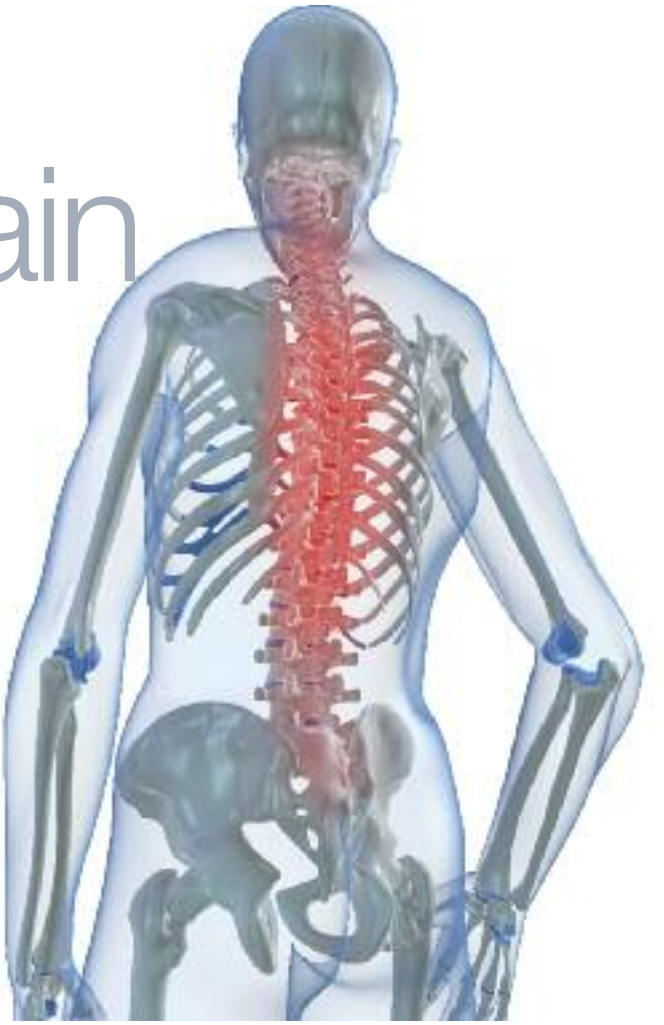
Regional pain syndrome

a disorder of pain sensitisation



GEOFFREY O. LITTLEJOHN MB BS(Hons), MD, MPH, FRACP, FRCP(Edin), FAFRM

Early recognition of regional pain syndrome as a disorder of pain sensitisation is needed so patients can be treated effectively.

MedicineToday 2011; 12(6): 72-80

Professor Littlejohn is Associate Professor of Medicine at Monash University and Director of Rheumatology at the Department of Rheumatology, Monash Medical Centre, Melbourne, Vic, and Adjunct Professor at Edith Cowan University, Perth, WA.

Series Editors: Dr Jane Zochling, MB BS, FRACP, MMed (ClinEpi), PhD, Research Fellow, Menzies Research Institute, University of Tasmania, Hobart, Tas. Professor Lyn March, MB BS, MSc, PhD, FRACP, FAFPHM, Professor of Medicine at the University of Sydney, Department of Rheumatology at Royal North Shore Hospital, Sydney, NSW.

Regional pain syndrome is a common pain syndrome that affects different areas of the body. Typical terms used to describe this syndrome include whiplash, repetitive strain syndrome or nonspecific low back pain. It is often triggered by a musculoskeletal injury or disease. Delayed or missed diagnosis is common and has an adverse impact on patient outcome. This article reviews regional pain syndrome and discusses it in the context of related pain syndromes of fibromyalgia and complex regional pain syndrome.

PAIN IN MUSCULOSKELETAL INJURY

Acute pain within the various components of the musculoskeletal system is a cardinal symptom of the pathophysiological processes involved with tissue damage, disease or dysfunction. Immediate activation of the inbuilt hard-wired innate pain system serves a primary protective function.[1] These pain pathways are intimately linked to withdrawal reflexes, removing the structure from danger. Shortly thereafter, pain responses in the brain relating specifically to the tissue damage allow for protective responses and therefore healing to occur.

