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A Multicenter Study on Neuropathic Pain in China: Characteristics and the Efficacy of Pregabalin

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Abstract

Background: This clinical study aims to analyse the characteristics of neuropathic pain patients across country nationwide and evaluate the efficacy and tolerability of pregabalin for the treatment of neuropathic pain. The GABA analogue, pregabalin, is being studied to try to establish standardized management of neuropathic pain as it is commonly used in postherpetic neuralgia in China.

Methods: Patients with neuropathic pain from 17 hospitals were included for four weeks. The demographics and baseline characteristics of patients were analyzed. The primary outcome was the difference in the pain intensity scores in the numerical rating scale from baseline to follow-up visits. Secondary outcomes included the differing visual analogue scale (VAS) of the short-form McGill Pain Questionnaire, sleep quality, anxiety and depression scores, and side effects during four weeks of follow-up.

Results: As 355 patients completed the 4-week follow up, various types of neuropathic pain intensity scores significantly decreased at the first week of treatment and improved through the course of the study. Meanwhile; the difference in the percentage change in patient global impression of change scores, mean sleep interference scores, anxiety and depression scores are all significantly higher after 4-week treatment. Most of the side effects went away during treatment as patients adjust to the medicine.

Conclusions: The data demonstrated that pregabalin was effective and well tolerated in Chinese patients with neuropathic pains. This study also analyzed the distribution features of neuropathic pain in a general population and established standardized management of neuropathic pain in China.

Keywords: Neuralgia; Treatment outcome; Quality of life

Abbreviations: PHN: Post Herpetic Neuralnia; PDN: Painful Diabetic Neuropathy; NeP: Neuropathic Pain; NRS: Numerical Rating Scale; VAS: Visual Analogue Scale; SFMPQ: Short-Form McGill Pain Questionnaire; PGIC: Patient Global Impression of Change; DSIS: Daily Sleep Interference Scale; HADS: Hospital Anxiety and Depression Scale; FM: Fibromyalgia; AE: Adverse Event.

Background

Neuropathic pain (NeP) is a term used for a group of conditions with a wide range of causes and different pain distributions. However, all these conditions are characterized by a lesion or other disease affecting the somatosensory nervous system peripherally or centrally [1]. NeP can be intense, unremitting and can have an impact on quality of life and functional status [2]. The common types of NeP are painful diabetic neuropathy (PDN), postherpetic neuralgia (PHN), trigeminal neuralgia. However; there are more types of NeP based on anatomical classification including peripheral origin and central origin [3]. NeP is common in daily clinical practice and makes up a high proportion in the out-patient neurology visits. To provide sufficient treatment, the type of pain the patient suffers from and its etiology should be evaluated by the physicians or medical providers. However, there is a lack of a general NeP demographic in China.

Pregabalin is a ligand of the auxiliary α2-δ subunit site of voltage-gated calcium channels, and hence acts as an inhibitor of α2-δ subunit-containing voltage-gated calcium channels. It has been shown the anticonvulsant, anxiolytic and analgesic effects and also has been found to be effective in the modulation of NeP [4-6]. Some of the randomized, multicentre, placebo-controlled trials have demonstrated pregabalin is effective in the management of neuropathic pain [7-9]. Pregabalin has been recommended as one of several first line agents for the treatment of the most common NeP conditions in some countries [10,11]. Although different clinical trials have shown the efficacy of pregabalin in the treatment of Chinese people with PHN [12,13], there are no known multicenter, clinical trials that evaluate the efficacy and safety of pregabalin for the treatment of other types of NeP in Chinese population.

In the United States, pregabalin is indicated for the treatment of NeP associated with PDN, PHN, for the management of fibromyalgia and as an adjuvant therapy for adult patients with partial seizures. In Europe, it is indicated for the treatment of peripheral and central NeP in adults, generalized anxiety disorder in adults, and as adjuvant

treatment in adults associated with partial seizures. Whereas in China, it is indicated as a therapy for NeP associated with PHN only.

This study aims at investigating the demographic characteristics of patients with NeP in China and evaluating the efficacy and tolerability of pregabalin for the treatment of other types of NeP together with PHN.

