A cross-sectional survey of health state impairment and treatment patterns in patients with postherpetic neuralgia

ROBERT VAN SEVENTER1, ALESIA SADOSKY2, MELANIE LUCERO3, ELLEN DUKES2

1Amphia Ziekenhuis, Department of Anaesthesiology, Breda, The Netherlands
2Global Outcomes Research, Pfizer Global Pharmaceuticals, 235 East 42nd Street, Mailstop 235/9/2, New York, NY 10017, USA
3Pfizer Consultant, Durham, NC, USA

Address correspondence to: A. Sadosky. Tel: (+1) 212 733 9491. Fax: (+1) 212 309 4423. Email: alesia.sadosky@pfizer.com

Abstract

Background: postherpetic neuralgia (PHN) develops in 8–24% of patients with herpes zoster. Few studies have evaluated the patient burden and treatment of PHN in general practice.

Objectives: to determine the patient burden of PHN with respect to pain intensity and impact on patient functioning and to characterise treatment patterns and health resource utilisation in general practice.

Methods: eighty-four patients with PHN were identified in general practice settings during an observational survey of neuropathic pain syndromes in six European countries. Patients answered a questionnaire that included: pain severity and interference items from the modified short form brief pain inventory (mBPI-SF); EuroQol (EQ-5D) survey; and questions related to current treatment, health status and resource utilisation. Physicians provided information on medications prescribed for PHN and pain-related co-morbidities (anxiety, depression and sleep disturbance).

Results: mean patient age was 71.0 ± 12.8 years, 76% were ≥65 years and 45% of patients had PHN ≥1 year. The mean pain severity index was 4.2, reflecting moderate pain despite 89% of patients taking prescription medications for PHN. Few medications with demonstrated efficacy against PHN (e.g. carbamazepine and gabapentin) were prescribed, often at suboptimal doses. Pain severity was associated with reduced EQ-5D health state valuation (P<0.001), greater pain interference on all domains (P<0.001) and increased health resource utilisation (P = 0.008).

Conclusions: PHN causes substantial patient burden expressed as interference with daily functioning and reduced health status associated with pain severity. This burden may result in part from suboptimal management strategies and suggests a need for more effective pain management.

Keywords: postherpetic neuralgia, herpes zoster, neuropathic pain, patient burden, quality of life, health status, elderly

Introduction

Herpes zoster (HZ) is characterised by painful blisters that erupt along a nerve path after reactivation of latent varicella zoster virus. HZ has an estimated incidence in the United States and Europe of 3.9–11.8/1,000 person-years in persons aged ≥60 years [1]. The acute pain of HZ significantly impacts patient function and quality of life [2, 3].

Postherpetic neuralgia (PHN), the most common complication of HZ, is a neuropathic pain frequently reported as lancinating, burning, shooting, stabbing, paroxysmal or electrical. It is often associated with abnormal sensory
perception (e.g. allodynia and/or hyperalgesia) and may persist as chronic pain after resolution of the HZ rash. Because different criteria are used to define PHN (pain at rash healing, 1 month after rash onset or 3 months after rash onset), the estimated incidence varies from 8 to 24% [4, 5]. The prevalence of PHN increases with older age [6, 7]; 47 and 73% of untreated adults with HZ over 60 and 70 years of age, respectively, may have PHN [8]. With the ageing of the population, a larger proportion of persons are at a risk of developing HZ and PHN. Medical management of pain presents unique challenges in an older population, and care is needed in the choice of therapies for neuropathic pain conditions [9].

The high incidence of HZ in older persons combined with the recognised impact of PHN on patient functioning and quality of life [1, 4, 5, 10–13] suggests that PHN may present a significant patient burden in a population already impaired in health status. Patient functioning and quality of life have been incorporated as outcomes in several studies of PHN [14–16]. However, few studies evaluated the patient burden and treatment of PHN in primary care, the usual locus of chronic pain management [17]. A US study conducted by postal questionnaire in patients recruited through advertisements showed substantial impact of PHN on health status domains related to patient functioning [13]. A second US study, adapting the brief pain inventory to assess HZ pain in patients recruited from different health care settings, showed an association between PHN and reduced patient function and quality of life [18].

