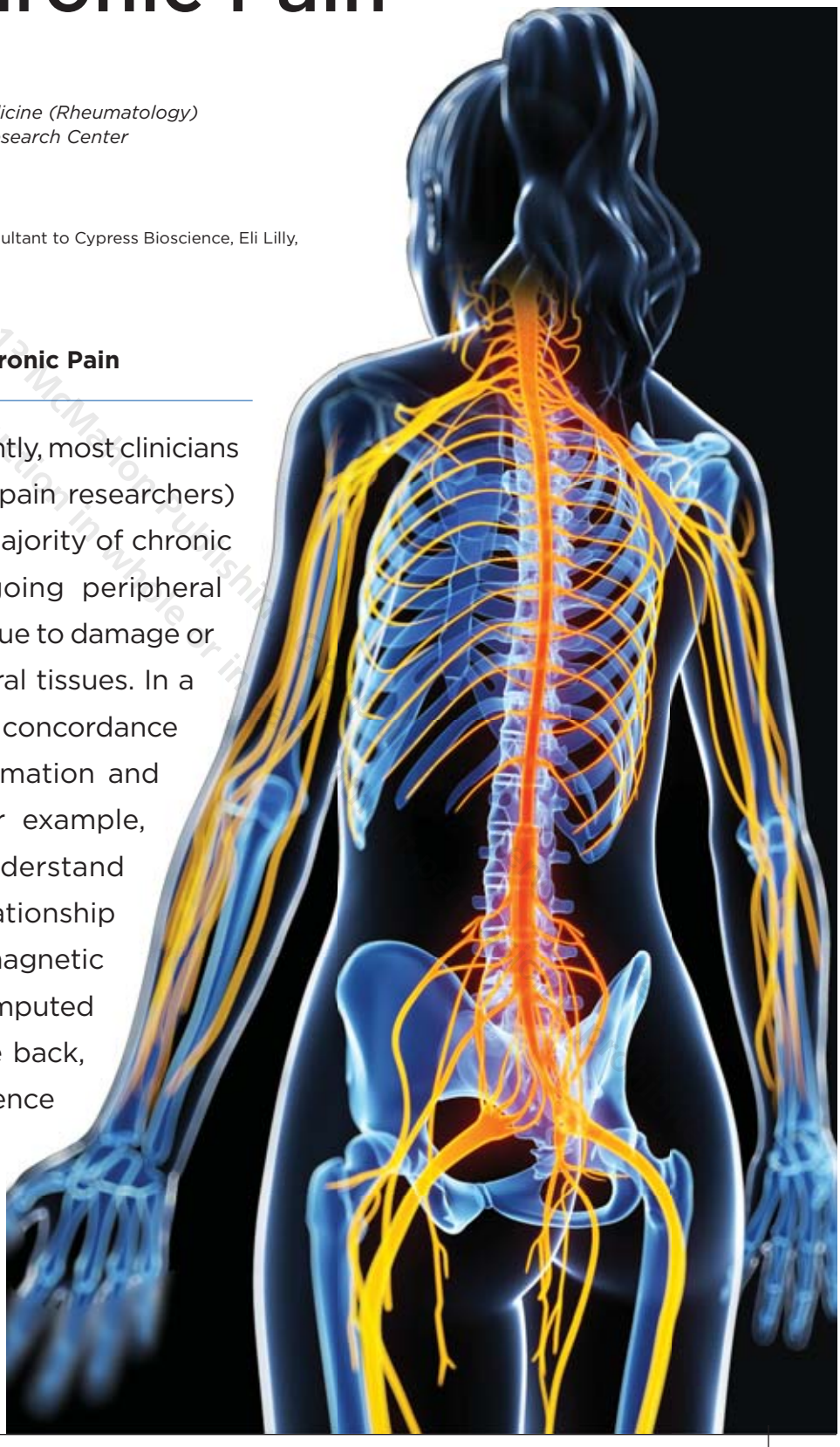
What Fibromyalgia Teaches Us About Chronic Pain

DANIEL J. CLAUW, MD

Professor of Anesthesiology and Medicine (Rheumatology)
Director, Chronic Pain and Fatigue Research Center
The University of Michigan
Ann Arbor, Michigan

Dr. Clauw has served as an advisor or consultant to Cypress Bioscience, Eli Lilly, Forest, Pfizer, and Wyeth.



