are altered in FM patients supports the opposing idea that FM symptoms are at least in part caused by alterations in CNS processing of the pain signal, including a dysregulation of pain modulatory systems. Nevertheless, the apparent dysregulation within these systems could be caused and/or perpetuated by a tonic activation related to the presence of ongoing widespread pain, so that the systems are saturated and cannot regulate further in response to external stimuli.

Since similar descending control systems, including attentional and emotional regulatory circuitry, affect multiple sensory modalities [113–119], a dysfunction (or saturation) in these systems could lead to the hypersensitivity in multiple sensory modalities. FM patients show reduced habituation to nonpainful tactile stimuli and increased cortical response to intense auditory stimuli, both of which have been linked to deficient inhibition of incoming sensory stimuli [120, 121]. Also in support of the idea of a central dysregulation or saturation of pain modulation are changes

in the opioid and dopamine neurotransmitter systems, both known to be involved in hedonic regulation [122].

Finally, the findings that FM patients not only perceive themselves to have altered memory and concentration (“fibrofog”), but also in fact perform poorly on multiple cognitive tests, even when depression is excluded as a contributing factor, suggest that there are alterations in brain function. The anatomical brain imaging studies that show reductions in gray matter in frontal regions important for cognitive function further indicate that this common symptom of FM is based on altered brain function. Together, the experimental evidence provides strong support for the idea that FM symptoms are related to dysfunctions in the central nervous system. The cause of these changes cannot be deduced from the available evidence, as it is correlational in nature. Did long-term ongoing pain cause the changes or did the changes cause the pain? Without a relevant animal model or long-term longitudinal studies, we cannot answer these questions. Nevertheless, we can at least say that fibromyalgia is real and that it is associated with multiple changes in the brain.

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Review Article

Early Life Adversity as a Risk Factor for Fibromyalgia in Later Life

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The impact of early life events is increasingly becoming apparent, as studies investigate how early childhood can shape long-term physiology and behaviour. Fibromyalgia (FM), which is characterised by increased pain sensitivity and a number of affective co-morbidities, has an unclear etiology. This paper discusses risk factors from early life that may increase the occurrence or severity of FM in later life: pain experience during neonatal life causes long-lasting changes in nociceptive circuitry and increases pain sensitivity in the older organism; premature birth and related stressor exposure cause lasting changes in stress responsivity; maternal deprivation affects anxiety-like behaviours that may be partially mediated by epigenetic modulation of the genome—all these adult phenotypes are strikingly similar to symptoms displayed by FM sufferers. In addition, childhood trauma and exposure to substances of abuse may cause lasting changes in developing neurotransmitter and endocrine circuits that are linked to anxiety and stress responses.

1. Introduction

The causes and underlying pathologies dictating and affecting the development of fibromyalgia (FM) are not yet clear, but as a syndrome affecting between 2 and 4% of the population, with a higher incidence in women [1, 2], it is a hot topic in pain research at this time. As discussed in detail elsewhere in this paper, FM constitutes a chronic pain syndrome, concomitant with a myriad of symptoms, including muscular stiffness and tenderness at specific locations, chronic fatigue, cognitive and mood disturbances, and insomnia. Documented pathophysiologies related to FM include aberrations in neuroendocrine systems, dysfunction in stress regulation and neurotransmitter function, and alterations in brain structure and connectivity. In addition, FM is linked to psychosocial and environmental triggering factors. This paper will explain and discuss some of the potential risk factors of early life adversity (ELA) that display markedly similar outcomes that constitute some of the later symptoms of FM. Pain researchers have clearly shown that noxious events during early life can cause a number of long-lasting changes in pain processing systems in the older organism, which could contribute to the increased pain sensitivity noted in FM patients. In addition, factors

such as premature birth and related exposure to stressors, maternal deprivation, and physical or substance abuse in the perinatal period can influence developing neurobiological and psychological states in a number of ways, often causing changes in adulthood similar to the disturbances seen in FM sufferers. Early life pain, hospitalisation, deprivation, emotional trauma, and abuse are discussed in this paper, with speculation about their potential impact upon fibromyalgia.

2. Risk Factor: Painful Experiences during Infant Development

It is well established that the experience of pain during infancy causes long-lasting alterations in pain processing that extend well into childhood and adulthood [3–5]. This adds weight to the need for effective understanding and management of pain in neonates, in order to minimise later consequences of early pain experience (see [6, 7]). Infants born with preexisting illnesses or under difficult circumstances, born preterm or needing early surgery, may all need hospitalisation for treatment. In addition, the incidence of premature birth and the necessary associated critical care has increased over the last 20 years [8], and the

technology to aid survival has meant that infants as young as 24 weeks postmenstrual age (PMA) can survive and develop on the neonatal intensive care unit (NICU). In these clinical settings, multiple painful procedures may be performed daily for routine monitoring, in addition to any necessary surgeries infants require—for example, Simons et al. [9] found that during the first 14 days of hospitalisation, neonates were subject to an average of 14 painful procedures per day. A more recent study [10] confirmed these findings, showing that neonates were exposed to a daily average of 16 painful and/or stressful procedures and that up to 80% of children were not given specific analgesia for these procedures. This high number of procedures, perhaps repeated over a number of weeks or months, affects the developing nociceptive circuitry of the infant in ways that cause long-lasting changes in pain processing (see [3]) and could explain some of the abnormalities in pain processing displayed by FM patients.

2.1. *The Effect of Painful Stimulation on the Human Neonate.*

Studies of ex-premature children provide compelling evidence for the long-term effects of human early pain experiences. Walker et al. [11] recently presented data on sensory sensitivity in a cohort of 307 extremely preterm infants born at less than 26 weeks postmenstrual age (PMA) in 1995 and followed throughout their lives so far (the UK EPICure cohort). Quantitative sensory testing (QST) established sensory thresholds in these children at age 11 and showed that these extremely preterm children had significantly *decreased* sensitivity to non-noxious mechanical and thermal stimuli compared to age- and sex-matched term born controls. A similar result has been seen in 9–12-year-old children who had previously experienced neonatal cardiac surgery—subjects were significantly less sensitive to nonnoxious mechanical and thermal stimuli at both the previously operated site and noninjured areas [12]. The foundations for this baseline hyposensitivity may be laid whilst children are being cared for on the NICU—following children with NICU experience at 4, 8, and 18 months of (corrected) age, dampened pain responses to immunisation and blunted nociceptive sensitivity to everyday bumps are seen, compared to full-term controls with no NICU experience [13, 14]. Hermann et al. [15] also found elevated heat pain thresholds (i.e., decreased sensitivity) in children who had been hospitalised for a prolonged period as infants and had undergone repeated painful procedures as part of their treatment.

Importantly and more relevant to FM, when pain-exposed neonates are reexposed to noxious stimuli in later life, *hypersensitivity* to the stimulus is observed. For example, when ex-NICU infants were tested on their perceptual sensitisation to heat pain, where a constant temperature is given for 30 seconds and the change in perception gauged at the end, neonatally hospitalised children showed increased sensitisation compared to nonhospitalised controls, who habituated to the thermal stimulus [15]. Interestingly, heat pain thresholds of all groups of children were increased in the presence of the children's mothers [16], highlighting the

importance of social support on the pain experience (which has also been shown to be effective in alleviating the impact of FM [17]). More studies confirm the hypersensitivity seen in ex-premature infants after noxious stimulation in the older child. For example, behavioural sensitivity to noxious mechanical stimuli at the heel persists for at least the first year of life after repeated NICU heel lance experience [18]. Deep somatic and visceral noxious stimulation resulting from early invasive surgery leads to sensitisation of pain responses to later surgery, particularly in regions of the body served by the same spinal nerves as those affected by the initial surgery [19]. These effects are not limited to surgical pain. Children who suffered from burn injuries in infancy (6–18 months of age) showed lower mechanical pain thresholds and greater perceptual sensitisation to both heat and mechanical pain stimuli at sites not originally affected by the burn at ages 9–16 [20]. An interesting study by Buskila and colleagues [21] may be particularly relevant to adult fibromyalgia patients: this study showed that ex-NICU neonates had, as 12–18 year olds, significantly more “tender points” and lower tenderness thresholds than matched full-term children. Seeing as FM diagnosis has been partly based on soreness at a certain number of “tender points”, it could be informative to follow these adolescents over time and assess later FM prevalence.

Summarizing the above, hypo- as well as hypersensitivity has been observed as a consequence of early life pain. The way in which sensory processing is altered by early life pain may be dependent on several factors. For example, the developmental time point at which injury is experienced can dictate the lasting effects of these injuries (see discussion of the “critical period” in the section “Early Life Exposure to Pain May Influence Fibromyalgia”). In addition, the type of noxious insult (surgical, burn, etc.) and therefore the relative proportion of nociceptors that are activated (i.e., C fibre or A delta nociceptors) may influence the exact nature of altered sensory processing. Finally, as detailed in the following section, it may be that discrete CNS systems are responsible for decreases in tactile and thermal sensitivities and the hyperalgesia seen in neonatally injured humans.

Animal models of neonatal pain show markedly similar effects as those seen in humans and are crucial to identify and understand cellular mechanisms that are impossible to study in humans. The development of nociceptive circuitry has been studied in-depth, and the neurobiology underlying long-lasting changes is becoming increasingly clear (see [3]).

2.2. *The Neurobiology Underlying Long-Term Effects Can Be Studied in Animal Models.*

The utility of animal models is illustrated by evidence showing that the generalised hyposensitivity to mechanical and thermal stimuli shown in humans with early life pain experience (e.g., [14]) is likely mediated by changes in the brainstem regions that modulate ascending afferent input, in particular the periaqueductal grey (PAG) and rostroventral medulla (RVM), which can either enhance or suppress nociceptive input from the spinal cord [22–25]. In the rat, these areas (PAG and RVM) mature over the first three weeks of age [26–28], which corresponds approximately to the time span from the third

trimester of gestation to adolescence in human [29, 30]. La Prairie and Murphy [31] injected carrageenan (which causes short-term inflammation lasting around 24 hours) into the hindpaw of male and female rats on the day of birth and saw that, in adulthood, the animals showed decreased sensitivity to thermal stimulation in both the previously injured and uninjured paws. In addition, increased levels of endogenous opioid mRNA were seen in the PAG of the adult animal, and blockade of brain opioid receptors with naloxone abolished this decreased pain sensitivity, leading the authors to speculate that neonatal inflammation induces an upregulation in endogenous opioidergic tone that is maintained into adulthood, so that the adult displays a system that is constitutively “dampening” afferent spinal cord input, leading to decreased pain responses [32].

This suggests that early pain can alter endogenous pain inhibitory circuitry. However, FM patients show hyperalgesia rather than hyposensitivity [33–36]. Enhanced nociceptive responsiveness is consistently observed in neonatally injured animals upon adult reinjury and likely results from a number of changes in nociceptive circuitry induced by early pain exposure, all of which result in a nervous system “primed” to respond in an enhanced manner to a new insult. For example, neonatal inflammation causes thermal hyperalgesia in rat pups that lasts from several weeks up to adulthood [37–39]. This inflammation and concomitant release of inflammatory and trophic molecules results in enhanced spinal neuronal responses to paw pinch in the adult, as well as increased primary afferent nerve fibre innervation of the dorsal horn of the spinal cord [40]. Inflammation-induced alterations in the developmental connectivity of the spinal cord [41] and/or sprouting of nerve fibres at the skin also result in an increased nociceptive response [42]. Neonatal skin wounds, like inflammation, cause drops in mechanical withdrawal thresholds at the site of injury and increase in dorsal horn receptive field size weeks after the wound had healed [43, 44], as well as causing release of nerve growth factors leading to hyperinnervation of the skin, and increased sensitivity to noxious stimuli in later life [45]. This is consistent with human studies showing hypersensitivity after injury in children, especially those with previous surgical history [19, 46, 47]. Therefore, the apparent contradiction between generalised decreased sensitivities and hyperalgesic responses to new noxious stimulation may in part be due to discrete CNS processing systems dictating behavioural responses, for example, enhanced endogenous pain inhibition at a brainstem level, but increased hypersensitivity/hyperinnervation at a spinal level.

2.3. Early Life Exposure to Pain May Influence Fibromyalgia. As explained above, whilst La Prairie and Murphy [31] showed that animals subject to neonatal inflammation showed generalised hypoalgesia to thermal stimuli at baseline in adulthood, when animals were reinjured as adults, animals were *more* sensitive to noxious thermal stimulation. Importantly, all of these effects were greatest in female animals. This finding might be relevant to fibromyalgia syndrome, as the incidence of FM is greater in women [48]. Furthermore, disturbances in descending pain modulation

have been reported in FM patients [49, 50] and patients show decreased blood serum levels of serotonin and lower CSF levels of serotonin and noradrenaline metabolites [51–54]. This may be relevant to FM, as there is a discrete descending serotonergic system projecting from the RVM that modulates spinal cord excitability [55–59]. Furthermore, noradrenergic signalling, originating from the locus coeruleus, has a role centrally in feedback inhibition of pain (see [60]).

The developmental timing of any injury determines potential long-term effects, leading to the concept of a “critical period” of nociceptive development, within which pain experience permanently alters pain processing (see [5, 61]). To illustrate, giving a skin incision to the hindpaw of a neonatal rat at postnatal days (P) 3 or 6 produces an increased pain response to a repeat incision 2 weeks later. If, however, the initial incision is performed after the critical period (at P10, 21, or 40 followed by repeat incisions 2 weeks later), the enhanced hypersensitivity to the later incision is not seen [61]. Understanding the concept of a “critical period” of nociceptive development may be useful for determining some of the root causes of fibromyalgia—as human infants born prematurely display long-term alterations in pain processing, it is possible that early pain experience within this time window contributes to some of the adult pain in FM. At this time, there is very little literature that attempts to delve into the neonatal and childhood life of current FM patients.

2.4. Adequate Pain Management of Neonates May Decrease FM Prevalence in Adults. In order to prevent these physiological disturbances, adequate pain management for human neonates is an important clinical issue. Pain management of neonates is a difficult area, as neonates cannot give verbal feedback on their pain experience, and are physiologically very different to the adult state that dictates dosage, metabolism and efficacy (i.e., [7]). Current treatments include morphine and benzodiazepines both for postsurgical pain and general sedation on the NICU [62], as well as non-pharmacological interventions such as the administration of sucrose for acute procedures including heel lance [63] (although the effectiveness of these interventions and the long-term effects of chronic exposure to sucrose and drugs such as morphine are not yet clear [64, 65]). The effects of these continue to be studied, and given the long-term effects of early pain as discussed above, adequate pain management for neonates might reduce various pain syndromes in later life, including fibromyalgia. The importance of adequate analgesia for neonatal procedures is illustrated in a seminal paper by Taddio et al. [46]. They performed a double-blind, randomized, controlled trial (RCT) on the effects of a topical anaesthetic (EMLA cream) used during male neonatal circumcision, which has traditionally been done without anaesthesia or analgesia. Looking at pain responses in the infants when they were later vaccinated at 4–6 months, boys who had been treated with the EMLA cream when circumcised showed lower pain responses than those who received no anaesthesia, and the circumcised groups both showed higher pain scores than uncircumcised controls.

3. Risk Factor: Premature Birth and Related Stressors

As discussed above, pain during the neonatal period can alter the nociceptive processing pathways of an organism for life, potentially impacting upon the development of fibromyalgia in later life. Many of the human studies mentioned in the previous section recruited infants born prematurely, needing the intensive care unit for survival. The NICU is a strange and abnormal environment in comparison to the womb, and premature infants are exposed to many stressful stimuli in addition to repeated nociceptive procedures, such as light, noise, tactile stimulation, surgery, medication, and maternal separation, all of which could feasibly affect development [66]. Indeed, even the act of nursing very premature infants (changing diapers etc.) causes increases in stress hormones [67]. In addition to the long-term effects of increased pain sensitivity in these children are effects upon stress regulatory systems, where a large body of evidence suggests that prematurity and the resulting experiences on the NICU can permanently alter in particular the hypothalamic-pituitary-adrenal (HPA) axis. As this is shown to be disturbed in FM patients [68–71], it is possible to speculate that premature birth in itself may influence the occurrence of FM in adults.

3.1. Premature Birth Impacts upon the Body's Response to Stressors. The HPA axis is the body's stress-response system. Cells of the hypothalamus produce corticotropin-releasing factor (CRF) in response to an environmental stressor, and a cascade of events ultimately causes adrenaline release and the production of the “stress hormone” cortisol. Under normal circumstances, adrenaline and cortisol release is terminated via a negative feedback circuit. In FM, however, HPA axis regulation appears to be abnormal. Whilst the precise dysfunctions in stress regulation via the HPA axis are not clear at this point (some studies find FM patients show hypocortisolism (see [72]), whilst others describe hypercortisolism and HPA hyperactivity [68, 69, 73]), what is clear is that HPA axis function is not normal in many patients. The discrepancy between findings of hyper- and hypocortisolism may be due to a number of factors. For example, disease-specific patient characteristics, such as symptom profiles and comorbidities, as well as disease-nonspecific characteristics, such as age, gender, personality traits, and socioeconomic background, can affect results. In addition, markers of HPA axis function differ between studies (e.g., basal levels or evoked cortisol responses) as do the time points of measurement (e.g., upon waking or following diurnal fluctuations), in addition to other technical details. In instances where the literature does not permit any conclusions on the direction, we refer to *alterations* in HPA axis function, rather than increases or decreases.

Nevertheless, the way in which premature birth alters cortisol levels and cortisol responses compared to term-born controls is relatively unambiguous. Grunau et al. [66] propose that early stressors such as those routinely experienced in the NICU can impact upon development of

the HPA axis by causing consistent release of adrenaline and cortisol and increase the “allostatic load” of the neonate—the concept of “allostasis” explaining how an organism's physiological systems fluctuate over time in order to meet the demands of external stressors, in an attempt to regain homeostasis (bodily equilibrium). The impact of chronic stress and the accompanying neuroendocrine responses may also ultimately cause long-lasting damage to bodily organs and contribute to chronic disease development [74]. In preterm neonates, this may manifest as a life-long shift in HPA axis balance.

Basal cortisol levels are often low in neonates on the NICU in comparison to term infants, which is unexpected considering the length of time that infants spend there and the stressful procedures the still-developing neonate is subject to [75, 76]. Grunau and colleagues have published a series of studies giving convincing evidence that NICU experience causes “resetting” of the endocrine stress systems, by measuring cortisol levels after noxious experiences in ex-preterm infants, either whilst still on the NICU (short-term effects), or in the months to years following. When a clinically required heel lance was done whilst infants were still on the NICU, the earliest premature infants born at less than 28 weeks gestational age (i.e., approximately 3 months premature) showed a dampened cortisol response to heel lance. In addition, higher cumulative exposure to neonatal procedural pain over the length of stay in the NICU was related to lower cortisol release to standard nursing procedures [77]. When immunised at 2–4 months (corrected) age, low gestation age (LGA) boys (<32 weeks), but not girls, showed lower cortisol concentrations than full-term infants after injections, although facial and heart rate responses did not differ between groups [78].

When studied over a longer period of time, we see that this early dampened cortisol response in premature infants changes to elevations in cortisol levels and responses when the children are older. At 8 months old, infants born at extremely low gestational age (≤ 28 weeks) with previously low basal cortisol levels, showed elevated basal levels as well as greater increases in cortisol response to stressors, compared to term infants. In these children, greater increases in cortisol were associated with higher numbers of skin-breaking procedures experienced in the past on the NICU [79]. Grunau et al. [80] followed the time course of this “switch” from low to high stress hormone levels and found that at 3 months corrected age, basal cortisol levels were lower than term controls, but, at 8 and 18 months, the youngest ex-premature infants had significantly higher cortisol levels than term controls. The authors speculate that the HPA axis has been “reprogrammed” by NICU experience. Recent work has replicated the finding that premature children born onto the NICU later have higher basal cortisol levels compared to term-born controls at both 18 months [81] and upon waking in 8–14 year old ex-premature infants [82].

Animal studies support the existence of a developmental shift from low to high cortisol levels after perinatal corticosteroid exposure, and these higher levels of cortisol seen in older animals are associated with increased levels

of corticotropin-releasing hormone (CRH) mRNA and glucocorticoid (GC) receptors in the amygdala (e.g., [83, 84]). In humans, this shift from low to high levels over development may be influenced by the fact that the mothers at risk of giving birth prematurely are routinely given corticosteroids to delay birth and enhance infant survival and lung function—an intervention which suppresses cortisol secretion in the infant when born [85] yet causes an increased cortisol response after heel lance at 24 hours after birth [86]. Further work is needed to address the impact of perinatal glucocorticoid exposure on the stress response axis in later life.

3.2. Prematurity May Contribute to Adult FM Symptoms via the HPA Axis. The above evidence highlights how premature birth and the stressors associated with it can influence the physiological response to stress and “reset” the balance of the HPA axis response. Seeing as FM patients routinely show imbalances in the stress response, it is reasonable to hypothesise that premature birth may be a risk factor for developing FM in later life. Indeed, Klingmann et al. [87] show that of 93 female FM patients, 62% reported a gestation length of <38 weeks, which was related to a lower cortisol response upon waking when compared to full-term FM patients. The authors speculate that enhanced glucocorticoid levels in the mother during pregnancy or in response to premature birth affect the development of the adrenal glands in the foetus/premature infant, rendering the HPA axis less capable of dampening stress responses to later stressors. This in turn may disinhibit responses to physical or psychological stress and affect brain function, resulting in enhanced responses to pain and increased fatigue levels. Support for this hypothesis comes from animal studies of prenatal glucocorticoid exposure, where dam rats are exposed to substances that increase HPA axis activity (such as glucocorticoid receptor agonists), in the third trimester of gestation. Results show that the adrenal glands and brain weight of the adult offspring are smaller, stress regulation is compromised, and cognitive dysfunction is seen in tests of memory as well as anxiety-like behaviour, with the effects exacerbated in female offspring [88–93].

3.3. Cognitive Symptoms of FM May Arise from Differences in Brain Development Caused by Premature Birth. One symptom of FM, colloquially called “fibro-fog” by sufferers, constitutes cognitive deficits, with patients complaining of difficulties in memory and attention that mimic the effects of an extra 20 years of ageing (e.g., [94, 95]). Additional evidence that prematurity may influence the development of FM comes from studies showing that the risks of cognitive and psychiatric impairment are much greater in ex-preterm infants. The EPICure cohorts (born at ≤25 weeks gestation) have recently had their cognitive abilities and psychiatric profiles investigated at 11 years of age. Results showed that the children born at the youngest preterm ages are at higher risk of ADHD, autism spectrum, and emotional disorders [96] and show increased incidences of learning impairments and poor academic attainment [97]. Other meta-analyses and epidemiological studies have confirmed

the increased risk for psychiatric symptoms and poorer academic performance in older childhood after premature birth [98–100].

Brain imaging of ex-preterm infants compared to full-term controls has shown underlying changes in brain structure and function that may help explain some of these deficits. Cortical surface area is decreased at full-term in extremely preterm infants [101], and the incidence of white matter abnormalities persisting past 18 months (corrected) age is increased [102]. Thalamic volume is also reduced in preterm children at term-equivalent age [103] and at 2 years of age, and connectivity between the thalamus and cortex may be disrupted in ex-preterm children [104]. Seeing as the premature brain is still developing at a rapid pace and as myelination occurs during late preterm maturation [105], it is likely that prematurity influences white matter development, helping to explain why later cognitive deficits may arise. If premature birth becomes a proven risk factor for fibromyalgia, the neural bases of “fibro-fog” may become better understood in the adult.

4. Risk Factor: Maternal Deprivation

As discussed above, early pain experience and prematurity may be risk factors for FM development in later life. Prematurity might be a risk factor in combination with the high exposure to additional stressors, including maternal deprivation. Relatively detailed information is available on the effects of maternal deprivation on the developing organism, and therefore maternal deprivation is discussed separately. Animal models of deprivation have proven extremely useful in illustrating the effects of deprivation from the primary caregiver (generally the mother) and the strong role for the fluidity of genetic expression during early life in the shaping of the adult phenotype. The study of epigenetics, or how the environment influences the activation and expression of different genes, has provided fascinating insights into this fluidity.

4.1. Maternal Deprivation in Animal Models Influences Later Stress Responses. Animal models of maternal deprivation often use rats and generally employ a paradigm whereby pups are separated from the mother for at least an hour per day, much longer than the 20–25 minutes of absence that dam (mother) rats are routinely away from the nest [106]. When neonatal rats are exposed to these prolonged periods of deprivation during the first weeks of life, a number of physiological and behavioural changes occur in the adult animal. For example, rats separated from the dam for 180 minutes per day from postnatal day (P) 2–14 show elevated levels of CRF mRNA as adults, which causes adrenaline and cortisol release via activation of the HPA axis [107, 108]. They also show more anxiety-like behaviours as adults and an increased propensity to consume alcohol [109, 110]. Accordingly, maternal deprivation has now been used to model various psychiatric states such as anxiety [111], addictive disorders [112], and schizophrenia [113], and a recent study by Uhelski and Fuchs [114]

showed that maternally deprived animals showed increased active avoidance of environments in which pain had been experienced, suggesting enhanced supraspinally mediated responses to pain. The importance of maternal presence is further illustrated by work with monkeys: infants reared in the absence of an adult caregiver but together with age-matched peers develop chronic anxiety-like behaviours and disordered cortisol levels to stressors (suggesting HPA axis imbalance), similar to FM symptoms [115]. Taken together, these data show that maternal deprivation has been associated with three important disturbances found among FM patients, namely, alterations in the HPA axis, increased anxiety, and increased pain responses [116].

