Curbside Consultation

Central Sensitization: When It Is Not "All in Your Head"

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Case Scenario

I have a busy morning during clinic, and I realize that a new patient has been added to my late afternoon schedule because of back pain, headache, abdominal pain, fatigue, and difficulty sleeping. A brief review of the medical record reveals that over the past years, this 32-year-old patient has been seen by primary care physicians, numerous specialists, and even in emergency medicine settings for various ongoing symptoms, including headache, neck pain, diffuse body aches, urinary frequency, dysuria, generalized fatigue, brain fog, and anxiety. Despite multiple investigations with negative results, the patient does not appear to have received any definitive diagnoses. Experiencing a moment of dread and anticipating a difficult patient encounter, I vent my frustration to my colleague, knowing that I will unlikely be able to offer any useful tests, explanations, or acceptable treatment recommendations. My colleague suggests that central sensitization could be a useful concept in understanding and explaining my new patient's various types of chronic pain.

Commentary

Patients and many physicians often think of chronic pain as a direct manifestation of ongoing tissue (nociceptive pain) or nerve (neuropathic pain) damage.[1] In recent years, a third type of pain—centralized or nociplastic pain—has been recognized.[1] Nociplastic pain is believed to be primarily generated by central sensitization, in which abnormal neural signaling causes the development and amplification of chronic pain as well as a variety of other symptoms that are often difficult to explain or to reconcile with traditional diagnostic tests. Central sensitization provides a robust conceptual and etiologic framework for chronic pain and many unexplained symptoms. The model facilitates patient engagement, builds trust, and may assist in acceptance of and adherence to a broader range of evidence-based therapies. Several chronic conditions (e.g., irritable bowel syndrome, functional dyspepsia, fibromyalgia, myalgic encephalomyelitis [formerly chronic fatigue syndrome], interstitial cystitis, chronic pelvic pain, chronic neck or back pain, chronic orofacial pain, headache, a variety of postinfectious syndromes) are believed to be attributable to ongoing nociplastic pain caused by central sensitization.[1-6]

PATHOPHYSIOLOGY

Central sensitization–based conditions develop when persistent or repeated sensory signals from the periphery cause alterations in how the brain and spinal cord process sensory stimuli. The resulting structural, functional, and neurochemical changes in the central nervous system (CNS) exacerbate the perception of pain or noxious stimuli.[2-5] Although a specific precipitating event cannot always be identified, several key pathologic processes that trigger central sensitization have been elucidated. These include altered cellular processes and cytokine concentration changes following an injury, immune activation following infections, sympathetic nervous system hyperactivity, perturbations of brain neuroplasticity, and endogenous opioid system changes.[1-5,7-10] Collectively, these changes cascade into the amplification of ascending (excitatory/pain) nervous system signaling from the periphery plus the reduction in normal descending (inhibitory/downregulatory) signaling from the CNS. Over time, because of neuroplasticity, a greater area of the CNS is activated by painful afferent signals, with a concomitant reduction in capacity to generate modulatory efferent signals. These changes lead to the development of chronic widespread pain, which extends beyond the site of the original insult and accounts for nonanatomic distribution patterns, often in the absence of identifiable tissue damage.[3,4,11]

PATIENT PRESENTATION

There is substantial individual variability in the presentation, impact, and severity of central sensitization. Central sensitization appears to be more common in individuals with coexisting chronic pain–related conditions, as well as psychosocial and socioeconomic risk factors. As a result,

Case scenarios are written to express typical situations that family physicians may encounter; authors remain anonymous. Send scenarios to afpjournal@aafp.org. Materials are edited to retain confidentiality.

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patients presenting with central sensitization–based conditions should be assessed (and offered treatment/advice) for substance and inappropriate analgesic use, intimate partner violence, resource scarcities, low income, and mental health disorders. These factors may predispose patients to central sensitization, precipitate central sensitization, or perpetuate symptoms with more frequent exacerbations.[11]

Patients typically experience diffuse waxing and waning migratory symptoms, which are often vague and unrelated to antecedent activities. Patients almost always develop allodynia (e.g., things that normally do not hurt now hurt), hyperalgesia (e.g., things that used to hurt now hurt more), and global sensory hyperresponsiveness (e.g., sensitivity to various stimuli from within and external to your body).[1-4,7-11] They may eventually develop additional, more generalized CNS symptoms such as cognitive difficulties (e.g., brain fog), disturbed sleep, chronic fatigue, anxiety, depression, or increased sensitivity to sound, light, or odors.[1-4,7-11] Central sensitization–induced nociplastic pain may coexist with or even replace the initial nociceptive or neuropathic elements of chronic conditions such as low back pain, migraine headache, and rheumatoid arthritis.[2,6,11] Furthermore, the interrelated nature of nociplastic symptoms may sometimes lead to a domino effect in which the flare-up of one symptom leads to the worsening of several others.

