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# Localised neuropathic pain in the primary care setting: a cross-sectional study of prevalence, clinical characteristics, treatment patterns, quality of life and sleep performance

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## ABSTRACT

**Background:** Localised Neuropathic Pain (LNP) is challenging to diagnose and manage in primary care. **Objective:** To describe clinical characteristics, treatment patterns, quality of life and sleep performance of patients with LNP and estimate its prevalence in primary care.

**Methods:** Cross-sectional study in 4 European countries. Patients were identified using a screening tool for LNP. Patients completed the EQ-5D VAS score and Chronic Pain Sleep Inventory (CPSI).

**Results:** There were 1030 LNP patients for analysis. They presented a median pain intensity of 6.0 (IQR 4.0–7.0) with a median duration of 30.9 months (IQR 12.0–75.3), despite 97% receiving pain treatment. Main sites affected were the limbs (62% upper/58% lower) and spine (41%). Main aetiologies were neuropathic low back pain (47%), post-surgical neuropathic pain (17%), and diabetic poly-neuropathy (12%). Thirty percent received a single analgesic (2% topical), while combinations comprised 43% systemic-systemic, 24% topical-systemic, 1% topical-topical. Medications included NSAIDs (45%), anticonvulsants (38%), WHO step 2 opioids (35%), and topical analgesics (27%). In the previous 6 months, 40% had switched treatment. The mean (SD) EQ-5D VAS score was 58 (22.3) and the mean (SD) EQ-5D summary score (UK tariff) was 0.62 (0.25). Patients had a CPSI mean index of 41/100, and sleeping pills were used by 33% of patients. The standardized prevalence of LNP by age and sex was 2.01% in the general population and 43.3% among chronic pain patients.

**Conclusions:** Many LNP patients reported pain intensities of six on a ten-point scale in average for durations longer than 2.5 years, with quality of life and sleep performance affected, with frequent treatment combinations and switches, suggesting suboptimal pain management.

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Localized neuropathic pain; analgesics; primary care; prevalence; quality of life; sleep performance

## Introduction

Chronic pain is a debilitating condition for the affected individuals and the society overall. The prevalence of chronic pain of neuropathic origin (i.e. neuropathic pain) has been shown to be 7–8% in the general population<sup>1–4</sup>. Neuropathic pain (NP) is often misdiagnosed or underdiagnosed and patients can experience a trail of treatment errors, with personal and social negative impact.

The NP aetiology can involve viral infections (e.g. herpes zoster, HIV), metabolic disorders (e.g. diabetes), inflammation (e.g. radiculopathy), cancer, post-surgical and traumatic sequelae, as well as events affecting the central nervous system (e.g. stroke, spinal cord lesions). Patients who suffer from NP often experience constant burning pain, intermittent stabbing, lancinating pains and allodynia<sup>2,3</sup>. Clinical signs and symptoms are similar across different NP conditions and several grading

scales and other diagnostic tools (e.g. Neuropathic Pain Scale) have been developed to assess the multiple domains of NP.

Localization (and size) are important characterizing features of NP. Mick et al. proposed to define Localized Neuropathic Pain (LNP) as “a type of neuropathic pain that is characterized by consistent and circumscribed area(s) of maximum pain”<sup>5</sup>. LNP arises due to damage to a peripheral nerve; but can also arise from a lesion to a nerve plexus or a nerve root. Post-herpetic neuralgia (PHN), painful diabetic polyneuropathy (DPN), neuropathic postsurgical pain, painful neuropathy in human immunodeficiency virus infection, neuropathic cancer pain and neuropathic low back pain (e.g. radiculopathy) are often characterized by localized pain. Although LNP is not yet commonly understood, nor mentioned in international and regulatory pain guidelines, a well-recognized definition of LNP could support the identification of patients and

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*a tool to identify such LNP patients could provide added value to health care professionals. This is important as appropriate identification of patients impacts treatment selection.*

General practitioners (GPs) are the first healthcare professionals that chronic pain patients visit, and pain represents about 40% of primary care consultations<sup>6</sup>. Only 2% of chronic pain patients are followed up by a pain specialist<sup>6</sup>. A screening tool based on the International Association for the Study of Pain (IASP) grading principles for NP (which focus on the evaluation of the NP history coupled with the distribution of symptoms and sensory signs) is used for a prompt initial identification of LNP in primary care<sup>1</sup>. The LNP screening tool consists of four questions about the history, the anatomy, the sensory examination, and the size of the painful area. If the medical history, the anatomy and the signs of pain make NP plausible and the painful area is constant and circumscribed the patient probably suffers from LNP. This screening tool has been validated against clinical diagnoses by pain experts and shown to be suitable for routine clinical use with a sensitivity of 83.2% and specificity of 88.2%<sup>7</sup>.

Current systemic treatment options for NP include anticonvulsants (gabapentin, pregabalin) and tricyclic antidepressants (amitriptyline, desipramine, nortriptyline) as first line treatment. Secondary or tertiary line treatments are serotonin–norepinephrine reuptake inhibitors (venlafaxine, duloxetine) and opioids (methadone, morphine, tapentadol and tramadol). Although systemic treatments have been proved to be effective in relieving pain and ameliorating the patient's quality of life (QoL), their tolerability is often limited by side effects. Topical treatments (e.g. lidocaine plasters or capsaicin patches, or cream formulations of gabapentin, amitriptyline or ketamine) can offer a valid therapeutic alternative for LNP while avoiding the systemic side effects of systemic analgesics<sup>8</sup>.

LNP can impact severely the QoL of affected patients. Furthermore, it is known that chronic pain patients experience significant sleep problems, mainly described as primary sleep disorders, including difficulties falling asleep, awakening by pain during the night or in the morning<sup>9–13</sup>. Self-reported health status and pain-related sleep disturbance may provide valuable insights when assessing the responses to treatment for chronic pain, including LNP. However, QoL as well as sleep difficulties among patients who experience LNP have not yet been fully described in literature.

Only sparse data are available in the literature about the features of LNP, its therapeutic management and its frequency in the primary care population in Europe. This study aimed to describe clinical characteristics and patterns of treatment of LNP patients identified among chronic pain patients in primary care. Patient's QoL and sleep performance were also evaluated. Additionally, the study attempted to estimate the prevalence of LNP in the primary care.

## Methods

### Study design

This is a non-interventional multicentre cross-sectional study in general practices in Europe. The total data collection period was approximately 10.5 months. Data were extracted

by GP personnel at the sites from patient medical records and patients who screened positive for LNP completed the EuroQol five dimensions questionnaire (EQ-5D) and the Chronic Pain Sleep Inventory (CPSI) at the screening visit. The study was approved by Central Ethics Committees in each of the participating countries.

