DOI: 10.1111/papr.13049

ORIGINAL ARTICLE

The Greek Neuropathic Pain Registry: The structure and objectives of the sole NPR in Greece

Athina Vadalouca MD, PhD, FIPP[1,2] | Evnomia Alexopoulou-Vrachnou MD[1,3] | Martina Rekatsina MD[1,4] | Irene Kouroukli MD, PhD, FIPP[1,5] | Sousana Anisoglou MD, PhD[1,6] | Fani Kremastinou MD, PhD[1,7] | Zoi Gabopoulou MD, PhD[1,8] | Panagiota Chloropoulou MD[1,9] | Georgia Micha MD, MSc, PhD[1,3] | Athanasia Tsaroucha MD, PhD[1,10] | Ioanna Siafaka MD, PhD[1,10]

[1]Hellenic Society of Pain Management and Palliative Care (PARH.SY.A.), Athens, Greece

[2]Pain and Palliative Care Center, Athens Medical Center, Private Hospital, Athens, Greece

[3]Department and Pain Clinic and PC, Oncological Hospital "St. Savvas", Athens, Greece

[4]Whipps Cross Hospital, Barts Health NHS Trust, London, UK

[5]Private Anesthesiologist, Zografou, Athens, Greece

[6]ICU and Pain Medical Center, Theagenion Hospital, Thessaloniki, Greece

[7]Anaesthesiology and Pain & Palliative Care, Ippokration General Hospital, Athens, Greece

[8]KAT Hospital Evaluation Pain Center, Athens, Greece

[9]General Hospital of Kavala, Kavala, Greece

[10]First Department of Anesthesiology, National and Kapodistrian University of Athens, Athens, Greece

Correspondence
Athina Vadalouca, Department of Anesthesiology, Pain Management and Palliative Care, Director of Pain and Palliative Care Center, Athens Medical Center Private Hospital, Athens, Greece and University of Athens, Lefkon Oreon, Gerakas, 15344 Athens, Greece.
Email: athinajva@gmail.com

Funding information
Pfizer Hellas SA

Abstract

Objectives: Neuropathic pain (NP) is a complex condition that impairs the patients' quality of life. Registries are useful tools, increasingly used as they provide high-quality data. This article aims to describe the Greek Neuropathic Pain Registry (Gr.NP.R.) design, the patients' baseline data, and real-world treatment outcomes.

Methods: The Gr.NP.R. collects electronically, stores, and shares real-world clinical data from Pain and Palliative Care centers in Greece. It is a web-based application, which ensures security, simplicity, and transparency. VAS, DN4, and Pain Detect were used for pain and NP assessment.

Results: From 2016 to 2020, 5980 patients with chronic pain, of cancer or non-cancer origin, were examined and 2334 fulfilled the NP inclusion criteria (VAS > 5, DN4 > 4, and Pain Detect ≥ 19). At the first visit, the mean age was 64.8 years, 65.5% were female patients, and 97.9% were Greek. The mean (SD) time from pain initiation to visiting the pain clinics was 1.5 (3.8) years. Most patients were undertreated. Following the patients' registration, the national guidelines were implemented. The majority of the prescribed medications were gabapentinoids (70.2%), especially pregabalin (62.6%), and opioids (tramadol, 55.3%). At visits 1 and 6, mean VAS was 7.1 and 5, and mean DN4 score was 5.6 and 3.5, respectively.

Conclusions: The Gr.NP.R. provides information on the demographics, clinical progress, treatment history, treatment responses, and the drugs of choice for patients with cancer and non-cancer NP. The collected data may help physicians plan the management of their patients.

KEYWORDS
first-line medications, neuropathic pain, pain registry, pregabalin

INTRODUCTION

Chronic pain, which is often associated with various diseases, remains one of the most prevalent medical conditions. It is estimated that 100 million American adults, almost one-third of the total population, and 27% of the EU population suffer from chronic pain.[1]

Chronic pain is a leading cause of disability worldwide. One of the most challenging types of chronic pain is neuropathic pain (NP), caused by a lesion or disease of the somatosensory system.[2] NP is a complex condition, which impairs the patients' quality of life multidimensionally. A systematic review estimated the prevalence of pain with neuropathic characteristics between 6.9% and 10% and the incidence (new cases) of neuropathic pain around 8 cases per 1000 person-years.[3] NP can be either peripheral, resulting from nerve injury or disease (e.g., lumbar radiculopathy, post-herpetic neuralgia, diabetic or HIV related neuropathy, or post-surgical pain), or central due to a lesion or disease of the spinal cord or brain (e.g., cerebrovascular disease, neurogenerative diseases, and spinal cord injury).[4] Several patient-reported questionnaires are used for the diagnosis of NP or neuropathic components to chronic pain, such as the DN4[5] and Pain Detect[6]; these tools guide the patient to describe the characteristic traits of neuropathic pain (such as burning, tingling, sensitivity to touch, pain caused by light pressure, electric shock-like pain, pain to cold or heat, and numbness) and allow the physician to distinguish between neuropathic and non-neuropathic pain with high specificity and sensitivity.[7]

Existing studies may not be representative of the population with NP. Therefore, it is of utmost importance that we decided to establish a neuropathic pain registry in Greece to systematically record and describe the most relevant aspects of chronic NP, as well as the real-world outcomes of clinical interventions followed by pain specialists.

In the last years, the use of registries and the recognition of their importance is increasing. Compared to randomized controlled trials, registries gather continuously real-world information from a large number of patients. They are increasingly used for ameliorating clinical conditions, supporting clinical and epidemiological research, and planning healthcare services.[8] Examples[9] of pain registries are the PAIN OUT,[10] the first international acute pain registry, the "Oslo University Hospital Pain Registry,"[11] the Quebec Pain Registry,[12] and the PainData[13] in Denmark.

