Ther Adv Musculoskel Dis
2017, Vol. 9(5) 115–127
DOI: 10.1177/1759720X17699199

Controversies and challenges in fibromyalgia: a review and a proposal

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Abstract: Fibromyalgia (FM) is the most commonly encountered chronic widespread pain (CWP) condition in rheumatology. In comparison to inflammatory arthritis (IA), it can seem ill defined with no clear understanding of the pathology and therefore no specific targeted treatment. This inevitably raises controversies and challenges. However, this is an outdated view perpetuated by poor teaching of pain at undergraduate and postgraduate levels, and the perennial problem of advances in relevant cross-speciality knowledge penetrating speciality silos. Research has provided a better understanding of the aetiopathology and FM is now regarded as a centralized pain state. Effective treatment is possible utilizing a multidisciplinary approach combining nonpharmacologic and pharmacologic treatments rooted in a biopsychosocial model. This article will provide a review of the mechanisms, diagnosis and treatment of FM, focus on some ongoing contentious issues and propose a change to the diagnostic terminology.

Keywords: Fibromyalgia, chronic widespread pain, central sensitisation, psychological factors, diagnostic criteria

Received: 9 July 2016; revised manuscript accepted: 4 February 2017.

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Introduction

Chronic widespread pain (CWP) syndromes have always been a challenge to patient and clinician alike. Every medical speciality has its own version and in rheumatology, fibromyalgia (FM) is the most commonly encountered. Furthermore, they often overlap with each other.[1–3]

When a patient is describing their pain experience, the default position of the clinician is to accept this at face value and to avoid imposing personal value judgements. However, the clinician also has to strive to avoid overmedicalization, including medicalizing symptoms and signs including pain that fall within the normal spectrum and thereby 'creating' disease, and ignoring psychological factors that may drive symptom presentation and illness behaviour thereby leading to overinvestigation and overtreatment. This also has to be balanced against labelling symptoms and signs as psychological and missing treatable 'organic' disease.

These complex factors when dealing with CWP provide the background to some of the controversies and challenges faced when treating FM (see box 1), and to this review.

Box 1. Challenges and controversies in fibromyalgia.

Controversies
- Whether FM should be considered a discrete entity or part of the CWP spectrum
- Differing clinical diagnostic criteria
- Mind–body dualism in the context of FM
- The WHO pain ladder was not designed for chronic noncancer pain and therefore its use in CWP should be discouraged

Challenges
- While understanding of CWP and FM continues to improve, the precise aetiopathogenesis remains unclear and continues to evolve
- Balancing the need to avoid overinvestigation and overmedicalization against missing other diagnoses or under treatment
- Recognizing the significant role of concurrent psychological diagnoses when present, and confronting the associated stigmatization
- FM in the presence of coexisting disease, for example IA
- Managing patient expectations and recognizing the limitations of the pharmacological treatment, particularly high strength opioids which should be avoided
- Development of services able to provide an individualized approach to FM/CWP rooted in a biopsychosocial model

CWP, chronic widespread pain; FM, fibromyalgia; IA, inflammatory arthritis; WHO, World Health Organization.

Epidemiology

There is ongoing debate whether FM should be considered as a discrete entity or as part of the CWP spectrum (see also 'Definition and diagnostic criteria' below). Therefore, the prevalence depends on whether FM or CWP are being investigated and which diagnostic criteria are utilized. The prevalence of CWP varies between 4% and 11% utilizing 'Manchester' or other CWP definitions.[4–6] The prevalence of FM in the general population varies between 2% and 8%.[7–10] There is a need for a standard definition of CWP/FM.[6] The challenge will be how to achieve an expert consensus on the definition and diagnosis of CWP and FM. Meanwhile there will continue to be disparity in research structure and therefore difficulty in comparative research work, and the extent and burden of CWP/FM in the community remains unclear.

