Fibromyalgia

Finding the silver lining around a common chronic pain disorder

HUAI LENG PISANIELLO MB BS
SAMUEL WHITTLE MB BS(Hons), MClinEpid, FRACP

Recent advances in understanding both the pathophysiology of fibromyalgia and multimodal therapies have significantly improved the management of this chronic and potentially disabling disorder.

Fibromyalgia is a chronic noninflammatory musculoskeletal condition defined by widespread pain and commonly accompanied by fatigue, sleep disturbance and physical and psychological distress.[1] Patients with fibromyalgia often report cognitive clouding or 'fibrofog' (a triad of poor concentration, impaired short-term memory and inability to multitask), which can be more debilitating than the pain.[2] Fibromyalgia is often associated with other pain disorders, including chronic headache, chronic fatigue syndrome, functional bowel or bladder syndromes and other regional pain syndromes (e.g. temporomandibular, neck, back and pelvic pain).[3]

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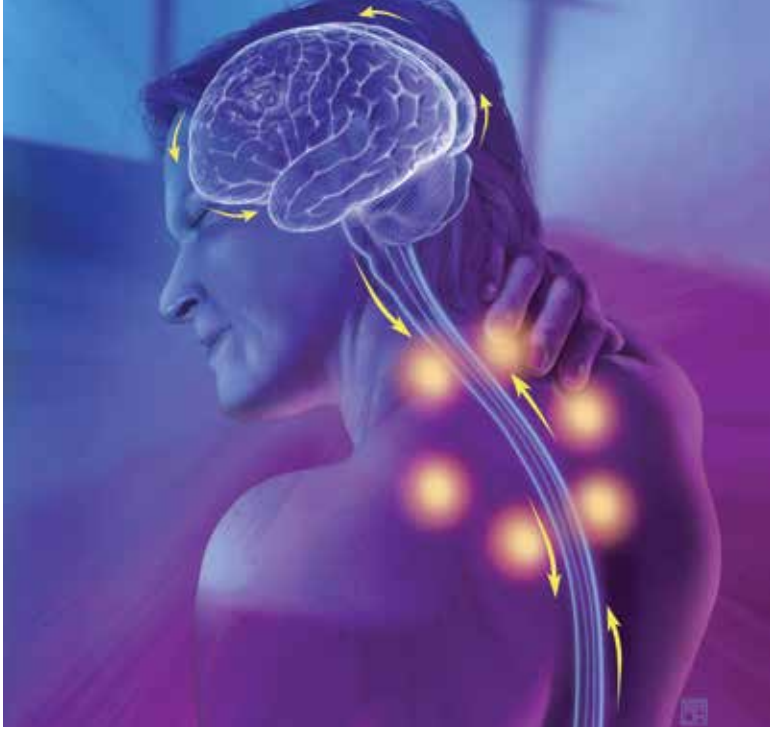
Dr Pisaniello is a Rheumatology Registrar at The Queen Elizabeth Hospital, Adelaide. Dr Whittle is a Senior Consultant Rheumatologist at the Queen Elizabeth Hospital, Adelaide; and a Clinical Senior Lecturer at the University of Adelaide, Adelaide, SA.

SERIES EDITORS: Dr Bethan Richards MB BS(Hons), FRACP, MMed(ClinEpi), MSportsMed, Senior Clinical Lecturer, The University of Sydney, and Head of Rheumatology, Institute of Rheumatology and Orthopaedics, Royal Prince Alfred Hospital, Sydney, NSW. Professor Lyn March, MB BS, MSc, PhD, FRACP, FAFPHM, Liggins Professor of Rheumatology and Musculoskeletal Epidemiology, Institute of Bone and Joint Research, University of Sydney, and Senior Staff Specialist Rheumatologist, Royal North Shore Hospital, Sydney, NSW.



