LITERATURE REVIEW

# Central Sensitization in Chronic Musculoskeletal Pain

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# CENTRAL SENSITIZATION IN CHRONIC MUSCULOSKELETAL PAIN


## ABSTRACT

**OBJECTIVE** – To discuss the role of central sensitization in chronic pain resulting from musculoskeletal injuries. Also, the clinical diagnosis and treatment options for central sensitization will be reviewed and discussed.

**DATA COLLECTION** – Data was collected by performing a PubMed search for relevant articles. The initial search was conducted by searching for the key word "central sensitization" with limits placed to include articles published within the past 10 years, written in English, and involving human subjects only. This search resulted in 407 potential articles which were briefly reviewed and the most relevant articles utilized. Articles were chosen based on their clinical relevance including successful diagnosis and treatment. Further articles were obtained by searching for chosen articles from the reference sections of the most relevant articles.

**RESULTS** – Central sensitization is a highly complex process that arises due to plastic changes within the central nervous system resulting in chronic pain in the absence of further tissue damage. This process is reversible especially in the early stages but after becoming firmly established requires treatment from multiple disciplines within the healthcare field. There is limited literature discussing easy to utilize diagnostic testing within the clinic. Also, documented effective treatment and resolution of central sensitization utilizing either manual therapy or pharmaceuticals is rare.

**CONCLUSIONS** – The processing of pain is a complex and in many ways individualized phenomenon. The development of central sensitization can occur as a result of enhanced or continual afferent input, dysfunctional descending inhibition, or a combination of these factors. Central sensitization results in secondary hyperalgesia and allodynia making both diagnosis and treatment difficult. Treatment must be targeted towards the true cause of dysfunction and often involves eliminating musculoskeletal dysfunction, aberrant central pain processing, along with therapy focused on psychological processing of pain. A targeted and careful exam will result in proper diagnosis so that the most effective treatment can be utilized.



**KEY TERMS** – Central Sensitization; Chronic Musculoskeletal Pain; Secondary Hyperalgesia; Allodynia.

## INTRODUCTION

In a normally functioning nervous system, damage or perceived damage to peripheral structures activates nociceptive neurons that relay information to the central nervous system resulting in an action to protect the body from further damage. This response and the feeling of pain are generally short lasting and should normally resolve. However, when the central nervous system is exposed to repeated stimuli from nociceptors or is exposed to an abnormally large amount of damage there can be plastic changes within the central nervous system that can lead to a prolonged experience of pain, hypersensitivity to non-painful stimuli, and pain felt in regions distant to the area of initial injury. This phenomenon has become known as central sensitization and represents a plastic change within the central nervous system that leads to sensitization of central structures resulting in abnormal pain response. This response is protective if it results in limiting the use of an injured area until the area is fully healed but becomes pathological if peripheral inflammation persists or is maintained in the absence of peripheral pathology.(1) The sensation of pain includes a combination of physical, psychological, and affective processes that causes the reaction to and experience of chronic pain to differ from individual to individual and increases the difficulty in making a definitive diagnosis of true cause in a chronic pain patient.

Peripheral tissue injury initially generates increased neuronal excitability peripherally which when severe or constant will lead to increased excitability of the spinal cord and central structures. Following damage to innervated tissues and persistence of pain there is an adaptation of unimodal nociceptors and the responsiveness of polymodal nociceptors is enhanced which leads to primary hyperalgesia or peripheral sensitization. (2) Sensitization of the nociceptive terminal neurons is responsible for primary hyperalgesia along with increased excitability of neurons within the dorsal horn.(3) This process is one of many that can lead to the development of changes within the central nervous system that can result in central sensitization. The sensitization of peripheral nociceptors must be

controlled or further injury to these structures must be eliminated otherwise sensitization of central structures can occur.

Injury in the periphery produces an inflammatory response that begins the process of healing. Inflammation also results in the release of potassium ions, substance P, bradykinin, prostaglandins, and other neurotransmitters that result in activation of neural structures. Peripherally, Aβ-fibers will begin to synthesize receptors that are normally only found in C-fibers and gene expression in the dorsal root ganglion causes an increase in synthesis of peripheral receptors. (4) This entire process results in increased nociceptive input into the central nervous system and with time can lead to plastic changes that lead to central sensitization. The physiology of processing nociceptive pain is a complicated one and beyond the scope of this review. This process involves processing from peripheral receptors, the spinal cord, and supraspinal centers. Changes can occur within each of these areas that are directly related to sensitization and the continual experience of pain. The longer a person has been affected by pain along with the severity of symptoms appears to be related to the amount of symptom spread in central sensitization. Sustained peripheral input into the central nervous system is one mechanist that is responsible for the maintenance of central sensitization.(5)

Central sensitization is a complex process and can involve changes in multiple areas within the central nervous system and can occur as a result of many different possible triggers. Recognized triggers include windup, temporal summation, dysregulated descending inhibitory pathways, and up regulated facilitatory modulation from the forebrain along with alterations within the spinal cord and dorsal horn neurons.(6) Peripheral sensitization leads to primary hyperalgesia and results in increased pain to thermal and mechanical stimuli whereas central sensitization leads to secondary hyperalgesia and results in increased pain to mechanical stimuli but not to thermal stimulation.(7) These differences are important when evaluating a patient with pain to determine the area of primary dysfunction so that a specifically targeted treatment can be utilized. Widespread hypersensitivity and allodynia to thermal and mechanical stimuli appear to be present in conditions associated with central sensitization. If peripheral sensitization

continues or is severe enough then plastic changes can occur in the dorsal horn neurons. This results in secondary hyperalgesia and pain may be felt in areas distal to the initial injury.