The Greek Neuropathic Pain Registry (Gr.NP.R.) is the first systematic effort of the Hellenic Society of Pain Management and Palliative Care (PARH.SY.A.) to record neuropathic pain in Greece as there is a knowledge-gap in the patients' profile and the treatment they receive. The registry collects data from thousands of patients with chronic NP, such as demographics and lifestyle factors, medical history, type of chronic NP, history of NP, pain medication, interventional techniques, and other treatments. Preliminary results from the registry were presented at the 10th World Congress of the World Institute of Pain (WIP),[14] where the authors concluded that the NP registry could be used to evaluate the long-term effectiveness and the safety of the drugs of choice in the clinical practice. The registry primarily aims to improve the therapeutic outcomes of the patients with NP by identifying sub-treated patients and optimizing their therapy. It is expected that this strategy will increase the proportion of patients with chronic NP resolution, reduce the time to symptom resolution, reduce the medication discontinuation rates due to adverse events, and subsequently will improve the patients' quality of life. Furthermore, the registry could help identify a pool of patients eligible for clinical studies. Finally, better management of the resources and minimization of the indirect costs of NP by increasing the patients' functionality and reducing patients' visits to a pain clinic can be expected. This article reports outcomes from patients with chronic cancer- and non-cancer NP, registered in a period of 4 years.

The authors of this registry followed the National therapeutic Guidelines for the treatment of NP, which were published in 2013 by PARH.SY.A.[15] and issued by the Hellenic Ministry of Health.[16]

Key Points

- Real-world data from patients with neuropathic pain in Greece are lacking.
- This is the first report from the Greek Neuropathic Pain Registry, which covers more than 2,000 patients for the period 2016-2020.
- The results show that patients with Neuropathic Pain in Greece are underdiagnosed and undertreated outside the specialists' pain clinics and that the specific therapeutic protocols need to be communicated to consultant GPs and other specialties.

METHODS

The Gr.NP.R. is a multicenter registry, which involves 7 tertiary Pain and Palliative Care Centers ("Agios Savvas" General Anticancer Hospital, "Aretaieio" University Hospital, Athens Medical Centre Private Hospital, "Ippokration" Hospital of Athens, "K.A.T" General Hospital, General Hospital of Kavala, and "Theagenio" Anticancer Hospital of Thessaloniki) in Greece. The centers operate regularly 2–5 times a week. All the investigators are members of PARH.SY.A.

The initiative to establish the first NP registry in Greece was undertaken by a selected workgroup, having in mind the safety of the data, the ease-of-use in everyday medical practice, and aiming to be an overall useful tool for the medical community. Following the submission of the application to the Hellenic Personal Data Protection Authority in 2014, laborious efforts were made to design the database structure. In parallel, a user-friendly website was created in collaboration with program developers. In 2015, educational videos with instructions for the users were developed. Users can access the registry via a personal computer (PC), tablet, or smartphone. Precautions for maximum protection of the registry data have been taken, implementing the Secure Lockets Layer (SSL) safety protocol for communication with the database, as well as custom personal codes provided by the database administrator. Physicians need to apply to the Scientific Committee and, after their approval, they become certified users of the registry. Finally, in May 2016, the registry was licensed by the Hellenic Data Protection Authority.

For inclusion in the study, the patients had to fulfill the following criteria: age 18 years or older, uncontrolled chronic pain, VAS score greater than 5, DN4 higher than 4, and Pain Detect score equal or higher than 19. DN4 and Pain Detect scores were assessed with the Greek validated questionnaires.[17,18] Patients who were not able to understand the registry's objectives or complete the questionnaires were excluded from the registry. Written informed consent was obtained from all patients.

At baseline, the following information was recorded: demographics, lifestyle factors, type of specialists who referred the patient and the number of patients self-referred to the clinic, etiology of the pain, pain intensity pain using the VAS (0–10), and medical history. We also recorded the time from symptoms initiation to referral or visit to a tertiary pain clinic, the pharmacological treatment, as well as the interventional and other treatments. The discontinuation rates of the drugs administered and the reasons for discontinuation were also recorded.

Patients were instructed to revisit the pain and palliative care clinic weekly for the first month (4 visits), and monthly for the next 2 months (maximum up to 6 visits). Pain intensity and type of pain were assessed at each follow-up visit with a VAS and the validated DN4 questionnaire.

Statistical analysis

All statistical analyses and generation of tables and patient data listings were performed using SAS release 9.4 (SAS Institute, Inc.). Summary statistics based on frequency tables were used for categorical variables. For continuous variables, descriptive statistics (mean, SD) were used.

TABLE 1 Sociodemographic characteristics of neuropathic pain in Greek pain clinics

Demographic characteristics	*N*	Percentage
Total enrolled patients	2334	100
Sex		
Male	806	34.5
Female	1528	65.5
BMI classification		
Underweight	64	2.7
Normal weight	687	29.4
Overweight	639	27.4
Obese	408	17.5
Not reported	536	23.0
Ethnicity		
Greek	2283	97.8
Other ethnicities	51	2.2
Lifestyle factors		
Smoker	496	21.3
Previous smoker	296	12.7
Non-smokers	1506	64.5
Alcohol consumption	36	1.5
Age (years)		
Mean (SD)	64.8 (15.6)	
Time from pain initiation to diagnosis (years)		
Mean (SD)	1.5 (3.8)	

Abbreviations: BMI, body mass index; *N*, number of patients.

