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Original article

Health status, function, productivity, and costs among individuals with idiopathic painful peripheral neuropathy with small fiber involvement in the United States: results from a retrospective chart review and cross-sectional survey

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Abstract

Objective:
To characterize the burden of idiopathic painful peripheral neuropathy with small fiber involvement (idiopathic SFN) by pain severity in the US.

Methods:
One hundred previously diagnosed idiopathic SFN subjects were enrolled during routine office visits. Subjects completed a one-time questionnaire, and investigators reported clinical characteristics and healthcare resource use, based on 6 month retrospective chart review. Annualized direct and indirect costs were estimated. Results were stratified across pain severity groups.

Results:
Mean age was 63.5 years; 53.0% were female; 76.0% had moderate or severe pain. Most common comorbidities were sleep disturbance/insomnia (37.0%), anxiety (34.0%), and depressive symptoms (33.0%). Overall mean health status (0.59; −0.11–1.00 scale), physical and mental health (31.7 and 45.6, respectively, 0–100 scale), sleep index (45.1; 0–100 scale), and pain interference with function (5.0; 0–10 scale) differed by pain severity, with worse outcomes among those with greater pain (all $p < 0.002$). 84.0% were prescribed $\geq$1 SFN medication. 16.0% were employed; mean overall work impairment was 36.9%. Annualized average adjusted direct and indirect costs per subject ($8055 and $13,733, respectively) differed by pain severity.

Conclusions:
Idiopathic SFN subjects with pain experience moderate or severe pain, which negatively impacts health status, function, and productivity, and leads to substantial direct and indirect costs.

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Burden – Costs – Function – Healthcare resource use – Health status – Idiopathic small fiber neuropathy – Neuropathic pain – Patient-reported outcomes – Productivity

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Introduction

Small fiber neuropathy (SFN) is a relatively common disorder of peripheral nerves, primarily affecting small somatic fibers, autonomic fibers, or both[1,2]. The clinical presentation is characteristically dominated by the onset of neuropathic pain and autonomic symptoms usually in adulthood, with relative preservation of most large fiber functions (i.e., relatively normal strength, tendon reflexes, position sense, and vibration sense), and normal nerve conduction[1,2]. Small fiber neuropathy can be caused by a variety of disorders, including glucose intolerance, lupus erythematosus, scleroderma, inflammatory bowel disease, celiac disease, human immunodeficiency virus (HIV), and toxin or toxic drug exposure, among others; however, in approximately half of the cases (5 to 8 million people in the US[3]) no cause can be established[1,2]. Such patients are diagnosed as having idiopathic SFN and may complain of tingling, numbness, burning pain, or sensitivity/pain to touch in the feet, usually with sensory loss on the skin[4].

Small fibers are not specifically assessed by traditional neurophysiological investigations, and thus SFN can be difficult to diagnose with conventional testing, such as nerve conduction studies and electromyography. The diagnosis of painful idiopathic SFN in clinical practice remains a clinical diagnosis based upon a history of pain starting in the feet (i.e., length-dependent polyneuropathy) and examination findings of hypoalgesia, hyperalgesia, or allodynia without signs or symptoms of large fiber disease[5]. Development of newer diagnostic tools, quantitative sensory testing (QST), and quantifiable nerve fiber density testing via skin biopsy can confirm the presence of SFN in a reliable fashion with good sensitivity and specificity[6–8]. Skin biopsy can be instrumental in helping to establish an SFN diagnosis among individuals with no known etiology for their neuropathy[9]; however, these tools are not commonly used in clinical practice[10].

A number of publications have provided evidence that neuropathic pain leads to high levels of pain, impaired quality of life, lost productivity, and increased costs[11–14]. However, painful idiopathic SFN remains under-studied compared with neuropathic pain populations of comparable size, such as painful diabetic peripheral neuropathy. To our knowledge, no studies have assessed both the humanistic and economic burden of painful idiopathic SFN.

The objective of this study was to comprehensively assess the humanistic and economic burden, by pain severity, of painful idiopathic SFN in the US by capturing sociodemographic and clinical characteristics, as well as the impact of idiopathic SFN on health status, normal function and activities, productivity, healthcare resource use (HRU), and direct and indirect costs.

Patients and methods

Study design and subjects

This cross-sectional, observational study recruited previously diagnosed idiopathic SFN subjects when they presented for routine office visits between September 2011 and March 2012 at one of 16 community-based US physician practices, including 5 general practitioners, 5 pain specialists, 4 neurologists, 1 endocrinologist, and 1 rheumatologist. Study sites screened all subjects with neuropathic pain who presented for office visits during the study period to assess eligibility.

Eligibility criteria for enrollment required subjects to be 18 years or older; to be able to read and understand English; and to have been diagnosed with idiopathic SFN at least 6 months prior to enrollment. Subjects were also required to

have been managed at the participating physician's practice for at least 6 months and to have experienced symptoms due to neuropathy (e.g., pain) for at least 3 months prior to the survey. Subjects were not eligible if they participated in an investigational drug study in the 6 months prior to enrollment, had a serious or unstable medical or psychological condition that would compromise participation in the study, or had a concomitant illness unrelated to idiopathic SFN that may confound the assessment of the subject's painful idiopathic SFN.

While investigators confirmed subjects had been previously diagnosed with painful idiopathic SFN, diagnosis in the clinical setting was likely based upon history and physical exam, rather than by confirmation by QST or skin biopsy. Individuals with SFN of known cause, including HIV, shingles, diabetes, or other hereditary forms of small fiber involvement were not considered for this sample.

This cross-sectional, observational study was conducted according to the Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects contained in the Declaration of Helsinki[15] and a central Institutional Review Board (IRB), Concordia Clinical Research (Cedar Knolls, NJ), approved this study.

Data collection

Upon enrollment, subjects completed a one-time questionnaire, including items related to demographics, symptom duration, nonprescription treatments, out-of-pocket costs (in the past 4 weeks) related to idiopathic SFN pain treatments, employment status and productivity, as well as the following validated patient-reported outcomes (PRO) measures:

- Brief Pain Inventory–Short Form (BPI-SF), an 11 item measure of pain severity (at its worst, at its least, on average, and currently) and pain interference with function (general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life) (0–10 scale; higher scores indicate worse outcomes)[16];
- 12-item Short-Form Health Survey version 2 (SF-12v2), 1 week recall, a 12 item measure of physical and mental health status via eight domains (physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health) and a physical and mental component score (0–100 scale; higher scores indicate better outcomes)[17];
- EuroQol 5-dimensions, 3 levels (EQ-5D-3L), a 5 item general health status and utility measure (−0.11 to 1.00 scale; higher scores indicate better outcomes)[18];
- Medical Outcomes Study Sleep Scale (MOS-SS), a 12 item measure of sleep outcomes, including 6 subscales (sleep disturbance, snoring, awakening short of breath or with a headache, sleep adequacy, somnolence, and sleep quantity) as well as the Sleep Problems Index (0–100 scale; higher scores indicate more sleep problems)[19]; and
- Work Productivity and Activity Impairment (WPAI) due to idiopathic SFN, a 6 item measure used to quantify overall work impairment (comprising absenteeism and presenteeism) and daily activity impairment (scores expressed as impairment percentages; higher scores indicate more productivity loss and greater impairment)[20].