Pathogenesis

The overall perception and experience of pain is dependent on a balance of peripheral nociceptive inputs central descending facilitation and inhibition of nociceptive sensory processing, cortical processing and the consequent emotional, psychological, autonomic, hormonal and behavioural response.[1,7,11–14] The understanding of FM has moved away from a predominantly peripheral musculoskeletal pathology towards a centralized pain state within the CWP spectrum. This does not deny the contribution of peripheral nociceptive mechanisms, and it is likely that many different pain mechanisms contribute to the FM/CWP or 'central' pain prone phenotype.[7] It rather emphasizes the role of maladaptive pain amplification through a variety of different mechanisms. The following outlines some of these.

Central pain mechanisms

There is an increasing body of neuroimaging study evidence in CWP and FM, and knowledge of central pain mechanisms; a full review is beyond the scope of this article. There are review articles available for more detailed reading.[15–19]

There is evidence for enhanced brain responses to experimental pain stimuli.[20,21] Other work demonstrates altered resting state[22–24] and pain induced functional connectivity.[25,26] Changes in brain morphology have been demonstrated. Grey matter volume changes in several areas have been noted, including cingulofrontal, amygdalae, postcentral gyri, hippocampi, striatal, superior frontal, anterior cingulate and insular.[27–31] Furthermore, decreases in cortical thickness and overall brain volume are more pronounced in patients with longer exposure to FM pain.[28,29,32] There is functional neuroimaging evidence for impaired descending inhibition[28,33] and enhanced ascending facilitation or 'wind up'.[15,34]

Evidence of altered function of brain neurotransmission has been demonstrated, including decreased availability of μ-opioid receptors,[35] elevated insular glutamate and reduced γ-aminobutyric acid (GABA),[36,37] and alterations in cerebral glutamate/glutamine, inositol, choline and N-acetylaspartate levels compared with healthy controls.[38] Changes in levels of molecules associated with the neurotransmission of pain have been documented in FM. These include increased cerebrospinal fluid substance P, glutamate and nerve growth factor, and decreased serotonin, norepinephrine, dopamine and GABA.[7,11]

These neuroplastic structural and functional changes may help to explain the transition from acute to chronic conditions and have implications for rehabilitation.[39,40]

Peripheral mechanisms

Peripheral factors are likely to contribute to both the initiation and maintenance of the centralized pain state. These might include subtle inflammatory activity and changes to the inflammatory cytokine network and glial cell activity.[7] There may be muscle nociceptive factors operating, such as peripheral ischaemia, microtrauma and enhanced nociceptor activity.[14,41]

Musculoskeletal factors

Patients with FM often become physically inactive as a consequence of pain, and may develop a maladaptive posture and gait.[42,43] This can become reinforced by fear-avoidance behaviours and kinaesiophobia (fear of movement).[44,45] This may lead to marked physical deconditioning, further deterioration of posture and gait, worsening musculoskeletal fitness and tone with further deterioration in posture, gait and fitness in an ever declining vicious circle. Patients may therefore also present with enthesopathies, bursitis and tendinopathies secondary to maladapted posture, gait and deconditioning, for example trochanteric bursitis. However, the patient with apparent FM

and recurrent enthesopathies and possible inflammatory signs or features in their history should prompt further review and investigation as necessary (see 'Coexisting conditions' below).

Sleep disturbance

Nonrestorative sleep and fatigue are common and distressing symptoms in FM. Studies demonstrate disruption to stage four non rapid eye movement sleep.[46] Sleep quality may be a mediator in the relationship between pain and emotional distress in some patients,[47] and patients with FM and poorer sleep have worse function and quality of life.[48]

Other mechanisms

Other potential mechanisms include dysfunction of the hypothalamic–pituitary axis (HPA). The main HPA abnormalities documented in FM include low free cortisol levels in 24 h urine samples; loss of the normal circadian rhythm with elevated evening cortisol level; insulin-induced hypoglycaemia associated with an overproduction of pituitary adrenocorticotropic hormone (ACTH); low levels of growth hormone; and insufficient adrenal release of glucocorticoids to stimulation by ACTH.[11] Although studies have been conflicting, there is evidence for autonomic dysfunction in FM.[26,49] Sympathetic dysfunction has been consistently described and may explain some features.[50,51] Familial aggregation has been noted in FM and family members of patients with FM may also have a history of chronic pain. Therefore genetics may also play a role in susceptibility to chronic pain states through genes that play a role in the transmission and processing of pain.[7,52]