The combination of the particular process involved, be it injury, inflammation or degeneration, and the specific muscle– tendon unit affected results in predictable clinical features of different disorders. These range from enthesitis or tenosynovitis to muscle strain. The healing and resolution of the symptoms of most common painful musculoskeletal disorders will usually take place over days to weeks. However, the intensity and duration of the nociceptor stimulation is

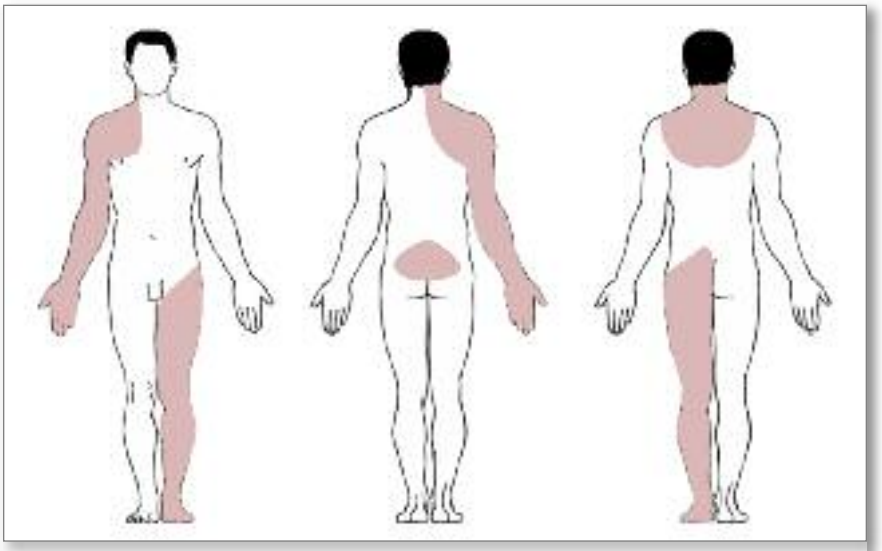


Figure 1. Common locations of regional pain syndrome.

SELECTED COMMONLY USED NAMES FOR REGIONAL PAIN SYNDROME BY REGION

Upper quadrant

- Repetitive strain injury/repetitive strain syndrome
- Cumulative trauma disorder
- Work-related upper limb pain
- Diffuse upper limb disorder

Cervical

- Whiplash-associated disorder (and variants)

Lumbar

- Low back pain
- Nonspecific low back pain

important because it may significantly modulate the healing time.

Continued nociceptor stimulation, such as through ongoing injury, can lead to a change in the stimulation threshold in the neurones that receive the pain message in the dorsal horn of the spinal cord. This important neurobiological process is called sensitisation and because it involves brain and spinal cord processes of the central nervous system the term central sensitisation is applied. In this situation, otherwise innocuous sensory inputs that have links to the sensitised dorsal horn pain-transmitting cells, particularly those coming from mechano - receptor A-beta fibres, will have their input translated into pain sensations. Therefore, with central sensitisation, touch and movement in the region of the injury will be painful. Through other mechanisms, there is regional spread of pain beyond the injured tissue.

Additionally, other disease processes, particularly inflammation, can not only activate the peripheral nociceptor itself but also increase its sensitivity to minor stimuli, known as peripheral sensitisation.

The above effects of peripheral and central sensitisation are normal and to some degree are to be expected after musculoskeletal injury or inflammation. However, the dorsal horn pain transmission centre, where the peripheral nociceptive input is first processed, may be further affected by a more potent control system that links to the brain. The brain has powerful downward control over processing in the dorsal horn and change in this 'pain brake' will augment, amplify and extend any pain response.