Methods

This observed, prospective, open-label, dose-flexible study was approved by the China Association of Health Promotion and Education as a public welfare program. Patients diagnosed as having NeP conditions were recruited in this study. Patients were included from 17 hospitals (Sun Yat-sen memorial hospital of Sun Yat-sen University, Chinese PLA general hospital, the first affiliated hospital of Harbin Medical University, Beijing Tian Tan Hospital of Capital Medical University, West China Hospital of Sichuan University, the third affiliated hospital of Sun Yat-sen University, Renji Hospital affiliated to Shanghai Jiao Tong University School of Medicine, the Second Affiliated hospital of Zhejiang University School of Medicine, Peking Union Medical College Hospital, Tongji Hospital of Tongji Medical College of Huazhong University of Science&Technology, the First People's Hospital of Foshan, the First Affiliated Hospital of Dalian Medical University, Peking University Third Hospital, Wuhan Union Hospital, the First Affiliated hospital of Zhejiang University, the First Affiliated Hospital of Xi'An Jiaotong University and Huashan Hospital of Fudan University) in the different provinces of China from January 1st to August 31st, 2016 following the approval of the Institutional Ethical Committee of General Hospital of each site. All patients provided written, informed consent before participating in the study. All consecutive patients reporting neuropathic pain who visited an outpatient center or admitted to hospital were invited to participate in the study. A study flow chart is illustrated in Figure 1.

Inclusion criteria

1. Confirmed diagnosis of neuropathic pain according to anatomical location. Divides neuropathic pain syndromes into two groups based on a central or peripheral location of the nervous system lesion 3.

2. Age equal to or greater than 18 years.

3. Duration of the pain at least three months.

4. Willing to provide a written informed consent to undergo the experimental procedures.

Exclusion criteria

1. The history of substance abuse.

2. Being pregnant or lactating.

3. Previous use of Pregabalin.

4. A surgical operation in the affected area within the last six months.

Procedures

After eligibility assessment, all patients initiated pregabalin open-label at a flexible-dose range from 75 mg QD-150 mg TID according to patients' pain severity for the first week. During the treatment, no other treatment was allowed, and the dose of pregabalin was adjusted throughout the trial increased to 600 mg/day according to patients' response and tolerance.

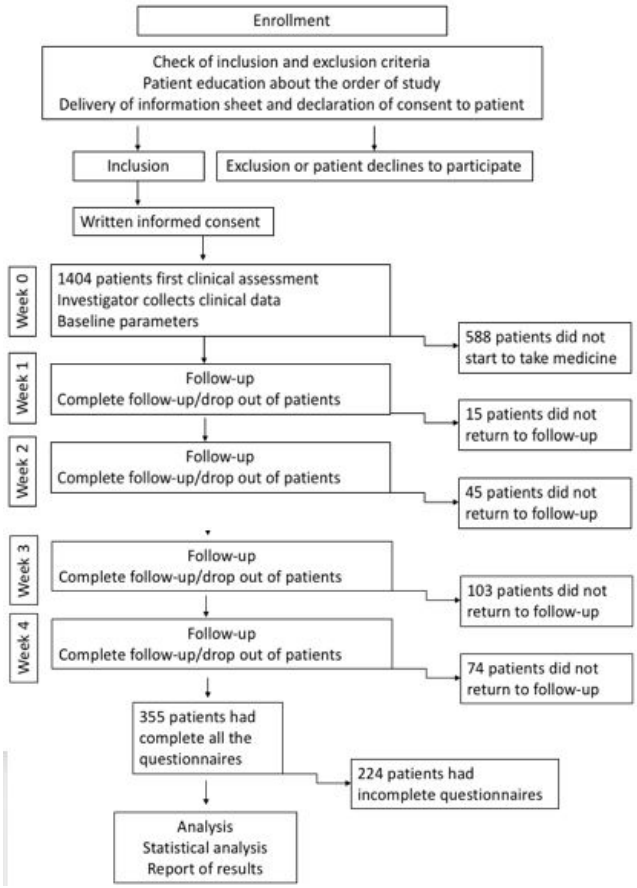

Figure 1: The study flow chart.

Patients were asked to complete daily pain diary throughout the study and would be followed up once a week after treatment for four weeks. The pain diary included the Numeric Rating Scale (NRS) and the visual analogue scale (VAS) of the Short-Form McGill Pain Questionnaire (SFMPQ) to score pain intensity. Patient Global Impression of Change (PGIC), Daily Sleep Interference Scale (DSIS) and Hospital Anxiety and Depression Scale (HADS) were also included.