### Study population

The study was conducted in France, Italy, Spain and UK, to provide a spectrum of health care systems in Europe. The following sampling strategies were used to identify sites in the participating countries: panel of GPs interested in research in France and Italy, while in the UK GPs were approached through the National Institute for Health Research Clinical Research Network (NIHR CRN) and centres in Spain were recruited from a list of geographically spread practices provided by the sponsor. The same site feasibility process was followed in all countries.

All patients  $\geq 18$  years old with a record in patient databases maintained in the participating general practices containing a diagnostic code in the previous six months consistent with suffering from chronic pain were identified using a comprehensive listing prepared from each of the Medical Dictionaries in use in the four study countries (e.g. ICD 9, ICD 10, and READ). Recruitment of patients spontaneously presenting to the GP with symptoms of chronic pain was also permitted.

A screening tool described in the literature to diagnose LNP was used<sup>1</sup>. Adults identified as having chronic pain were invited for screening with the LNP tool. Those who screened positive were asked to provide informed consent and those who provided written informed consent were asked to self-report on their health status through the EQ-5D and CPSI questionnaires<sup>12</sup>. Characteristics of patients who screened positive for LNP were extracted by the GP site, including demographic, lifestyle, medical history, clinical characteristics of pain, and previous and current treatment characteristics.

### Study endpoints and data collection instruments

An electronic Case Report Form (eCRF) using the OXON validated EDC platform (OXON Epidemiology was the Contract Research Organization in charge of the study on behalf of Grunenthal) was used to collect data from GPs (or their staff) and patient responses the self-administered patient questionnaires and create the study database for analysis.

### Clinical and treatment characteristics

Data on duration of chronic pain, site of LNP, aetiology (PHN, DPN, neuropathic LBP, postsurgical neuropathic pain, cancer surgery neuropathic pain) and comorbidities at screening were extracted. Intensity of pain at screening was assessed by the GP at the screening visit in an 11-point Numeric Rating Scale (0 = No pain; 10 = Worst imaginable pain). Intensity was categorized into mild (1–3 points), moderate (4–6 points) and severe (7–10 points).

Analgesic treatments at screening and in the six months preceding screening were collected as individual agents and whether they were given in combination or monotherapy. Additionally, treatments were classified into topical (topical monotherapy/topical-topical combinations) or systemic (systemic monotherapy/systemic-systemic combinations). Changes in the analgesic treatment in the six months pre-screening were documented.

### Quality of life

The EQ-5D questionnaire is a standardized instrument for measuring generic health status and has been extensively used in pain research. It includes two components, health state description and evaluation. In the description part, patients were required to report on five dimensions (5D) of their health status, namely mobility (walking ability), self-care (the ability to wash or dress by oneself), usual activities (performance in work, study, housework, etc.), pain/discomfort (how much pain or discomfort they experience), and anxiety/depression (how anxious or depressed they are), on a scale 1–5 (from no problems to extreme problems). Patients self-rate their level of severity for each dimension using a five-level scale. In the evaluation part, patients evaluated their overall health status, on a scale 0–100, using the EQ-5D visual analogue scale (VAS)<sup>14</sup>.

### Sleep performance

The Chronic Pain Sleep Inventory (CPSI) is validated as a study instrument to evaluate quality of sleep in patients experiencing chronic pain. The CPSI incorporates 5 items: trouble falling asleep, needing sleep medication, awakenings due to pain in the night and morning, and overall quality of sleep. Respondents self-rate their quality of sleep for each of the 4 items, on a scale 0–100 (from sleeping not affected to low quality of sleep) for trouble falling asleep, needing sleep medication, and awakenings due to pain in the night and morning, and on a scale 100–0 for item 5 (overall quality of sleep). A Sleep Problems Index was computed using items 1, 3, and 4. A CPSI validation study supports the scoring of a reliable single index from 3 of the 5 CPSI items that all attribute sleep problems to pain<sup>12</sup>.

### Prevalence

**Reference population.** For all GPs who accepted to participate in the study, the number of registered patients  $\geq 18$  years old were retrieved and summarized overall and by gender and age groups. Registration with a GP is a requirement of the healthcare system in all study countries, but France. In this country the GP Reference Population consists of the total number of patients who attended each participating GP clinic in the last year.

**Chronic pain population.** Patients identified with a record of chronic pain, through pre-defined ICD or READ code records available for the 6 months preceding screening or

spontaneous attendance to the clinic during the study period with symptoms compatible with chronic pain.

**LNP population.** Patients who screened positive for LNP with the study screening tool.

### Data analysis

The sample size was planned to ensure with  $\alpha=0.05$  that the study targeted a total of 1000 LNP patients (250 patients per country) to allow precisions of  $\pm 1.9$ – $3.2\%$  for categorical primary outcomes (i.e. use of a specific analgesic treatment) ranging from 10 to 50%, respectively. For continuous variables, this size allows the detection of small differences in the 11-point VAS of pain intensity ( $d=0.06$ ) or in the EQ-5D index score ( $d=0.02$ ) according to published standard deviations<sup>15,16</sup>.

The main analysis was descriptive. Results were provided according to the main patient characteristics (e.g. gender-age groups), clinical characteristics of pain (duration, location, intensity) and treatment patterns identified at screening.

The crude prevalence of LNP among the reference population (i.e. population prevalence) was calculated as the number of eligible LNP patients divided by the reference population. The prevalence of LNP among chronic pain patients was calculated as the number of eligible LNP patients divided by the number of patients with chronic pain. The crude prevalence was standardized using the direct method (the European population projection to 2015 from the 2011 census stratified by age and sex was used as the reference population).

### Results

Thirty-six general practices were selected in France ( $n=6$ ), Spain ( $n=11$ ), UK ( $n=10$ ) and Italy ( $n=9$ ). The number of patients identified with chronic pain in the 10.5 months data collection period was 3298, of which 2841 were screened for LNP; 1102 screened positive and 1030 LNP patients were included in the analysis (Figure 1).

### Patient characteristics and disease status at screening

The distribution of patients diagnosed as LNP by the screening tool by country was 20.7% ( $n=213$ ) in France, 28.3% ( $n=291$ ) in Italy, 32.9% ( $n=339$ ) in Spain and 18.2% ( $n=187$ ) in the UK. The median (Q1–Q3) age was 61.0 (49.0–72.0) years and the proportion of females was 63.2%. Current or past alcohol dependence/abuse was reported in 6.4% of patients at attendance while 40.8% of patients were current or ex-smokers.