The participating physician or site coordinator reviewed the subject's medical chart for clinical characteristics, such as idiopathic SFN diagnosis date, duration of idiopathic SFN, and comorbidities, as well as idiopathic SFN prescription treatments and other idiopathic SFN-related HRU over the past 6 months.

Costing algorithms

Standard costing algorithms were used to assign 'per-unit' costs (2012 US$) to units of HRU and lost productivity to calculate costs.

Indirect costs included work-related lost productivity due to absenteeism, presenteeism and changes in employment status (i.e., disability; unemployment; early retirement; and reduced work schedule) due to idiopathic SFN. Indirect costs were calculated by applying (1) the average hourly wage values, obtained through the Bureau of Labor Statistics[21], to absenteeism and presenteeism from the WPAI as described by Lofland *et al.*[22], and subject-reported time since change in employment status due to idiopathic SFN; as well as (2) the average monthly disability payment from the Social Security Administration to subject-reported time disabled due to idiopathic SFN[23].

Direct costs attributable to idiopathic SFN included costs to payers for physician and other healthcare provider visits; prescription medications; transcutaneous electrical nerve stimulation (TENS) device; outpatient tests and procedures; emergency room visits; hospital outpatient visits; and hospitalizations; as well as out-of-pocket costs to subjects for medical care and nonmedical resources (child care, help with house and/or yard work, and help with activities of daily living) related to idiopathic SFN.

Direct costs were calculated using per-unit costs obtained from the 2012 Red Book, discounted average wholesale price (AWP) (plus a dispensing fee)[24], the fiscal year (FY) 2012 Medicare Physician Fee Schedule (MPFS), the FY 2012 Medicare Hospital Outpatient Prospective Payment System (OPPS), and the FY 2012 Medicare Hospital Inpatient Prospective Payment System (IPPS). Costing algorithms assigned a per-unit cost (2012 US$) to HRU to calculate direct costs, with

the exception of subject-reported out-of-pocket costs, which did not need to be monetized, and per subject costs were then annualized.

Statistical methods

Data analysis was performed using PC-SAS version 9.1.3 (SAS Institute, Cary, NC). To describe the sample, summary statistics were reported, and average pain severity scores on the BPI-SF were used to classify subjects into one of three pain severity groups based on established cut-points for individuals with neuropathic pain (0–3, mild; 4–6, moderate; and 7–10, severe)[25,26]. To evaluate the association between pain severity and outcomes, the Kruskal–Wallis (continuous variables) and chi-square or Fisher's exact (categorical variables) tests were applied.

Multiple (adjusted) linear regression was used to examine the association between pain severity and costs. For the adjusted model, the following pool of covariates was introduced for the forward stepwise regression using SAS default entry and exit criteria of 0.15: age, sex, race, ethnicity, pain severity, employment status, ability to walk, insurance coverage, idiopathic SFN prescription drug coverage, worker's compensation, time since diagnosis, and comorbid conditions (see Table 2 for a list of comorbid conditions). Details about the components of the final models can be found in Table 6. Statistical significance was evaluated at the 0.05 level.

Results

Demographic and clinical characteristics

One hundred idiopathic SFN subjects were enrolled in the study; Table 1 presents the demographic and clinical characteristics of the entire sample overall and by pain severity.

Table 1. Demographic and clinical characteristics, overall and by average pain severity*.

Characteristic	Overall ($N=100$)	Mild ($n=23$)	Moderate ($n=43$)	Severe ($n=33$)	p Value†
Age, years, mean (SD)	63.5 (14.6)	66.8 (15.7)	62.2 (14.5)	61.9 (13.4)	0.4859
Female, *n* (%)	53 (53.0)	10 (43.5)	19 (44.2)	24 (72.7)	0.0264
Race, *n* (%)					0.1238
White	89 (89.0)	19 (82.6)	42 (97.7)	27 (81.8)	
Black or African American	5 (5.0)	1 (4.3)	1 (2.3)	3 (9.1)	
American Indian or Alaska Native	2 (2.0)	1 (4.3)	0 (0.0)	1 (3.0)	
Multiracial	1 (1.0)	1 (4.3)	0 (0.0)	0 (0.0)	
Other	3 (3.0)	1 (4.3)	0 (0.0)	2 (6.1)	
Health insurance, *n* (%)	95 (95.0)	23 (100.0)	42 (97.7)	29 (87.9)	NA
NeP prescription coverage, *n* (%)	91 (91.0)	22 (95.7)	41 (95.3)	27 (81.8)	0.1160
BPI-SF Pain Severity Index, mean (SD)	5.2 (2.4)	1.7 (1.2)	5.2 (0.8)	7.6 (1.0)	NA
Time since SFN diagnosis, months, mean (SD)	87.9 (65.0)	78.2 (68.3)	86.7 (60.7)	89.4 (57.6)	0.5330
Time since first healthcare provider visit related to SFN, months, mean (SD)‡	98.4 (75.4)	94.2 (75.6)	94.9 (76.3)	99.3 (67.3)	0.8456
Time since first experienced SFN symptoms, months, mean (SD)‡	103.6 (76.9)	105.5 (78.1)	99.4 (79.1)	101.1 (66.5)	0.8702
Comorbid conditions, *n* (%)§					
Sleep disturbance/insomnia	37 (37.0)	8 (34.8)	13 (30.2)	16 (48.5)	0.2749
Anxiety	34 (34.0)	3 (13.0)	14 (32.6)	17 (51.5)	0.0111
Depressive symptoms	33 (33.0)	4 (17.4)	14 (32.6)	15 (45.5)	0.0946
Restless legs syndrome	29 (29.0)	5 (21.7)	13 (30.2)	11 (33.3)	0.6341
Headache/migraine	28 (28.0)	3 (13.0)	13 (30.2)	12 (36.4)	0.1457
Chronic low back pain	18 (18.0)	2 (8.7)	11 (25.6)	5 (15.2)	0.2365
Irritable bowel syndrome	14 (14.0)	2 (8.7)	6 (14.0)	6 (18.2)	0.6591
Chronic fatigue syndrome	12 (12.0)	2 (8.7)	6 (14.0)	4 (12.1)	0.9245
Fibromyalgia	10 (10.0)	0 (0.0)	4 (9.3)	6 (18.2)	0.0748
Cognitive dysfunction	9 (9.0)	4 (17.4)	3 (7.0)	2 (6.1)	0.3616
Major depressive disorder	8 (8.0)	1 (4.3)	6 (14.0)	1 (3.0)	0.2266
Raynaud's syndrome	2 (2.0)	1 (4.3)	1 (2.3)	0 (0.0)	0.7075
Other comorbidities	4 (4.0)	0 (0.0)	2 (4.7)	2 (6.1)	0.6792

*Mild, moderate, and severe classification was based on the Brief Pain Inventory–Short Form average pain severity score (mild = 0–3; moderate = 4–6; and severe = 7–10). One subject did not respond to all required items needed to calculate an average pain severity score and thus was not included in any analysis by pain severity category.
†p Values are from the Kruskal–Wallis test for continuous variables and the Fisher's exact test for the categorical variables; mild versus moderate versus severe.
‡Overall: $n=99$, mild: $n=22$.
§As more than one response may be selected, the sum of percentages across response options may exceed 100.
BPI-SF, Brief Pain Inventory–Short Form; GP, general practitioner; NA, not available; NeP, neuropathic pain; SD, standard deviation; SFN, small fiber neuropathy.