Rethinking the Origin of Chronic Pain

Until relatively recently, most clinicians (and even many pain researchers) considered the majority of chronic pain to be due to ongoing peripheral nociceptive activity (eg, due to damage or inflammation) in peripheral tissues. In a few instances, this lack of concordance between damage/inflammation and pain is well known. For example, nearly all clinicians understand that there is a poor relationship between the results of magnetic resonance imaging or computed tomography scans of the back, and the presence or absence of lumbar pain.[1]

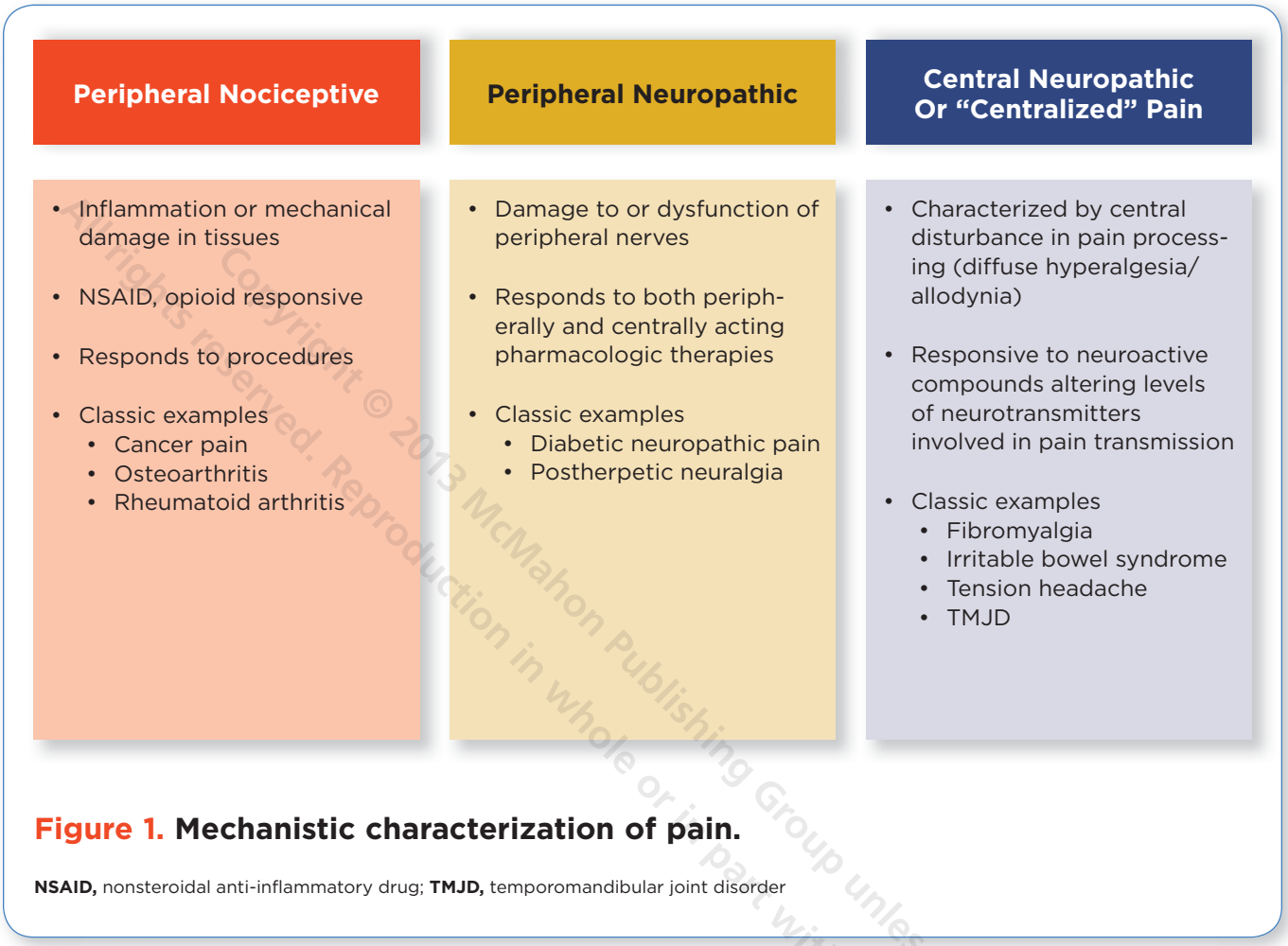


Figure 1. Mechanistic characterization of pain.

NSAID, nonsteroidal anti-inflammatory drug; **TMJD,** temporomandibular joint disorder

However, very few realize that there is not a single chronic pain state where any radiographic, surgical, or pathologic description of peripheral nociceptive damage has been reproducibly shown to reliably identify which individuals will be experiencing pain, or how severe that pain will be. The reason for this appears to be that both the peripheral and central nervous systems (PNS/CNS) play critical roles in determining which nociceptive input detected by sensory nerves in the peripheral tissues will lead to the perception of pain in humans. Many individuals with significant peripheral nociceptive input will not experience pain, and others without any identifiable peripheral nociceptive input will experience severe pain.

A central tenet of this review is that within any specific diagnostic category, individual patients may have markedly different peripheral nociceptive and neural contributions to their pain. Thus, just as low back pain has long been acknowledged to have multiple potential mechanisms and thus has sometimes been referred to as a *mixed pain state*, it is becoming more likely that all chronic pain syndromes may in fact be mixed pain states. This term implies that within each diagnostic category, individuals may have markedly different reasons for their pain. Some individuals will have pain primarily due to peripheral nociceptive input, whereas in others peripheral (eg, peripheral sensitization) or CNS factors (central sensitization, or centralization, of pain

