Short-Term Outcomes of Mirogabalin in Patients with Peripheral Neuropathic Pain: A Retrospective Study

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Abstract

Background: Mirogabalin, which is approved for the treatment of peripheral neuropathic pain in Japan, is a ligand for the α2δ subunit of voltage-gated calcium channels. Both pregabalin and mirogabalin act as nonselective ligands at the α2δ-1 and α2δ-2 subunits. Mirogabalin has a unique binding profile and long duration of action. Pregabalin has been reported to produce intolerable adverse effects in some patients. This study investigated outcomes associated with mirogabalin in patients with peripheral neuropathic pain who withdrew from treatment with pregabalin.

Methods: We retrospectively assessed peripheral neuropathic pain in 187 patients (58 men, 129 women) who were treated with mirogabalin. All patients had been treated with pregabalin and withdrew from therapy due to lack of efficacy or adverse events. The mean age of patients was 72.3 years (range, 30–94 years), and mean duration of disease was 37 months (range, 3–252 months).

Results: After treatment with mirogabalin for 1 week, numeric rating scale (NRS) scores decreased significantly compared with baseline, and continued to decrease over time . After 8 weeks, NRS scores improved by ³30% from baseline in 113 patients (69.3%). Twenty-four patients (12.8%) stopped mirogabalin treatment due to adverse events. Somnolence (26.7%), dizziness (12.3%), edema (5.9%), and weight gain (0.5%) were noted as adverse events of mirogabalin.

Conclusions: The results of this investigation indicate that mirogabalin is safe and effective for reducing peripheral neuropathic pain.

Background

The International Association for the Study of Pain defined neuropathic pain as “pain caused by a lesion or disease of the somatosensory nervous system” [1]. Neuropathic pain results in multiple symptoms, including spontaneous neurological pain, allodynia, hyperalgesia, and numbness, and results in decreases in quality of life (QOL) [2]. In addition, neuropathic pain may become intractable [2]. Chronic low back pain is known to be due to neuropathic as well as nociceptive pain mechanisms [3, 4]. Patients with neuropathic pain show higher ratings for pain intensity, with more co-morbidities such as depression, panic/anxiety disorder, and sleep disorders [4]. It is thus important to determine which factors contribute to neuropathic pain at an early stage and start appropriate drug therapy [5]. Unfortunately, current treatment methods are not always satisfactory [5].

Pregabalin is a ligand for the α2δ subunit of voltage-sensitive calcium channels, and is recommended as the first-line drug for neuropathic pain in guidelines around the world [6]. It decreases the release of neurotransmitters such as glutamate, noradrenalin, and substance P, leading to pain relief [7]. Pregabalin has been used in patients with neuropathic pain and shown to be a cost-effective treatment [8, 9] that has a positive impact on QOL [10]. It is generally well tolerated [11], and most adverse events are mild to moderate [12]. Pregabalin binds to α2δ-1 and α2δ-2 subunits of presynaptic, voltage-dependent calcium channels, which are widely distributed throughout the central and peripheral nervous systems [13]. The

most frequently reported side effects of pregabalin include dizziness and somnolence, which are related to the central nervous system (CNS) [13]. Therefore, the clinical utility of pregabalin may be limited by CNS adverse events [13].

Mirogabalin, which is a potent and specific ligand for the $\alpha_2\delta$ subunit of the voltage-gated calcium channels, is an orally administered gabapentinoid developed for the treatment of peripheral neuropathic pain in Japan [14, 15]. This agent has the distinguishing feature of binding persistently to the α2δ-1 subunit, which plays an important role in neuropathic pain [15]. This new drug is reportedly well tolerated and well absorbed by oral administration, and was first approved for peripheral neuropathic pain in 2019.

Although there are many positive reports associated with pregabalin, some patients have been reported to withdraw from treatment due to adverse events [13]. No reports regarding the adverse effects that lead to treatment discontinuation of mirogabalin in patients with peripheral neuropathic pain have been published. In the present study, we examined the outcomes of mirogabalin as a rescue drug in patients with peripheral neuropathic pain who withdrew from pregabalin treatment.

