

Efficacy of pregabalin and gabapentin for neuropathic pain in spinal-cord injury: an evidence-based evaluation of the literature

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Abstract

Background Spinal-cord injury (SCI) is a leading cause of neuropathic pain (NP). Current pharmaceutical treatments for NP in SCI patients are not effective. Two promising options are gabapentin (GP) and pregabalin (PB). Their predominant mechanism of action is believed to be the inhibition of calcium currents, leading in turn to reduced neurotransmitter release and attenuation of postsynaptic excitability. This could explain much of their efficacy in the treatment of both seizure disorders and pain syndromes. However, evidence for their efficacy in attenuating NP of SCI is still controversial.

Objective To efficiently integrate valid information and provide a basis for rational decision making, through determining PB and GP efficacy in treating NP in SCI.

Methods Literature was systematically reviewed. Medline, Embase, CINAHL and Cochrane Database were searched using search terms ‘gabapentin’, ‘pregabalin’, ‘neurontin’, ‘lyrica’, ‘neuropathic pain’ and ‘spinal-cord injury’. Studies were assessed independently by two authors.

Results Five studies were eligible for inclusion. Two of them studied PB and three GP. Both GP and PB appear to be efficacious for NP in SCI. A clear comparison between

the two drugs could not be performed. The literature data suggest that PB is more efficacious than GP in many important variables for NP in SCI, although PB use is followed by more side effects than GP. PB reduced Visual Analogue Score (VAS) in both studies ($P < 0.001$ and $P = 0.016$). On the other hand, for GP a maximum dosage of 3,600 mg/day reduced VAS score ($P = 0.000$), whereas a maximum dosage of 1,200 mg/day failed to do so.

Conclusion There is a lack of studies comparing GP and PB in treating NP in SCI. This systematic review indicates the possible efficacy of PB and GP in NP of SCI. Recommendations for future research to inform clinical practice should include cost-effectiveness studies and dose-response analysis in order to determine the schema employed and the duration of treatment.

Keywords Gabapentin · Lyrica · Neurontin ·
Neuropathic pain · Pregabalin · Spinal-cord injury ·
Systematic review

Introduction

Neuropathic pain (NP) is pain initiated or caused by a primary lesion or dysfunction in the nervous system [1]. It has heterogeneous causes such as spinal-cord injury (SCI), stroke, multiple sclerosis, diabetes mellitus and neoplasia [2]. NP is believed to be mediated by multiple mechanisms. It has been suggested that abnormal spinothalamic function with altered sensitivity to temperature and pinprick, neuronal hyperexcitability, excessive firing of pain-mediating nerve cells and insufficient segmental and non-segmental inhibitory circuits are involved [3–5]. The final result is an abnormal pain perception leading to clinical symptoms such as burning, stabbing, and stinging and pain that is similar in quality to electric shock [2].

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SCI is one of the leading causes of NP. It is estimated that NP at or below the level of the injury occurs in up to 40% of patients with SCI [6]. It is an intractable type of pain and its prevalence differs, depending on the time since the injury and on the localisation of the pain in relation to the level of the injury [6, 7]. It causes emotional and physical discomfort and is associated with depressive symptoms leading to greater pain intensity [8]. Thus, search for effective treatment options is of a high priority.

Various pharmaceutical treatments have been proposed, such as opioids, anti-depressants, anti-convulsants, baclofen, non-opioid analgesics, alfa-adrenergic agonists and ketamine. However, efficacy is still not satisfactory and the use of many of these agents is often limited by significant side effects [9].

Two promising treatment options are gabapentin and pregabalin. Gabapentin (Neurontin) is an anti-convulsant drug that has become a treatment of choice to manage NP. There are data indicating the efficacy of gabapentin for postherpetic neuralgia [10], diabetic neuropathy [11], cancer pain and other chronic pain states. Preclinical studies in rat models with SCI indicated that gabapentin reduced allodynia [12]. Many clinical studies have been conducted to determine the efficacy of gabapentin on NP in SCI, including retrospective studies [13], uncontrolled open-label trials [14] and randomised controlled trials [15, 16]. However the data are still controversial and some researchers question gabapentin's role in attenuating NP of SCI [13, 15]. Gabapentin is proven to be well tolerated and results in few side effects and lack of toxicity on any specific organ [9–11, 15–18].