via augmented pain processing in the spine and brain) may be playing an equally or even more prominent role in their pain and other symptoms.

Making this distinction is critical from a clinical standpoint because both the drug and non-drug therapies that will work for any given chronic pain patient might be much better guided by a nuanced view of the mechanisms of the pain rather than knowing from which of these diagnoses the patient is suffering. This is not a new concept, having first been raised more than a decade ago by Mitchell Max, and later Clifford Woolf and others.[2,3] However, these authors opined that we should do this in the future; this review suggests that we might finally have made enough scientific progress in the pain field to begin implementing these techniques in clinical practice.

Figure 1 briefly describes at least 3 different underlying mechanisms that can be operative in chronic pain states: peripheral nociceptive, peripheral neuropathic, and central neuropathic (or centralized) pain. Some authors use the term *neuropathic pain* for any pain of neural origin, whereas others reserve this term for conditions where there is identifiable damage to the nervous system. We acknowledge this, but prefer to use the term *central* (or centralized) *pain* to refer to the fact that the CNS (rather than the PNS) is prominently involved in maintaining the pain. This distinction between peripheral *neuropathic pain* (where peripherally directed therapies such as topical treatments, injections, and/or surgery might be helpful, and should be considered) and *central neuropathic pain* (where these generally are not options) is extremely important.

Of note, although specific diagnoses are noted in Figure 1 as being considered peripheral nociceptive, peripheral neuropathic, or central neuropathic (centralized), this is meant to indicate the category in which each of the diagnoses has historically been considered to reside. Again, the emphasis of this review is that some individuals with any chronic pain state have evidence that they have centralized their pain and should likely be treated with centrally acting treatments, whereas other individuals with conditions such as fibromyalgia or irritable bowel syndrome (IBS) may have peripheral contributions to their pain that may need to be identified and treated.