Psychological factors

Psychosocial and behavioural issues can contribute to and modify the presentation and treatment of FM. Patients are more likely to suffer depression, anxiety, obsessive–compulsive disorder and post-traumatic stress disorder.[2,3,7] They may have a negative body image perception.[53,54] Catastophizing, reduced self-efficacy, hypervigilance and kinaesiophobia can be additional complicating factors.[2,7,47] The familial aggregation noted above could also be transmitted through modelling and learning. Unfortunately there is still a stigma attached to a psychological label, and patients may be reluctant to admit to such problems or consider psychological approaches. Some doctors may share similar stigmatizing attitudes with the potential result that the patient is overinvestigated, overmedicalized and undertreated psychologically.

In common with other CWP and 'functional' syndromes, FM is often subject to the mind–body dualism controversy.[3,55] Many patients with FM would meet the Diagnostic and Statistical Manual for Mental Disorders 5 criteria for somatic symptom disorder, but reliability and validity is questionable.[56,57] The increasing knowledge being gained from cognitive neuroscience is providing new insights into the psychiatric and psychological concepts, and can be used to support either stance. With the neuroscience revolution of the past few decades, it seems increasingly absurd to attempt to dissect a distressed chronic pain patient into either a psychological or organic disease state. If the science has shown us anything, it is that both factors are equally important, and that a biopsychosocial approach is required.[2,58]

A more recent challenge is the effect of the internet and mass global communication. There is unlimited access to a wealth of health information and advice, good or bad, true or false. This may reinforce abnormal health beliefs, and patients may come to the clinic with preconceived internet based self diagnoses and demands for inappropriate or dubious treatments. Patients with FM/CWP are more likely to have health-related anxiety, and excessive internet use exacerbating health anxiety has been termed 'cyberchondria'.[59,60]

Definition and diagnostic criteria

The definition of FM continues to evolve reflecting the changes in understanding and shifts in diagnostic criteria. The American College of Rheumatology (ACR) 1990 diagnostic criteria required the presence of pain on both sides of the body and above and below the waist present for at least 3 months, with the presence of at least 11 out of a possible 18 tender points and not better explained by any other disorder.[61] They are not intended to replace the 1990 criteria, but to address the changing face and definition of FMS. The newer 2010 ACR diagnostic criteria[62] define FM as a CWP condition associated with fatigue, sleep and cognitive disturbance and a variety of somatic symptoms.

Challenges and controversies

Once the technique for tender point testing and their location is known, the 1990 criteria are simple to administer and score.[63] However, tender points are not unique to patients with FM and are associated with psychological distress and female sex independent of age.[11,64,65]

The 2010 criteria utilizes a widespread pain index and symptom severity scale comprising rating for three symptoms (fatigue, sleep, cognitive) and somatic symptoms.[62] Forty-one possible somatic symptoms are listed for consideration, but no detail is given on how to rate their presence as mild, moderate or severe, leaving this to the clinician. Some organizations have produced questionnaires for patient self administration, listing the criteria and all 41 somatic symptoms. However, the criteria were not intended for self administration, and the symptom severity score should not be assessed by listing the given examples and creating a tick list. Subsequently Wolfe produced a 'How to use the new ACR FM diagnostic criteria' document[63] covering these aspects in more detail. A modified version of the 2010 criteria has removed the physician's estimate of the extent of somatic symptoms and substituted a sum of three specific self-reported symptoms, making it simpler to use and maintaining sensitivity.[66–68] Compared with the 1990 and 2010 criteria, the modified 2010 criteria identify a higher FM prevalence and a greater proportion of men with the condition.[69]

As reflected by the changing ACR criteria, an ongoing controversy is whether FM should be considered as a discrete disorder or is better regarded as part of the spectrum of CWP.[49,70,71] It is well recognized that many chronic pain syndromes have overlapping features with each other,[72] and many patients with FM may also have other chronic pain syndromes such as irritable bowel syndrome,[73] chronic fatigue,[74] migraine,[75] craniofacial pain,[76] chronic pelvic pain[77] and other chronic regional pain problems.[1,78] The 2010 criteria conceptualize core fibromyalgic symptoms as part of the spectrum of central pain sensitization,[7] moving the diagnosis of FM towards the CWP continuum. Furthermore neuroimaging studies are providing increasing evidence for changes and dysfunction in central brain structures and mechanisms in FM[15] and CWP.[19]