RESULTS

From 5980 patients with cancer and non-cancer chronic pain who visited the pain and palliative care clinics from May 2016 to July 2020, we included 2334 patients who met the registry's selection criteria and were followed-up for up to 6 visits. Most of the patients were female (65.5%), of Greek ethnicity (97.9%), and the mean age was 64.7 years. Body mass index (BMI) classification at visit 1 showed that 29.4% of the patients had normal weight, and 44.9% were above the normal (25 kg/m^2). A small proportion of patients were smokers (21.3%), and 1.5% consumed alcohol regularly. The mean (SD) time from pain initiation to referral to the pain clinics was 1.5 (3.8) years. Table 1 presents the sociodemographic characteristics of the patients.

Nearly one third of the patients were referred to the pain clinics by general practitioners (624 patients, 26.7%), whereas more than one third (891, 38.2%) self-referred, 276 (11.8%) were referred by oncologists, 217 (9.3%) by orthopedic surgeons, 114 (4.9%) by dermatologists, 95 (4.1%) by diabetologists, 48 (2.1%) by neurologists, 25 (1.1%) by neurosurgeons, 22 (0.9%) by rheumatologists, and 22 (0.9%) by other specialties (22, 0.9%; Figure 1).

The most frequent NP type was peripheral (96.9% of the overall patient population), followed by cancer NP

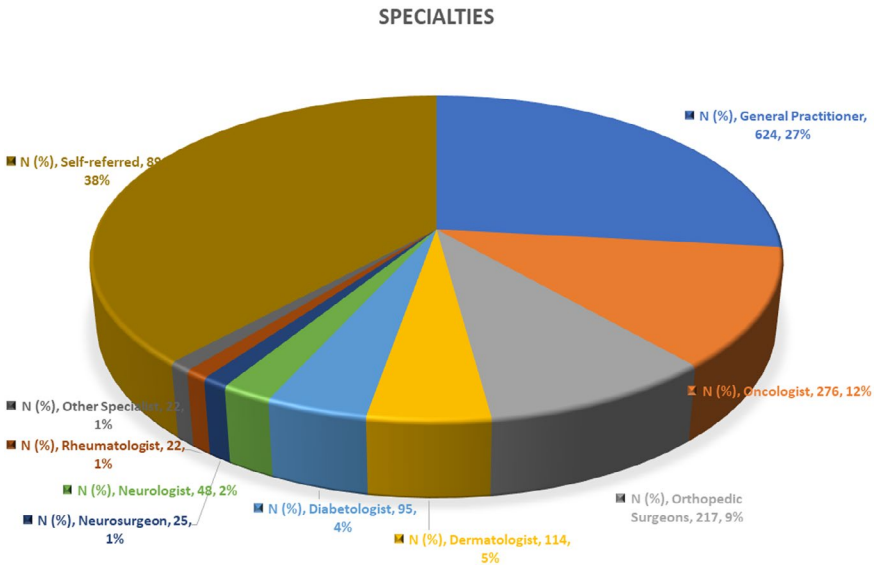

FIGURE 1 Referring specialties

(7.8%), and special NP syndromes (7.7%), whereas 4.2% of the patients suffered from central NP. Radiculopathy was the most prevalent etiology of peripheral NP, accounting for 48.5% of the patients, followed by peripheral neuropathy (chemotherapy-induced neuropathy [CIPN + survivors], 17.6%), post-herpetic neuralgia (9.2%), and post-operative pain (11.7%). Cancerous infiltration was the most frequent etiology for cancer NP, accounting for 60.7% of the cases. Pain of central neuropathy was most often attributed to multiple sclerosis (24.2%) and stroke (21.2%). The clinical characteristics of pain are shown in Table 2.

Patients were followed up regularly after their recruitment, and pain assessments were performed at each visit. Figure 2 shows the percentage of patients per visit.

Pain assessments were performed at each visit with 2 questionnaires, and the mean scores appear in Figures 3 and 4. The mean VAS score was 7.1 at visit 1, and 5 at visit 6 (reduced by 29.6%), and the mean DN4 score was 5.6 at visit 1, and 3.5 at visit 6 (reduced by 37.5%).

The drugs used for NP treatment before and after the patients' recruitment to the registry appear in Table 3 by frequency. Most patients (almost 60%) had not received any medication for NP before their first visit to the pain clinics. Weak opioids (codeine and tramadol) were the most commonly used drug for these patients (11.0%), followed by gabapentinoids (9.9%).

Following the patients' examination, the majority of the prescribed medications were gabapentinoids (70.2% overall, 62.6% pregabalin, and 7.6% gabapentin) and weak opioids (55.3%). Maximum medication dose was prescribed, during visits, to the majority of patients on COX-2 inhibitors (71.8%), and paracetamol (59.9%), 34.7% of the patients on nonsteroidal anti-inflammatory drug (NSAIDs; Diclofenac and Lornoxicam), 32.7% of the patients on venlafaxine, and 4.8% and 1.1% of the patients on pregabalin and gabapentin, respectively. The median starting dose for each medication and the maximum prescribed dose is shown in Table 4.

Patients discontinued treatment more frequently when on NDAIDs (33.7%), COX-2 inhibitors (23.1%), combination of oxycodone-paracetamol (22.4%), and opioids (19.3%), mainly due to lack of effectiveness and adverse events. Discontinuation rates were lower for patients on pregabalin (8.4%, mainly due to adverse events) and paracetamol (6.6%, due to ineffectiveness; Table 5).

Pharmacological treatment is fundamental in NP management, but as for every chronic pain, NP requires an interdisciplinary approach. In our registry, interventional techniques and other treatments (third line treatment) were applied to a very small portion of the patients with NP (Table 6). The most common treatment was acupuncture (8.3% of the patients).