Fibromyalgia as the Prototypical Centralized Pain State

The term *central pain* was originally used to describe individuals who developed pain after a stroke or spinal cord lesion. In this case, central referred to the fact that the lesion leading to pain occurred within the CNS—either spinal cord or brain. More recently, however, the term has expanded to describe any CNS dysfunction or pathology that may be contributing to the development or maintenance of chronic pain. Another term that often has been used to describe this same phenomenon is *central sensitization*. Using this term can cause some confusion because just like central pain, the original meaning of central sensitization in the pain field referred to a specific spinal cord mechanism that is now realized to be one of many potential causes of augmented CNS pain processing.[4]

Central pain, as newly defined, originally was thought to be confined to individuals with idiopathic or functional pain syndromes, such as fibromyalgia, headache, IBS, temporomandibular joint disorder, and interstitial cystitis.[5,6] These pain syndromes have been shown to be familial/genetic, and to strongly coaggregate in individuals and families.[7,8] The symptoms experienced by individuals with central pain syndromes have been well characterized and consist of multifocal pain (with a high current and lifetime history of pain in many bodily regions), and a cluster of co-occurring somatic symptoms (ie, fatigue, sleep disturbances, memory difficulties).[8,9] Even if individuals are identified as having a new onset of a regional pain syndrome, closer questioning often reveals very high rates of pain in other bodily regions, and other somatic symptoms in addition to pain.[9]

Using a large Swedish twin registry, Kato and colleagues performed a series of studies first showing the comorbidities with chronic widespread pain. They later examined a number of these central, or functional, pain syndromes and the relationship of symptoms to those of depression and anxiety.[10] These studies clearly demonstrated that functional somatic syndromes such as fibromyalgia, chronic fatigue syndrome, IBS, and headache have latent traits (eg, multifocal pain, fatigue, memory, and sleep difficulties) that are different from (but overlap somewhat with) psychiatric conditions such as anxiety and depression. The notion that there are 2 overlapping sets of traits, one being pain and sensory amplification and the other being mood and affect, also is supported by genetic studies of idiopathic pain syndromes.[7]

Current evidence suggests that genetic factors are approximately 50% responsible for overall sensitivity to experimental pain, and that the same genes that have been identified as increasing sensitivity to