Methods

Participants

This retrospective study included outpatients with peripheral neuropathic pain who consulted our hospital between April 2019 and October 2019. Data were collected from medical records. The diagnosis of peripheral neuropathic pain was based on a history of neuropathic pain and confirmatory findings on examination. Inclusion criteria were diagnosis of peripheral neuropathic pain based on the flow chart of the grading system for neuropathic pain [16], lack of efficacy with pregabalin (Lyrica®, Pfizer Inc., Tokyo, Japan) or withdrawal from treatment with pregabalin due to adverse events, and willingness to answer the questionnaire. Exclusion criteria included dementia, delirium, or other conditions that made it difficult to complete a self-reported written questionnaire. Patients with severe chronic disease that interfered with treatment (e.g., cardiovascular disease, renal failure, or other disqualifying conditions) were also excluded. At baseline, patients completed a self-reported questionnaire and provided demographic and clinical information. This study was approved by the Kurashiki Municipal Hospital ethics committee, and written informed consent was waived because of the retrospective design.

Procedure

Treatment protocol

At least 1 month after withdrawing from pregabalin, treatment with mirogabalin (Tarlige®, Daiichi Sankyo, Inc., Tokyo, Japan) was prescribed. Patients received mirogabalin 10 mg/day orally for the first week. In patients with decreased renal function, the dose of mirogabalin was decreased to 5 mg/day. Depending on patient age and symptoms, the dose of mirogabalin was decreased or increased as required to between 2.5 mg and 15 mg/dose twice daily. All patients visited the hospital at 1, 2, 4, and 8 weeks to

ensure compliance with the study regimen. Patients with an adequate effect received the same dose of mirogabalin. In patients with an inadequate effect, the dose of mirogabalin was increased up to 30 mg/day. If adverse events were observed, the dose was decreased. In this study, no other conservative treatments (non-steroidal anti-inflammatory drugs and rehabilitation) or surgery were performed. During the study, only the dispensing pharmacist had knowledge of the patient codes. The manufacturer and provider of mirogabalin (Daiichi Sankyo, Inc., Tokyo, Japan) was not involved in the protocol development, data collection and management, statistical analysis, or manuscript preparation.

Clinical assessment

The numeric rating scale (NRS) for pain self-assessment is a widely used, valid, and reliable tool to measure chronic pain intensity [17]. Scores range from 0 to 10, with 0 representing no pain and 10 representing the worst pain imaginable. NRS scores were obtained at baseline, 1, 2, 4, and 8 weeks of treatment. We also evaluated adverse events of mirogabalin. The neuropathic pain screening questionnaire (NeP score), developed by Ogawa et al., was used for the peripheral neuropathic pain survey (Table 1) [18-20]. Patients' answers to questions in seven domains were weighted and scored. The likelihood of neuropathic pain was determined based on total score, as follows: ≥5 = highly likely to have neuropathic pain; 4 = likely to have neuropathic pain; 3 = possibility of neuropathic pain; ≤2 = unlikely to have neuropathic pain. A score ≥4 was judged as representing neuropathic pain [19].

Statistical analysis

Factors associated with withdrawal of mirogabalin treatment due to adverse events were identified using univariate analyses between patients who continued treatment and withdrew from treatment. Differences among treatment course (NRS) were compared using one-way analysis of variance with the Bonferroni post-hoc test. Moderate improvements in pain are considered to be ~30%–50% pain relief, whereas >50% pain relief is considered a good outcome [21, 22]. Therefore, we divided patients into two groups with pain relief <30% or ≥30% after 8 weeks of treatment with mirogabalin. Normally distributed variables were compared using Student's t test, and non-normally distributed variables were compared using the Mann-Whitney U test. The $\chi 2$ test was used to compare sex, diagnosis, and presence or absence of diabetes mellitus between groups. Differences of $p < 0.05$ were considered significant. Statistical analysis was conducted using SPSS software version 25.0 for Windows (IBM Corporation, Armonk, NY, USA).

Results

Participants

Of 195 outpatients with peripheral neuropathic pain who visited our hospital, 187 met the inclusion criteria and were included in this study (95.9%, Table 2). Patients included 58 men and 129 women with a mean age of 72.3 years (range, 30–94 years) at the time of the baseline examination. The mean pain duration from onset until consultation was 37 months (range, 3–252 months). In this study, 134 patients had lumbar canal stenosis, 33 had cervical spondylotic myelopathy, 10 had lumbar disc herniation, 9 had

carpal-tunnel syndrome, and 1 had post-operative pain. Adverse events leading to the discontinuation of pregabalin and subsequent use of mirogabalin included somnolence (97 patients), dizziness (50 patients), edema (7 patients), weight gain (3 patients), epigastralgia (2 patients), and fatigue (2 patients). Thirty-two patients switched to mirogabalin due to lack of efficacy with pregabalin.