These considerations suggested a need to better understand treatment patterns and patient burden in general practice settings in Europe. The purpose of the present analysis was to evaluate the impact of PHN on patient functioning and to characterise associated treatment patterns in patients recruited from primary care settings in six European countries.

Subjects and methods

The sample consisted of 84 patients with PHN identified during a larger observational, cross-sectional study of broad neuropathic pain syndromes [19]. Sampling was limited to general practitioners and non-pain specialists. Patients were recruited from community-based practices in France, Germany, Italy, the Netherlands, Spain and United Kingdom. We assessed patient-reported functional health and well-being, pain experience, medication use and health resource utilisation specifically for PHN (e.g. physician visits and telephone consultations).

Physicians were screened for their interest in study participation, and a feasibility assessment was conducted to determine their ability to identify patients for inclusion. Physician training by teleconference included reviewing the study objectives, physician responsibilities, patient eligibility criteria and administrative procedures. The clinical case report form provided definitions of PHN with reference to patient-reported pain descriptors and pain location.

The study protocol was approved by local ethics committees. Participating physicians invited patients to participate in the study during routine care visits. Eligible patients were identified by physicians based on the presence of neuropathic pain and report of symptoms consistent with allodynia (pain in reaction to non-noxious stimuli such as the light touch of a cotton ball) and hyperalgesia (exaggerated pain reaction to mild pain stimuli) and/or the patient’s use of specific words (e.g. burning, shooting, stabbing or tingling) that typically describe neuropathic pain. PHN was defined as neuropathic pain in the area of a spinal nerve dermatome or cranial nerve tract lasting >3 months after crusting of the skin lesions associated with HZ. Symptom duration of ≥3 months and up to the week before the survey was required.

Exclusion criteria were participation in an investigational drug study within the past 30 days, presentation with or a history of a serious or unstable medical or psychological condition that would compromise participation in the study and presence of a concomitant illness unrelated to PHN (e.g. neurological disorder or other pain condition) that would likely confound the assessment of PHN. Patients were eligible if they had other chronic pain conditions such as osteoarthritis or migraine headaches, provided they could distinguish between PHN pain and the other conditions.

Patients who consented completed a questionnaire as described below. Physicians provided clinical information regarding the duration of disease and prescribed medications for PHN and common pain-related co-morbid conditions (e.g. anxiety, depression or sleep disturbance).

Patient questionnaire

The questionnaire included: 11 items from the modified short form brief pain inventory (mBPI-SF) [20–22]; the EuroQol (EQ-5D) [23]; and additional questions as described below. Validated translations of the mBPI-SF and EQ-5D survey were used, and the remaining questions were translated and reviewed for accuracy by native speakers.

Modified short form brief pain inventory

Pain severity, assessed using the mBPI-SF, was measured using an 11-point numeric rating scale ranging from 0 (no pain) to 10 (pain as bad as you can imagine). Items included current pain, worst, least and average pain over the previous 24 hours. The pain severity index was calculated as the average of the four ratings. Pain severity cut-points were 1–3 for mild pain, 4–6 for moderate pain and 7–10 for severe pain [24].

The remaining items measured pain-related interference over seven health status domains using 11-point numeric rating scales ranging from 0 (does not interfere) to 10 (completely interferes). The mean of these seven ratings measured the patient’s overall level of pain interference (pain interference index).

EuroQol survey

The EQ-5D survey assessed the overall functioning and well-being with respect to mobility, self-care, usual activities,
pain or discomfort and anxiety or depression [23]. Domains were rated using a 3-point ordinal scale, and the resulting profile was used to calculate health state valuations based on precalculated scoring coefficients [25]. We used scoring coefficients generated in the United Kingdom to assign health state valuations to patients. Health state valuations ranged from –0.59 (worst health state) to 1.00 (best health state).

Additional questions
Specific questions addressed patients’ overall health rating and health resource utilisation. Patients rated their current health on a scale of 0–100, where 0 represented ‘worst possible health’ and 100 represented ‘perfect health’; patients also provided a health rating under the hypothetical scenario of having complete relief of PHN pain.