Use of analgesic treatments (past and current) was reported in 97.2% of patients. LNP patients presented a median (Q1–Q3) pain intensity of = 6.0 (4.0–7.0) and a median (Q1–Q3) duration of 30.9 months (12.0–75.3). Figure 2 shows the categorized distributions of duration of pain (Panel A) and intensity (Panel B). The main anatomical sites affected were the upper and lower limbs (62.3 and 58.2%), and the spine (dorsal skin area of the vertebrae from the neck to the sacrum)

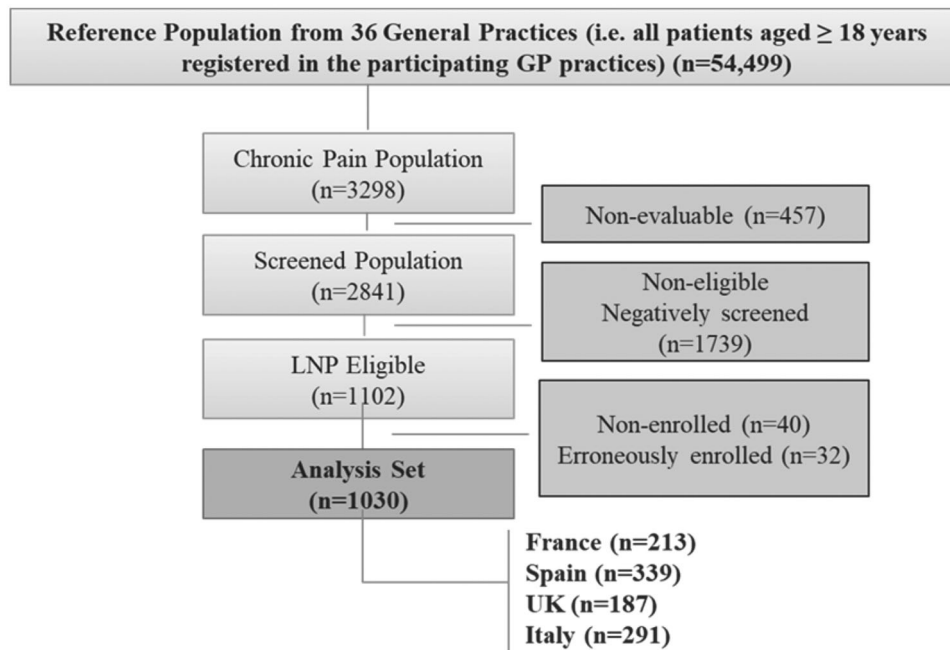


Figure 1. Flowchart of study conduct.

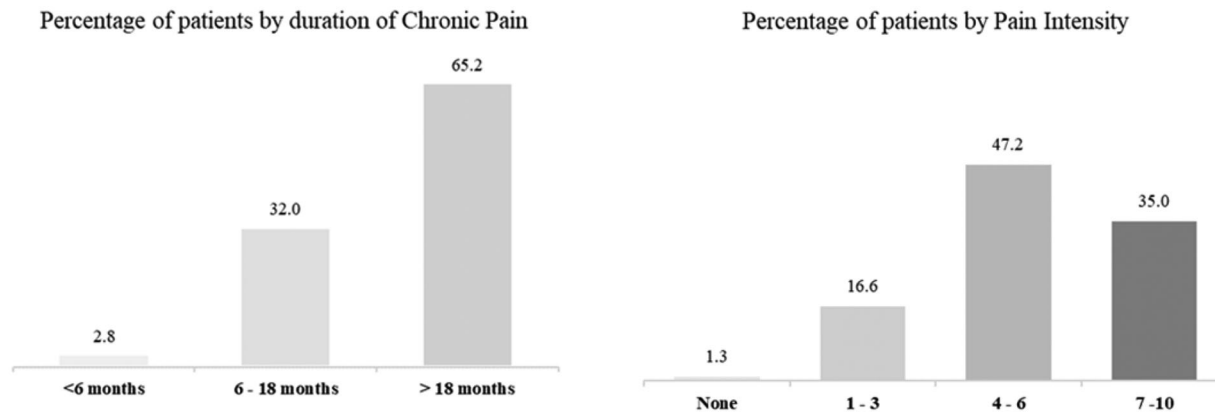


Figure 2. Percentage of LNP patients by: duration of pain (panel A), pain intensity (panel B).

(41.1%). Neuropathic LBP (47.3%), other neuropathies (27.1%), postsurgical neuropathic pain (17.4%), and DPN (12.2%) were the most frequent types of LNP. The most frequent comorbidities included cardiovascular diseases (32.4%), arthritis (osteoarthritis, rheumatoid arthritis (RA), psoriatic arthritis) (31.8%), depression (28.3%) and diabetes (20.9%). Other patient characteristics are presented in Table 1.

### Analgesia pre-screening

In the 6 months before screening, 98.1% of 1001 patients on treatment received systemic therapies and 15.4% topical (Table 2); among systemic medications used 60.0% had received NSAIDs, 47.6% WHO step 2 opioids, 36.8% anticonvulsants, 18.5% antidepressants, 13.9% corticosteroids, and 13.4% WHO step 3 opioids; and 13.3% lidocaine 5% plaster among topical medications. Topical treatments were less used in patients with high pain intensities (20.4% score 1–3, 17.2% score 4–6 and 11.2% score 7–10). The results were reversed for systemic treatments at screening (93.8% score

1–3, 98.7% score 4–6 and 99.2% score 7–10). Combinations were more frequently used than monotherapies (51.7 vs. 48.3%), and increasing in patients with longer duration of the disorder (41.4, 47.3, and 53.3% in patients with duration <6 months, 6–18 months and >18 months, respectively). The longer the duration the higher the percentage of patients on two and more different combinations (patients on one single combination were 66.7, 64.1, and 49.7% with duration <6 months, 6–18 months and >18 months, respectively). Switching in the 6 months prior to screening was reported for 39.4% of patients. The percentage of patients switching treatment was 33.3, 27.5, 46, and 43% of patients receiving topical medication at screening, systemic monotherapy, systemic-systemic combinations and topical-systemic combinations respectively.