Mirogabalin dose

Fifty-nine patients received mirogabalin 10 mg/day orally for the first week, and 128 patients received mirogabalin 5 mg/day due to decreased renal function. Nineteen patients increased the dose of mirogabalin to 30 mg/day due to lack of efficacy; none of these patients experienced severe adverse events with the increased dose.

Treatment with mirogabalin

Adverse events associated with mirogabalin included somnolence (50 patients, 26.7%), dizziness (23 patients, 12.3%), edema (11 patients, 5.9%), epigastric pain (2 patients, 1.1%), weight gain (1 patient, 0.5%), and fatigue (1 patient, 0.5%). Twenty-four patients (12.8%) withdrew from mirogabalin treatment because of adverse events. We investigated factors associated with withdrawal of mirogabalin treatment due to adverse events. There were no significant differences in age, sex, body mass index (BMI), or diagnosis between patients who discontinued mirogabalin and those who continued its use (Table 3). Patients who discontinued mirogabalin had a significantly lower incidence of somnolence ($p = 0.0017$) and significantly higher incidences of dizziness ($p = 0.015$) and edema ($p = 0.012$) with pregabalin compared with those who continued mirogabalin. Compared to patients who continued mirogabalin, patients who discontinued mirogabalin also had significantly higher incidences of dizziness ($p = 0.0069$) and edema (0.016), which contributed to withdrawal of treatment.

We also investigated changes in NRS scores after treatment with mirogabalin for 8 weeks. After treatment with mirogabalin for 1 week, NRS scores decreased significantly compared with baseline ($p < 0.0001$, Figure 1), and subsequently continued to decrease over time. After 8 weeks, NRS scores improved by ³30% compared with baseline in 113 patients (69.3%). We divided patients into two groups to identify factors associated with an improvement in NRS score <30% and ³30% after 8 weeks (Table 4). There were no significant differences in age, sex, diagnosis, or BMI between groups, but the NeP score was significantly higher in patients who experienced pain relief <30% ($p = 0.0047$).

Discussion

In this study, we used mirogabalin to treat patients with peripheral neuropathic pain who withdrew from pregabalin treatment due to lack of efficacy or adverse events. Mirogabalin is a new drug for the treatment of peripheral neuropathic pain, and to our knowledge, there have been no reports of its clinical

outcomes for patients who stopped treatment with pregabalin. Mirogabalin exerted a significant analgesic effect within 1 week after the start of treatment and was associated with mild CNS adverse effects.

Guidelines for the pharmacologic management of neuropathic pain recommend α2δ subunit of voltage-gated calcium channels, serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants as first-line agents, neurotropin and tramadol as second-line agents, and opioids as third-line agents [23]. Several other scientific associations and guidelines recommend gabapentinoids as first-line drugs for the treatment of neuropathic pain [24–27]. Mirogabalin, the ligand for the α2δ subunit (α2δ-1 and α2δ-2) of voltage-sensitive calcium channels in the CNS, was approved as a molecular target for pain relief in peripheral neuropathic pain in 2019 in Japan. Mirogabalin reportedly relieved diabetic peripheral neuropathic pain in a dose-dependent manner in Asian patients with diabetic peripheral neuropathic pain and was associated with only mild adverse events [28]. It was also shown to be effective and well tolerated in the management of postherpetic neuralgia in Asian patients [29]. In the present study, which included only patients who withdrew from pregabalin treatment due to adverse events or lack of efficacy, we found that mirogabalin was an effective analgesic, and that few patients stopped treatment due to adverse events.

In vitro studies of its pharmacologic action demonstrated that mirogabalin had a higher binding affinity for the human and rat $\alpha_2\delta$ subunit than pregabalin [15]. In a dissociation rate analysis, the dissociation half-lives of mirogabalin from the α2δ-1 and α2δ-2 subunits were 11.1 hours and 2.4 hours, respectively, compared with 1.4 hours for pregabalin in both cases [15]. These reports indicate that mirogabalin has potent and selective binding affinities for the human and rat $\alpha_2\delta$ subunit, and slower dissociation rates for the α2δ-1 subunit than the α2δ-2 subunit compared with pregabalin [15]. These findings support our finding that even patients who had discontinued pregabalin because of its CNS effects experienced fewer adverse events due to these effects when they were treated with mirogabalin. It has also been reported that continued oral mirogabalin treatment decreases the pain threshold over time [15]. In animal models of fibromyalgia, mirogabalin treatment has been shown to significantly decrease the pain score due to chronic allodynia [30]. In this study, the analgesic effect of mirogabalin was evident after only 1 week, which is a good result for patients with chronic pain.