The mean (SD) age was 63.5 (14.6) years in the sample, and a majority (53.0%) of subjects were female. The mean (SD) subject-reported pain severity score was 5.2 (2.4) overall; using aforementioned established cut-points, 76.0% of subjects were classified as having moderate or severe pain. Severe pain was more common among females. A majority (78.0%) of subjects reported suffering (moderately – 21.0%, strongly – 39.0%, or very strongly – 18.0%) from a burning sensation (data not shown). Similarly, the majority (78.0%) of subjects reported suffering (moderately – 22.0%, strongly – 42.0%, or very strongly – 14.0%) from a tingling or prickling sensation in the area of their pain (data not shown).

Subjects had an average (SD) of 3.3 (2.1) comorbid conditions, and the most frequently reported in our sample included sleep disturbance/insomnia (37.0%), anxiety (34.0%), and depressive symptoms (33.0%). Restless leg syndrome and headache/migraine were also reported by more than one-quarter of the sample. Only anxiety differed across the pain severity groups ($p = 0.0111$).

On average (SD), subjects had been diagnosed with idiopathic SFN 7.3 (5.4) years prior to enrollment in the study (Table 1), and it took idiopathic SFN subjects 5.2 months from first experiencing neuropathic pain symptoms to see a healthcare professional (HCP) for their neuropathic pain symptoms (Table 1). The majority of subjects reported being diagnosed by a neurologist (39.0%) or pain specialist (14.0%), with the remaining 47.0% of subjects being diagnosed by a primary care physician (27.0%), endocrinologist (6.0%), orthopedist (4.0%), rheumatologist (2.0%), surgeon (2.0%), podiatrist (2.0%), neurosurgeon (1.0%), physiatrist/physical medicine and rehabilitation specialist (1.0%), or other physician (2.0%) (data not shown). On average, it took nearly 1 year from the first neuropathic pain visit to receive an idiopathic SFN diagnosis (Table 1). In total, the mean time from subjects' first experience of idiopathic SFN symptoms to the time of physician diagnosis was 1.3 years.

Health status and function

The mean (SD) BPI-SF pain interference index was 5.0 (2.7) overall; a statistically significant difference was observed across pain severity groups ($p < 0.0001$) and pain interference with function increased with pain severity (Figure 1). In the overall sample, 5 of the 7 pain interference with function domains had (mean) scores >5.0: sleep (5.8), walking ability (5.5), normal work (5.5), general activity (5.2) and enjoyment of life (5.2) (data not shown). Significant differences across pain severity groups were observed for each of the seven pain interference with function domains (all $p < 0.0001$), with higher scores among those with higher pain severity (Table 2).

The mean (SD) SF-12v2 Physical Component Summary (PCS) and Mental Component Summary (MCS) were 31.7 (11.4) and 45.6 (12.2), respectively. In the overall sample, the SF-12v2 domains most impacted with (mean) scores <40.0 were physical functioning (29.3), vitality (36.1), bodily pain (37.8) and role physical (38.0) (data not shown). A statistically significant

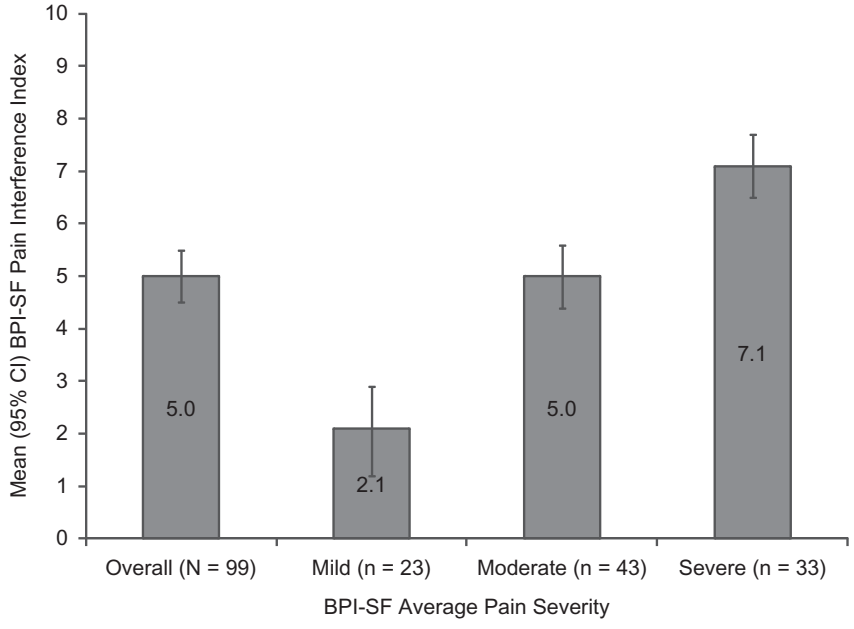

Figure 1. Brief Pain Inventory–Short Form (BPI-SF) Pain Interference Index scores stratified by BPI-SF average pain severity score (mild = 0–3, moderate = 4–6, and severe = 7–10). One subject did not respond to all required items needed to calculate an average pain severity score and thus was not included in any analysis by pain severity. The BPI-SF Pain Interference Index scored on a 0–10 scale. $p < 0.0001$ across pain severity groups.

Table 2. Patient-reported pain interference with function, physical and mental health status, and sleep, by average pain severity*.

Outcome	Mild ($n=23$)	Moderate ($n=43$)	Severe ($n=33$)	p Value†
BPI-SF Pain Interference with Function Domains‡				
General Activity	1.8 (2.00)	5.2 (2.41)	7.4 (2.15)	<0.0001
Mood	1.0 (1.68)	4.0 (2.76)	6.9 (2.54)	<0.0001
Walking Ability	2.3 (2.51)	5.6 (2.75)	7.8 (1.73)	<0.0001
Normal Work	2.0 (2.50)	5.7 (2.52)	7.5 (1.97)	<0.0001
Relations with Other People	1.1 (1.95)	3.6 (2.91)	5.5 (2.77)	<0.0001
Sleep	3.4 (3.80)	5.7 (2.95)	7.6 (2.56)	<0.0001
Enjoyment of Life	2.9 (3.03)	5.3 (2.97)	6.8 (2.56)	<0.0001
SF-12 Domains§				
Physical Functioning, Mean (SD)	55.4 (37.66)	27.9 (31.91)	12.9 (21.76)	<0.0001
Role Physical, Mean (SD)‖	63.0 (33.17)	35.1 (27.50)	23.1 (23.41)	<0.0001
Bodily Pain, Mean (SD)	67.4 (30.56)	37.2 (24.62)	16.7 (19.43)	<0.0001
General Health, Mean (SD)	63.3 (23.48)	49.3 (28.94)	35.5 (24.35)	0.0010
Vitality, Mean (SD)‖	53.3 (26.44)	36.3 (25.42)	24.2 (22.95)	0.0005
Social Functioning, Mean (SD)	78.3 (27.49)	52.3 (29.79)	35.6 (27.97)	<0.0001
Role Emotional, Mean (SD)	82.6 (28.89)	60.5 (33.73)	48.9 (33.85)	0.0015
Mental Health, Mean (SD)‖	72.8 (20.52)	63.7 (18.48)	47.7 (23.27)	0.0001
MOS-SS Subscales**				
Sleep Disturbance	29.7 (25.13)	48.3 (21.27)	60.2 (28.06)	<0.0001
Sleep Adequacy	51.7 (28.23)	47.4 (20.94)	33.3 (24.32)	0.0150
Sleep Somnolence	34.5 (21.71)	39.4 (23.36)	52.9 (25.49)	0.0099
Snoring	32.2 (31.76)	39.1 (34.07)	42.4 (36.66)	0.6400
Shortness of Breath or Headache	0.9 (4.17)	14.4 (19.68)	27.3 (33.47)	0.0002
Sleep Quantity††	7.0 (1.74)	6.7 (1.52)	6.0 (1.61)	0.1262

