Fibromyalgia or chronic widespread pain: Does it matter?

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Fibromyalgia or chronic widespread pain: Does it matter?

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The question whether Fibromyalgia syndrome (FMS) is a distinct clinical entity in the context of chronic widespread pain (CWP) have remained challenging after decades of research and several diagnostic criteria that have attempted to clarify FMS. A recent study has raised more challenges on the issue, proposing that diagnosis of FMS in patients representing with CWP is not informative or helpful for clinical practice and such a differentiation will provide little or no significance regarding the choice of effective and safe therapies. This proposal will be further discussed here by reviewing the recent advances in the field of pain medicine. These advances have collectively provided compelling evidence that all individuals with chronic pain, even those classically categorized as originating from peripheral/nociceptive origins have common central contributions to their pain and associated comorbidities. The recent understanding of the pain mechanisms has also provided important implications on classification and management of pain. Centrally acting agents have been recommended as first-line treatment options for FMS and potential use of these agents has been expanded to other chronic pain disorders. After having reviewed the recent advances in the pain field, distinction between CWP and FMS still seems not to be useful in clinical practice, as effective treatment in an individual patient might be much guided by dominant underlying mechanisms rather than specific diagnosis the patient is suffering. The conditions representing with CWP in the absence of definitive objective confirmation may then be classified under one heading such as "CWP", "chronic pain syndrome" or "central pain", when considering their similar pattern of clinical presentation, commonality of central sensitization to their pathophysiology and their similar response to centrally acting analgesics. Future research should be directed toward classification of CWP based on the validated measurements of different aspects of pain. Such a classification may help clinicians identify the patients who will preferentially respond to peripheral or centrally acting analgesics and may therefore assist in advancing a more individualized and pain mechanism focused treatment in the clinical setting.

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Do we have to name fibromyalgia syndrome (FMS) as a distinct entity in somebody with chronic widespread pain (CWP)? What is the purpose of this differentiation? Does such a differentiation provide any significance in determining the effective and safe therapies? Should we tailor the treatment according to the specific diagnosis or to the different aspects of pain in an individual patient? These questions have remained challenging after decades of research and several consensus reports that have attempted to clarify FMS. Because of the lack of gold standard for definition of FM and absence of objective abnormalities the value of the FMS concept for diagnosis and treatment has been subject to discussion for several decades. Recent advances in the field of pain medicine have added more

challenges to the issue.

In their recent study, Arzu Yagiz On and colleagues at Ege-University have also raised this issue [1]. They reported a survey of 284 patients with CWP, who had admitted to Physical Medicine and Rehabilitation, Algology and Rheumatology clinics of a university hospital. They applied the American College of Rheumatology (ACR) 1990 and 2010 criteria for FMS [2, 3] in these patients, including those with regional painful disorders and systemic inflammatory diseases. The findings may be summarized as follows: 1) almost all patients with CWP may be diagnosed as FMS by using the clinical criteria, regardless of whether they have accompanying painful disorders. 2) Many patients that would not satisfy the TP criterion of the 1990 criteria may be diagnosed as FMS by using the 2010 criteria. 3) Although the 2010 criteria exclude the concept of secondary FMS, co-expression of FMS may be unrecognized in many patients with systemic inflammatory disorders by using the 1990 criteria. 4) Severity of pain-associated symptoms assessed by the 2010 criteria is considerably high in all patients with CWP regardless of the accompanying painful disorders, thus the symptoms are not specific to FMS. 4) TP counts are associated with greater symptom severity and depression in patients with CWP. With these findings they came to the conclusion that attempting to delineate a diagnosis of FMS in patients representing with CWP is not informative or helpful for clinical practice and such a differentiation will provide little or no significance regarding the choice of effective and safe therapies. On the other hand, the authors emphasized the significance of assessing the number of TPs in patients with CWP, as they may represent more severe end of the spectrum of CWP. They suggested that future attempts should be directed toward definition/classification of CWP instead of FMS to formulate effective treatment strategies. This paper thus seems to strongly support the arguments against FMS as a separate disorder but raises more challenges on the issue.