Pregabalin (Lyrica) is also an anti-convulsant that has great bioavailability and safety profile and limited drug interactions. Recently, pregabalin was shown to be effective in randomised clinical trials for post-herpetic neuralgia [19–22] and diabetic peripheral neuropathy [23]. Preclinical data suggest that it reduces neurotransmitter release in hyperexcited neurons [24–26]. Two clinical studies indicate pregabalin efficacy for NP of SCI [27, 28]. A recent review also supports this efficacy, but fails to systematically review the literature and include a comparison with gabapentin [29].

Gabapentin and pregabalin are structurally related compounds. Both drugs are derivatives of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), with gabapentin originally designed as a GABA-mimetic agent that could freely cross the blood–brain barrier. Gabapentin recently has received considerable attention as a potential analgesic for neuropathic pain [30]. Pregabalin can be considered as a successor to gabapentin, at least in terms of its basic chemical structure and therapeutic profile. Multiple modest cellular effects have been proposed for gabapentin and pregabalin, including modest actions on the GABAergic system [31] and on voltage-gated potassium channels [32], but a single mechanism of action is believed to predominate their pharmacology and to explain much of their efficacy in

the treatment of both seizure disorders and pain syndromes: inhibition of calcium currents via high-voltage-activated channels containing the $\alpha_2\delta$ -1 subunit, leading in turn to reduced neurotransmitter release and attenuation of post-synaptic excitability. This mechanism has consistently been observed at therapeutically relevant concentrations in pre-clinical studies of gabapentin and pregabalin [33, 34].

In order to efficiently integrate valid information and provide a basis for rational decision-making, the literature was systematically reviewed to determine the efficacy of pregabalin and gabapentin in the treatment of NP in SCI.

Methods

Search strategy

We systematically searched MEDLINE and EMBASE from 1980 to January 2008, as well as CINAHL and the Cochrane Controlled Trials Register (CCTR). In order to identify relevant studies, we used as search terms ‘gabapentin’, ‘pregabalin’, ‘neurontin’, ‘lyrica’, ‘neuropathic pain’ and ‘spinal-cord injury’. The reference lists of selected studies and review articles were reviewed for additional citations. No language and publication status restrictions were applied.

Study selection

Studies were assessed independently by two authors (EA, DK) who also independently extracted the data. Eligibility was determined by reading each abstract identified by the search and conclusions were reached by consensus. A study was eligible for inclusion in this review if it was a randomised controlled trial following certain eligibility criteria. Cohort studies, case reports, case series, observational studies and experimental models were excluded. Eligibility criteria were as follows:

1. Population

The studies should have enrolled male and female patients over the age of 18 with SCI suffering from neuropathic pain at or below the level of injury.

2. Intervention

We included studies that compared pregabalin and gabapentin at a licensed therapeutic dose with vehicle or another active treatment.

3. Outcome

The outcomes under analysis were all variables determining efficacy, such as reduction in pain scores and pain relief and improvement in health status and quality of life.

Results

Out of 17 studies retrieved, 5 were eligible for inclusion in our review (see Table 1) [15, 16, 27, 28, 35]. Two of them studied pregabalin and three gabapentin. The three studying gabapentin had a crossover design [15, 16, 35]. Most of the excluded studies were reviews, open-label studies and case series.