*Mild, moderate, and severe classification was based on the Brief Pain Inventory–Short Form average pain severity score (mild = 0–3; moderate = 4–6; and severe = 7–10). One subject did not respond to all required items needed to calculate an average pain severity score and thus was not included in any analysis by pain severity category.
†p-values are from the Kruskal–Wallis test; mild versus moderate versus severe.
‡Lower scores indicate a better subject-reported outcome.
§Higher scores indicate a better subject-reported outcome.
‖Moderate: $n=42$.
**Higher scores indicate more of the concept being measured. Higher scores for 'Sleep Adequacy' and 'Sleep Quantity' represent better sleep outcomes; whereas higher scores for the other scales indicate poorer sleep outcomes.
††Moderate: $n=41$.
BPI-SF, Brief Pain Inventory–Short Form; MOS-SS, Medical Outcomes Study Sleep Scale; SD, standard deviation; SF-12, Short Form, 12 items; SFN, small fiber neuropathy.

difference was observed in health status across pain severity levels for the PCS ($p<0.0001$) and MCS ($p=0.0010$; Figure 2), as well as for each of the eight individual domains (all $p<0.002$), with lower scores among those with higher pain severity (Table 2). The mean (SD) EQ-5D-3L health state utility was 0.59 (0.23) overall and decreased as pain severity increased. Similar to the PCS and MCS, a statistically significant difference across pain severity levels was observed in health status measured by the EQ-5D-3L ($p<0.0001$; Figure 3).

The mean MOS-SS Sleep Problems index score was 45.1 (20.3); sleep problems worsened at increasing levels of pain ($p<0.0001$; Figure 4). The sleep domains most affected were sleep disturbance, sleep adequacy, and sleep somnolence (means 47.5, 43.8 and 42.5, respectively; data not shown). In each of the sleep domains measured by the MOS-SS, subjects with severe pain had the worst mean scores (Table 2). A statistically significant difference was observed across pain severity levels for sleep disturbance, sleep adequacy, sleep somnolence, and shortness of breath or headache (all $p<0.02$; Table 2).

Lost productivity and changes in employment status

The majority of subjects were not employed for pay. Nearly half (49.0%) were retired, 23.0% were disabled, and less than a quarter (16.0%) were employed; employment status differed significantly by pain severity ($p=0.0138$, Figure 5). Overall, approximately a quarter of the sample reported that SFN had negatively impacted their employment status, and this impact differed by pain severity ($p=0.0296$), with a greater impact among severe subjects (Table 3). For example, 95.7% of mild subjects reported no change in employment status due to SFN compared to 60.6% of severe subjects, and 4.3% of mild subjects reported being disabled due to SFN compared to 27.3% of severe subjects.

WPAI scores for overall work impairment, which consists of absenteeism and presenteeism, and overall activity impairment are presented in Table 3. Among employed subjects ($n=16$), mean (SD) WPAI overall work impairment due to idiopathic SFN was 36.9% (31.3%).

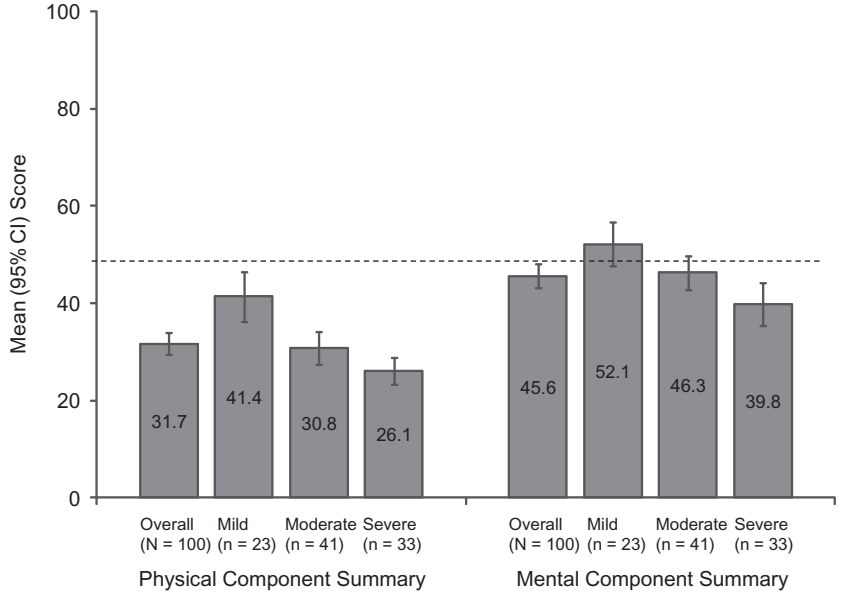

Figure 2. Summary scale scores on the 12 item Short Form Health Survey stratified by Brief Pain Inventory–Short Form (BPI-SF) average pain severity score (mild = 0–3, moderate = 4–6, and severe = 7–10). One subject did not respond to all required items needed to calculate an average pain severity score and thus was not included in any analysis by pain severity. Summary scores are scored on a 0–100 scale (higher scores indicate better health status); population norms are indicated by the broken horizontal line. Physical Component Summary: $p < 0.0001$ and Mental Component Summary: $p = 0.0010$ across pain severity groups.