### Analgesia at screening

At the screening visit, 97.9% of 1001 treated patients received systemic therapies and 29.4% topical; 44.6% NSAIDs,

**Table 1.** Patient characteristics and disease status.

	Statistic	Overall
Reason for consultancy	<i>n</i> ( <i>n</i> missing)	1022 (8)
Invited to screening	<i>n</i> (col%)	609 (59.59)
Spontaneous attendance	<i>n</i> (col%)	413 (40.41)
Gender	<i>n</i> ( <i>n</i> missing)	1030 (0)
Male	<i>n</i> (col%)	379 (36.80)
Female	<i>n</i> (col%)	651 (63.20)
Age	<i>n</i> ( <i>n</i> missing)	1030 (0)
Mean (SD)		60.2 (15.32)
Median (Q1–Q3)		61.0 (49.0–72.0)
Min–Max		19–98
18–45	<i>n</i> (col%)	189 (18.35)
46–65	<i>n</i> (col%)	423 (41.07)
66–75	<i>n</i> (col%)	240 (23.30)
More than 75	<i>n</i> (col%)	178 (17.28)
BMI (Kg/m <sup>2</sup> )	<i>n</i> ( <i>n</i> missing)	1028 (2)
Mean (SD)		27.5 (5.44)
Median (Q1–Q3)		26.8 (24.0–30.0)
Min–Max		15.2–53.4
≤30.0 Kg/m <sup>2</sup>	<i>n</i> (col%)	777 (75.58)
>30.0 Kg/m <sup>2</sup>	<i>n</i> (col%)	251 (24.42)
Smoking status	<i>n</i> ( <i>n</i> missing)	1027 (3)
Ex-smoker	<i>n</i> (col%)	211 (20.55)
Never smoked	<i>n</i> (col%)	608 (59.20)
Current smoker	<i>n</i> (col%)	208 (20.25)
+ ≤10 year	<i>n</i> (col%)	84 (40.19)
+ >10 years	<i>n</i> (col%)	125 (59.81)
+ Missing	<i>n</i>	2
+ <10 cigarettes/day	<i>n</i> (col%)	100 (48.08)
+ ≥10 cigarettes/day	<i>n</i> (col%)	108 (51.92)
+ Missing	<i>n</i>	0
Alcohol abuse/dependence	<i>n</i> ( <i>n</i> missing)	1023 (7)
Current	<i>n</i> (col%)	20 (1.96)
Past	<i>n</i> (col%)	45 (4.40)
Never	<i>n</i> (col%)	958 (93.65)
Sleeping aid medication in the past	<i>n</i> ( <i>n</i> missing)	1029 (1)
Yes	<i>n</i> (col%)	344 (33.43)
No	<i>n</i> (col%)	685 (66.57)
Aetiology of LNP	<i>n</i> ( <i>n</i> missing)	1027 (3)
Post–herpetic neuropathy	<i>n</i> (col%)	96 (9.35)
Painful diabetic poly–neuropathy	<i>n</i> (col%)	125 (12.17)
Neuropathic low back pain	<i>n</i> (col%)	486 (47.32)
Postsurgical neuropathic pain (non–cancer)	<i>n</i> (col%)	179 (17.43)
Cancer surgery neuropathic pain	<i>n</i> (col%)	37 (3.60)
Other neuropathy	<i>n</i> (col%)	278 (27.07)
Comorbidities	<i>n</i> ( <i>n</i> missing)	1030 (0)
Diabetes	<i>n</i> (col%)	215 (20.87)
Cardiovascular diseases	<i>n</i> (col%)	334 (32.43)
Cerebrovascular diseases	<i>n</i> (col%)	56 (5.44)
Depression	<i>n</i> (col%)	291 (28.25)
Cancer	<i>n</i> (col%)	58 (5.63)
Arthritis (osteoarthritis, rheumatoid arthritis (RA), psoriatic arthritis)	<i>n</i> (col%)	327 (31.75)
Fibromyalgia	<i>n</i> (col%)	101 (9.81)
Ankylosing spondylitis	<i>n</i> (col%)	20 (1.94)
Other inflammatory disorder	<i>n</i> (col%)	153 (14.85)
Other condition	<i>n</i> (col%)	241 (23.40)

37.8% anticonvulsants, 35.4% WHO step 2 opioids, 20.4% lidocaine 5% plaster, 20.0% WHO step 3 opioids, 16.4% antidepressants, 9.4% corticosteroids. Capsaicin patches were used rarely, 3.2%. As shown in Table 3, combinations were more frequently used than monotherapies (70.3 vs. 29.7%), 2.1% were on topical monotherapy, 27.6% on systemic monotherapy, 43.1% on systemic-systemic combinations, 24.4% on topical-systemic combinations and 0.7% on topical-topical combinations (combinations of two or more topical analgesic treatments). Patients with shorter durations of the disorder received more monotherapy (55.2% in patients with

**Table 2.** Analgesic treatment pre-screening.

	Statistic	Overall
Patients with medications in the previous 6 months	<i>n</i>	1001
Medicines in the 6 months before screening*		
Systemic treatment	<i>n</i> (col%)	982 (98.10)
Anticonvulsants	<i>n</i> (col%)	368 (36.76)
Antidepressants	<i>n</i> (col%)	185 (18.48)
SNRIs	<i>n</i> (col%)	110 (10.99)
2nd Ladder opioids	<i>n</i> (col%)	476 (47.55)
3rd Ladder opioids	<i>n</i> (col%)	134 (13.39)
NSAIDs	<i>n</i> (col%)	601 (60.04)
Corticosteroids	<i>n</i> (col%)	139 (13.89)
Other systemic medication	<i>n</i> (col%)	204 (20.38)
Topical treatment	<i>n</i> (col%)	154 (15.38)
Lidocaine 5% plaster	<i>n</i> (col%)	133 (13.29)
8% capsaicin plaster	<i>n</i> (col%)	27 (2.70)
Other topical medication	<i>n</i> (col%)	4 (0.40)
Patients undertaking pain management activities	<i>n</i> (col%)	38 (3.69)
Treatment switches in 6 months	<i>n</i> ( <i>n</i> missing)	1029 (1)
None	<i>n</i> (col%)	624 (60.64)
Yes	<i>n</i> (col%)	405 (39.36)
Patients on combined therapies	<i>n</i> ( <i>n</i> missing)	1029 (1)
No	<i>n</i> (col%)	497 (48.30)
Yes	<i>n</i> (col%)	532 (51.70)
Number of combinations	<i>n</i> ( <i>n</i> missing)	532 (0)
Only 1	<i>n</i> (col%)	289 (54.32)
Two	<i>n</i> (col%)	137 (25.75)
More than two	<i>n</i> (col%)	106 (19.92)
Number of medicines in combination	<i>n</i> ( <i>n</i> missing)	532 (0)
Two	<i>n</i> (col%)	317 (59.59)
Three or more	<i>n</i> (col%)	227 (42.67)
Combinations including topical treatment	<i>n</i> ( <i>n</i> missing)	532 (0)
No topical treatment	<i>n</i> (col%)	294 (55.26)
Lidocaine 5% plaster	<i>n</i> (col%)	136 (25.56)
Alone	<i>n</i> (col%)	3 (2.21)
Anticonvulsants	<i>n</i> (col%)	51 (37.50)
Antidepressants	<i>n</i> (col%)	20 (14.71)
SNRIs	<i>n</i> (col%)	18 (13.24)
2nd Ladder opioids	<i>n</i> (col%)	58 (42.65)
3rd Ladder opioids	<i>n</i> (col%)	21 (15.44)
NSAIDs	<i>n</i> (col%)	82 (60.29)
Corticosteroids	<i>n</i> (col%)	16 (11.76)
Other	<i>n</i> (col%)	0 (0.00)
8% Capsaicin plaster	<i>n</i> (col%)	14 (2.63)
Other topical treatment	<i>n</i> (col%)	104 (19.55)

<6 months vs. 27.5 and 29.6% in patients with 6–18 months and >18 months of pain duration, respectively).