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Epidemiology and pathophysiology

The prevalence of fibromyalgia is estimated to be 2 to 5% in the general population.[4,5] The societal impact of fibromyalgia is substantial and is comparable to that of other common chronic medical conditions such as diabetes mellitus and rheumatoid arthritis. Suboptimal management of fibromyalgia can result in increased health care costs, chronic disability and reduced work productivity through absenteeism or unemployment.[6] Fibromyalgia can occur in any age group, including childhood, and can affect both sexes. First-degree relatives of patients with fibromyalgia have an eightfold increased likelihood of developing fibromyalgia and other chronic pain disorders.[7] Environmental factors that may trigger fibromyalgia include acute physical stress (e.g. acute pain), psychological stress (e.g. deployment to war), or infections (e.g. Epstein-Barr virus), although in many cases, a single trigger is not identified.[8] Fibromyalgia frequently develops in individuals with other painful musculoskeletal conditions such as osteoarthritis, rheumatoid arthritis or systemic lupus erythematosus.

While advances have been made, we are still far from fully understanding the mechanisms that create the complex, multifaceted and distressing set of symptoms that characterise fibromyalgia. Causal influences are likely to occur at multiple levels (including genetic, neural, hormonal, whole-brain, whole-person, interpersonal and societal) and interact in complex and unpredictable ways. A wide array of functional, chemical and structural brain neuroimaging techniques has been studied in the evaluation of central nervous system (CNS) pain processing areas in fibromyalgia, but at present these remain research tools only. In particular, functional magnetic resonance imaging using the blood-oxygen-level-dependent (BOLD) method has shown augmented sensitivity to painful pressure in patients with fibromyalgia compared with controls.[9] Altered levels of neurotransmitters have also been demonstrated in patients with fibromyalgia. Notably, most of the neurotransmitters that mediate sensory sensitivity also control sleep, mood, memory and alertness.[10]

It is unlikely that a single pathophysiological process will be found that explains all cases of fibromyalgia. Therefore, despite

1. PATIENT SELF-REPORT SURVEY FOR THE ASSESSMENT OF FIBROMYALGIA IN EPIDEMIOLOGICAL AND CLINICAL STUDIES

- According to the modified American College of Rheumatology (ACR) 2011 diagnostic criteria, a patient has fibromyalgia if they meet the following three conditions:[17]
  - Widespread Pain Index (WPI) ≥7 and Symptom Severity Score (SSS) ≥5; or WPI of 3 to 6 and SSS ≥9
  - The patient's symptoms have been present at a consistent level for at least three months
  - The patient does not have a disorder that would otherwise explain the pain.
- A patient's WPI score is based on the number of anatomical areas in which the patient reports having had pain over the past week. The 19 areas to be assessed comprise left and right shoulder girdles, upper arms, lower arms, hips (buttock or trochanter), upper legs, lower legs and jaw; and the chest, abdomen, upper back, lower back and neck. The WPI score will be between 0 and 19.
- A patient's SSS is determined by adding together two symptom measures. The first is the level of severity during the past week of each of three symptoms – fatigue, waking unrefreshed and cognitive symptoms – based on the following scale: 0=no problem; 1=slight or mild problem (generally mild or intermittent); 2=moderate (considerable problems, often present and/or at a moderate level); 3=severe (pervasive, continuous, life-disturbing problems). The possible total is 0 to 9. The second is the total number during the past six months of other somatic symptoms – headaches, pain or cramps in the lower abdomen and depressed mood – with a possible total of 0 to 3. The final SSS score is between 0 and 12.

the many similarities in clinical presentation, medical practitioners must adopt a detailed and curious approach to the particular biomedical and life-course circumstances of each individual with fibromyalgia.

A useful conceptual model for the primary mechanism underlying fibromyalgia is abnormal amplification of pain in the CNS ('centralised' pain), resulting in allodynia (a pain experience elicited by a stimulus that is not normally painful) and hyperalgesia (an increased response to a painful stimulus).