DISCUSSION

Clinical registries collect real-world data longitudinally and give information, which can improve the patient's health care and help address problems for different stakeholders in the healthcare system (patients, physicians, and payers).[19]

The Gr.NP.R. by PARH.SY.A. is the first organized attempt to collect data from patients with chronic cancer and non-cancer NP who visit pain and palliative care centers in Greece. The first results are reported here in an effort to map the disease's landscape and present information on patient demographics, clinical characteristic of the disease, treatment patterns, and outcomes.

Data from 2334 patients were collected from May 2016 to July 2020 in 7 pain and palliative care clinics.

TABLE 2 Clinical characteristics of neuropathic pain in Greek pain clinics

Type of NP[a]	*N*	Percentage
Peripheral NP	**2262**	**96.9**
Radiculopathy (low back pain, neck pain, sciatica, thoracic)	**1098**	48.5
Cervical	172	7.6
Thoracic	86	3.8
Lumbosacral	753	33.3
Sciatica	108	4.8
Post-herpetic neuralgia	**208**	9.2
Plexopathy (Brachial plexus avulsion)	**15**	0.7
Peripheral neuropathy	**436**	19.3
Chemotherapy-induced (CIPN + survivors)	399	17.6
Diabetic	29	1.3
Other etiologies	8	0.4
Mononeuropathy (Carpal tunnel syndrome)	**8**	0.4
Postoperative (postsurgical, surgery from cancer)	**265**	11.7
Post-traumatic	**73**	3.2
Other (osteoarthritis, autoimmune disease, CRPS(II), diabetic mononeuropathy)	**159**	7.0
Central NP	**99**	**4.2**
Multiple sclerosis pain	24	24.2
Stroke pain	21	21.2
Spinal cord injury	8	8.1
Other (Parkinson, phantom limb, myelopathy, syringomyelia)	46	46.5
Cancer NP	**183**	**7.8**
Cancerous infiltration	111	60.7
Postradiotherapy	72	39.3
Special syndromes (fibromyalgia, trigeminal neuralgia)	**179**	**7.7**

Note: Percentages of the subcategories are calculated over the respective category's number of patients (2262, 99, 183, and 179, respectively).

Abbreviations: Central NP, neuropathic pain of central nervous system; CIPN, chemotherapy-induced peripheral neuropathy; CRPS, complex regional pain syndrome; NP, neuropathic pain; *N*, number of patients.

[a]Percentages for the 4 major NP types (peripheral, central, cancer, and special syndromes) are calculated over the total number of patients ($N = 2334$). Many patients presented with more than 1 of the 4 major NP manifestations, hence the sum patients in the 4 categories is higher than 2334. Similarly, the sum of the 4 minor categories in radiculopathy is 1119 (not 1098). This is due to patients presenting more than one category of pain (the 4 minor categories are not mutually exclusive).

Bold values are N/A: No statistical analysis was done. *P*-values are not available.

Most patients were female (65.5%), higher than that reported in epidemiological studies,[7] and in-line with Momi et al.[20] who reported that sex is a risk factor for the development of NP. Furthermore, the mean age of the patients was 64.8 years, a typical age group of patients with NP, reinforcing the suggestion that increased age is a risk factor for NP.[20] Almost 1 in 5 patients were smokers, which is lower to the smoking prevalence in Greece (37% according to an EU survey in 2017).[21] However, this difference could be attributed to the higher representation of women in our patient-group and the patients' high mean age. We also observed that a low proportion of our patients were regular alcohol consumers (1.5%). Finally, almost all patients were of Greek ethnicity. PARH.SY.A. has been educating patients on pain management for more than 23 years; all educational material and advertisements are published only in Greek web sites. As a result, patients who do not speak Greek may not be aware of our pain clinics.

The mean time from pain initiation to diagnosis was 1.5 years. A similar study in Germany, published in 2009, investigated patients with headache, low back pain, and NP, and reported that the average time from pain symptoms to the first consultation with their general practitioner (GP) was 3 years, and it took 9 more years on average for patients to be referred to a specialized pain center.[22] The reduced time from symptoms to diagnosis might be due to the wider use of the NP-specific questionnaires from pain specialists following the Greek linguistic validations.[17,18] However, there is still an unmet need to reduce the time to patients' visit to specialized pain clinics and diagnosis.

The clinical characteristics of NP are in line with observations from other studies; the most prevalent NP type is peripheral in origin, most commonly radiculopathy,[23,24] followed by chemotherapy-induced peripheral