Are CWP and FMS really distinct entities in terms of clinical manifestations and underlying pathophysiology? Are the management approaches really identical for FM and other CWP conditions? To be able to address these questions, it is first necessary to briefly go over the recent advances in the study of pain mechanisms, as they have substantially changed our general understanding and management of chronic pain conditions. Particularly, identification of the contribution of central pain processing mechanisms, such as loss of descending analgesic activity and central pain augmentation or sensitization to the generation of chronic pain syndromes has provided new insights into the pathogenesis of chronic pain and offered new diagnostic and therapeutic opportunities. I would like to specifically address the clinical implications of central sensitization phenomenon for the diagnosis and treatment of FMS and other chronic pain disorders.

Central Sensitization (CS) is a proposed physiological phenomenon in which dysregulation in the central nervous system (CNS) causes an abnormal augmentation of pain, leading to hypersensitivity to peripheral noxious stimuli as well as nonnoxious stimuli [4, 5]. Manifestations of CS include widespread reduction in thermal and mechanical pain thresholds, exaggerated response to a noxious stimulus, pain after the end of a stimulus, and a spread of sensitivity to normal tissue. The term CS was first introduced by Clifford Woolf and his colleagues in 1980s [6-8]. Since then, remarkable progresses in genetics, neurochemistry, neurophysiology, molecular biology, immunology and neuroimaging have significantly advanced our understanding of CS [5]. CS helped to explain pathophysiological mechanisms of chronic pain disorders that are unexplained by organic cause, thus commonly referred as “functional syndromes”. Much of our understanding has been gained through pieces of research into FMS. The presence of CS has been repeatedly identified using quantitative sensory testing methods, functional neuroimaging techniques and various electrophysiological techniques in FMS [9-20]. The data overall have provided a strong evidence that CS play a major role in the generation of generalized sensitivity in patients with FMS. Yunus came to realise that these “unexplained” conditions shared overlapping symptoms such as memory and concentration difficulties, headache, sleep disturbances, fatigue, anxiety and depression, suggesting that they may share CS etiology [21]. He proposed the term “Central Sensitivity Syndrome” (CSS) to collectively describe these poorly understood disorders [21]. With this model, FMS has been widely accepted as a prototypical CCS [22]. Other members of the CSS family include chronic fatigue syndrome, irritable bowel syndrome (IBS), temporomandibular joint disorder (TMD), tension headache/migraine and other overlapping conditions [23]. A growing body of evidence has revealed CS to be a common central mechanism among CSS members [24-27]. Further, epidemiologic studies have demonstrated high comorbidity of CWP with various kinds of diseases that are secondary to or associated with CS [28-31]. These findings have strongly suggested shared etiologic mechanisms for the clinical comorbidities and psychoaffective correlates associated with CWP. Genetic studies using a very large sample of twins have provided consistent evidence of genetic factors underlying the comorbidity of all the various pain syndromes [30, 32-36]. The concept of CS has also gained great importance in explaining the generation of widespread pain hypersensitivity in a variety of conditions with structural pathology, where pain was classically believed to be

