Identifying central mechanisms in musculoskeletal pain

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Central pain has an important role in the pathophysiology of numerous musculoskeletal pain disorders and should be considered in patients who present with persisting pain, stiffness and other key symptoms suggestive of central sensitisation.

Key points

- **Central pain, which predominantly results from abnormal neurophysiological processes in the central nervous system, has an important role in the pathophysiology of numerous musculoskeletal pain disorders.**
- **Referred pain underlies many musculoskeletal pain presentations and involves central mechanisms within the spinal cord.**
- **Fibromyalgia is the prototypical example of central pain; many of the symptoms and signs of fibromyalgia are essentially those of referred pain.**
- **Fibromyalgia should always be considered in patients with persisting pain, stiffness and other characteristic symptoms.**
- **Identification of central pain mechanisms as a component of a patient's presentation shifts management towards strategies that target central pain modulation.**

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To provide optimal management of patients with musculoskeletal pain it is first essential to identify the main mechanism causing the pain. Central pain, which is pain that predominantly results from abnormal neurophysiological processes in the central nervous system, has an important role in the pathophysiology of numerous musculoskeletal pain disorders. Identification of central pain mechanisms in a patient's presentation will shift management towards strategies that target central pain modulation.

In this article we review briefly the sensory systems involved in musculoskeletal pain and their role in central sensitisation; discuss the role of referred pain in linking peripheral nociception to central pain; and describe the clinical features of fibromyalgia, the most common example of chronic musculoskeletal pain resulting from abnormality of central pain-related mechanisms.

Sensory systems and central pain

Two fundamentally different sensory systems are important in musculoskeletal pain:

- the first involves nociceptors, which when activated provide input into the spinal cord and brain, leading to pain
- the second involves mechanoreceptors, which normally provide sensory input, such as light touch or proprioception, to the brain.

The mechanoreceptor sensory system is also critically involved in central pain. This occurs through the mechanism of central sensitisation, whereby there is increased responsiveness in the pain transmission nerves of the spinal cord. This process allows otherwise innocuous sensory stimuli to 'gain access' to the pathways involved in pain transmission to the brain. For instance, when there is central sensitisation in the neurones of the spinal cord, light touch to the skin or gentle movement of a joint will induce pain through sensory input from the mechanoreceptors.

Central sensitisation can be caused by prolonged stimulation of peripheral nociceptive fibres (for example, when there is persisting inflammation in a joint and the pain is felt in a wider regional

Table 1. Important pain types in chronic musculoskeletal pain

Pain type	Examples	Main mechanism
Nociceptive pain	Inflammatory arthritis	Activation/modulation of peripheral nociceptor
Neuropathic pain	Diabetic neuropathy Post-zoster neuralgia	Damage to components of the peripheral or central somatosensory nervous system
Central pain	Fibromyalgia Regional pain syndrome	Sensitisation of spinal cord pain transmission neurones due to altered modulation from the brain

distribution than the joint itself). The more common cause of central sensitisation, however, results from a change in modulatory influences, such as stress or sleep disturbance, on spinal cord neurones from the brain through the descending pathways linking the brain stem to the spinal cord.[1]

Chronic musculoskeletal pain can result primarily from peripheral mechanisms or central mechanisms, or from a combination of both (Table 1). Neuropathic pain is not further discussed in this article.

Referred pain and central mechanisms

Referred pain underlies many musculoskeletal pain presentations, involves central mechanisms within the spinal cord, and is important in the understanding of the mechanisms involved in fibromyalgia.[2] As noted previously, in the presence of central sensitisation peripheral mechanoreceptor input, such as muscle or joint movement, is translated into pain.[1] Similarly, when there is central sensitisation, mechanoreceptor input from deep spinal structures will be translated into pain, but in this case it involves the mechanism of referred pain.