Chronic pain results from a combination of nociceptive processes, psychological factors, and social factors. The major clinical features of centrally maintained nociceptive pain include hypersensitivity of the injured tissues, mechanoallodynia, thermal hyperalgesia, hyperpathia, secondary hypersensitivity, and neurogenic inflammation, autonomic dysregulation, and motor phenomena.(3) This process is progressive and is reversible in early stages. The non-segmental distribution of pain and hyperalgesia to areas distant to the initial injury reflects the plastic changes within the central nervous system rather than psychosomatic pathology in chronic pain patients.

Neuropathic pain is sometimes used as a term that is related to central sensitization. Neuropathic pain as defined by the International Association for the Study of Pain in 1994 is pain initiated or caused by a primary lesion or dysfunction of the nervous system. Central sensitization results from changes within the central nervous system itself and this system may be altered or damaged in central sensitization and cause neuropathic pain conditions.

Specific and known signs of central sensitization include hyperalgesia, allodynia, and wind-up.(1) Hyperalgesia is an exaggerated painful experience to a normally painful stimuli. Allodynia is the experience of pain to an otherwise painless stimulus. Wind-up occurs as the result of continual input into the central nervous system and results in increased painful sensations as a result of the maintained input. Wind-up does not involve peripheral sensitization and is a potent spinal mechanism of pain amplification.(1) Secondary hyperalgesia occurs in uninjured areas following wind-up due to the dorsal horn neurons receiving input from more than one nerve or root and their receptive fields reach outside the boundaries of peripheral nerves and dermatomes. These sensations can be local to the initial injury, in a region innervated by related spinal areas or even widespread. All of these signs will point to the potential of central sensitization complicating diagnosis and treatment.

Central sensitization itself is a relatively new explanation for the maintenance of pain in patients with chronic pain disorders that cannot be explained by peripheral tissue damage. The process can be

operationally defined as “an amplification of neural signaling within the central nervous system that elicits pain hypersensitivity”.(8) This process is also useful to explain painful conditions that are experienced in areas distal to an initial area of tissue damage but that appears to be related to the initial tissue insult. The response of the nervous system to pain is not static and chronic noxious input leads to alterations due to the plasticity of neural structures. Activation of N-methyl D-aspartate (NMDA) receptors is linked to expression of Cyclooxygenase-2 (COX-2) in the cord which affects the entire cord and not just the receptors associated with tissue damage.(9) This is how multiple areas of the central nervous system may respond to and be affected by nociceptive stimuli.

An appropriate summary of the processes behind central sensitization can be found in an article written in 2010 by Geoff M. Schneider et al and is summarized as follows:

> “Alterations in neuronal excitability in the spinal cord, secondary to ongoing peripheral nociception, has been hypothesized as a mechanism of central hyperexcitability. Contributing to central hyperexcitability is the activation of NMDA receptors, and subsequent release of COX-2 in the spinal cord, as well as the activation of glial cells. Clinical manifestations of central hyperexcitability are represented by lowered pain thresholds in areas distant from the site of tissue injury (secondary hyperalgesia) and allodynia. Another contributing factor to central hyperexcitability stems from higher brain centers and is represented by the imbalance on descending facilitatory and inhibitory pathways. Structural injury secondary to trauma may lead to an inflammatory response characterized by the release of inflammatory mediators such as substance P, prostaglandins, and bradykinin. As a result of this inflammatory response, peripheral nociceptors may become sensitized. With long periods of nociception, primary hyperalgesia may be maintained as peripheral nerve fibers such as A-fibers, assume C-fiber characteristics.” (10)

According to functional imaging studies there are multiple areas within the central nervous system that show altered activity in patients with known disorders related to central sensitization. From

the dorsal horn to the supraspinal centers, chronic pain does not affect one area alone. One study used fMRI in such patients and detected increased activation in the contralateral brainstem, cerebellum, bilateral thalamus, contralateral primary and secondary somatosensory cortices, bilateral posterior insula, anterior and posterior cingulated cortices, right middle frontal gyrus, and right parietal association cortex in experimentally induced secondary hyperalgesia as found in central sensitization.(7) There are also many structures within the midbrain that show altered activity in patients with altered pain processing. Structures such as the periaqueductal gray area and the nucleus cuneiformis within the mesencephalic reticular formation are known to have a substrate for bidirectional modulation of pain processing and can either facilitate or inhibit nociception.(7) These areas show altered function in patients with signs and symptoms associated with central sensitization. Another study showed that brainstem activity contributes to maintenance of central sensitization in humans whereas activity in somatosensory cortex reflects the perception of pain intensity that is increased as a result of central sensitization.(11) This same study also determined that output from the mesencephalic reticular formation will activate descending pathways in the rostroventral medulla that enhances nociceptive processing at the level of the dorsal horn which completes the spinal-bulbar circuit to maintain central sensitization.(11)

The structures within the cord and the dorsal root ganglion are also capable of plastic changes and have altered function in patients with central sensitization. Peripherally the firing of nociceptive C-fibers into the dorsal horn will cause a pain response and result in altered functioning within this loop to ensure that further damage does not occur. As sensitization progresses there is a sensitization of the peripheral nociceptive receptors, ectopic firing of the dorsal root ganglion cells, changes in the characteristics of non-nociceptive neurons, and anatomic changes in the superficial layers of the dorsal horn.(3) These changes progress over time and are more easily reversed in early phases. After the process of central sensitization continues, these structures will more easily utilize this pattern of increased pain and function as if the pain state is the normal resting state of the nervous system.