Presentation

There is a female preponderance in FM, which typically presents with chronic widespread musculoskeletal pain. Pain may be described as aching, burning or sore. Patients usually describe sleep disturbance and fatigue. Tactile sensitivity and generalized 'tenderness' is often displayed, and there may be complaints of general sensory sensitivity, for example to light, sound, smell etc.[79] A history of other chronic pain syndromes such as headache, migraine, noncardiac chest pain, heartburn, dysmenorrhoea, and irritable bowel syndrome may be present. Dyscognition or 'fibro-fog' is a common complaint.[1] Other symptoms can include paraesthesias, restless legs, morning stiffness, and sensation of tissue swelling.

Examination

The aim of the physical examination is to rule out any other potential conditions and confirm the diagnosis. Therefore, a full general medical examination is required with particular attention to the musculoskeletal system. 'Red flag' symptoms and signs suggest alternative diagnoses and require appropriate investigation. These include symptoms of significant weight change, fever, sleep apnoea or signs of significant muscle weakness or wasting, abnormal gait, focal neurological signs, abnormal reflexes, synovitis or joint swelling, rashes, lymphadenopathy and cardiac murmurs.

Depending upon the diagnostic criteria utilized, various questionnaires and a tender point count may need to be administered.

Differential diagnosis

This includes:

(1) inflammatory arthritis (IA) and spondyloarthropathies,
(2) autoimmune connective tissue disease,
(3) myositis,
(4) myopathies,
(5) primary generalized osteoarthritis,
(6) polymyalgia rheumatica,
(7) hypothyroidism,
(8) malignancies.

Coexisting conditions: considerations and challenges

FM can coexist with other conditions such as osteoarthritis and IA.[11,80–82] Joint hypermobility syndrome is increasingly recognized in the context of FM, and vice versa.[83–89] It can be challenging to both the doctor and patient to work out

which aspects of their pain are due to which condition.[23] Patients with IA and FM can be at risk of overtreatment of one condition and undertreatment of the other in either direction, and the patient with FM who subsequently develops an IA may be at risk of delayed diagnosis. Patients with rheumatoid arthritis (RA) and FM have higher Disease Activity Score (DAS28) scores[90,91] and worse outcomes.[92]

The various inflammatory outcome measures utilized such as DAS28 in RA, Bath Ankylosing Spondylitis Disease Activity Index and Psoriatic Arthritis Response Criteria scores require patient pain ratings and cannot differentiate inflammatory from noninflammatory pain, and clinical judgement is still required.[93–96] In DAS28 scores, the tender count has been noted as a particular issue.[82,93,95,97] A patient with CWP/FM is likely to rate any measures of pain and effect on quality of life measures consistently very highly, particularly if there is associated anxiety or depression.[97] Therefore patients are at risk of having apparently 'failed' a Disease modifying anti-rheumatic drug (DMARD) treatment when in fact it was having a beneficial effect. Expensive DMARD medications may be subject to forms of rationing in some countries. Thus there is the potential for some patients with active IA and CWP which was not recognized to have apparently failed all available biologic medications due to the inadequacy of currently used outcome measures; these patients may run out of treatment options and not be eligible for further biologic treatment. In this scenario, the recognition and treatment of the CWP becomes particularly important.

A challenge in IA clinics is to recognize coexistent FM/CWP so that this can be appropriately managed and considered when completing outcome measures. An index of suspicion should be maintained in the patient with IA when there is a consistently high tender joint count but minimal swollen joint count, very high pain visual analog scale (VAS) but minimal elevation of inflammatory markers.[23,95] A further challenge is to improve outcome measures such that coexistent FM/CWP can be taken into account.