primarily due to peripheral nociceptive input. Osteoarthritis (OA) is a good example for such a disorder. Discordance between apparent structural peripheral pathology and the level of pain, high presence of comorbid somatic symptoms and failure to respond to conservative interventions in some individuals have suggested that central factors may be playing a pivotal role in OA [37-42]. Indeed, evidence of CS has been demonstrated in patients with OA, by using sensory testing and functional neuroimaging techniques [43-46]. Some data, including the observation of widespread pain sensitivity have suggested that central pain-processing defects may alter the pain response in rheumatoid arthritis patients [47-49]. Reduced perception threshold to noxious and innocuous stimuli have also been demonstrated in many local pain conditions including patello-femoral pain syndrome [50], tendinitis [51], lateral epicondylitis [52, 53], carpal tunnel syndrome [54, 55], chronic low back pain [56], servical whiplash [57] and shoulder impingement syndrome [58]. Furthermore, studies have demonstrated that altered sensory transmission may result in structural and functional changes within different subcortical and cortical areas implicated in sensory transmission, perception and motor control in local pain conditions. In their pioneering study, Arzu Yagiz On and her colleagues have provided evidence that corticomotor excitability can be enhanced in patients with chronic knee pain [59]. They showed that transcranial magnetic stimulation evoked larger motor evoked potentials in the quadriceps on the affected side in patients with chronic patellofemoral pain syndrome, suggesting an increased excitability at the cortical level. Subsequent studies of corticospinal excitability have been performed in subjects with various local pain conditions including ACL deficiency [60], recurrent low back pain [61-63] and rotator cuff tears [64], all supporting this finding. Furthermore, functional imaging evidence has demonstrated structural changes in areas that influence pain perception and behavior in subjects with chronic low back pain [65]. These findings have provided evidence that the neuroplastic changes amplifying sensory transmission contribute to the pathophysiology of some chronic pain conditions possibly even in the absence of any continued anatomical/structural insult to musculoskeletal structures [37, 38, 66-69]. Changes in central pain processing also helped to explain why some individuals with regional pain later develop CWP when no structural cause can be discerned [65, 66, 68-70]. These advances collectively provide compelling evidence that all individuals with chronic pain, even those classically categorized as originating from peripheral/nociceptive origins have common central contributions to their clinical presentations.

Because FMS and other chronic widespread and regional pain syndromes share common mechanisms, they are also presumed to share common clinical presentations. Indeed, measures of CS have been found to be strongly correlated with duration and intensity of pain and reported to be highly predictive of clinical pain intensity in many chronic musculoskeletal pain disorders including FMS [37, 38, 71, 72]. Many studies have also shown significant correlations between measures of CS and comorbid somatic symptoms such as poor sleep [25, 73], concentration and memory difficulties [74] and depression [75]. Although somatic and cognitive symptoms have been recognized as defining features of FMS, they are not unique to FMS but also encountered in patients with various pain conditions including those with inflammatory disorders or regional pain [39, 42, 76-87,].

The recent growth in our understanding of the mechanisms responsible for pain has also provided important implications on classification and management of pain. New drugs have being developed based on the pathophysiology of CS, which produce analgesia by normalizing hyperexcitable central neural activity [88]. The concept of mechanism-based classification of pain has been proposed to improve the treatment of pain by facilitating the selection of clinical interventions known or hypothesized to target the dominant underlying mechanisms responsible for its generation [89-91]. Specific diagnoses have been classically categorized as peripheral/nociceptive, peripheral/neuropathic or central neuropathic pain based on the dominant underlying mechanism of pain in each of these diagnoses. Although the term “peripheral and central neuropathic pain” originally required evidence for a disease process or lesion affecting the peripheral or central somatosensory system [92], some authors recently use the term “neuropathic pain” for any pain of neural origin and some propose the term central or centralized pain to refer any CNS dysfunction or pathology that may be contributing to the development or maintenance of chronic pain [93, 94]. As FMS has been categorized as a prototypical central pain state, much of the evidence in treatment of central pain has been based on FMS treatment trials [95-100]. Current evidence-based guidelines for managing FMS have been developed based on the recognition that centralized pain poses unique challenges in the fields of pain management. Centrally acting agents such as TCAs, pregabalin, duloxetine and milnacipran have been recommended as first-line treatment options by these guidelines [101-103]. However, a huge shift has taken place towards a person/patient centered management of pain, with the recognition that individual patients within a specific diagnostic category may present a combination of various types of pain with markedly different nociceptive and neural contributions [94, 104]. The patient may not necessarily fit neatly into traditional categories such as FMS or OA, as different types of pain that require different treatment approaches may coexist in a given individual. This is important since treatment of an individual with OA, RA or

CLBP, for example, with focus on peripheral pathology alone will not provide satisfactory treatment if they also have CS that needs centrally acting treatments [49]. In contrast, treatment of an individual previously diagnosed as having FMS with centrally acting treatments alone may not be satisfactory if a kind of peripheral pain coexists. Identification of nociceptive or neural contributions to pain is therefore critical even if a prior diagnostic label has been attached to the individual suffering from chronic pain, to offer an effective treatment.