The clinical features that make up referred pain are well known and assessed in everyday practice (Table 2). Pain generation from any deep tissue, be it in the viscera or a somatic part of the body, particularly the spine, will be referred to the body surface in a characteristic manner. Although the pain does not occur in the distribution of a dermatome, it does still relate to the level of the innervated structure involved, hence symptoms and signs are segmental. For instance, tissue damage in the myocardium causes pain to the left arm, chest wall or jaw in a distinctive manner. Nociceptor activation emanating from a spinal facet joint disorder will refer to the same body segment as the facet joint – for example, the shoulder girdle and arm if the pain is generated in the lower neck.

There are many components to referred pain, not all of which relate just to pain. These include segmental dysaesthesia (unpleasant abnormal sensations), which might manifest as pins and needles or numbness, or segmental muscle tightness. Importantly, there is abnormal tenderness to palpation within the segmental region involved in referred pain (Table 2).

The mechanism of referred pain seems to be important for symptom generation in fibromyalgia. As shown in Tables 2 and 3, many of the symptoms and signs of fibromyalgia are essentially those of referred pain.

Clinical features of the central pain syndrome fibromyalgia

Fibromyalgia in both its more common widespread form and its less common regionalised form is the prototypical example of central pain.[3] It is common, occurring in 3 to 5% of the population, and affects about four times as many women as men. Typical features of central pain include the pain symptom itself, which is usually widespread or segmental and described as dull aching or burning, with intermittent localised sharp pains. Other common symptoms include muscular stiffness. Clinically, patients will have non-neuroanatomical sensory dysaesthesia. This might manifest as tingling and numbness affecting all five digits or glove and stocking sensory change in the peripheries.

The pain of fibromyalgia is accompanied by widespread abnormal tenderness. This is usually elicited by gentle palpation in areas that are already known to be sensitive such as the mid-trapezius area or the anterior chest wall, among others. These areas, known as tender points, become more tender than usual in fibromyalgia.

Widespread or segmental abnormal tenderness is typical of central pain and has its origins in the mechanism of referred pain. Muscles are often tight and there may be localised muscular regions, known as trigger points, which are easily identified as tight bands and which cause pain on palpation.[4] Trigger points are thus different from tender points; the latter occur in many tissues, not just muscle, and result from widespread lowering of the pain threshold, the key feature of central pain.

There is no muscle wasting or weakness in patients with fibromyalgia beyond that which is caused by the pain.

Table 2. Typical clinical features of referred pain

Clinical feature	Characteristics	Examination
Pain	Segmental, dull, heavy, aching, occasionally lancinating and sharp	
Dysaesthesia	Segmental 'pins and needles' and/or 'numbness'	Symptoms and signs non-neuroanatomical (nondermatomal), may be 'glove and stocking' sensory change
Tenderness	Segmental soft-tissue tenderness	Some areas within the symptomatic segment more tender than others
Muscle stiffness	Muscles tight	Segmental joint movements stiff, muscle co-contraction, spinal movement stiff

Dermatographia is a useful sign in central pain states, such as fibromyalgia, and is elicited by gently stroking the fingernail over the upper back and watching for a wheal and flare response to occur within the next 10 seconds.[5] Although there is overlap with normal, patients with central pain have a brisk and early response to this stimulus, which is caused by release of substance P from activated nerves causing vasodilatation after mechanical stimulation.

Table 3. Key clinical musculoskeletal features in fibromyalgia

Clinical feature	Characteristics	Examination
Pain	Segmental, dull, heavy, aching, occasionally lancinating and sharp	
Dysaesthesia	Segmental 'pins and needles' and/or 'numbness'	Symptoms and signs non-neuroanatomical (nondermatomal)
Tenderness	Segmental soft-tissue tenderness	Some areas more tender
Muscle stiffness	Muscles tight	Muscle and spinal movement stiff
Dermatographia	Exaggerated wheal and flare	Segmental, bilateral even if regional

Table 3 lists the key clinical pain-related presenting symptoms and signs in patients with fibromyalgia.