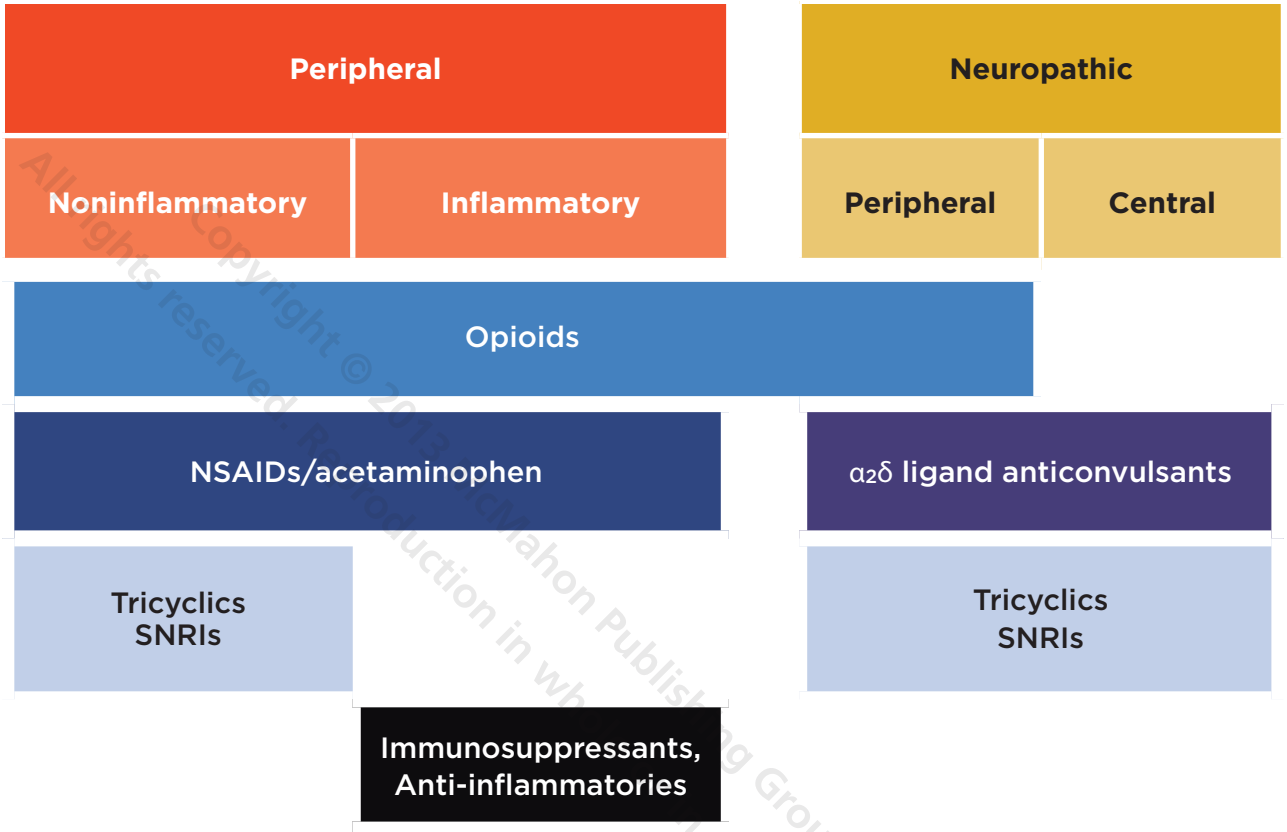


Figure 2. Drugs for pain based on underlying mechanisms.

NSAID, nonsteroidal anti-inflammatory drug; **SNRI,** serotonin-norepinephrine reuptake inhibitor

experimental pain also make individuals more likely to develop chronic pain over the course of their lifetime. There are at least 5 sets of genes that have been shown to both change an individual's pain sensitivity and increase their likelihood of developing one or more chronic pain states. These include *COMT* (an estrogen-sensitive enzyme that may play a more prominent role in females); a number of sodium channel mutations; GTP cyclohydroxylase (*GCHI*); types 2 and 3 adrenergic receptors; and a potassium channel gene (*KCNS*).[11-16] The genes have been most consistently shown to confer a higher risk for pain sensitivity or the development of chronic pain, but not all studies have confirmed these findings.[15,17,18]

As with most illnesses that may have a familial or genetic underpinning, environmental factors may play a prominent role in triggering the development of fibromyalgia and other central pain states. Environmental stressors temporally associated with the development of either fibromyalgia or chronic fatigue syndrome include early life trauma; physical trauma (especially involving the trunk); certain infections such as hepatitis C, Epstein-Barr virus, parvovirus, and Lyme disease; and emotional stress. The disorder also is associated with other regional pain conditions or autoimmune disorders.[19-21] Of note, each of these stressors only triggers the development of fibromyalgia and/or chronic fatigue syndrome in approximately 5% to 10% of individuals

who are exposed; the overwhelming majority of individuals who experience these same infections or other stressful events regain their baseline state of health.

Although fibromyalgia, IBS, and other central pain states were originally felt to be autoimmune or inflammatory diseases (ie, fibrositis, spastic colitis) and then later believed not to be, recent findings are leading to a reconsideration of whether subtle inflammatory or peripheral changes may be responsible for some of the symptoms seen. Furthermore, studies suggest that maintenance of central augmentation requires persistent noxious peripheral input, even in syndromes such as IBS and fibromyalgia, which are characterized by the absence of well-defined, localized, pain-causing lesions.[22] A recent study of 68 patients with fibromyalgia and myofascial pain syndromes and 56 patients with fibromyalgia and regional joint pain showed that peripheral trigger-point injections and hydroelectrophoresis ameliorate fibromyalgia pain and increase pain thresholds at sites distant from the therapeutic interventions, providing further evidence that painful peripheral stimuli contribute to the perpetuation of central augmentation interventions.[23]