Emotional distress has a controlling effect on this process and can drive a series of events that result in central sensitisation with altered 'downstream' musculoskeletal symptoms and function. Under these circumstances, chronic pain states or pain syndromes may arise and particularly may involve the musculo - skeletal tissues.[2]

PAIN SYNDROME

A pain syndrome is a predictable and characteristic collection of symptoms and clinical signs, predominately pain, for which there is no identifiable primary nociceptive cause (that is, tissue damage). In other words, there is no identifiable local or proximal tissue pathology that causes the ongoing pain. Pain syndromes involving the musculoskeletal system occur because of the process of sensitisation described above.

REGIONAL PAIN SYNDROME

The term regional pain syndrome denotes a characteristic set of clinical features that are localised to one region of the musculoskeletal system, most commonly the low neck or back or the upper or lower quadrant (Figure 1). Regional pain syndrome falls within a spectrum of disorders that includes complex regional pain syndrome and fibromyalgia syndrome.

Nomenclature and descriptors

It should be noted that regionalised musculoskeletal disorders that have a defined mechanism or pathophysiology, such as injury, strain, inflammation or degeneration, are not pain syndromes. The term 'regional pain syndrome' is descriptive only and used in preference to other terms that inappropriately attempt to link the syndrome to a putative cause (see the box on this page).

There are no validated classification or diagnostic criteria for regional pain syndrome, but practical clinical criteria

PRACTICAL CLINICAL CRITERIA FOR REGIONAL PAIN SYNDROME

Essential features

- Regional pain
- Regional allodynia (abnormal tenderness to light touch), including areas of focal tenderness (tender points) within the region
- Clinical features not neuroanatomical, involved region consistently links to spine
- Significant emotional distress

Common features

- Sensory dysfunction (dysaesthesia)
- Muscle dysfunction (tightness, trigger points)
- Spine dysfunction (stiffness, referred sensory symptoms)

can be used to help in its diagnosis (see the box on this page).[3] The 2010 American College of Rheumatology diagnostic criteria for fibromyalgia encompass regional pain syndrome if the patient has more than three pain regions and very high rates of poor sleep, fatigue, cognitive change and related symptoms.[4]

Although many criteria for chronic pain syndromes require symptom duration of three months to ensure that tissue-damage contributions are minimised, for regional pain syndrome the presence of the defined clinical features denotes the syndrome as being present. Early identification is therefore emphasised as an important part of optimal management of affected patients.

Regional pain syndrome is characterised by regional pain and tenderness. It is usually triggered by an injury to a component of the muscle–tendon unit of the neck, shoulder, upper limb or back, for example supraspinatus tendinitis, forearm muscle strain or strain of a pain-sensitive structure of various types in the low neck or back. The tissue-damage component of the initial injury usually resolves but regionalised pain, from the spine to a periphery, may persist.

The pain may be described as constantly aching, dull or burning with short-lived sharper lancinating episodes. The pain is usually aggravated by activity, constrained posture of the affected part, weather or emotional changes. The pain is often accompanied by non-neuroanatomical dysaesthesia, such as sensations of numbness, tingling, pins and needles, and glove and stocking sensation changes. These symptoms are common sources of inappropriate investigation and treatment. The proximal spine is often tight, as are muscles in the region of pain. There may be subtle swelling of the forearm or hand and discolouration of the periphery, such as blotchy red or white palms.

Examination shows no evidence of a unifying tissue-damaging lesion to explain all symptoms. There is no muscle wasting and the neurological examination is normal. The key clinical sign is pain on gentle palpation in the whole region involved; some regions (not only muscle) will be more sensitive than others, usually termed tender points, but all regions are abnormally tender.

Other bodily regions not involved in the regional pain syndrome are not abnormally tender. The spine and shoulder/hip girdle may be tight but intrinsic movements are normal. Dermatographia, where a low-level stimulus such as stroking with the fingernail will cause a brisk and exaggerated wheal and flare response in related paraspinal areas, is common.