A question then arises, "how can the clinicians identify whether central mechanisms contributes to the clinical features in a given individual with chronic pain?" Although sophisticated research methods including QST testing, brain imaging and electrophysiological techniques can be used for this purpose, they are not easily accessible for use in daily practice. There are excellent reviews on clinical approaches the clinicians should take when evaluating a patient who represents with chronic pain [93, 105, 106]. These reviews have collectively emphasized that much of the same information attained via aforementioned sophisticated research methods can also be roughly obtained by performing a history and physical examination [94]. Because CWP is the fundamental feature of central pain mechanisms, identification of CWP should be a routine part of history taking when seeing patients with chronic pain, even those with local pain syndromes or associated symptomatology. Indeed, CWP is the entry point for the care pathway recommended for the patients with chronic pain, including FMS [105, 106]. In most of the studies, CWP was defined using the ACR-1990 criteria, as pain lasting three months or more, affecting both sides of the body, and sites above and below the diaphragm, plus pain in the axial skeleton [2, 107], a few defined CWP using the ACR-2010 criteria of a widespread pain index of ≥ 6 or 7 [3, 107, 108]. In a recent study, Visser and colleagues calculated the percentage pain surface area (PPSA) from the body diagram drawn by patients and defined CWP if PPSA $\geq 20\%$ [108]. Increased sensitivity to other sensory stimuli such as bright light, noises, odors, diffuse tenderness or decreased pressure pain threshold can also be easily assessed by history and physical examination [93, 94]. Presence of allodynia and hyperalgesia are other clinical features of central pain mechanisms that should be assessed. Although the clinical utility of tender point (TP) examination in patients reporting CWP has been the subject of contemporary debate, it represents one method for evaluating the presence and spread of mechanical hyperalgesia [11]. In a recent study it has been demonstrated that the presence of mechanical hyperalgesia influences symptomatology in CWP and that the severity of clinical expression is related to a threshold of TPs [109]. The authors therefore suggested that a high TPC or reduced threshold of TPs points to a predominantly central pain mechanism in CWP pathophysiology. Recognizing symptoms of centralized pain, such as disturbed sleep, fatigue, cognitive difficulties and altered bowel movements is particularly important, as it can indicate the need for adding therapeutic interventions directed at treating centralized pain. Recent evidence based guidelines on FMS recommended that treatment choices should target the most prominent comorbid symptoms in a patient tailored approach [101-103]. Amitriptyline or pregabalin could be preferred for those with sleep disturbances, duloxetine for those in depressed mood, and duloxetine or pregabalin for those with anxiety [97]. Appropriate measures and batteries may also be used to identify separate domains of pain [110]. In their series of recent studies, Brummett and colleagues have used 2011 survey criteria for FM [111] to identify central contributions of pain in patients with OA and chronic low back pain [112-114]. The Central Sensitization Inventory (CSI) is a self-report screening instrument that was recently developed to help identify patients with Central Sensitivity Syndromes and to alert clinicians that presenting symptoms may be related to CS [115]. CSI identifies key comorbid symptoms associated CS, and quantifies the degree of these symptoms. It was found to have high reliability and validity and a cut-off score of 40 out of 100 yielded a good sensitivity for correctly identifying CSS subjects [115, 116]. The tools such as the PainDETECT questionnaire (PD-Q) may also be used to identify central pain sensitization in individuals with patients with CWP. Although PD-Q was originally developed to detect neuropathic pain in patients with chronic low back pain [117], subsequent studies have found that PD-Q of ≥ 19 reflected increased pain sensitization in patients with chronic musculo-skeletal pain including FMS [118-122]. It has been demonstrated in a recent study that, significantly more patients with CWP had above-threshold PD-Q scores and conversely, a high PD-Q score was strongly predictive of CWP [108].