Investigations

Laboratory investigations and imaging are directed towards the exclusion of other conditions according to the history and examination findings. A challenge in CWP/FM is to avoid overinvestigation of polysymptomatology, and multiple referrals feeding into revolving door 'doctor-shopping', reinforcement of health anxiety[59,60] and potential iatrogenic harm.[98,99] This has to be balanced against appropriate investigation and referral. This is often particularly difficult for doctors when faced by the demanding patient with several pages printed out from the internet.

Another area of controversy with relevance to FM is vitamin D. Low vitamin D is recognized in association with CWP and FM and there is ongoing debate concerning its potential role.[100,101] It remains unclear what is a normal level of vitamin D, and when it should be replaced or supplemented.[102,103] However, when there is clear vitamin D deficiency there is general consensus that this should be appropriately treated.

Treatment

There are published guidelines for the treatment of FM, the main ones being European League Against Rheumatism (EULAR) 2008, revised 2016,[104,105] American Pain Society (APS) 2005,[106] German Association of the Scientific Medical Societies (AWMF) 2012,[58,107] Israeli[108] and Canadian Pain Society 2013.[109] While there is heterogeneity, they do agree that the main treatment should be multidisciplinary with a nonpharmacologic focus, balancing cautious pharmacologic input when required with patient education and engagement.[7,110–112] There are differences between the guidelines on the strength of recommendations for pharmacologic therapies, and on the types of nonpharmacologic therapies. The recently revised EULAR guidelines note that many recommendations were based upon expert opinion, and in the revision have recommendations underpinned by high-quality reviews and meta-analyses.[105]

The following is a summary of treatment strategies (see also Figure 1), and readers are referred to the individual guidelines, which also provide the evidence base for their recommendations.

Nonpharmacologic therapies

The most studied nonpharmacologic therapies which are all recommended by the guidelines[105–109] are exercise, patient education and psychological treatment, particularly cognitive behavioural therapy (CBT). All encourage a multidisciplinary approach. Patients with more