Distinct from the tender areas and tender points, indicating regional lowering of the pain threshold, there may be some specifically sensitive palpable tight muscle bands known as trigger points, especially in the region of the spine, shoulder girdle or upper forearm.

The differential diagnosis should include consideration of a single lesion that could cause the clinical features – for example, spinal pathology. Many patients with an injury to an upper limb muscle–tendon unit will develop superadded regional pain and tenderness, for example, to the whole upper quadrant. Therefore, quite commonly an injury can coexist with regional pain syndrome, making management of affected patients complex. This situation often occurs in the context of injury at work or a motor vehicle accident when an otherwise straightforward musculoskeletal injury occurs in the context of considerable psychosocial stress.

Workers' compensation, litigation and disability issues force extreme and unique pressures onto the pain axis, promoting change in the brain control of the spinal pain system. This results in amplification of otherwise innocuous sensory inputs, including those from mechanoreceptors. When these inputs come from deep spinal structures there is consequent amplification of normal low-level referred regionalised pain and tenderness. Approaches to the management of patients with chronic pain in this environment are subject to vested interest and confusion. Different outcomes and pathways in patients with the same initial problem will occur according to multiple subtle factors.

The essential pathophysiology of regional pain syndrome, therefore, is sensitisation of pain-related neural pathways in the spinal cord and brain.[5] This in turn relates to decreased tonic control of pathways from the brain that otherwise inhibit spinal cord pain-related inputs. It is the emotion-influenced parts of the brain, such as the anterior cingular and insular cortexes, that have potent control over this pathway and provide the link between emotional distress and the development of regional pain syndrome. Regional pain syndrome is therefore a 'top-down' amplification of regional pain and other sensory systems. It may be