Role of Central Factors in Classic Peripheral Nociceptive Input Disorders

Historically, the "disease" of osteoarthritis (OA) has been viewed primarily as damage to the cartilage and bone. As such, the magnitude of damage or inflammation of these structures should predict symptoms. Population-based studies suggest otherwise; 30% to 50% of individuals with moderate to severe radiographic changes of OA are asymptomatic, and approximately 10% of individuals with moderate to severe knee pain have normal radiographs.[24,25] Psychological factors do account for some of this variance in pain and other symptoms, but only to a small degree.[26,27] This failure of peripheral damage, inflammation, or even psychological factors to explain the presence, absence, or severity of chronic pain should not be surprising. To date, no chronic pain state involves a strong relationship between peripheral factors and the level of pain reported.

The work done to date supports the hypothesis of OA as a mixed pain state, and in some individuals CNS factors are highly influential. Central factors may be playing a pivotal role in OA, which helps to explain the fact that comorbid somatic symptoms known to be associated with central pain conditions (eg, fatigue, sleep problems) are very commonly present in OA, and are not explained by a purely peripheral model of this disorder.[28,29] Moreover, both quantitative sensory testing and functional neuroimaging studies suggest that patients with OA display diffuse hyperalgesia to mechanical or heat stimuli, some of which normalizes following hip arthroplasty. This further suggests that the central factors were being at least partly driven by peripheral nociceptive input.[30-33] Finally, recent randomized controlled trials have demonstrated that compounds that alter pain neurotransmitters centrally such as serotonin and norepinephrine (eg, duloxetine [Cymbalta, Lilly], milnacipran [Savella, Forest], tricyclics) are efficacious in OA.[34,35]

Basing Pharmacologic Therapy on Underlying Mechanism(*s*) of Pain

Figure 2 shows the classes of drugs that seem most effective in different underlying mechanisms of pain. For peripheral nociceptive, noninflammatory pain states such as OA, treatment guidelines typically recommend first using acetaminophen, and then nonsteroidal anti-inflammatory drugs (NSAIDs). It is now generally thought that acetaminophen is safer, but less effective, than NSAIDs. Although opioids previously had been considered to be very useful for pain refractory to these treatments, the latest meta-analyses of opioids in OA challenge this notion, and generally recommend against opioid use.[36]

Although older studies supported the fact that tricyclic compounds may be effective in OA, these drugs have significant toxicity, especially in the elderly. Because of this, newer drugs that also are likely working by increasing serotonergic and noradrenergic activity, such as tramadol and duloxetine, are more commonly used. Although many in the pain field strongly suspect that these latter *centrally acting* analgesics (this term is used cautiously because most analgesics have potential peripheral and central mechanisms) will be more effective in individuals with peripheral nociceptive pain that has centralized to date, there have been no studies that have definitively proved this.

In inflammatory, peripheral pain states such as rheumatoid arthritis, a whole host of anti-inflammatory or disease-modifying drugs also are used in addition to the above drugs. It is likely that these drugs both directly decrease pain by reducing inflammation, and also reduce peripheral sensitization that may occur due to ongoing inflammation.

The classes of drugs that preferentially work for neuropathic or centralized pain states again include the serotonin-norepinephrine reuptake inhibitors (eg, tricyclics, tramadol, duloxetine) as well as the $\alpha_2\delta$ calcium channel ligands (pregabalin [Lyrica, Pfizer] and gabapentin).

Peripheral pain syndromes (including both inflammatory and noninflammatory peripheral pain, and peripheral neuropathic pain) also can be treated with topical agents or injections. Injections of corticosteroids, hyaluronic acid preparations (for OA in joints that can be injected), agents that ablate nerves, or capsaicin (effective in both OA and neuropathic pain) are all therapeutic options.

