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Systematic Review

An evaluation of gabapentin and pregabalin usage in the treatment of neuropathic pain related to spinal cord injury

Yasin Emre Kaya

Abant Izzet Baysal University Faculty of Medicine, Department of Orthopaedic and Traumatology, Bolu, Turkey

Abstract

Aim: In the present study, we aimed to systematically evaluate the effects of gabapentin and pregabalin, which are believed to be safe and well-tolerated and have analgesic, anticonvulsant, and anxiolytic effects, in the treatment of neuropathic pain after spinal cord injury despite their high side effect profiles.

Material and Methods: A literature search of numerous electronic databases was performed. A combination of key words was used to retrieve studies published until November 1, 2018 correlated with the point of interest. The key words used were as follows: "spinal cord injury," "neuropathic pain," "gabapentin," and "pregabalin." Studies that met the inclusion criteria and were Level of I clinical trials were included in the study. The included studies were statistically evaluated.

Results: In total, 125,515 publications were retrieved using the aforementioned key words. 19 studies on the use of gabapentin and pregabalin for the treatment of neuropathic pain associated with spinal cord injury were retrieved through.

Conclusion: Studies suggested that available treatment modalities did not provide satisfactory outcomes for patients with neuropathic pain related to spinal cord injury. However, gabapentin and pregabalin were preferred as the first-line drugs in the treatment of neuropathic pain. The efficacy of gabapentin in the treatment of neuropathic pain after spinal cord injury has only been investigated in a few recent studies; data in these studies are not sufficiently clear and will need further clarification.

Keywords: Gabapentin; Neuropathic Pain; Pregabalin; Spinal Cord Injury.

INTRODUCTION

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage (1).

Primarily by orthopaedic surgeons and other spine surgeons cannot consider the pain of patients as real pain in situations when they do not detect an objective finding and may explain its presence by psychological reasons. However, pain perception may vary according to many factors, such as sex, religion, language, race, and sociocultural environment, and it may be encountered at different thresholds that vary from person to person. The quality of life of patients may be adversely affected by chronic pain, and this may cause economic losses due to the loss of millions of working days each year (2).

Pharmacological therapy has a beneficial effect on 75–85% of patients receiving pain treatment. The choice of analgesic agents should be made in accordance with the severity of the pain and stepwise treatment principles. According to the World Health Organization's stepwise treatment procedure (3), non-steroidal anti-inflammatory drugs and acetaminophen are included in the primary treatment of pain. If pain control cannot be provided or pain cannot be treated with these agents, weak opioids and second-line drugs, such as codeine and tramadol, can be added to the therapy. When pain control is still not achieved, the pain treatment may be continued with strong opioids, such as fentanyl and morphine. Non-analgesic adjuvant drugs, such as antidepressants, anticonvulsants, neuroleptics, corticosteroids, and anxiolytics, may also be added (3).

Invasive therapies may be applied to patients when pain control cannot be achieved with current pharmacological treatment. These methods include stellate and sphenopalatine block, lumbar sympathetic block, celiac and splanchnic block, superior hypogastric block, thoracic block and ganglion impair block. Furthermore, various invasive techniques, such as facial median nerve blocks, epidural and spinal blocks, transforaminal injections,

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Corresponding Author: Yasin Emre Kaya, Abant Izzet Baysal University Faculty of Medicine, Department of Orthopaedic and Traumatology, Bolu, Turkey, **E-mail:** yemrek@hotmail.com

peripheral nerve blocks, facet block with radiofrequency thermocoagulation, radiofrequency thermocoagulation to the dorsal root ganglion, intradiscal radiofrequency thermocoagulation, and port-pump systems, can also be included (4).

However, a tolerance to analgesic drugs, one of the pharmacological treatment modalities, may sometimes develop (5), and recovery may not be achieved with pharmacological treatments or invasive techniques. Despite the availability of innovative medical treatments, progress in pharmacotherapy has been limited (6). For these reasons, researchers continue to focus on novel pain control methods.