Molecular changes in nociceptive terminals, ectopic firing of afferent pain fibers at the level of the dorsal root ganglia and physiologic changes of the NMDA receptor, perpetuate chronic pain.(3)

Central sensitization is maintained by nociceptive input and physiologic changes in the NMDA receptors. The dorsal horn neurons have been shown to be responsible for a portion of induction and maintenance of the central sensitized state. The NMDA receptors within the dorsal horn play a major role in this sensitization. With maintenance of nociceptive input into the dorsal horn, the magnesium blockade of the NMDA receptors is lifted as a result of cumulative depolarization.

Although central sensitization can result from increases in nociceptive input from C-fiber afferents of many structures, activation of nociceptors innervations from deep tissues such as muscles and joints influence central pain processing to a greater extent and can produce longer lasting effects than superficial tissues like skin.(1,8,12,13) Temporal summation of deep musculoskeletal structures has been shown to be more potent in causing chronic widespread pain and effects within the central nervous system than temporal summation of superficial structures such as the skin.(13) This knowledge is useful when assessing a patient with chronic pain following injury and understanding that it is critical to know which structures could have been effected and damaged. It becomes necessary to envision all musculoskeletal structures from the skin to the deepest structures and be able to use clinical judgment to determine how the mechanism of initial injury could have led to damage of the deepest structures. This is why a focused history and patient interview are critical in evaluating a patient who has had chronic injury. Understanding the date of onset, mechanism of injury, and area of trauma can all be related to symptoms following significant trauma. With cutaneous injury a higher frequency of pain stimulation is necessary to produce central sensitization whereas when deep soft tissues are injured this frequency of nociceptive stimulation is not required to sensitize the central nervous system and thus it is easier for central sensitization to occur.(13)

Another such common mechanism that can induce chronic pain conditions besides a blunt traumatic incident is incongruence between sensory stimulation and motor patterns.(14) The central nervous system monitors sensory input and produces appropriate motor effects to cause a match between afferents and efferents. With a mismatch between intention, proprioception, and visual feedback there is an increased activation of central structures that results in excess afferency within the system.(14) When

there is an interruption within the motor control system caused by instability and improper mechanics of motion it leads to abnormalities in the sensory-motor functioning. In susceptible individuals this may be enough to cause painful states even in the absence of acute trauma or known injury. It is necessary when treating such cases to recognize the abnormal motion pattern so that treatment can focus on stabilization and coordination of muscle control to decrease the constant mismatch of sensory information that may be exacerbating the chronic pain. The feed-forward and feedback neuronal controls are in constant action and when a mismatch occurs between the two, sensory input can lead to the sensation of pain.(14) Since many proprioceptors are found within the deep supporting structures of joints, this is another form of increased sensory input from deep structures which have an increased effect on central structures.

Injury to soft tissues causes characteristic pain which differs from regional pain syndromes that occur along with sensory symptoms that are not always accounted for based on the mechanism of injury. Whenever central sensitization is known to account for symptoms of widespread pain both the peripheral musculoskeletal and central nervous systems are linked in symptom presentation. One variable that typically connects these two systems is the emotional and psychological state of the patient.

Central sensitization leads to a number of physiologic changes within the neural structures. There are also changes within the neuroimmune system that can contribute to sensitization associated with chronic pain. Pain conditions that cause a patient's behavioral hypersensitivity to stimuli will also create an activation of immune cells both centrally and peripherally in an attempt to mediate the pain.(15) Immune activation along with the other factors released as a response to pain can induce the further expression of other pain mediators within the central nervous system which further sensitizes the central structures. As immune cells infiltrate into the central nervous system it creates further activation of neurons which perpetuates sensitization.(15)

Central sensitization is a highly complex process that affects multiple structures throughout the central nervous system. This process increases the difficulty in both diagnosis and treatment of a patient. Knowing that there are multiple systems throughout the body that may experience altered function and the fact that each individual will experience pain in their own way can help a physician in understanding

their patient better and allow them to reach more consistent results through treatment. Keeping an open mind will also allow different specializations in the health care field to work together in targeting all areas that are affected by the process of central sensitization.

**PATHOPHYSIOLOGY**

Central sensitization is a complex process affecting multiple areas of the nervous system from the dorsal horn of the spinal cord to many supraspinal regions. There is no single defining mechanism in the development of central sensitization but the process is instead a series of events that occurs throughout the central nervous system. The process of plastic changes within the nervous system leading to central sensitization and chronic pain can be considered a disease of the nervous system itself. The plasticity of the nervous system allows for the development of chronic pain but should also indicate the possibility of reversal of the condition. There are many biochemical and neurological processes that result from and cause a centrally sensitized state and the basic pathophysiology of this condition will be presented in this review. The activation of NMDA receptors, release of nitric oxide, enhanced release of substance P and excitatory amino acids combined with increased expression of certain neuronal receptors are the best signaling mechanisms that are engaged in central sensitization.(16)

Sensitization of the nervous system begins with sensitization of the peripheral receptors. The process then affects nervous tissue along the path from these sensitized peripheral neurons through the dorsal horn, up the cord, into the brainstem, and through the pain processing centers of the cortex . The major mechanisms that underlie nociceptive central pain are autosensitization of nociceptive receptors, ectopic firing of dorsal root ganglion cells, calcium-induced molecular cascades from excess nociceptor glutamate, phenotypic change of afferent Aβ-fibers and dorsal root ganglion cells to the characteristics of those associated with pain, changes in gene expression of sodium channels and neuropeptides both at nociceptive terminals and at the dorsal root ganglion, and anatomic changes of the superficial layers of the dorsal horn.(3)

