

## Biomarkers for Chronic Neuropathic Pain and Their Potential Application in Spinal Cord Stimulation (SCS) Therapy

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### Abstract

Chronic neuropathic pain disorders represent a common long-term disability globally. Its treatment has limited success because of its poorly understood mechanisms. Moreover, the effectiveness of neuropathic pain management regimens and procedures have been difficult to determine to date, due to the subjectivity related to pain perception, and a lack of standardized assessment of neuropathic pain. However, one of the most effective and popular management strategies of chronic neuropathic pain in recent times is spinal cord stimulation (SCS), a form of neuromodulation. This review aims to understand which substances inside the human body increase and decrease with increasing neuropathic pain. Through identifying those biomarkers and finding correlations between neuropathic pain and those components, we would like to apply our knowledge to develop a biomarker profile which will ultimately help to see prognosis or predict success of spinal cord stimulation therapy in patients suffering from chronic neuropathic pain.

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### Introduction

The latest report from International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage”, while chronic neuropathic pain is defined as “pain caused by a lesion or disease of the somatosensory system”, which represents a broad category of pain syndromes encompassing a wide variety of peripheral or central disorders.<sup>1-3</sup> Clinically, neuropathic pain syndromes are characterized by the combination of positive and negative phenomena. The positive phenomena include various painful symptoms, paresthesia and/or dysesthesia, which, by definition, are abnormal nonpainful sensations (e.g., tingling, numbness, pins and needles), while negative phenomena usually include neurological sensory deficits in the painful area, together with other deficits (motor, cognitive etc.), depending on the location of the lesion.<sup>3</sup> Chronic neuropathic pain disorders represent a common long-term disability globally; however, the lack of accurate

prevalence and incidence data result from broad heterogeneity of NP studies, differences in definitions and evaluation methods used.<sup>4</sup> Nonetheless, several epidemiological studies have shown that their prevalence in the general population may be 1 to 10%, and accounting for 20 to 35% of individuals with chronic pain syndromes.<sup>3-11</sup> Chronic neuropathic pain treatment has limited success because of its poorly understood mechanisms.<sup>1</sup>

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Moreover, the effectiveness of neuropathic pain management regimens and procedures have been difficult to determine till to date, due to the subjectivity related to pain perception, and a lack of standardized assessment of neuropathic pain.<sup>3,4,12,13</sup> Pharma industries strive continuously on development of new molecules to control neuropathic pain; symptoms also improve by available drug treatments. However, tricyclic antidepressants (TCAs), Calcium channel  $\alpha_2\delta$  ligands, common analgesics and opioids carry significant adverse events, if they are used as long-term therapy.<sup>14,15</sup> Among the latest alternative options are lesional surgery at the dorsal root entry zone or a number of neuromodulation procedures.<sup>15-17</sup> However, one of the most effective and popular neuromodulation management strategies in recent times is spinal cord stimulation (SCS) therapy, which is able to actually decrease neuropathic pain in many syndromes such as in failed back surgery syndrome (FBSS), complex regional pain syndrome (CRPS) type I and II, postherpetic neuralgia and pure radicular pain.<sup>17-20</sup> One consensus on pathophysiology of chronic neuropathic pain is that pain is caused often by inflammation and/or nerve injury, which invariably relates to biological expression of cytokines, neurotransmitters, and structural proteins.<sup>15,21</sup> Hence, there must be changes in some of the biomarkers levels associated with neuropathic pain before and after SCS therapy. This review aims to understand which substances inside the human body increase and decrease with increasing neuropathic pain and act inversely in spinal cord stimulation (SCS).

### **Spinal Cord Stimulation (SCS) Therapy**

Advanced modalities for the treatment of chronic pain like neuromodulation has developed rapidly since the evidence on the electrical inhibition of

pain by the stimulation of the dorsal column which was published almost 55 years back.<sup>22</sup> In traditional practice of SCS therapy, the objective is to replace the pain sensation with paresthesia that requires mapping of stimulation to the specific region of pain.<sup>15,22</sup> The anticipation is that the electrical current alters pain processing by masking the sensation of pain with a comfortable tingling or paresthesia. The stimulation is provided either through electrodes that are placed percutaneously into the epidural space or through a surgical paddle lead that is delivered via a laminotomy.<sup>17,19,23,24</sup> These devices deliver stimulation frequencies between 2 and 1200Hz; however, in most cases, frequencies have been utilized at 40-60Hz.<sup>17,19,23,24</sup> Patients typically undergo a trial of such neuromodulation with an external power source and if the trial proves to be positive and compelling, they subsequently have a subcutaneously implanted pulse generator (very similar to a pace-maker) for the long-term therapy.<sup>23,24</sup> While it is generally believed that spinal cord stimulation inhibits pain transmission in the dorsal horn, the exact mechanisms by which SCS relieves neuropathic pain is unknown.<sup>15,23,24</sup> However, the main goals of spinal cord stimulation are to improve physical function and quality of life.<sup>18,24</sup>

### **Biomarkers Associated with Chronic Neuropathic Pain**

Current advanced research suggests that different biomarkers e.g., cytokines, either positively or negatively correlate with the chronic pain phenomena.<sup>21,25</sup> However, that negative or positive correlation mainly depends on the characteristics of the cytokines.<sup>25</sup> Cytokines are signaling proteins, either pro-inflammatory or anti-inflammatory in nature, and they help mediate activation, differentiation, and proliferation of the immune cells.<sup>25</sup>

Table-I below shows important roles played by different biomarkers: pro-inflammatory cytokines such as IL-1 $\beta$ , IL-6, IL-2, IL-33, CCL3, CXCL1, CCR5, and TNF- $\alpha$ , and anti-inflammatory cytokine, IL-4, and the CCL3-neutralizing antibody, as found in different literature.<sup>26-36</sup> We know that the immune system depends on the balance between pro-inflammatory and anti-inflammatory forces.<sup>25</sup> Higher levels of pro- and lower levels of anti-inflammatory cytokines have been demonstrated in patients with chronic neuropathic pain conditions.<sup>26-36</sup> Given that fact, it is assumed that SCS therapy reverse the situation, i.e., increase the levels of anti- and decrease pro-inflammatory components.

**Table-I:** Role of different biomarkers in chronic neuropathic pain<sup>26-36</sup>

Cytokines/ Chemokines	Pain	Diagnosis
TNF- $\alpha$	Increased	Neuropathic Pain/CRPS Fibromyalgia
IL-1 $\beta$	Increased	Tension Headache Neuropathic Pain/CRPS
IL-2	Increased	Neuropathic Pain/CRPS
IL-6	Increased	Fibromyalgia Neuropathic Pain/CRPS Tension Headache Chronic Constriction Injury
IL-8	Increased	Fibromyalgia Tension Headache
IL-33	Increased	Chronic Constriction Injury
CXCL1	Increased	Chronic Constriction Injury
CCL3	Increased	Chronic Constriction Injury
CCR5	Increased	Chronic Constriction Injury
IL-10	Decreased	Neuropathic Pain/CRPS Fibromyalgia
IL-4	Decreased	Neuropathic Pain/CRPS

## Conclusion

Evidence suggests that chronic pain either inflammation-induced or nerve injury-induced can be mobilized by the application of the spinal cord

stimulation (SCS) therapy. From above-mentioned roles of the biomarkers, we assume that during the SCS procedure, there is a relative reduction of some of the pro-inflammatory cytokines, while some of the anti-inflammatory cytokines increase. Observing those biomarkers levels in the body will ultimately help to see prognosis or predict success of spinal cord stimulation (SCS) therapy in patients suffering from chronic neuropathic pain.

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