Fibromyalgia often occurs in the context of emotional distress. Patients have a mix of symptoms that relate firstly to the background central processes and related symptoms that can cause the spinal cord pain modulation (sensitisation) and secondly to the amplified peripheral sensations that result from the central sensitisation. Of note in central pain there is amplification not only of pain but also of many other sensory symptoms (Box 1). In particular, the triad of poor quality sleep, high levels of fatigue and cognitive dysfunction, manifesting as poor memory or concentration, are common clues to central sensitisation and subsequent central pain. The amplified sensations in many other organ systems are an additional clue.

Contextual clues to central pain

Central pain, and particularly fibromyalgia, should always be considered in patients presenting with persisting pain, stiffness and other symptoms if they have significant ongoing life stress or poor coping in the context of normal stress. It should also be considered in patients who have persisting pain after a prolonged viral-like illness or physical trauma.[3]

Box 2 lists some common clinical scenarios in patients with central pain. The presence of these should alert the clinician to the possibility that central pain mechanisms might be contributing to the patient's overall clinical presentation.

Central pain is also a common comorbidity of a number of other disorders, including irritable bowel syndrome, irritable bladder syndrome, restless legs syndrome, temporomandibular joint syndrome, regional pain syndromes, intolerance to foods and drugs, and neurogenic hypotension, among others.

Fibromyalgia is 10 times more common in patients with chronic illness, particularly if that illness is painful or distressing.[3] Hence there is an increased rate of fibromyalgia in patients with rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease and chronic viral infection such as hepatitis C, HIV infection, multiple sclerosis and a host of other similar chronic illnesses. An increased rate of fibromyalgia also occurs in patients with certain chronic psychological and psychiatric disorders, including depression and, particularly, anxiety disorders.

In patients with any of the yellow flags listed in Box 2, the presence of a specific trigger needs to be sought. Over 80% of patients with fibromyalgia have a trigger that they recall was present when they first developed the condition. Motor vehicle accidents, work injury, other chronic illness, stress and other life predicaments associated with loss of control are often reported. Patients developing pain-related symptoms in such context should be assessed for central pain.

1. Symptom groups characterising fibromyalgia

Central symptoms

Poor sleep
Fatigue
Fuzzy head
Poor memory and concentration
Emotional distress
Mood disturbance

Amplified peripheral sensations

Pain
Other sensory symptoms
- Increased sensitivity to:
  - light
  - noise
  - odours
  - tinnitus
- Peripheral dysaesthesia
- Swelling
- Eye irritability – 'dry', gritty
- Nausea
- Bowel/bladder irritability

2. Yellow flags: common clinical scenarios in patients with central pain

Psychosocial

Positive family history – e.g. mother with fibromyalgia
Family, work, personal stressors
Sleep disturbance
Vulnerable personality – e.g. poor coping skills/catastrophising
Current or previous substance abuse
Current or previous mood disorder
Past events that might link to stress reaction

Medical

Previous pain syndrome – e.g. migraine, TMJ, regional pain syndrome
Chronic medical illness – e.g. SLE, RA, IBD
Pain-related work predicament
Physical trauma in emotion-linked setting – e.g. spine injury
Poor recovery from viral illness
Other central sensitivity syndromes – e.g. restless legs syndrome, irritable bowel syndrome, irritable bladder syndrome, neurogenic hypotension, chemical intolerance

Abbreviations: IBD = inflammatory bowel disease; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; TMJ = temporomandibular pain syndrome.

Table 4. Suggested guide to investigations in patients with widespread pain

Appropriate setting	Investigation
All patients	FBE, ESR, CRP, TSH, T4, renal and liver function
If baseline tests are abnormal, or if features of CTD	Antinuclear antibody
If synovitis present	Rheumatoid factor/CCP antibody
If patient is weak, or on statins	Creatine kinase level
If high risk factors for vitamin D deficiency	Vitamin D
If menopause suspected	Oestrogen, FSH, LH
If spinal pain is present in context of red flags – e.g. previous malignancy, features of spinal infection, inflammation or abnormal neurology	Imaging

Abbreviations: CCP = cyclic citrullinated peptide; CRP = C-reactive protein measurement; CTD = connective tissue disorder; ESR = erythrocyte sedimentation rate; FBE = full blood examination; FSH = follicle-stimulating hormone level; LH = luteinising hormone level; TSH = thyroid-stimulating hormone measurement; T4 = thyroxine level.