Physicians provided information about current prescription medications for PHN, and patients provided information about the use of non-prescription medications and other therapies including acupuncture, topical lotions, herbs or vitamins, devices such as those for electroneural stimulation (e.g. transcutaneous electroneural stimulation [TENS] or spinal cord stimulation) and exercise. Patients also evaluated the efficacy of prescription medications (extremely effective, very effective, somewhat effective, a little effective and not effective) including information on treatment adherence and medication satisfaction. Other questions included the frequency of neuropathic pain-related physician visits and telephone consultations during the past 4 weeks and evaluation by pain specialists.

Statistical analyses
Summary statistics were utilised to describe the study sample: means ± standard deviations were provided for continuous variables and frequency distributions for categorical variables.

One-way analysis of variance models for continuous outcomes and chi-square tests for categorical outcomes were used to evaluate the association between pain severity (categorised as mild, moderate or severe) [24] and other outcomes. Statistical significance was evaluated at the 0.05 level, with no adjustments for multiple comparisons, given the descriptive nature of the study. All analyses were performed using PC-SAS version 8.0 (SAS Institute, Cary, NC, USA).

Results
The sample consisted of 84 patients: 48% males and 52% females. The mean age was 71.0 ± 12.8 years: 76% of patients were ≥65 years of age. Sixty-five percent of patients were retired, 12.6% employed at least part-time and the rest disabled (3.8%), full-time homemakers (17.5%) or other (1.3%). Almost half the patients (45%) had PHN for >1 year.

The mean pain severity index was 4.2 indicating moderate pain. Fifty-nine per cent of patients reported moderate-to-severe pain as their overall pain within the prior 24 hours as indicated by their pain index severity scores; 78% of patients reported their worst pain within the prior 24 hours as moderate or severe in intensity.

Patients reported pain interference on all seven health status domains that was significantly associated with greater pain severity (Figure 1; $P<0.001$). The most affected domains were mood, sleep and general activity; the least affected domains were walking ability and relations with other people.

Most patients (89%) received at least one prescription medication for neuropathic pain, and polypharmacy was common (Table 1). More than half of the patients (52%) were prescribed antiepileptic medications (Table 1) including gabapentin (38%) and carbamazepine (23%), which are recommended for neuropathic pain [9]. Mean daily doses were low; 1032.3 ± 508.2 mg of gabapentin and 500.0 ± 309.1 mg of carbamazepine. Other commonly prescribed medications for PHN included anti-inflammatory and opioid agents (64%), sedative or hypnotic medications (32%), amitriptyline (21%) and other antidepressants (26%). More than one-third of patients (37%) received some form of prescription medication for PHN for >1 year, and a similar

Figure 1. Mean pain interference scores for domains of daily functioning on the modified short form brief pain inventory (mBPI-SF) by pain severity; $*P<0.001$ for the association between pain severity and interference.
Table 1. Patterns of treatment for postherpetic neuralgia