Research into the use of different drugs has gained momentum due to the inability to control chronic pain with current analgesics and also the side effects of analgesics, such as tolerance, dependence, gastrointestinal dysfunction, cognitive impairment, and the narrow therapeutic window (7).

The discovery of the cannabinoid (CB) receptor in the rat brain has taken its place within these novel studies. CB agonists and antagonists are believed to play a significant role in the field of CB pharmacology and physiology, so studies have begun to focus on this matter. In parallel with progress being made with allosteric ligands, the endocannabinoid (ECB) system has emerged as a major modulator of many physiological processes and has gained popularity as a result of the development of highly specific and potent orthosteric ligands. The role of the ECB system, particularly in regard to medical cannabis, in human physiology has been investigated through pharmaceutical chemistry and pharmacomolecular studies (8).

Fowler et al. investigated the pharmacology of the ECB system and reported that knowledge of this system and its physiological effects had greatly increased (9). They suggested that topical CB1 and CB2 agonists might be therapeutically useful, and that the non-steroidal anti-inflammatory agent indomethacin produced effects secondary to the activation of the ECB system (9). Subsequently, it was reported that oleamide had the same painkiller effects as anandamide, based on the fact that the oleamide enzyme, a fatty acid amide hydrolase inhibitor, could degrade oleamide to anandamide, which influences the nutrients' endogenous anandamide levels (10).

Preclinical and clinical studies using cannabis-related treatment have been reported to produce both analgesia and anti-inflammatory effects with a relief of clinical symptoms in animal models of arthritis (11). However, researchers have emphasized that the progress in the cannabis-based therapeutics is in its initial stages, and further research is required to determine the efficacy and safety profile in patients (11).

Many studies have suggested that the ECB system affects physiological processes, including pain feeling, motor control, recall and learning, immune and inflammatory responses, and nerve protection (12–15). In parallel with the aforementioned studies, research has also been carried out on CBs and the ECB system in the treatment of spinal cord injury (SCI), a devastating disease which has no standard treatment (16–19).

The ECB system has been reported to be expressed in the intact spinal cord and is significantly up-regulated after spinal cord damage (16-19). Moreover, some studies have suggested that endogenous activation of this system prevents secondary damage after SCI, and treatments with ECBs or synthetic CB receptor agonists render much better functional outcome in experimental models (16-19).

The present study aimed to systematically evaluate the effects of gabapentin (GBP) and pregabalin (PGB), which are the preferred pharmacological agents in clinics despite their high side effect profiles, in the treatment of pain related to SCI. The goal was to provide information on the treatment of the pathology causing central neuropathic pain (NeP) secondary to SCI and the recovery of potentially lost functions.