### Quality of life

The mean EQ-5D VA S score was 58.4. The longer the duration and higher the intensity of pain the greater the impact on QoL for all dimensions and the EQ-5D VAS score. The mean EQ-5D VAS score was 73.7 in patients on topical monotherapy, 62.9 on systemic monotherapy, 58.7 on systemic combinations and 50.8 on topical combinations (Figure 3).

### Sleep performance

Sleeping problems were of mild severity (mean index 41.2) with an overall quality of sleep mildly affected (50.4±27.7). The overall quality of sleep was 67.7 in patients on topical monotherapy, 51.3 on systemic monotherapy, 52.7 on

**Table 3.** Analgesic treatment at screening.

	Statistic	Overall
Overall	<i>n</i> (row%)	1030 (100.0)
Patients with medications for pain	<i>n</i> /valid <i>N</i> (%)	1001/1030 (97.2)
Time on current therapy (months)	<i>n</i> ( <i>n</i> missing)	1001 (0)
Mean (SD)		12.69 (25.21)
Median (Q1–Q3)		5.34 (2.13, 10.98)
Min-Max		(0.00, 311.48)
Type of therapy	<i>n</i> ( <i>n</i> missing)	1001 (0)
– Monotherapy	<i>n</i> /valid <i>N</i> (%)	297/1001 (29.67)
– Combinations	<i>n</i> /valid <i>N</i> (%)	704/1001 (70.33)
Treatment pattern at assessment	<i>n</i> ( <i>n</i> missing)	1001 (0)
Single medication topical treatment	<i>n</i> /valid <i>N</i> (%)	21/1001 (2.10)
Single medication systemic treatment	<i>n</i> /valid <i>N</i> (%)	276/1001 (27.57)
Combination with topical medication	<i>n</i> /valid <i>N</i> (%)	251/1001 (25.07)
Combination without topical medication	<i>n</i> /valid <i>N</i> (%)	453/1001 (45.25)
Type of medications (monotherapy/comb)*		
Topical		
Lidocaine 5% plaster	<i>n</i> /valid <i>N</i> (%)	204/1001 (20.4)
8% Capsaicin plaster	<i>n</i> /valid <i>N</i> (%)	32/1001 (3.2)
Other topical treatment	<i>n</i> /valid <i>N</i> (%)	62/1001 (6.2)
Systemic		
Anticonvulsants	<i>n</i> /valid <i>N</i> (%)	378/1001 (37.8)
Tricyclic antidepressants	<i>n</i> /valid <i>N</i> (%)	164/1001 (16.4)
SNRIs	<i>n</i> /valid <i>N</i> (%)	120/1001 (12.0)
Opioids for mild to moderate pain	<i>n</i> /valid <i>N</i> (%)	354/1001 (35.4)
Opioids for moderate to severe pain	<i>n</i> /valid <i>N</i> (%)	200/1001 (20.0)
Non-steroid anti-inflammatory drugs	<i>n</i> /valid <i>N</i> (%)	446/1001 (44.6)
Corticosteroids	<i>n</i> /valid <i>N</i> (%)	94/1001 (9.4)
Other systemic treatment	<i>n</i> /valid <i>N</i> (%)	201/1001 (20.1)
Monotherapy – combinations		
Topical		
Lidocaine alone	<i>n</i> /valid <i>N</i> (%)	14/1001 (1.4)
Capsaicin alone	<i>n</i> /valid <i>N</i> (%)	6/1001 (0.6)
Other topical treatment alone	<i>n</i> /valid <i>N</i> (%)	1/1001 (0.1)
Systemic		
Anticonvulsants alone	<i>n</i> /valid <i>N</i> (%)	79/1001 (7.9)
Antidepressants alone	<i>n</i> /valid <i>N</i> (%)	29/1001 (2.9)
SNRI alone	<i>n</i> /valid <i>N</i> (%)	10/1001 (1.0)
2nd Step opioids alone	<i>n</i> /valid <i>N</i> (%)	40/1001 (4.0)
3rd Step opioids alone	<i>n</i> /valid <i>N</i> (%)	19/1001 (1.9)
NSAIs alone	<i>n</i> /valid <i>N</i> (%)	98/1001 (9.8)
Corticosteroids alone	<i>n</i> /valid <i>N</i> (%)	4/1001 (0.4)
Other systemic treatment alone	<i>n</i> /valid <i>N</i> (%)	19/1001 (1.9)
Combinations – medications		
Combinations with topical treatments	<i>n</i> /valid <i>N</i> (%)	251/1001 (24.4)
Combinations of topical treatments only	<i>n</i> /valid <i>N</i> (%)	7/1001 (0.7)
Combinations of two topical treatments	<i>n</i> /valid <i>N</i> (%)	4/1001 (0.4)
Combinations of three topical treatments	<i>n</i> /valid <i>N</i> (%)	3/1001 (0.3)
Combinations of topical and systemic	<i>n</i> /valid <i>N</i> (%)	244/1001 (24.4)
Combinations of lidocaine with systemic	<i>n</i> /valid <i>N</i> (%)	183/1001 (18.3)
Comb of lidocaine with 2 systemic	<i>n</i> /valid <i>N</i> (%)	51/1001 (5.1)
Comb of lidocaine with 3 systemic	<i>n</i> /valid <i>N</i> (%)	132/1001 (13.2)
Most commonly used combinations with lidocaine		
Lidocaine + NSAID	<i>n</i> /valid <i>N</i> (%)	19/1001 (1.9)
Lidocaine + 3rd step opioids	<i>n</i> /valid <i>N</i> (%)	14/1001 (1.4)
Lidocaine + 2nd step opioids + NSAID	<i>n</i> /valid <i>N</i> (%)	11/1001 (1.1)
Lidocaine + anticonvulsants + 3rd step opioids + NSAID	<i>n</i> /valid <i>N</i> (%)	11/1001 (1.1)
Lidocaine + anticonvulsants + NSAID + other	<i>n</i> /valid <i>N</i> (%)	30/1001 (3.0)
Lidocaine + another comb of systemic treat	<i>n</i> /valid <i>N</i> (%)	115/1001 (11.5)
Comb of capsaicin with systemic treat	<i>n</i> /valid <i>N</i> (%)	15/1001 (1.5)
Comb of capsaicin with 2 systemic treat	<i>n</i> /valid <i>N</i> (%)	11/1001 (1.1)
Comb of capsaicin with 3 systemic treat	<i>n</i> /valid <i>N</i> (%)	4/1001 (0.4)
Most commonly used combinations with CAPSAICIN		
Capsaicin + lidocaine	<i>n</i> /valid <i>N</i> (%)	7/1001 (0.7)
Capsaicin + 2nd step opioids	<i>n</i> /valid <i>N</i> (%)	4/1001 (0.4)
Capsaicin + other combinations	<i>n</i> /valid <i>N</i> (%)	3/1001 (0.3)
Combinations of systemic treatments only	<i>n</i> /valid <i>N</i> (%)	431/1001 (43.1)
Combinations of 2 systemic treatments	<i>n</i> /valid <i>N</i> (%)	245/1001 (24.5)
Combinations of 3 systemic treatments	<i>n</i> /valid <i>N</i> (%)	186/1001 (18.6)
Most commonly used Systemic medicines in systemic combinations*		
2nd step opioids in any comb of syst med	<i>n</i> /valid <i>N</i> (%)	239/1001 (23.9)
NSAID in any comb of syst medicines	<i>n</i> /valid <i>N</i> (%)	207/1001 (20.7)
Anticonvulsants in any comb of syst med	<i>n</i> /valid <i>N</i> (%)	198/1001 (19.8)
Other systemics in any comb of syst med	<i>n</i> /valid <i>N</i> (%)	144/1001 (14.4)
Corticosteroids in any comb of syst med	<i>n</i> /valid <i>N</i> (%)	68/1001 (6.8)