Clinical diagnosis

Globally, despite a better understanding of this condition, barriers to recognition of symptoms of fibromyalgia and lack of confidence in the diagnosis and management of fibromyalgia are still present.[11] Given the variability of symptom presentation and unpredictable disease trajectory, fibromyalgia can present as a diagnostic and management challenge for healthcare professionals. Prompt diagnosis of fibromyalgia may improve health satisfaction by providing a sense of relief for the patient at receiving a formal diagnosis, and avoiding unnecessary investigations and referrals.[12-15]

The original American College of Rheumatology classification criteria, published in 1990, emphasised objective measurement of tender points and were intended for research classification.[1] Subsequent diagnostic criteria were formulated in 2010, followed by further modification in 2011, and these were designed for clinical use, focusing on symptom-based questions rather than tender points (Box 1)[16-17] The new criteria embrace the concept of fibromyalgia as a continuum of symptoms ('fibromyalgia-ness') characterised by CNS sensitisation ('centralisation').[18] These simplified, quantitative criteria may facilitate a diagnosis of fibromyalgia in primary care by assessing the patient's symptoms without the need to perform a formal tender point count.

2. PRACTICAL POINTS IN MANAGING FIBROMYALGIA

- Fibromyalgia may impact on the patient's ability to work and conduct social relationships, but ongoing encouragement and support for participation in these activities is strongly recommended.
- Symptoms of fibromyalgia can be unpredictable and may vary without a clear relationship to stressors or other triggering factors.
- Avoid excessive use of caffeinated stimulants in patients with symptoms of 'fibrofog'.
- Careful clinical evaluation of new symptoms in fibromyalgia is important to exclude other medical conditions.
- Prescribe exercise in small doses at a self-paced intensity, and with a planned duration (rather than to exhaustion), and with gradual dose increases.
- Start low and go slow with any medications used in fibromyalgia treatment.
- Avoid opioid-based therapy.
- Treat any other peripheral sources of nociceptive pain (e.g. osteoarthritis), if present.
- The goal of any intervention should be improvement of function rather than abolition of pain.
- Specialist referral may be required in complex, atypical or refractory cases.

In clinical practice, fibromyalgia should be suspected in patients with multifocal musculoskeletal pain that is not explained by other causes, particularly inflammatory diseases. It should be stressed that fibromyalgia is not a diagnosis of exclusion, and a detailed history and physical examination is crucial for recognising the pattern of symptoms that is characteristic of fibromyalgia and also other conditions with symptoms that mimic fibromyalgia.[19] In the physical examination, it is essential to be able to differentiate soft tissue tenderness and concerning clinical signs not typical for fibromyalgia such as synovitis or muscle weakness. The presence of allodynia (e.g. pain induced by inflation of the sphygmomanometer cuff) is often a clue to the diagnosis.[20] Serological tests or imaging are not necessary in the diagnosis unless clinically relevant to exclude other possibilities or comorbidities associated with fibromyalgia.[17]

Management

The integration of nonpharmacological and pharmacological treatments as well as the patient's active involvement are cornerstones for effective management of symptoms of fibromyalgia and in improving quality of life. Practical points in managing fibromyalgia are listed in Box 2.

TABLE. RECOMMENDED PHARMACOLOGICAL TREATMENT FOR FIBROMYALGIA

Medication	Dose and titration	Side effects
Amitriptyline*	10 to 25 mg orally in the early evening. Increase the daily dose as tolerated by 25 mg monthly up to a maximum of 50 mg daily	Dry mouth, weight gain, constipation, urinary retention, drowsiness
Dosulepin (dothiepin)*	25 mg orally in the early evening. Increase the daily dose as tolerated by 25 mg monthly up to a maximum of 75 mg daily	
Pregabalin*	25 to 75 mg orally in the early evening If tolerated, increase to twice daily (after three to seven days), and then gradually increase up to a maximum daily dose of 450 mg in two divided doses	Dizziness, increased somnolence, dry mouth, weight gain
Gabapentin*	100 to 300 mg orally in the early evening. If tolerated, increase (not more frequently than every four days) from daily to three times daily, to a maximum daily dose of 2400 mg in three divided doses	
Duloxetine*	30 mg orally daily. If tolerated, increase in a month to 60 mg daily and to a maximum of 60 mg twice daily	Nausea, headache, palpitations, fatigue, hypertension
Milnacipran	12.5 mg orally daily. If tolerated, increase incrementally over a week to 50 mg twice daily and up to a maximum dose of 100 mg twice daily	Nausea, constipation, hot flush, hyperhidrosis, palpitations, dry mouth, hypertension