The primary measure of efficacy was the score on the NRS scale of 0 (No pain) and 10 (Worst possible pain), and the secondary efficacy parameters included the VAS of the SFMPQ, DSIS, PGIC, and anxiety and depression score. The side effects were also recorded throughout the 4-week treatment by the patient or observed by the investigator at each visit to assess the tolerability of pregabalin.

Descriptive summaries were used for analysis of mean pain, sleep interference, and anxiety and depression score over time. The treatment effect as measured by the variables PGIC and the reduction in the mean pain score sleep interference and anxiety and depression score were analyzed by Student's t-test for differences at the 5% significance level.

Results

In total, 1,404 individuals fulfilled the inclusion criteria as mentioned above and received pregabalin in a flexible dose according to their pain severity. All of them completed the demographic survey at baseline.

Demographic

Of the 1,104 participants enrolled; 802 (57.12%) were women. The age ranges from 18 to 88 years of which the most common age period was 51-61 (25%). Their mean age was 51.7±15.6 years old. There were thirteen categories in the survey: PHN (14%), Trigeminal neuralgia (10%), postradiation plexopathy (6%), poststroke pain (4%), posttraumatic neuralgias (4%), PDN (3%), Multiple sclerosis-related pain (2%), Chemotherapy-induced polyneuropathy (2%), Entrapment neuropathies (1%), Nerve compression or infiltration by tumor (1%), others peripheral origin neuropathic pain (11%), other central origins neuropathic pain (19%) and unclassified neuropathic pain (43%) (Table 1). 816 of all enrolled patients had valid data in the pain localization (Table 2). Head and neck were the most popular distribution of pain (50%). Following were the four limbs (24%), truncus (13%), the whole body (3%) and other (10%). The pain severity was defined as mild (NRS pain score ≤ 3) 8%, moderate (NRS pain score 4-6) 41% and severe (NRS pain score (NRS pain score ≥ 7) 51%.

Characteristics	N (%)
Age,y	
:::::;30	140 (10%)
31-40	197 (14%)
41- 50	295 (21%)
51-60	351 (25%)
61-70	267 (19%)
71-80	112 (8%)
>80	42 (3%)
Gender	602 (42.88%)
Male Female	802 (57.12%)
Clinical type	
PHN	197 (14%)
Trigeminal neuralgia	140 (10%)
Postradiation plexopathy	84 (6%)
Poststroke pain	56 (4%)
Posttraumatic neuralgias	56 (4%)
PON	42 (3%)
Multiple sclerosis-related pain	30 (2%)
Chemotherapy- induced polyneuropathy	28 (2%)
Entrapment neuropathies	14 (1%)
Nerve compression or infiltration by tumor	13 (1%)
others peripheral origin neuropathic pain	98 (7%)
other central origin neuropathic pain	197 (14%)
neurophatic pain unclassified	449 (32%)

Table 1: Patient demographic and baseline characteristics. **PHN:** Postherpetic Neuralgia; PDN: Painful Diabetic Neuropathy

Characteristics	N (%)
Distribution of pain	
head and neck	408 (50%)
truncus	106 (13%)
four limbs	196 (24%)
the whole body	24 (3%)
others	82 (10%)
Pain severity category (NRS)	
mild (3)	65 (8%)
moderate (4-6)	335 (41%)
severe (7)	416 (51%)

Table 2: Distribution and severity category of pain.

Efficacy

Of all the participants, there were 355 patients completed 4-week follow up and valid questionnaires. We analyzed each patient endpoint pain score compared with the baseline pain score in each neuropathic pain classification (Table 3).