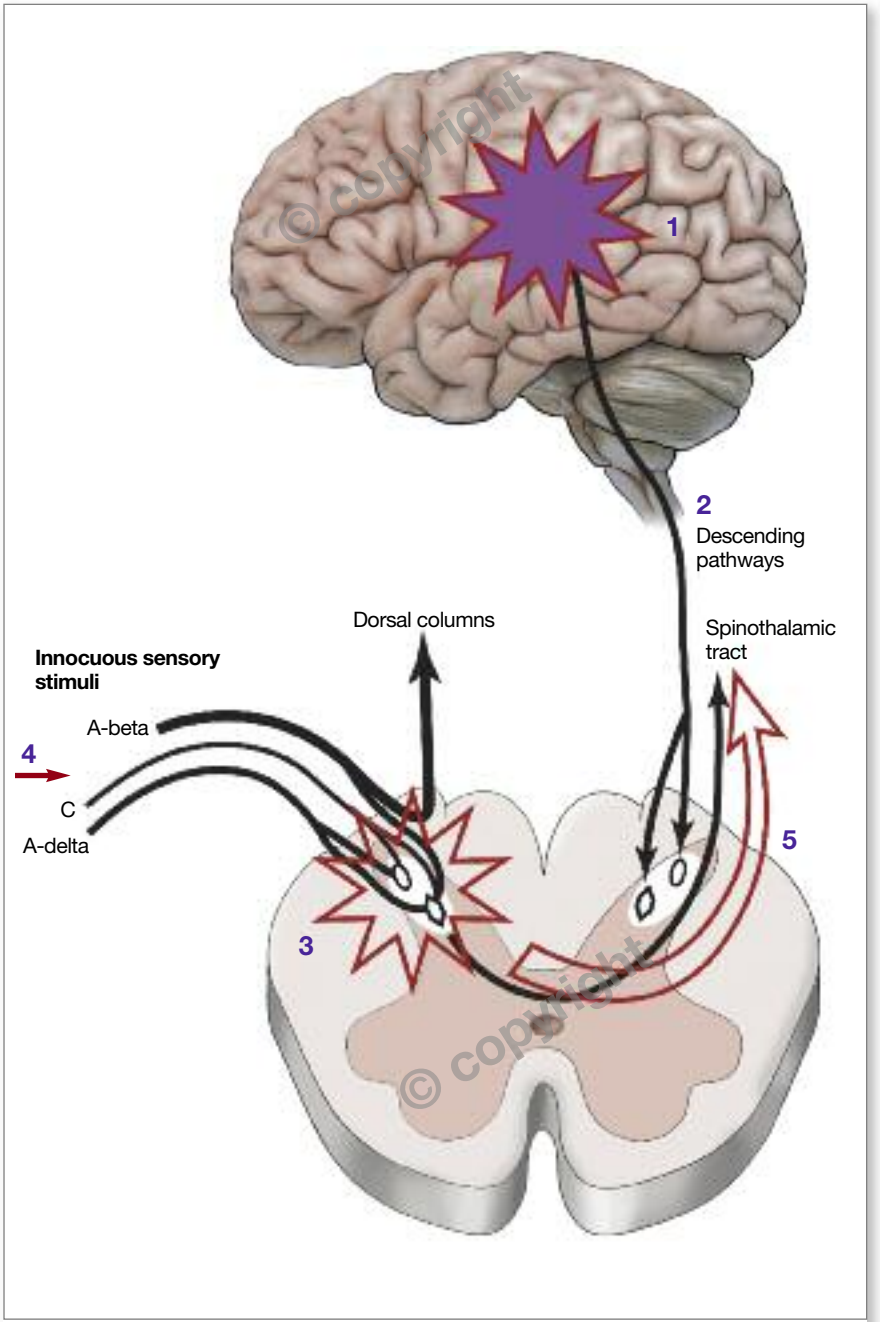


Figure 2. Mechanism of ongoing pain in regional pain syndrome. Central emotion-related brain areas (1) change the function of the descending pain-control system (2) causing sensitisation of deeply placed pain-related projection neurons in the spinal cord (3). Sensory stimuli have important connections to this region (3) and thereby innocuous stimuli (4) can gain 'access' to the pain system with muscle/joint movement now becoming painful (5). A-beta fibres are mechanoreceptors and C and A-delta fibres are nociceptive fibres. Red star shape indicates sensitisation. Red arrow indicates pain.

triggered by local injury but there is no significant ongoing primary peripheral source of nociception causing the syndrome (Figure 2).[6]

COMPLEX REGIONAL PAIN SYNDROME

Complex regional pain syndrome shares many features with regional pain syndrome.[3,7] The term 'complex' denotes a condition that usually has more significant peripheral clinical features such as swelling, colour change or sweating, and with possibly more severe soft tissue tenderness. There is generally less proximal abnormality. In addition, very localised regions, such as the patella or digits, may be involved. No direct regional link to the spine is necessary, although it is common.

Different terms have been used to describe complex regional pain syndrome at different times, usually reflecting the current understanding of the perceived mechanisms of the disorder at the time. Currently, complex regional pain syndrome type I (generally previously known as reflex sympathetic dystrophy) is used for the most common type (90%) and type II (previously known as causalgia) if nerve injury is involved (10%). Criteria for the diagnosis of complex regional pain syndrome include combinations of characteristic symptoms and signs (see the box on page 78).

Patients with regional pain syndrome affecting the upper quadrant will often also fulfill criteria for complex regional pain syndrome. In other regions, such as the neck or low back, the distinction in criteria between regional pain syndrome and complex regional pain syndrome is clearer. The overlap between regional pain syndrome and fibromyalgia, with its widespread pain, and complex regional pain syndrome, with its more intense local symptoms, is indicative of all these conditions being due to the common process of sensitisation of the pain-related nervous system. Therefore, although the names differ, the underlying process is

TYPICAL DIAGNOSTIC CRITERIA FOR COMPLEX REGIONAL PAIN SYNDROME[8]

Continuing pain, disproportionate to any inciting event, and no other diagnosis to better explain signs and symptoms. Plus at least one symptom in three of the following categories and one sign in two or more of the following categories:

- Sensory: hyperaesthesia, hyperalgesia (to pinprick), allodynia to light touch, deep somatic pressure and/or joint movement.
- Vasomotor: temperature asymmetry, skin colour changes
- Sudomotor/oedema: oedema, sweating changes
- Motor/trophic decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin).

similar, as is the management of affected patients.