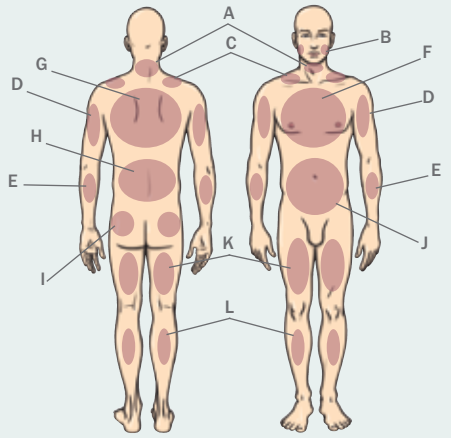
Many patients presenting with what appears to be a local musculoskeletal problem in the periphery will have contributing central pain mechanisms. This is particularly common in those with pain in the lumbar spine/trochanteric area and shoulder girdle area, where there may be some otherwise subclinical pre-existing pathology.[6]

Evaluate for an alternative explanation

Physical examination is important to determine whether an underlying medical condition is responsible for

3. 2011 modification of the 2010 American College of Rheumatology diagnostic criteria for fibromyalgia[7,10]

Pain in the last week*			
Region	Centre	Right	Left
Neck (A)	❑		
Jaw (B)		❑	❑
Shoulder girdle (C)		❑	❑
Upper arm (D)		❑	❑
Lower arm (E)		❑	❑
Chest (F)	❑		
Upper back (G)	❑		
Lower back (H)	❑		
Hip (I)		❑	❑
Abdomen (J)	❑		
Upper leg (K)		❑	❑
Lower leg (L)		❑	❑



Widespread pain index score (WPI; 0 – 19) = _____

Symptoms in the last week†				
Symptom	Score (0-3) ‡			
Fatigue	0	1	2	3
Wakening unrefreshed	0	1	2	3
Cognitive symptoms	0	1	2	3
Other symptoms				
– Headache	1			
– Abdominal pain	1			
– Depression	1			

Total symptom severity score (SSS; 0 – 12) = _____

Polysymptomatic distress score (fibromyalgianess score)

= WPI _____ + SSS _____ = _____

Fibromyalgia diagnosis = WPI ⩾7 ❑ plus SSS ⩾5 ❑

OR

WPI ⩾3 ❑ plus SSS ⩾9 ❑

Criteria filled = Yes/No

Comments:

* Tick appropriate box and count

† Symptoms present at similar level for three months – yes/no; no other explanatory diagnosis – yes/no.

‡ Scoring system: 0 = no problem, 1 = slight or mild problems, generally mild or intermittent, 2 = moderate, considerable problems, often present and/or at a moderate level, 3 = severe, pervasive, continuous, life-disturbing problem.