Whenever peripheral tissue damage occurs there is a release of neurotransmitters that leads to an inflammatory response which results in tissue healing. If damage is severe or nociceptive input frequent enough then some of these neurotransmitters will be released within the dorsal horn. These neurotransmitters induce gene expression which will result in increased synthesis of peripheral receptors. As this occurs some of the Aβ -fibers will synthesize receptors that are normally only found on C-fibers.(17) The Aβ -fibers will also sprout connections within the dorsal horn to terminate in the superficial laminae which typically only receive innervations from C-fibers. These two processes are responsible for input into the central nervous system from the periphery which results in normally innocuous stimuli being interpreted as potentially damaging and cause the sensation of pain. Structural changes in pain systems occur after injury and are affected by local increased production of growth factors from fibroblasts, macrophages, and lymphocytes which are retrogradely transported back to the dorsal root ganglion and substantia gelatinosa.(3) The neurons in lamina I of the dorsal horn receive input from C-fibers for processing nociception. These areas then send projections to the parabrachial area and periaqueductal gray area of the brainstem. These two areas are associated with affective and autonomic responses to pain and although sensory and psychological aspects of pain are separable the neural pathways that contribute to these aspects of pain are inter-linked.(18) In addition to physiologic changes in leading to central sensitization there are a series of neuroimmune responses that contribute to the process. Hypersensitivity activates immune cells and neuroimmune activation along with cytokine production leads to further expression of pain mediators.(15)

Glutamate is an excitatory amino acid and is a neurotransmitter that is found throughout the entire nervous system which is essential for pain processing at every level.(19) Glutamate is released in the dorsal horn from sensory afferent neurons in response to noxious stimuli. It quickly binds to and activates N-methyl D-Aspartate (NMDA) receptors in the dorsal horn. Activation of the NMDA receptors is an essential step in initiation and maintenance of central sensitization.(1) Normally there is a $Mg^{2+}$ plug on the NMDA channels which requires sustained depolarization of the membrane for its removal. Whenever the $Mg^{2+}$ is released from NMDA receptors an ion channel is opened which allows

$Ca^{2+}$ to flow inward. This process results in activation of intracellular protein kinases and enhanced channel conductance which contributes to prolonged membrane depolarization.(20) Activation of NMDA from repetitive or high frequency nociception results in wind-up within the spinal cord which causes sensitization of the dorsal horn.

Glial cells are the immunocompetent component of the central nervous system and are activated following tissue injury.(21) Whenever glial cells are activated they secrete substances that excite the dorsal horn neurons. Glial cells secrete cytokines, nitric oxide, excitatory amino acids, prostaglandins, and ATP. It has been found that standing chronic pain causes significant activation of glial cells which was most prominent at the level of original injury but extended throughout the entire length of the spinal cord.(21) Glial cells are also known to express chemokines that promote pain sensitivity. Spinal glial cell activation is an important component in the development and maintenance of central sensitization.

Within the supraspinal centers of the central nervous system, brainstem activity contributes to the maintenance of central sensitization and activity in the somatosensory cortex reflects the perceptual consequences of central sensitization.(11) In central sensitization, the spinal dorsal horn initiates input to supraspinal centers which attempt to either facilitate or inhibit the processing of nociception. As these inputs increase or are maintained the output from nuclei within the brainstem activate descending pathways from the rostroventral medulla which enhances nociceptive processing at the level of the dorsal horn and maintains central sensitization.(11) Activity in the somatosensory cortex and anterior cingulate cortex are related to the intensity of pain perception and the increased activity in these cortical areas reflects increased intensity of pain experience with central sensitization.(11) The reticular formation within the brainstem also contributes to the development and maintenance of central sensitization.(7) In states of central sensitization it was found that activation increased in the nucleus cuneiformis, periaqueductal gray area, and superior colliculi.(7) These areas have the ability to participate in bidirectional modulation of pain and can either facilitate or inhibit nociception. Studies using fMRI have detected increased activation in contralateral brainstem, cerebellum, bilateral thalamus, contralateral primary and secondary somatosensory cortices, bilateral posterior insula, anterior and posterior cingulate

cortices, right middle frontal gyrus, and right parietal association cortex in experimentally induced secondary hyperalgesia.(7) Inappropriate cognitions, emotions and behavior like catastrophizing, hypervigilance, avoidance behavior, and somatisation perpetuate the decreased inhibition within the brainstem.(22)

As can be seen, the spinal cord and specifically the dorsal horn is an important area in the process of pain transmission as a site where afferent input and descending facilitation and inhibition meet. In response to significant painful stimuli nociceptive neurons release neurotransmitters in the dorsal horn and these chemicals are known to contribute to the plasticity of the spinal neurons.(16) The plasticity of the nervous system results in alterations in pain processing that is responsible for long standing chronic pain and secondary hyperalgesia. The many varying symptoms found in patients with chronic pain can be explained by the bidirectional connections found between the nociceptive nervous system, the immune system, the sleep regulating system, and the stress regulating system.(23) With such an interrelated connection it is easy to see why patients present with such a wide array of symptoms and conditions that can all be stemming from chronic pain that has resulted in central sensitization.