Pregabalin for NP in SCI

An outcome assessment for the most important variables for pregabalin efficacy is presented in Table 2. The article by Vranken and colleagues indicates that there was a statistically significant decrease in mean pain score at endpoint for pregabalin treatment (VAS score) [28]. The pregabalin group also showed a statistically significant improvement for the Euro Quality of Life-5 Dimensions (EQ-5D) utility score and Euro Quality of Life-5 Dimensions Visual Analogue Scale (EQ-5D VAS) score compared with the placebo group, suggesting an overall increase in health status [28]. They also report that of the eight domains of the Short-Form Health Survey Questionnaire 36 (SF36) pregabalin treatment led to a significant improvement in the bodily pain domain. On the other hand, the PDI (assessment of disability) outcome did not differ between both groups at the end of the trial [28].

Siddall and colleagues also indicate that pregabalin was superior to placebo on the endpoint mean pain score [27]. The mean reduction from baseline to endpoint on each of the five Short-Form McGill Pain Questionnaire (SF-MPQ) scales and the mean reduction from baseline to endpoint in the sleep interference score was greater in the pregabalin group compared to the placebo [27]. Finally, the mean reduction from baseline to endpoint in the Hospital Anxiety and Depression Scale (HADS) anxiety score was greater in the pregabalin group than in the placebo, but there was no significant difference in the HADS depression score [27].

Overall, a great problem of both studies was study design, as all patients were permitted to remain on existing pain therapies except the ones receiving gabapentin, who were required to discontinue treatment. As Kruszewski and colleagues point out, this intentionally produced a gabapentin withdrawal state [36].

Gabapentin for NP in SCI

An outcome assessment for the most important variables for gabapentin efficacy is presented in Table 2. Levendoglu and collaborators indicate that gabapentin reduced the intensity as well as the frequency of pain [16]. Gabapentin showed efficacy by positively influencing Neuropathic Pain Scale (NPS), Lattinen Test (LQ) and Visual Analogue Scale

(VAS) and relieved all neuropathic pain descriptors except the itchy, dull, sensitive, and cold types [16]. It also improved quality of life, since it positively influenced all LQ parameters including subjective pain intensity, pain frequency, disability due to pain and sleep quality. All patients completed this study.

On the other hand, Tai and colleagues indicate that gabapentin had some beneficial effects only on certain types of neuropathic pain and that there was a significant decrease in ‘unpleasant feeling’ but a non-significant decrease in ‘pain intensity’ and ‘burning sensation’ [15]. No significant difference was found among other pain descriptors during the gabapentin and placebo treatment [15]. This study, however, had a very small sample size (seven patients), a low maximum dosage of gabapentin (1,800 mg/day), poor outcome measure (only NPS) and generally poor study design.

Rintala and his team evaluated both amitriptyline and gabapentin [35]. They report that for pain intensity (VAS score) there was no significant difference between gabapentin and diphenhydramine therapy, and that in the amitriptyline group, pain intensity was significantly lower than in the gabapentin or diphenhydramine groups [35]. They also indicate that for patients with high baseline Centre for Epidemiologic Studies Depression Scale-Short Form score (CESD-SF), amitriptyline was more effective than diphenhydramine, and there was a non-significant trend suggesting that amitriptyline may be more effective than gabapentin [35]. Gabapentin was no more effective than diphenhydramine. They also report that there was no significant difference among the medications for those with lower CESD-SF scores [28]. Although this study was well designed, it has various limitations, as Rintala et al. point out [35]. Only 22 patients completed all three phases, an active placebo was used, and most importantly, a low maximum dosage of gabapentin was administered [35]. Rintala et al. used a maximum dosage of 1,200 mg/day [35], whereas Levendoglu et al. [16] administered a maximum dose of 3,600 mg/day, a factor that may explain the difference in gabapentin efficacy. It is worth noting that with a maximum dosage of 3,600 mg/day, each individual side effect did not differ significantly between gabapentin and placebo group with the most common side effect being weakness [35]. Therefore, in our opinion, the dose used by Rintala et al. was not sufficient. Another limitation of Rintala’s study was that all measures were based on self-reports.

In conclusion, the above-mentioned data indicate that maximum dosage and dose-response relationship for gabapentin efficacy in NP of SCI are of great importance. The data also indicate that gabapentin, when used at a maximum dosage of 3,600 mg/day with non-rapid dose escalation (4-week titration period), as Levendoglu et al.