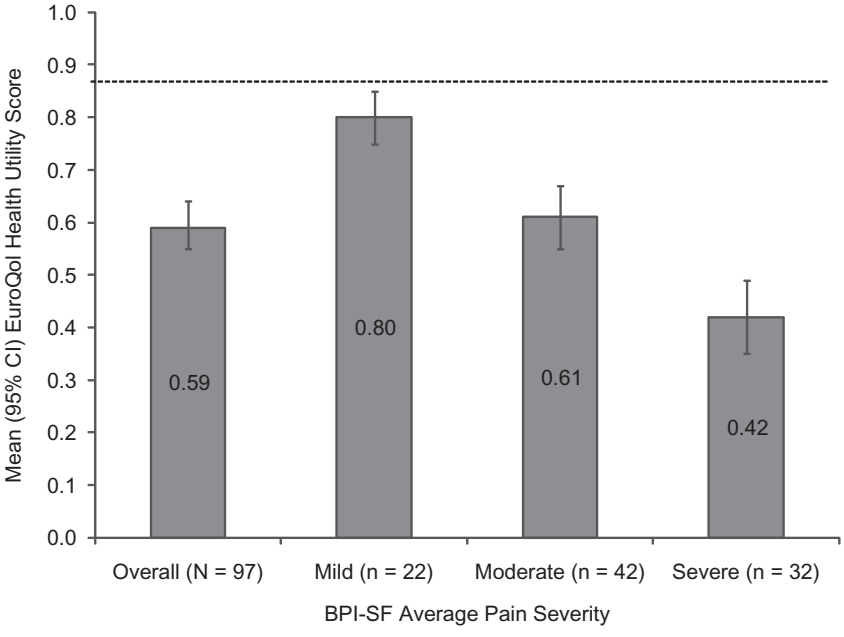

Figure 3. EuroQol health state utility scores stratified by Brief Pain Inventory–Short Form (BPI-SF) average pain severity score (mild = 0–3, moderate = 4–6, and severe = 7–10). One subject did not respond to all required items needed to calculate an average pain severity score and thus was not included in any analysis by pain severity. EuroQol is scored on a −0.11 to 1.00 scale (higher scores indicate better health status); population norm is indicated by the broken horizontal line. $p < 0.0001$ across pain severity groups.

Across all subjects, mean (SD) WPAI activity impairment due to idiopathic SFN was 51.9% (29.6%); the difference was statistically significant ($p < 0.0001$) across pain severity groups and worsened at increasing levels of pain.

Healthcare resource use

The mean (SD) number of idiopathic SFN-related physician office visits per subject in the 6 months

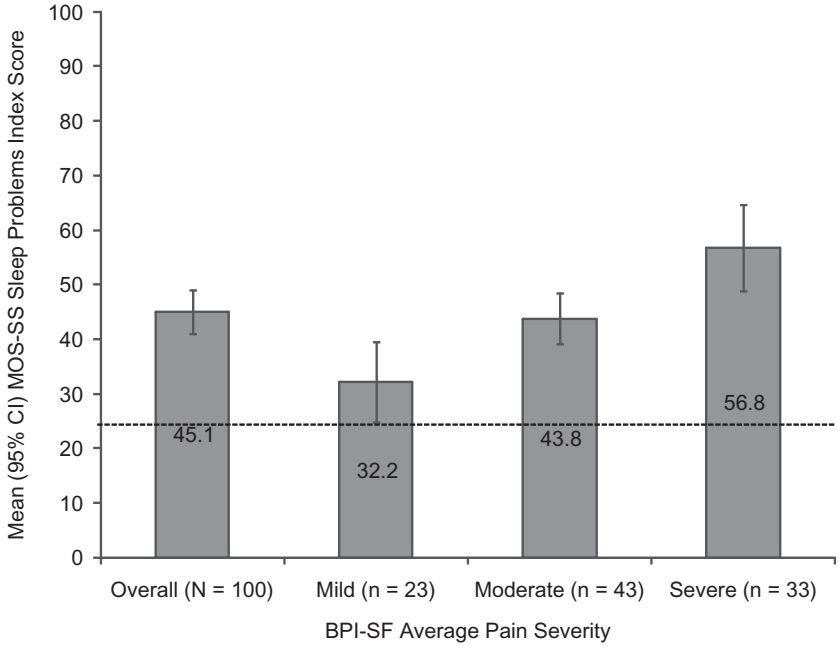

Figure 4. Medical Outcomes Study Sleep Scale (MOS-SS) Sleep Problems Index score stratified by Brief Pain Inventory–Short Form (BPI-SF) average pain severity score (mild = 0–3, moderate = 4–6, and severe = 7–10). One subject did not respond to all required items needed to calculate an average pain severity score and thus was not included in any analysis by pain severity. The MOS-SS Sleep Problems Index is scored on a 0–100 scale (higher score indicates greater sleep problems); population norm is indicated by the broken horizontal line. $p < 0.0001$ across pain severity groups.

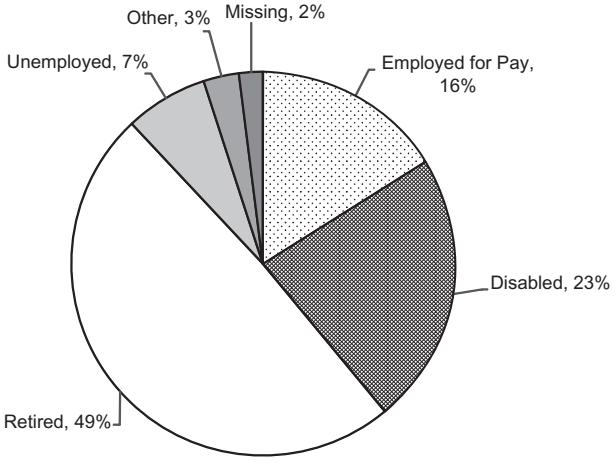

Figure 5. Overall employment status among the study subjects ($N = 100$). Employment status differed significantly by pain severity ($p = 0.0138$), with 26.1% of mild, 20.9% of moderate, and 3.0% of severe subjects employed for pay; 4.3% of mild, 18.6% of moderate, and 42.4% of severe subjects disabled; 56.5% of mild, 48.8% of moderate, and 42.4% of severe subjects retired; and 8.7% of mild, 7.0% of moderate, and 6.1% of severe subjects unemployed. Two moderate subjects and one severe subject selected 'other', and one mild subject and one severe subject had missing data.

prior to enrollment was 2.7 (2.2), and the mean (SD) number of office-based tests and procedures performed in the same 6 months was 0.6 (1.4; Table 4). However, no significant difference in use of these resources was observed across the pain severity groups (Table 4).

A majority (84.0%) of subjects were prescribed at least one medication for the management of their idiopathic SFN in the 6 months prior to enrollment, and approximately half (51.0%) of the subjects reported taking nonprescription medications for their idiopathic SFN in the 4 weeks prior to enrollment (data not shown). The mean (SD) number of medications prescribed per subject over the past 6 months was 1.7 (1.3) overall, and for nonprescription medications, patients reported a mean of 1.0 (1.3) medications over the past 4 weeks (Table 4). Statistical significance was observed across the pain severity groups for prescription medications ($p = 0.0117$) but not for nonprescription medications ($p = 0.1099$; Table 4).

Figure 6 shows that the most frequently prescribed medication classes were antiepileptics (52.0%) and opioids (47.0%). Among antiepileptics, gabapentin (67.3% of those taking an antiepileptic) and pregabalin (32.7% of those taking an antiepileptic) were the most commonly prescribed (data not shown). Opioids were further classified into strong short-acting, weak short-acting, and long-acting classes; the most commonly prescribed of the opioid classes were strong short-acting opioids (Figure 6). The most frequently taken nonprescription medications were vitamins (27.0%), ibuprofen (21.0%), and acetaminophen (18.0%; data not shown).

Table 3. Impact on employment status, work productivity, and activity impairment due to small fiber neuropathy, overall and by average pain severity*.