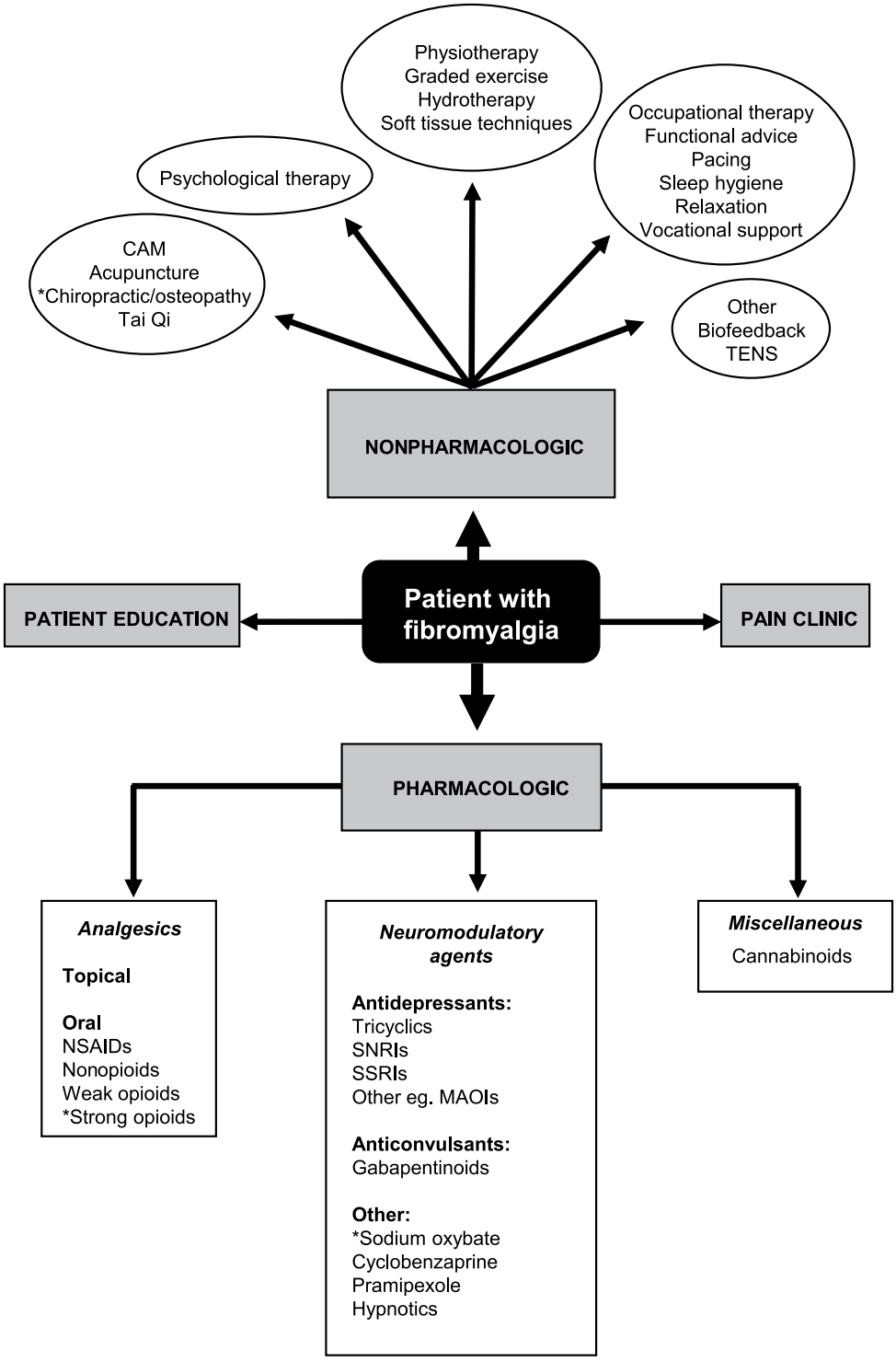

Figure 1. Treatment approaches for the patient with FM.
Please note, the diagram is based upon the references alluded to in the text. The order of options presented is not evidence weighted or preferential; please see individual guidelines. *, EULAR revised guidelines recommendation indicate 'strong against' the therapy.
CAM, complementary alternative medicine; EULAR, European League Against Rheumatism; FM, fibromyalgia; MAOI, monoamine oxidase inhibitor; NSAID, nonsteroidal anti-inflammatory drug; SNRI, serotonin norepinephrine uptake inhibitor; SSRI, serotonin selective reuptake inhibitor; TENS, transcutaneous electrical nerve stimulation.

severe disease and those whose condition fails to respond to initial treatment will need an individualized approach rooted in a holistic biopsychosocial model.

The use of complementary and alternative medicine (CAM) continues to be challenging and controversial, and all the guidelines mention it. The Canadian guidelines encourage patients to discuss CAM, and that the practitioner should be tolerant of disclosure but inform them that there is currently insufficient evidence to recommend CAM for FM. The revised EULAR guidelines provide recommendations based upon available evidence.

Some patients will struggle to make or maintain progress. They may require specialist referral[111] such as rheumatology, psychology, psychiatry or to a pain clinic for further advice and consideration of an outpatient or inpatient based pain management programme. This provides more intensive input aimed to improve long-term self-managed coping skills.[113]

Pharmacologic

The aim is to provide a balance of medications that help the patient to cope with their symptoms, complementing the nonpharmacologic therapies and patient education (Figure 1). The evidence base is poor. Patient expectations should be managed, as although a symptom-based medication approach may ameliorate symptoms, it will not 'cure' the pain. Medication will require cautious dose escalation and monitoring of short- and long-term side effects, and discontinuation of ineffective drugs or those with intolerable side effects. Few medications are licensed for FM and many continue to be prescribed off license.

Neuromodulatory medications. These include the antidepressant (tricyclic, selective serotonin norepinephrine uptake inhibitor (SNRI), serotonin selective reuptake inhibitor (SSRI)] and anticonvulsant classes of medications. Amitriptyline has some evidence[110] and is recommended in all the guidelines,[114] and therefore is worthwhile considering particularly for patients with FM and sleep disturbance. The serotonin norepinephrine uptake inhibitors (SNRIs) have better evidence than SSRIs,[7] and may benefit from their effect on both serotonin and noradrenaline on the descending modulatory pathways. Gabapentin and pregabalin are also commonly used in FM and CWP.