Table 1 The five studies eligible for inclusion in this review

Citation	Patients	Methodology	Intervention/control	Dosing regimen	Outcome measures	Tolerability/safety	Limitations
Siddall et al. 2006 [27]	70 PB, 67 placebo	12-week multicentre parallel group, double-blind clinical trial	PB/placebo	Flexible dose 300, twice daily BID, 150 mg/day for week 1, up to 600 mg/day if needed	Mean pain score, sleep interference, SF-MPQ, HADS	Discontinuation: 21% from PB group, 62% more than placebo, significantly more adverse side effects	Patients allowed to remain on existing pain therapy but had to discontinue GP
Vranken et al. 2007 [28]	11 PB, 10 placebo	4-week double-blind clinical trial	PB/placebo	Flexible dose, twice-daily escalating doses (150, 300, 600 mg/day) titrated at 3-day interval	Pain score (VAS), health status (EQ-5D), quality of life (SF-36)	Mild or moderate side effects did not differ significantly between treatment groups	Patients allowed to remain on concomitant analgesic treatment, but had to discontinue GP
Levendoglu et al. 2004 [16]	20 patients	18-week double-blind crossover clinical trial	GP/placebo	4-week medication/placebo titration period (900, 1,800, 2,400, 3,600 mg/day 3 times daily), 4-week stable dose (maximum tolerated dose), 2-week wash out, 4-week titration, 4-week stable dose period	Pain score (VAS), pain score (NPS), disability and quality of sleep (LQ)	Each individual type of side effect did not differ significantly between treatment groups	Small number of patients
Tai et al. 2002 [15]	7 patients	10-week double-blind crossover clinical trial	GP/placebo	4-week medication/placebo, 2-week wash-out period (1,800 mg/day maximum dosage)	Pain score (NPS)	Side effects did not differ significantly	Very small sample size, poor outcome measures, poor study design
Rintala et al. 2007 [35]	38 patients (26 completed GP phase)	10-week double-blind triple crossover clinical trial	GP/amitriptyline/active placebo (diphenhydramine)	4-week medication with increasing daily dose, 5–8 weeks constant dose (up to 1,200 mg/day 3 times daily) for GP, 9 weeks of decreased dose, 10 weeks of washout	Pain score (VAS), pain score (NRS), depression (CESD-SF)	Amitriptyline side effects differed significantly and caused withdrawal	Use of active placebo with similar side effects; only 58% of participants completed all three phases

PB Pregabalin, GP gabapentin, SF-MPQ short-form McGill Pain Questionnaire, HADS Hospital Anxiety and Depression Scale, VAS Visual Analogue Scale, EQ-5D Euro Quality of Life-5 dimensions, SF36 Short-Form Health Survey Questionnaire 36, NPS Neuropathic Pain Scale, LQ Lattinen Test, NRS numeric rating scale, CESD-SF Center for Epidemiologic Studies Depression Scale-Short Form