Assessment	Baseline	1st week	2nd week	3rd week	Endpoint	p-value
PHN	6.38	5.43	4.68	3.82	2.62	< 0.05
Trigeminal neuralgia	6.64	5.2	4.58	4.02	2 .91	<0.05
Postradiation plexopathy	6.14	4.99	4.27	3.46	2.35	<0.05
Poststroke pain	6.2	5.11	4.32	3.55	2.46	<0.05
Posttraumatic neuralgias	6.26	5.12	4.37	3.22	2.12	<0.05

PDN	6.7	5.36	4.48	3.69	2.7	<0.05
Multiple sclerosis- related	6.44	5.05	4.2	3.38	2.24	<0.05
Chemotherapy-induced polyneuropathy	6.56	5.44	4.31	3.32	2.1	<0.05
Entrapment neuropath ies	6.01	4.96	3.78	3.02	2.07	<0.05
Nerve compression or infiltration by tumor	6.67	5.41	4.65	3.48	2.24	<0.05
Other peripheral origin neuropathic pain	6.92	5.09	4.54	3.77	3.04	<0.05
Other central origin neuropathic pain	6.24	5.07	4.69	3.92	2.88	<0.05
Other unclassified neuropath ic pain	6.64	5.42	4.71	3.69	2.76	<0.05

Table 3: Pain score changes in each classification at weekly follow-up. **PHN:** Postherpetic Neuralgia; PDN: Painful Diabetic Neuropathy

The data showed that the pain scores at endpoint for all the classifications of neuropathic pain groups were significantly lower than those at baseline. The mean pain scores significantly decreased at first week after the treatment, and this reduction was remained through the entire treatment period. As a second efficacy parameter, the patient global impression of change showed the statistical improvement observed in the first week after pregabalin treatment, and it was maintained throughout the following treatment (Figure 2).

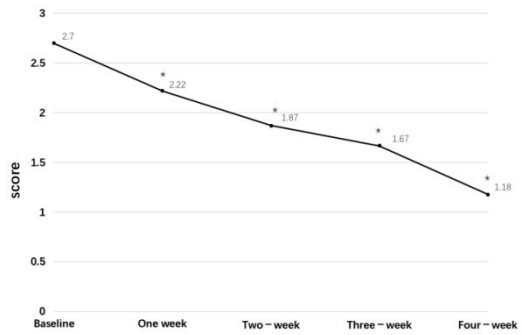

Figure 2: Patient global impression of change SF-MPQ. The patient global impression scores decreased at the first week after pregabalin treatment and maintained throughout the following treatment (* p<0.05).

Furthermore; we analyzed the efficacy of pregabalin for patients with different pain severity. As we can see from the results, patients at endpoint improved with flexible-dose pregabalin compared with baseline among different pain severity groups (Table 4).

Assessment	Baseline Pain Score	Pain Score at endpoint	p-value
Mild pain	2.07	1.6	<0.05
Moderate pain	5.73	2.51	<0.05
Severe pain	7.5	2.98	<0.05

Table 4: Pain score changes in different pain severity.

Improvement in the quality of life

In addition to measuring the efficacy of the pregabalin, we also evaluated the quality of life in participants during treatment. At endpoint, the sleep disorder index in different pain severity groups was significantly lowered than the baseline. It showed that pregabalin effectively improved patient's sleep quality (p<0.05) (Table 5). Pregabalin-treated patients had numerically better outcomes of HADS scores at endpoint compared with baseline among the mild pain, moderate pain and severe pain groups (p<0.05) (Table 6).

Assessment	Baseline Sleep Disorder Index	Sleep Disorder Index at endpoint	p-value
Mild pain	5.29	143	< 0.01
Moderate pain	4.86	1.98	<0.01
Severe pain	5.43	2.28	<0.01

Table 5: Sleep disorder index changes in different pain severity.

Assessment	Baseline Depression Index	Depression Index at endpoint	p-value
Mild pain	7.17	2.14	<0.01
Moderate pain	8.79	2.76	<0.01
Severe pain	9.74	3.1	<0.01

Table 6: Depression index changes in different pain severity.

Safety and tolerability

The number of adverse event (AE) and all kinds of AEs recorded by patients and investigators throughout the study are shown in Table 7. The most frequent AEs among pregabalin-treated patients were dizziness (12.8%), somnolence (8.5%), numbness in the hands, arms feet or legs (5.9%) and vertigo (5.1%). Most of these side effects went away during treatment as patients adjust to the medicine. The percentage of patients who were reduced dose or temporary withdrawal from AEs was 8.5%.

