

# Central Sensitization in Functional Chronic Pain Syndromes: Overview and Clinical Application

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## ■ ABSTRACT:

The purpose of this review and clinical application article is to offer nurses up-to-date knowledge on peripheral and central sensitization in chronic functional pain syndromes, and to discuss therapies that have shown efficacy in treating various aspects of these disorders. Central sensitization is a result of changes in the peripheral and central nervous system due to noxious stimuli, such as illness or trauma. Once these changes occur, treatment for the associated syndromes requires a multimodal approach that includes behavioral pain psychology, physical therapy, and pharmacological agents that specifically target neuroinflammation, pain modulation, and amplification of pain pathways. More research needs to be conducted on the basis and patient perception of functional pain syndromes to reduce the morbidity and significant disability associated with these illnesses. Nurses have the opportunity to be at the forefront of this research because of their holistic and multidimensional approach to patient care, assessment, and symptom management.

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## OBJECTIVE AND DATA SOURCES

The objective of this review is to discuss and define the concept of central sensitization as it pertains to functional pain syndromes, as well as to discuss the treatment options, future research objectives, and implications for nursing. A literature review was conducted applying a systematic approach utilizing the following databases: CINAHL, MEDLINE, EMBASE, and Google Scholar. The terms "central sensitization," "peripheral sensitization," and "functional pain syndromes" were employed in this search. Following a systematic screening process based on relevance to the topic and level of evidence, 25 articles were chosen for this overview and clinical application article.

## INTRODUCTION

Chronic pain is a serious health concern in both pediatric and adult populations that often is associated with high levels of functional disability and morbidity

(King et al., 2011). The International Association for the Study of Pain (IASP) defined chronic pain as a condition that occurs for more than 3 months (Merskey & Bogduk, 1994). Many chronic pain disorders are without any detected anatomical cause, and therefore are deemed “functional pain syndromes.” Recent research has implicated a set of central nervous system (CNS) events that are linked to chronic pain conditions such as fibromyalgia, irritable bowel syndrome, and interstitial cystitis, to name a few (Phillips & Clauw, 2011). This neural process is known as central sensitization, and the syndromes that are associated with its occurrence are called disorders of central sensitization (CS).

CS is a pathological pain state that is also known as pain memory because the sensation of pain lasts long after the initial stimulus. CS is thought to be the variable that most contributes to the evolution from acute to chronic pain (Noel et al., 2015). In this process, synaptic neuroplasticity occurs, which is the alteration of neurons based on environmental and genetic factors. Neuroplasticity in chronic pain syndromes has been a strong interest of pain clinicians and researchers in recent decades. It is now understood that a set of pathological conditions leads to CS. The process begins with peripheral sensitization and advances to early- and then late-phase CS leading to allodynia (pain with light touch) and diffuse hyperalgesia (widespread increased sensitivity to painful stimuli) (Woolf, 2007; Woolf, 2011).

## PERIPHERAL SENSITIZATION

Increased neuro-excitability in a localized area is known as peripheral sensitization (PS). PS is an exaggerated pain response limited to the area of injury (Ji et al., 2003). The progression to PS is a result of noxious stimuli such as injury, illness, or inflammation. PS begins with the sensitization of nociceptors, which are neurons that respond specifically to noxious stimuli. This process results in a lower threshold of the peripheral nociceptor terminals following tissue injury (Woolf, 2011). After trauma, a group of inflammatory messengers including prostaglandins, cytokines, leukotrienes, and bradykinin are released (Bridgestock & Rae, 2013). These chemicals are the result of persistent activation of microglial cells in the contralateral thymus of the brain that initiate neuroinflammation as a result of injury or illness (Cooper & Clark, 2013). The resultant inflammatory messengers cause alterations in neuron-specific, voltage-gated sodium channels that subsequently produce reduced activation potentials and increased membrane excitability (Ji et al., 2003). Elevated neural-excitability in PS

triggers reduced pain thresholds, leading to a heightened response to pressure and heat stimuli (Hermann et al., 2006). Sensitivity to these sensations can bring about fear and avoidance of previously enjoyed activities that may elicit increased pain through minor trauma.

## CENTRAL SENSITIZATION

CS now is understood to be responsible for pain hypersensitivity outside of the original area of injury. This also is known as secondary hyperalgesia (Woolf, 2011). The progression from PS to CS has a clear association with memory, and in fact shares common molecular processes resulting in neuroplasticity of neurons within the limbic region of the brain (Ji et al., 2003).

CS is separated into acute- and late-phase sensitization. In acute-phase CS, the activation potential of neurons in the dorsal horn of the spinal cord is lowered through increased glutamate transmission by N-methyl-D-aspartate (NMDA) and  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptors. A rise in the amino acid glutamate and substance P reduces the activation threshold and intensifies the opening characteristics of various ion channels, leading to an upsurge in neuron excitability (Woolf, 2007; Argoff, 2008). The increase in synaptic glutamate also results in the death of inhibitory neurons that would usually help modulate pain signals. Inhibitory neurons are replaced by greater numbers of afferent excitatory neurons that allow pain signals to flourish (Henry et al., 2011).

Late-phase CS involves an alteration of gene expression within dorsal horn neurons (Woolf, 2007). This is important to understand because after these changes in gene regulation occur in late-phase CS it becomes more difficult to recover fully from hyperalgesia. The alteration in gene expression leads to changes in the dorsal root ganglia, giving these nonafferent neurons the capacity to induce CS without nociceptive input (Ji et al., 2003). Continued afferent outflow without inhibitory response results in greater pain transmission to the brain, specifically in the insula, the area that is responsible for interpretation of various sensory information (Henry et al., 2011).

## CLINICAL PRESENTATION

CS is heterogeneous in clinical presentation, with various degrees of pain, affected sites, and disability. Patients with CS often are referred to a chronic pain clinic for ongoing pain that does not correspond with objective findings such as swelling, trauma, or

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