(continued)

Table 3. Continued.

	Statistic	Overall
Antidepressants in any comb of syst med	n/valid N (%)	79/1001 (7.9)
3rd step opioids in any comb of syst med	n/valid N (%)	88/1001 (8.8)
SNRI in any comb of systemic medicines	n/valid N (%)	71/1001 (7.1)
Most commonly used comb of systemic medicines		
NSAI + corticosteroids	n/valid N (%)	42/1001 (4.2)
NSAI + 2nd step opioids	n/valid N (%)	36/1001 (3.6)
Anticonvulsants + 2nd step opioids	n/valid N (%)	32/1001 (3.2)
2nd step opioids + other syst treatments	n/valid N (%)	27/1001 (2.7)
Anticonvulsants + 2nd step opioids + other	n/valid N (%)	23/1001 (2.3)
Anticonvulsants in another comb of syst treat	n/valid N (%)	66/1001 (6.6)
Other comb of syst treatments	n/valid N (%)	242/1001 (24.2)

\*The categories listed below are not mutually exclusive. All percentages are calculated for patients with current treatment.

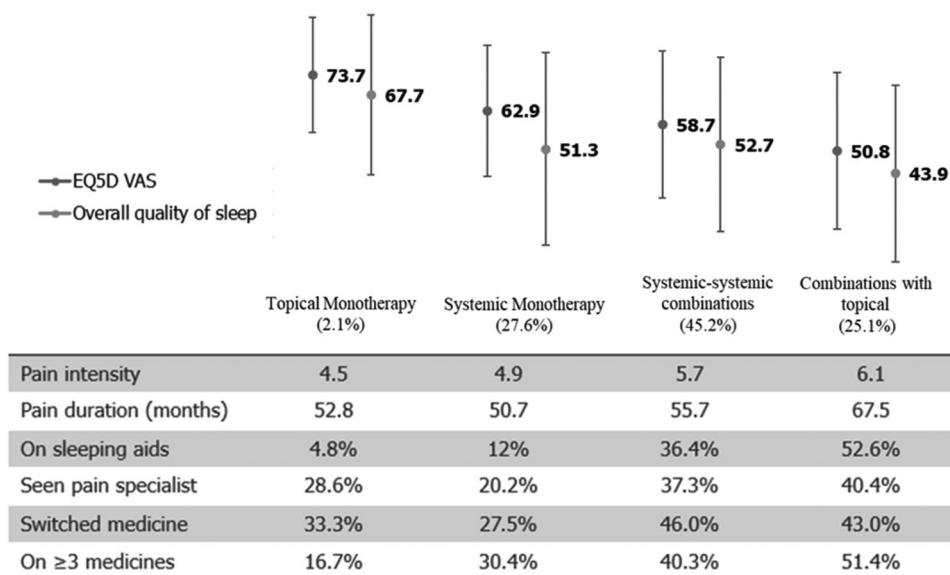


Figure 3. EQ-5D VAS and CPSI Item 5 by type of analgesia at screening. \*The vertical lines represent 95% confidence intervals

Table 4. Prevalence overall and by country.

Country	Prevalence of LNP		Prevalence of chronic pain
	General population (%)	Chronic pain (%)	General population (%)
Background estimates	1.6	19 <sup>1</sup>	12–30 <sup>13</sup>
Overall	2.01	43.30	6.05
France	1.10	45.06	
Italy	2.04	39.79	
Spain	2.42	54.07	
UK	4.17	35.95	

systemic combinations and 43.9 on topical combinations (Figure 3).

Sleeping aid medications were used in 33.4% of patients in the prior 6 months and by 32.2% at screening.

### Prevalence

As shown in Table 4, the standardized prevalence of LNP by age and sex in the general population was 2.01%; 2.45% in females and 1.54% in males, higher in France (4.2%) and Italy (2.42%) and lower in the UK (1.1%). The standardized prevalence of LNP by age and gender among chronic pain patients was 43.3%; 41.7% in females and 45.1% in males

higher in Italy (54.1%) and the UK (45.1%) and lower in France (35.9%) and Spain (39.8%).

### Discussion

This cross-sectional study described clinical characteristics and treatment patterns of LNP patients and estimated its prevalence in GP practices across 4 EU countries. The study results provide a better understanding of current pain management strategies and treatment decisions for LNP patients in a real-world setting.

Use of this screening tool to diagnose LNP was appropriate given the high sensitivity and specificity found in a validation study against clinical expert opinion<sup>7</sup>.



LNP patients suffered pain intensities of six on a ten-point scale in average for durations longer than 2.5 years, mostly affecting the upper and lower limbs and the spine. LNP had its origin mainly in neuropathic LBP, postsurgical neuropathic pain and DPN coexisting with comorbidities such as cardiovascular diseases, arthritis (osteoarthritis, rheumatoid arthritis (RA), psoriatic arthritis), depression and diabetes. In particular, almost half of the patients diagnosed with LNP with the screening tool and included in the study had LBP, being largely treated with NSAIDs. Most of the neuropathic back pain patients had LNP in addition to a nociceptive pain component, a fact that might explain the high use of NSAIDs in this population. Furthermore, this finding may be explained by the great variability of clinical practice in Europe but may also be attributed to the misclassification of non-localized neuropathic LBP cases as LNP by the screening tool. Although, some consider LBP to be infrequently associated with LNP, except in post-surgical cases, pain specialists in Mick et al.<sup>1</sup> found the proportion of patients with neuropathic LBP reported by the GPs was lower than what was observed in this study, but still substantial (27.4%)<sup>1</sup>.