Productivity (%)	Overall ($N=100$)	Mild ($n=23$)	Moderate ($n=43$)	Severe ($n=33$)	p Value†
Employed for pay, *n* (%)	16 (16.0)	6 (26.1)	9 (20.9)	1 (3.0)	0.0213
Impact of SFN on employment status, *n* (%)					0.0296
No change	71 (71.0)	22 (95.7)	28 (65.1)	20 (60.6)	
Reduced hours	2 (2.0)	0 (0.0)	2 (4.7)	0 (0.0)	
Disabled	14 (14.0)	1 (4.3)	4 (9.3)	9 (27.3)	
Retired early	3 (3.0)	0 (0.0)	3 (7.0)	0 (0.0)	
Unemployed	4 (4.0)	0 (0.0)	3 (7.0)	1 (3.0)	
Missing	6 (6.0)	0 (0.0)	3 (7.0)	3 (9.1)	
WPAI					
Overall work impairment‡,§					0.2980
n	15	6	8	1	
Mean (SD)	36.9 (31.3)	23.8 (31.6)	43.9 (31.0)	60.0 (NA)	
Activity impairment‡					<0.0001
n	98	23	42	33	
Mean (SD)	51.9 (29.6)	18.7 (21.0)	54.3 (26.3)	72.1 (15.8)	

*Mild, moderate, and severe classification was based on the Brief Pain Inventory–Short Form average pain severity score (mild = 0–3; moderate = 4–6; and severe = 7–10). One subject did not respond to all required items needed to calculate an average pain severity score and thus was not included in any analysis by pain severity category.
†*p* Values are from the Kruskal–Wallis test; mild versus moderate versus severe.
‡The Overall Work Impairment score is based on subjects who provided a value for presenteeism and/or absenteeism unless all values were 0; higher values indicate greater impairment.
§Among those employed for pay.
NA, not applicable; SFN, small fiber neuropathy; SD, standard deviation; WPAI, Work Productivity and Activity Impairment.

Table 4. Healthcare resource utilization for small fiber neuropathy, overall and by average pain severity*.

Resource Use†	Overall ($N=100$)	Mild ($n=23$)	Moderate ($n=43$)	Severe ($n=33$)	p Value‡
Medications					
Prescription medications prescribed, mean (SD)§	1.7 (1.3)	1.0 (0.8)	2.0 (1.4)	1.8 (1.1)	0.0117
Non-prescription medications used, mean (SD)‖	1.0 (1.3)	0.5 (0.8)	1.1 (1.4)	1.2 (1.4)	0.1099
Office visits§					
Physician office visits for SFN, mean (SD)	2.7 (2.2)	2.2 (1.6)	2.6 (2.3)	3.2 (2.5)	0.3294
Non-physician office visits for SFN, mean (SD)	0.3 (1.2)	0.3 (0.9)	0.4 (1.3)	0.3 (1.2)	0.9026
Outpatient tests or procedures, mean (SD)§	0.6 (1.4)	0.4 (1.5)	0.7 (1.6)	0.5 (0.9)	0.3642

*Mild, moderate and severe classification was based on the Brief Pain Inventory–Short Form average pain severity score. One subject did not respond to all required items needed to calculate an average pain severity score and thus was not included in any analysis by pain severity category.
†No hospitalizations or hospital outpatient visits were reported, and one emergency room visit was reported by a moderate pain subject.
‡*p* Values are from the Kruskal–Wallis test; mild versus moderate versus severe.
§During the past 6 months.
‖During the past 4 weeks.
SD, standard deviation.

Costs

The unadjusted total indirect and direct costs and cost components are presented in Table 5. The unadjusted mean (95% confidence interval [CI]) annualized indirect cost per subject for the overall sample was $13,459 ([$9158, $17,759]). The indirect per subject costs were highest among those with moderate and severe pain, although the difference across pain severity groups was not statistically significant (mild: $5819; moderate: $16,043; severe: $15,824; $p=0.2348$). The primary driver of indirect costs was lost productivity due to idiopathic SFN disability (53.6%; data not shown). The unadjusted mean (95% CI) annualized direct cost per subject for the overall sample was $8055 ($5440, $10,671) and increased as pain severity increased (mild: $3375; moderate: $8085; severe: $11,481; $p=0.0100$). The primary driver of direct costs was prescription drugs (68.4%), followed by out-of-pocket medical costs to subjects (17.8%; data not shown).

Results from the regression analysis can be found in Table 6. A subset of comorbidities were predictive of direct costs; similarly, certain comorbidities and covariates related to employment were predictive of indirect costs. Total average annualized adjusted direct costs per subject were $6501 for mild, $7855 for moderate, and $9602 for severe, and for indirect costs, the values were $7574, $16,871, and $13,522 for mild, moderate and severe, respectively. There was a statistically significant difference in annualized adjusted indirect costs per subject for subjects with mild and moderate pain severity ($p=0.0360$; Figure 7).

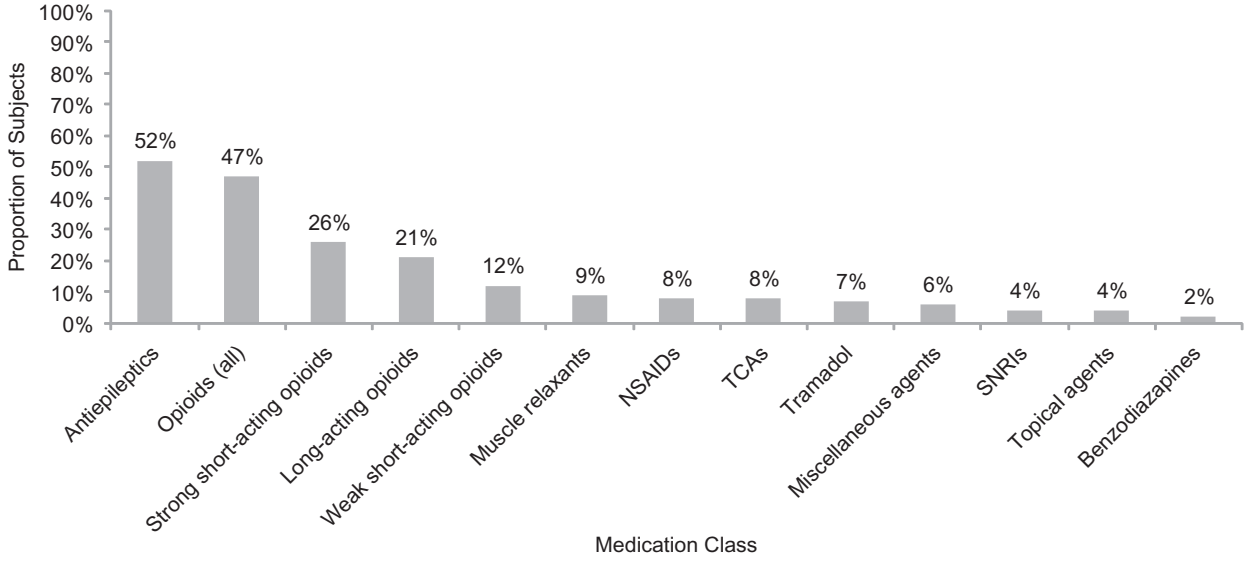

Figure 6. Pain-related medications prescribed for small fiber neuropathy ($N = 100$). Figure includes all reported classes with ≥2% of subjects prescribed one or more medications in the class. Opioids (all) include strong short-acting opioids, long-acting opioids, and weak short-acting opioids. NSAIDs, nonsteroidal antiinflammatory drugs; SNRIs, serotonin–norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants.