Short-term separation of pups conversely causes opposite effects to longer maternal deprivation. If pups are subject to only 15 minutes of deprivation, the adult animals display more social contact and better stress-coping abilities compared to animals deprived for longer periods [117–121]. These effects seem to be mediated by the maternal style of the dam upon reunion with the pups—mothers of pups separated for short periods engage in more licking/grooming and arched-back nursing (LG-ABN) when reunited compared to dams of pups separated for more prolonged periods. Dams that engage in high levels of this nursing style produce offspring that show more efficient stress regulation, as measured by corticosterone (the animal equivalent of CRH) responses to stress and feedback sensitivity of the HPA axis [122, 123]. In fact, the maternal LG-ABN style (either high or low) causes individual differences in stress responsiveness and emotionality that remain stable in the adult offspring [124] and is in itself a trait that is passed on to female offspring. Cross-fostering studies, where pups from low or high LG-ABN dams are reared by dams showing the opposite LG-ABN behaviour illustrate that female offspring will show nursing styles akin to their “foster” dam rather than their biological dam [125]. Further evidence for the fluidity of these behavioural phenotypes comes from evidence that low LG-ABN dams rearing litters in a socially-enriched environment produce offspring showing enhanced exploration and licking/grooming behaviour of their own offspring [126].

The effects upon adult phenotype that depend on maternal style are regulated by changes in DNA methylation of the infant genome, leading to activation or silencing of certain genes, and alterations in levels of, for example, glucocorticoid receptors [122], neurotrophic factors and specific neurotransmitter receptors in the hippocampus [127]. Serotonin (5-HT) turnover (as seen by measures of 5-HT levels compared to levels of 5-HT metabolites) is also increased in maternally deprived animals [128], and expression and levels of serotonin receptors and transporter proteins altered [129, 130]. This is particularly relevant to FM, as the serotonergic system has been implicated in the affective components associated with FM—cerebrospinal fluid levels of 5-HT metabolites are decreased in patients [53], serotonin antagonists are effective drugs for some FM patients with no associated depressive comorbidities [131], and increased incidence of a specific genetic polymorphism in the 5-HT transporter gene has been identified in FM patients [132], although the exact disorders in serotonergic

signalling are not yet clear [133]. However, some of the heterogeneity in FM patients may arise due to epigenetic alterations that occurred during early infancy. To date, no research has been conducted on this specific question.

4.2. Quality of Maternal Attachment Affects Pain Processing. The quality of the relationship between child and primary caregiver (generally the mother) can also dictate emotional reactivity throughout life and the type of attachment style that an individual will form with others throughout their life. Bowlby first developed the idea of “attachment theory”, studying the bond between child and mother and suggested that a secure attachment style is the most beneficial for infant development [134, 135]. Since then, studies have shown that disordered attachment styles are linked to chronic pain and problems coping with pain (see [136]). For example, chronic pain patients with high levels of avoidant attachment self-scored pain intensity more highly, and patients with fearful attachment styles display increased levels of pain catastrophising, linked to anxiety levels [137, 138]. In acute pain tests, adults showing secure attachment styles rated pain as less intense and anxiogenic [139]. Importantly for FM, secure attachment formation is linked to the dopamine and opiodergic system in both animals and humans [140, 141], suggesting that a secure early attachment between infant and parent could be protective against developing FM in later life. Hallberg and Carlsson [142] indeed mention the overrepresentation of individuals with insecure attachment styles in the chronic pain patient population.

5. Risk Factor: Childhood Physical and Psychological Trauma

Physical and sexual abuse during childhood are well-documented risk factors in the development of fibromyalgia [143–146], and two recent meta-analyses link childhood incidence of physical and sexual abuse with FM [147, 148]. Early life abuse carries with it the burden of a number of other behavioural and pathological problems, including increased incidence of depression, posttraumatic stress disorder, alcoholism, substance abuse, obesity, ill health, and suicide ([149; see 150]). A number of these are also comorbidities in FM. It is possible that the impact of early abuse and trauma contributes to FM via disruption of neurotransmitter systems such as the serotonergic and dopaminergic systems and impacts stress-management via the HPA axis [151–155].

5.1. A High Incidence of Childhood Abuse Is Reported in FM Patients. Self-report studies, where patients are questioned on their childhood history, consistently show increased early life adversity in FM patients. Goldberg et al. [156] found that three different groups of chronic pain patients (facial pain, myofascial pain, and FM), all had a history of abuse in nearly 50% of cases, rising to 65% in the fibromyalgia group. In particular, females with an alcoholic parent were likely to be members of the FM group. Hallberg and Carlsson [142] conducted in-depth interviews with 22 FM patients

and describe “abundant examples of early loss (and...) high degree of responsibility early in life,” and Anderberg et al. [157] found that, of 40 female FM patients, 51% had experienced very negative childhood or adolescence life events, compared to 28% in healthy age-matched women. Nicolson et al. [158] found an association of self-reported childhood abuse and neglect with FM patients’ daily cortisol levels, finding the most disordered cortisol responses in the patients reporting the highest levels of sexual and emotional abuse. This suggests that early abuse further impacts upon the HPA axis, which shows aberrant functionality in FM in patients with no history of abuse [71]. Childhood rape has also been strongly associated with a lifetime diagnosis of FM [147].

The loss of a parent during early childhood is an emotionally traumatic event and is associated with altered daily cortisol levels in the adult, particularly in men [159, 160]. Poor quality family relationships during childhood also cause changes in cortisol release in response to a stressful event [161]. In addition, early-life stress and trauma has been shown to be a significant predictor of levels of CRF in cerebrospinal fluid (CSF) in non-FM subjects [162], and Danese et al. [163] found an association between early-life maltreatment and adult blood levels of C-reactive protein, a marker of inflammation. Specific to fibromyalgia, McLean et al. [164] showed that women with FM who reported sexual or physical abuse in their personal histories had differences in CSF levels of CRF compared to nonabused FM women, and Weissbecker and colleagues [165] found that a similar group of FM women abused in childhood had disordered diurnal cortisol levels.

However, studies based on the self-report of FM patients can be difficult to verify. Adult life experiences may bias memories from early life, and it is possible that FM patients, due to their current pain and comorbid states, become self-centred and preoccupied with the pain, and potentially overemphasise traumatic memories [166, 167]. Longitudinal studies following children and young people who have suffered from documented abuse, for example, children in social care, would be useful in order to avoid this confound. Epidemiological studies of socioeconomic position (SEP) during childhood have shown that lower SEP during childhood is a predictor of chronic widespread pain in later life [168]. Whilst socioeconomic status incorporates a large number of factors, trauma-related hospitalisations are more prevalent in children from lower socioeconomic statuses who have less access to appropriate healthcare [169–172].

6. Risk Factor: Perinatal Exposure to Substances of Abuse

Serotonin is not the only neurotransmitter system altered in fibromyalgia—dopamine and opioid neurotransmitter disturbances are also reported that may, in part, result from interference with these developing systems during pre- or early postnatal life. Dopamine responses of FM patients to painful stimuli are lower than those of healthy subjects [173],

and low CSF levels of dopamine (as well as serotonin and norepinephrine) metabolites are seen in patients [52]. Furthermore, the opioid system is closely linked to dopaminergic signalling, constitutes an important endogenous antinociceptive system, and is altered in FM [174, 175]. Exposure to a number of substances during early life will impact upon the development of these neurotransmitter systems. For example, exposure of the foetus to alcohol induces dysfunction in dopaminergic and serotonergic systems and will persistently affect the development of the HPA axis [176–178], all of which are, as mentioned, disturbed in FM.

6.1. Early Opioid Exposure Causes Long-Lasting Changes in Nociceptive Systems. Early exposure to opioids, such as exposure of the foetus to heroin or methadone during pregnancy, or prolonged morphine administration after birth, for example, on the NICU, causes lasting changes in opioid signalling. If exposure occurs prenatally, it can result in the newly born infant undergoing withdrawal symptoms very soon after birth, the so-called neonatal abstinence syndrome (NAS) [179]—an effect mirrored in animal models of early drug dependence [180]. Morphine is used in the NICU to provide sedation in neonates requiring mechanical ventilation and to improve tolerance of ventilation and comfort of the infant. The lasting effects of this are not yet well-characterised [65, 181], although it is known that chronic morphine administration causes changes in mu-opioid receptor density and sensitivity that desensitises older animals to opiate analgesia [182, 183]. As the opioidergic and dopaminergic systems are crucial for endogenous modulation of pain, and this modulation seems to be disordered in fibromyalgia, longitudinal studies of early life exposure to opioids may help explain some of the disturbances in opioid function seen in FM. Positron emission tomography (PET) studies would be useful to investigate if the altered opioid receptor activity seen in FM patients is related to early life opioid exposure. Harris and colleagues [175, 184] have shown that FM patients show alterations in mu-opioid receptor availability, but a history of opioid use was one of the exclusion criterion for these studies, meaning that the impact of early life exposure to opioids is not yet known in terms of later FM prevalence.

6.2. Dopamine Overexposure during Early Life Affects HPA Axis Function, and May Be Mediated by Epigenetic Factors. Dopaminergic drugs such as cocaine and amphetamine increase anxiety-like behaviours in animal models of abuse during pregnancy [185], and cocaine activates the HPA axis by potentiating adrenocorticotropin hormone (ACTH) release, which in turn stimulates the adrenal glands to produce adrenaline and cortisol [186]. Increasing evidence now suggests that prenatal exposure to drugs of abuse (including alcohol, cocaine, and amphetamine) may be toxic to developing dopamine-rich areas such as the basal ganglia (see [187]). After birth, studies on the development of the dopamine system suggest that functional connectivity in the young animal, particularly to frontal cortical areas, is not mature until adolescence or later [188, 189], and it is

possible that the balance between tonic and phasic dopamine release will also be affected by exposure of the developing system to excessive dopamine activation, impacting upon later pain control mechanisms [190]. Therefore, early life exposure to increased levels of dopamine could help explain the aberrant dopaminergic functionality seen in FM patients [173, 191]. Interestingly, genetic polymorphisms linked to FM include the *val¹⁵⁸met* polymorphism (in the gene coding for catechol-o-methyltransferase, an enzyme that metabolises dopamine) [192] and the dopamine D4 receptor [193]. Considering that epigenetic effects impact upon stress regulation in maternally deprived animals, it is possible to speculate that early life events cause epigenetic changes, which may interact with the above polymorphisms to produce an adult phenotype at increased risk of developing FM. Indeed, self-report studies of FM patients show higher levels of reported parental drug and alcohol abuse in comparison to other groups of other chronic pain patients [194, 195].

7. Conclusions

Fibromyalgia is classified as a disorder of pain processing and stress regulation, often along with comorbidities of anxiety and depression; the amount of evidence that links early life adversity to pain, stress, and emotional problems in later life strongly suggests that these adverse events and traumas could increase the risk of developing FM in adulthood. At this point, research has shown that FM patients self-report high levels of early adversity and indicates that early life circumstances affecting later pain processing and stress regulation may be more prevalent in FM. However, there is little evidence to conclusively link the two, for example, by proving that maternal deprivation or increased stress during pregnancy increases the incidence of FM.

This paper has focused on the evidence showing that painful procedures during early life cause long-lasting changes in pain processing and suggests that high exposure to painful experiences in early life may partially explain the increased pain sensitivity shown by FM patients. In addition, childhood adversities and maternal deprivation are also discussed in terms of the effects they have on stress-regulatory systems in the older organism, so again are potentially sources of the disorders in cortisol levels and stress response seen in FM patients. As previously mentioned, the precise dysfunctions in stress regulation via the HPA axis are not yet clear in FM patients, but what is clear is that the body's stress regulatory systems are compromised, and it is possible that the precise nature and combination of each individual's childhood experience may be contributing to the overall symptomatology of FM.

Exposure of the developing brain to perinatal stress and glucocorticoids during critical periods of development may affect the long-term function of areas involved in stress regulation such as the hippocampus and amygdala and help explain the "fibrofog" and anxiety disorders prevalent in FM. Furthermore, impairments in stress regulation caused by early exposure to stressors such as increased maternal cortisol levels, pain, or maternal deprivation may also partially

explain the increased pain sensitivities seen in FM patients. Finally, as pain is itself a stressor, the pain experienced by FM patients may be acting in a positive feedback manner to further increase anxiety levels and impact upon stress regulation. Whilst FM is unlikely to be due to a single factor, it is possible that the factors outlined in this paper, concomitant with a number of other factors such as a genetic predisposition to enhanced pain sensitivity, stressful life experiences in adult life, and the influence of sex hormones, may combine or interact to create a phenotype at higher risk of developing this form of chronic pain. Teasing apart potential influences and their mechanisms may help treat sufferers or, in fact, decrease the risk of future suffering.

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Review Article

A Comprehensive Evaluation of Standardized Assessment Tools in the Diagnosis of Fibromyalgia and in the Assessment of Fibromyalgia Severity

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Standard assessments for fibromyalgia (FM) diagnosis and core FM symptom domains are needed for biomarker development and treatment trials. Diagnostic and symptom assessments are reviewed and recommendations are made for standards. Recommendations for existing assessments include the American College of Rheumatology FM classification criteria using the manual tender point Survey for diagnosis, the brief pain inventory average pain visual analogue scale for pain intensity, the function subscale of the revised fibromyalgia impact questionnaire (FIQR) for physical function, the patient global impression of change and FIQR for overall/global improvement, the hospital anxiety and depression scale depression subscale for depression, the multiple ability self-report questionnaire for cognitive dysfunction, the fatigue severity scale for fatigue, the FIQR for multidimensional function/health-related quality of life, the jenkins sleep scale for sleep disturbance, and the fibromyalgia intensity score for tenderness. Forthcoming assessments including the FIQR for diagnosis, NIH PROMIS, and FIBRO Change scales are discussed.

1. Introduction

Fibromyalgia (FM) is one of the most challenging disorders to manage. Treatment advances are needed to improve the care of FM patients. FM is currently a very subjective disorder, and the development of biomarkers could improve care by simplifying FM diagnosis and objectively quantifying symptom severity. Numerous FM biomarkers have been proposed [1]. However, a recent review characterized the current state of FM biomarker development as an “abyss” [1]. Biomarker development has been limited by the lack of universal, “gold standard” definitions for FM clinical diagnosis and symptom severity against which biomarkers can be compared. Similarly, a standard set of assessments for all core FM symptom domains is needed for inclusion in treatment trials to develop better therapies and improve the ability to make efficacy comparisons between treatments. Unfortunately, consensus on standard assessments in research to quantify the severity of FM symptoms is lacking, and recommendations for standard assessments have not

been made previously. This paper represents one author’s review of the available literature and his recommendations for current and future assessments to clinically diagnose FM and measure the severity of FM symptoms in research to enable development of new therapies and biomarkers. The recommendations made in this paper are intended to be a starting point for discussions in a group such as outcome measures in rheumatology (OMERACT) rather than the final articulation of standards to be used. While none of the assessments discussed herein are perfect, consensus within the FM research community must be reached if timely advances for improving patient care are to be made.

2. Recommended FM Clinical Diagnostic Criteria

FM is a very complex disorder. In addition to widespread pain and tenderness, FM patients also typically suffer from

numerous other symptoms that can include, but are not limited to, fatigue, cognitive dysfunction (fibrofog), disturbed (nonrestorative) sleep, depression, anxiety, stiffness, tenderness and functional disability [2]. The number and severity of associated symptoms varies from patient-to-patient, making development of unified diagnostic criteria difficult. While not originally intended for clinical diagnosis, the American College of Rheumatology (ACR) FM classification criteria have been used in the clinic to identify FM patients since their publication in 1990 [3]. These criteria include the presence of widespread pain for at least 3 months and pain upon palpation of at least 11 of 18 tender points with 4 kg/cm² of force. However, performance of the classification criteria in clinical diagnosis is poor, failing to identify almost half of FM patients [4].

New ACR FM diagnostic criteria have been proposed to simplify clinical diagnosis by doing away with the need for performing the tender point examination. The new criteria diagnose FM by evaluating the distribution of body pain in combination with symptom severity [5]. While these new criteria have been provisionally accepted by the ACR, final acceptance is awaiting validation studies. However, these new criteria have been criticized for their lack of precision or mechanistic features and complete symptom focus [6–8]. Also, diagnosis via the new criteria is based on a physician's subjective assessment of the extent and severity of the patient's somatic symptoms [9]. Therefore, FM diagnosis using the new criteria is likely to differ from one physician to another. Due to these issues, the new diagnostic criteria cannot be recommended until validation studies are completed.

Though not perfect, the 1990 ACR classification criteria have been used to identify FM patients for inclusion in clinical trials for the past 20 years, and broad consensus exists for its use. At least part of the poor performance of the 1990 ACR criteria in clinical diagnosis is likely due to nonstandard performance of the tender point examination. Performance of the tender point exam can be improved by using the manual tender point Survey (MTPS) method [10]. The MTPS has been shown to reduce variability in performance of the tender point exam and identify FM patients with high sensitivity and specificity [10]. The MTPS consists of standardized components including (1) location of the tender point sites, (2) patient and examiner positioning, (3) order of tender point examination, (4) pressure application technique, and (5) pain severity rating scores in which FM patients rate pain severity upon digital palpation of each tender point on a verbal 11-point numerical rating scale (NRS) from 0 (no pain) to 10 (worst pain), with a pain severity score of at least 2 required to count a tender point as positive. Until the new FM diagnostic criteria are validated, the 1990 ACR fibromyalgia classification criteria utilizing the MTPS are recommended for the diagnosis of FM patients in research studies (Table 1).

3. Recommended FM Core Symptom Domains

As previously discussed, FM is a complex disorder with numerous symptoms occurring along with widespread pain

and tenderness [2]. Since effective FM management requires a treatment regimen that addresses not only pain but all associated FM symptoms [11], multiple biomarkers will likely be necessary to evaluate all FM symptom domains. While phase-three FM treatment trials have evaluated multiple symptom domains (Table 2), the symptoms assessed across trials have been inconsistent. This is likely because the US Food and Drug Administration (FDA) has made the improvement of pain the primary consideration for approval of FM medications, and a required core set of symptom domains for evaluation in FM treatment trials does not exist. Discrepancies in symptoms assessed by treatment trials can lead to bias, since researchers tend to only evaluate symptoms likely to be improved by the treatment under investigation and ignore symptoms likely to be made worse. A required core set of symptom domains are needed so that a comprehensive set of FM biomarkers can be developed and bias in treatment trials can be reduced.

Recommendations for a core set of FM symptom domains to be assessed in treatment trials have been made previously (Table 1) [12]. These recommendations arose from a Delphi exercise of FM patients and expert clinicians to determine symptoms that should be evaluated in all treatment trials [2]. While it may be advisable for additional symptoms to be evaluated in some circumstances (e.g., anxiety for an antidepressant trial), a core set of 9 symptom domains were recommended for assessment including pain intensity, physical function, patient global impression of change, cognitive dysfunction (fibrofog), fatigue, multidimensional function/health-related quality of life (HRQoL), sleep disturbance, tenderness and depression (Table 1). Since consensus for these core domains exists, it is recommended that biomarkers be developed to evaluate these 9 symptom domains.

4. No Recommended Assessments for FM Core Symptom Domains Currently Exist

While recommendations for core symptom domains exist, there are no accepted standards for assessments to evaluate these domains. Standard measures are needed against which biomarkers can be compared for development and to allow direct comparisons between treatment trial results. Published work to develop a consensus set of FM outcome measures has been limited to two papers [13, 14]. The work by Choy et al. pooled data from 10 fibromyalgia treatment trials to determine the construct validity of questionnaires that have been used to assess change in a number of FM symptom domains including pain, patient global, fatigue, multidimensional function (which included HRQoL), sleep, depression, physical function, tenderness, fibrofog, anxiety, and stiffness [13]. The authors did not compare questionnaires to one another, and no specific recommendations for assessments were made. Instead, pooled psychometric properties of questionnaires for each symptom domain were assessed. Support was found for construct validity of self-report questionnaires for pain, fatigue, depression, physical function, and multidimensional function. However, support

TABLE 1: 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.

TABLE 2: Assessments used to evaluate fibromyalgia symptom severity in medication trials.

Symptom	Medication used in treatment trials			
	Pregabalin	Duloxetine	Milnacipran	Sodium oxybate
Fatigue	MAF	MFI	MFI	Fatigue VAS
Fibrofog	—	—	MASQ	—
Sleep	MOS-Sleep	—	JSS, MOS-sleep	FOSQ, JSS
Depression	BDI, HADS-D	BDI-II, HAMD17	BDI	—
Anxiety	HADS-A	Beck Anxiety Inv.	Beck anxiety inv.	—
Pain	Pain VAS, Pain NRS	BPI-mod short form	Pain VAS, McGill pain quest.	Pain VAS
Physical disability	FIQ, F-HAQ	FIQ, SDS	FIQ, MDHAQ	FIQ
Global/QOL	FIQ, CGI-C, PGI-C, SF-36	EQ-5D, FIQ, CGI-S, PGI-I, SF-36	FIQ, PGI-C, SF-36	FIQ, CGI-C, CGI-S, PGI-C, SF-36
Tenderness	MTPS-FIS	—	—	TPI

BDI: beck depression inventory, BPI: brief pain inventory, CGI-C: clinician global impression of change, CGI-S: clinician global impression of severity, EQ-5D: EUROQOL 5-D QUESTIONNAIRE, F-HAQ: fibromyalgia health assessment questionnaire, FIQ: fibromyalgia impact questionnaire, FIS: fibromyalgia intensity scale, FOSQ: Functional outcomes of sleep questionnaire, HADS: hospital anxiety and depression scale (-D denotes depression subscale, -A denotes anxiety subscale), HAMD17: 17-item hamilton rating scale for depression, Inv.: inventory, JSS: jenkins sleep scale, MAF: multidimensional assessment of fatigue, MASQ: multiple abilities self-report questionnaire, MDHAQ: multi-dimensional health assessment questionnaire, MFI: multidimensional fatigue inventory, MOS-sleep: medical outcomes studies sleep scale, MTPS: manual tender point survey, NRS: numeric rating scale, PGI-C: patient global impression of change, PGI-I: patient global impression of improvement, QOL: quality of life, QUEST.: questionnaire, SDS: sheehan disability scale, SF-36: short form health survey, TPI: tender point index, VAS: visual analogue scale.

was not found for use of full-length sleep questionnaires (including the medical outcomes studies (MOS) sleep scale). The lack of support for sleep questionnaires was because many items assessed sleep problems such as snoring and shortness of breath that are not relevant to most FM patients. The authors recommended either using the sleep disturbance subscale of the MOS sleep scale in isolation or developing a new FM-specific sleep questionnaire for use in clinical trials. Validity could also not be determined for fibrofog, anxiety, or stiffness assessments because these domains were measured by only one instrument in the trials (the multiple abilities self-report questionnaire (MASQ), anxiety subscale of the hospital anxiety and depression scale (HADS), and stiffness subscale of the fibromyalgia impact questionnaire (FIQ), resp.).

The work by Carville and Choy reviewed 185 FM trials to identify assessment instruments for core FM domains

that were sensitive to change for both pharmacologic and nonpharmacologic treatments [14]. The authors only compared the 5 assessments that were most often used for each core symptom domain, significantly limiting the questionnaires that were evaluated since concordance of assessments across trials was low. Across all domains including pain, patient global, fatigue, sleep, and anxiety, visual analogue scales (VASs) were found to be sensitive to change. For pain, the FIQ, tender point count, and pressure point threshold were insensitive to change. While evaluation of depression questionnaires was limited due to the use of multiple different assessments across trials and the exclusion of patients with significant depression from many trials, the Hamilton and Center for Epidemiologic Studies Depression scales were found to be more sensitive to change than the Beck depression inventory (BDI). All anxiety scales analyzed were insensitive to change in pharmacologic trials

including the Beck anxiety inventory, state trait anxiety index (STAI) and the FIQ anxiety subscale. For fatigue, Likert scales showed good sensitivity, but the FIQ fatigue subscale did not. For health-related quality of life, the physical component of the short form36 was sensitive to change in pharmacologic studies, but the mental component score was not. For sleep, the FIQ sleep item was sensitive to change in nonpharmacologic trials but not in pharmacologic trials. For evaluation of multidimensional function, the global FIQ score was moderately sensitive to change in both pharmacologic and nonpharmacologic trials. While the analyses in this work are instructive, no specific recommendations for assessment measures were made.

5. Recommended Pain Intensity Assessment

The initiative on methods, measurement, and pain assessment in clinical trials (IMMPACT) has provided recommendations for questionnaires to be used in interpreting the clinical importance of therapeutic outcomes in clinical trials of chronic pain treatments that may be applicable to FM [15]. IMMPACT recommends assessment of four core chronic pain outcome domains including (1) pain intensity, (2) physical functioning, (3) emotional functioning, and (4) participant ratings of overall improvement. A 0 to 10 NRS was recommended to assess pain intensity, but no specific recommendations for the wording of instructions or anchors of the NRS were made. To ensure uniformity across FM trials, I recommend wording from the average pain NRS of the brief pain inventory (BPI) to be used which asks “please rate your pain by circling the one number that best describes your pain on average” and has anchors that vary from “no pain” to “pain as bad as you can imagine” since this wording can help limit recall bias and reduce ceiling effects commonly seen in FM patient trials [16].

6. Recommended Physical Functioning Assessment

IMMPACT recommends the multidimensional pain inventory (MPI) [17] and the interference scale of the (BPI) [16] for assessment of physical functioning unless a well-validated disease-specific measure is available. Since the FIQ physical functioning subscale is a well-validated FM-specific measure that has been used to assess physical functioning in all FM clinical trials (Table 2) [18], it is reasonable to use it to assess physical functioning. However, the FIQ physical functioning subscale has been criticized for its gender bias, nonlinearity, nonunidimensionality, and systematic underestimation of functional impairment by inclusion of infrequently performed activities [19]. The FIQ was recently revised as the FIQR to address some of these criticisms and allow for computerized administration [20]. Therefore, the FIQR physical functioning subscale is recommended for assessment of physical function in FM patients.

7. Recommended Overall/Global Improvement Assessments

The patient global impression of change scale (PGIC) is IMMPACT recommended for evaluating participant ratings of overall improvement in pain treatment trials [15]. The PGIC uses a 7-point Likert scale that varies from 1 “very much improved” to 7 “very much worse” to quantify patient global response to treatment [21]. The PGIC is a standard assessment in clinical trials, and various forms of the PGIC have been used in all FM treatment trials (Table 2). A specific form of the PGIC has been linguistically validated into 12 languages to allow for use in FM research worldwide [22], and this form of the PGIC is recommended to assess overall/global improvement in combination with the FIQR (Table 1).