Table 2 Outcome assessment of the five studies included in this review

Citation	VAS	NPS	LQ	SF36	SF-MPQ	HADS
Siddall et al. 2006 [27] ^a	Mean pain scores changed from 6.73±1.4 to 6.27±2.1 for placebo, 6.54±1.3 to 4.62±2.1 for PB (<i>P</i> <0.001)	NU	NU	NU	Significant mean reduction on all five scales with PB (<i>P</i> <0.002)	Significant mean reduction in anxiety score with PB (<i>P</i> =0.043), no significant difference in depression score (<i>P</i> =0.482)
Vranken et al. 2007 [28] ^a	Mean pain intensity scores changed from 7.4±1.0 to 7.3±2.0 for placebo, 7.6±0.8 to 5.1±2.9 for PB (<i>P</i> =0.016)	NU	NU	Significant improvement in bodily pain domain (<i>P</i> =0.009), no significant improvement in physical, role, health, vitality, social, emotional, mental domains	NU	NU
Levendoglu et al. 2004 [16] ^b	Mean pain relief at the end of GP treatment 60.7±12.7%; placebo 10.3±2.8% (<i>P</i> =0.000)	Significant difference for all other descriptors of NP (<i>P</i> <0.05) except itchy, dull, sensitive and cold NP types	Significant decrease with GP in subjective pain intensity (<i>P</i> <0.001), pain frequency (<i>P</i> <0.05), disability due to pain (<i>P</i> <0.001), increase in sleep quality (<i>P</i> <0.001)	NU	NU	NU
Tai et al. 2002 [15] ^b	NU	Significant decrease in unpleasant-feeling variable, trend toward statistical significance in pain intensity and hot sensation, no significance in other pain descriptors	NU	NU	NU	NU
Rintala et al. 2007 [35] ^b	Mean pain ratings at end: amitriptyline 3.46±2.09, GP 4.85±2.86, diphenhydramine 5.11±2.54; significant difference for amitriptyline, no significant difference between GP and diphenhydramine	NU	NU	NU	NU	NU

PB Pregabalin, GP gabapentin, NP neuropathic pain, NU not used in the study, VAS Visual Analogue Scale, NPS Neuropathic Pain Scale, LQ Lattinen Test, SF36 Short-Form Health Survey Questionnaire 36, SF-MPQ Short-Form McGill Pain Questionnaire, HADS Hospital Anxiety and Depression Scale

^a Pregabalin treatment

^b Gabapentin treatment

[16] suggest, is quite efficacious and with minimal side effects in treating NP of SCI. Thus, the schema employed by Levendoglu et al. could be a proposed treatment as well as a drug schema to be used in future studies evaluating gabapentin. On the other hand, the lower maximum gabapentin dosages with more rapid dose escalation used by the other two studies [15, 35] clearly are not efficacious and should be abandoned as treatment options.

Side effects

Safety and tolerability are issues of great importance when treating NP in SCI because of the chronicity of the condition and the already heavily affected health status of SCI patients.

Gabapentin was generally well tolerated with mild side effects. Levendoglu et al. [16] indicate that each individual side effect did not differ significantly between gabapentin and placebo group with the most common side effect being weakness. Tai et al. [15] also came to the same conclusion. Lastly, Rintala et al. [35] reported that the only side effect that differed significantly from the placebo group was nausea. However, one must keep in mind that this was a triple crossover clinical trial and that diphenhydramine was used as an active placebo [35], a fact that could have obscured possible significant differences regarding the side effects of gabapentin and amitriptyline. Furthermore, withdrawal because of possible side effects occurred five times during the gabapentin phase. Another important fact is that increased spasticity was reported significantly less often during gabapentin therapy than with the other two medications [35]. This evidence is quite important and will be further evaluated in the 'Discussion' section.

On the other hand, pregabalin shows a different safety/tolerability profile. Vranken et al. reported that the most frequent adverse effects were those related to the central nervous system such as dizziness, decreased intellectual performance, somnolence and nausea [28]. They also indicated that the effects were mild or moderate in intensity and that their incidence did not differ significantly between treatment groups [28]. However, this trial lasted only for 4 weeks and included a small number of patients (11 pregabalin, 10 placebo). Siddall et al. reported that side effects were generally mild or moderate in intensity and that somnolence and dizziness were the two most common adverse events [27]. They also reported that somnolence resulted in the withdrawal of four patients from pregabalin and none from placebo. Edema and clinically significant weight gain were also reported [27]. More serious side effects were present and reported in 19% of the pregabalin group [27]. What is interesting is that one patient had a withdrawal reaction manifesting as spasticity with impaired coordination. Overall, the group discontinuing treatment

due to pregabalin was 62% larger than those discontinuing treatment due to placebo [27]. One also must keep in mind that in both pregabalin studies patients were allowed to remain on existing pain therapy.