APPROACH TO CARE

Nociplastic changes are at least partially reversible, with management strategies aimed at desensitizing the CNS at structural, functional, and chemical levels. Given the complexity of the nociplastic changes, an extended time frame (months to a year) for appreciable reversibility is expected. Patients should be made aware of the anticipated duration to ensure understanding, motivation/commitment, and the setting of realistic expectations. Treatment should begin with a detailed discussion of central sensitization that is incorporated into a structured, thoughtful, and empathic interaction *(Table 1)*; this helps validate the patient and helps explain discrepancies

TABLE 1

Initial Approach to the Care of Patients With Central Sensitization

Suggested steps	Comments and examples
Have a basic understanding of the role of central sensitization in common chronic conditions	The understanding and framework of central sensitization can be used in daily patient care, especially when faced with challenging chronic conditions (e.g., fibromyalgia, chronic fatigue, irritable bowel syndrome, functional dyspepsia, chronic low back pain)
Review the medical record in advance and recognize an acute flare-up of a chronic condition, which may be partially related to central sensitization	Clinical presentations may be highly variable; some patients may have continuous symptoms, whereas others may have flare-ups that last only a few days, with months or years between episodes
Listen to, anticipate, and address patient's fears or concerns about symptoms and underlying conditions	Patients may be concerned that symptoms are caused by or could develop into cancer or irreparable damage if not treated
Suggest possibility of central sensitization and introduce the concept: "I wonder whether you might have central sensitization." "Have you ever heard of central sensitization?" "I'd like to review some of your symptoms and perform an examination to see whether you have any evidence of something called central sensitization."	Do not offer a diagnosis until after completing a detailed history and targeted physical examination, including appropriate diagnostic testing where indicated

continues

*—Moseley GL, Butler DS. Fifteen years of explaining pain: the past, present, and future. *J Pain.* 2015;16(9):807-813.

TABLE 1 *(continued)*

Initial Approach to the Care of Patients With Central Sensitization

Suggested steps	Comments and examples
Obtain an expanded history focused on symptoms suggestive of central sensitization: Pain disproportionate to apparent structural damage or pathology, particularly if self-reported moderate to severe pain Post-exertional malaise or worsening of symptoms after even mild physical, mental, or emotional activity Centrally mediated symptoms: pain, disturbed sleep, memory changes (e.g., brain fog), fatigue, headache, bowel symptoms, dizziness, anxiety	Inconsistent or unpredictable responses to prior interventions Widespread nonanatomic distribution on a patient-drawn pain chart Worsening symptoms with opioids Nonmusculoskeletal hypersensitivity (e.g., temperature, light, noise, stress)
Perform a physical examination designed to elicit findings and signs suggestive of central sensitization Definitive physical findings are uncommon but should not be missed; a careful examination is a valuable ritual and helps convey empathy	Inconsistent or confusing findings on physical examination Signs of allodynia (e.g., discomfort with gentle touch or brushing of skin with cotton) Signs of widespread hyperalgesia Heightened sensitivity to heat or cold stimuli Signs of hyperresponsiveness
Use the explaining pain principles strategy with the patient, which refers to a range of educational interventions that aim to change the understanding of what pain actually is, what function it serves, and what biologic processes are thought to underpin it* Incorporate central sensitization into your explanatory model and patient education using the explaining pain principles strategy	Highlight the following features: Pain and symptom physiology Role and function of the nervous system in pain and symptom amplification Disparate nature of central sensitization–based symptoms, often with unremarkable findings Interrelatedness of symptoms and conditions, including mood and sleep disorders Specifically make clear that you are not saying that "it's all in your head," attributing hypochondriasis, or suggesting that "you will just have to live with it" (most people can eventually partially improve)
Explain the limited role of testing	Discuss previous testing, highlighting reassuring results, but do not describe as negative results
Using your expertise, patient symptoms, and diagnostic results, translate the symptoms into named diagnoses	Ask, "What have other doctors told you is your diagnosis(es)?"
Emphasize expanded treatment options	Promote evidence-based, multimodal treatment strategies, including medication and nonmedication modalities (Tables 2 and 3)
Routinely follow up with your patient to ensure ongoing understanding of central sensitization and adherence to agreed-on treatment strategies; address any new issues as they arise	Schedule a follow-up visit, and assure continuity (either with yourself or with the patient's regular physician)

*—Moseley GL, Butler DS. Fifteen years of explaining pain: the past, present, and future. *J Pain.* 2015;16(9):807-813.

between their symptoms and objective clinical findings.[2-4,6,11] It also allows for a physiologic framework and explanation on which additional treatment strategies are based.