REGIONAL PAIN SYNDROME AND OTHER IMPORTANT MUSCULOSKELETAL PAIN SYNDROMES

Fibromyalgia is more common than regional pain syndrome, affecting 2 to 4% of people. It is a syndrome of widespread pain and tenderness occurring in patients with emotional distress, poor sleep, increased fatigue, altered cognition and enhanced sensory systems. Many patients with fibromyalgia are prone to regional pain syndrome and likewise many with regional pain syndrome will develop fibromyalgia.

Myofascial pain syndrome is a common disorder of muscles characterised by tightening and bunching of muscle fibres and it is associated with exquisite pain on palpation of so-called trigger points.[9] This may cause altered movement or pain. The problem is usually present in the mid-belly of the muscle and usually occurs after injury or with overuse or postural strain. Many patients with regional pain syndrome also have myofascial pain syndrome in muscles affected by the regional pain process and need to have this treated in conjunction with the regional pain syndrome. Ergonomic considerations and physical therapies are the mainstay of treatment but these therapies are not effective if the patient with regional pain syndrome is not managed appropriately.

Spinal referred pain may be both a contributor to and a consequence of regional pain syndrome. Patients with tight spinal regions may need treatment with stretching, strengthening or relaxation programs to diminish symptoms. Imaging of patients with regional pain syndrome will show the usual 30% or more abnormalities with MRI, CT or plain x-ray, usually unrelated to the clinical presentation. In the context of regional pain syndrome features, extreme care should be taken if considering invasive procedures, such as nerve blocks, denervation, surgery or protracted physical therapies, because regional pain syndrome is not responsive and will usually be aggravated by these approaches.

MANAGEMENT OF REGIONAL PAIN SYNDROME

There is limited evidence-based literature on therapy for regional pain syndrome, due to classification and logistic issues. Many patients with regional pain syndrome are involved in medicolegal deliberations, which makes high quality studies difficult to perform.

Once established, regional pain syndrome can be difficult to manage, hence prevention and early diagnosis remain priorities. Accurate diagnosis, a label specifically incorporating the term 'pain syndrome' and careful education are essential for effective management. The patient needs to understand that the pain is from changes in pain control and not due to a tissue abnormality in the symptomatic region. Of utmost importance is the need to exclude or treat other conditions that might coexist with or mimic the features of regional pain syndrome. Having done this, it is also essential to avoid excessive investigation.

The principles of management of patients with regional pain syndrome are essentially the same as those of other similar pain syndromes, particularly fibromyalgia.[10] Regional pain syndrome differs, however, in that an initial triggering injury might be taken by the healthcare professional and patient alike to be the continuing source of the pain, which can result in expensive, frustrating and illogical management, with poor outcomes. These predicaments often lead to emphasis on medicolegal deliberations rather than effective self-management-derived outcomes.

Common management strategies are based on the four principles of education, exercise, mechanism-targeted drug therapy and psychological treatments (see the box on page 80). These same principles also apply to the related pain syndrome of complex regional pain syndrome, where other interventions may be required (this is beyond the scope of this article). Patients need to know that

MANAGEMENT PRINCIPLES FOR PATIENTS WITH REGIONAL PAIN SYNDROME

Diagnosis and education

- Consider regional pain syndrome as a possible diagnosis in high-risk situations (i.e. work or motor vehicle injuries)
- Ensure accurate diagnosis
- Identify any unresolved nociceptive stimulus but avoid unnecessary investigation
- Provide careful explanation of pain syndrome and indicate expected good outcome

Physical management

- Encourage activity and involve a physical therapist
- Avoid passive physical therapies
- Plan resumption of normal activities