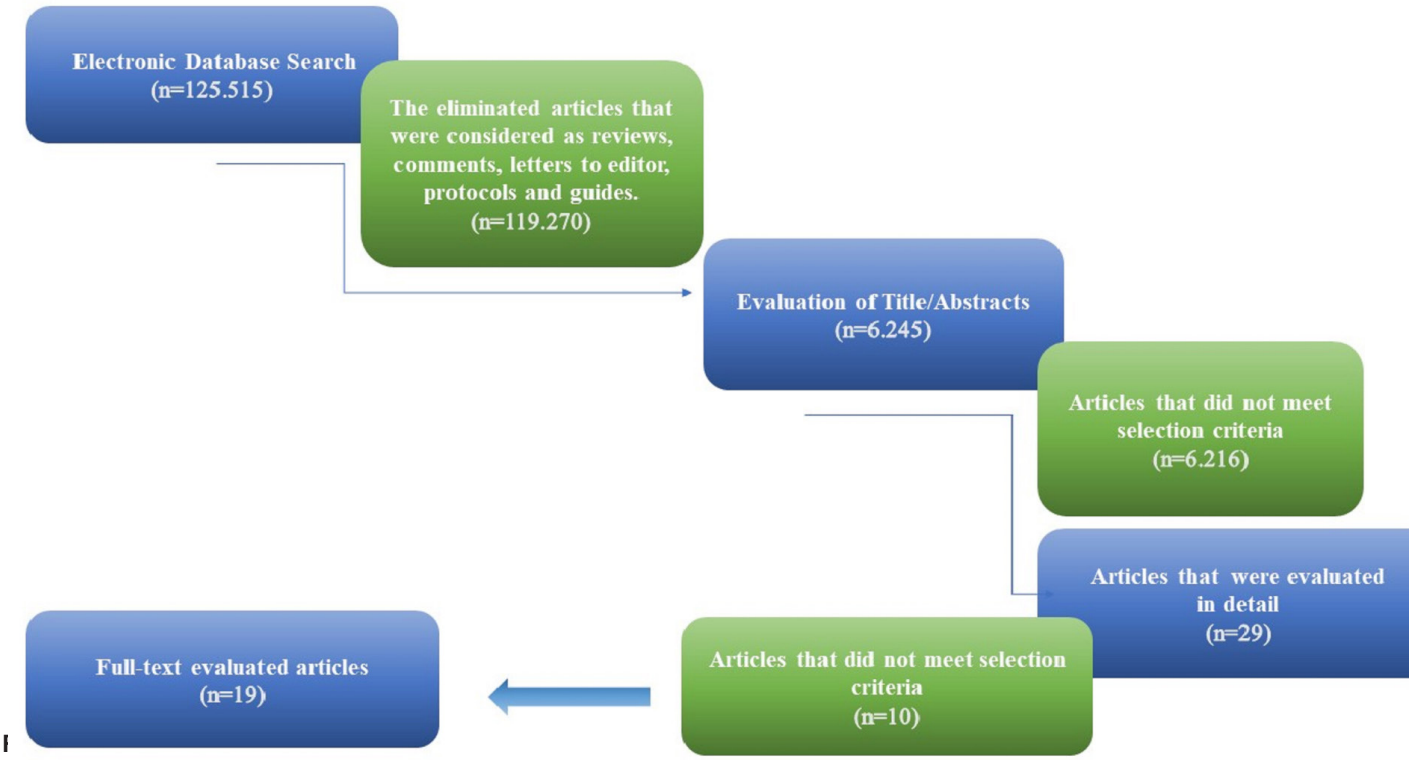
MATERIAL and METHODS

A broad literature search of numerous electronic databases, including Cochrane Collaboration, Cochrane Library, Ovid, Medline, ProQuest, the National Library of Medicine at the National Institutes of Health, and PubMed, was performed. A combination of key words was used to retrieve studies correlated with the point of interest. The keywords used were as follows: “spinal cord injury,” “neuropathic pain,” “gabapentin,” and “pregabalin.”

The headings and abstracts of all studies on the use of GBP and PGB in the treatment of central NeP secondary to SCI were reviewed. The full texts of the appropriate studies were retrieved according to the headings and abstracts, and then the decision of whether to include or exclude these studies was made after a comprehensive review (20–22).

Letters to the editor, bibliographies, reviews, and meta-analyses were excluded from the study. Critical appraisal checklists were used to assess and analyze the quality of the selected studies. Evaluations performed independently by the authors were compared (20–23), and then a consensus was reached by the authors. Next, the obtained data were summarized, and the findings were compiled in a clear and understandable manner using tables. The present study was performed using the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (20-25).

The screening process of the studies that did not meet the inclusion criteria and therefore were left out of our systematic review is presented in Figure 1.



RESULTS

We retrieved 67,655 publications using the keyword "spinal cord injury (SCI)." In addition, 41,118, 6,198 and 3,151 studies were retrieved using the key words "neuropathic pain," "gabapentin," and "pregabalin," respectively. Of the studies performed before 1 October 2018, the date of the oldest study was 9 January 2002.