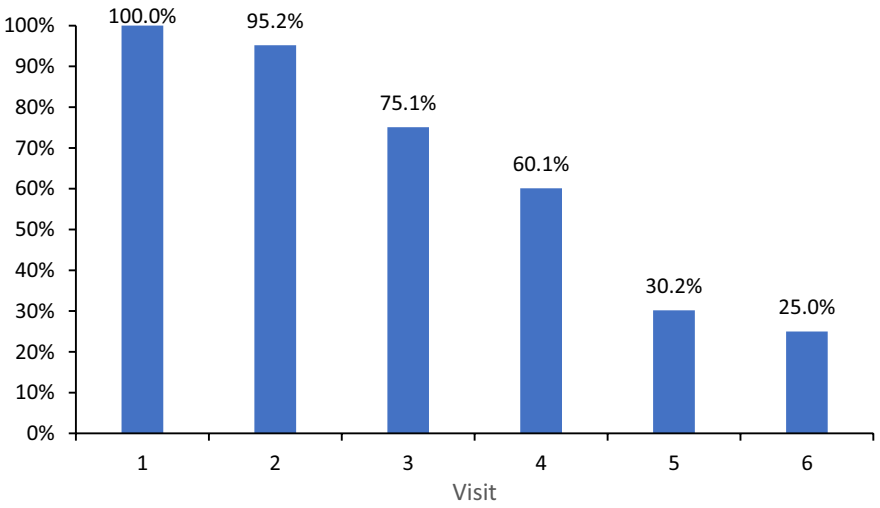

FIGURE 2 Percentage of patients per visit

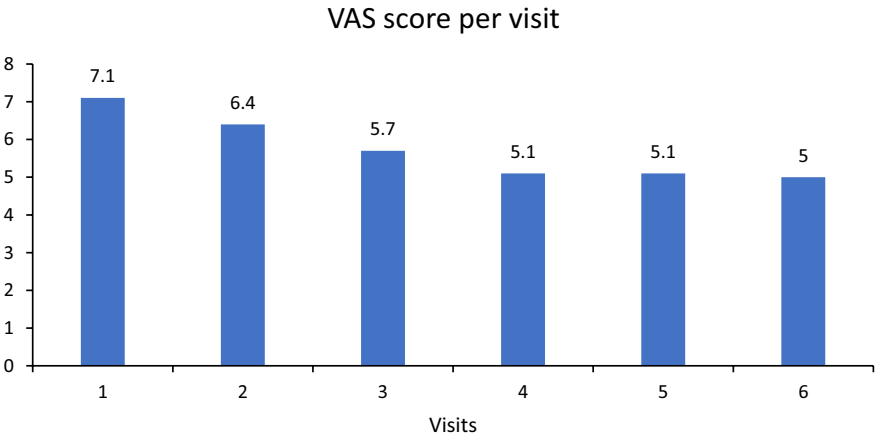

FIGURE 3 Average VAS score by visit

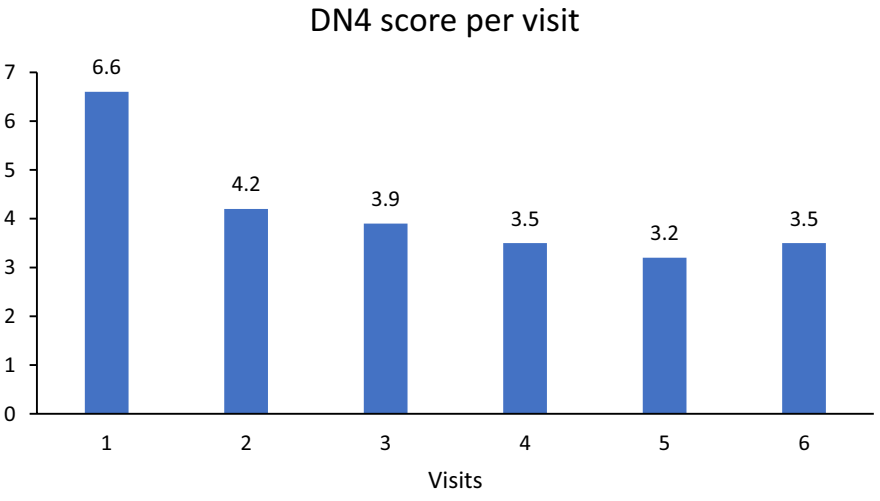

FIGURE 4 Average DN4 score by visit

TABLE 3 Frequency of drugs used for NP before and after patients' participation in the Gr.NP.R.

Drug	*N* (%) Treatment administered before visiting pain clinic	*N* (%) Treatment administered after visiting pain clinic
Weak opioids[a]	257 (11.0%)	1291 (55.3%)
Pregabalin	181 (7.8%)	1462 (62.6%)
Paracetamol	92 (3.9%)	723 (31.0%)
NSAIDs	87 (3.7%)	95 (4.1%)
Duloxetine	80 (3.4%)	253 (10.8%)
Strong opioids[b]	78 (3.3%)	544 (22.3%)
Gabapentin	50 (2.1%)	177 (7.6%)
Venlafaxine	28 (1.2%)	37 (1.6%)
COX-2 inhibitors	28 (1.2%)	412 (17.7%)
Lidocaine (patch)	21 (0.9%)	282 (12.1%)
Tricyclic antidepressants	15 (0.6%)	10 (0.4%)
Capsaicin (patch)	11 (0.5%)	23 (1.0%)

Note: Denominator: Total number of patients (*N* = 2334).

Abbreviation: Gr.NP.R., Greek Neuropathic Pain Registry; NP, neuropathic pain; NSAIDs, non-steroidal anti-inflammatory drugs.

[a]Weak opioids include codeine and tramadol.

[b]Strong opioids include fentanyl, tapentadol, buprenorphine, and morphine.

TABLE 4 Median starting and maximum drugs' doses for patients in pain clinics

Drug	Median starting dose	Max dose given	Percentage of patients who received the maximum dose
Opioids (Tramadol) (mg)	150.0	400.0	14.9
Opioids (Tapentadol) (mg)	50.0	600.0	
Opioids (Fentanyl) (μg/h) (patch)	50.0	250.0	
Opioids (Buprenorphine) (μg) (patch)	35.0	100.4	
Pregabalin (mg)	100.0	600.0	4.8
Paracetamol (mg)	3000.0	4000.0	59.9
COX-2 inhibitors (Celecoxib) (mg)	200.0	400.0	71.8
Lidocaine (patch)	1.0	3.0	10.3
Duloxetine (mg)	30.0	120.0	4.3
Gabapentin (mg)	900.0	3600.0	1.1
Oxycodone + Paracetamol (mg)	15.0	40.0	5.1
NSAIDs (Diclofenac) (mg)	50.0	100.0	34.7
NSAIDs (Lornoxicam) (mg)	8.0	16.0	
Venlafaxine (mg)	30.0	150.0	32.4
Capsaicin (patch)	1.0	3.0	8.7
Tricyclic antidepressants (mg)	25.0	75.0	30.0

Abbreviation: NSAIDs, non-steroidal anti-inflammatory drugs.

neuropathy,[25,26] post-herpetic neuralgia,[27] and postoperative pain.[28–30]

A very small proportion of patients was directed from our clinics to the third line treatment, such as interventional techniques and other complementary and alternative therapies. It is important to know that from the 7 centers included in the study, interventional techniques, such as spinal cord stimulation and totally implanted drug delivery systems (IDDS), are used in only 2 of them.