* Not TGA approved for fibromyalgia.

Nonpharmacological approach

Patient education, low-impact graded exercise, certain forms of cognitive behavioural therapy (CBT), stress reduction and good sleep hygiene improve symptoms and function in patients with fibromyalgia.[7] These interventions represent the cornerstone of management of fibromyalgia.

Reliable fibromyalgia e-resources are widely available to help with patient education and self-management. For example:

- MOVE muscle, bone and joint health; formerly Arthritis Victoria (www.move.org.au/conditions-and-symptoms/fibromyalgia)
- American College of Rheumatology patient information (www.rheumatology.org/I-Am-A/Patient-Caregiver/Diseases-Conditions/Fibromyalgia)
- University of Michigan Chronic Pain and Fatigue Research Center Fibroguide (www.fibroguide.med.umich.edu).

Pharmacotherapy

Many drugs used in fibromyalgia tend to provide only modest benefit and are often poorly tolerated. However, pharmacotherapy may play an important role in the multimodal management of fibromyalgia. The drugs with the strongest evidence for efficacy in fibromyalgia are predominantly centrally-acting agents, which is consistent with the concept of fibromyalgia as a centralised pain disorder. Evidence has shown modest benefit with the use of low-dose tricyclic medications (amitriptyline, dosulepin [dothiepin]), gabapentinoids (pregabalin, gabapentin) and serotonin noradrenaline reuptake inhibitors (SNRIs; duloxetine, milnacipran).[21-25] It should be noted that selective serotonin reuptake inhibitors (SSRIs) are not effective for the management of pain in fibromyalgia. In Australia, these medications are not specifically approved for fibromyalgia under the PBS. At present, only milnacipran is approved by the TGA for treating fibromyalgia. Combinations of drugs with different modes of action are occasionally used in fibromyalgia. Combination therapy should be approached with caution due to the risk of pharmacokinetic and pharmacodynamic interaction and may indicate a need for specialist referral. Low-dose initiation of individual drugs with gradual titration to the most effective and tolerable dose is recommended (Table). The choice of drug should be individualised to the patient's symptoms, the presence of other comorbidities and potential drug interactions. Treatments directed at peripheral sources of nociception (e.g. NSAIDs, opioids and corticosteroids) are generally ineffective in treating fibromyalgia pain and, hence, are not recommended in the treatment of fibromyalgia.

Conclusion

While fibromyalgia can be a challenging condition to treat, recent advances in our understanding of the pathophysiology and the role of both nonpharmacological and pharmacological interventions have been of great value. A deep, nuanced, individualised approach to caring for the individual with fibromyalgia is not only therapeutically useful, but also enriches the experience for the interested practitioner. A patient-centred multidisciplinary approach to management in the primary care setting offers the promise of improved long-term outcomes for individuals with fibromyalgia and is perhaps the key to revealing this painful condition's silver lining. MT

References

A list of references is included in the website version of this article (www.medicinetoday.com.au).