8. Recommended Depression Assessment

The Beck depression inventory (BDI) is the IMMPACT recommended depression assessment for pain treatment trials [15]. The BDI was recommended based on its excellent psychometric properties, extensive use in pain clinical research, and responsiveness to change in pain clinical trials. The BDI consists of 21 multiple choice items, with each item answered by choosing which of four statements best describes the way the patient feels [23]. The BDI was designed to assess the severity of current depressive symptoms, with scores ranging from 0 to 63 with higher scores indicating more severe depression. The original BDI evaluated symptoms over the past week, but this time frame was increased to two weeks for the current version of the BDI, the BDI-II, for consistency with *Diagnostic and Statistical Manual on Mental Disorders (DSM-IV)* criteria for major depressive disorder [24]. The BDI-II was also modified to include assessments for all nine *DSM-IV* criteria (the original BDI only met six of the nine criteria). The BDI-II has been linguistically validated into 12 languages for use in international FM treatment trials [22]. Normative data on the BDI and BDI-II are available.

While the BDI is recommended for use in pain treatment trials and has been used in FM trials (Table 2), it is not recommended to quantify depression severity in FM patients due to its lack of unidimensionality. The BDI does not specify patients answer on the basis of their depressive symptoms but to comment on how they “...have been feeling.” Only one of the 21 BDI-II items specifically addresses feelings of sadness, the rest of the items query general physical and mental concepts not specific for depression including tiredness/fatigue, concentration difficulty, sleep changes, and loss of energy. Given the myriad of coexisting FM symptoms, it is likely the BDI functions as more of a general measure of symptomatology in FM patients rather than a specific measure of depression symptom severity. This view is supported by a study comparing the BDI to a computerized diagnostic interview schedule (C-DIS) for diagnosing major depressive disorder (MDD) in FM patients [25]. The C-DIS is a reliable method for identifying individuals with MDD

[26, 27]. This study found that while the C-DIS detected MDD in 22% of FM patients, the BDI estimate was much higher at 55%. The authors felt that the BDI overestimated the presence of MDD because numerous BDI items evaluate nondepressive symptoms that are part of the FM syndrome process and that the BDI lacked utility as a unidimensional measure of depression in FM patients. Factor analyses of the BDI have identified three dimensions, including negative attitudes toward self (also termed general depression), performance impairment and somatic concerns [28, 29]. The BDI-II has also been shown to be multidimensional, composed of two first-order factors representing cognitive and noncognitive symptoms [24, 30]. It is very important that assessments used in treatment trials and to develop biomarkers be unidimensional to ensure specificity. Given the lack of specificity of the BDI for assessing depression symptoms, it cannot be recommended to quantify depression severity in FM trials.

The HADS depression subscale has been used previously to evaluate change in depressive symptoms in FM treatment trials (Table 2). The HADS was originally developed to quantify the severity of anxiety and depressive symptoms in nonpsychiatric hospital clinic patients [31]. To prevent somatic disorders common in these patients from falsely affecting scores, symptoms of anxiety and depression that relate to physical disorders were excluded to ensure unidimensionality of the anxiety and depression subscales that have been confirmed by factor analysis in multiple populations [32]. The HADS includes 7 items each to assess anxiety and depressive symptoms (the HADS-A and HADS-D, resp.), with each item answered on a four-point (0 to 3) scale so that possible scores range from 0 to 21 for both anxiety and depressive symptoms with higher scores indicating more severe symptoms. The HADS has been translated into a number of languages allowing for its use in international trials.

While the HADS-D has not been specifically validated in FM patients, its validity to quantify depression symptoms has been shown in a variety of patient populations including somatic, psychiatric, and primary care patients and in the general population [32]. The HADS-D also has proven validity in its ability to reflect change in depression severity in treatment trials [33]. An analysis of data from three pregabalin FM trials supports diagnostic validity of the HADS by showing that, using a standard cutoff score of ≥ 11 on the HADS-D to identify patients with MDD, 27% of enrolled patients in the trials had MDD, a percentage consistent with previously reported MDD rates in FM patients when gold-standard diagnostic assessments are done [34]. Similarly, 38% of patients in the FM pregabalin trials were found to have an anxiety disorder using the HADS-A, consistent with previously published rates in FM patients [34, 35]. Based on this, the HADS-D is recommended for assessment of depressive symptoms in FM patients (Table 1).

9. Cognitive Dysfunction Assessments

Core FM domains that lack published recommendations for self-report questionnaires include cognitive dysfunction,

fatigue, multidimensional function/HRQoL, sleep, and tenderness. While numerous assessments exist for each domain in the literature, most were developed for use in patient populations other than FM. This is significant, since concepts and psychometric properties of a measure may not hold across patient populations. While cognitive dysfunction is a significant problem for many FM patients, assessment in large clinical trials has been hindered by the time and expertise required to perform the complex neurocognitive tests that can quantify cognitive dysfunction in FM [36]. The multiple ability self-report questionnaire (MASQ) is the only self-report questionnaire that has been used in FM clinical trials to assess cognitive dysfunction [37]. The MASQ is a self-report measure comprising items to assess five cognitive domains including language, visuoperception, verbal memory, visual memory, and attention. While originally written in English, the MASQ has been translated and linguistically validated into 12 different languages to facilitate its use in international FM studies [22]. For this reason, the MASQ is recommended for assessment of cognitive dysfunction in fibromyalgia trials. However, it is hoped that computerized batteries of neurocognitive tests will soon become available to provide more objective measures of cognitive function for use in clinical trials [36] since self-assessment is poorly correlated with objective measures of cognitive function and has poor discriminating ability for patients with mild cognitive impairment [38].

10. Fatigue Assessments

Numerous self-report questionnaires have been used to assess fatigue severity in FM treatment trials including the multidimensional fatigue index (MFI) [39], the multidimensional assessment of fatigue (MAF) [40], and the fatigue severity scale (FSS) [41]. While none of the fatigue questionnaires were developed in FM patients, the MFI was developed in chronic fatigue syndrome patients who have fatigue symptoms similar to those seen in FM. The MAF was developed in rheumatoid arthritis patients, while the FSS was developed in patients with multiple sclerosis and systemic lupus erythematosus. All three scales are available in numerous languages, allowing for their use in international FM studies.

The MFI is a 20-item scale that covers 5 dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity. Four items in each subscale are answered on a 5-point Likert scale with item scores summed to yield subscale scores and a total score that varies between 20 and 100 with higher scores indicating more severe fatigue symptoms. The MFI is reliable and valid in FM patients [42], and it has been linguistically validated into 12 languages to enable use in international FM studies [22]. Normative data for the MFI is available for multiple subgroups including the general population [43].

The MAF is a 16-item scale (14, 10-point NRSs and 2, 4-point Likert scales) that measures 4 dimensions of self-reported fatigue: severity (2 items), distress (1 item), timing (2 items; how often fatigue occurs and change in

fatigue over the past week), and degree of interference with activities of daily living (11 items including household chores, cooking, bathing, dressing, working, socializing, sex, leisure, shopping/errands, walking, and exercise other than walking) [40]. The global fatigue index (GFI), a measure of global fatigue severity derived from 15 of the MAF items, has a scoring range that varies from 7.5 to 50 with higher scores indicating more severe fatigue. While the GFI technically varies from 1 to 50, patients can only score a 1 if they have no fatigue; the lowest possible score for a patient with fatigue is 7.5. The MAF and a user's guide are freely available from the developer's website (<http://www.son.washington.edu/research/maf/>). The MAF is available in 25 different language versions for various regions of the world, allowing for use in international research. While no published validation studies of the MAF in FM patients exist, a study of the MAF in 663 FM patients presented at EULAR in 2002 supports use of the MAF in the assessment of FM patients [44].

The FSS is a 9-item unidimensional measure of fatigue that is the most often used fatigue-specific scale in chronic diseases [41, 45]. The FSS measures fatigue by quantifying the impact of fatigue on specific types of functioning rather than the intensity of fatigue-related symptoms [46]. Each item is scored on a 7-point NRS, and the FSS score is derived by averaging all items to yield a score from 1 to 7 with higher scores indicating more severe fatigue symptoms. The FSS is freely available in English from the original paper [41] and has been translated into multiple languages. Validity and reliability of the FSS in FM patients has been demonstrated [47].

While all 3 scales were designed to measure fatigue symptoms, they differ considerably in their composition and foci. While the MFI is the most comprehensive of the 3 fatigue scales, questions have been raised about its dimensional structure, and it appears that MFI may only discriminate between two fatigue dimensions [48]. Also, the MFI does not specify patients' answer on the basis of their fatigue symptoms but to comment on how they "...have been feeling lately." Only two of the 20 MFI items specifically address feelings of tiredness, the rest of the items query general physical and mental concepts not specific to fatigue. Given the myriad of FM symptoms that contribute to physical and mental disability, it is likely that the MFI functions as more of a general symptom measure than a specific measure of fatigue in FM patients. On the basis of these limitations, the MFI cannot be recommended to quantify fatigue severity in FM patients.

In contrast to the MFI, both the MAF and the FSS instruct patients to answer questions based on their fatigue symptoms, and every question specifically asks about fatigue, making the MAF and FSS more specific fatigue measures than the MFI. The MAF and FSS have both been recommended for the measurement of fatigue in chronic illnesses based on their good psychometric properties and demonstrated ability to detect change over time [49]. However, a comparison of fatigue measures concluded that the FSS had the most robust psychometric properties of 19 reviewed fatigue measures, including both the MAF and the MFI, and

had the best ability to act as an outcome measure sensitive to change with treatment [49].

The FSS is the recommended fatigue severity measure in multiple disorders with associated fatigue including systemic lupus erythematosus [50] and Parkinson's disease [51]. The FSS is also easier to score than the MFA and is shorter. For this reason, the FSS is the recommended fatigue assessment for use in FM patients.

11. Multidimensional Function/HRQoL Assessments

The FIQ is recommended as a primary efficacy endpoint measure in FM clinical trials [52] and is the standard assessment measure for multidimensional function/HRQoL in FM patients, having been cited in over 300 papers and translated into 14 languages. The FIQ is a 20-item self-report questionnaire that quantifies global FM disease severity by measuring the degree to which FM interferes with a patient's life over the past week [18]. The FIQ is divided into 11 items to assess physical function, 2 "day-of-the-week" items to quantify the number of days patients "felt good" or "missed work," and 7 VASs to assess symptoms of fatigue, sleep quality, depression, anxiety, stiffness, pain, and work disability. The FIQ has been translated into numerous languages enabling its use internationally [22].

While the FIQ is universally used in FM trials, problems with the questionnaire exist. FIQ scoring is complex. The 11 physical function items are each scored on a 4-point Likert scale ranging from "always" (score of 0) to "never" (score of 3). Scores on the physical function items are summed, divided by the number of questions answered, and then multiplied by 3.33 to yield a 0-to-10 composite physical function score. The "felt good" "day-of-the-week" item is reverse scored (to obtain the number of days patients felt bad), and the result is multiplied by 1.43 to yield a 0-to-10 score. The "missed work" "day-of-the-week" item is derived by multiplying the number of days by 1.43 to yield a 0-to-10 score. The VASs are scored by measuring the distance from the beginning of the line to the patient's mark in centimeters. FIQ global scores are derived by summing the 0-to-10 composite physical function, "day-of-the-week," and VAS item scores to yield a 0-to-100 score with higher scores indicating more severe FM. In order to maintain a maximum possible score of 100, an "equalization calculation" is used if patients did not answer all 10 sections by multiplying the global score by 10 and dividing by the number of sections answered. Content problems in the FIQ have also been raised [20]. The physical function items were originally intended for women living in affluent countries and assumed possession of an automobile, vacuum cleaner, and washing machine. Also, questions now considered relevant to FM symptomatology including cognitive dysfunction, tenderness, balance problems, and environmental sensitivity were not included in the original FIQ. Finally, the original FIQ was developed as a pen-and-paper questionnaire and is incompatible with computer administration.

To address shortcomings of the original FIQ, the authors have published a revised FIQ, the FIQR [20]. The FIQR uses 21 NRS questions to evaluate the same three domains as the FIQ (physical function, overall impact, and symptoms) but differs from the FIQ by having modified physical function questions and the inclusion of questions on memory, tenderness, balance, and environmental sensitivity. The NRS structure of the FIQR questions simplify scoring and calculation of the subset domain and global scores. As in the FIQ, the FIQR yields a 0-to-100 score with higher scores indicating more severe FM. The FIQR has comparable scoring characteristics to the original FIQ, making comparison of results between the FIQ and the FIQR possible. The FIQR has the added functionality of computer-based administration, and there is a disease-neutral version of the FIQR, the SIQR, that can be used in population studies to identify and study FM patients who have not been previously diagnosed [53]. For these reasons, the FIQR is the recommended multidimensional function/HRQoL assessment for use in FM patients.

12. Sleep Assessments

Sleep problems are almost universal in FM, occurring in 95% of patients [2]. Since disturbed sleep can worsen numerous other FM symptoms including pain, depression, and physical disability [2], accurately assessing sleep dysfunction is vital. Three sleep assessments have been used in FM trials (Table 2); the MOS sleep scale [54], the functional outcomes of sleep questionnaire (FOSQ) [55], and the Jenkins sleep scale (JSS) [56]. All three scales are available in numerous languages, allowing for their use in international FM studies.

The MOS Sleep Scale is a 12-item questionnaire designed to evaluate key sleep domains by assessing sleep latency (2 items), duration, quality (4 items), snoring, awakening short of breath or with headache, and daytime somnolence (3 items) over the past month [54] or week [57]. All items are answered on a 6-point Likert scale from 1 = "all of the time" to 6 = "none of the time" except for the time to sleep and number of hours of sleep questions which are answered in minutes and hours, respectively. Seven subscales are derived to evaluate sleep disturbance, snoring, shortness of breath or headache, adequacy, somnolence, quantity, and optimal sleep. A sleep problems index can also be calculated from 9 of the items to generate a 0 to 100 score that quantifies overall sleep problems with higher scores indicating worse sleep problems. As previously discussed, an analysis of FM assessment measures showed the MOS sleep scale lacked construct validity to assess change in sleep symptoms in FM treatment trials [13]. This was because the MOS Sleep Scale evaluates numerous problems, such as snoring and shortness of breath, that are not relevant to many FM patients. The analysis concluded that the sleep disturbance subscale may be useful in isolation, but the MOS sleep scale as a whole was not recommended for use in FM patients. Another evaluation of the MOS sleep scale provided some evidence for content validity in FM, but modifications to the scale were recommended to improve the psychometric properties

and relevance in FM patients [58]. Based on these analyses and the availability of other sleep questionnaires, the MOS sleep scale is not recommended for quantifying the severity of sleep symptoms in FM patients.

The FOSQ is a 30-item self-report questionnaire designed to measure the impact of daytime sleepiness on activities of daily living in people with sleep disorders using functional status categories including general productivity, activity level, vigilance, social outcomes, and intimacy and sexual relationships [55]. Each item queries level of difficulty with an activity due to being "sleepy or tired" and is answered from 1 = "yes, extreme (difficulty)" to 4 = "no (difficulty)." FOSQ scores range from 5 to 20 with lower values indicating worse functioning. The FOSQ was developed in patients with disorders of excessive sleepiness, primarily obstructive sleep apnea, recruited from university sleep disorder clinics [55]. The FOSQ has never been validated in FM patients. This is significant, as the FOSQ instructions state that "when the words 'sleepy' or 'tired' are used, it describes the feeling that you cannot keep your eyes open, your head is droopy, you want to nod off, or you feel the urge to nap. These words do not refer to the tired or fatigued feeling you may have after you exercised." FM patients commonly have severe worsening of fatigue after exercise not seen in typical patients that is likely to significantly interfere with their ability to correctly complete the questionnaire. For this reason, the FOSQ cannot be recommended until validation and reliability studies are completed in FM patients.

The JSS is a 4-item self-report questionnaire designed to measure how often a subject has experienced sleep problems in the past month [56]. JSS items evaluate trouble falling asleep, staying asleep, waking up several times, and awakening unrefreshed with each item scored on a 5-point Likert scale from 0 = "not at all" to 5 = "22–31 days." Scores vary from 0 to 20 with higher scores indicating more frequent sleep problems. The JSS has been studied in FM patients and found to be valid, reliable, and able to detect change after treatment [59]. Of the three sleep questionnaires that have been used in phase III FM trials, the JSS is recommended for assessment of sleep symptoms in FM patients (Table 1). However, the JSS has been criticized for possible high-recall bias because it requires patients to rate frequency over the past month. To limit recall bias, an alternative scoring scheme has been proposed and provisionally validated in FM patients by scoring each item either "not at all," "less than 1/2 the time," or "greater than 1/2 the time" [59]. However, further testing of this alternate scoring scheme is needed before it can be recommended for use in assessing FM patients.

13. Tenderness Assessments

Tenderness is a defining feature of FM patients, defined by the 1990 ACR criteria as pain upon palpation at standard tender point sites with 4 kg/cm² of force [3]. However, decreases in the number of tender points have been shown to correlate poorly with patient improvement in FM treatment trials [52, 60]. This is likely because tender point counts do not specifically measure tenderness but are a more general

measure of distress influenced by cognitive and emotional aspects of pain perception [61, 62].

Change in the severity of pain at tender point sites has been shown to be a better measure of tenderness than change in the number of tender points. The manual tender point survey (MTPS) is a standardized approach to performing the tender point exam in which FM patients rate pain severity upon digital palpation of each tender point on a verbal 11 point NRS [10]. Pain severity ratings from the 18 tender points are averaged to yield a Fibromyalgia Intensity Score (FIS) that varies from 0 to 10 with higher scores indicating more severe tenderness. The MTPS/FIS has been used in a pregabalin FM treatment trial, and decreases in FIS scores with treatment were seen [63]. The tender point index (TPI) is a similar tenderness measure to the FIS that supports its use [3]. For the TPI, patients are asked to rate pain on a 0 to 4 scale upon digital palpation of each of the standard 18 FM tender points, and pain scores for all tender points are summed to yield a 0 to 72 score with higher scores indicating more severe tenderness. Significant decreases in TPI scores with active treatment compared to placebo were demonstrated in a small milnacipran FM trial [64], but no other trials have used the TPI.

While newer assessments currently under development may prove superior for evaluating tenderness, such as the multiple random staircase-evoked pain measure [60], they remain unproven. The MTPS/FIS is the currently recommended tenderness assessment for FM trials since it is standardized, can be performed with minimal training, and does not require specialized equipment.

14. Recommended Evaluations and the PROMIS of Future Assessments

As previously discussed, it is currently challenging to compare results across different treatment trials since different measurement tools are commonly used that often have noncomparable or noncombinable scores. This limitation of clinical trials is well known and not exclusive to FM. Two routes have been taken to solve this problem: (1) require a standard set of existing assessment tools to be used in treatment trials or (2) develop a new set of assessment tools for use in clinical trials. While groups like IMMPACT have taken the first route and made recommendations for the use of existing assessment tools [15], these recommendations have typically not been followed because regulatory bodies like the US Food and Drug Administration have not made them mandatory. This is likely due to the fact that, as we have seen in the case of FM, assessments that work well for one condition do not work well for others. Because of this, the FDA would need to develop a different set of recommended assessments for use in treatment trials of every condition.

The US National Institutes of Health roadmap project Patient-Reported Outcomes and Measurement Information System (PROMIS) has taken the second route to address the need for uniform assessment measures in clinical trials. PROMIS is a 5-year cooperative group program of research designed to develop, validate, and standardize item banks to

measure patient-reported outcomes relevant across common medical conditions [65]. The PROMIS network is working to combine items from the best of all current patient self-report questionnaires to create a set of standard symptom severity assessments for use in clinical trials. In addition to improving the ability to compare results from one trial to another, use of PROMIS is expected to reduce the sample size requirements of trials needed to demonstrate minimal clinically important differences by 20% to 50%. PROMIS also has great potential in clinical practice to rapidly and reliably assess response to interventions and to inform treatment decisions. PROMIS is particularly well suited for use in FM treatment trials, as assessments have been developed for all core FM symptom domains [66], and field testing of PROMIS item banks in >3500 FM patients is nearing completion (private communication with David A. Williams, University of Michigan, Ann Arbor, MI, USA). Assuming PROMIS item banks are shown to be valid and reliable in FM patients, they will be the recommended assessment standard for core FM symptom domains in addition to the FIQR and PGIC for global improvement.

While PROMIS is being developed, the Athens insomnia scale (AIS) should be studied for use in assessing sleep disturbance in FM patients [67]. The AIS is a recently developed 8-item self-report sleep questionnaire based on ICD-10 insomnia diagnostic criteria that has been recommended for use in therapeutic trials based on its superior feasibility, validity, and psychometric properties compared to 44 other sleep questionnaires including those discussed above [68]. The AIS cannot only quantify the severity of sleep problems but also be used to diagnose patients with insomnia [67]. The AIS has a 5-item subscale, the AIS-5, that is a unidimensional measure of nighttime sleep problems similar to the JSS, and scores on the two scales are highly correlated [67]. However, the AIS is superior to the JSS since it also has 3 items that measure the severity of daytime symptoms related to poor sleep that are lacking in the JSS, and assessing the severity of daytime symptoms is important to evaluate in patients with sleep problems. However, recommendation of the AIS must await validation and reliability testing in FM patients.

High ceiling effects are typically seen when assessments are used to quantify symptom severity in FM patients. As an example, the ceiling effect on the JSS total score was found to be 27% in an FM treatment trial [59]. Assessments with high ceiling effects are problematic because they limit the ability to adequately evaluate patients with severe symptoms and measure symptom worsening (e.g., an FM patient with a maximal JSS score at baseline is treated and, even though their sleep symptoms worsen, the JSS score remains unchanged from baseline which is wrongly interpreted as no change in symptom severity). Patient impression of change scales have been shown to be superior to other questionnaire types in evaluating change in patients with severe symptoms [69]. The FIBRO Change Scale have been proposed as a way to use patient impression of change scales to better evaluate change in FM patient symptoms in response to therapy [70]. The FIBRO change scale includes seven patient impressions of change scales to assess key FM symptoms including fatigue, fibrofog, sleep dysfunction, depression,

anxiety, stiffness, and pain each answered on a 0 to 10 scale from 0 = “very much improved,” 5 = “no change” and 10 = “very much worse.” A similar scale could be developed incorporating patient impression of change items for all 9 core FM symptom domains that could reduce the problem of questionnaire floor and ceiling effects in biomarker development and therapeutic efficacy evaluations. However, such a scale will require validation studies in FM patients before it can be recommended.

15. Conclusions

Objective biomarkers and new treatments are needed to improve the diagnosis and management of FM. However, research standards for FM clinical diagnosis and core FM symptom domain assessments are needed to enable development of biomarkers and new treatments. Since standards for FM diagnosis and symptom assessment do not exist, these recommendations are intended as a starting point for discussions that will lead to the development of standards. While none of the assessments discussed herein are perfect, consensus within the FM research community must be reached if timely advances for improving patient care are to be made. The 1990 ACR FM classification criteria performed using the manual tender point survey (MTPS) standardized method incorporating the fibromyalgia intensity score (FIS) is the recommended method for clinical diagnosis since the 1990 criteria are well established, and the method can be performed without any specialized equipment. Recommended assessments for core FM symptom domains include the brief pain inventory average pain visual analogue scale for pain intensity, the physical function subscale from the revised fibromyalgia impact questionnaire (FIQR) for physical function, the patient global impression of change (PGIC) and FIQR for overall/global improvement, the depression subscale of the hospital anxiety and depression scale (HADS-D) for depression, the multiple ability self-report questionnaire (MASQ) for cognitive dysfunction, the fatigue severity scale (FSS) for fatigue, the FIQR for multidimensional function/health-related quality of life, the Jenkins Sleep Scale (JSS) for sleep disturbance, and the MTPS-FIS for tenderness. It is hoped that these recommendations will provide an impetus for the development of universally accepted standards of FM clinical diagnosis and symptom domain assessments that can provide the foundation for the development of objective FM biomarkers and new more effective treatment regimens.

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Review Article

Dysfunctional Neurotransmitter Systems in Fibromyalgia, Their Role in Central Stress Circuitry and Pharmacological Actions on These Systems

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Fibromyalgia is considered a stress-related disorder, and hypo- as well as hyperactive stress systems (sympathetic nervous system and hypothalamic-pituitary-adrenal axis) have been found. Some observations raise doubts on the view that alterations in these stress systems are solely responsible for fibromyalgia symptoms. Cumulative evidence points at dysfunctional transmitter systems that may underlie the major symptoms of the condition. In addition, all transmitter systems found to be altered in fibromyalgia influence the body's stress systems. Since both transmitter and stress systems change during chronic stress, it is conceivable that both systems change in parallel, interact, and contribute to the phenotype of fibromyalgia. As we outline in this paper, subgroups of patients might exhibit varying degrees and types of transmitter dysfunction, explaining differences in symptomatology and contributing to the heterogeneity of fibromyalgia. The finding that not all fibromyalgia patients respond to the same medications, targeting dysfunctional transmitter systems, further supports this hypothesis.

1. Fibromyalgia as a Stress-Related Disorder

Fibromyalgia is characterized by heightened pain perception, including widespread hyperalgesia, in particular to deep-pressure stimuli, enhanced temporal summation, and reduced pain-inhibiting effects of heterotopic noxious stimulation (often termed diffuse noxious inhibitory control, DNIC) [1]. Fibromyalgia has often been described as a stress-related disorder, and altered stress systems have been viewed as causal for pain and other symptoms experienced in this condition [2]. The body's two stress systems, the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system, are indeed altered in fibromyalgia [1]; however, results on the specific changes are heterogeneous. For both systems, hyper- as well as hypoactivity in basal functioning and acute stress responses has been reported (e.g., [3–8]). Concerning the HPA axis, it has been suggested that prolonged periods of stress associated with heightened basal tone and exaggerated acute stress responses (hyperreactivity) are followed by the development of a hyporeactive HPA axis,

thus potentially explaining inconsistent findings regarding the HPA axis [9].