Only 30.8% of the patients were prescribed medication for NP, and less than 10% were prescribed any of the first-line medications recommended in the national guidelines, before the first visit to the specialist pain clinics. Almost half of the patients with peripheral NP had low back pain. Furthermore, a very low percentage of patients with diabetic neuropathy were referred to our registry (1.3%). There is a need to train physicians of other specialties in the contemporary treatment strategies for patients with NP in Greece, which would improve the outcomes and reduce healthcare costs.

In Greece, PARH.SY.A. issued and published online[15] in 2013, the guidelines for the treatment of chronic NP,

TABLE 5 Discontinuation rates and reasons for discontinuation

Drug	Discontinued[a]	Adverse events	Cost	Ineffectiveness	Patient preferences	Unknown
Opioids	323 (19.3%)	32 (1.9%)	0	49 (2.9%)	10 (0.6%)	232 (13.8%)
Pregabalin	123 (8.4%)	31 (2.1%)	0	12 (0.8%)	7 (0.5%)	73 (5.0%)
Paracetamol	48 (6.6%)	3 (0.4%)	0	10 (1.4%)	0	35 (4.8%)
NSAIDs	32 (33.7%)	2 (2.1%)	0	9 (9.5%)	0	21 (22.1%)
Duloxetine	47 (18.6%)	14 (5.5%)	1 (0.4%)	3 (1.2%)	1 (0.4%)	28 (11.1%)
Gabapentin	23 (13.0%)	3 (1.7%)	0	1 (0.6%)	3 (1.7%)	16 (9.0%)
Venlafaxine	5 (13.5%)	2 (5.4%)	0	1 (2.7%)	1 (2.7%)	1 (2.7%)
COX-2 inhibitors	95 (23.1%)	2 (0.5%)	0	5 (1.2%)	1 (0.2%)	87 (21.1%)
Lidocaine	36 (12.8%)	5 (1.8%)	2 (0.7%)		1 (0.4%)	28 (9.9%)
Tricyclic antidepressants	1 (10.0%)	0	0	0	0	1 (10.0%)
Capsaicin (patch)	1 (4.3%)	0	0	0	0	1 (4.3%)
Oxycodone + Paracetamol	35 (22.4%)	7 (4.5%)	0	7 (4.5%)	0	21 (13.5%)

Abbreviation: NSAIDs, non-steroidal anti-inflammatory drugs.

[a]Frequency of patients who discontinued over the total number of patients treated with each drug.

TABLE 6 Interventional techniques and other treatments

Treatment	*N* (%)
Nerve blockages	
Peripheral nerve blocks	85 (3.6%)
Trigger points	62 (2.7%)
Epidural infusion	62 (2.7%)
Implanted spinal drug delivery systems	
Epidural PCA	14 (0.6%)
Subarachnoid	3 (0.1%)
Spinal cord stimulation	1 (0.04%)
Other therapies	
Psychological support	190 (8.1%)
Acupuncture	194 (8.3%)
Physical therapy	94 (4.0%)
TENS	7 (0.3%)
Shiatsu	34 (1.5%)
Reflexology	32 (1.4%)
Yoga	2 (0.1%)
Occupational therapy	1 (> 0%)
Music therapy	1 (> 0%)
Other therapy	74 (3.2%)

Abbreviations: PCA, patient-controlled analgesia; TENS, transcutaneous electrical nerve stimulation.

which have been adopted by the Hellenic Ministry of Health in the therapeutic protocols for the management of NP.[16] The guidelines specify the treatment for different types of NP for example, in post-herpetic neuralgia, pregabalin and not gabapentin is considered first-line therapy along with tramadol, tramadol-paracetamol and capsaicin patches and combinations of these drugs, whereas serotonin-norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs) are reconsidered as second line. In peripheral diabetic neuropathy, pregabalin, tramadol, and tramadol-paracetamol are recommended as first-line treatment, whereas gabapentin and the SNRIs (venlafaxine and duloxetine) are second line treatments. In chronic back pain with neuropathic characteristics and postsurgical NP, pregabalin (and not gabapentin), tramadol, tramadol-paracetamol, and capsaicin are first-line treatments (and short term COX-2 for chronic back pain).[16] Following the patients' referral to our registry, almost all received treatment according to the current guidelines. The only discrepancy was that lidocaine 5% was most often prescribed instead of capsaicin 8%; the reason is that capsaicin supplies were discontinued in Greece at the time of the patients' recruitment.

In our registry, medication was altered for most patients to reflect the current guidelines and the neuropathic specific approved treatments (weak opioids and gabapentinoids). As a result, 55.3% of the patients were treated with weak opioids and 62.6% with pregabalin, both first-line medications for NP. Adjustments were also made to the starting dose of the medication when the symptoms were not alleviated.

Pregabalin is a frontline therapy for NP according to our National Guidelines. Evidence shows the efficacy of pregabalin in post-herpetic neuralgia, painful diabetic neuralgia, and mixed or unclassified post-traumatic NP and cancer NP.[31–33] Pregabalin treatment can start at 100 mg and dose increases every 3–7 days are allowed up to 600 mg (in 2 or 3 daily doses). However, the median starting dose of pregabalin was 100 mg and only 4.8% of the patients on pregabalin received the maximum allowed dose.