Analgesic medication. The use of opioids in CWP is an ongoing controversy[115] and the guidelines vary in their recommendations. Weak nonopioids such as paracetamol, or paracetamol combined with a weak opioid such as codeine, are often used as adjuvant medication, as per the World Health Organization (WHO) pain ladder. However, this approach has limitations in FM (see below). NSAIDs are often ineffective, and the potential adverse effects of gastrointestinal ulceration and cardiovascular risk have to be considered. Tramadol may be beneficial for some patients but the problems associated with opioid use and its potential interaction with SNRIs to cause the serotonin syndrome must be considered.

Strong opioids are not recommended by the German and EULAR guidelines, discouraged by the Canadian guidelines and only considered if other medicinal and nonmedicinal therapies have been exhausted in the APS guidelines. They are often poorly effective for the pain and there are significant potential long-term adverse effects including increased risk of mortality,[116,117] reduction of testosterone[118] and opiate-induced hyperalgesia.[119] The WHO pain ladder was designed for cancer pain, and not intended for use in chronic pain. Thus the concept and particularly the opiate rung is not appropriate for CWP/FM.[117,120]

If a patient is gaining various medications at increasing doses for little further impact on pain but accruing short- and long-term adverse effects, or is on high-dose strong opioids then referral to a pain clinic should be considered.

Proposal

There is good evidence that FM should be regarded as part of the CWP spectrum. This provides a clearer understanding of the condition, the common overlap with other chronic pain conditions and that it has to be treated accordingly for both the musculoskeletal aspects and in a broader holistic biopsychosocial pain management model. This approach is already being championed internationally with proposals on how to construct and optimize

appropriate clinical services for bodily distress syndromes/medically unexplained symptom clinics.[121] The CWP/central sensitization model has implications for the diagnostic labels utilized. It is no longer appropriate to continue diagnosing chronic pain conditions in isolation of each other or their CWP component. This denies the increasing body of research evidence, and potentially denies the patient recognition and treatment of their CWP.

Therefore, a proposal and a challenge to the wider medical community when seeing a patient with CWP is to consider changing the diagnostic terminology from specific isolated chronic pain conditions to a central CWP label with a descriptive subcategory. For example, chronic pain and irritable bowel syndrome become CWP-IBS predominant; a patient with chronic pain, IBS and CFS becomes CWP-IBS, fatigue predominant. Rheumatologists should consider taking a lead and use the diagnosis of CWP-FM predominant. This may set an example for other specialities to follow.

Why is this proposal relevant, and how should it be considered and evaluated? It could be considered as another step in the ongoing evolution of the Descartian mind–body dualism debate that continues to challenge medicine through the ages. If it provides a better description of the patient with CWP/FM and thus allows for a fuller holistic approach to that patient, then it should be seen as relevant to current practice and adopted. Only time and the clinical community on an individual and wider level can determine whether it is something they wish to adopt. Even if this proposal does nothing other than promote further debate, discussion and stimulation of thought when faced by a patient with CWP/FM, it will have been worthwhile.

Conclusion

While the teaching of pain at undergraduate and postgraduate levels remains suboptimal[122] and rheumatology moves towards an increasing immunological focus, many trainee and experienced rheumatologists can feel overwhelmed when faced by a distressed patient with fibromyalgia. However, there is now much improved understanding of FM and other centralized pain states (see Box 2). Effective treatment is possible utilizing combined nonpharmacologic and pharmacologic approaches rooted in a biopsychosocial model.

Box 2. Conclusions.

- Central and peripheral mechanisms contribute to the development of FM and other centralized pain states
- Optimal clinical diagnostic criteria remain elusive and continue to evolve
- Psychological conditions when present can significantly influence the presentation and treatment of FM
- Effective treatment is possible utilizing combined nonpharmacologic and pharmacologic approaches rooted in a biopsychosocial model

FM, fibromyalgia.

Acknowledgements

Thanks are due to Dr Piper, Dr Wolman and Professor Ikkos for their review and suggestions.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The author declares that there is no conflict of interest.

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