With recognition of person/patient centered mechanism-based management of pain, potential use of centrally acting drugs has been expanded to other chronic pain disorders. Duloxetine, which primarily works centrally, has been shown to be effective in the treatment of osteoarthritis [123-125] and chronic low back pain [125-133]. Another centrally acting drug Pregabalin has also been demonstrated to be an effective treatment of various chronic musculoskeletal pain disorders, particularly of chronic low back pain [134-141]. Current treatments for central pain are likely play an increasing role in pain management among patients with inflammatory rheumatic disease such as RA, although the current evidence is limited [49]. Centrally acting non-pharmacological therapies such as cognitive behavioral therapy, mindfulness meditation and neuroscience education have currently a major role in the management of centralized

pain and chronic pain in general [105, 142-144].

After having reviewed the recent advances in the pain field discussed above, I would like to go back to the beginning asking the question, "Is it necessary to diagnose FMS in the clinical context of CWP or does it not make a difference?". I still believe that this distinction seems to be not useful from the viewpoint of clinical practice, as it will not facilitate the selection of appropriate interventions and/or discourage the selection of inappropriate ones. As discussed above, an effective treatment in an individual patient might be much guided by dominant underlying mechanisms responsible for pain rather than the level of pain or specific diagnosis the patient is suffering [94, 104, 145]. Optimal personalized care may require pharmacological and non-pharmacological strategies aiming at treating centralized pain in an individual even if a formal diagnosis of fibromyalgia has not been made and even in the presence of an inflammatory or structural disease such as RA, OA or CLBP. Rationally treating a patient suffering from chronic pain should therefore require focusing on an individual not on a disease. My suggestion does not mean to ignore currently available diagnostic criteria for FMS. Previous studies, including ours demonstrated that the patients with CWP who had satisfied the TP criterion of the ACR 1990 seemed to have greater disease burden with more severe pain, more comorbidities and pain related medications, and worse overall health comparing to those who had not [1, 146-151]. In their recent study, Jimenez *et al.* found that patients fulfilling the modified 2010 only had worse symptom profile than those fulfilling the 1990 criteria only [152]. They also found that the patients fulfilling both diagnostic criteria had the worst profile. These studies suggest that FMS criteria may be used as a useful marker in terms of determining current or potential morbidity that deserves special consideration. However, further evidence is needed to assure that there is a fundamental qualitative difference between FMS and CWP.

Nevertheless, naming of the disease the patient was diagnosed is an important matter for both the clinician and the patient. So another question arises, "What term should then be used in the clinical context where pain and hyperalgesia is of widespread distribution and where the amplification of nociceptive signals in the central nervous system that contribute to widespread pain?". As Yunus emphasized in his recent review [23], the terms "functional" or "somatization" seem nonsensical, based on the fact that symptoms of these disorders are explicable by their pathophysiology. Some authors [5, 23] defends using the term CS, while others [153], suggest use of other terms, e.g. 'central pain,' 'central augmentation' and 'central amplification' instead of CS to describe these conditions. My suggestion is that these conditions might be classified under one heading such as "CWP", "chronic pain syndrome" or "central pain", when considering their comorbidities, their similar pattern of clinical presentation, commonality of central sensitization to their pathophysiology and their similar response to centrally acting analgesics, in the absence of definitive objective confirmation. Indeed, the term FMS is often used synonymously to mean CWP or vice versa in recent articles [30, 105, 107, 108, 143]. Moreover, the individuals with CWP could move through various categories of chronic pain syndrome with time [154]. In their recent cohort, Edgar Adams and colleagues demonstrated that many patients with CWP transitioned into/out of FM over 2 years period, reflecting the waxing and waning nature of FM that further complicates diagnosis [155]. Nevertheless, because patients usually seek for an "organic" disease for their pain, both the clinicians and the patients may not like to have a vogue, obscure or subjective diagnosis. Future research should therefore be directed toward classification of CWP based on the validated measurements of different aspects of pain. Development of objective laboratory and clinical indices to make an irrefutable diagnosis of central sensitization will help to classify the patients with CWP. Such a classification may help clinicians identify the subsets of patients who will preferentially respond to peripheral or centrally acting analgesics and may therefore assist in advancing a more individualized and pain mechanism focused treatment in the clinical setting.

Conflicting interests

The author has declared that no competing interests exist.

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