**DIAGNOSIS**

An accurate diagnosis is of the utmost importance for any patient who enters a health care facility. When diagnosing a patient's condition the physician must obtain accurate and important information from the patient in the form of subjective and objective data. In the case of a patient with chronic pain as a result of central sensitization this diagnosis becomes increasingly difficult when you consider the amount of structures that may be affected and the limited knowledge in thoroughly understanding how the multiple systems of the body influence each other to create the experience of pain. The experience of pain will vary from patient to patient regardless of the severity or similarities between injuries and especially in the case of chronic pain will involve multiple systems that are difficult at times to assess.

Chronic painful conditions can be classified into one of three broad categories for the initial stage of diagnosis: nociceptive pain from tissue damage in the presence of a fully functional nervous system, neuropathic pain where the nervous system itself is damaged, and chronic pain without a known somatic background.(24) Although the cause of chronic pain is difficult to definitively diagnose an attempt must be made to categorize its cause so the most effective treatment can be chosen. Along with the usual and customary intake and evaluation of all patients, a physician must make an extra effort in order to accurately determine the absolute cause of chronic pain which may include performing a more detailed history and examination and the utilization of pain questionnaires.

Although clinical judgment and a thorough patient health history along with a physical examination are the most critical component of patient management, patients with chronic pain require more effort in the diagnosis phase of care. When a chronic pain state is maintained by a dysfunction within the nervous system itself then symptoms may be exaggerated and localized to areas distant from the dysfunctional nerve tissue which necessitates a physician's careful examination of multiple areas including central structures that the patient may believe are unrelated to their condition.

Criteria for clinical classification of suspected neuropathic pain disorders are as follows:(25)

- Definite = Pain located in a neuroanatomical area and fulfilling at least two of the following
    - Decreased sensibility in all/part of painful area
    - Present or former disease knowing to cause nerve lesion, relevant for the pain
    - Nerve lesion confirmed by neurophysiology, surgery or neuroimaging
- Possible = Pain located in a neuroanatomical area and fulfilling at least two of the following
    - Decreased sensibility in all/part of the painful area
    - Unknown etiology
    - Present or former diseases knowing to cause either nociceptive or neuropathic pain, relevant for the pain
    - Radiating pain or paroxysms

- Unlikely = Pain fulfilling at least two of the following
    - Pain located in a non-neuroanatomical area
    - Present or former disease knowing to cause nociceptive pain in the painful area
    - No sensory loss

These criteria can be helpful in initially defining a patient's root cause of pain but are not an endpoint in the diagnosis.

The symptoms of widespread sensory hypersensitivity are a good indication that there are changes in the central nervous systems processing of pain. This hypersensitivity can be found as a result of decreased pain thresholds to pressure, temperature, motion, and other types of stimulation. With the understanding that widespread hypersensitivity is associated with central sensitization it is important to be able to test such hypersensitivity to properly diagnose a patient's condition. One set of testing tools that can be used is pressure algometry and thermal pain threshold measurements. Pressure algometry is a clinical tool that measures pressure pain threshold. This threshold is defined as the minimal amount of pressure that produces pain. An algometer can be used and pressure increased until the patient first notices pain and this level is noted as the threshold. Thermal pain threshold is the temperature that first produces pain. Thermal pain thresholds are much more difficult to measure clinically. These measures are important however because a patient with the presence of both mechanical and cold hypersensitivity may not respond well to physical treatment alone.(26)

Patients who show generalized hypersensitivity earlier after an acute injury are more likely to have persistent moderate to severe pain symptoms in the future.(27) In patients that are at higher risk of developing chronic sensitization it is more important to implement treatment in the early phases of acute pain conditions. This is why questionnaires concerning early symptoms may help further guide diagnosis.

In the case of cervical spine injuries some patients will experience relief of pain while others will continue to have long-term cervical pain which can progress to more widespread hyperesthesia and whiplash associated disorders (WAD). These disorders display symptoms related to central sensitization

and appear to be experienced more frequently in individuals who have injured the deeper musculoskeletal structures of the cervical spine. When comparing normal controls to those with WAD, range of motion testing of the cervical spine differentiates between such individuals.(28) This study showed that patients with WAD had decreased ranges of motion in the cervical spine, especially in the sagittal plane and range of motion was able to significantly discriminate between asymptomatic patients and those with persistent chronic pain.(28) Another study testing poor prognosis to cervical spine injuries found that cervical range of motion loss was the only measure of motor function that could predict higher pain and disability in patients at six months post-injury.(29) This same study also found that cold hyperalgesia and an impaired sympathetic vasoconstrictor response were the strongest sensory variables capable of predicting long term disability from cervical spine injury. These reports suggest that by simply measuring ranges of motion following musculoskeletal injury, a clinician can differentiate between patients likely to develop central sensitization and chronic pain later. Obtaining this information early will allow treatment to focus on decreasing the likelihood of developing abnormal symptoms following injury.

Another factor that can help determine patients who are at risk of developing chronic widespread pain is dysfunction of the hypothalamic-pituitary-adrenal (HPA) system. The HPA system is responsible for responding to stresses upon the body whether they are psychological or physical. Abnormalities in functioning of the HPA axis are associated with an increased risk of developing chronic widespread pain in the future.(30) Failure to suppress this axis and reversal of the normal diurnal rhythm are both associated with this dysfunction. The inability to control stressors accompanied by abnormal cortisol control put a person at risk of developing widespread pain. This is one factor that explains why two people with similar modes of injury and damage to similar structures may have differing symptoms. This also could be an explanation for the fact that some patients will completely recover from an injury while still others will experience chronic pain. When treating patients it is important to consider the functioning of the HPA axis when addressing areas that are in need of treatment to address all aspects of the pain condition. Measuring or calculating the diurnal changes in cortisol will test the functioning of this system and help understand the body's ability to control its normal function.