The cost-effectiveness of pregabalin versus gabapentin in the management of peripheral NP, associated

with post-herpetic neuralgia and diabetic neuropathy, has been studied in the Greek healthcare setting.[34] Pregabalin demonstrated a reduction in days with moderate to severe pain when compared to gabapentin. The authors concluded that the treatment of pain associated with peripheral diabetic neuropathy and post-herpetic neuralgia with pregabalin is a cost-effective intervention for the social security in Greece compared to gabapentin.

This change in the treatment and the subsequent dose modifications were followed by a spectacular improvement in the patients' pain intensity and symptoms (burning, tingling, sensitivity to touch, pain caused by light pressure, electric shock-like pain, pain to cold or heat, and numbness); mean VAS score was reduced from 7.1 to 5 (−29.6%), and DN4 from 5.6 to 3.5 (−37.5%; Figures 3 and 4). We did not assess the patients symptoms with the Pain Detect scores at follow-up visits, although it has been used as a monitoring tool for NP symptoms because it is time-consuming and the main information is already captured by the DN4 questionnaire.[17] Almost 60% of the patients completed their visit schedule in 4 visits (1 month), and only 25% required 6 visits (Figure 2). Finally, a small proportion of patients discontinued their treatment, highlighting the effectiveness of the current guidelines.

CONCLUSIONS

The Gr.NP.R. has been active since May 2016, and 2334 patients have been registered up to July 2020. The first results reveal that patients with NP in Greece are underdiagnosed and undertreated outside the specialists' pain clinics and that the specific therapeutic protocols issued by the Ministry of Health need to be communicated to consultant GPs and other specialties.

Implementing the therapeutic protocols for the treatment of the registered patients resulted in spectacular clinically meaningful decreases in the pain scores and low discontinuation rates.

The registry can provide data to evaluate the long-term effectiveness, safety, and tolerability of the drugs of choice (pregabalin, tramadol, lidocaine 5%, capsaicin 8%, gabapentin, and duloxetine) and the combination treatment in the clinical practice.

We had lower than expected number of patients, which can be attributed to the small number of anesthesiologists, the fact that pain clinics are not officially established, and that most of the pain clinics operate twice per week. There is a need to expand our registry to more centers and include all patients with chronic pain.

It is important that the Gr.NP.R. gains acceptance from competent National Authorities Information of the medical community through data recorded for clinical management improvement, and entry of a sufficient number of patients aiming at the publication of articles from our system's data.

Our mission is to make the Registry of Patients with chronic NP available in every country through European or global scientific societies.

ACKNOWLEDGEMENTS

The authors would like to thank the patients for their participation in the study. The analysis was done by Ioannis Katagas, an employee of HeADS S.A.

CONFLICTS OF INTEREST

Funding for the purchase of the registry's software and medical writing of this manuscript was provided by Pfizer Hellas SA. Prof. Vadalouca is a speaker for Pfizer, Menarini, Astellas, Vianex, Angelini, and Prostracan. Dr. Alexopoulou-Vrachnou: declares that she has been the Official Speaker on behalf of the following pharmaceutical companies: Pfizer, Takeda, Vianex, Anabiosis-Prostracan, Brain Therapeutics, and Mylan. Dr. Rekatsina declares no conflicts of interest. Dr. Kouroukli is a speaker for Janssen, Nycomed, Astellas, Vianex, and Pfizer. Dr. Anisoglou is a speaker for Vianex, Angelini, Pfizer, and anaBIOsis-Kyowa Kirin. Dr. Kremastinou is a speaker in collaboration with the following companies: Astellas, Menarini, and Vianex. Dr. Gabopoulou is a speaker for Menarini and Astellas. Dr. Chloropoulou declares no conflicts of interest. Dr. Micha declares no conflicts of interest. Prof. Tsaroucha is a speaker for Vianex. Prof. Siafaka is a speaker for Pfizer, Menarini, Astellas, Vianex, Angelini, Prostracan, and Brain-Therapeutics.

ORCID

Athina Vadalouca https://orcid.org/0000-0001-8761-2234

REFERENCES

1. Park PW, Dryer RD, Hegeman-Dingle R, Mardekian J, Zlateva G, Wolff GG, et al. Cost burden of chronic pain patients in a large integrated delivery system in the United States. Pain Pract. 2016;16(8):1001–11.
2. Treede R-D, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology. 2008;70(18):1630–5.
3. van Hecke O, Austin SK, Khan RA, Smith BH, Torrance N. Neuropathic pain in the general population: a systematic review of epidemiological studies. Pain. 2014;155(4):654–62.
4. Smith BH, Torrance N. Epidemiology of neuropathic pain and its impact on quality of life. Curr Pain Headache Rep. 2012;16:191–8.
5. Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain. 2005;114:29–36.
6. Freynhagen R, Baron R, Gockel U, Tölle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin. 2006;22(10):1911–20.
7. Colloca L, Ludman T, Bouhassira D, Baron R, Dickenson AH, Yarnitsky D, et al. Neuropathic pain. Nat Rev Dis Prim. 2017;3:17002.