Great heterogeneity in treatment patterns was observed in the study across countries, which seems to reflect a lack of consensus on the diagnosis and management of LNP and the heterogeneity of treatment recommendations, prescribing habits and access to certain medications. Additionally, despite most patients in the study were on analgesic medication, a median pain intensity of six out of ten and durations longer than 2.5 years were observed. Neuropathic pain guidelines recommend first-line treatment with tricyclic antidepressants or calcium channel  $\alpha_2$ - $\delta$  ligands<sup>17</sup>, and topical medications (in case of LNP). The treatment algorithm by Allegri et al. proposes topical analgesic agents as first-line therapy in LNP with systemic treatments added to enhance the effect or replace topical agents<sup>18</sup>. However, the use of topical medications in the present study was limited to the less severe cases in monotherapy or in combination with systemic medications as severity increased. NSAIDs were the main treatments reported in the study while anticonvulsants and antidepressants were less frequently used. This trend was also observed in Mick et al.<sup>1</sup>. These observations are interesting since guidelines on neuropathic pain do not support the use of NSAIDs due to limited evidence. Multiple combinations and switches in pharmacotherapy were reported.

This highlights the need for prompt diagnosis of LNP and use of treatment regimens specifically designed to relieve pain in LNP patients to eventually improve quality of life and sleep performance.

QoL and sleep performance were affected in patients with LNP. QoL was far from the score in the general population for each participating country: 66.3 vs. 76.8 in France, 55.9 vs. 77.1 in Italy, 53.6 vs. 75.0 in Spain, and 59.3 vs. 82.8 in the UK<sup>19</sup>. Patients on topical monotherapy were close to the average in published population norms. The severity of sleeping problems was mild overall however one third of patients relied on sleeping aid medication to fall asleep

Use of topical monotherapies was mainly reported in patients with LNP of mild intensity or short durations and

with stable QoL. As intensity or duration of pain increased, patients were more likely to be treated with systemic medications. The results showed that as LNP becomes chronic with longer durations or greater intensity, pain starts affecting other QoL dimensions, also increasingly using sleeping aid medications, antidepressants, 3rd step opioids and non-pharmacological therapies.

LNP was considered highly prevalent among chronic pain patients in primary care centres participating in the study (43.3%) while the prevalence of chronic pain observed in the study was lower (6.1%) compared to previous studies (12–32%)<sup>13,16,20</sup> and appears to be more in the range of prevalence figures for chronic pain of neuropathic origin (6.9% in<sup>16</sup>). This may be due to a bias in the selection with LNP patients being more likely to be screened. This is particularly striking in France where the prevalence of chronic pain reported was 2.2%, which may be the result of the private nature of participating sites in France.

In summary, the considerable prevalence of LNP in primary care revealed its clinical significance based on a new diagnostic screening instrument, yet remains challenging to manage, with treatment patterns that diverge from treatment guidelines. The results of the study indicate the need for strengthened education efforts among GPs with particular emphasis on the diagnosis and management of LNP.

Additionally, this suggests that further evaluation (e.g. a comparative observational study) of the ability of the screening tool to identify undiagnosed and under-treated LNP patients, may lead to better treatment and improvement of quality of life and sleep.

The study has some limitations. There is potential bias in extrapolating the study results to LNP in the secondary care setting. However, most cases of chronic pain of LNP origin are managed in primary care (only 2% of chronic pain patients are treated by a pain specialist<sup>1</sup>, usually the more severe cases).

Site selection strategies were adapted to the specific needs of the country e.g. in Italy and France a panel of GPs interested in research was used to recruit patients while in Spain the sampling list was provided by Grunenthal. This resulted in heterogeneity in the type of sites participating in the study and their contribution to the reference population for the estimation of prevalence. For example, in France only private centres with no established patient catchment population database participated in the study mostly recruiting patients spontaneously as they attended to clinic – France only contributed 10% to the general population in the study.

The size of the study populations allowed an acceptable level of precision for the study primary endpoints. However, a large number of comparisons was performed with no adjustment for multiple comparisons. Therefore, some findings may be due to the play of chance and should therefore be interpreted with caution and clinical relevance.

Treatment patterns in the LNP population may be affected by variability in treatment recommendations across countries, cultural considerations with respect to prescribing habits and access to certain treatments due to

reimbursement status e.g. prescription conditioned by reimbursement in the UK resulted in limited use of topical treatments.

Opportunistic recruitment of patients was permitted to minimize the potential for selection bias towards patients who require less frequent medical attention.

## Conclusion

The study results provide a better understanding of current pain management strategies and treatment decisions for LNP patients in a real-world setting. Many LNP patients suffered from moderate pain for long durations, mostly affecting the upper and lower limbs and the spine. Neuropathic low back pain, postsurgical neuropathic pain and diabetic polyneuropathy were the main causes coexisting with comorbidities such as CVDs, arthritis (osteoarthritis, rheumatoid arthritis (RA), psoriatic arthritis), depression and diabetes. QoL and sleep performance were affected in patients with LNP with one third relying on sleeping aid medications to sleep.

Treatment patterns seem sub-optimal for LNP with mainly NSAIDs being used. Use of topical monotherapies was reported in patients with LNP of mild intensity or short durations and with QoL. As intensity or duration of pain increased, patients were more likely to be treated with systemic medications. Results showed that as LNP becomes more chronic with longer durations or greater intensity, pain starts affecting other QoL dimensions, increasingly using sleeping aid medications, antidepressants, 3rd ladder opioids and non-pharmacological therapies.

This highlights the need for early and rapid diagnosis of LNP and use of treatment regimens specifically designed to relieve pain in LNP patients to improve quality of life and sleep performance. To achieve this, education efforts among GPs should be strengthened with particular emphasis on the diagnosis and management of LNP according to current guidelines.

The prevalence of LNP in the general population and in chronic pain patients was high, which may partially be a result of the use of a screening tool either detecting cases that would otherwise remain undiagnosed or misclassifying non-localized LBP of neuropathic origin as LNP.

## Transparency

### Declaration of funding

OXON Epidemiology is scientific service provider/CRO that conducts observational studies for the pharmaceutical industry and was funded to conduct this study for Grünenthal GmbH. OXON Epidemiology is responsible for the overall conduct and deliverables.