Summary

Advances in our understanding of pain over the past decade are finally making the dream of personalized analgesia closer to reality. Using clues from a history and physical examination, clinicians can now, at a minimum, identify the subsets of individuals with heretofore considered "peripheral" pain syndromes, and treat these individuals with more centrally than peripherally directed pharmacologic and nonpharmacologic approaches. However, more work is necessary to determine if we can extrapolate our understanding of conditions such as fibromyalgia and OA more broadly, and if these segmentation techniques really do identify subsets of patients who will preferentially respond to peripherally or centrally acting analgesics.

References

1. Boden SD, McCowin PR, Davis DO, et al. Abnormal magnetic-resonance scans of the cervical spine in asymptomatic subjects. A prospective investigation. *J Bone Joint Surg Am.* 1990;72(8):1178-1184.
2. Max MB. Is mechanism-based pain treatment attainable? Clinical trial issues. *J Pain.* 2000;1(3 suppl):2-9.
3. Woolf CJ. Pain: moving from symptom control toward mechanism-specific pharmacologic management**.** *Ann Intern Med.* 2004;140(6):441-451.
4. Woolf CJ, Thompson SW. The induction and maintenance of central sensitization is dependent on *N*-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. *Pain.* 1991;44(3):293-299.
5. Clauw DJ, Schmidt M, Radulovic D, et al. The relationship between fibromyalgia and interstitial cystitis. *J Psychiatric Res.* 1997;31(1):125-131.
6. Hudson JI, Pope HG. The concept of affective spectrum disorder: relationship to fibromyalgia and other syndromes of chronic fatigue and chronic muscle pain. *Baillieres Clin Rheumatol.* 1994;8(4):839-856.
7. Diatchenko L, Nackley AG, Slade GD, et al. Idiopathic pain disorders—pathways of vulnerability. *Pain.* 2006;123(3):226-230.
8. Williams DA, Clauw DJ. Understanding fibromyalgia: lessons from the broader pain research community. *J Pain.* 2009;10(8):777-791.
9. Warren JW, Howard FM, Cross RK, et al. Antecedent nonbladder syndromes in case-control study of interstitial cystitis/painful bladder syndrome. *Urology*. 2009;73(1):52-57.
10. Kato K, Sullivan PF, Evengard B, et al. A population-based twin study of functional somatic syndromes. *Psychol Med.* 2009;39(3):497-505**.**
11. Amaya F, Wang H, Costigan M, et al. The voltage-gated sodium channel Na(v)1.9 is an effector of peripheral inflammatory pain hypersensitivity. *J Neurosci.* **2**006;26(50):12852-12860.
12. Costigan M, Belfer I, Griffin RS, Dai F, et al. Multiple chronic pain states are associated with a common amino acid-changing allele in KCNS1. *Brain.* 2010;133(9):2519-2527.
13. McLean SA, Diatchenko L, Lee YM, et al. Catechol *O*-methyltransferase haplotype predicts immediate musculoskeletal neck pain and psychological symptoms after motor vehicle collision. *J Pain.* 2011;12(1):101-107.
14. Tegeder I, Costigan M, Griffin RS, et al. GTP cyclohydrolase and tetrahydrobiopterin regulate pain sensitivity and persistence. *Nat Med.* 2006;12(11):1269-1277.
15. van Meurs JB, Uitterlinden AG, Stolk L, et al. A functional polymorphism in the catechol-O-methyltransferase gene is associated with osteoarthritis-related pain. *Arthritis Rheum.* 2009;60(2):628-629.
16. Zubieta JK, Heitzeg MM, Smith YR, et al. COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. *Science.* 2003;299(5610):1240-1243.
17. Hocking LJ, Smith BH, Jones GT, et al. Genetic variation in the beta2-adrenergic receptor but not catecholamine-*O*-methyltransferase predisposes to chronic pain: results from the 1958 British Birth Cohort Study. *Pain.* 2010;149(1):143-151.
18. Nicholl BI, Holliday KL, Macfarlane GJ, et al. No evidence for a role of the catechol-*O*-methyltransferase pain sensitivity haplotypes in chronic widespread pain. *Ann Rheum Dis.* 2010;69(11):2009-2012.
19. Ablin K, Clauw DJ. From fibrositis to functional somatic syndromes to a bell-shaped curve of pain and sensory sensitivity: evolution of a clinical construct. *Rheum Dis Clin North Am.* 2009;35(2):233-251.