Pregabalin vs. gabapentin

A clear comparison between gabapentin and pregabalin cannot be performed. There is not a study directly comparing them. The above-mentioned data suggest that pregabalin is more efficacious than gabapentin in many important variables for NP in SCI. However, methodological errors in all studies make this statement less than conclusive. On the other hand, it is clear that pregabalin use is followed by more side effects than gabapentin, some of them also quite serious. Dosing may play an important role. Dose-response relationship and cost effectiveness are not well established yet.

Discussion

There is a lack of studies, especially randomised controlled trials, comparing gabapentin and pregabalin in treating NP in SCI. The published studies are heterogeneous, use different measure scales, and most importantly, a number of them were poorly designed, especially for the evaluation of gabapentin. Furthermore, the fact that all patients in pregabalin studies were permitted to remain on existing pain therapies except the ones taking gabapentin is a great drawback that can not be ignored. The above evidence-based evaluation indicates the possible efficacy of both pregabalin and gabapentin in NP of SCI.

As far as safety and tolerability are concerned, gabapentin seems to be advantageous. Although poor design and heterogeneity are obstacles in comparing both drugs, serious side effects appeared only in pregabalin treatment. Overall, both drugs had few side effects compared to other treatment options for NP in SCI, such as tricyclic anti-depressants and opioids [37]. Opioids, although a well-established treatment, have side effects such as analgesic tolerance, withdrawal reactions after discontinuation and possibility of addiction that cannot be ignored. [38]. Amitriptyline, a tricyclic anti-depressant, is another agent that has been associated with significant analgesia in different animal models. Although amitriptyline has been a drug of choice for treating pain in people with SCI, only a few studies have described the effect of amitriptyline on chronic pain syndromes in the SCI population. These include two randomised controlled trials [35, 39]. Cardenas and collaborators conducted the first randomised controlled trial of the effectiveness of amitriptyline in relieving pain in patients with SCI and concluded that amitriptyline was not efficacious in relieving pain or improving the quality of life

of participants with SCI. The results of that study differed from those of the study of amitriptyline by Rintala et al. who found that amitriptyline was relatively cost effective and more effective than gabapentin in relieving neuropathic pain at or below the level of injury in participants with SCI who have considerable depressive symptomatology. The pain, however, was not completely eliminated, even in those participants for whom amitriptyline was an effective antidepressant therapy. Furthermore, amitriptyline has considerable side effects, some of which can be serious, particularly in the SCI population (strong anti-cholinergic activity, cardiovascular effects, lowering of the epileptic seizure threshold).

Spasticity is a factor of SCI that is quite important. Data suggest that gabapentin may be effective in controlling some features of spasticity in patients with SCI [40, 41]. Increased spasticity was reported significantly less often during gabapentin therapy than with the other two medications [35]. On the other hand, pregabalin does not seem to exhibit this feature. What is interesting is that in a pregabalin trial, one patient had a withdrawal reaction manifesting as spasticity with impaired coordination [27].

Dosage and schema employed seem to be of great importance, especially for gabapentin. Levendoglu et al. administered a maximum dose of 3,600 mg/day with more efficacy and non-significant side effects, compared to the other two studies, which used 1,800 and 1,200 mg/day respectively. So it appears that quantification of dose-response relationship for efficacy and adverse effects is of great importance.

Future studies with larger sample sizes and possibly higher dosages of GP may help further determine the efficacy of gabapentin and pregabalin in the treatment of SCI-related neuropathic pain. Since pregabalin and gabapentin are still expensive, cost-effectiveness studies should be performed too. Furthermore, individual symptoms of neuropathic pain (including allodynia, burning pain, shooting pain and hyperalgesia) were not scored following pregabalin treatment. In our opinion, a symptom-based analysis should be performed for gabapentin and pregabalin because these specific symptoms may respond differently to treatment.

In this review, it was not possible to draw any conclusions regarding a dose-response effect of pregabalin and gabapentin in central neuropathic pain. However, it is quite clear that recommendations for future research to inform clinical practice should include dose-response analysis, in order to determine the schema employed, the duration of treatment or the method of assessing improvement.

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