The α2δ-1 subunit plays an important role in the onset and pathological persistence of neuropathic pain. α2δ-1 expression levels that correlated with tactile allodynia development were significantly increased in spinal cord injury rats [31]. Knockdown of the α2δ-1 subunit by antisense oligodeoxynucleotides reportedly inhibits tactile allodynia in rat models [31, 32]. Overexpression of the α2δ-1 subunit resulted in enhanced currents, altered kinetics, and voltage-dependence of voltage-gated calcium channel activation in sensory neurons; exaggerated and prolonged dorsal horn neuronal responses to mechanical and thermal stimulations at the periphery; and pain behaviors [33]. As far as we are aware, no study has addressed the association between the α2δ-2 subunit and pain. Edvardson et al. reported the importance of the α2δ-2 subunit, dominantly expressed in the cerebellar Purkinje cells, in the normal physiology of the human brain [34]. Binding to the α2δ-1 subunit contributes to analgesic effects, whereas binding to the

α2δ-2 subunit appears to contribute to undesirable CNS effects, such as somnolence [35–37]. Those studies indicate that gabapentinoids exert their analgesic effect via the α2δ-1 subunit, and the α2δ-1 subunit thus plays a major role in neuropathic pain. These findings suggest that the α2δ-2 subunit may be implicated in the CNS adverse events commonly seen in pregabalin treatment. These findings also suggest that the selective actions of mirogabalin on the α2δ-1 and α2δ-2 subunits may maximize its effect while minimizing CNS adverse events. The potent binding affinity of mirogabalin with the α2δ-1 subunit and its long dissociation half-life from the α2δ-2 subunit may thus make mirogabalin an attractive agent for the treatment of peripheral neuropathic pain. Although 12.8% of patients in the present study discontinued because of adverse events, mirogabalin was generally well tolerated.

Although the results of the present study suggest that mirogabalin might be an alternative treatment option for the treatment of peripheral neuropathic pain, the present study has some limitations. First, this study is a case series without a comparison or placebo group. Thus, the results cannot be clearly attributed to mirogabalin. Second, this study had a short observation period. Although most patients treated with mirogabalin for 8 weeks maintained their weight within ± 5% of their baseline weight, weight gain can be an issue with mirogabalin when used for a longer period. A third limitation was a lack of determination of the best screening questionnaire for neuropathic pain. Neuropathic pain screening questionnaires include painDETECT [4], the spine painDETECT questionnaire, which is a screening tool for neuropathic pain caused by spinal disorders [38], and the NeP score used in this study. We considered that if the NeP score was high, there would be little decrease in NRS score after mirogabalin treatment, making it suitable as a baseline index. However, the use of other neuropathic pain screening questionnaires might lead to different results. We consider that assessment and diagnosis of the neuropathic pain should be followed by the identical algorithm widely used as a current international standard for the diagnosis of neuropathic pain, specifically 1) range of pain is neuroanatomically plausible, 2) a lesion or disease of the somatosensory system is suggested, and 3) objective findings of sensory damage are observed in the neuroanatomically innervated region of the damaged nerve, or tests are performed to give a diagnosis of neurological lesion or disease that accounts for neuropathic pain. Despite these limitations, mirogabalin, a recently developed agent, showed promising results in patients with peripheral neuropathic pain.

Conclusions

This investigation indicated that mirogabalin is safe and effective for reducing peripheral neuropathic pain in patients who withdrew from treatment with pregabalin due to adverse events or lack of efficacy.

Abbreviations

QOL
quality of life; CNS:central nervous system; NRS:Numeric rating scale; BMI:body mass index

Declarations

Ethics approval and consent to participate

The Kurashiki Municipal Hospital ethics committee approved this research.

Consent for publication

Not applicable.

Availability of data and materials

All data used and analyzed during this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

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Tables

Table 1. Neuropathic pain screening questionnaire

Q1	There is a pinprick-like pain
Q2	There is an electric shock-like pain
Q3	There is a tingling burning pain
Q4	There is pain with strong numbness
Q5	A light touch with clothing or cold wind causes pain
Q6	The site of pain has decreased or increased sensation
Q7	The site of pain shows skin swelling and/or discoloration to red or purple

Each of the items is scored on a 5-point scale (0=never; 1=slight; 2=moderate; 3=strong; 4=very strong). The total score can range from 0 to 28 points, with higher scores indicating greater pain.