Following injury to musculoskeletal structures patients differ in their physical and psychological responses to pain. By measuring physical and psychological impairment early in this process it may be necessary to separate patients into subgroups so that the most appropriate treatment can be tailored to the patient even with treatment of acute injuries. If a clinician can predict which patients are at risk of developing chronic symptoms then the appropriate management can begin early in the healing process in an attempt to avoid central plastic processes from leading to central sensitization. A combination of physical and psychological factors along with indicators of age and initial symptom intensity are all important in determining outcome following musculoskeletal injuries.(29) It is important to utilize testing of pain intensity as well as functional disability levels to determine the extent that a patient is affected by their injury. The combination of symptoms and systems affected in a patient require a multi-professional approach to treatment. A patient with high levels of chronic pain and disability, movement loss, sensory disturbances, and psychological alterations following injury will need multiple disciplines within the health care realm to provide a complete treatment program.(29) Early detection of concomitant psychosocial problems is an integral part of treatment of chronic pain and management of psychosocial stressors must be involved in the treatment plan.(24)

A good screening tool is helpful when trying to distinguish the type of pain a patient is experiencing and diagnosing the cause of chronic pain that may be a result of central sensitization. A number of screening tools have been developed for neuropathic pain.(31) These tests include:

- Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)
- Neuropathic Pain Questionnaire (NPQ)
- Douleur Neuropathique en 4 questions (DN4)
- painDETECT
- ID-Pain

All of these tools vary in their sensitivity and specificity, however they are all able to discriminate patients with neuropathic pain from those with other chronic pain conditions.(31) The utilization of

neuropathic pain screening tools allows a physician to further separate patients into sub-groups based on the root cause of their pain so as to more specifically and successfully treat the patient.

Specifically, the painDETECT screening questionnaire is a simple tool that can distinguish neuropathic pain conditions based on a few key symptoms and signs. It also provides information on the cause of a chronic pain condition without the necessity of a physical examination. The questionnaire consists of seven questions, pain description, pain location, and intensity of pain. This tool is simple to use and can reliably predict the likelihood of a neuropathic component to chronic pain conditions.(32) It is simple to use because it can be performed by the patient as part of their intake paperwork and the results do not need any prior physical examination to be accurate.

To more accurately and specifically diagnose neuropathic pain requires expensive equipment that is typically only utilized in laboratories for research purposes. Quantitative sensory testing (QST) allows the tester to determine a patient's minimal stimulus level that provokes a sensation of pain.(33) This type of testing allows for a specifically controlled range of sensory stimulation, a specific timing of stimuli, and allows for quick measuring of the patient's response. QST is not appropriate for use in clinics but has provided information on testing neuropathic pain components in chronic pain states. With QST a clinician is able to test cold versus hot hyperalgesia, pressure pain thresholds, and temporal summation of pain and specifically evaluate the severity of the hyperalgesic state.

Specific diagnosis of a true cause of a patient's chronic pain is both necessary and difficult. The fact that multiple areas from the periphery through the supraspinal pain processing centers including processing of emotions can undergo plastic changes allows for endless possibilities in diagnosis of dysfunction. A clinician is forced to spend more time initially in diagnosis of chronic musculoskeletal pain in order to successfully manage and treat a patient and avoid exacerbation of a central sensitization state through inappropriate input into the system.

## TREATMENT

Information on treatment and the successful resolution of chronic central sensitization is difficult to find. It is known that nervous structures are able to undergo plastic transformation and develop a memory of processing so as to operate in a more efficient manner. Whenever these processes are the cause of chronic pain then the efficiency of the system, although protective initially, becomes the cause of dysfunction. Treatment of such a condition requires both patience and consistency to begin to cause plastic changes within the system for the benefit of the patient. Both the patient and clinician must be absolutely comfortable discussing the course of care and willing to make any necessary changes along the way to most completely resolve symptoms.

The major clinical concern with sensitization of central structures is that the patient will experience peripherally located pain despite the fact that peripheral structures are intact and the true dysfunction is within the central nervous system. This becomes an obstacle of treatment because central structures are difficult to quickly treat with a single modality. Because of the complex pathologic mechanisms and wide variety of patient presentation in chronic pain conditions an optimal and uniform treatment is not easy to develop. For this reason a carefully conducted history and physical exam are the most important tools in clinical practice to assist in diagnosis and development of an appropriate treatment plan. Also, the screening tools mentioned previously are useful in proper diagnosis so that an appropriate course of treatment can begin. Management and treatment of chronic pain requires a strong relationship between the patient and their treating physicians.

Considering the fact that so many structures are affected and can undergo plastic changes within the entire nervous system both peripheral and central structures must be addressed throughout treatment. Initially treatment must focus on removal of the peripheral injury that began and may be perpetuating the sensitization process. Once this issue is controlled then the central structures which include emotions and affect must be treated to fully reverse or halt the process of sensitization and the fear of continual pain.