Stress increases the risk of developing fibromyalgia, dependent on different predispositions (e.g., genetic makeup and gender) [2]. However, it is still unclear which physiological processes mediate the relationship between experienced stress and the development of fibromyalgia. Changes in the autonomic and HPA stress systems are often considered as such mediators, with chronic stress exposure altering the functioning of these stress systems, causing fibromyalgia symptoms [2, 10]. In line with this view, the cardinal symptom of the condition seems to be related to alterations of the HPA axis: reported levels of clinical pain have been shown to be associated with concentrations of corticotropin-releasing hormone (CRH) in the cerebrospinal fluid (CSF) [11] and to salivary cortisol levels [12].

Nevertheless, prospective studies are scarce and available results do not allow conclusions on causal relationships [13]. In addition, in contrast to pain, other prominent symptoms associated with fibromyalgia, such as fatigue, depressivity,

and perceived stress, appear not to be related to measures of HPA axis function [11, 12]. It is, therefore, conceivable that fibromyalgia symptoms are associated with altered autonomic and HPA axis stress systems but that these altered stress systems do not necessarily cause the symptoms. Stress-related changes in other physiological systems, for example, neurotransmitter systems, might be additionally involved in symptom development. Further, stress-related changes in such other systems may develop in parallel to changes in the autonomic and HPA axis systems or even precede them, thereby contributing to or causing fibromyalgia symptoms.

In support of these considerations, some evidence suggests that dysfunction of the body's autonomic and HPA axis stress systems are related to some of the risk factors for developing fibromyalgia, such as early-life stress [14] rather than playing a causal role in the pathogenesis of fibromyalgia. For example, salivary cortisol levels in a cross-sectional study were shown to differ depending on the presence or absence of early-life trauma (physical or sexual abuse) but did not differentiate between fibromyalgia patients and healthy controls [12]. Similarly, CRH concentrations in the CSF have been shown to be strongly related to the presence or absence of early-life trauma (physical or sexual abuse) [11]. Regarding the sympathetic system, evidence in healthy volunteers suggests that reduced heart rate variability may be a predisposing factor for the development of fatigue, pain, and depressive symptoms rather than the underlying cause of these symptoms [15].

2. Dysfunctional Transmitter Systems in Fibromyalgia

Cumulative evidence points at alterations in neurotransmitter systems in fibromyalgia (see Figure 1), which is interesting because the main symptoms of fibromyalgia, that is, heightened pain perception, fatigue, sleep disturbances, and depressive as well as anxiety-related symptoms, are closely linked to these neurotransmitters.

The key symptom and main diagnostic criterion for fibromyalgia is chronic widespread pain. Several neurotransmitters and modulators are substantially involved in pain processing. For example, central serotonin and noradrenalin are important in endogenous pain inhibitory pathways [19, 20] and serotonin plays also an essential role in descending pain facilitation via the 5HT₃ receptor [21, 22]. Substance P is a neuropeptide that is important for spinal nociception. It coexists with the excitatory neurotransmitter glutamate in primary nociceptive afferents [23] and causes sensitization of dorsal horn neurons [24, 25]. Not surprisingly, glutamate itself plays an important role in nociception, as it has excitatory and sensitizing effects [26]. In addition, glutamate has some inhibitory effects in descending pain pathways [21]. Although it has to be acknowledged that the exact effects and modulatory actions of these transmitters depend on receptor subtypes and CNS site [21, 22], serotonin, noradrenalin, substance P, and glutamate have been shown to be altered in fibromyalgia in ways that could explain patients' increased pain sensitivity. CNS levels of serotonin and noradrenalin

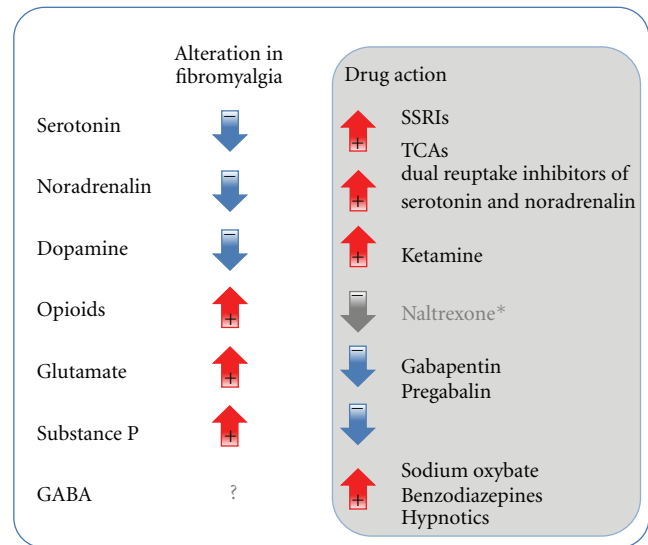


FIGURE 1: Alterations in transmitter systems found in fibromyalgia patients in terms of increased or decreased activity and action of drugs used in fibromyalgia on these transmitters systems in terms of activity increase or decrease. *The positive effect of naltrexone, an opioid antagonist, on fibromyalgia symptoms is suggested to be mediated through disinhibiting effects on HPA axis activity, rather than by its effect on the opioid system (cf. [16–18]).

appear to be lowered, indicated by decreased levels of metabolites in the CSF and of serotonin and noradrenalin in blood [27–30], possibly contributing to dysfunctional descending pathways and resulting in attenuated descending inhibition (cf. [31]). CSF concentrations of substance P and glutamate have been repeatedly found to be increased in fibromyalgia patients [32–34]. With respect to glutamate, proton magnetic resonance spectroscopy studies could show that this neurotransmitter is elevated in pain processing regions such as the insula, amygdala, and cingulate cortex [35–39]. Supporting the hypothesis that a hyperactive glutamate system contributes to increased pain sensitivity, and maybe other symptoms of fibromyalgia, elevated glutamate levels in the insular cortex have been observed to be correlated with low pressure pain thresholds [39] as well as with high scores on the fibromyalgia impact questionnaire (FIQ, [40]) [37].

Similar to serotonin and noradrenalin, dopamine activity has been demonstrated to be attenuated in fibromyalgia (see [41] for review): CSF levels of dopamine [28] and presynaptic dopamine function are reduced (examined with positron emission tomography (PET)) [42], and dopamine responses to acute pain are diminished in fibromyalgia patients [43]. Since inactivation of D2 receptors has been shown to lead to hyperalgesia [44], these findings may suggest that dysfunctional dopaminergic neurotransmission contribute to patients' pain symptomatology.

Particularly important for the endogenous control of nociception are endogenous opioids, as they decrease transmission of nociceptive signals in several pathways and nuclei [21, 45]. Counterintuitively, opioid activity appears

to be increased in fibromyalgia as indicated by increased CSF and blood serum opioid levels [46], upregulation of opioid receptors [47], and reduced cerebral mu-receptor binding at rest (indicative of increased release) [48]. It is not readily conceivable how an overactive opioid system would contribute to fibromyalgia symptoms. Indeed, elevated levels of opioids might be a consequence of pain, rather than a cause, since similar findings have been obtained in other chronic pain conditions [49, 50]. Nevertheless, mu-opioid receptor binding potentials have been found to be negatively correlated with measures of affective pain in fibromyalgia [48], perhaps explaining the emotional connotation of pain in fibromyalgia. Another important neurotransmitter of antinociception is GABA [51], the main inhibitory neurotransmitter in the CNS. Although direct investigations are not yet available, pharmacological studies have shown a certain effectiveness of GABAergic agents for pain, sleep, and fatigue, suggesting that this inhibitory neurotransmitter system might also be impaired in fibromyalgia.

In addition to increasing pain sensitivity, alterations in serotonin, noradrenalin, and substance P may contribute to disturbances in sleep or mood in fibromyalgia patients. Serotonin and noradrenalin are strongly associated with circadian rhythms (see [52] for review), and serotonin is recognized as a mediator of deep sleep [53]. Moreover, a deficient serotonin system is strongly associated with major depression [54]. Increased levels of intracerebral substance P have been associated with increased anxiety-like behavior in animals [55], and accordingly, NK1-receptor blockade (NK-receptors are the receptors for substance P) is associated with reduced anxiety [56].

3. The Role of Altered Transmitters in Stress Systems

Dysregulated neurotransmitter systems have been suggested to play a role in the etiology and pathogenesis of stress-related pathologies including fibromyalgia (cf. [57, 58]). For example, deficient noradrenergic modulatory function is hypothesized to increase the vulnerability to stress-related pathology [58]. In line with this hypothesis, all of the neurotransmitters systems found to be altered in fibromyalgia exert influences on the sympathetic nervous system or the HPA axis stress system (see [52, 59] for review; see Table 1).

Serotonin and noradrenalin have been shown to have a mainly excitatory influence on acute stress responses and both are key in circadian rhythm of the HPA axis [52, 59–61]. Dopamine has excitatory influences on the basal tone of the HPA axis and enhances acute stress responses, as demonstrated in various animal and human studies (e.g., [62–64]). Another excitatory neurotransmitter in CNS stress circuits is glutamate even though glutamate is present also in inhibitory stress circuits [52, 65–67]. It is hypothesized that an optimal “glutamate tone” is required, whereby too little or too much results in HPA activation [52]. GABA and substance P both inhibit HPA axis functioning: they have a tonic inhibitory influence on the HPA axis and terminate acute HPA stress responses (GABA [68–70]; substance P

[59, 71, 72]). Evidence suggests that opioids diminish stress-induced autonomic stress responses [57, 73], but for the HPA axis, both inhibitory and excitatory effects have been found [74, 75], presumably depending on receptor subtypes and type of stressor [74–76].

The transmitter disturbances observed in fibromyalgia could readily explain hyporeactivity of both stress systems, as found in fibromyalgia (see above; [1]). Transmitters that regulate circadian rhythm and enhance acute stress responses such as serotonin, noradrenalin, and dopamine are reduced in fibromyalgia, while substance P, which inhibits basal tone and acute responses of the HPA axis, is increased. Similarly, opioids, which are increased in fibromyalgia, inhibit acute sympathetic and HPA axis stress responses.

In contrast, these transmitter aberrations cannot easily explain a hyperactivity of the stress systems, which has equally been shown in fibromyalgia [1]. This might be because the view presented in the preceding paragraph is very simplistic. The specific effect of a neurotransmitter may be only weakly related to its global level (which is the measure often obtained in human studies) but depends on factors such as receptors subtype, brain region, concentration relative to other neurochemicals, and the type of stressor. For example, evidence suggests functional differences of serotonin receptor subtypes in HPA axis regulation [61, 77], and the modulatory function of serotonin appears to be dependent on specific brain regions and stressors [60]. The same has been suggested for dopamine [63, 78–80] and glutamate [66, 81–84]. Similarly, the differential inhibitory and excitatory effects of opioids have been suggested to be due to different opioids acting through different opioid receptors in addition to a dependence on stimulus conditions [74–76].

The situation gets even more complicated if one takes into account changes in neurotransmitter functioning due to chronic stress that in turn affect sympathetic and HPA axis stress responses. Chronic stress leads to attenuated HPA axis responses that are mediated by serotonergic neurotransmission, in contrast to the serotonin-mediated increase of acute HPA axis responses under normal conditions [52, 60, 61]. Noradrenalin release seems to be increased by chronic stress through sensitized noradrenergic neurons, leading to enhanced autonomic and HPA axis excitability [52, 58, 85–87]. In otherwise healthy organisms, the experience of chronic stress has been demonstrated to result in increased as well as decreased dopaminergic activity depending on receptor subtype and brain region [88]. In general, dopaminergic responses to stressors seem to be enhanced after exposure to chronic stress [78], which could lead to hyperreactive stress systems, since these systems are excited by dopamine. In accordance with increased levels of endogenous opioids and substance P found in fibromyalgia, opioids [57, 89] and substance P [52, 90] have been found to be increased in response to chronic stress, leading to an attenuation of HPA axis reactivity. Results on changes of glutamate and GABA systems due to chronic stress are not conclusive: some glutamate [91–93] and GABA [94–96] receptors subunits are upregulated, while others are downregulated with chronic stress depending on brain regions.

TABLE 1: Overview of the effects of the neurotransmitter systems found to be altered in fibromyalgia on HPA axis activity and the effects of drugs used in fibromyalgia, targeting these transmitter systems, on HPA axis activity. Information on effects on the sympathetic nervous system is not included, because results are scarce. The specific effect of the transmitters depends on different aspects of HPA axis activity, that is, basal tone and circadian rhythm or acute stress responses. In addition, under conditions of chronic stress, the transmitter effects on the HPA axis are often altered. The table represents a simplistic summary of the evidence found on transmitter actions on HPA axis activity. Despite a vast number of studies, the precise mechanisms of neurotransmitters on HPA axis functioning remain only incompletely understood [52]; transmitter actions depend on receptor subtypes, brain regions, and type of stressor.

Transmitter system	Effect on HPA axis activity in terms of		HPA axis activity under chronic stress*	Effect of drugs on HPA axis activity*
	basal tone and circadian rhythm	acute stress responses		
Serotonin	excitatory (↑) and inhibitory (↓)	excitatory (↑)	inhibitory (↓)	excitatory (↑) and inhibitory (↓)
Noradrenalin	excitatory (↑) and inhibitory (↓)	excitatory (↑)	excitatory (↑)	excitatory (↑) and inhibitory (↓)
Dopamine	excitatory (↑)	excitatory (↑)	excitatory (↑)	?
Opioids	excitatory (↑)	inhibitory (↓)	inhibitory (↓)	excitatory (↑)
Glutamate	?	excitatory (↑)	?	excitatory (↑) and inhibitory (↓)
GABA	inhibitory (↓)	inhibitory (↓)	excitatory (↑)	?
Substance P	inhibitory (↓)	inhibitory (↓)	inhibitory (↓)	?

* Chronic stress as well as drugs have differential effects on basal tone, circadian rhythm, and acute responses to stress but most studies do not differentiate these aspects. Accordingly, this table does not differentiate in these instances.

These diverse results strongly suggest that chronic stress does not affect transmitters and stress systems uniformly. In fact, the diversity of the results on chronic stress-induced changes in transmitter functioning favoring in some instances hypoactive, and in other instances, hyperactive stress systems are reminiscent of the range that is found regarding the activity of the stress systems in fibromyalgia patients. So perhaps whether the sympathetic nervous system and/or the HPA axis is hyper- or hypoactive in a given individual depends on the ratio of dysfunctions in different transmitter systems, rather than absolute transmitter levels. For example, hyperactivity of the HPA axis could be associated with alterations in glutamate and opioids that are more pronounced than changes in serotonin, noradrenalin, and dopamine. The different transmitter dysfunctions may also change as a function of time, which could then contribute to stress systems alterations that are not constant over time (cf. [9]). Individual patients might exhibit varying degrees and types of transmitter dysfunction, and indeed, fibromyalgia patients are recognized to be a heterogeneous group. Accordingly, categorization of fibromyalgia patients into subgroups has been suggested. Generally, fibromyalgia patients are subdivided into a group with a predominant pain phenotype (strong hyperalgesia) without or only mild related psychopathological findings and into patients with (major) depression although different ways of categorizing and different numbers of subgroups have been suggested [97–99]. In any case, most studies on dysfunctional neurotransmitters as well as on stress systems in fibromyalgia have not taken any subcategorization into account even though it seems reasonable to assume that these subgroups differ not only with respect to their symptoms but also regarding the mechanisms underlying the condition. Considering that transmitter alterations seem to be strongly related to

symptoms, it seems conceivable that subgroups of fibromyalgia patients are characterized by different transmitter alterations and that the ratio of dysfunctions in different transmitter systems varies between subgroups. The observation that not all fibromyalgia patients respond to the same medications (Figure 1). Further supports the notion that subgrouping might be important in studies on fibromyalgia.

4. Pharmacological Interventions in Fibromyalgia Targeting Dysfunctional Transmitter Systems

Pharmacological compounds that raise serotonin and noradrenalin concentrations such as tricyclic antidepressants (TCAs) and dual reuptake inhibitors of serotonin and noradrenalin are relatively effective treatments of fibromyalgia, improving mainly pain, sleep, and fatigue although not in all patients (see [100–102] for review). Interestingly, the beneficial effects of these medications are independent of effects on mood (e.g., [103, 104]). Selective serotonin reuptake inhibitors (SSRIs) are less effective compared to TCAs and dual reuptake inhibitors. Moreover, newer SSRIs (e.g., citalopram), which are even more selective for serotonin reuptake inhibition, appear to be even less effective compared to older SSRIs (e.g., fluoxetine and paroxetine) [101]. Taken together, reuptake inhibition of noradrenalin seems to be more important compared to reuptake inhibition of serotonin. Therefore, it would be interesting to investigate the effects of selective noradrenalin reuptake inhibitors (e.g., reboxetine) on fibromyalgia symptoms, which has not yet been done to the best of our knowledge. Moreover, antidepressants such as TCAs or SSRIs, dampen HPA axis activity in patients with major depression [105]. If this was

also true in patients with fibromyalgia, another factor for the choice of medication would be the HPA axis activity status of an individual patient.

A very interesting finding is that 5-HT₃ receptor *antagonists* are effective in fibromyalgia patients with a primary pain phenotype (without depression) but not in fibromyalgia patients with depression [97]. 5-HT₃ antagonists act antihyperalgesic probably through a reduction of descending pain facilitation [22]. The finding that some fibromyalgia patients respond to 5-HT₃ antagonists does not necessarily fit with the finding of decreased serotonin activity in fibromyalgia. So, perhaps fibromyalgia patients with a primary pain phenotype, who respond to 5-HT₃ antagonists, do not have decreased serotonin levels and only those in whom depressive symptoms dominate the clinical picture would show decreased serotonin levels when subgrouped. However, one has to be cautious with this hypothesis, because serotonin concentrations could potentially vary across different CNS sites.

Glutamate and substance P disturbances in fibromyalgia might be targeted by pregabalin. Pregabalin binds to the $\alpha_2\delta$ subunit of voltage-dependent calcium channels and decreases the release of a variety of neurotransmitters, including glutamate and substance P [106, 107] by reducing the calcium influx into nerve terminals. Pregabalin is effective particularly for pain and sleep. Interestingly, only small or no effects on anxiety symptoms have been found in fibromyalgia [108–112] although pregabalin is known to have anxiolytic effects [113] and is approved by the European Union for the treatment of anxiety disorders.

Other pharmacological treatments have been tested in fibromyalgia patients but evidence is weaker [100]. Ketamine is an interesting molecule: typically conceived as a NMDA receptor antagonist, it has recently been demonstrated to act mainly as a D2 dopamine receptor agonist in low doses [114]. Such low doses lead to reductions in experimental and clinical pain in approximately half of the tested fibromyalgia patients [115–117]. A study on the NMDA receptor antagonist dextromethorphan failed to demonstrate positive effects on experimental pain in fibromyalgia patients [118], suggesting that the beneficial effects of ketamine might indeed be related to its dopaminergic properties. The effects of ketamine on the HPA axis vary: while high doses consistently increase HPA axis activity, doses comparable to those used in fibromyalgia have been found to enhance or dampen effects HPA axis functioning (e.g., [119–121]).

Interestingly, naltrexone, an opioid antagonist, has shown some beneficial effect on fatigue and perceived stress in fibromyalgia patients [122]. Since naltrexone disinhibits HPA activity [16–18], it could be postulated that it might be particularly effective in patients with low HPA axis activity and in whom fatigue is the predominant symptom rather than pain.

Disturbances of GABAergic neurotransmission have not yet been directly investigated in fibromyalgia. Nevertheless, a certain effectiveness of sodium oxybate (γ -hydroxybutyrate) (e.g., [123–125]), which acts as a GABA_B receptor agonist, benzodiazepines [126], which enhance the effect of GABA, and (nonbenzodiazepine) hypnotics [127–129], which act

as GABA_A receptor agonists, for pain, sleep, and fatigue has been observed. Benzodiazepines and hypnotics that act at GABA_A receptors dampen HPA axis activity (e.g., [130–133]). Interestingly, zolpidem, which acts selectively at the GABA_A α_1 receptor subunit, has been shown to enhance HPA axis activity [131, 132]. Presumably, this differential effect depends on the drug's effect on a specific GABA receptor subunit and the net effect of the nonselective drugs results from by action on different receptor subunits [131, 132]. It would be interesting to investigate whether the effects of selective and nonselective drugs targeting GABAergic neurotransmission are different in fibromyalgia patient subgroups with hypo- or hyperactive stress systems.

5. Stress-Induced Changes in Transmitter Systems as a Pathogenic Factor in Fibromyalgia?

Because transmitter changes seem to be closely related to fibromyalgia symptoms and could, at least partly, explain alterations observed in the HPA axis as well as the sympathetic system, dysregulated neurotransmitter systems may play a pathogenic role in fibromyalgia (cf. [57, 58]). Indeed, chronic stress induces changes in relevant neurotransmitters, as discussed above. In this theoretical framework, stress-induced changes in transmitter systems would cause pain as well as other symptoms in fibromyalgia and contribute to the observed changes in the sympathetic as well as HPA stress system. In addition, chronic stress also directly modifies the HPA axis and the autonomic nervous system, and the stress systems are likely to influence the transmitter systems. Consider, for example, substance P: chronic stress leads to an increase in substance P [52, 90] and can cause a hyporeactivity of the HPA axis. But because substance P itself inhibits the HPA axis, the causal relationship remains unclear. Different scenarios are conceivable: the first one is, the “serial stress system-based view” in which changes in the functioning of the autonomic and HPA axis stress systems, as a result of chronic stress, cause fibromyalgia symptoms and alter transmitter systems. In this scenario, changes in the stress systems precede and cause fibromyalgia symptoms and dysfunctional transmitter systems, considering dysfunctional transmitters systems not as causally relevant for the pathogenesis of fibromyalgia. The second scenario is, the “serial transmitter-based view” in which changes in transmitter functioning, as a result of chronic stress, cause fibromyalgia symptoms and alter autonomic and HPA axis stress systems. In this second scenario, dysfunctional stress systems are not considered as causally relevant for the pathogenesis of fibromyalgia in that dysfunctional transmitter systems precede and cause fibromyalgia symptoms and altered stress systems. Lastly, we have the “parallel view” in which chronic stress is considered to cause dysfunctional transmitter as well as autonomic and HPA axis stress systems in parallel. Neither changes in transmitter systems nor in stress systems precede each other, but changes in the systems interact and both dysfunctional transmitter and stress systems finally cause fibromyalgia symptoms.

The current evidence does not conclusively favor one model. Longitudinal studies in fibromyalgia that track the development of disturbances in transmitters as well as stress systems over time would be important in order to test these models. Further, any study on the topic is likely to substantially benefit from subcategorizing fibromyalgia patients. Similarly, treatment studies should investigate well-defined subgroups of patients, ideally selected based on specific biochemical alterations that are hypothesized to be impacted by the specific therapy. Although—or maybe because—this is a long “to-do” list, it has to be acknowledged that research in recent years has already made great advances in uncovering CNS alterations and potential mechanisms that might contribute to the complex clinical phenomenon of fibromyalgia.

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Review Article

A Mechanism-Based Approach to Prevention of and Therapy for Fibromyalgia

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Fibromyalgia syndrome (FMS) is characterized by pain referred to deep tissues. Diagnosis and treatment of FMS are complicated by a variable coexistence with regional pain, fatigue, sleep disruption, difficulty with mentation, and depression. The widespread, deep pain of FMS can be a consequence of chronic psychological stress with autonomic dysregulation. Stress acts centrally to facilitate pain and acts peripherally, via sympathetic vasoconstriction, to establish painful muscular ischemia. FMS pain, with or without a coexistent regional pain condition, is stressful, setting up a vicious circle of reciprocal interaction. Also, stress interacts reciprocally with systems of control over depression, mentation, and sleep, establishing FMS as a multiple-system disorder. Thus, stress and the ischemic pain it generates are fundamental to the multiple disorders of FMS, and a therapeutic procedure that attenuates stress and peripheral vasoconstriction should be highly beneficial for FMS. Physical exercise has been shown to counteract peripheral vasoconstriction and to attenuate stress, depression, and fatigue and improve mentation and sleep quality. Thus, exercise can interrupt the reciprocal interactions between psychological stress and each of the multiple-system disorders of FMS. The large literature supporting these conclusions indicates that exercise should be considered strongly as a first-line approach to FMS therapy.

1. Mechanistic Base of FMS Prevention and Therapy

Clinical diagnosis of fibromyalgia syndrome (FMS) has relied heavily upon tender point counts, a convenient evaluation of pain sensitivity that has come under scrutiny in terms of reliability and validity [1]. Tender point testing is designed to provide objective evidence for hypersensitivity to palpation of deep tissues, consistent with patient reports of ongoing pain referred to deep tissues. The location of ongoing pain changes over time but is widespread in the aggregate. The pain is chronic but is not always present. These features suggest that deep tissues are chronically sensitized and are easily brought to threshold for activation of nociceptors. Accordingly, tests of deep pressure sensitivity with control over the stimulus and thorough psychophysical evaluations reveal allodynia and hyperalgesia for stimulation of a muscle within the aggregate distribution of FMS pain. When muscular indentations are controlled in duration and force, FMS subjects report lower pain thresholds [2]

and substantially more pain for suprathreshold stimulation than control subjects [2–8]. Repetitive stimulation at the threshold force for pain during a single indentation produces higher ratings by FMS subjects, compared to repetitive threshold stimulation for control subjects. Pain is longer in duration for FMS subjects following a series of repetitive muscular indentations. These observations [8] provide diagnostic verification of the ongoing deep muscular pain that brings FMS patients to the clinic.