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( n ) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physician-reported NP prescription medications</strong></td>
<td></td>
</tr>
<tr>
<td>Current NP prescription medication</td>
<td>75 (89.3)</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>18 (21.4)</td>
</tr>
<tr>
<td>Other antidepressants</td>
<td>22 (26.2)</td>
</tr>
<tr>
<td>Sedatives/hypnotics</td>
<td>27 (32.1)</td>
</tr>
<tr>
<td>Analgesics</td>
<td>54 (64.3)</td>
</tr>
<tr>
<td>Opioids and opioid compounds</td>
<td>17 (20.2)</td>
</tr>
<tr>
<td>NSAIDs or COX-2s</td>
<td>28 (33.3)</td>
</tr>
<tr>
<td>Antiepileptic medications</td>
<td>44 (52.4)</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>32 (38.1)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>19 (22.6)</td>
</tr>
<tr>
<td><strong>Duration of NP prescription medication use</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;3 months</td>
<td>24 (29.6)</td>
</tr>
<tr>
<td>3–6 months</td>
<td>19 (23.5)</td>
</tr>
<tr>
<td>7–12 months</td>
<td>8 (9.9)</td>
</tr>
<tr>
<td>13–35 months</td>
<td>17 (21.0)</td>
</tr>
<tr>
<td>≥36 months</td>
<td>13 (16.0)</td>
</tr>
<tr>
<td><strong>Physician-reported concomitant prescription medications</strong></td>
<td></td>
</tr>
<tr>
<td>Current concomitant prescription medications</td>
<td>31 (36.9)</td>
</tr>
<tr>
<td>Prescribed medications for anxiety</td>
<td>12 (14.3)</td>
</tr>
<tr>
<td>Prescribed medications for sleep disturbance</td>
<td>14 (16.7)</td>
</tr>
<tr>
<td>Prescribed medication for depression</td>
<td>5 (6.0)</td>
</tr>
<tr>
<td><strong>Patient-reported other NP medications</strong></td>
<td></td>
</tr>
<tr>
<td>Non-prescription medications</td>
<td>31 (36.9)</td>
</tr>
<tr>
<td>Physical treatments</td>
<td>24 (28.6)</td>
</tr>
<tr>
<td>Topical lotions/creams</td>
<td>36 (42.9)</td>
</tr>
<tr>
<td>Herbs, vitamins and supplements</td>
<td>21 (25.0)</td>
</tr>
<tr>
<td>Devices</td>
<td>16 (19.0)</td>
</tr>
<tr>
<td>Exercise</td>
<td>14 (16.7)</td>
</tr>
</tbody>
</table>

NP, neuropathic pain; NSAIDs, non-steroidal anti-inflammatory drugs.

*Neither the treatment categories nor the subcategories are mutually exclusive.

bPrescribed either antidepressants, sedatives/hypnotics (benzodiazepines, buspirone or other hypnotics) or analgesics (tramadol, any opioids or opioid compounds, non-steroidal anti-inflammatory drugs or COX-2 inhibitors) for concomitant anxiety, depression or sleep disturbance.

proportion (37%) received concomitant prescription medications for anxiety, depression or sleep disturbance related to PHN (Table 1).

Eighty-five per cent of patients reported taking their prescription medication for PHN ‘all’ or ‘most of the time’.

Only 39% of patients reported their prescription medication as ‘extremely effective’ or ‘very effective’.

Many patients reported using other medications/treatments for their PHN (Table 1); 37% reported taking over-the-counter medications (e.g. paracetamol or aspirin), and similar proportions reported use of topical lotions or creams (43%), physical treatments (29%) or herbs/vitamins/supplements (25%).

Pain had a significant impact on health status including functioning and well-being. Patients reported an overall mean EQ-5D health state valuation of 0.60 ± 0.29 (–0.59 to +1.00 scale), and a significant association was observed between increasing pain severity and decreasing EQ-5D health state valuation (Figure 2; \( P<0.001 \)). Similarly, a significant association was observed between increasing pain severity and pain interference; pain interference index scores were 1.3, 3.8 and 6.2 for mild, moderate and severe pain, respectively (\( P<0.001 \)).

Patients placed significant value on obtaining relief from their PHN. On a 0–100 scale, patients estimated a 29% increase in their health-rating score (improvement from 61.7 ± 20.3 to 79.7 ± 19.8; \( P<0.0001 \), paired \( t \)-test) if they could experience complete relief from their PHN.

PHN directly impacted medical resource utilisation within the past 4 weeks; 68% of patients visited their physician at least once, 30% had telephone consultations for their PHN and 30% saw a pain specialist. A significant association was observed between increasing pain severity and greater number of telephone consults (\( P = 0.008 \)), with a similar trend between pain severity and physician visits (\( P = 0.078 \)).

**Discussion**

These findings demonstrate a substantial patient burden of PHN, consistent with previously reported neuropathic pain conditions including diabetic peripheral neuropathy [12, 19, 26] and PHN [13]. Patient burden, expressed as impairment of function and reduced quality of life, was significantly associated with pain severity as indicated by poorer health status (EQ-5D) and increased pain interference with functioning (mBPI-SF Pain Interference scores) with increasing neuropathic pain severity. Additionally, a substantial proportion of patients were prescribed medications for depression, anxiety and sleep disturbance related to PHN, conditions considered co-morbid with chronic pain including neuropathic syndromes [11, 27].