8. Hoque D, Kumari V, Hoque M, Ruseckaite R, Romero L, Evans SM. Impact of clinical registries on quality of patient care and clinical outcomes: a systematic review. PLoS One. 2017;12(9):e0183667.
9. Vadalouca A, Rekatsina M. Neuropathic pain registries improve pain management and provide more efficacious planning of healthcare services. Pain Ther. 2020;9(1):1–6.
10. Zaslansky R, Rothaug J, Chapman CR, Bäckström R, Brill S, Fletcher D, et al. PAIN OUT: the making of an international acute pain registry. Eur J Pain. 2015;19(4):490–502.
11. Granan LP, Reme SE, Jacobsen HB, Stubhaug A, Ljoså TM. The Oslo University Hospital Pain Registry: development of a digital chronic pain registry and baseline data from 1712 patients. Scand J Pain. 2019;19(2):365–73.
12. Choinière M, Ware MA, Pagé MG, Lacasse A, Lanctôt H, Beaudet N, et al. Development and implementation of a registry of patients attending multidisciplinary pain treatment clinics: The Quebec Pain Registry. Pain Res Manag. 2017;2017:1–16. https://doi.org/10.1155/2017/8123812
13. Vægter HB, Høybye MT, Larsen SK, Hansen OB, Pedersen CB, Jensen P, et al. PainData: a clinical pain registry in Denmark. Scand J Pain. 2017;16(1):185.
14. Siafaka I, Rekatsina M, Vrachnou E, Kouroukli I, Anisoglou S, Kremastinou F, et al. Registry for patients with chronic neuropathic pain, preliminary results from the Greek registry. Pain Practice. 2020;20 S1:ID296, p. 42.
15. Greek registry for neuropathic pain website (Greek only). https://grpalliative.gr/mnp/. Accessed 15 Oct 2020.
16. Hellenic Ministry of Health; 2018. https://www.moh.gov.gr/articles/health/domes-kai-draseis-gia-thn-ygeia/kwdikopoihseis/therapeytika-prwtokolla-syntagografhshs/diagnwstika-kai-therapeytika-prwtokolla-syntagografhshs/5418-diagnwstika-kai-therapeytika-prwtokolla-syntagografhshs-epwdynwn-syndromwn
17. Sykioti P, Zis P, Vadalouca A, Siafaka I, Argyra E, Bouhassira D, et al. Validation of the Greek version of the DN4 diagnostic questionnaire for neuropathic pain. Pain Pract. 2015;15(7):627–32.
18. Linguistic validation certificate; Pain DETECT questionnaire. Mapi Research Institute; 2008.
19. Lübbeke A, Carr AJ, Hoffmeyer P. Registry stakeholders. EFORT Open Rev. 2019;4(6):330–6.
20. Momi SK, Fabiane SM, Lachance G, Livshits G, Williams FM. Neuropathic pain as part of chronic widespread pain: environmental and genetic influences. Pain. 2015;156(10):2100–6.
21. Special Eurobarometer 458 – Wave EB87.1 – TNS opinion & social, May 2017.
22. Schulte E, Hermann K, Berghöfer A, Hagmeister H, Schuh-Hofer S, Schenk M, et al. Referral practices in patients suffering from non-malignant chronic pain. Eur J Pain. 2010;14(3):308.e1–10.
23. de Andrés J, de la Calle JL, Pérez M, López V. Clinical characteristics, patient-reported outcomes, and previous therapeutic management of patients with uncontrolled neuropathic pain referred to pain clinics. Pain Res Treat. 2014;2014:1–15.
24. Leadley RM, Armstrong N, Lee YC, Allen A, Kleijnen J. Chronic diseases in the European Union: the prevalence and health cost implications of chronic pain. J Pain Palliat Care Pharmacother. 2012;26(4):310–25.
25. Girach A, Julian TH, Varrassi G, Paladini A, Vadalouka A, Zis P. Quality of life in painful peripheral neuropathies: a systematic review. Pain Res Manag. 2019;2019:1–9.
26. Brozou V, Vadalouca A, Zis P. Pain in platin-induced neuropathies: a systematic review and meta-analysis. Pain Ther. 2018;7(1):105–19.
27. García-González AI, Rosas-Carrasco O. Herpes zoster (HZ) y neuralgia posherpética (NPH) en el adulto mayor: particularidades en la prevención, el diagnóstico y el tratamiento [Herpes zoster and post-herpetic neuralgia in the elderly: Particularities in prevention, diagnosis, and treatment]. Gac Med Mex. 2017;153(1):92–101.
28. Breivik H, Stubhaug A. Management of acute post-operative pain: still a long way to go!. Pain. 2008;137(2):233–4.
29. Fletcher D, Stamer UM, Pogatzki-Zahn E, Zaslansky R, Tanase NV, Perruchoud C, et al. Chronic post-surgical pain in Europe: an observational study. Eur J Anaesthesiol. 2015;32(10):725–34.
30. Stamer UM, Ehrler M, Lehmann T, Meissner W, Fletcher D. Pain-related functional interference in patients with chronic neuropathic post-surgical pain: an analysis of registry data. Pain. 2019;160(8):1856–65.
31. Derry S, Bell RF, Straube S, Wiffen PJ, Aldington D, Moore RA. Pregabalin for neuropathic pain in adults. Cochrane Database Syst Rev. 2019;1:Art. No.: CD007076.
32. Raptis E, Vadalouca A, Stavropoulou E, Argyra E, Melemeni A, Siafaka I. Pregabalin vs. opioids for the treatment of neuropathic cancer pain: a prospective, head-to-head, randomized, open-label study. Pain Pract. 2014;14(1):32–42.
33. Bannister K, Sachau J, Baron R, Dickenson AH. Neuropathic pain: mechanism-based therapeutics. Annu Rev Pharmacol Toxicol. 2020;6(60):257–74.
34. Athanasakis K, Petrakis I, Karampli E, Vitsou E, Lyras L, Kyriopoulos J. Pregabalin versus gabapentin in the management of peripheral neuropathic pain associated with post-herpetic neuralgia and diabetic neuropathy: a cost-effectiveness analysis for the Greek healthcare setting. BMC Neurol. 2013;13:56.