FMS pain can arise from peripheral influences of the autonomic nervous system [9, 10] in response to aversive mood states (e.g., anxiety, fear, sorrow, and depression) that are referred to generally as mental suffering or distress. Distress activates the hypothalamopituitary axis (HPA) and sympathetic nervous system to generate physiological adaptations referred to as psychological stress reactions [11]. Stress, when chronic, results in cardiovascular dysfunction [12–16] with reduced peripheral blood flow as a result of vasoconstriction [17–19] and reduced endothelium-dependent vasodilatation [20, 21]. Also, chronic stress

produces mitochondrial damage and pathological changes in the vasculature that reduce blood flow [22]. Resting levels of peripheral vasoconstriction are particularly high for females, relative to males [23–29], and FMS primarily is a female pain disorder [10]. Consistent with a predisposition toward peripheral vasoconstriction, females are particularly susceptible to Raynaud's syndrome [30, 31], characterized by excessive cutaneous vasoconstriction and pain in response to ambient cold. Also, peripheral artery disease (PAD) with reduced peripheral blood flow is more prevalent for women [32, 33]. Over time, reduced peripheral blood flow can lead to development of muscular ischemia [34, 35].

Phasic peripheral vasoconstriction, when robust, is painful, as demonstrated by the cold pressor test. Recordings of muscle nerve sympathetic activity (MSA) during ice water immersion of a hand or foot have shown that pain and MSA activity are highly correlated [36]. Similarly, acute muscular ischemia is painful, as evidenced by the submaximal effort tourniquet test [37]. Thus, when psychological stress and peripheral vasoconstriction become chronic and establish muscular ischemia, with sensitization of nociceptors [38, 39], muscular pain is easily evoked [9]. In turn, nociceptive input (e.g., from ischemic muscles) increases sympathetic vasoconstrictor outflow to muscles [40, 41], reinforcing the ischemia. Pain from vasoconstriction and muscular ischemia can explain the referral of FMS pain to deep tissues.

In addition to ongoing or spontaneous muscular pain, psychophysical testing of FMS individuals has revealed widespread cutaneous hyperalgesia [42]. A parsimonious explanation for this effect is that nociceptive input from deep tissues sensitizes spinal neurons having convergent input from the skin, resulting in cutaneous hyperalgesia within the distribution of deep FMS pain [43]. The most thoroughly studied form of central sensitization is temporal summation (windup), a form of central synaptic magnification that requires repetitive or tonic nociceptive input to central neurons [43]. This phenomenology has led to proposals that central sensitization underlies FMS pain [42] and also is responsible for the widespread cutaneous hyperalgesia that accompanies regional pain conditions [44]. However, central sensitization from nociceptive driving does not readily explain the widespread cutaneous hyperalgesia that accompanies regionally localized pain conditions [37, 45–59]. Spinal neurons supplying areas of cutaneous hypersensitivity can be located distant from a source of regional pain. For example, central nociceptive pathways from the foot and the face originate separately from the spinal cord and brain stem, with different thalamic relays to the cerebral cortex. In spite of this separation, temporomandibular pain is associated with enhanced sensitivity to nociceptive stimulation of the foot [56], and patients with irritable bowel syndrome are hypersensitive to stimulation of the face [54] (J. Riley, A. Mauderli, and C. Vierck, unpublished observations). Thus, a source of facilitation other than direct synaptic driving by nociceptive input (e.g., temporal summation) is required to generate widespread cutaneous hyperalgesia from a regional source of pain. The stress and autonomic dysregulation that accompany localized chronic pain can account for widespread hyperalgesia [58, 60–66, 66–68] and

development of FMS pain after onset of a regional pain condition [50].

2. Status of FMS Muscles

The relationships outlined above indicate that a primary objective of FMS prevention and therapy should be to reduce sympathetic vasoconstriction and muscular ischemia, resulting in a loss or reduction of widespread deep pain and hyperalgesia. Prevention applies to the development of FMS in association with chronic stress (e.g., from a regional pain condition), and reducing stress and increasing blood supply to peripheral tissues should be therapeutic if FMS has developed. The need to increase blood flow to peripheral tissues is strongly supported by demonstrations of muscle pathophysiology among FMS patients. Microcirculation is deficient for FMS individuals, as indicated by reductions in capillary density, capillary permeability, and blood flow, resulting in low tissue oxygenation [69–73]. The normal increase in blood flow during dynamic and static exercise (hyperaemia) is attenuated for FMS subjects [74]. Intramuscular concentrations of pyruvate and lactate are increased for subjects with FMS and are negatively correlated with pressure pain thresholds (PPTs) for muscle [2]. Expression of genes that detect muscle metabolites signaling pain and fatigue is increased following exercise by FMS individuals [75]. The strength and endurance of FMS subjects is decreased and is associated with high ratings of exercise induced pain [76, 77]. During and following dynamic exercise, muscle tension of FMS subjects is increased [76]. Inflammatory activity is altered toward an overproduction of proinflammatory cytokines [77–82]. Mitochondrial dysfunction of FMS individuals has been described, with a CoQ₁₀ deficiency in blood mononuclear cells, increased oxidative stress, and mitophagy [83]. Thus, peripheral pathology associated with chronically reduced blood flow to deep tissues clearly can be a factor in generation of FMS pain.

3. Exercise Effects on Muscles

Long-term programs of exercise have beneficial effects on stress and its effects on muscles of individuals with FMS and other conditions of ischemic muscular pain. Cardiovascular consequences of acute stress have been shown to be attenuated following a bout of exercise [17, 84–88]. For individuals with hypertension, a condition associated with chronic stress, exercise decreases sympathetic output to muscles [89] and decreases peripheral vascular resistance [90]. Thus, sympathetic activation by acute or chronic stress can be attenuated by exercise. Exercise promotes angiogenesis and attenuates symptoms of intermittent claudication and ischemic muscle pain associated with peripheral artery disease [91]. Muscular contraction induces secretion of vascular endothelial growth factor (VEGF), an essential contributor to capillary growth in skeletal muscles [92]. Accordingly, capillary density is increased by long-term exercise programs [93, 94]. Exercise increases expression of genes involved in mitochondrial biogenesis [95]. Also,

oxygen consumption (VO_2) is increased during exercise, to meet increased energy needs, and it remains elevated for hours following exercise—particularly when the exercise is distributed in time [96]. Blood flow to an exercised muscle is increased [97–100], along with VO_2 [101], with little generalization to uninvolved muscles, avoiding hypotension [102]. The increase in blood flow in proportion to the relative activity of different muscle groups is referred to as functional sympatholysis, which declines with age [103]. Also following exercise, there is generalized sympathoinhibition [104] and prevention or reversal of endothelial dysfunction [105, 106]. Important functions of the endothelium that are enhanced by exercise include vasodilation, regulation of neovascular growth, and inflammatory control [105, 107].

4. Temperature Regulation and Blood Flow to Muscles

Control over blood flow to peripheral tissues is a fundamental component of temperature regulation. Cold environmental temperatures generate vasoconstriction, and warm temperatures elicit vasodilation, resulting in heat retention or loss, respectively [108]. The implications of temperature regulation for FMS are obvious. Individuals with FMS should stay warm, and exercise generates body heat. Studies of sauna heat therapy have revealed significant improvement in blood flow (endothelium-dependent dilation) [109–111] and reductions in FMS pain [112, 113]. Exercise in warm water is an effective therapeutic procedure for FMS [114], with long-term reductions in pain [115]. Exercise in water is well tolerated by FMS individuals, as it limits stress on weight bearing joints and provides resistance in proportion to the speed of movements.

5. Exercise Therapy for Distress and Depression

In addition to widespread pain and hyperalgesia, FMS is associated with disrupted control over numerous physiological and psychological functions. Accordingly, there has been a shift in emphasis away from seeing FMS strictly as a pain disorder toward regarding it as a multisystems disorder [1, 116]. Symptoms frequently associated with FMS pain include sleep disruption, depression, fatigue, and altered mentation (fibrofog). Mechanistically, these multiple symptoms of FMS can be seen as products of FMS pain and the stress inevitably associated with pain. Sleep disruption, inactivity, and fatigue are predictable consequences of chronic pain [117] and stress [118–120]. Similarly, depression [118, 121, 122] and memory disturbances [123, 124] can result from chronic stress. Thus, FMS fundamentally is a disorder involving reciprocal interactions between pain and stress. Pain can result from or be enhanced by chronic stress [49, 66, 125–132], and pain produces stress [64, 133–137], which has widespread influences on biological systems [11, 62].

Mood disorders both elicit stress and are consequences of stress. Distress, the driving force for chronic psychological stress with HPA and sympathetic activation, is attenuated by exercise programs for individuals relatively free of autonomic

dysregulation [138] or with hypertension [139] or chronic pain [140, 141]. Depression, a mood disorder which often accompanies chronic pain, including FMS, is associated with autonomic dysregulation [142] and with cardiovascular disease [143]. Depression can evolve from chronic stress [121, 144, 145] and from chronic pain [146, 147], and it is a risk factor for chronic pain [142, 148, 149]. Stress, chronic pain and depression frequently coexist and are considered to be reciprocally related [150], each facilitating the other. As depression increases, so do pain complaints, and as pain episodes increase in intensity, frequency, duration, or variety, depression becomes more likely [151]. Exercise can disrupt these interactions by reducing pain [114, 140, 141, 152–156] and depression [114, 140, 141, 152, 153, 156–159]. Conversely, depression occurs more frequently for sedentary individuals [160] or when a long-term program of exercise is interrupted for as little as 2 weeks [161].

6. Stress, Exercise, and Mentation

Psychological stress can either facilitate or interfere with learning and memory, depending upon the timing of HPA activation relative to the event to be learned or remembered, and the magnitude and duration of stress are critical variables [124, 162]. While acute stress can be beneficial, chronic stress is detrimental to learning and memory. Activation of the HPA by psychological stress prominently involves the prefrontal cortex, amygdale, and hippocampus, with feedback regulation via corticosteroid receptors in these structures [123]. Chronic activation of corticosteroid receptors within the prefrontal cortex results in neuronal damage, impairing learning and memory [163, 164]. The hippocampus is a component of the cerebral circuitry mediating psychological stress and is a crucial structure for memory consolidation. Stress reduces neurogenesis in the hippocampus [165, 166], impairing memory and contributing to the pathophysiology of depression [167]. Depression and cognitive decline are linked phenomena [168].

Beneficial effects of exercise on mentation have been documented thoroughly [169]. Large surveys have revealed an inverse relationship between cognitive decline (including Alzheimer's dementia) and levels of exercise. Prospective studies have similarly shown an inverse relationship between objective fitness measures and cognitive decline. The largest effect sizes were for executive functions such as planning, working memory, and multitasking. Investigations of exercise programs for individuals with dementia have revealed beneficial effects on cognitive tests, increased cerebral blood flow, and spared brain volume. A dose-response relationship pertains to exercise duration/intensity and quality of life for older individuals [170].

Laboratory animal experiments have revealed mechanisms for exercise effects on mentation [168]. In brief, exercise induces a cascade of growth factor signaling that enhances cognitive function and attenuates depression by stimulating neuroplasticity and neurogenesis and improving blood flow. The growth factors IGF-1, BDNF, and VEGF are increased peripherally and centrally by exercise. IGF-1

increases BDNF signaling in response to exercise, enhancing neurogenesis and synaptic plasticity in the hippocampus and thereby facilitating learning and memory. Peripheral IGF-1 and VEGF are necessary for exercise-induced prevention of peripheral risk factors for cognitive decline, such as hypertension, hyperglycemia and inflammation.

7. Stress, Exercise, and Sleep

Psychological stress, pain, and sleep disruption are reciprocally related. Stress increases pain sensitivity [60, 66, 67, 171] and disrupts sleep [120, 172]; sleep disruption results in stress [173] with increased pain sensitivity [117, 174, 175]; pain produces stress [58, 61–64, 66, 68] and sleep disruption [117, 175–178]. Given the beneficial effects of exercise on stress and pain, reviewed above, it is not surprising that exercise has been reported to improve sleep latency, quality, efficiency, and duration and reduce next day tiredness [178–184].

8. Methodological Considerations for Prevention of and Therapy for FMS Pain

Ideally, a preventative/therapeutic regimen would not only have beneficial effects on stress, autonomic dysregulation, and pain but would directly or indirectly attenuate the multisystem aspects of FMS such as sleep disruption, depression, fatigue, and fibrofog. Exercise has the potential to accomplish these goals, but it is difficult to convince an FMS patient that an acutely painful activity will reduce pain in the long run. FMS pain can be increased during a bout of exercise [77, 185, 186], and pain sensitivity can be increased at the conclusion of exercise [77, 187]. Peripheral receptors that contribute to muscular pain and fatigue [38] are expressed and detected in leukocytes following exercise by individuals with FMS [75]. These effects are to be expected during and after working ischemic muscles. However, despite the barrier of activity-induced pain, carefully structured exercise programs can attenuate FMS pain and associated symptoms. Gradual introduction to an exercise protocol is especially important for FMS patients with chronic fatigue syndrome (CFS), for whom exertion can cause postexercise malaise for several days.

Numerous studies of exercise effects on FMS symptoms have been summarized in meta-analysis reviews that critically evaluate the experimental methods and summarize the results. The benefits of mild to moderate exercise programs for FMS uniformly include enhanced well being, improved physical fitness, and reduced disability [140, 141]. Because deconditioning commonly accompanies FMS [65], a strong case can be made for exercise as a standard component of FMS therapy. Furthermore, pain and/or tender point counts clearly are decreased by most exercise paradigms [114, 140, 141, 152–156]. The success rate of exercise for pain is important, relative to therapies that rely exclusively on pharmacological agents with side effects and inherent difficulties associated with long-term usage [156]. However, individual differences in response to exercise result in a

moderate overall (average) effect on FMS pain [141, 154, 156, 188]. Individual variability is considerable with respect to the severity, duration, and variety of FMS symptoms at the inception of treatment, and the duration of chronic pain is an important consideration. Also, the type and frequency of exercise and long-term compliance of the subjects influence the benefits of exercise therapy.

Typical experimental protocols for aerobic exercise have conducted supervised sessions 2 or 3 times per week [153–155], with varying recommendations for and documentation of exercise at home. Low to moderate levels of aerobic exercise, as defined by heart rate and blood pressure recordings, have been recommended [152–155]. Direct comparisons with strength training or stretching exercises have concluded that aerobic procedures provide better results [141, 154]. The reasons for this conclusion are not clear, because assessments of presumed mechanistic bases for FMS are not included. For example, what are the relative effects of aerobic and strength exercises on indices of stress, autonomic regulation, and peripheral blood flow, and how are these effects related to reduction of deep muscular pain? In terms of peripheral mechanisms of FMS such as widespread muscular ischemia, it seems that an exercise protocol should enhance peripheral circulation globally, rather than for a specific set of muscles. This goal may be met by whole body aerobic exercise or strength training of multiple muscle groups, but documentation is needed. Also, summaries of exercise therapy for FMS have strongly recommended tailoring of parameters of exertion for each patient [153, 154, 156, 188]. More specifically, (1) a level of exercise which is painful for a subject will discourage participation and may be deleterious [188]; (2) it is important to have exercise options that are adaptable to frequent use by individuals with different daily routines and/or physical limitations; (3) because chronic stress and autonomic dysregulation are relentless, exercise routines are likely to be most effective if conducted frequently so that peripheral blood flow is increased over a significant portion of each day.

The optimal schedule of exercise likely will depend upon the duration of increased blood flow that can be expected to accompany and follow each exercise period. Exercise training appears not to affect muscle blood flow at rest [189]. Thus, exercise therapy for FMS is at an important juncture, needing thorough investigations of long-term effects of different forms of exercise on blood supply to deep tissues. It is encouraging that studies involving standardized schedules of infrequent exercise have revealed attenuation of FMS symptoms, but there is little to be gained by continued study of set exercise paradigms with a fixed set of parameters that are chosen arbitrarily.

The optimum benefits of exercise for FMS surely will depend upon repeated, daily periods of exertion, but regularly scheduled laboratory sessions will be necessary to evaluate and adjust paradigms of exercise. Tolerance for exercise (exercise induced pain) can be assessed, both to maximize continued participation and to measure beneficial effects of exercise. If peripheral blood flow is increased over time with exercise, the threshold for exercise-induced pain should increase. Also, there should be a period free of clinical

pain following each exercise period [186], and charting the time-course of this effect in relation to changes in blood flow to deep tissues would be instructive for design and modification of the exercise protocol. Resting levels of blood flow to muscles, as well as changes in blood flow in response to exercise or nociceptive stimulation, are regarded here as crucial information.

Previous studies have relied upon tender point counts as a measure of deep pain sensitivity, but a psychophysical test of pain during and after well-controlled compression of several muscle groups can provide more useful information on effects of exercise, over time, on sensitization of nociceptors in deep tissues. Psychophysical tests of sensitivity to cutaneous stimulation (e.g., temporal summation during repetitive stimulation) provide information on the central sensitization that is driven by tonic nociceptive input. Techniques for detection of biomarkers of gene expression have been shown to be particularly informative concerning levels of receptor expression and immune activation that are associated with muscular fatigue and pain [75, 190]. These means for evaluation of mechanisms have provided opportunities to approach FMS as a medical condition. Until recently, there were questions as to whether FMS is psychosomatic, without an identifiable organic basis, in contrast to regional pain conditions with histories of injury to the painful tissues. Ironically, the mechanistic bases of FMS appear to be identifiable and may also be correctable, in contrast to many regional pain conditions without available therapies that can silence the source of nociceptive input.

9. Summary and Therapeutic Implications

Fibromyalgia is a multiple-system disorder. FMS patients complain of chronic pain referred to deep tissues (and pain from exercise or palpation of muscles) and commonly present with depression, fibro fog, and sleep disruption. FMS patients frequently are in a deconditioned state with fatigue, and the widespread deep pain of FMS often coexists with one or more regional pain conditions. It is not feasible to treat each of these disorders separately (e.g., with pharmacological agents directed specifically to treat each disorder). This conundrum forces consideration of whether there is a fundamental mechanism for the symptoms that define FMS as a multiple-system disorder. Evidence summarized here identifies chronic psychological stress with autonomic dysregulation as the root cause of FMS, providing opportunities for mechanism-based prevention and therapy [191]. Pain referred to deep tissues is considered the primary symptom of FMS. Chronic stress reduces peripheral blood flow, resulting in widespread muscular ischemia, and muscular pain is a powerful stressor. Stress, with autonomic dysregulation and pain, also establishes central influences that enhance depression, impair mentation and sleep, and increase pain. Therefore, a therapy that reduces stress and/or pain could alleviate each of the multiple-system disorders of FMS. Remarkably, exercise exerts beneficial effects on stress and pain and the other FMS disorders. Reports documenting these effects are part of an extensive literature providing

evidence for exercise as an effective therapy for many chronic diseases of a deconditioned modern society [192].

Investigations typically report moderate overall effects of exercise on FMS symptoms, attributable to the use of standardized exercise protocols despite considerable variability between patients. The use of fixed exercise protocols appears to suit scientific purposes but conflicts with a necessity to tailor exercise to each individual for the maximal therapeutic effect. Thus, it is recommended that different forms, frequencies, durations, and intensities of exercise be evaluated in terms of sustained normalization of peripheral blood flow for FMS individuals. Once an optimal pattern of exercise is established, it can be utilized with measurements of peripheral blood flow to guide individual variations in the exercise protocol over time. It can be expected that effective exercise protocols for pain reduction will differ between subjects and over time, as dictated by blood flow to muscles.

A mechanistic approach to FMS therapy and research minimizes the importance of a control group for comparison with treatments such as exercise. The therapeutic goal is to alleviate FMS, and important scientific goals are to evaluate relationships between FMS and suspected biological mechanisms for the FMS symptoms. At this point, these comparisons can be more instructive than group comparisons with and without exercise. For evaluation of FMS pain, it will be important to evaluate elicited ischemic pain in addition to standard verbal reports of ongoing pain. Well-controlled pressure stimulation of muscles with psychophysical evaluation of pain threshold and the suprathreshold intensity and duration of muscular pain is more informative than pressure point counts. Measurements of peripheral blood flow and exercise-induced expression of biomarkers for receptor expression and immune activation [75] are informative concerning peripheral effects of exercise. Assessments of distress, depression, sleep quality, and mentation provide a tracking of central effects of exercise.

Correction of deconditioning with exercise is beneficial for FMS patients, but available evidence indicates that psychological stress and peripheral vasoconstriction must be attenuated to alleviate pain referred to deep tissues. This paper has not covered techniques to relieve psychological stress directly, but they can be effective in combination with exercise, attenuating reciprocal interactions with pain and each of the multiple-system disorders of FMS.

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Review Article

Genetics and Gene Expression Involving Stress and Distress Pathways in Fibromyalgia with and without Comorbid Chronic Fatigue Syndrome

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In complex multisymptom disorders like fibromyalgia syndrome (FMS) and chronic fatigue syndrome (CFS) that are defined primarily by subjective symptoms, genetic and gene expression profiles can provide very useful objective information. This paper summarizes research on genes that may be linked to increased susceptibility in developing and maintaining these disorders, and research on resting and stressor-evoked changes in leukocyte gene expression, highlighting physiological pathways linked to stress and distress. These include the adrenergic nervous system, the hypothalamic-pituitary-adrenal axis and serotonergic pathways, and exercise responsive metabolite-detecting ion channels. The findings to date provide some support for both inherited susceptibility and/or physiological dysregulation in all three systems, particularly for catechol-O-methyl transferase (COMT) genes, the glucocorticoid and the related mineralocorticoid receptors (NR3C1, NR3C2), and the purinergic 2X4 (P2X4) ion channel involved as a sensory receptor for muscle pain and fatigue and also in upregulation of spinal microglia in chronic pain models. Methodological concerns for future research, including potential influences of comorbid clinical depression and antidepressants and other medications, on gene expression are also addressed.

1. Introduction

The concept that fibromyalgia syndrome (FMS) may involve inherited susceptibility is not new, nor is the related hypothesis that FMS pathogenesis involves a genetic susceptibility combined with environmental exposure that triggers further changes in expression of the same gene(s) or other interacting genes [1–3]. These environmental events might include one or several of the following: traumatic injury, bacterial or viral infection, surgery, or chronic intermittent life stressors. All of these environmental events increase stress exposure (defined as the external events themselves) and distress (defined by the individual's physiological and emotional responses to stressful events). Increased distress is also a consequence of the chronic pain of FMS itself and its cost to normal work, family, and social functioning [4, 5]. This distress may be greater in those individuals with specific

biological predispositions that alter function of the two main stress pathways, the sympathetic (adrenergic) and hypothalamic-pituitary-adrenal (HPA) axes [6]. Distress is certainly greater in those with psychobiological predispositions, such as depression, anxiety, and pain catastrophizing, all of which are intercorrelated with each other and with severity of disability [7]. The focus of this report is on the genetic factors that may underlie these susceptibilities (inherited DNA) and on the gene-environment interactions that can lead to altered gene expression (mRNA) and thereby change the neural and immune pathways that regulate the primary symptoms of muscle pain and fatigue.

In order to rigorously test for possible genetic and gene expression contributions in FMS, it is vital that within the broadly inclusive FMS patient definition, key patient subgroups must be carefully defined to be as homogeneous as possible. Diagnosis of FMS is currently undergoing some

evolution, but is based largely on subjective reports of widespread pain involving muscles and joints that last for 3 months or longer. Research on genes and gene expression in FMS may identify objective biomarkers for the disorder, as well as indicate pathways that are dysregulated and thus are potential targets for therapeutic intervention. Many patients meeting the older American College of Rheumatology (ACR) criteria for FMS, which requires widespread hyperalgesic response to Tender Point testing [8], also meet the Fukuda et al. and Reeves et al. [9] criteria for chronic fatigue syndrome (CFS); this percentage has been reported from 21–80%, with less overlap in primary care and population studies but approaching 70% in specialized referral clinics [10]. It has even been suggested that FMS, CFS, and other overlapping somatic disorders like irritable bowel syndrome (IBS), and other noncardiac chronic pain conditions should be classified as a single disorder labeled “bodily distress syndrome” [11]. The more recent recommendations for clinically defining FMS without requiring Tender Point testing and highlighting fatigue as one of the central constellation of symptoms [8, 12, 13] is likely to further increase the overlap of CFS and FMS. With the broader definition of FMS, however, there is also a greater likelihood of inclusion of subgroups with differing etiologies involving disparate genetic and gene expression profiles. Because of the overlap in these syndromes, in the present report, we will summarize the literature on genetic allelic differences and gene expression in both FMS and CFS, with an emphasis on stress-related genes that may indicate dysregulation in three interacting neural pathways: the adrenergic nervous system known to be activated during many types of physical and mental stress, the serotonin and HPA axis linked to distress through depression, and the purinergic and other ion channel receptors (e.g., acid sensing ion channel (ASIC) and transient vanilloid-1 or capsaicin receptors (TRPV1)) that our own research linked to increased pain and fatigue symptoms in patients with CFS and comorbid FMS following moderate physical activity. Table 1 lists the various stress-related genes addressed in this review.

2. Functional Importance of Adrenergic and Ion Channel Receptors in the Pain and Fatigue of FMS and CFS

Adrenergic receptors are best known for their function as components of the efferent sympathetic pathway, with greatest emphasis on the heart and vasculature as the target organs. A change in central sympathetic activity initiates an increase or decrease in neural activity to β -1 receptors in the myocardium altering heart rate and contractile force, and to α receptors in arterial and venous vessels, influencing constriction and dilation and thereby altering blood flow to specific tissues and venous return to the heart. Equally important in the regulation of blood flow are the vascular β -2 receptors which enhance dilation when activated, a response that principally occurs in response to increased circulating levels of norepinephrine and epinephrine. The levels of these circulating amines reflect the sum of both

adrenal production and local release from postganglionic sympathetic nerve fibers, but may also reflect the rate of metabolism which varies as a function of key enzymes, particularly catechol-O-methyl transferase (COMT). What is less commonly noted is that vascular β -2 receptors are also critical components of the metabolic pathway that causes blood flow to increase in a specific muscle when that muscle's activity increases and more metabolites of activity are produced (local autoregulation). Because this local autoregulation is so firmly tied to increases and decreases in local metabolic activity, this necessarily involves communication between the vascular β -2 receptors and the sensory ion channel receptors that are involved in detection and signaling of increases in metabolites of muscle activity that occur as we exercise first to fatigue and then (if exercise is unabated) to muscle pain.