Nineteen studies on the use of GBP and PGB in the treatment of NeP associated with SCI were retrieved from electronic databases (26–33, 35–40). However, these studies, the full texts of which were reviewed, did not meet the inclusion criteria, and they were not Level -1 clinical trial or studies. Therefore, a statistical assessment was not performed, but descriptive results were presented (Table 1).

DISCUSSION

NeP was first defined as pain triggered or induced by a primary lesion or dysfunction in the peripheral or central nervous system by the International Association for the Study of Pain in 1994. It is currently defined as pain emerging as a direct result of a wound or disorder affecting the somatosensory system (6, 41). In the clinical field, PGB and GBP, which reduce the release of presynaptic transmitters by binding to the voltage-gated calcium channel alpha-2-delta-1 (α2δ-1) subunit, are frequently prescribed for the treatment of central NeP after SCI. Although these pharmaceuticals are designed to act as gamma amino butyric acid (GABA) analogues, they block the release of calcium channel-mediated neurotransmitters at the presynaptic end, without acting on GABA receptors (19).

In the present study, we aimed to systematically evaluate the effects of GBP and PGB, which are preferred in clinics despite their high side effect profiles, in the treatment of NeP related to SCI.

Amr conducted a controlled, double-blind study (36) and reported that serious, persistent, chronic pain was an important problem for persons involved in the long-term care of SCI patients and also that gabapentin, an anticonvulsant, and ketamine were widely used for treating chronic pain.

However, Amr underlined that there were no studies that focused on the effectiveness of GBP in treating NeP after SCI. He examined the safety and efficacy of administering a low-dose ketamine infusion along with oral gabapentin for treating chronic pain after SCI. In that study, 40 patients with NeP secondary to SCI were randomly divided into two groups, and the participants in Group 1 received 80 mg of ketamine infusion which was diluted in 500 cc normal saline for five-hour period daily for one week and 300 mg of gabapentin three times daily (36).

Following the administration of 300 mg of GBP three times daily to cases in Group 2, a placebo infusion was administered three times daily, and then 300 mg of GBP was re-administered. Subsequently, the Visual Analogue Scale (VAS) was used to evaluate the intensity of the pain in each group. Pain scores were markedly reduced in both groups compared with their scores prior to treatment (36).

Table 1. A detailed review of articles' full texts.

Author(s)	Cases	Center(s)	Study design (Randomized, controlled, double blind trial)	Level of Injury	Comparison drug(s)	The effect of the drug(s).
Gruenthal M, et al.[26] (1997)	25	1	Yes,	Not specified	Gabapentin, but not placebo	The data obtained suggest that gabapentin may be useful in the management of spasticity associated with SCI.
Tai Q, et al.[27] (2002)	7	1	Yes	C2 (2); C5 (2); C6 (1); C8 (1); T7(1)	Gabapentin and placebo	Gabapentin has some beneficial effects on certain types of NeP.
Ahn SH, et al.[28] (2003)	31	1	Yes	C4 (2); C5 (3); C6 (1);C7 (2); C8 (1); T2 (1); T3 (2); T4 (1); T8 (1); T9 (1); T11 (3); T12 (2);L1 (2); L2 (2); L3 (1)	Gabapentin, but not placebo	Gabapentin may be effective in decreasing NeP.
Levendoglu F, et al.[29] (2004)	20	1	Yes	Not specified	Gabapentin and placebo	Gabapentin can be added to the list of first-line medications for the treatment of chronic NePin SCI patients.
Siddall PJ, et al.[30] (2006)	137	1	Yes	Not specified	Pregabalin and placebo	Pregabalin was effective in NePwith SCI.
Rintala DH, et al.[31] (2007)	38	1	Yes	Not specified	gabapentin and amitriptyline and placebo	Gabapentin was no more effective than placebo in neuropathic pain in SCI patients. Amitriptyline is more efficacious in relieving NePthan placebo.
Silver M, et al.[32] (2007)	3	1	Yes	Not specified	gabapentin and amitriptyline and placebo	Lamotrigine added to gabapentin, a tricyclic antidepressant, or a nonopioid analgesic did not demonstrate efficacy as an adjunctive treatment of NeP.
Vranken JH, et al.[33] (2008)						
Norrbrink C, et al.[35] (2009).	35	3	Yes	Not specified	antidepressant drugs antiepileptic drugs cyclooxygenase-2-inhibitors nonsteroidalantiinflammatory drugs	No between-group dierences in pain aect were observed.
Amr YM.[36] (2010)	40	1	Yes	C5-C8 (3) T1-T12 (11) L1-L5 (22) S1-S5 (4)	Ketamine, Gabapentin	There was no statistical difference between the groups at 3 weeks and 4 weeks after infusion termination.
Parsons B, et al.[37] (2013)	356	1	Yes	Not specified	Pregabalin and placebo	Pregabalin reduced NePdue to SCI.
Cardenas DD, et al.[38] (2013)	220	60	No	Between to C2-T12 levels.	Pregabalin and placebo	pregabalin is effective and well tolerated in patients with NePdue to SCI.
Min K, et al.[39] (2016)	55	1	Yes	Not specified	Oxcarbazepine, Pregabalin and placebo	Oxcarbazepine and pregabalin were significantly more effective, for SCI patients.
Schug SA, et al.[40] (2017	2	1	Yes	Not specified	Pregabalin and placebo	A little difference was observed in the extent of therapeutic response to pregabalin between patients who received concomitant NeP medications and patients who did not receive concomitant NeP medications.