20. Buskila D, Neumann L, Vaisberg G, et al. Increased rates of fibromyalgia following cervical spine injury. A controlled study of 161 cases of traumatic injury. *Arthritis Rheum.* 1997;40(3):446-452.

21. Clauw DJ, Chrousos GP. Chronic pain and fatigue syndromes: overlapping clinical and neuroendocrine features and potential pathogenic mechanisms. *Neuroimmunomodulation.* 1997;4(3):134-153.

22. Staud R, Nagel S, Robinson ME, Price DD. Enhanced central pain processing of fibromyalgia patients is maintained by muscle afferent input: a randomized, double-blind, placebo-controlled study. *Pain.* 2009;145(1-2):96-104.

23. Affaitati G, Costantini R, Fabrizio A, et al. Effects of treatment of peripheral pain generators in fibromyalgia patients. *Eur J Pain.* 2011;15(1):61-69.

24. Creamer P, Hochberg MC. Why does osteoarthritis of the knee hurt—sometimes? *Br J Rheumatol.* 1997;36(7):726-728.

25. Hannan MT, Felson DT, Pincus T. Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee**.** *J Rheumatol.* 2000;27(6):1513-1517.

26. Creamer P, Hochberg MC. The relationship between psychosocial variables and pain reporting in osteoarthritis of the knee. *Arthritis Care Res.* 1998;11(1):60-65.

27. Creamer P, Lethbridge-Cejku M, Costa P, et al. The relationship of anxiety and depression with self-reported knee pain in the community: data from the Baltimore Longitudinal Study of Aging. *Arthritis Care Res.* 1999;12(1):3-7.

28. Allen KD, Renner JB, DeVellis B, et al. Osteoarthritis and sleep: the Johnston County Osteoarthritis Project. *J Rheumatol.* 2008;35(6):1102-1107.

29. Zhang Y, Jordan JM. Epidemiology of osteoarthritis. *Rheum Dis Clin North Am.* 2008;34(3):515-529.

30. Arendt-Nielsen L, Nie H, Laursen MB, et al. Sensitization in patients with painful knee osteoarthritis. *Pain.* 2010;149(3):573-581.

31. Gwilym SE, Filippini N, Douaud G, et al. Thalamic atrophy associated with painful osteoarthritis of the hip is reversible after arthroplasty: a longitudinal voxel-based morphometric study. *Arthritis Rheum.* 2010;62(10):2930-2940.

32. Gwilym SE, Keltner JR, Warnaby CE, et al. Psychophysical and functional imaging evidence supporting the presence of central sensitization in a cohort of osteoarthritis patients. *Arthritis Rheum***.** 2009;61(9):1226-1234.

33. Kosek E, Ordeberg G. Lack of pressure pain modulation by heterotopic noxious conditioning stimulation in patients with painful osteoarthritis before, but not following, surgical pain relief. *Pain.* 2000;88(1):69-78.

34. Chappell AS, Ossanna MJ, Liu-Seifert H, et al. Duloxetine, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: a 13-week, randomized, placebo-controlled trial. *Pain.* 2009;146(3):252-260.

35. Fishbain D. Evidence-based data on pain relief with antidepressants. *Ann Med.* 2000;32(5):305-316.

36. Furlan AD, Sandoval JA, Mailis-Gagnon A, et al. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. *CMAJ***.** 2006;174(11):1589-1594.