In addition to their role in efferent activity, both α -2 and β -2 adrenergic receptors have been implicated in animal models of neuropathic and inflammation-induced pain [14–17]. Rahman et al. [18] conclude that in healthy individuals, a spinal pathway including α -2 receptor activity provides a tonic inhibition of neuronal responses to mechanical pain, and this inhibition is lost after peripheral nerve injury. In regard to β -2 adrenergic receptor involvement, this may differ depending upon whether the chronic pain state is new or well established. Coadministration into the temporomandibular joint (TMJ) of the inflammatory agent, carrageenan, together with a β -2 adrenergic receptor antagonist, prevents the chronic TMJ hyperalgesia that typically follows carrageenan alone [17]. However, in established neuropathy induced by sciatic nerve cuff, chronic administration of β -adrenergic receptor agonists reduce mechanical allodynia via β -2 receptor activity [19].

Until recently, no solid candidates for the molecular pathways signaling these sensations that we all have experienced have been confirmed. A significant breakthrough occurred, however, when McCleskey and colleagues found that ASIC3 receptors have the appropriate characteristics to detect such ischemia; they are extraordinarily sensitive to protons (acid), and they are expressed highly in dorsal root ganglion (DRG) neurons that innervate skeletal muscle and the myocardium [20, 21]. They noted that ASIC3 sensitivity to acid is greatly enhanced if extracellular lactate and adenosine triphosphate (ATP) are also present. Subsequently, Sluka and colleagues confirmed that ASIC3 is also important in detecting hyperalgesia in skeletal muscle using a model of chronic pain induced by inflammation. They also demonstrated that exercising their mice to fatigue made these animals more likely to develop hyperalgesia after acidic saline injections [22–24]. In related work, Hayes, Kaufman and colleagues confirmed in cat that ATP-sensitive P2X and ASIC but not P2Y receptors on muscle afferents are important in pressor responses and changes in muscle blood flow induced by chemoreflexes similar to those occurring during muscle activity [25, 26]. Extending this basic research on ASIC and P2X receptors, Light and colleagues [27] recently showed that mouse DRG neurons innervating muscle respond poorly to a single metabolite like lactate, but respond much better to physiological levels of *combinations* of the normal

TABLE 1: Stress-related genes studied for DNA or mRNA effects in FMS, CFS, or related disorders.

Adrenergic receptors		α -1, α -2A, α -2C, β -1, β -2, β -3
Catechol-O-methyltransferase		COMT
Cytokines		IL6, IL10, LTa, CD14, TLR4
Dopamine receptors, enzyme, and transporter		DRD1, DRD2, DRD3, DRD4, DBH, SLC6A3
Glucocorticoid and mineralocorticoid receptors		NR3C1, NR3C2
Ion channels	Purinergic	P2X4, P2X5, P2X7
	Acid sensing	ASIC1a, ASIC3
	Transient vanilloid receptor	TRPV1
Opioid receptors (kappa and delta)		OPRK1, OPRD1
Serotonin receptors, synthesis gene and transporter		HTR2a, HTR3a, HTR3b, TPH2, SLC6A4

metabolites of muscle work including acid, ATP, and lactate. By applying specific antagonists for ASIC3, P2X, and TRPV1 receptors, Light et al. also confirmed that these different ion channel receptors *work together in concert* to signal increases in the levels of these metabolites. Furthermore, two types of DRG neurons innervating muscle were seen: one that responded to low metabolite levels (and may signal fatigue), and another that responded maximally to higher metabolite levels (and thus may signal muscle pain).

For the P2X receptors, in addition to their role as part of a receptor complex detecting potentially painful levels of metabolites, they also contribute to the establishment of chronic pain state by influencing the function of spinal microglia [28]. Microglia become activated under many conditions, including trauma, inflammation, and infection, during which they release chemical mediators including proinflammatory cytokines. Following experimentally induced inflammation, peripheral nerve injury or autoimmune models of neuritis, P2X4 expression is enhanced in activated spinal microglia, and administration of P2X inhibitors leads to a reduction in the hyperalgesia that otherwise follows such injury [29–32]. This research on P2X4 involvement in chronic pain conditions has been somewhat limited by the lack of a specific P2X4 receptor antagonist and has thus turned instead to mouse models where the P2X4 gene has been disrupted. These P2X4 $-/-$ mice show normal responses to acute noxious stimuli, but reduced responses to both chronic inflammatory pain induced by intraplantar injection of Freund's adjuvant and to neuropathic pain induced by spinal nerve injury [29, 32]. Furthermore, following inflammatory treatments, P2X4-deficient mice fail to show the expected increase in prostaglandin E2, a potentially important step in the initiation of inflammatory pain [31].

As noted by Light et al. [27], a third ion channel receptor is part of the metabolite detecting complex, TRPV1, or the capsaicin receptor. Fujii et al. [33] have reported that inflammatory pain and delayed onset muscle soreness in rats is blocked by both ASIC and TRP receptor antagonists. Thus, upregulation of P2X4, ASIC3 and TRP receptors in the DRG could contribute to exaggerated sensitivity to metabolites linked to fatigue and muscle pain sensations, and upregulation of the same receptors on microglia could play an important role in the establishment of chronic

pain following inflammation, nerve injury or autoimmune conditions.

3. Genetic Polymorphisms Linked to FMS Susceptibility or Subgroup Differences

Early research on genetic susceptibility in FMS focused on serotonergic pathways. The rationale for this focus was partly that effective and approved pharmacological treatments for FMS included drugs commonly classified as serotonin and norepinephrine reuptake inhibitors (SNRIs). Although a few of the studies have been positive [34], the majority of investigations on genes involving serotonin function have not shown any association with FMS. For example, Frank et al. [35] found no evidence of any difference in frequency of polymorphisms involving the serotonin receptors 3A or 3B while Tander et al. [36] similarly saw no FMS difference in serotonin receptor 2A polymorphisms, and Gürsoy [37] found no links to serotonin transporter gene variants. In the most recent investigation, reported by Nicholl et al. [38] and Holliday et al. [39], two serotonergic gene SNPs for serotonin receptor 2A and serotonin synthesis gene TPH2 were related to somatic symptoms in the general population and in patients with chronic wide spread pain (CWP). There were of course very different clinical definitions used for FMS in the negative studies versus CWP and somatic symptoms in the latest positive studies, and none of these studies have clearly defined the characteristics of the subgroups where the serotonin SNPs are seen. It was recently shown that female patients with CFS only have increased serotonergic tone (defined by increased prolactin response to tryptophan infusion) while those with CFS who have comorbid FMS (CFS+FMS) have normal serotonergic tone by this test [40]; note that this study used the older ACR criteria for FMS including Tender Point exam. Thus, any future research on serotonergic genes or other serotonin-related biomarkers in FMS using the new broader definition for the disorder must acknowledge the importance of subgrouping based on either Tender Points or some other tests of hyperalgesic response.

The second system to receive intense attention for genetic polymorphisms was the other system directly altered by SNRIs, the adrenergic nervous system. Here too outcomes

have generated mixed positive and negative findings [41], which we believe are largely due to differences in FMS samples, possibly involving whether the sample included larger versus smaller percentages who had comorbid CFS. The adrenergic gene that has received the most attention in FMS to date is the val(158)met single nucleotide polymorphism (SNP) for COMT, the primary enzyme that metabolizes and inactivates catecholamines. Gürsoy et al. [42] reported that specific polymorphisms for this COMT gene differed in frequency among FMS patients versus controls. They further reported that these polymorphisms were unrelated to clinical depression or other psychiatric disorders in their sample. Cohen et al. [43] replicated this finding in a larger sample of 209 female FMS patients compared to 152 of their own nonaffected relatives, and they showed that the met allele was linked to increased number of positive Tender Points. More recently, Finan et al. [44] have linked specific COMT haplotypes to catastrophizing, suggesting that this gene influences cognitive coping strategies. Other studies have shown that these as well as other gene haplotypes associated with reduced COMT enzymatic activity are linked to greater sensitivity to experimental pain among healthy women, and greater risk of developing musculoskeletal disorders including FMS and temporomandibular disorder (TMD) [45–48]. In contrast, studies using patients having the broader diagnosis of CWP with no attention to Tender Point have generally not found any association with COMT haplotypes even with very large samples [49, 50]. This appears to suggest that the characteristics of hyperalgesia and/or allodynia as reflected by responses to Tender Point testing and to experimental pain tasks may be importantly related to the COMT haplotypes and their links to development of TMD and FMS. Further large-scale prospective longitudinal research on the role of COMT-related genes in the pathogenesis of TMD and FMS is in progress, and will provide more definitive tests of the role of these genes.

Additional research on adrenergic genes has indicated that haplotypes influencing α -1a adrenergic receptor and the β -2 adrenergic receptor differ in patients with FMS. Vargas-Alarcón et al. [51] examined SNPs for α -1, β -2, and β -3 receptors in samples of Spanish and Mexican FMS patients versus controls. Of these, only the β -2 adrenergic receptor SNPs were differentially expressed in the FMS patients from both locations while in the Spanish patients only, there was also increased frequency of one of the 3 α -1 adrenergic receptor SNPs studied. In a prospective study, Herlyn et al. [52] reported an association of the same α -1 receptor polymorphism, the rs1048101, with increased risk of development of complex regional pain syndrome following fracture of the radius. Polymorphisms for the adrenergic receptors α -2A and α -2C have both been linked to IBS and to broader somatic complaints including pain in these patients [53]. Xiao et al. [54] found that the Gly16Arg polymorphism for the β -2 adrenergic receptor was less frequent in FMS than controls. Those FM patients carrying the alternative Arg16Arg polymorphism showed lower intracellular cyclic AMP functioning. It is important to note that Nackley et al. [47] found that β -2 adrenergic receptors are involved in the increase in pain sensitivity that results from diminished

COMT activity. Thus, it is possible that the combined presence of genes that downregulate both β -2 receptors and COMT activity in the same individual may more greatly enhance pain sensitivity and risk for FMS than either gene polymorphism individually. Our research group [55] demonstrated short-term reduction in clinical pain ratings in patients with FMS (including 40% with comorbid CFS) and TMD following β -receptor blockade with low-dose propranolol (which blocks both β -1 and β -2 receptors). Subsequently, Tchivileva et al. [56] used a double-blind crossover design to compare one week of propranolol versus placebo treatment, and similarly found that total pain ratings of TMD patients were decreased by the β -adrenergic antagonist; they also found that propranolol did not alter sensitivity to experimental pain in all TMD patients, but did reduce it in those with the COMT haplotype linked to decreased enzyme production.

Altogether, these findings indicate that genetic haplotypes for α and β -adrenergic receptors and COMT confer an inherent susceptibility and are related to risk of developing chronic musculoskeletal and gastrointestinal pain disorders including FMS, TMD, and IBS. Future FMS research should include larger and better characterized samples so that it can be determined whether these risks differ depending on the presence or absence of comorbid CFS, IBS, orthostatic intolerance, and other clinical factors linked to altered autonomic/adrenergic function.

Another central pathway that has received some attention among genetic studies in FMS and related disorders is the dopaminergic pathway. Zubieta et al. [57] reported that the SNPs linked to reduced COMT activity were associated with changes in effects of mu-opioid transmitters on experimental pain. Wood et al. [58] had observed that FMS patients show abnormal dopamine responses to pain. Although Triester et al. [59] found that healthy subjects with specific SNPs for the dopamine transporter gene were less tolerant to noxious cold, Ablin et al. [60] found no evidence for differences among Israeli FMS patients in haplotypes for the dopaminergic transporter gene or for the substance P receptor. However, genetic variants of the dopamine receptor-4 (DRD4) have been associated with FMS or with an overlapping disorder, migraine headaches, in several studies [61–63]. Other dopamine receptor and transporter gene SNPs were not linked to migraine in Spanish samples [64, 65] but dopamine transporter and dopamine beta-hydroxylase gene SNPs did show an association to migraine with aura in other European samples [66].

The purinergic receptors are another broadly influential pathway deserving of attention in genetic studies of FMS and other disorders involving chronic pain and fatigue. IFN-gamma has been shown to upregulate P2X4 receptors (both expression and protein) in vascular endothelial cells [67]. Furthermore, flow-mediated dilation is impaired in P2X4 knockout mice, which have higher BP and have altered nitric oxide (NO) function, even excreting less NO in urine [68]. In one study, a polymorphism linked to lower expression of the P2X7 receptor was associated with subgroups of patients, with both systemic lupus erythematosus and rheumatoid arthritis having poor apoptotic function [69]. Also, SNPs

for the P2X7 receptor gene have been associated with clinical anxiety and both monopolar and bipolar depression disorders [70–73]. Yet to date, there have been no published studies of which we are aware examining genetic variants of any purinergic receptor genes in FMS, CWP, CFS, IBS, migraine, or any other overlapping multisymptom disorder.

4. Gene Expression Research

Gene expression as opposed to genetic SNPs (mRNA rather than DNA) is typically determined through one of two major methods: microarray where the full genome is assessed together, and quantitative real-time polymerase chain reaction (qPCR) where selected primers for specific genes are examined individually. The micro-array approach is attractive for multisymptom disorders like FMS where dysregulation in many physiological systems may potentially be involved, simply because all of them can be examined at once. The primary drawback to microarray for FMS research, however, is that due to examining such a huge number of outcome measures in the same study, it is necessary to use a very large patient and control sample and/or to lump together multiple genes to assess as a single pathway, in order to control for a tremendous statistical problem of false-positive findings. Some authors ignore the false positive problem, and report each gene as though it were an independent test; for example, Gow et al. [74] studied only 8 CFS patients versus 7 controls using the full 33,000 gene sequences from the Affymetrix array, and report that these groups differ significantly in 366 genes (roughly 1% of genes tested). This is very likely one of the factors that has led to frequent nonreplication of results. In contrast, the number of genes examined using qPCR is usually 1–40, and they are typically selected on the basis of representing a specific pathway where prior research has indicated a functional difference. Several studies have reported that from 1–6 genes related to immune function were upregulated in leukocytes of CFS patients compared to controls [75–78]. One option, employed by Kerr and colleagues to examine patients with CFS, is to use microarray for an initial study to identify pathways where multiple gene show differential expression, and then follow this with qPCR on the strongest candidate genes within those pathways [79, 80]. However, Frampton and colleagues [81] have recently found that even using a 44-gene profile generated from their original research, its utility in prospectively distinguishing CFS patients from controls in a new test was only fair (correctly identifying only about 60% of those tested).

One important advantage for gene expression protocols is that one can examine the mRNA levels before and after a challenge. Many genes are upregulated or downregulated quite rapidly in response to normal physiological events, like physical exercise, pain, emotional stress, exposure to an infectious agent, toxins, and many others. In this way, the dysregulation that may be too subtle for detection in the resting state can be revealed. In an early investigation using micro-array to examine gene expression changes in response to an exercise challenge, the Centers for Disease Control

(CDC) research group elected to use a moderate bicycle exercise task (using 70% percent of age-predicted maximum heart rate) rather than a maximal exercise task, which has long been the preferred option for exercise scientists focusing on the cardiovascular system [82]. Their rationale for this decision, which is compelling, was that a submaximal exercise task has 3 key advantages over a maximal exercise test. First, even debilitated patients can complete moderate exercise on a stationary bicycle. Second, it can be performed for an extended period of time (here, 20 min) and duration can be matched across subjects while maximal tests are briefer (7–12 min) and the duration for deconditioned CFS patients may average only 60–75% of that in controls, which could by itself contribute to gene expression differences. Third, this type of exercise is more typical of the activities of daily living that cause postexertional malaise (defined as worsening fatigue, pain, or feelings of sickness), a key symptom of CFS. This CDC-based study observed increased expression of genes in a number of pathways at 24 hours after the exercise in the 5 CFS versus 5 controls, of which the most relevant were ion transport and ion channel activity genes. A more recent case-control study with another small sample (8 CFS patients versus 7 controls) using the same exercise protocol but with qPCR assays for mRNA at 6 hours after the exercise showed increased activity in a pathway linked to complement activation [83]. Using a different Bayesian approach to analyze the same data set, which looked for genes that differed at baseline as well as in response to the challenge, Lin and Hsu [84, 85] found differences in the glucocorticoid receptor gene NR3C1. It should be noted that both Goertzel et al. [85] and Rajeevan et al. [86] had previously reported that NR3C1 haplotypes were differentially present in CFS patients while Macedo et al. [87] observed that a related gene SNP for NR3C2, the mineralocorticoid receptor, was differentially present in FMS patients and this was linked to lower baseline gene expression of both NR3C1 and NR3C2.

To date, the only research examining leukocyte gene expression responses after exercise in patients with FMS-only and patients with CFS plus comorbid FMS has been by our University of Utah research team [88–90]. The 1994 Fukuda et al. criteria plus the Reeves criteria [9] were used to define CFS, including persistent or relapsing fatigue of 6 months duration or longer that results in substantial restriction of life activities, and is accompanied by at least 4 of these 8 additional symptoms: unusual worsening of fatigue, pain, or general unwellness following exertion, impaired memory or concentration, muscle pain, joint pain, unrefreshing sleep, change in headaches, sore throat, and tender lymph nodes. To define FMS, patients had to have widespread muscle/connective tissue pain, including all 4 body quadrants (bilateral, upper, and lower body) for 3 months or longer, and hyperalgesic responses to pressure at Tender Points (with pain reported for at least 11 of 18 Tender Points) [91]; activity-restricting fatigue was not involved in the definition of FMS, and the FMS-only group reported only milder fatigue that rarely limited life activities. We modeled our 25-minute moderate exercise stressor after the one used by the CDC research, but extended the blood sampling times to include 0.5, 8, 24, and 48 hours after the exercise,

corresponding with the typical duration of after the exertional malaise reported by many CFS patients. In our recent investigation, [89], we have also employed a much larger sample including 48 patients with CFS only or CFS with comorbid FMS, and 18 patients with FMS only who report some daily mental or physical fatigue but do not meet criteria for CFS. As our primary comparison group, we tested 49 healthy controls who were age-matched to the CFS and CFS+FMS patients. Because of the risks and problems associated with asking patients to be withdrawn from antidepressant medications, 30 of 48 CFS patients (63%) and 13 of the 18 FM-only patients (72%) were tested while continuing their usual antidepressants; however, to mitigate possible confounding effects of these medications, 11 of 49 control subjects (23%) also had been diagnosed and were currently on medication for clinical depression. We also included another deconditioned patient group, 20 multiple sclerosis (MS) patients who reported daily fatigue that significantly impacted functioning [90]. The genes selected for qPCR assay included adrenergic receptors and COMT, sensory ion channel receptors P2X4, P2X5, ASIC3, and TRPV1, and several cytokine and immune genes including IL10, IL6, lymphotoxin- α (LT α), Toll-like receptor-4 (TLR4), and cluster of differentiation-14 (CD14). At baseline, there were no differences in gene expression between any of the CFS groups or the MS group versus the controls. As depicted in Figure 1, healthy controls (including those on medication for clinical depression) showed no significant increases after moderate exercise in any of the genes under study, despite a trend based on some healthy subjects showing an increase in β -1 adrenergic receptor expression. In contrast, the majority of patients with CFS only or CFS+FMS showed postexercise increases in most of the sensory ion channel genes and all of the adrenergic receptor and COMT genes, as well as IL10, differing from controls in all of these responses. Importantly, patients with CFS only and CFS+FMS showed nearly identical increases in all genes except ASIC3, which increased only in the CFS+FMS group. These postexercise increases were evident as rapidly as half an hour after the moderate exercise task, and persisted for the full 48 hours.

These differences from controls were also evident when comparisons involved reduced samples matched for actual work performed to attain 70% of their predicted maximum heart rate, thereby controlling for differences in fitness level [89]. Postexercise severity of clinical pain and fatigue ratings in CFS-only and CFS+FMS patients were correlated with increases in gene expression, especially with P2X4, α -2A and β -2 receptors ($r = +0.43$, $+0.48$, and $+0.44$ for pain, and $r = +0.51$, $+0.60$, and $+0.47$ for fatigue, resp.; $P < 0.01$) [89].

Unlike those with CFS+FMS, patients with FMS only showed no significant increases in any gene after moderate exercise (see Figure 2). The other patient group, the MS patients, showed modest and transitory increases in α -2A and β -1 adrenergic receptors, but these were significantly lower overall than the increases in the CFS groups, and they had no increases in any of the sensory ion channel genes. The MS group responses were in fact very similar to 10 healthy controls who exercised for 25 minutes at much higher intensity, 85% of their age-predicted maximum heart rate,

who likewise increased β -1 adrenergic receptor expression, but not any sensory receptor. The very modest responses of this high-intensity control group contradict the possibility that, although our moderate exercise task was individually adjusted to evoke a similar cardiovascular response, it was still a more intense stressor for the CFS patients and this resulted in their greater gene expression changes.

Increases in P2X4, P2X5, TRPV1, and ASIC3 plus exaggerated COMT, α -2A, and β -2 adrenergic receptor expression following moderate exercise have been a unique profile in CFS and CFS+FMS patients, not evident in any other patient group with chronic fatigue or pain that we have examined to date. Both the adrenergic receptor and ion channel gene expression was directly correlated with the severity of postexertional fatigue and pain reported by the CFS group. It is notable that our gene expression responses did identify a subgroup among the CFS patients showing decreases rather than increases in α -2A adrenergic receptors lasting for 48 hours; this subgroup did not show increases in any other genes, and they were much more likely to have a clinical history of orthostatic intolerance than other CFS patients. These clinical and gene expression differences provide a helpful starting point for individualized treatment options. Surprisingly, despite their shared fibromyalgia and the fact that both groups reported postexercise increases in pain and fatigue, the FMS-only group was unlike the CFS+FMS group and showed no postexercise increases in these genes.

However, the FMS-only patients did show evidence of dysregulation in the sensory ion channel pathway at baseline prior to exercise. These patients showed increased expression of both P2X4 and TRPV1 receptors at baseline, along with increased IL10 [89]. It is possible that these patients differed from the CFS+FMS primarily in their ability to cope with their sensations of fatigue. If so, they would report less fatigue severity as a chronic symptom, and be able to remain more active in daily life activities. Even though all patients and controls were instructed to refrain from formal exercise beyond slow walking for 48 hour before and 48 hours after our exercise test, the FMS-only patients may have been functional enough to have baseline responses that were nevertheless elevated by more activity while the CFS+FMS and CFS-only groups did not. This possibility might be best addressed in future research by use of activity logs and objective documentation such as with the Actigraph monitoring systems.

We have interpreted these observations as indications of dysregulation in the primary metabolite-detecting neural pathway that senses products of muscle activity including protons, lactate, and ATP. Large-scale increases in P2X4, P2X5, TRPV1, and ASIC3 receptors in the DRG would potentially increase sensitivity to even low levels of these metabolites such that even activity as mild as upright posture and slow walking in CFS or CFS+FMS patients could produce sensations of fatigue and muscle pain that normal individuals would only feel during extreme activity [92]. One major problem with this research is that directional changes in gene expression are tissue specific, and it is not possible to obtain samples of DRG or other neural tissues from living human individuals without causing irreversible damage.

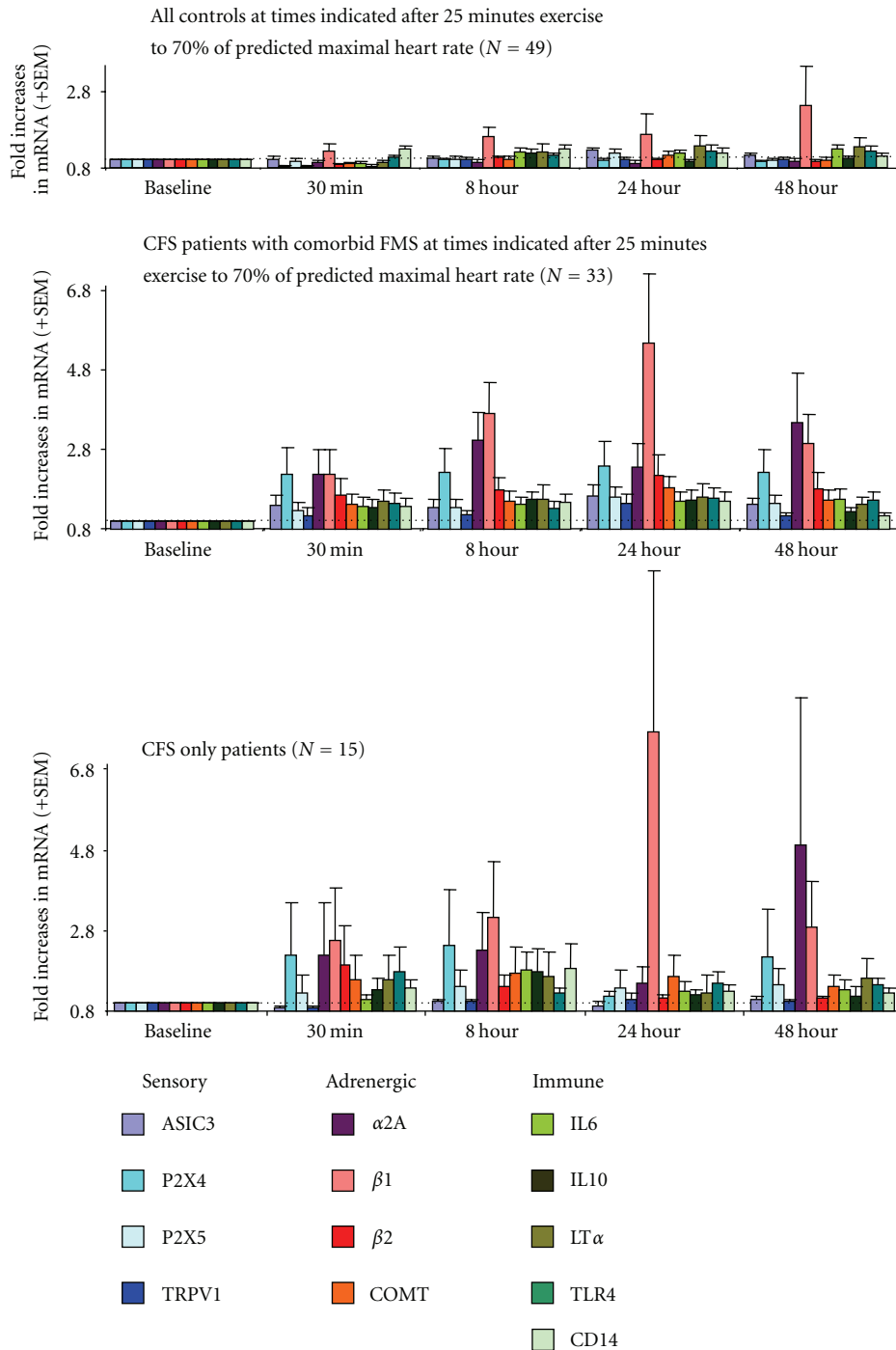


FIGURE 1: Increases in leukocyte gene expression at 30 minutes, 8 hours, 24 hours, and 48 hours after moderate intensity exercise in healthy controls (top), CFS+FMS patients (middle), and CFS-only patients (bottom). Data for each gene (see color codes) are depicted as fold increases from preexercise baseline at each of the 4 sampling times; thus, 2.0 = twice as much expression as at baseline, and so forth. CFS+FMS and CFS only significantly greater than controls for P2X4, P2X5, TRPV1, α -2A, β -1, β -2 adrenergic receptors, COMT, and IL10 assessed as area under the curve across all 4 postexercise sampling times ($P < 0.05$). CFS+FMS greater than CFS-only and controls for ASIC3 ($P < 0.05$). Data are adapted from results reported by Light et al. [89].