The sustained moderate-to-severe pain levels suggest suboptimal pain management. This is supported by the considerable patient burden observed despite most patients receiving prescription medications for their PHN. This finding may in part be attributed to the use of agents having no demonstrated efficacy for the treatment of neuropathic pain.
pain (e.g. 33% of patients were taking non-steroidal anti-inflammatory drugs or COX-2 inhibitors for their PHN).

Similarly, suboptimal doses of neuropathic pain medications including gabapentin and carbamazepine may have contributed to inadequate pain management [9, 10]. Few patients reported adequate therapeutic efficacy of their prescribed medications, which may explain why non-prescription adjunctive treatments including over-the-counter analgesics, topicals and supplements were taken to obtain pain relief.

Twenty-one per cent of patients were taking amitriptyline, which has demonstrated efficacy in neuropathic pain, albeit at higher doses than the mean daily dose of 32.4 ± 17.4 mg observed here. According to the Beers modified criteria [28], amitriptyline is considered inappropriate for use in the age group represented in this analysis (≥65 years) and is not recommended for treatment of neuropathic pain in older patients [9]. Potentially inappropriate use of medications for painful neuropathic disorders was recently reported in older adults, where 35% of patients with PHN were prescribed amitriptyline [29].

Our observation of inadequate pain control, pain interference with functioning and suboptimal treatment was consistent with a US postal survey of patients with PHN, where only half of patients reported taking prescription medication for PHN in the prior week, despite moderate levels of pain severity and pain interference [13]. The association of pain severity with pain interference and EQ-5D health state valuation observed in both the postal survey and current study suggest that suboptimal treatment of PHN is common.

Suboptimal pain management and patient burden were similarly reported by Gilron et al. [30] in a Canadian study of patients with neuropathic pain treated by general practitioners. Seventy-three per cent of patients complained of inadequate pain control and only 16% tried any of the newer pharmacologic agents available for neuropathic pain. Approximately 30% of patients saw a pain specialist, similar to the present study, indicating that few patients were being referred to and treated by physicians familiar with new and/or appropriate treatment options. In the current analysis, inadequate management of PHN and increased resource utilisation were demonstrated by the significant association between pain severity and telephone consults and the trend towards more physician visits with increasing pain severity.

This study has several limitations. The small number of patients may limit the ability to detect potentially significant associations. Other limitations include the potential for selection and recall bias, where patients were actively seeking medical care (possible selection bias), and some information from the survey was collected by self report (possible recall bias). Furthermore, pain is a complex and multidimensional experience, and our focus on pain severity may not have captured the full impact of pain on patient burden. The use of >3 to distinguish between moderate and mild pain severity and interference was consistent with that reported in other studies. The cut-point correlated with resource utilisation and patient outcomes in painful diabetic peripheral neuropathy [20, 24] and demonstrated agreement with activities of daily living and quality of life in an HZ-specific adaptation of the BPI [18].

In conclusion, this study demonstrates substantial patient burden associated with PHN. The burden was significantly greater when pain was less controlled and likely resulted from suboptimal or inappropriate management strategies. Our results demonstrate a need for more effective management strategies in patients presenting with PHN, such as physician education related to neuropathic pain mechanisms and treatment options, and familiarity with current neuropathic pain management guidelines.

**Key points**
- Most patients with postherpetic neuralgia (PHN) reported moderate or severe pain and suboptimal health and functioning despite taking prescribed medications for the treatment of PHN.
- Patient burden was significantly associated with pain severity: health valuation was poorer and pain interference with functioning was greater with increasing pain levels.
- Use of prescription medications with no known efficacy in neuropathic pain and in general lower than recommended doses of medications with neuropathic pain efficacy was reported.
- Better management strategies including physician education could reduce the burden of PHN.

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**Conflicts of interest**
There were no conflicts of interest.

**References**