The biopsychosocial model of pain considers the bidirectional relationships in chronic pain conditions between biologic, psychologic, and social factors and accounts for the multiple influences of chronic pain states.(34) Treatment therefore requires multiple specialties within the health care field all working together to address all of these areas. A multidisciplinary approach to care of chronic pain conditions is an absolute necessity. This approach requires a physical medicine component that provides comprehensive musculoskeletal examinations considering postural and motion imbalances along with a psychologic component that assesses the emotional state as it relates to pain sensitivity.(34)

One important key in developing treatment for a patient with known secondary hyperalgesia is ensuring that whichever treatment protocol is utilized the treatments must not induce any pain for the patient. A central nervous system that is sensitized to many types of input will not be able to revert back to a normal state with continual nociceptive input. Any technique that causes nociceptive stimulation will likely result in pain amplification which will only enhance and perpetuate the underlying disorder causing chronic pain. To this end it is important that a comprehensive treatment program allows for open communication between the patient and physician and regular adjustments in treatment protocol to allow gradual gains in symptom control.

There are multiple modes of treatment to address symptoms of chronic pain caused by central sensitization and patients who have been in pain and have had multiple therapies fail in the past are generally willing to try any form of treatment if they believe it will decrease pain. This will include medication, surgery, manual medicine, alternative approaches to therapy, and eastern medicine. The most appropriate treatment type must be utilized and a physician who has a basic knowledge of these areas and the willingness to refer to and consult with multiple professionals is best suited to treat and manage the care of a patient with central sensitization.

According to one study, central sensitization can be prevented or treated by the following approaches: block or reduction of the nociceptive input from the injured areas, specific pharmacological intervention on the cord mechanisms, pharmacologic or psychologic interventions at supraspinal level and descending modulatory system.(9) This article does not consider manual methods for the reduction of

centrally sensitized structures within the musculoskeletal system. The inclusion of manual medicine with this multidisciplinary approach would cover all areas of potential dysfunction through comprehensive treatments.

Manual therapy is an important part of the thorough treatment of patients with chronic pain and central sensitization from injury to musculoskeletal structures. Specifically manual therapy is important to halt progression of an acute injury into secondary hyperalgesia by treatment of acute damage to prevent central sensitization from occurring, finding and preventing processes involved in development of central sensitization in subacute conditions, and as a part of the comprehensive management involving multiple divisions of the health care system to manage patients who have a central sensitization disorder.(22)

Considering conditions where muscle or joint control is incongruent with central processing such as in arthritic conditions and musculoskeletal injuries it is important to manage the dysfunction in motion to minimize abnormal afferent input. Home exercise routines can be given to patients, however without a trained and skilled practitioner to provide guidance the desired effect of normal motion may not be achieved. One study found that there was a difference in symptom relief when comparing groups of patients with hyperalgesia following whiplash associated disorders. The study compared a group of patients receiving a multimodal physical therapy program with a group treated with a self-management program consisting of at home exercises and found that improvement in the pattern of muscle control was only evident in the group exercising under the guidance of a therapist.(35) The therapy program consisted of low load exercises to re-educate muscle control, exercises to retrain kinesthetic sense, and low velocity mobilizing techniques of involved structures and all therapies were performed at a intensity that did not produce pain. Another key finding was that a sub-group of patients with both widespread mechanical and cold hyperalgesia had the least improvement in pain and disability compared with the group with widespread mechanical hyperalgesia alone.(35) This may indicate that the presence of both mechanical and cold hyperalgesia indicates a poorer response to manual therapy alone. It also reiterates the importance of classifying patients before beginning a generic trial of care.

Since many chronic pain conditions may be maintained by plastic changes to the central nervous system, interventions that can favorably affect central pain processing are desirable in such conditions. One such form of treatment is spinal manipulative therapy that has the potential to positively alter afferent input into the cord. One study found inhibition of temporal summation but not of Aδ-fiber pain perception was found immediately following spinal manipulative therapy which suggests modulation of dorsal horn excitability.(36) This effect was found following spinal manipulative therapy and not following riding a stationary bicycle or performing back extension exercises alone. Spinal manipulative therapy affects the dorsal horn by inhibiting temporal summation which decreases the continuous nociceptive input into the cord and may effectively alter the neuroplastic changes associated with central sensitization and provide counter-irritation in the cord.(36) This effect was found to be a local one and only effected the immediate area and dermatomes related to the area of manipulation. Specific manipulation to the spine can affect the dorsal horn and central structures and this is beneficial when sensitization within the dorsal horn is determined to be a cause of hyperalgesia, especially in the early stages of pain processing.

Exercise in a normal healthy individual should result in decreased pain sensitivity for a period of time following the activity. In patients with conditions associated with widespread hypersensitivity there may be an opposite response to exercise. Patients with fibromyalgia and known hypersensitivity are found to experience decreased pressure pain thresholds following isometric exercise.(37) These effects were found to be on the ipsilateral and contralateral exercised extremity. It is not known whether this is a result of deficient inhibition or enhanced pain facilitation. Regardless, a clinician should use caution with generically prescribing exercise to patients experiencing chronic pain.

Exercise is also important in re-training muscle control and improving the central processing of matching motor control with sensory feedback. Joint hypermobility is known to cause microtrauma and results in increased nociceptive input into the central nervous system.(22) Exercise programs must be carefully implemented with the understanding that muscle nociceptors are highly susceptible to ischemia and patients at risk for development of chronic pain related to central sensitization must gradually

increase the intensity of exercise to minimize the risk of causing widespread muscle ischemia. Patients with diagnosed chronic fatigue syndrome have symptoms related to central sensitization which includes lowered pain thresholds. One study compared the post-exertional pain thresholds following graded treadmill exercise and found that a group of control patients had increased pain threshold while patients with chronic fatigue showed decreased threshold even though there was not a significant difference in thresholds between the groups before exercise.(38) This shows a dysfunction in the central pain processing mechanism in certain conditions and is another example of why specific treatment programs must be developed.