Leukocytes, in contrast, are easily obtained without risk on a repeated basis, but we are compelled to use them as indirect markers of these critical neural cells. To reinforce our interpretation, we must depend on research in animal models

where the hypothesized parallel changes in leukocyte and DRG genes can be directly confirmed or refuted. A recently emerging literature, however, supports the use of gene expression profiles from leukocytes as useful surrogates to

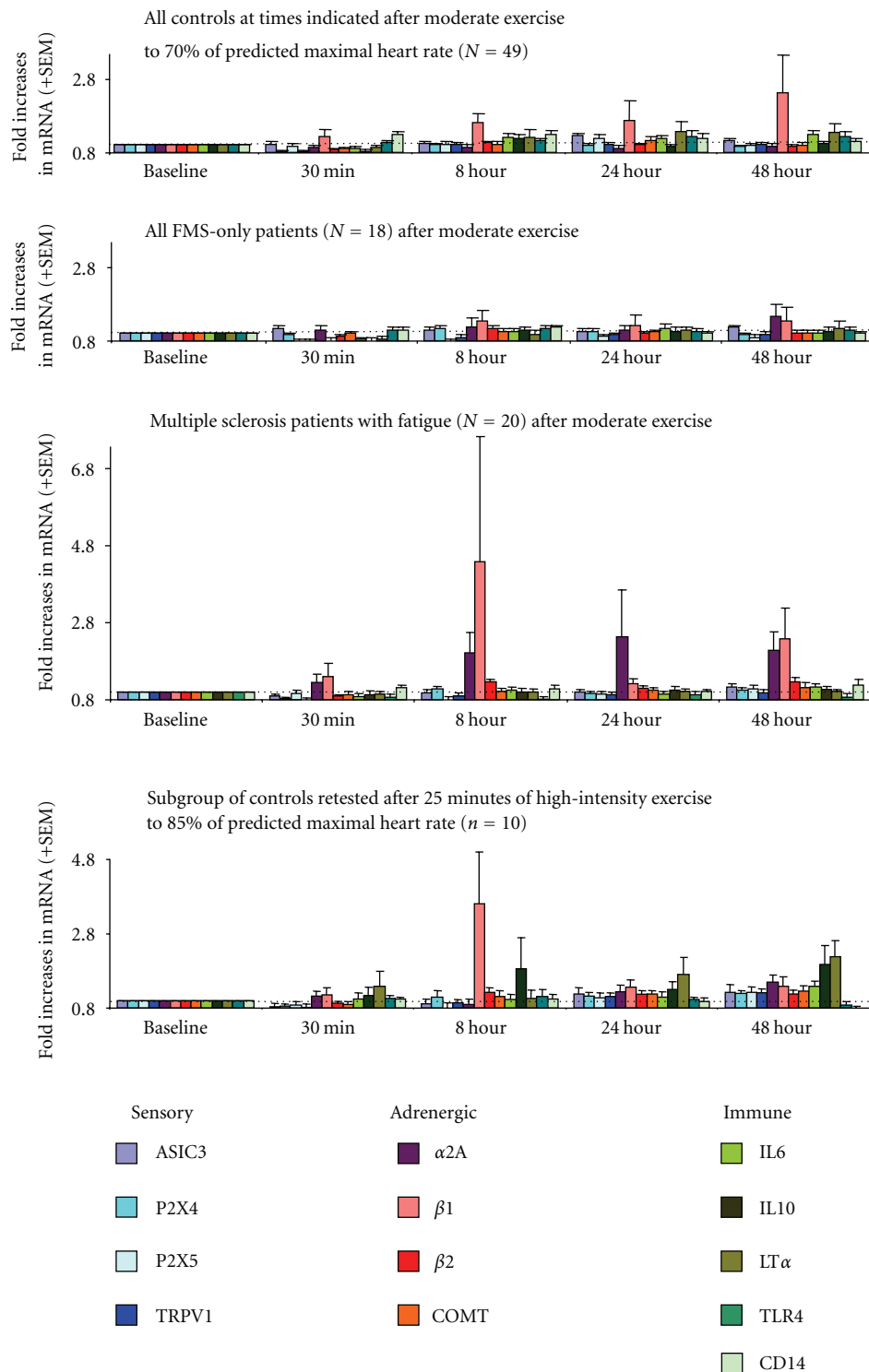


FIGURE 2: Increases in leukocyte gene expression at 30 minutes, 8 hours, 24 hours, and 48 hours after moderate intensity exercise in healthy controls (top), FMS only patients (upper middle), multiple sclerosis patients (lower middle), and after higher intensity exercise in healthy controls (bottom). FMS-only do not differ from moderate exercise controls in any gene. MS patients significantly greater than moderate exercise controls for α -2A, β -1 and β -2 adrenergic receptors ($P < 0.05$). High-intensity controls significantly greater than moderate intensity controls for adrenergic receptors, LT α and IL10 ($P < 0.05$) but not for any sensory gene. CFS+FMS combined with CFS-only patients from Figure 1 significantly greater than high intensity controls for ASIC3, P2X4, TRPV1, α -2A and β -2 adrenergic receptors, and COMT ($P < 0.05$). Data are adapted from Light et al. [89], White et al. [90], and unpublished observations.

neuronal expression for genes linked to pain affect and mood [93–95], thus strengthening use of this approach in the context of FMS. In all studies of gene expression, there is also the additional limitation that this is an indication that processes have been engaged in an effort to increase or decrease the production of a specific receptor or other protein, and that changes in actual protein levels may not always occur.

5. Methodological Issues for Future Research on Genetics and Gene Expression of FMS

One of the difficult issues for this area of research is that many patients with FMS, CFS, and related multisymptom disorders develop clinical depression secondary to their chronic disabling pain and fatigue symptoms, which make performing the usual activities of work and family life difficult or even impossible. When attempting to separate biological effects of depression from the effects of their primary disorder, some investigations have elected to study only those FMS patients who do not meet criteria for clinical depression [40, 55]. This strategy is vulnerable to the criticism that by eliminating FMS patients with depression, the sample may be biased and nonrepresentative, and especially may include only less severely affected FMS patients. Another approach which may be more expensive in terms of resources but more valid is to include patients with clinical depression who do not meet criteria for FMS, CFS, or any other multisymptom disorder as a second comparison group, along with healthy controls. This latter approach could be especially useful when attempting to match the patient and comparison groups for a number of other characteristics, including current or prior use of certain medications, affective state, and use versus avoidance of traditional medical treatment for chronic conditions. Using patients with clinical depression who do not meet criteria for FMS as a comparison group is also extremely important because of the hypothesis that CFS and FMS may be severe somatization variants of major depressive disorder, a possibility which many CFS and FMS patients dispute [96, 97]. A different concern applies to investigations in which the FMS patients are required to stop all their medications for an extended period of time, because the more severely affected patients may be unwilling or unable to do this. However, if all FMS patients are tested while using a specific medication and none of the controls are tested on this medication, gene expression differences between groups could be due to the medication and not the diagnosis. For example, Salemi et al. [98] found that both kappa- and delta-opioid receptor genes had higher expression in skin of patients with FMS versus healthy controls. However, because the report does not clarify medication use or recent cessation, the differences could also be due to more FMS patients either currently using opioid medications or, equally problematic, having receptors that are in a “withdrawal state” due to stopping these medications for only a few days prior to the study. In contrast, one of the better designed studies to date by Macedo et al. [87] reported reduced leukocyte gene expression of both the glucocorticoid receptor NR3C1 and

the mineralocorticoid receptor NR3C2 in patients with FMS, all of whom stopped their antidepressants for at least 2 weeks prior to testing. This study was also especially well designed in that they concurrently tested the functionality of the corticosteroid pathway by measuring basal serum and saliva cortisol levels and examining responses to dexamethasone. Finally, they looked for genetic polymorphisms for these receptors, and found an excess of one allele for the mineralocorticoid receptor, which was then linked to diminished expression of both these related genes NR3C2 and NR3C1. In our research on gene expression differences in patients with FMS (including 72% tested on SSRI or SNRI antidepressants), we have recently compared this group to patients with moderate to severe clinical depression persisting despite SSRI and SNRI treatment as well as to healthy individuals including a subgroup with milder depression that was well controlled by antidepressants (Light et al., unpublished observations). We observed that the FMS and the treatment-refractory depressed patients differed from the controls in expression of a number of the same genes, including similar increased expression of the ASIC1a gene. In mice, genetically disrupting ASIC1a or administering an ASIC1a antagonist reduced depressive-like behaviors in the forced swim test while restoring ASIC1a to the amygdala with a viral vector reversed this effect [99]. In our FMS and depressed patients, this similar increase in ASIC1a expression may reflect common neural dysregulation that contributes to both of these disorders, or instead may reflect the consequences of persisting depressive symptoms. Importantly, the effects do not appear linked to antidepressant use, since this factor was not reliably related to ASIC1a expression in any of our statistical models.

One weakness of the exemplary study by Macedo et al. [87] was a failure to examine their patients for clinical information that might more closely identify the specific clinical characteristics of the FMS who showed this genetic and genomic profile; specifically, it would have been very desirable to know whether they also met criteria for comorbid CFS or other overlapping disorders. We feel very strongly that in a heterogeneous syndromic disorder like FMS, research is greatly strengthened when meaningful subgroups can be differentiated. The findings can then be more specifically useful for clarifying factors linked to pathogenesis and prognosis. The well-defined subgroups together with the genetic and genomic data, when combined, can also provide a clear rationale for individualized physiological targets for treatment.

To date, most of the research summarized above has taken a single blood sample from patients and controls, and examined gene SNPS (DNA) or gene expression (mRNA). Gene expression responses to exercise have rarely been employed, and gene expression responses have not been assessed to any other types of challenge. Future research should continue to examine gene expression responses to exercise and other physical challenges, including pain stimuli and psychological stressors which have particular relevance in hypotheses about FMS onset and progression. When exercise is used as the challenge, it is important to consider both submaximal and maximal exercise tasks as valid options,

depending upon the specific goals of the study. We reiterate that submaximal exercise is closer to the usual physical activity of daily life that leads to worsening of muscle pain and fatigue for 24–48 hours in patients but not healthy individuals, and thus may be better than maximal exercise at revealing physiological pathways that are dysregulated in patients versus controls. If possible, longitudinal research should be encouraged in which both genetic and gene expression measures are obtained in subjects who are still healthy but have genetic SNPs previously linked to FMS susceptibility (for NR3C2, serotonin, COMT, or other haplotypes), and gene expression responses reexamined after a period of years when a subgroup of these individuals may meet criteria for FMS.

As a final point of emphasis, there is a critical need to continue to integrate genetic and genomic clinical research with closely associated research in animal models of FMS—what has been called “reverse translational research.” At this time, for example, research with animal models is critical in the development and testing of new receptor antagonists, such as a specific antagonist for P2X4 receptors. This type of pharmacological tool could be important both for its research and therapeutic possibilities in FMS. Genetic mutant and knockout mouse models are also extremely valuable to help elucidate multiple physiological pathways that are influenced by any genetic or genomic variations of interest. As stated previously, virtually all gene expression research in humans is based on leukocytes, and must acknowledge the limitation that this may or may not parallel gene expression changes in other organs and tissues, like the DRG, spinal cord, or specific brain regions of interest. Parallel studies in animal models can explore gene expression changes in neural tissues and thus greatly reinforce the clinical findings. Thus, much more translational clinical research and reverse translational basic research on adrenergic and purinergic genes and gene expression is encouraged for expanding our understanding of the physiological and environmental factors that initiate and maintain the chronic symptoms of FMS, and to lay the foundation for treatments that are more effective and have fewer side effects for each individual patient.

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Review Article

Fibromyalgia: When Distress Becomes (Un)sympathetic Pain

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Fibromyalgia is a painful stress-related disorder. A key issue in fibromyalgia research is to investigate how distress could be converted into pain. The sympathetic nervous system is the main element of the stress response system. In animal models, physical trauma, infection, or distressing noise can induce abnormal connections between the sympathetic nervous system and the nociceptive system. Dorsal root ganglia sodium channels facilitate this type of sympathetic pain. Similar mechanisms may operate in fibromyalgia. Signs of sympathetic hyperactivity have been described in this condition. Genetic factors and/or distressful lifestyle may lead to this state of sympathetic hyperactivity. Trauma and infection are recognized fibromyalgia triggers. Women who suffer from fibromyalgia have catecholamine-evoked pain. Sympathetic dysfunction may also explain nonpain-related fibromyalgia symptoms. In conclusion, in fibromyalgia, distress could be converted into pain through forced hyperactivity of the sympathetic component of the stress response system.

1. Introduction

The key issue in fibromyalgia (FM) research is to define why people suffering from this illness have so much pain. FM is a stress-related disorder [1]. Patients who have FM often associate the onset of their illness to a particularly stressful situation such as physical or emotional trauma [2–4] or to different types of infections [5]. Additionally, they are frequently immersed in a distressful life style [6]. This article reviews scientific evidence suggesting that, in FM, distress becomes pain through malfunction of the sympathetic component of the stress response system. The following topics will be analyzed.

- (i) Definition of stress, distress, and allostasis.
- (ii) The sympathetic nervous system as a key element of the stress response system.
- (iii) The autonomic nervous system as a complex adaptive system.
- (iv) Animal models linking the development of sympathetic pain to physical or emotional trauma and to different types of infections.

- (v) Dorsal root ganglia sodium channels as key elements in sympathetically maintained pain.
- (vi) Physical and emotional distress in FM.
- (vii) Genetic and clinical data suggesting that FM is a sympathetically maintained neuropathic pain syndrome.
- (viii) Conclusions.

2. Stress, Distress, and Allostasis

The term stress is used in various ways and has different interpretations. Stress has been used to describe the cause (stressor) or the effect (stressed) of a phenomenon. An acceptable physiological definition of stress could be “any stimuli, physical or emotional, that threatens homeostasis” [7]. The term distress is also ambiguous. It was coined by Selye to describe maladaptive responses to stress leading to somatic and/or psychological harm [8]. The emotional component of distress is manifested as anxiety, exhaustion, and/or depression. There are other medical terms related to stress such as allostasis (the additional effort necessary to maintain equilibrium) and allostatic load (the price the body pays for being forced to adapt to adverse psychosocial

or physical situations). These terms may also be pertinent in the study of FM pathogenesis [9]. Stress, distress, and allostasis have both physical and emotional connotations. Novel approaches to understanding complex diseases such as FM steer clear from the Cartesian mind-body dualism, and instead embrace a scientific holistic approach [10].

3. Sympathetic Nervous System as a Key Element of the Stress Response System

Vertebrate animals, including humans, try to accommodate to stressful situations through the allostatic action of their stress response system. This dynamic system is composed principally of a hormonal element, the hypothalamic-pituitary-adrenal axis, and a neural component, the sympathetic and parasympathetic nervous systems [1, 11]. Both parts of the stress response system are closely integrated and complementary. This review will focus on the sympathetic nervous system, since riotous activation of this system in FM could theoretically convert distress into pain.

The sympathetic nervous system is the “accelerating” part of the autonomic nervous system. Its antagonistic calming counterpart is the parasympathetic nervous system. The autonomic nervous system is in charge of maintaining homeostasis through the harmonious and opposing actions of these two branches. This balance maintains internal organ functions, and also maintains the vital signs.

Structures in the central nervous system that generate patterns of autonomic response have been identified. These pattern generators are located at multiple levels in the central nervous system, including the hypothalamus and locus coeruleus, and they can be combined in temporal and spatial patterns to subserve a wide range of behavioral needs [11].

The peripheral sympathetic nervous system consists of a rich neural network that originates in the thoracolumbar section of the spinal column. The preganglionic sympathetic neurons have cell bodies within the horns of the spinal gray matter. Nerve fibers from these cell bodies extend to three types of ganglia grouped as paired paravertebral sympathetic chains, various unpaired distal plexuses, and terminal or collateral ganglia near the target organ. Sympathetic postganglionic fibers innervate the trunk and limbs via the spinal nerves. The sympathetic distribution to the head and neck comes from the three ganglia of the cervical sympathetic chain. The unpaired prevertebral ganglia reside in the abdomen and pelvis, anterior to the vertebral column, and are the celiac, superior mesenteric, aorticrenal, and inferior mesenteric ganglia. Postganglionic fibers arising from synaptic links of the upper thoracic sympathetic fibers in the vertebral ganglia form the terminal cardiac, esophageal, and pulmonary plexuses. The postganglionic fibers from the celiac, superior, and inferior mesenteric plexuses innervate the viscera of the abdomen and pelvis. The adrenal medulla and other chromaffin tissue are homologous to the sympathetic ganglia.

The sympathetic network is highly interconnected. Nerve trunks unite the paravertebral ganglia to each other, so that,

in response to physical and/or mental stressors, sympathetic activation induces a diffuse amplified response that puts the whole organism in a state of high alert, ready to fight or flight. Sympathetic hyperactivity induces nervousness, pupil dilation, tachycardia, skin and visceral vasoconstriction, and muscle vasodilation in addition to many other reactions [12].

Catecholamines (norepinephrine and epinephrine) are the main postganglionic sympathetic neurotransmitters acting on a delicate dampening synaptic structure, the adrenergic receptor. Adrenergic receptors are G coupled proteins that are fundamental in maintaining homeostasis. These receptors are broadly classified as alpha and beta receptors. Alpha adrenergic receptors are more directly related to vasoconstriction whereas beta receptors increase cardiac output and vasodilation. Adrenergic receptors are expressed not only in the sympathetic nervous system, but also in virtually every cell type of the body. Lymphocytes and platelets have adrenergic receptors that are responsive to catecholamines. Hence, sympathetic activation may have coagulation and immune consequences [13].

Sympathetic nervous system dynamics are difficult to assess. Static blood or urinary measurements of catecholamines are unable to follow the constantly changing activity of the sympathetic nervous system. Fortunately, there is a new dynamic method based on computers that is able to estimate sympathetic and parasympathetic influence on heart rhythms. This method is called heart rate variability (HRV) analysis. As will be discussed later, diverse HRV studies have found abnormalities of the sympathetic nervous system in FM patients.

4. The Autonomic Nervous System as a Complex Adaptive System

Science is an ever changing discipline. The current linear-reductionist medical model appears unable to understand FM and similar maladies. Complexity is a new scientific paradigm that will probably have an impact on the practice of medicine. Complexity originated from the computer's awesome ability to perform calculations that are far beyond the capability of the human brain. Complexity recognizes that the universe is full of complex systems that work in an apparent disorderly way in an effort to adapt to the changing environment. In these complex systems, the magnitude of the response is not proportional to the intensity of the stimulus, therefore, linear algorithms are futile. Similarly, for complex systems, the whole is different from the sum of its parts, therefore, reductionist approaches are useless. The only way to understand a complex system is with a holistic approach, viewing the system dynamics in its entirety and assessing its adaptation to the environment. Therefore, holism has now scientific basis. Healthy complex systems have disorderly elastic behavior. If a complex system evolves into an orderly predictable behavior, it suffers degradation and ultimately dies.

Complexity may change some medical dogmas. The current medical view proposes that disease appears when there is disorder in the function of the body. Complexity proposes

the contrary: disorder is healthy and uniformity leads to disease. Existing linear clinical-pathologic correlations view structural damage as the essence of disease. New paradigms propose that disease is dysfunction.

Complexity science paradigms may help us to understand FM. The autonomic nervous system can be viewed as a complex adaptive system. It is a hierarchic and decentralized self-regulatory system, from cells to neurons and from neurons to nerve system. Each level upholds a measure of independence while contributing to a higher level of organization. As will be discussed later, autonomic alterations in FM suggest degradation of this adaptive system, with the presence of rigid sympathetic hyperactivity. From a philosophical perspective, FM can be viewed as a failed attempt of our main complex adaptive system to accommodate to a hostile environment [14].

5. Animal Models Linking the Development of Sympathetic Pain to Physical or Emotional Trauma and to Different Types of Infections

Animal models demonstrate that physical trauma and distress can lead to chronic pain through aberrant sympathetic transmission. Sciatic nerve ligation is a standard model used to study neuropathic pain [15]. In rats, sciatic nerve injury induces abnormal connections between the sympathetic nervous system and the nociceptive system. These short-circuits take place in the rich synaptic paravertebral nodules called dorsal root ganglia. Under normal circumstances, there is not significant sympathetic innervation of dorsal root ganglia. Things change dramatically after nerve injury: there is sympathetic fiber sprouting via nerve growth factor overexpression. In such instances, catecholamines or sympathetic activity are able to induce pain and hyperalgesia [16].

Dorsal root ganglia may also act as a sanctuary for infective agents. Herpes virus may lay dormant for years in these sites. Upon reactivation, herpes may induce dorsal root ganglia neuroplasticity. Postherpetic neuralgia may be the resulting painful manifestation. A similar mechanism may operate in cases of chronic Lyme's disease [17].

Sodium channels located in dorsal root ganglia are the molecular gatekeepers of pain detection at peripheral nociceptors. Nine sodium channel subunits have been identified (Nav1.1–Nav1.9), each with a unique central and peripheral nervous system distribution. An isoform (Nav1.7) encoded in gene SCN9A of chromosome 2q24.3 is predominantly expressed in the dorsal root ganglia pain-sensing neurons and sympathetic ganglia neurons. A single Nav1.7 mutation (L858H) induces electrical hyperactivity of sensory neurons in dorsal root ganglia and, at the same time, produces hyporeactivity of sympathetic ganglia neurons. Several sodium "channelopathies" have been associated to rare painful dysautonomic syndromes such as primary erythromalgia and paroxysmal extreme pain disorder (formerly familial rectal pain syndrome) [18].

Animal models also show how distress can lead to pain. In rats, unpredictable noise can induce catecholamine-mediated chronic mechanical hyperalgesia [19].

These animal models illustrate how physical or emotional distress, as well as different types of infections, can induce sympathetically-dependent chronic pain conditions. Emerging evidence suggests that similar mechanisms may be operative in FM.

6. Physical and Emotional Distress in FM

Both physical and emotional stressors are frequent FM triggers. Bodily trauma, particularly a whiplash injury during automobile accident, is a recognized FM trigger [3, 4]. Also, different types of infections have been associated with the development of FM [20]. Agents implicated include viruses (e.g., hepatitis C, HIV, herpes) and *Borrelia*, the latter is the infecting agent in cases of Lyme's disease [21]. Women with FM have increased incidence of prior sexual or physical abuse [22].

Moreover, FM patients are often immersed in a stressful lifestyle. A prospective investigation found that the development of this illness was associated to workplace bullying, high workload, and low decision-making possibilities [23]. Anxiety and depression are frequent FM companions. Furthermore, many FM patients appear to have created their own "lifestyle stress" by physically or mentally overexerting themselves, being too perfectionist or overcommitted at work, or engaging in disproportionate self-sacrificing behavior [6].

7. Genetic and Clinical Data Suggesting That FM Is a Sympathetically Maintained Neuropathic Pain Syndrome

Different groups of investigators have described sympathetic nervous system dysfunction in patients suffering from FM. Most investigations used HRV analysis as a probing tool. From the literature review, a clear pattern of sympathetic abnormalities in FM emerges: basal sympathetic hyperactivity accompanied by blunted sympathetic response to different types of stressors. HRV alterations suggestive of sympathetic dysfunction are perhaps the most consistent alteration described so far in FM. We have proposed that this abnormal sympathetic behavior may explain all symptoms and that FM is a sympathetically maintained neuropathic pain syndrome [1]. Mechanisms whereby sympathetic dysfunction leads to fibromyalgia multisystem features are outlined in Figure 1.

The International Association for the Study of Pain defines neuropathic pain as "Pain initiated or caused by a primary lesion or dysfunction in the nervous system." Following linear algorithms, a group of experts from the same society recently redefined neuropathic pain as "pain arising as the direct consequence of a lesion or disease affecting the somatosensory system," and a grading system of "definite," "probable," and "possible" neuropathic pain was introduced. This linear redefinition emphasizes "damage" over "dysfunction" as the essence of disease [24]. As already stated, in contrast to this point of view, new scientific paradigms suggest that disease is dysfunction.