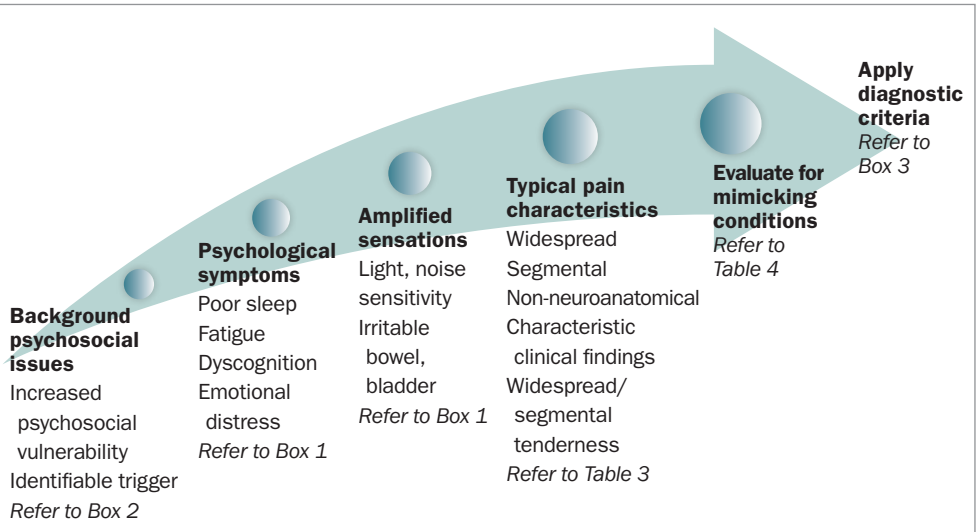


Figure. Considerations in the diagnosis of fibromyalgia.

all of the patient's symptoms. This is complicated in people who already have several established conditions such as osteoarthritis, degenerative spinal pain and inflammatory arthritis that give rise to local pain. In such settings, fibromyalgia is a common concomitant and the two types of pain need to be differentiated to allow for targeted pain management.

Diagnosis is more straightforward in younger people who have no other conditions that could cause similar symptoms, although disorders that mimic fibromyalgia must still be considered.

Table 4 provides a guide to investigations in patients presenting with widespread pain.

Diagnostic criteria for fibromyalgia

Many of the clinical features mentioned above have been found to be valid components contributing to diagnostic criteria for fibromyalgia. A 2011 modification of the 2010 American College of Rheumatology diagnostic criteria is useful in clinical practice (Box 3).[7-9] The patient's pain sites over the previous week and the severity of key symptoms are recorded, rated and the scores added together. A diagnosis of fibromyalgia is made if the score reaches prevalidated levels. The polysymptomatic distress score, also called the fibromyalgianess score, is the combined score of the widespread pain index and the symptom severity score and provides a numerical assessment of any patient's tendency to have fibromyalgia-like symptoms, even if they do not reach the criteria for fibromyalgia.

The older 1990 American College of Rheumatology classification criteria for fibromyalgia are also valid but require an accurate count of the number of tender point sites, which many clinicians do not evaluate.[10]

The diagnosis of central pain, as typified by fibromyalgia, is aided by considering several contextual clues. The first clues to consider are the background yellow flags that signal conditions linking stress to fibromyalgia. Other clues include the symptoms and signs of emotional distress that cause central sensitisation, the symptoms that reflect consequent amplified sensory symptoms, and, particularly, the characteristic clinical signs of widespread or segmental pain and tenderness. Validated diagnostic criteria can then be applied to confirm a diagnosis. The figure summarises these points.

Importance of identifying central pain and pain modulation

Identification of central pain mechanisms as a component of a patient's presentation shifts management towards strategies that target central pain modulation. These strategies include an emphasis on pain education, pain psychology and exercise and consideration of pain modulatory medication.

Descending pathways from the brain modulate pain-related centres in the spinal cord. Two main pathways are involved. One principally involves opioidergic mechanisms and the other involves serotonin and noradrenaline mechanisms. This second pathway links to the emotional centres in the brain and is abnormal in central pain syndromes such as fibromyalgia. Medications that target this mechanism – for example, low-dose amitriptyline and serotonin-noradrenaline reuptake inhibitors (used off label) – are useful in managing the central pain of fibromyalgia. In contrast, there is poor response to opioids in patients with fibromyalgia as the opioidergic systems are not affected.[3]

Gabapentinoids, such as gabapentin and pregabalin, are other examples of pain modulatory medication; they target central sensitisation at the level of the spinal cord and also the brain, and are used off-label for central pain.

Further discussion of management beyond these principles is not within the scope of this article.

Conclusion

Pain arising from central mechanisms is common and can be identified through targeted clinical history and examination. Central pain can occur by itself or in conjunction with many other chronic disorders. Treatment of central pain requires different strategies than other types of pain. PMT

References

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

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