SCI: Spinal Cord Injury, NeP: Neuropathic pain symbolized

Group 1 revealed marked pain score amelioration than Group 2 for all measurements. However, there was no statistical difference in terms of the intensity of the pain between the groups three and four weeks after terminating the infusions (36). Amr suggested that both drugs were well tolerated in both groups, and side effects did not require any medical treatment. Furthermore, he concluded that the usage of low-dose ketamine adjuvant to GBP for the treatment of post-SCI pain was safe and effective at reducing the pain, but this effect ceased compared with the placebo at two weeks following infusion termination (36).

Norrbrink and Lundeberg (35) investigated the effectiveness and safety of tramadol in treating NeP after SCI. They included 35 patients with NeP associated with SCI in a randomized, double-blind, and placebo-controlled trial. Of these patients, 23 were treated with tramadol, while 12 received a placebo. Participants were given either 50 mg of tramadol or one placebo tablet three times daily. The reported pain severity was lower in patients treated with tramadol than it was in those treated with a placebo at four weeks following the treatment initiation. However, 43% of patients in the tramadol group and 17% of patients in the placebo group withdrew from the study due to serious adverse effects. Norrbrink and Lundeberg suggested that tramadol might be given for NeP secondary to SCI only after the usage of gabapentin/pregabalin; more importantly, they reported that titration should be gradual and specific to reduce the occurrence of potential adverse events (35).

Rintala et al. (31) investigated the hypothesis that amitriptyline and GBP were more efficient in treating NeP than placebo, diphenhydramine. They administered amitriptyline, GBP, and diphenhydramine to 38 patients with SCI and then measured the severity of pain using the VAS.

In addition to this scale, depressive symptomatology was evaluated using the Center for Epidemiologic Studies Depression Scale-Short Form (CESD-SF). They reported that the initial VAS scores for patients with low CESD-SF scores were 4.61, while for those with a high score, it was 7.41. Rintala et al. also indicated that amitriptyline was more effective than diphenhydramine in patients with high initial CESD-SF scores at week 8 (31). They suggested that amitriptyline might be more potent than gabapentin; however, that these results were not statistically significant. In addition, they reported that there was no significant difference between the drugs in patients with low CESD-SF scores. Rintala et al. concluded that amitriptyline was more potent in treating NeP than diphenhydramine in patients with considerable depressive symptomatology (31).