Table 2. Patient characteristics

Variables	n=187
Age (years)	72.3±12.4 (30–94)
Sex, female/male	129 / 58
Diagnosis	
LCS	134
CSM	33
LDH	10
CTS	9
Others	1
BMI (kg/m^2)	23.1±4.2 (18–33)
DM	17

LCS, lumbar canal stenosis; CSM, cervical spondylotic myelopathy; LDH, lumbar disc herniation; CTS, carpal-tunnel syndrome; BMI, body mass index; DM, diabetes mellitus. Data are expressed as mean ± standard deviation (range) or n (%).

Table 3. Univariate analyses comparing factors associated with continuation or withdrawal of treatment with mirogabalin

Variables	Continued treatment (n=163)	Withdrew from treatment (n=24)	P value
Age (years)	71.8±12.7 (30–94)	75.0±9.9 (49–91)	0.23[a]
Sex, female/male	110 / 53	19 / 5	0.25[b]
Diagnosis			0.98[b]
LCS	118	17	
CSM	28	5	
LDH	9	1	
CTS	8	1	
Others	1	0	
BMI (kg/m^2)	22.9±4.1 (18–33)	23.2±3.9 (19–31)	0.78[a]
DM	15	2	0.89[b]
Adverse events with pregabalin			
Somnolence	92 (56.4%)	5 (20.8%)	0.0017[b]
Dizziness	39 (23.9%)	11 (45.8%)	0.015[b]
Edema	4 (2.5%)	3 (12.5%)	0.012[b]
Weight gain	3 (1.8%)	0 (0%)	0.51[b]
Others	2 (1.2%)	2 (8.3%)	
Lack of efficacy with pregabalin	27 (16.6%)	5 (20.8%)	0.61[b]
NeP score (Points)	7.0±1.7 (6–12)	6.9±1.7 (6–12)	0.80[b]
Primary dose of mirogabalin (mg)	3.1±1.2 (5–10)	3.3±1.8 (5–10)	0.52[b]
Adverse events with mirogabalin			
Somnolence	44 (27%)	6 (25%)	0.84[b]
Dizziness	16 (9.8%)	7 (29.2%)	0.0069[b]
Edema	7 (4.3%)	4 (16.7%)	0.016[b]
Epigastric pain	0 (0%)	2 (8.3%)	<0.0001[b]
Weight gain	1 (0.6%)	0 (0%)	0.70[b]
Fatigue	1 (0.6%)	0 (0%)	0.70[b]

LCS, lumbar canal stenosis; CSM, cervical spondylotic myelopathy; LDH, lumbar disc herniation; CTS, carpal-tunnel syndrome; BMI, body mass index; DM, diabetes mellitus; NeP, neuropathic pain. Data are expressed as mean ± standard deviation (range) or n (%). [a]Student's t test; [b]Chi-squared test.

Table 4. Univariate analyses of patients with or without 30% pain relief by mirogabalin

Variables	<30% pain relief (n=50)	≥30% pain relief (n=113)	P value
Age (years)	72.9±11.9 (45–88)	71.3±13.0 (30–94)	0.46[a]
Sex, female/male	30 / 20	82 / 31	0.11[b]
Diagnosis			0.75[b]
LCS	35	83	
CSM	11	17	
LDH	2	7	
CTS	2	6	
Others	0	1	
BMI (kg/m^2)	22.7±4.2 (18–33)	23.0±3.8 (19–31)	0.79[a]
DM	4	11	0.72[b]
NeP score (Points)	7.4±2.1 (6–12)	6.6±1.4 (6–12)	0.0047[a]
Primary doze (mg)	3.1±1.5 (5–10)	3.1±1.1 (5–10)	0.97[a]
Max dose (mg)	6.6±3.8 (5–30)	6.4±3.8 (5–30)	0.76[a]
Adverse events	24 (48%)	42 (37.2%)	0.13[b]
Somnolence	17 (34%)	27 (23.9%)	
Dizziness	6 (12%)	10 (8.8%)	
Edema	2 (4%)	5 (4.4%)	
Weight gain	1 (2%)	0 (0%)	