Discussion

This is the first study to comprehensively evaluate the burden of painful idiopathic SFN with respect to health status, function, lost productivity, and costs among US adults. We found significant associations between pain severity and burden, with worse subject-reported health status and function and greater adjusted direct and indirect costs at increasing levels of pain.

Although subjects were actively managed, results suggest subjects with idiopathic SFN, particularly those with more severe pain, experienced substantially poorer health status than the general US population, as reflected by lower scores on the SF-12 MCS and PCS and EQ-5D-3L relative to US normative values: 49.5, 49.7, and 0.87, respectively (shown in Figures 2 and 3)[27,28]. Decrements in health status among those with severe pain were also seen across all the individual SF-12 domains. Subject-reported physical and mental health status in this study was comparable to subjects with painful diabetic peripheral neuropathy (pDPN)[14]. In both the idiopathic SFN sample in the current study and the pDPN sample described by Gore *et al.*, physical functioning and bodily pain were among the SF-12 domains most negatively affected[14].

Sleep outcomes were also significantly worse among subjects with greater pain severity. Compared with US normative data of 25.8 on the MOS-SS Sleep Problems Index[13,19], idiopathic SFN subjects had substantially higher (i.e., worse) scores (shown in Figure 4). Similar findings have been reported for pDPN subjects; Gore *et al.*[14] reported that subjects with pDPN have worse sleep outcomes compared with the general US population.

Indirect costs due to lost productivity associated with idiopathic SFN accounted for the majority of total costs across pain severity groups, although the contribution of indirect costs to the total cost per subject was most pronounced among those with moderate and severe pain. Notably, indirect costs were driven largely by the impact of idiopathic SFN on employment status, and more specifically by disability due to idiopathic SFN, rather than by absenteeism and presenteeism among those employed. Subjects also showed significant increase in overall activity impairment and pain interference with function with increasing pain severity, establishing a clear relationship between pain and activities of daily living and function in this patient population. Overall, idiopathic SFN subjects in our sample reported that pain substantially interfered with normal work and they appeared to experience similar levels of absenteeism and presenteeism compared to data previously reported for pDPN subjects[13,14].

Prescription medications and other HRU related to idiopathic SFN resulted in substantial total direct costs per subject attributable to this condition. This study's findings suggest that the direct costs of idiopathic SFN may be higher than those of other peripheral neuropathy conditions. While not a direct comparison, a recent claims analysis found that the mean all-cause annual direct costs for Medicare subjects with various types of peripheral neuropathic pain, other than diabetic peripheral neuropathy, were approximately $9800 once patients had the diagnosis for 6 months[29]. Our study estimates total annual direct costs to be close to this number, although our study

Table 5. Annual per-patient direct, indirect, and total costs, overall and by average pain severity*.

Cost (US$)	Overall ($N = 100$)	Mild ($n = 23$)	Moderate ($n = 43$)	Severe ($n = 33$)	p Value†
Direct Costs					
Total Direct Medical Costs to Payer‡					0.0280
Mean (SD)	6123 (12,649.3)	2306 (3016.2)	6079 (9149.3)	9022 (18,937.5)	
Median (IQR)	2511 (860, 5353)	1180 (419, 2860)	2871 (1601, 6676)	2585 (1005, 7412)	
Total Direct Costs to Subject§					0.1593
Mean (SD)	1932 (2720.6)	1069 (1164.7)	2006 (2081.2)	2459 (3928.9)	
Median (IQR)	1073 (312, 2574)	520 (130, 1651)	1170 (455, 3185)	1300 (286, 2431)	
Total Direct Costs‖					0.0100
Mean (SD)	8055 (13,180.3)	3375 (3541.2)	8085 (10,231.5)	11,481 (19,031.1)	
Median (IQR)	3725 (2047, 7641)	2487 (661, 4738)	4138 (2781, 7829)	5181 (2187, 17,733)	
Indirect Costs					
Indirect Costs using the WPAI:SHP**					0.1524
Mean (SD)	2531 (8441.5)	3331 (10,046.4)	3640 (10,060.0)	606 (3478.7)	
Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	
Total Indirect due to Changes in Employment††					0.0724
Mean (SD)	10,927 (21,218.8)	2488 (11,932.2)	12,402 (20,962.3)	15,218 (25,327.1)	
Median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 34,115)	0 (0, 44,408)	
Total Indirect Costs‡‡					0.2348
Mean (SD)	13,459 (21,673.2)	5819 (15,032.7)	16,043 (21,397.6)	15,824 (25,190.4)	
Median (IQR)	0 (0, 29,753)	0 (0, 0)	0 (0, 44,408)	0 (0, 44,408)	
Total Costs					
Total Direct and Indirect Costs§§					0.0153
Mean (SD)	21,514 (29,300.3)	9193 (15,823.7)	24,128 (26,731.8)	27,305 (37,154.1)	
Median (IQR)	5128 (2265, 42,320)	2497 (661, 7571)	5859 (2889, 47,929)	7711 (2850, 46,212)	

*Mild, moderate and severe classification was based on the Brief Pain Inventory–Short Form average pain severity score. One subject did not respond to all required items needed to calculate an average pain severity score and thus was not included in any analysis by pain severity category.
†p Values are from the Kruskal–Wallis test; mild versus moderate versus severe.
‡Total Direct Medical Costs to Payer includes: Physician Visits for NeP, Other Healthcare Provider Visits for NeP, Prescription Medications for NeP, Outpatient Tests and Procedures for NeP, Emergency Room Visits for NeP, Hospital Outpatient Visits for NeP, and Hospitalizations for NeP.
§Total Direct Costs to Subject includes: Direct Medical Costs to Subject for NeP, Child care, Help with house and/or yard work, and Help with activities of daily living.
‖Total Direct Costs includes: Direct Medical Costs to Payer and Direct Costs to Subject.
**The Lofland *et al.* approach is used to calculate the average hourly cost of work impairment: (WPAI:SHP lost productivity score) × (national average hourly wage [$21.35; http://www.bls.gov/oes/current/oes_nat.htm#00-0000]) per Lofland *et al.*[22] This cost is then multiplied by the sum of the number of hours present and the number of hours absent due to NeP to calculate the overall work impairment cost per week (the total number of hours may not equal 40 hours a week). This cost is then multiplied by 26 weeks to get the 6 month cost.
††Total Indirect Costs due to Changes in Employment includes: Lost Productivity due to Disability, Unemployment, Early retirement, and Reduced Work Schedule.
‡‡Total Indirect Costs includes: Overall Work Impairment, Disability, Unemployment, Early retirement, and Reduced work schedule.
§§Total Direct and Indirect Costs includes: Total Direct Costs and Total Indirect Costs.
IQR, inter-quartile range; SD, standard deviation.

sample was younger than the Medicare population, and our study estimated direct costs specific to idiopathic SFN[29]. Given the marked comorbidity profile seen among idiopathic SFN subjects, future research of the incremental humanistic and economic burden associated with common comorbidities is warranted.