In a randomized, double-blind, placebo-controlled trial, Silver et al. (32) evaluated the efficacy and tolerability of lamotrigine supplemented with GBP and a tricyclic antidepressant in patients whose NeP was not adequately managed by the drugs used in the treatment of NeP. Patients with NeP from diabetic peripheral neuropathy, post-herpetic neuralgia, traumatic/surgical nerve injury, incomplete SCI, trigeminal neuralgia, multiple sclerosis, or human immunodeficiency virus-associated peripheral neuropathy, who had a mean pain score 4 or above on an 11-point numerical rating scale were given 200, 300, or 400 mg of flexible lamotrigine daily adjuvant to their treatment with GBP and a tricyclic antidepressant (32). They reported that there was no statistically significant difference in the average change of pain-intensity score from starting to week 14 between lamotrigine and placebo (32). Silver et al. also found that differences between lamotrigine-treated patients and placebo-treated patients were not statistically significant for secondary measurements (32). They underlined that lamotrigine was well tolerated and that 400 mg of lamotrigine supplemented with GBP and a tricyclic antidepressant daily did not show efficacy as an adjuvant treatment of NeP (32).

Levendoglu et al. evaluated the efficacy of gabapentin in the treatment of NeP after SCI in a prospective, placebo-controlled, double-blind, crossover, randomized, clinical trial (29). Patients were given maximum tolerated doses after a four-week stable dosing period, a crossover administration of four weeks of drug/placebo, and another four weeks of unchanged dosing after a two-week washout period (29). Unlike other studies, Levendoğlu et al. evaluated 20 paraplegic patients with SCI at the lumbar and thoracic level who were between 20 and 65 years of age and had NeP for about 6 months (29). The authors proposed that GBP decreased the intensity of pain, alleviated all NeP descriptors apart from the itchy, sensitive, dull types, and improved the patients' life quality (29). They also stressed that GBP could be considered as a first-line drug for patients with SCI in the treatment of NeP and was a promising novel agent that might offer advantages over currently available treatments (29).

Ahn et al. (28) investigated the effect of GBP on NeP refractory to conventional analgesics in 31 patients who suffered from NeP after SCI or cauda equina syndrome. They divided the patients, who were treated with conventional analgesics, such as antidepressants, anticonvulsants, membrane stabilizers, and neuroleptics, but not reached a satisfactory result after administration of drug for about two weeks, into two groups. Patients with a pain duration that was less than six months served as Group 1 (n = 13), and patients with a duration of pain more than six months made up Group 2 (n = 18) (28).

Ahn et al. administered conventional analgesics GBP for an initial 18-day period, then a five-week period at a dose of 1800 mg/day (28). They measured the efficacy of GBP using a pain score and a sleep disturbance score via the VAS every two weeks for up to eight weeks in their two groups. They stated that the average pain and the average sleep disturbance scores for Group 1 was decreased more than those in Group 2 from two to eight weeks. They also reported that a decrease in the pain score of 2 or more patients was observed in 8 out of 9 patients who reported

sleep disturbance in Group 1 and 8 out of 13 patients with sleep disturbance in Group 2 (28). Ahn et al. concluded that GBP had some adverse effects, such as somnolence, but they were mild or moderate in intensity, and that GBP might be useful in reducing NeP resistant to conventional analgesics in some patients with SCI who had symptoms lasting less than six months. Moreover, they underlined that GBP may not result in serious side effects that would restrict its usage in patients with SCI (28).

Tai et al. (27) indicated that NeP after SCI was a common complaint and that GBP was reported to be beneficial in the treatment of NeP, but no studies had evaluated its efficacy after SCI. For this reason, they performed double-blind, prospective, crossover, randomized, and placebo-controlled clinical trial (27).