In addition to patient education, treatment strategies for central sensitization–based conditions comprise a multimodal approach that includes medication and nonmedication strategies targeting the central (nociplastic) and peripheral (nociceptive) mechanisms of pain and symptoms[2,3,7,11,12] *(Tables 2 and 3)*. These approaches are implemented with the hopes of

TABLE 2

Pharmacologic Treatment Strategies for Central Sensitization

Medications*	Comments
Neuromodulators†	Block central opioid receptors
Amitriptyline	Improve fatigue and sleep
Duloxetine (Cymbalta)	Improve pain
Gabapentin	Reduce paresthesia
Gamma-hydroxybutyric acid (GHB)	Reduce neuroimmune activation
Milnacipran (Savella)	Slow intestinal transit time
Naltrexone (Revia; low dose)	
Nortriptyline	
Pregabalin (Lyrica)	
Muscle relaxant	Improves pain, muscle tension, and sleep
Cyclobenzaprine	
Gut antispasmodic agents	For use in irritable bowel syndrome–related conditions
Dicyclomine	Improve postprandial abdominal pain, gas, bloating, fecal urgency
Hyoscyamine	Relax gastrointestinal small bowel and colonic activity
Peppermint oil	Aids with abdominal pain, bloating, irregular bowel habits, pain with defecation, incomplete evacuation
Analgesics	Short duration courses or as-needed dosing recommended
Acetaminophen	Target specific peripheral pain generators
Nonsteroidal anti-inflammatory drugs	
Antiemetic agents	For concomitant nausea experienced in various central sensitization–related conditions (e.g., irritable bowel syndrome, fibromyalgia, chronic migraines, chronic fatigue, functional dyspepsia)
Anticholinergics	
Antihistamines	
Phenothiazines	
Serotonergic antagonists	
Migraine agents‡	Various classes available for abortive or prophylactic purposes
Triptans	
Ergot alkaloids	
Selective serotonin receptor agonists	
Calcitonin gene-related peptide monoclonal antibodies	

*—Medication option(s) should be targeted to symptoms present and individualized for patients given their comorbid conditions; options here are a starting point.
†—The modulators listed are the most commonly used medications for central sensitization–based conditions. Variable degrees of symptomatic effectiveness, along with common potential adverse effects, have been reported.
‡—Migraine agents are listed as most to least commonly used.

retraining the maladaptive underlying changes associated with central sensitization.

Patients and physicians benefit from moving beyond an illness narrative that focuses mainly on symptoms, often resulting in prolonged diagnostic odysseys, to a mindset based on understanding, acceptance, engagement, and rehabilitation with mutual goals of improving function and overall quality of life. Although central sensitization should not be viewed as a uniform or homogenous process, it provides an explanatory model relaying the interrelatedness of various symptoms and conditions, highlights the role of the CNS in sensory amplification, and helps facilitate better acceptance of evidence-based treatment strategies.

Case Resolution

Before seeing the patient, the physician should review the resources about central sensitization and then be purposeful and focused about following a specific framework during the office visit[1,2,13,14] *(Table 1)*. At the initial patient visit, after completing a detailed history and physical examination, it is helpful to describe the term central sensitization as a diagnostic framework. After the physician reassures themself (based on the history, examination, and medical records) and the patient that nothing new or threatening to the patient's health is happening, further discussion of central sensitization is warranted. This should include its wide range of symptoms, its effect on overall functioning and well-being, and the ways in which the CNS can be desensitized. Most importantly, the physician should specifically arrange a follow-up visit, either with themself or their colleague, within a few weeks to continue the conversation.

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TABLE 3

Nonpharmacologic Treatment Strategies for Central Sensitization

Treatment modality	Comments
Patient education	Neuroscience review Explanation of pain physiology Explanation of neuroplasticity and its role in therapy
Physical therapy	Referral for treatment of specific sites of pain generation (e.g., low back, neck, shoulder, hip) Minimizes deconditioning Strength and aerobic training Increases daily functional abilities, independence, and quality of life
Occupational therapy	Focus of therapy includes daily schedule development, moderation (time, activity, daily tasks), energy conservation (avoidance of "crash and burn"), resource management, reduction of fatigue, and brain fog Usually recommended in conjunction with physical therapy and cognitive behavior therapy
Cognitive behavior therapy	Managing the cycle of thoughts, emotions, and behaviors associated with chronic symptoms Implementation of behavioral modification therapies Often directed by a trained psychologist or occupational therapist
Relaxation therapies Biofeedback therapy Paced breathing Deep breathing Mindfulness Guided imagery Muscle relaxation	Therapy options aimed at calming central sensitization Reversal of anatomic pain processing areas and sensory pathways Altering neurotransmitter concentrations Reduction of sympathetic pathways and activation of parasympathetic pathways

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