The second leading cause of high direct costs was out-of-pocket medical costs to subjects. Although the vast majority of subjects reported having both health insurance and prescription coverage, these results suggest that subjects incur high out-of-pocket costs for prescription medication co-pay costs and/or the purchase of over-the-counter treatments to manage their pain. Over half of the subjects in the study were supplementing their prescribed medications with over-the-counter treatments. Yet, on average, subjects reported high levels of pain and impaired health status, suggesting an ongoing unmet need in this patient population.

Limitations

Several limitations are inherent to the cross-sectional study design and are important to acknowledge. Subjects were actively seeking care (presented at a routine office visit) and were required to have a diagnosis of idiopathic SFN for at least 6 months in order to capture HRU. As such, findings presented may not be generalizable to other individuals with idiopathic SFN who are not seeking treatment, who do not regularly visit their physician. Finally, individuals with SFN of known cause were not included in this population, and thus the findings of this study may not be generalizable to all SFN conditions.

Study sites were made aware of the study sponsor prior to contracting. Though unlikely, the potential for selection bias among the study sites also should be acknowledged. This cross-sectional study required a 6 month retrospective review of subjects' medical records, which

Table 6. Model coefficients for adjusted annual costs.

Regression Models	*b*	SE	*t*	*p* Value
Total Direct Costs				
Overall Model				
Intercept	1414.64	1556.13	0.83	0.3658
Headache/Migraine	5212.35	2587.70	4.06	0.0470
Restless Leg Syndrome	4824.82	2438.29	3.92	0.0509
Anxiety	7527.45	2461.99	9.35	0.0029
Other Comorbidities	34,300.00	6379.98	28.9	<0.0001
Pain Severity Model				
Intercept	−1316.07	3383.52	0.15	0.6983
Pain Severity*	1404.49	1578.99	0.79	0.3762
Headache/Migraine	5960.47	2648.80	5.06	0.0270
Fibromyalgia	−6050.64	3917.27	2.39	0.1261
Restless Leg Syndrome	5411.16	2468.91	4.80	0.0311
Anxiety	7684.53	2556.43	9.04	0.0035
Other Comorbidities	33,453.00	6370.15	27.58	<0.0001
Total Indirect Costs				
Overall Model				
Intercept	27,016.00	9160.44	8.70	0.0041
Age	−462.26	134.03	11.89	0.0009
Employment Status	3028.07	2000.58	2.29	0.1338
Worker's Compensation	39,009.00	8614.56	20.5	<0.0001
Headache/Migraine	20,925.00	4023.79	27.04	<0.0001
Raynaud's Syndrome	24,101.00	11,940.00	4.07	0.0466
Other Comorbidities	15,969.00	9832.09	2.64	0.1079
Pain Severity Model				
Intercept	24,570.00	10,311.00	5.68	0.0194
Pain Severity*	2886.36	2367.26	1.49	0.2260
Age	−386.22	127.81	9.13	0.0033
Worker's Compensation	37,561.00	8569.97	19.21	<0.0001
Headache/Migraine	18,862.00	3994.98	22.29	<0.0001
Raynaud's Syndrome	24,141.00	12,041.00	4.02	0.0481
Other Comorbidities	14,716.00	9888.07	2.21	0.1403

*In the pain severity models, pain severity was forced into the model in order to obtain the LS mean estimate by pain severity level.
SE, standard error.

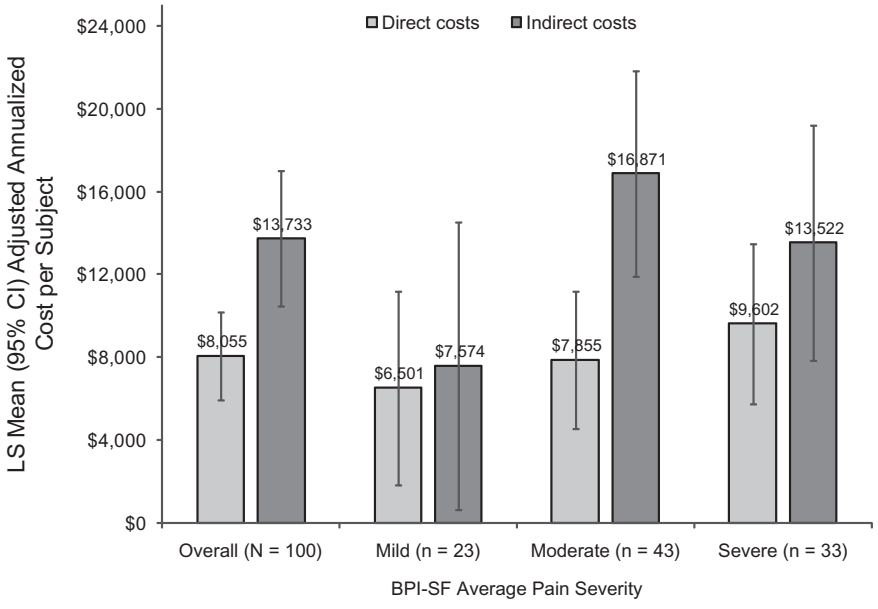

Figure 7. Mean adjusted annualized direct and indirect costs stratified by Brief Pain Inventory–Short Form (BPI-SF) average pain severity score (mild = 0–3; moderate = 4–6; and severe = 7–10). One subject did not respond to all required items needed to calculate an average pain severity score and thus was not included in any analysis by pain severity. $p < 0.0001$ across pain severity groups for both direct and indirect costs. Values are least squares mean estimates from multiple linear regression adjusted for confounding demographic and clinical variables. Specifically, covariates for direct costs: pain severity (mild/moderate/severe only) and comorbidities (headache/migraine, fibromyalgia [mild/moderate/severe only], restless leg syndrome, anxiety, other); and for indirect costs: age, pain severity (mild/moderate/severe only), workers' compensation, employment status (overall only), and comorbidities (headache/migraine, Raynaud's syndrome, other).

likely led to underreporting of HRU. The subject's medical record may not include all visits to other physicians, HCPs, or facilities, including idiopathic SFN-related tests and procedures, and medications prescribed outside of the study site.

Costs were assigned to HRU using standard algorithms, which may have over- or under-estimated costs. Finally, since lost productivity and out-of-pocket costs were based on subject recall, recall bias may have resulted in cost over- or under-estimation.

Conclusion

Despite receiving active management, the majority of subjects with painful idiopathic SFN in this study reported moderate or severe pain, on average, and suboptimal levels of overall health status, function, and well-being. Outcomes worsened among subjects with higher pain severity. Further, the economic burden, particularly indirect costs, of painful idiopathic SFN was substantial. These findings indicate that idiopathic SFN subjects with pain experience comparable burden to other more commonly studied neuropathic pain conditions and highlight the unmet need for more effective management of idiopathic SFN.

Transparency

Declaration of funding
This study was funded by Pfizer Inc.

Declaration of financial/other relationships
A.S. and B.P. have disclosed they are paid employees of Pfizer Inc. C.S., R.M., and S.D. have disclosed that they are employees of Covance Market Access Services Inc., a company that received funding from Pfizer for its role in conducting the study and developing the manuscript. S.N. and A.A. have disclosed that they were paid investigators for the study but were not financially compensated for their publication-related activities. B.R.S., M.T., and E.N. have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article.

JME peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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