Tai et al. included seven patients with NeP after SCI that lasted for more than 30 days and applied them GBP for four week and placebo for two-week washout period (27). They recorded daily pain levels using the Neuropathic Pain Scale and then evaluated the obtained data using the Wilcoxon signed-rank test. They found that GBP was effective in some types of NeP and that there was a notable decline in "unpleasant feelings" and a tendency toward a reduction in the "pain density" and a "burning sensation" for four week treatment of gabapentin compared to those treated with the placebo. Tai et al. concluded that GBP decreased some types of NeP related to SCI and that trials including larger sample sizes, and using higher dosages might be beneficial in determining the efficacy of GBP for the treatment of NeP after SCI (27).

Gruental et al. (26) examined the effects of GBP on spasticity in patients with SCI. Patients (n=25) with spasticity and SCI were given oral GBP in this study. They evaluated the patient replies by gauging the Ashworth Spasticity Scale, muscle stretch reflexes, and the existence of clonus and reflex replies to noxious stimuli. The patient evaluations were performed using a Likert Scale, and it was concluded that GBP administration resulted in an 11% decline in spasticity when assessed using the Ashworth Spasticity Scale and a 20% decline when measured with a Likert Scale. They reported that the obtained data demonstrated that GBP might be beneficial in the treatment of spasticity correlated with SCI (26).

Schug et al. (40) noted that patients with NeP are often treated with multiple agents with the aim of reducing pain and any comorbidities that might exist. They reported that PGB is prescribed as a first-line drug for NeP, but few research had investigated the effects of PGB. They performed seven randomized, placebo-controlled trials of PGB for the treatment of postherpetic neuralgia and two trials for the treatment of NeP related to SCI. They measured the severity of patients' pain and pain-related sleep interference (PRSI) over 24 hours on a scale from 0–10. Their study monitored patients for the occurrence of adverse events and analyzed the data obtained from clinical trials. They compared changes in the pain and PRSI scores of patients who were given NeP drugs and also in those who were not. They reported that wide adverse events were present for each group and that PGB markedly ameliorated pain and PRSI scores compared with placebo. In particular, they emphasized that there was little difference in the therapeutic response to PGB between patients who were given concomitant NeP drugs and patients who were not (40).

Min et al. (39) performed a prospective, randomized, crossover study where they examined 55 patients and 66 locations of NeP to determine the differences in drug effects according to the pain features of patients with SCI. They classified the pain using four spontaneous features and three stimulated pain features.

Min et al. used oxcarbazepine, a sodium channel blocker, and PGB, a calcium channel α2-δ ligand medication, and divided patients into two groups based upon whether stimulated pain was present or absent (39). They indicated that oxcarbazepine was markedly more beneficial for patients without stimulated pain than in those without it for burning, pricking and electrical pain. The effect of PGB was not different in the presence or absence of stimulated pain for all pain groups without burning pain. PGB was markedly more useful in electrical pain, allodynia, and heat hyperalgesia than oxcarbazepine. Min et al. concluded that the phenotype of NeP was related with the efficacy of different treatments and that symptom-based treatment could result in more effective analgesia (39).

Parsons et al. (37) investigated the tolerability, efficacy and safety of PGB in patients with central NeP after SCI. They compared the efficacy of PGB and placebo in patients with NeP related to SCI using an experimental design that lasted 12 or 16 weeks (37). Their study compared the efficacy by examining the following: the average change in pain from the beginning to end-point; the duration accommodated mean change in pain; the rate of patients with 30% or 50% decreases in their pain score from beginning to end-point; and the Patient Global Impression of Change score at end-point. They treated 174 patients with a placebo and 182 patients with PGB. They concluded that the average change in pain from beginning to end-point was ameliorated in the PGB-treated patients compared to the placebo-treated patients, and this difference was statistically significant (37).

Cardenas et al. (38) investigated the effectiveness and tolerability of PGB for the treatment of central NeP related to SCI. They treated randomly patients with chronic NeP after SCI with 150–600 mg/d PGB or the same amount of placebo for 17 weeks. They classified the pain according to the neurologic level of injury (38).

