

## **Drug Treatment of Neuropathic Pain in Patients with Spinal Cord Injury**

**Abdullah Erman Yagiz<sup>1</sup>, Nilgul Ustun<sup>1</sup>**

1. Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Mustafa Kemal University, Hatay, Turkey

Corresponding Author: Abdullah Erman Yagiz

Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Mustafa Kemal University, Hatay, Turkey

E-mail: ermanyagiz@gmail.com

### **Abstract**

Neuropathic pain develops as a result of a lesion or a disease in somatosensory nerve system. It can develop over one-half of the patients with spinal cord injury (SCI). It can be classified into 3 categories as follows: pain below the level of lesion, at the level of lesion and above the level of lesion. In these patients, treatment is directed to available symptoms, findings and underlying mechanisms. The most commonly used agents include antidepressants, anticonvulsants and opiates. In the present manuscript, we will provide literature data about the effects of these agents on neuropathic pain observed in patients with SCI.

**Keywords:** Spinal cord injury, treatment of neuropathic pain.

### **Introduction**

Neuropathic pain develops due to a lesion or disease of the somatosensory nerve system. It occurs over 50% of the patients with spinal cord injury (SCI) (1,2). The patients suffer from a sharp, throbbing and burning pain. Neuropathic pain can be classified into 3 categories in the context of localization of lesion in patients with SCI. a) Pain below the level of lesion: Pain is experienced at diffuse and local regions with sensorial denervation below the level of spinal injury. b) Pain at the level of lesion: The pain is located at normal margins of adjacent 2-4 segments at the level of injury or at denervated band. c) Pain above the level of lesion: Pain is experienced at the preserved regions with sensorial innervations above the level of spinal injury (3,4).

Frequently, the management of neuropathic pain is challenging and requires a distinct approach than

nociceptive pain (5). The goal of the therapy should be to relieve available symptoms and signs, and it should be directed to underlying mechanisms. The majority of the recommended drugs are adjuvant analgesics in which analgesia is not primary indication, including antidepressants, anticonvulsants and opiates (5,6).

### **Antidepressants**

Tricyclic antidepressants are frequently used in the management of pain disorders. Their therapeutic activity is based on the inhibition of presynaptic norepinephrine and serotonin reuptake (7). In addition, these agents antagonize N-methyl-D-aspartate receptors (8). They also have antagonistic effects on cholinergic, histaminergic, alpha-1-adrenergic and serotonergic receptors (6).

There are studies regarding amitriptyline, a tricyclic antidepressant, in the management

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of neuropathic pain seen in patients with SCI. In a randomized, double-blinded, placebo-controlled study, no improvement was reported by 6-weeks amitriptyline therapy (10-125 mg per day). This outcome was attributed to low dose of amitriptyline and inadequate assessment of neuropathic pain (9). In another randomized, double-blinded, placebo-controlled study, the effectiveness of amitriptyline was compared to placebo and gabapentin. A moderate effectiveness was found only in a subgroup of patients with depressive symptoms, which was linked to antidepressant activity of amitriptyline (10). Adverse effects developed in both studies, including dry mouth, constipation, aggravated spasticity and dysuria (11). In conclusion, it has been suggested that amitriptyline is effective in only depressive patients in the context of pain management after SCI (12).

Trazodone, a selective serotonin reuptake inhibitor, has less anti-cholinergic and cardiovascular adverse effects when compared to non-selective amitriptyline. It was failed to show a significant effectiveness in the management of SCI-related burning sensation and paresthesia in a double-blinded, placebo-controlled study (13). In a randomized, double-blinded, placebo-controlled study on duloxetine, a selective serotonin-norepinephrine reuptake inhibitor, a significant improvement was detected in allodynia, while no significant improvement was demonstrated in tactile and pressure pain as well as pain intensity (14).

**Anticonvulsants**

Although gabapentin is an analogue of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, it has been found that it has no effect on GABA receptors. It exerts its effects by modulating synthesis and release of GABA in brain; high affinity for calcium channels; inhibition of sodium channels;

and alteration in neurotransmitter levels (6).