Pharmacological treatment

- Provide neuroactive medication (low-dose tricyclic antidepressants, serotonin–noradrenaline reuptake inhibitors and alpha-2-delta ligands)
- Provide analgesia: simple (e.g. paracetamol, which might be ineffective) or complex (e.g. opioids, which are often unhelpful for sensitisation pain)

Psychological strategies

- Identify and manage psychosocial stressors
- Address social predicaments and involve a psychological therapist
- Use a patient-centred approach

they have a potentially reversible problem; they should understand the concept of sensitisation as a mechanism of their pain and recognise the input of societal constraints and personal reactions to their significant life predicaments as potent stressors and amplifiers of pain-related mechanisms.

The positive effects of activity, particularly aerobic fitness, on sensitisation, muscle stretch and regional muscle symptoms must be emphasised. Activity avoidance due to fear of further injury or aggravation holds many people back.

Medications shown to modulate pain in this setting include tricyclic antidepressants and related dual serotonin–noradrenaline reuptake inhibitors, such as duloxetine (all used off label). Other effective drugs include those modulating alpha-2-delta ligands, such as pregabalin and gabapentin (used off label). Opioid medications can interfere with positive psychological drive and its use must be carefully considered in patients with this disorder. As in fibromyalgia, many patients do not respond to opioids because the endogenous system is already fully activated.

Psychological treatments are the mainstay of management and will range from commonsense explanations and pragmatic strategies, usually delivered using a team approach, through to complex cognitive behaviour programs in the minority of cases. The goal is to educate and upskill the patient to continue self-management. Gaining control of the situation for the patient is critical in reducing the emotional distress that drives the altered pain-control pathways. However, other powerful forces, such as controlling health professionals and the requirements of the legal safety net system, may negate this.

Outcomes vary but improvement is expected in most affected patients. The patients have to take an active role in their own management and extrinsic stressors need to be minimised.

CONCLUSION

Regional pain syndrome is a pain disorder that is well-characterised and has a high-impact. Early diagnosis is aided by anticipation of pain sensitisation in high-risk situations, such as work-related injuries or traffic accidents, where safety net deliberations and disputes are common, and in psychologically vulnerable persons. Patient outcomes are significantly improved when the disorder is recognised early and treated as a disorder of pain sensitisation rather than one of peripheral nociception. MT

REFERENCES

1. Littlejohn GO. Musculoskeletal pain. J R Coll Physicians Edinb 2005; 35: 340-344.
2. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain 2011; 152(Suppl): S2-S15.
3. Littlejohn G. Regional pain syndrome: clinical characteristics, mechanisms and management. Nat Clin Pract Rheumatol 2007; 3: 504-511.
4. 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 (Hoboken) 2010; 62: 600-610.
5. Apkarian V, Robinson JP. Low back pain. Pain: Clinical Updates 2010; 18(6): 1-6.
6. Littlejohn GO, Guymer E. Fibromyalgia: mechanisms and management. Medicine Today 2009; 10(10): 15-26.
7. Littlejohn GO. Complex regional pain syndrome. In: Klippel JH SJ, Crofford LJ, White PH, eds. Primer on the Rheumatic Diseases,13th ed. New York: Springer; 2008; pp. 509-513.
8. Harden RN, Bruehl S, Stanton-Hicks M, Wilson PR. Proposed new diagnostic criteria for complex regional pain syndrome. Pain Med 2007; 8: 326-331.
9. Srbely JZ. New trends in the treatment and management of myofascial pain syndrome. Curr Pain Headache Rep 2010; 14: 346-352.
10. Guymer E, Littlejohn G. Fibromyalgia: current diagnosis and management. Expert Rev Clin Immunol 2009; 5: 181-192.

COMPETING INTERESTS: Professor Littlejohn and the Monash Medical Centre have received honoraria for involvement in research and educational activities from Pfizer and Eli Lilly.