Cardenas et al. accepted the primary outcome measure as the duration-accommodated mean change in pain. The secondary outcome measures that they took into account were the change in average pain score from beginning to end-point, the rate of patients with a 30% decrease in the average pain score at end-point, the patient's overall score changes at end-point, and the change in the average PRSI

score from beginning to end-point (38).

Cardenas et al. suggested that PGB treatment resulted in statistically significant ameliorations compared to placebo for primary and secondary outcome measures and that notable pain amelioration was evident as early as week 1 and continued during the treatment process. Adverse events due to PGB were in conformity with its safety profile and were mild to moderate in intensity. However, PGB was efficient and well-tolerated in patients with NeP after SCI (38).

Vranken et al. (33) investigated the efficacy of PGB in patients with central NeP after SCI. They treated 40 patients with increasing doses of either PGB or the same amount of placebo capsules. They started the treatment with either 150 mg of PGB or placebo per day in both groups. They continued the treatment by titrating patients to a higher dose when pain relief was insufficient. There was a statistically significant decline in the average pain score at end-point for PGB treatment compared to placebo, and that PGB treatment resulted in a statistically significant amelioration for the EQ-5D and SF36. They concluded that when applied in a flexible-dose regime, PGB led to a significant reduction in pain as well as ameliorations in the health status of patients with severe central NeP (33).

Siddall et al. (30) investigated the effect of PGB in central NeP associated with SCI. They treated patients with a flexible dose of PGB or placebo two times daily for 12 weeks. The end-point average pain score obtained from patients' last seven days records was evaluated as primary efficacy variable. The average end-point pain score was decreased in the PGB-treated group than in the placebo-treated group. Siddall et al. administered an average PGB dose (460 mg/day) after a three-week stabilization period. PGB gave rise to ameliorations in interfered sleep and anxiety, and more patients were reported broad amelioration at the end-point in the PGB group; the most common adverse effects of PGB were transient somnolence and dizziness. They concluded that PGB administered at doses ranging from 150–600 mg/day was beneficial in decreasing central NeP and ameliorating sleep, anxiety, and overall health status in patients with SCI (30).

In light of these findings, it is evident that available treatment modalities did not provide satisfactory outcomes for patients with NeP related to SCI. However, GBP, an anticonvulsant, has been used as the first-line drug in the treatment of NeP. The efficacy of GBP in the treatment of NeP after SCI has only been investigated in a few recent studies. Except for the study conducted by Levendoğlu et al. (29), all these studies had a retrospective study design, used a low evidential value, or administered a lower dose of GBP in a small number of participants. Therefore, the treatment of patients with central NeP remains a clinical problem despite the use of anticonvulsants and antidepressants.

The effects of PGB on pain reduction, tolerability, health status, and quality of life were evaluated in patients with central NeP related to brain or SCI in a randomized, double-blind, placebo-controlled trial. The findings in the literature demonstrated that the side effect profile of PGB was higher than that of GBP, whereas the efficacy of PGB treatment was higher in many variables compared with GBP treatment. The VAS score of patients cured with PGB was decreased; however, the VAS score of patients cured with a higher dose of GBP was also decreased. There were insufficient studies to compare the efficacy of GBP and PGB in patients with NeP related to SCI. This systematic review handled the efficacy of PGB and GBP in patients with NeP after SCI. Future studies on this matter should include a cost-effectiveness analysis and a dose-response analysis as well.

CONCLUSION

The treatment of NeP due to SCI, where patients have sensations such as sharp or cramping pain, fever, burning, stinging, throbbing, tingling, numbness, or electric shock is of significant importance. GBP and PGB are often prescribed for the current treatment of patients with NeP after SCI in clinics. The dominant action mechanism of these pharmaceuticals is believed to lead to an inhibition of calcium currents, a reduction of neurotransmitter release, and alleviation of postsynaptic excitability, and they should be prescribed by clinicians after carefully considering their side effect profiles and determining appropriate dosing and treatment period.

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Yasin Emre Kaya ORCID: 0000-0002-5412-8355;

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