In a prospective, randomized, double-blinded, placebo-controlled study on gabapentin including 20 patients with SCI, it was found that gabapentin decreased the pain frequency and intensity as well as improved quality of life. In that study, gabapentin was titrated up to 3600 mg per day (15). In another prospective, randomized, double-blinded, placebo-controlled study, 7 patients were included. A significant decrease was found in pain intensity and burning sensation, while no significant difference was found in other pain parameters. In that study in which gabapentin dose was escalated up to 1800 mg per day, the negative outcome was attributed to smaller sample size and low maximum dose titration (16). Gabapentin was not found to be more effective than placebo in a randomized, double-blinded in which amitriptyline, gabapentin and placebo were compared (10). In these studies, the most frequent adverse effects included somnolence, asthenia, dizziness, gastrointestinal disorders, dry mouth, weight gain and peripheral edema (11).

Pregabalin is GABA derivative which is related to gabapentin in structural manner; thus, it has close pharmacological profile and similar anticonvulsant and analgesic activity with gabapentin. The predominant mechanism of action is to decrease release of neurotransmitters such as glutamate, substance P and calcitonin gene-related peptide by binding presynaptic calcium channels. This attenuates neuronal hyperexcitability and causes abnormal synchronization. Thus; anticonvulsant, analgesic and anxiolytic activity occur (5).

In a multi-center, placebo-controlled study on 137 patients with SCI by using 150-600 mg per day pregabalin, it was found that pregabalin was effective in neuropathic pain and caused improvement in sleep, anxiety and general health status of the patients. The most commonly observed

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adverse effects included mild to moderate somnolence and dizziness (17). In another randomized, double-blinded, placebo-controlled study on 40 patients, a clinically significant decrease in pain and an improvement in health status were observed by pregabalin (150-600 mg per day). The most frequent adverse effects were dizziness, reduced intellectual performance, somnolence and nausea. The incidences of these adverse effects were in a range from mild to moderate and no significant difference was found between treatment groups regarding adverse effects (18).

In a double-blinded, placebo-controlled study, 20 patients with SCI were treated by valproate (600-2400 mg per day). However, no significant improvement was found in chronic central pain. Dizziness was observed in 4 patients, while gastroenteritis occurred in one patient after 2-weeks treatment (19). In a randomized, double-blinded, placebo-controlled study on lamotrigine, it was found that lamotrigine (200-400 mg per day) improved pain exclusively in a subgroup of patients with incomplete SCI. Vast majority of the patients well tolerated lamotrigine, while cutaneous rash occurred in one patient (20). In a randomized, double-blinded, placebo-controlled study on levetiracetam, an anti-epileptic agent, including 36 patients, it was found that there was no significant decrease in neuropathic pain and spasm intensity after SCI (21).

**Opiates**

The studies on effectiveness of opiates in neuropathic pain in SCI patients are limited. Morphine, an opium derivative, exerts its analgesic effect by binding and activating mu receptor (12). In a double-blinded, placebo-controlled study, it was found that morphine (0.3 mg/kg) decreased the affective component of pain (22). In

another double-blinded, placebo-controlled study, it was found that morphine (9-30 mg per day) decreased brush-induced allodynia, while it had no effect on other stimulated pain such as mechanical or thermal allodynia/hyperalgesia (23). In a double-blinded, placebo-controlled study, it was reported that alfentanil markedly decreased persistent and stimulated pains (24). In a study in which the effectiveness of high (8.9 mg per day) and low (2.7 mg per day) doses of the potent opioid levorphanol were evaluated, the decrease in the intensity of neuropathic pain by high dose was found to be significant when compared to low dose. However, higher complication rates including personality disorders, fatigue, confusion and dizziness was found in the high dose group (25).

**Conclusion**

The neuropathic pain in patients with SCI is an important complication which has a significant impact on function and quality of life. It seems that gabapentin and pregabalin are the most effective agents among those used in the treatment. Amitriptyline, a tricyclic antidepressant, can be recommended in patient having a depression component. Care should be taken to use opiates in the treatment of chronic pain such as neuropathic pain due to its addiction potential and adverse effects, which are effective in the management of acute pain. In patients with SCI, there are limited numbers of studies evaluating management of neuropathic pain; thus, further studies are needed in this issue.

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