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References

1. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 1990; 33: 160-172.
2. Kravitz HM, Katz RS. Fibrofog and fibromyalgia: a narrative review and implications for clinical practice. Rheumatol Int 2015; 35: 1115-1125.
3. Aaron LA, Buchwald D. Chronic diffuse musculoskeletal pain, fibromyalgia and co-morbid unexplained clinical conditions. Best Pract Res Clin Rheumatol 2003; 17: 563-574.
4. Queiroz LP. Worldwide epidemiology of fibromyalgia. Curr Pain Headache Rep 2013; 17: 356.
5. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 1995; 38: 19-28.
6. Skaer TL. Fibromyalgia: disease synopsis, medication cost effectiveness and economic burden. Pharmacoeconomics 2014; 32: 457-466.
7. Arnold LM, Hudson JI, Hess EV, et al. Family study of fibromyalgia. Arthritis Rheum 2004; 50: 944-952.
8. Clauw DJ. Fibromyalgia: a clinical review. JAMA 2014; 311: 1547-1555.
9. Gracely RH, Ambrose KR. Neuroimaging of fibromyalgia. Best Pract Res Clin Rheumatol 2011; 25: 271-284.
10. Phillips K, Clauw DJ. Central pain mechanisms in the rheumatic diseases: future directions. Arthritis Rheum 2013; 65: 291-302.
11. Hayes SM, Myhal GC, Thornton JF, et al. Fibromyalgia and the therapeutic relationship: where uncertainty meets attitude. Pain Res Manag 2010; 15: 385-391.
12. Annemans L, Wessely S, Spaepen E, et al. Health economic consequences related to the diagnosis of fibromyalgia syndrome. Arthritis Rheum 2008; 58: 895-902.
13. Hughes G, Martinez C, Myon E, Taieb C, Wessely S. The impact of a diagnosis of fibromyalgia on health care resource use by primary care patients in the UK: an observational study based on clinical practice. Arthritis Rheum 2006; 54: 177-183.
14. White KP, Nielson WR, Harth M, Ostbye T, Speechley M. Does the label 'fibromyalgia' alter health status, function, and health service utilization? A prospective, within-group comparison in a community cohort of adults with chronic widespread pain. Arthritis Rheum 2002; 47: 260-265.
15. Macfarlane GJ, Kronisch C, Dean LE, et al. EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis 2016; Jul 4. Epub ahead of print (doi: 10.1136/annrheumdis-2016-209724).
16. Wolfe F, Clauw DJ, Fitzcharles MA, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res 2010; 62: 600-610.
17. Wolfe F, Clauw DJ, Fitzcharles MA, et al. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR Preliminary Diagnostic Criteria for fibromyalgia. J Rheumatol 2011; 38: 1113-1122.
18. Wolfe F. Fibromyalgianess. Arthritis Rheum 2009; 61: 715-716.
19. Arnold LM, Clauw DJ, McCarberg BH. Improving the recognition and diagnosis of fibromyalgia. Mayo Clin Proc 2012; 87: 488-496.
20. Chandran AB, Coon CD, Martin SA, Mcleod LD, Coles TM, Arnold LM. Sphygmomanometer-evoked allodynia in chronic pain patients with and without fibromyalgia. Nurs Res 2012; 61: 363-368.
21. Arnold LM. Duloxetine and other antidepressants in the treatment of patients with fibromyalgia. Pain Med 2012; 13: 115-124.
22. Hauser W, Petzke F, Sommer C. Comparative efficacy and harms of duloxetine, milnacipran, and pregabalin in fibromyalgia syndrome. J Pain 2010; 11: 505-521.
23. Arnold LM, Clauw DJ, Wohlreich MM, et al. Efficacy of duloxetine in patients with fibromyalgia: pooled analysis of 4 placebo-controlled clinical trials. Prim Care Companion J Clin Psychiatry 2009; 11: 237-244.
24. Tzellos TG, Toulis KA, Goulis DG, et al. Gabapentin and pregabalin in the treatment of fibromyalgia: a systematic review and a meta-analysis. J Clin Pharm Ther 2010; 35: 639-656.
25. Geisser ME, Palmer RH, Gendreau RM, Wang Y, Clauw DJ. A pooled analysis of two randomized, double-blind, placebo-controlled trials of milnacipran monotherapy in the treatment of fibromyalgia. Pain Pract 2011; 11: 120-131.