The most appropriate course of treatment of chronic pain conditions related to central sensitization should incorporate multiple specialties and modalities. Treatment may involve nonpharmacological therapies, pharmacological therapies, as well as personal interventions. In early musculoskeletal pain conditions it is important to initiate mobilization and physical therapies the manage symptomatology. Patient education and psychological interventions may also be important, especially in a population of patients who are at risk of developing chronic pain syndromes. First-line pharmacological agents for treating neuropathic pain conditions includes tricyclic antidepressants, gabapentin, topical lidocaine, tramadol, and opiods.(39) These agents may be absolutely necessary for the treatment of established central sensitization and research is continually testing medications and their effectiveness in targeting the central nervous system. One article that reviewed central pain states that treatment is difficult and lists basic principles of treatment as elimination of initial nociceptive input, use of nonsteroidal anti-inflammatory drugs, use of tricyclic antidepressants, use of other prescription medications to control pain, dorsal column stimulation, along with intrathecal therapies.(3)

When managing a patient with coexistent physical deconditioning, insomnia, and psychological comorbidity it is important to be direct with the patient about what to expect with treatment and what the physician expects from them in managing their own condition. Frequent reassessment is critical in appropriate management. Nonpharmacological management of chronic pain patients always requires an open relationship between the patient and physician to avoid increasing symptoms and frustration of both

the doctor and patient. Another confounding factor in management of chronic pain is that many patients with chronic pain have a decreased sleep schedule and every effort should be made to normalize the patients sleep pattern.(39) Loss of sleep and un-rest at night may be responsible for perpetuating the condition.

Treatment of widespread pain that has progressed into a chronic state and is maintained by central sensitization will always be difficult to manage. One problem comes when one of the initiating triggers of pain is a specific injury and the patient and physician continually treat the initial area as the source of continuing pain. This can result in expensive and frustrating management with poor outcomes and management of such conditions requires a proper diagnosis followed by patient education, mechanism target pharmacologic treatment, physical management, and psychological therapies.(40)

In an effort to be comprehensive in managing patients with chronic pain all components of pain must be addressed including the physiology, sensory, affect, cognition, and behavioral components involved. The only way to effectively treat patients with symptoms of central sensitization leading to chronic pain is to be a persistent physician which includes taking a complete history, thorough physical exam, development of a comprehensive treatment plan, and following up with the patient to constantly assess treatment adherence and effects.(12)

Manual therapy including manipulation, mobilization, massage, and neural dynamics are responsible for biomechanical and neurophysiological effects that control pain. A mechanical stimulus in the form of manual therapy is capable of initiating neurophysiological effects that are responsible for the outcomes associated with manual therapy.(41) One important factor in deciding to utilize manual therapy in the treatment of chronic pain is that there are many different techniques that can be used. Although the mechanism of pain control from manual therapy is not well understood, it is known that the choice of technique is not as important as identifying an individual who is likely to respond to such treatment.(41) Manual therapy has been shown to create both a mechanical and neurophysiological response that affects the peripheral, spinal, and supraspinal mechanisms in pain control and production.(41) Despite the fact

that these responses aren't well understood in the literature, there appears to be an opportunity to positively treat all areas involved in both peripheral and central sensitization to chronic pain.

It can be difficult to know when or how to continue with manual therapies in a patient with chronic pain when treatment has not eliminated the pain or the patient feels that they are not getting any significant relief. All patients will not reach a pain free level of therapy or even a pre-injury state of functioning however a goal should be to achieve optimal functioning based on the patient and their needs. In the realm of manual medicine it is important to focus on functionality rather than pain status, especially in patients with chronic pain related to central sensitization. An appropriate strategy for managing such patients is to focus on changes in a validated functional outcome measure when treating musculoskeletal pain.(42) Regular review of functional improvement allows the physician to determine if the working diagnosis and treatment are appropriate or if another specialty should be consulted in the patient's comprehensive care.

Another method of treatment in controlling pain is acupuncture and electroacupuncture. One study found that secondary hyperalgesia caused by experimentally induced central sensitization could be controlled through the use of electroacupuncture to specific points.(43) This study found that the effects were specific to controlling secondary hyperalgesia and not primary hyperalgesia. If it is determined that the patient's condition is the result of centrally maintained hypersensitivities then acupuncture may be able to specifically target these structures in decreasing sensitization. Acupuncture provides a non-invasive form of treatment for targeting central structures in the management of chronic pain.

Therapies and treatment of central sensitization following musculoskeletal injuries must specifically address the dysfunctional area responsible for the experience of chronic pain. No specialty or physician has been able to successfully treat every patient the same and achieve optimal results. The differences from one patient to the next will require differing treatment protocols and each physician must be willing to evaluate progress and make regular necessary changes to optimize results. Considering the fact that manual medicine and spinal manipulative therapy have relatively low side effects when utilized properly in the appropriate patient they are an excellent source of treatment of chronic pain conditions.

Central structures are critical to address through treatment and spinal manipulative therapy can positively affect such structures which can result in improvement without the need for invasive procedures. Manual medicine that solely concentrates on peripheral structures and does not look to assess spinal structures associated with pain will not provide the treatment necessary to affect central structures involved in the process of central sensitization.

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