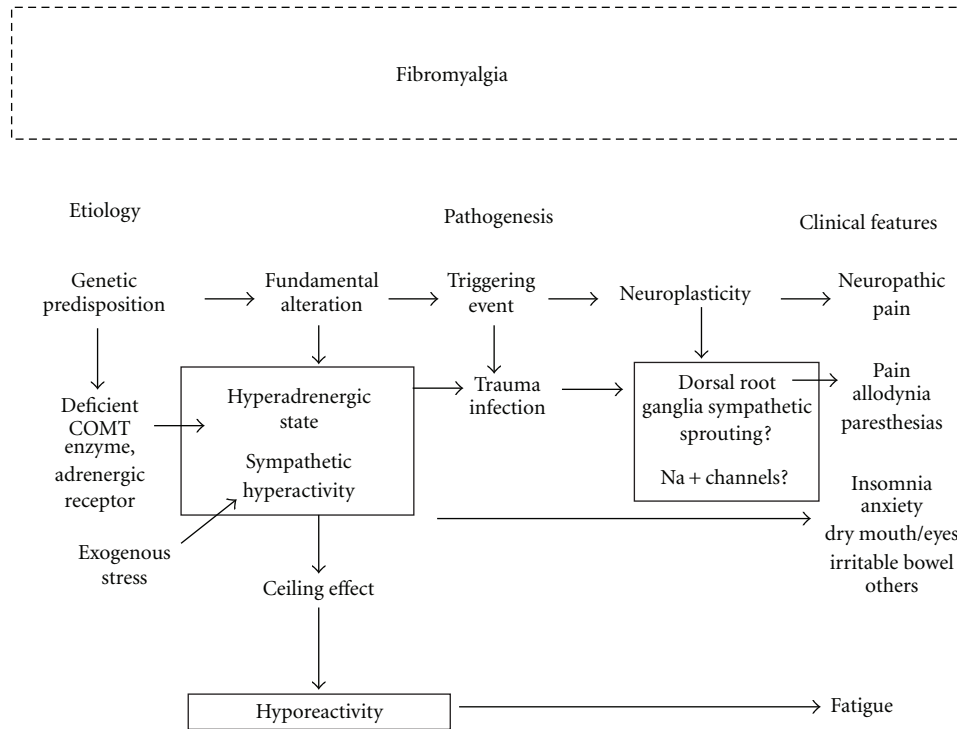


FIGURE 1: Theoretical etiopathogenetic mechanisms in fibromyalgia. See text for details. COMT: catechol-*O*-methyltransferase.

We propose that FM is a neuropathic pain syndrome based on the following three arguments.

- (1) FM is a stimulus-independent pain state. There is no structural damage that could explain the pain intensity.
- (2) The presence of allodynia as an essential feature of FM.
- (3) The presence of paresthesias as a distinctive feature of FM.

It seems difficult to ascribe an etiology other than neuropathic pain to a syndrome with such characteristics.

Among neuropathic pain syndromes, we propose that FM pain is sympathetically maintained based on the following three issues.

- (1) The high frequency of physical or psychological trauma as a triggering event [2–4].
- (2) The signs of ongoing sympathetic hyperactivity [1].
- (3) A double-blind study showing that norepinephrine injections rekindle FM pain [25].

Genetic studies support the concept of FM as a sympathetically maintained pain syndrome. Catechol-*O*-methyltransferase (COMT) is the enzyme in charge of clearing catecholamines from the system. In healthy individuals, pain perception is related to COMT gene haplotypes linked to a defective catecholamine clearing enzyme. A prospective study demonstrated that healthy individuals with such gene haplotypes are prone to develop chronic pain syndromes, such as temporomandibular joint disorder [26]. Several

groups of investigators have shown COMT gene alterations in FM patients [27, 28]. It should be noted, however, that this association was not found in a study of individuals with chronic widespread pain [29]. The reason for this discordance remains to be explained. Additionally, people suffering from FM have gene polymorphisms associated to defective adrenergic receptors [30].

The concept of FM as a sympathetically maintained neuropathic pain syndrome may offer new avenues for research. Firstly, this concept validates FM symptoms. Few physicians would doubt the validity of postherpetic neuralgia, even in the absence of ostensible tissue damage. Additionally, the fruitful animal and human research on the pathogenesis of neuropathic pain and sympathetic pain can be applied to the study of FM.

Recent genetic studies suggest that severe FM may be a sodium channelopathy. When compared to healthy controls, Mexican women with FM have different gene polymorphisms of sodium channels located in dorsal root ganglia and in sympathetic ganglia [31]. This new finding may have therapeutic implications. Sodium channel blockers may become useful therapeutic agents for FM. Currently available sodium channel blockers are weak and nonspecific. Selective tetrodotoxin-resistant channel blockers are being developed and may in the future constitute an important therapeutic option for FM pain [18].

8. Conclusions

FM can be viewed as a failed attempt of our main complex adaptive system to accommodate to a hostile environment.

A disease in which distress is transformed into pain through sympathetic system rigidity. Proposed mechanisms whereby this transformation takes place are summarized in Figure 1. Certain COMT or adrenergic receptor gene polymorphisms predispose to persistent hyperadrenergic state. Physical or emotional trauma may act as triggering events. Different types of infections may also set off the disease. Such stressors are confronted by the main element of the stress response system, the sympathetic nervous system. Resulting chronic sympathetic hyperactivity leads to aberrant dorsal root ganglia neuroplasticity, establishing abnormal connections between the sympathetic nervous system and the nociceptive system. Altered expression of sodium channels takes place. A clinical syndrome of sympathetically maintained neuropathic pain syndrome develops. Sympathetic hyperactivity may also explain other FM symptoms such as anxiety, insomnia, and irritable bowel. Sympathetic hyporeactivity to stress may explain the constant fatigue.

This fibromyalgia dysautonomic paradigm demands a holistic type of therapy in an effort to regain complexity of our main adaptive system and, thus, improving basal sympathetic tone [10]. Specific sodium channel blockers may become valuable agents to relieve the most vexing manifestation of FM: chronic widespread pain.

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Research Article

Affective-Cognitive Behavioral Therapy for Fibromyalgia: A Randomized Controlled Trial

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A randomized controlled trial was conducted to assess the efficacy of an individually administered form of cognitive behavioral treatment for fibromyalgia. In an additive design, 76 patients diagnosed with fibromyalgia were randomly assigned to either the experimental treatment (affective-cognitive behavioral therapy, 10 individual sessions, one per week) administered concurrently with treatment-as-usual or to an unaugmented treatment-as-usual condition. Statistical analysis conducted at the end of treatment (3 months after the baseline assessment) and at a followup (9 months after the baseline assessment) indicated that the patients receiving the experimental treatment reported less pain and overall better functioning than control patients, both at posttreatment and at followup. The implications of these findings for future research are discussed.

1. Introduction

Fibromyalgia (FM) is a prevalent and disabling syndrome. It is characterized by widespread musculoskeletal pain, multiple tender points, sleep disturbance, fatigue, and stiffness [1, 2]. The prevalence of FM has been estimated to be about 2% of the population [2]. Patients meeting criteria for FM have been shown to overuse health care services and experience high rates of disability [3–5].

At present, FM appears to be extremely challenging to treat [6]. Although some pharmacological and nonpharmacological treatments have produced moderate benefits, no intervention has yet been demonstrated capable of generating clinically significant improvement in the majority of FM patients [6]. The controlled clinical trial literature suggests that pharmacological agents provide some relief to FM patients, though the magnitude of these effects is modest [7, 8]. Psychosocial interventions also have shown some promise in alleviating FM symptoms, with exercise programs and cognitive-behavioral treatments appearing most potent

[8, 9]. Notwithstanding, empirical reviews of the efficacy of cognitive-behavioral treatment (CBT) for FM have revealed mixed results, some showing low-to-medium effect sizes [9, 10], others showing no effect [11]. Because, to date, CBT for FM has been administered in groups, the efficacy of *individually administered* CBT for FM has not been assessed within a controlled experimental design. We hypothesized that an individually administered, intensive, and individualized CBT treatment would achieve more powerful effects than previous group-administered CBT.

We developed an individually administered (CBT) for FM that includes relaxation training, activity regulation, facilitation of emotional awareness, cognitive restructuring, and interpersonal communication training. The elicitation and exploration of affect is an approach rarely used in CBT [12]. We, however, have found this component to be a powerful clinical tool with patients who cannot or do not willingly access and experience emotion, indeed so powerful that we have sometimes labeled our approach affective-cognitive behavioral therapy (ACBT) [13]. In this investigation, we

hypothesized that ACBT would reduce pain intensity and improve other symptomatology over and above the effects of treatment as usual in patients with FM.

2. Materials and Methods

2.1. Study Design. We conducted a randomized, controlled treatment trial, using an additive design [14], in which patients diagnosed with FM received 1 of 2 treatments: (1) 10 weekly sessions of individually administered ACBT in addition to treatment-as-usual (TAU) or (2) TAU alone. Participants were assessed three times during the course of the study: at baseline, 3 months after baseline (posttreatment), and 9 months after baseline (followup).

2.2. Study Population and Settings. Participants were referred to the study by their treating rheumatologists. Men and women, ages 18 to 70, who met ACR criteria for FM, as diagnosed by their rheumatologists and confirmed by a medical history review, were eligible for the study. Individuals manifesting any of the following were excluded from the study: pain from traumatic injury or structural or regional rheumatic disease, rheumatoid arthritis, inflammatory arthritis, autoimmune disease, unstable medical or psychiatric illness, active suicidal ideation, a history of psychosis, current psychoactive substance dependence, or a medication regimen that had not been stable for at least 2 months prior to baseline. Women who were pregnant or attempting to conceive also were excluded from the study. Participation in psychotherapy concurrent with the period between the baseline and posttreatment appointment, which occurred 3 months after baseline, was not permitted.

The study took place in an academic medical clinic at Robert Wood Johnson Medical School (RWJMS). The study was approved by RWJMS's institutional review board. Written informed consent was obtained from all participants.

2.3. Treatment Conditions. The ACBT is a 10-session, individually-administered, manualized intervention designed for patients with functional somatic symptoms. The treatment, which we developed, is described in detail elsewhere [13]. The treatment manual allows for adaptation and adjustment to the individual pattern of symptoms and life situations presented by the patients.

2.4. Randomization and Masking. Participants were randomly assigned to ACBT + TAU or TAU using a computer-generated random number sequence. Neither blocking nor stratification was used. Study personnel administering questionnaires were masked to participants' treatment condition.

2.5. Initial Assessment. Participants were assessed at baseline, just before treatment began. Demographic characteristics and baseline levels of the outcome measures (described below) were assessed. The Hollingshead four-factor index was employed to measure participants' socioeconomic status [15]. It is a widely used measure calculated from

an individual's (and his/her working spouse's, if applicable) educational background and occupational history.

2.6. Outcome Measures. The primary outcome measure was a 10 cm visual analog scale of pain (VAS) anchored at its lowest point by the expression "no pain" and at its highest point by the phrase "very severe pain." Participants were asked to rate their level of pain over the preceding seven days. The VAS has been used widely in FM clinical trials to measure pain severity and appears to be sensitive to change [16].

Secondary measures included the Medical Outcomes Study (MOS) SF-36 Physical Functioning Scale (MOS-PF), the Chronic Pain Self-Efficacy Scale (CPSE), the Beck Depression Inventory (BDI), and the Beck Anxiety Inventory (BAI). Physical functioning was assessed with the physical functioning subscale of the MOS SF-36, a 36-item self-report questionnaire assessing various aspects of quality of life. The MOS SF-36 has been validated across a wide range of conditions including fibromyalgia [17, 18]. Self-efficacy for pain management was assessed with the pain management subscale of the Chronic Pain Self-Efficacy Scale (CPSE) [19]. Current level of depression was assessed with the Beck Depression Inventory (BDI), a 21-item self-report questionnaire measuring various aspects of depression. The BDI has been used widely in the depression and fibromyalgia literatures and is considered psychometrically sound [20, 21]. Current level of anxiety was measured with the Beck Anxiety Inventory (BAI). The BAI is a 21-item self-report scale assessing the affective, cognitive, and physical symptoms of anxiety which has demonstrated sound psychometric properties [22, 23].

Because patients' expectations for treatment outcome may be associated with response to treatment [24], they were assessed with the Expectation Rating Scale [25]. The Expectation Rating Scale is made up of three statements to which patients respond by placing a mark on a 10 cm VAS [25].

2.7. Statistical Analysis. Differences between groups on baseline characteristics were tested using unpaired *t*-tests for continuous variables or χ^2 tests for categorical variables. An intent-to-treat approach, based on data from all randomized participants, was used in all analyses. The treatment condition (ACBT + TAU or TAU) served as the independent variable contrast in all analyses, in what is typically referred to as an additive design, in which both levels of the independent variable possess a common element to which, in one group, a putatively therapeutic agent is added [14]. Groups were compared on the primary and secondary outcome variables at the posttreatment and at follow-up appointments, 3 months and 9 months after baseline, respectively. In all, 12 participants were lost to attrition (see Figure 1). Missing data were imputed via the last observation carried forward method. Bonferroni's correction was used to control for the effect of multiple comparisons on overall experiment-wise error rate, which was set as $P < .05$. All tests of statistical significance were 2-tailed, and all statistical analyses were performed using SAS, version 8 (SAS Institute Inc, Cary, NC).

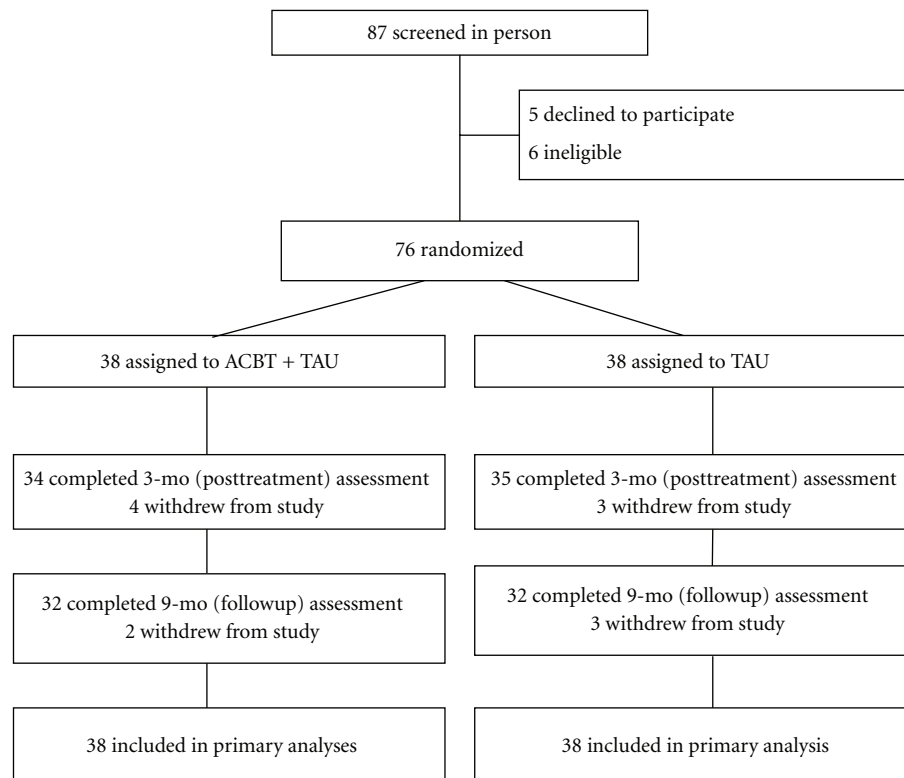


FIGURE 1: Flow of participants through the study.

3. Results

There were no significant differences on any baseline characteristics between the two treatment groups (Table 1), suggesting that outcome findings related to treatment were not confounded by any demographic variable. Most participants were middle-aged women who had experienced widespread pain for an average of 11.5 years.

A one-way analysis of covariance with one fixed effect (ACBT + TAU versus TAU), using baseline scores as the covariate, was conducted on the primary outcome measure (VAS) at posttreatment. The main effect for treatment was highly significant, $F(1, 73) = 45.94$, $P < .0001$, Hedges's $g = 0.90$, with patients receiving ACBT + TAU indicating less pain than those receiving TAU. At followup the difference between treatment conditions continued to be highly significant, $F(1, 73) = 52.83$, $P < .0001$, Hedges's $g = 0.95$ (see Figure 2).

The data were also examined from the perspective of clinical significance, using the criterion of 30% improvement. At posttreatment 25 patients (65.8% of the intent-to-treat sample) in the ACBT + TAU group, showed at least 30% improvement from baseline on the VAS, whereas only 2 patients (5.2%) in the TAU group improved by 30%. At followup 24 patients in the ACBT + TAU group (63.2%) were at least 30% improved from baseline on the VAS, whereas only one assessed patient (2.6%) in the TAU group continued to be improved by 30%.

In Table 2, a summary is presented of all analyses of primary and secondary dependent variables. The overall pattern

of results shows a relatively strong effect for the ACBT upon pain in FM, an effect that continues at followup. Significant but weaker effects were discovered for all the secondary targets at posttreatment, but a Bonferroni correction would have rendered the effect on the CPSE pain management scale less than significant at followup, when correcting for multiple comparisons (see Figures 3 and 4).

4. Discussion

Our findings suggest that an intensive individually-administered ACBT produces significant improvement in self-reported pain in FM. The treatment's impact on self-reported physical functioning, self-efficacy, depression, and anxiety was statistically significant but smaller. Our data are consistent with recent reviews that have found CBT to be perhaps the most effective psychosocial treatment for FM [9]. The effect size found for ACBT on VAS pain severity was both large and durable compared to those reported in other studies examining CBT, although findings on the other study variables were more or less in line with results of earlier research. The VAS is often considered to be the instrument of choice in studying treatment of FM patients [16], although there is enough variability in the way the VAS is presented to study patients, for example, differing anchor points, that comparisons across studies are rendered somewhat problematic. If we simply look within our own sample nonparametrically, using a 30% improvement on the VAS as the criterion,

TABLE 1: Baseline characteristics of the participants*.

	ACBT + TAU <i>n</i> = 38	TAU <i>n</i> = 38	<i>P</i> value
Age, mean (SD), y	47.79 (9.28)	50.21 (10.14)	n.s.
Female, no. (%)	34 (89.47)	33 (86.84)	n.s.
Race/ethnicity, no. (%)			
White	30 (78.95)	28 (73.68)	n.s.
African american	2 (5.26)	0 (0.00)	
Hispanic	3 (7.89)	6 (15.79)	
Other	3 (7.89)	4 (10.53)	
Education, no. (%)			
Graduate degree	10 (26.32)	6 (15.79)	n.s.
College degree	10 (26.32)	12 (31.58)	
Some college	9 (23.68)	13 (34.21)	
High school or less	9 (23.68)	7 (18.42)	
Married, no. (%)	19 (50.00)	21 (55.26)	n.s.
Employed, no. (%)	16 (42.11)	21 (55.26)	n.s.
Hollingshead SES, mean (SD)	47.51 (10.20)	49.61 (9.61)	n.s.
Expectation Rating Scale, mean (SD)	17.20 (5.21)	16.09 (6.86)	n.s.

ACBT indicates affective cognitive behavioral therapy, TAU indicates treatment as usual, Hollingshead SES indicates Hollingshead socioeconomic status scale score.

*Data are presented as No. (%) unless otherwise indicated.

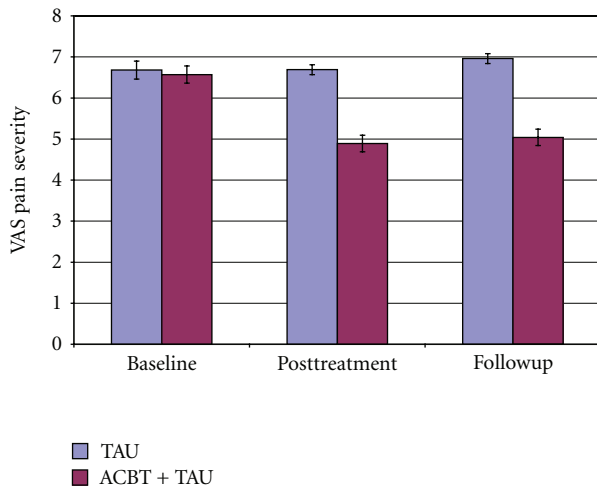


FIGURE 2: Mean and standard error of the mean of the Visual Analogue Scale (VAS) for pain severity TAU indicates treatment as usual. ACBT indicates affective cognitive-behavioral treatment.

the ACBT augmentation of TAU is clinically quite significant, given that TAU was almost entirely without benefit in our sample. Several other studies of treatment for FM have found TAU to yield no clinically significant improvement [26, 27].

Given the structure of the experimental design, however, we cannot infer with certainty that factors unique to ACBT were causal elements in the observed changes or that ACBT

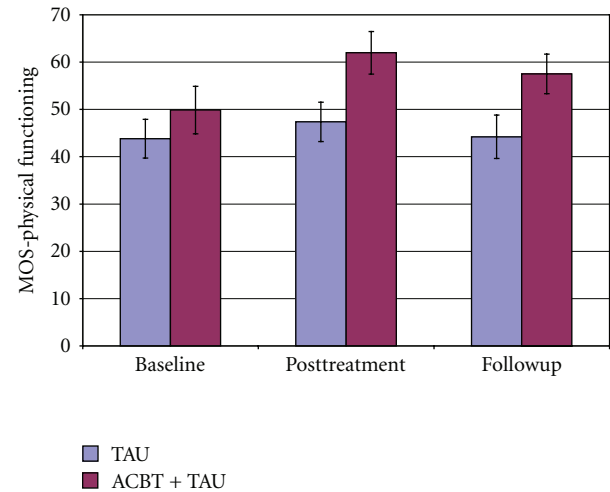


FIGURE 3: Mean and standard error of the mean of the MOS-physical functioning scale TAU indicates treatment as usual. ACBT indicates affective cognitive-behavioral treatment.

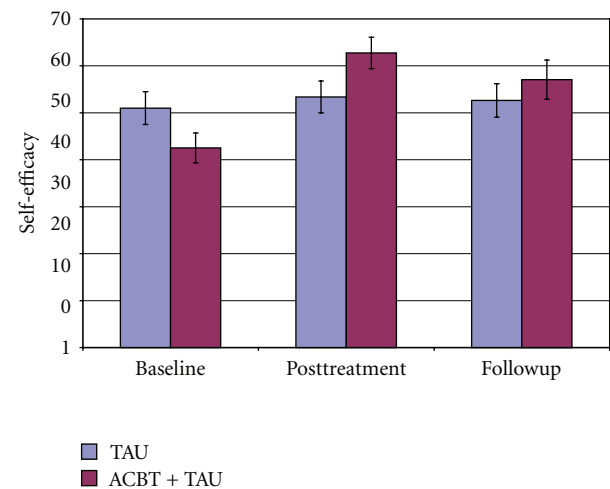


FIGURE 4: Mean and standard error of the mean of the self-efficacy for pain management scale. TAU indicates treatment as usual. ACBT indicates affective cognitive-behavioral treatment.

administered without TAU would be an effective treatment. What we observed was the successful augmentation of TAU by ACBT. Given that generally, and especially in our study, TAU is not an efficacious treatment for FM, our findings suggest that future research should examine the potential utility of treatments such as the one evaluated here. One question that could be addressed is whether additional ACBT sessions, either in the form of an extended treatment or “booster sessions” occurring in the months following the initial intervention, would yield greater therapeutic impact.

There are a variety of reasons why ACBT may have been especially beneficial to our patients. Because each of our patients received 10 individual sessions with the same therapist, perhaps a somewhat stronger bond may have developed between patient and therapist than is often seen in group-administered CBT. The use of extensive relaxation training

TABLE 2: Summary of outcomes.

Outcomes		<i>F</i>	<i>P</i>	Hedges' <i>g</i>
Visual analogue scale for pain severity	Posttreatment	45.94	<.0001	0.90
	Followup	52.83	<.0001	0.95
MOS SF-36 physical functioning	Posttreatment	13.25	<.0005	0.35
	Followup	9.89	<.0024	0.28
Self-efficacy for pain management	Posttreatment	10.42	<.0019	0.65
	Followup	4.13	<.0459	0.40
Beck depression inventory	Posttreatment	11.03	<.001	0.56
	Followup	15.70	<.0002	0.60
Beck anxiety inventory	Posttreatment	11.79	<.001	0.45
	Followup	12.04	<.0009	0.62

and exploration of emotions gives our treatment [13] some of the ambience of standard psychotherapy as it is practiced in the generic clinical arena, rather than the somewhat psychoeducational feeling that group-administered CBT can sometimes possess. Whether relationship factors per se added to the therapeutic power or simply inclined participants to indicate more symptom relief is impossible to say but raises questions that could be systematically examined in subsequent research. The failure to find higher expectations for treatment among ACBT + TAU patients suggests that the treatment effect was not due to mechanisms implicated in the response to placebos.

The durability of our treatment effect upon pain may have had to do with the more intensive, individualized treatment that individually administered sessions can provide. The very use of relaxation training throughout treatment and the strong emphasis given to it as a valuable stress management skill that should be regularly applied in one's life and be a permanent part of one's coping repertory may give our patients a tool that is effective in reducing the discomfort associated with FM. Whether the component of our treatment that places patients in closer touch with emotions that are often suppressed or denied is a factor in treatment efficacy is a question to be answered in future research. From a practical clinical standpoint, it would appear that our approach to cognitive behavioral therapy, ACBT, can be individually administered to FM patients with some likelihood of improving their symptoms.

5. Conclusion

An individually administered affective-cognitive behavioral treatment resulted in sustained improvement in pain and related symptomatology in a sample of patients with FM who had been referred for treatment by their rheumatologists. Additional research is needed to replicate our findings and to explore some questions raised. Is intensive, individually administered CBT a more powerful treatment for FM than treatment provided in patient groups? Are the factors that are stressed in our treatment, creating high competence in relaxation methods and emphasizing the patient's emotional self-awareness, important to success in the psychosocial treatment of FM?

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