Grünenthal GmbH, Aachen, Germany, the sponsor of the study, provided financial assistance through an unrestricted educational program to support clinicians in collating their individual patient data and interpreting results and to OXON Epidemiology to design and conduct the study, perform the statistical analysis, and interpret the results.

### Declaration of financial/other relationships

GM has received honoraria from Grünenthal GmbH, Mundipharma, Pfizer, and Astellas. MSerpell has received honoraria from Astellas, Grünenthal GmbH, NAPP, and Pfizer for speaking at meetings. His institution has received research support in the past 5 years from commercial studies sponsored by Astellas, Grünenthal GmbH, and NAPP. RB has received grants/research support from Pfizer, Genzyme GmbH, Grünenthal GmbH, and Mundipharma. He is a member of the EU Project No 633491: DOLOR-isk; a member of the IMI "Europain" collaboration, whose industry members are Astra Zeneca, Pfizer, Esteve, UCB-Pharma, Sanofi Aventis, Grünenthal GmbH, Eli Lilly, and Boehringer Ingelheim Pharma GmbH & Co. KG; and, via the German Federal Ministry of Education and Research (BMBF), a member of the ERA\_NET NEU-RON/IM-PAIN Project, German Research Network on Neuropathic Pain, NoPain system biology, and German Research Foundation (DFG). He has received speaking fees from Pfizer, Genzyme GmbH, Grünenthal GmbH, Mundipharma, Sanofi Pasteur, Medtronic Inc. Neuromodulation, Eisai Co. Ltd., Lilly GmbH, Boehringer Ingelheim Pharma GmbH & Co. KG, Astellas, Desitin, Teva Pharma, Bayer-Schering, MSD GmbH, and Seqirus. He has been a consultant for Pfizer, Genzyme GmbH, Grünenthal GmbH, Mundipharma, Allergan, Sanofi Pasteur, Medtronic Inc. Neuromodulation, Eisai Co. Ltd., Lilly GmbH, Boehringer Ingelheim Pharma GmbH & Co. KG, Astellas, Novartis, Bristol-Myers-Squibb, Biogenidec, AstraZeneca, Merck, AbbVie, Daiichi Sankyo, Glenmark Pharmaceuticals, Seqirus, Teva Pharma, Genentech, and Galapagos NV. VM has received honoraria and fees for the provision of expert opinion from Grünenthal GmbH, Mundipharma, Menarini, Archimedes Pharma, Takeda, and Ferrer. GH has nothing to disclose. IM, EA, and NQ are employees of OXON Epidemiology. MSohns is employee of Grünenthal GmbH. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

### Author contributions

GM, MSerpell, RB, VM, and GH were the Scientific Advisory Committee of the study. They supervised the study design, review and interpretation of the results, and the manuscript. EA, NQ, and IM participated in the design, interpretation of results, drafting and review of the manuscript. Ignacio Méndez conducted the statistical analysis. MSohns was involved in the conception of the study, was responsible for the follow-up of the project from Grünenthal and the coordination with OXON Epidemiology, and the Scientific Advisory Committee. She participated as well in the review of the manuscript.

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## References

- [1] Mick G, Baron R, Correa-Illanes G, et al. Is an easy and reliable diagnosis of localized neuropathic pain (LNP) possible in general practice? Development of a screening tool based on IASP criteria. *Curr Med Res Opin.* 2014;30(7):1357–1366.
- [2] Gilron I, Watson CPN, Cahill CM, et al. Neuropathic pain: a practical guide for the clinician. *CMAJ.* 2006;175(3):265–275.
- [3] Baron R, Binder A, Wasner G. Neuropathic pain: diagnosis, pathophysiological mechanisms, and treatment. *Lancet Neurol.* 2010; 9(8):807–819.
- [4] Attal N, Bouhassira D, Baron R. Diagnosis and assessment of neuropathic pain through questionnaires. *Lancet Neurol.* 2018; 17(5):456–466.
- [5] Mick G, Baron R, Finnerup NB, et al. What is localized neuropathic pain? A first proposal to characterize and define a widely used term. *Pain Manag.* 2012;2(1):71–77

- [6] Pickering G, Martin E, Tiberghien F, et al. Localized neuropathic pain: an expert consensus on local treatments. *Drug Des Devel Ther.* 2017;11:2709–2718.
- [7] Mayoral V, Pérez-Hernández C, Muro I, et al. Diagnostic accuracy of an identification tool for localized neuropathic pain based on the IASP criteria. *Curr Med Res Opin.* 2018;34(8):1465–1473.
- [8] Bhaskar A, Mittal R. Local therapies for localised neuropathic pain. *Rev Pain.* 2011;5(2):12–20.
- [9] O'Connor AB. Neuropathic pain: quality-of-life impact, costs and cost effectiveness of therapy. *Pharmacoeconomics.* 2009;27:95–112.
- [10] Pilowsky I, Crettenden I, Townley M. Sleep disturbance in pain clinic patients. *Pain.* 1985;23(1):27–33.
- [11] Wittig RM, Zorick FJ, Blumer D, et al. Disturbed sleep in patients complaining of chronic pain. *J Nerv Ment Dis.* 1982;170(7):429–431.
- [12] Kosinski M, Janagap CC, Gajria K, et al. Psychometric testing and validation of the Chronic Pain Sleep Inventory. *Clin Ther.* 2007;29(11):2562–2577.
- [13] Breivik H, Collett B, Ventafridda V, et al. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain.* 2006;10(4):287–333.
- [14] Vartiainen P, Mäntyselkä P, Heiskanen T, et al. Validation of EQ-5D and 15D in the assessment of health-related quality of life in chronic pain. *Pain.* 2017;158:1577–1585.
- [15] Kendrick DB, Strout TD. The minimum clinically significant difference in patient-assigned numeric scores for pain. *Am J Emerg Med.* 2005;23(7):828–832.
- [16] Torrance N, Lawson KD, Afolabi E, et al. Estimating the burden of disease in chronic pain with and without neuropathic characteristics: does the choice between the EQ-5D and SF-6D matter? *Pain.* 2014;155(10):1996–2004.
- [17] Dworkin RH, O'Connor AB, Audette J, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. *Mayo Clin Proc.* 2010;85(3 Suppl):S3–S14.
- [18] Allegri M, Baron R, Hans G, et al. A pharmacological treatment algorithm for localized neuropathic pain. *Curr Med Res Opin.* 2016;32(2):377–384.
- [19] Janssen B, Szende A. Population norms for the EQ-5D. In: König HH, Vilagut G, Ramos-Goñi JM, et al., editors. *Self-reported population health: an international perspective based on EQ-5D.* Dordrecht: Springer Netherlands, 2014. p. 19–30.
- [20] Cruccu G, Truini A. A review of neuropathic pain: from guidelines to clinical practice. *Pain Ther.* 2017;6(Suppl 1):35–42.