LCS, lumbar canal stenosis; CSM, cervical spondylotic myelopathy; LDH, lumbar disc herniation; CTS, carpal-tunnel syndrome; BMI, body mass index; DM, diabetes mellitus; NeP, neuropathic pain. Data are expressed as mean ± standard deviation (range) or n (%). [a] Student's t-test; [b] Chi-squared test

Figures

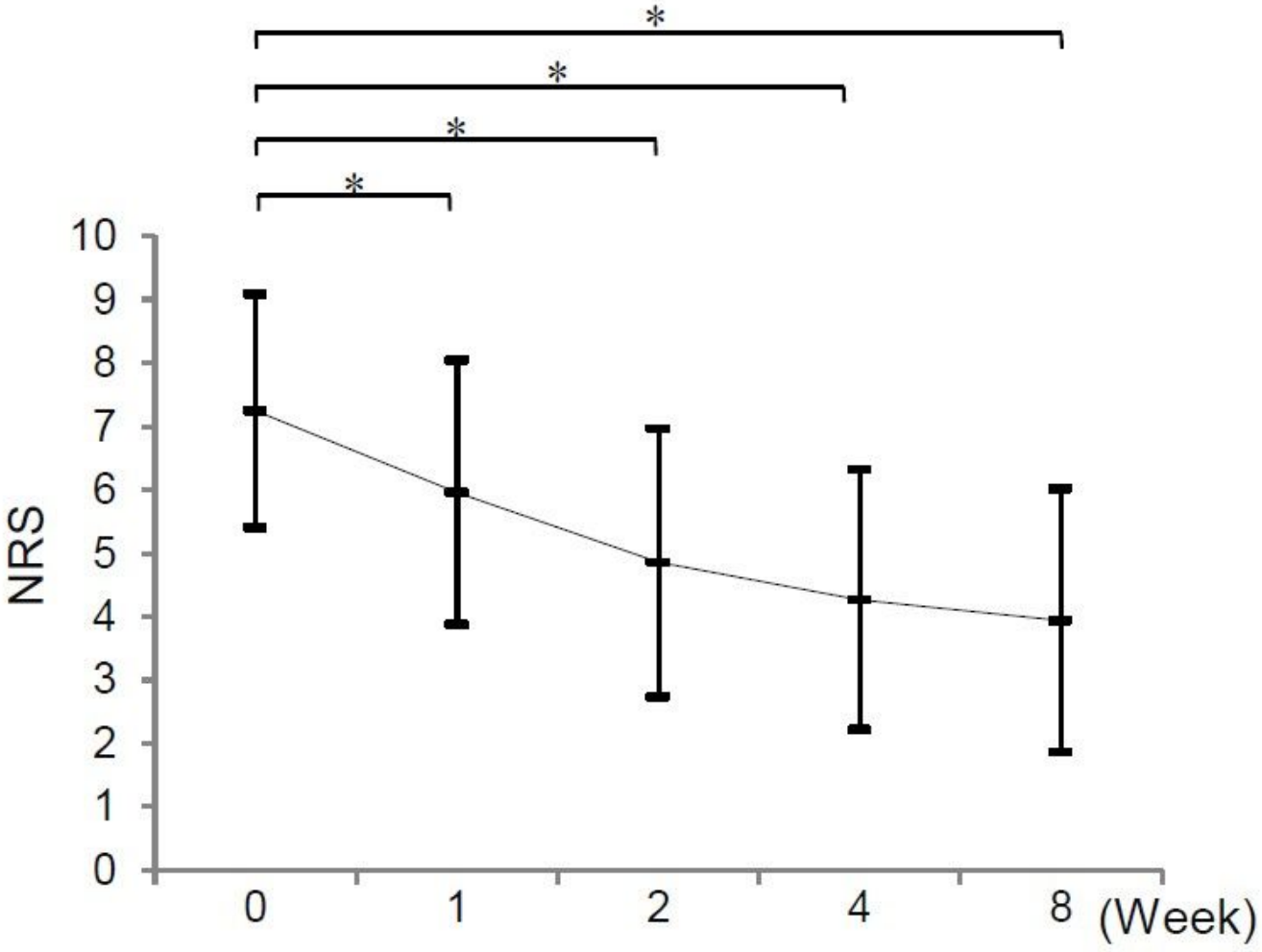

Figure 1

Scores on the Numeric Rating Scale (NRS) were significantly reduced after 8 weeks of treatment with mirogabalin. Data are expressed as mean ± standard deviation. *p < 0.05.