Type of AE	N (%)

Any AE	126 (35.5%)
More common AEs (;;::5% incidence)	
dizziness	45 (12.8%)
Somnolence	30 (8.5%)
numbness in the hands, arms, feet,or legs	21 (5.9%)
vertigo	18 (5.1%)
Less common (<5% incidence)	
dry mouth	6 (1.7%)
unsteady walk	2 (0.6%)
lack of coordination	1 (0.3%)
loss of bladder control	1 (0.3%)
peripheral edema	2 (0.6%)
Reduced dose or temporary withdrawal due to AEs	30 (8.5%)

Table 7: Patients with adverse events **AE:** Adverse Event

Discussion

This study was designed to determine the characteristics of NeP in a general population in China, and to evaluate the efficacy and tolerability of pregabalin in the management of different kinds of NeP, including the PHN which is currently the only indication of pregabalin. The data we presented in this study was based on 17 hospitals across the country, it can additionally provide extensive information for physicians and other healthcare providers on types of NeP populations. The pain characteristics of patients who reported chronic pain (grouped as different kinds of neuropathic pain) and their sex, age-group, pain site, pain severity category, sleep quality and depression index were collected and analyzed. Our study shows the effectiveness of pregabalin in the management of NeP in a large Chinese population, and meanwhile pregabalin produced significant improvement in different types of NeP including PHN, PDN, trigeminal neuralgia, postradiation plexopathy, poststroke pain, and other kinds of neuropathic pain. Previous studies have demonstrated pregabalin resulted in improvement in patients with PHN in China [14], and pregabalin was clinically meaningful in terms of improvement in pain in patients with fibromyalgia (FM), PDN, PHN in the USA 14 and Europe [15]. However, there are rare studies on the patients with other types of neuropathic pain in the large population of Chinese. In this open-label, multi-center, prospective study, patients receiving flexible-dosing pregabalin, guided by clinicians' responses to efficacy and tolerability issues 6, the data demonstrated PDN, trigeminal neuralgia, postradiation plexopathy, or other kinds of neuropathic pain together with PHN all showed significant results for the primary endpoint, the percent change in mean pain score compared with baseline strongly suggest the clinically meaningful improvement. The pain reduction occurred within the first week of practice, and it was remained through the 4-week study. Based on our findings and general clinical practice, flexible dosing of pregabalin allowed for dosage adjustment to optimize tolerability and efficacy. The results provide additional clinical evidence concerning utility pregabalin to different types of neuropathic pain in Chinese.

The improvement on the pain score was in line with the results on secondary parameter of sleep disturbance and of depressed mood. Both of the pain and quality of life were improved as early as the first week and sustained through the course of the study. PGIC measures were also elevated at each time point measured. Most paitents with NeP suffers from sleep and mood disorders which increase the pain feeling, and therefore sleep disturbance and emotional disorder are also the important therapeutic goal in the treatment of the NeP. Our study demonstrated that pregabalin effectively improved the overall sleep interference score at the first week of the practice. Improvement of the sleep quality decreases pain scores and increases overall health status indirectly, as the data showed the improved PGIC scores in our study. Most side effects from pregabalin were dizziness and somnolence, which went away when patients' bodies adjust to the medicine. Overall, pregabalin was safe and well tolerated.

Limitations

An important issue of this study is the high rate of outpatients drop-out. Two reasons are identified. The primary reason is the drug cost, since the drug wasn't covered in the basic medical insurance in China when the study was underway. Therefore, some of the patients with mild-moderate neuropathic pain dropped out the study because of the costs. The second one is perceived improvement which is related to the decreased compliance. For these reasons, the results of the present study have limitations and we need to establish the randomized placebo-controlled study and manage to decrease the drop-out rate in future studies.

Conclusion

This prospective study analyzed the distribution features of NeP in general population, established a standardized management of NeP in China and shared clinical experiences in the management of NeP with pregabalin. Pregabalin is effective and well tolerated without new side effects were identified.

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Significance

Our study analyzed the distribution features of neuropathic pain in general population, established a standardized management of neuropathic pain in China and shared clinical experiences in the treatment of neuropathic pain with pregabalin.

Declarations

Ethics approval and consent to participate

Study participants provided informed written consent prior to study enrolment. The study was approved by the China Association of Health Promotion and Education as a public welfare program. All patients provided written informed consent at study screening before receiving any study medication.

Consent for publication

All authors have agreed to the current submission.

Availability of data and materials

Data can be made available upon request.

Competing Interest

The authors declare that they have no competing interests.

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