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Healthcare Resource Utilization and Costs of Spinal Cord Injury with Neuropathic Pain in a Medicare Population

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Abstract

Objective: Evaluation of healthcare resource utilization (HRU) and costs in patients with neuropathic pain (NeP) secondary to spinal cord injury (SCI) in a Medicare population.

Methods: Using data from the MarketScan Medicare Database between January 1, 2006 and June 30, 2011, patients with NeP following SCI (SCI-NeP cohort) were identified based on an ICD-9-CM diagnostic code indicative of SCI, and NeP (index event) within 12 months based on ICD-9-CM code 338.0x (central neuropathic pain) or a claim for an NeP-related antiepileptic or NeP-related antidepressant drug, and propensity score-matched to SCI patients without NeP (SCI-only). Pre-index demographic and clinical characteristics were compared between the cohorts. HRU and expenditures were compared for 12 months post-index. Generalized linear models and ordinary least squares models evaluated the association between characteristics and outcomes.

Results: The matched cohorts included 1,418 patients (approximately 54% male, mean age 77 years). During the 12 month follow-up period, SCI-NeP patients showed significantly greater use of evaluated medications (P<0.01), and significantly higher HRU (P<0.05), including 20% and 18% increased odds of hospitalization and emergency department visits, respectively. Mean (SD) total all-cause healthcare expenditures for this period adjusted for covariates showed an annual incremental economic burden of $6,808 (95% confidence interval $4,143, $9,764) per patient with NeP.

Conclusions: Medicare patients with NeP secondary to SCI have significantly higher HRU and costs relative to SCI patients without NeP. Medicare patients represent a population with special needs regarding therapeutic choices that may benefit from an integrated approach to NeP management.

Keywords: Spinal cord injuries; Neuropathic pain; Burden of illness; Medicare

Introduction

Spinal cord injury (SCI), defined as damage or trauma to the spinal cord resulting in loss or impairment of normal motor, sensory, or autonomic function, is one of the most costly chronic conditions. Medical costs for SCI have been estimated at $340,787-$1,044,197 the first year and $41,393-$181,328 in subsequent years, depending on level of injury [1]. In addition to the high medical costs, SCI also substantially reduces patient functioning and quality of life [2-4].

Chronic pain is a common complication of SCI. In particular, neuropathic pain (NeP), which results from a lesion or disease of the somatosensory nervous system related to the injury, develops in approximately 50% of SCI patients[5,6]. The presence of NeP further compromises function and increases disability [7]. Reviews and guidelines for the treatment of NeP following SCI have been published [5,8,9], and recommended pharmacotherapy includes antidepressants, antiepileptic drugs, opioids, and intrathecal medications [1,9-11]. However, NeP is often intractable and remains one of the most challenging aspects of patient management; since complete pain reduction is seldom achieved, the main goal of treatment is reduction of pain to an acceptable level. Currently, only pregabalin, an antiepileptic drug, has received FDA approval in the US for treatment of NeP associated with SCI [12].

SCI generally occurs in a population approaching middle age, with an average age at injury of 42.6 years [1], although recent studies indicate a trend toward a higher average age of newly injured persons and all persons who are currently alive with SCI [13,14]. This age increase may be due, at least in part, from the greater occurrence of new onset SCI observed in older patients, mainly a result of falls [15] and the reported increase in survival among SCI patients [13]; life expectancy among individuals with SCI, although below that of the general population, is substantial for persons surviving at least 1 year post-injury [1]. One recent population-based study found SCI incidence among adults age 65 and older was higher than previous reports, with cumulative incidence in older adults at 79.4 per million in 2007 going to 87.7 by the end of 2009, attributable mainly to falls (40.5%), and that the older adults also experienced worse outcomes than younger adults [16]. Consequently, specific challenges related to the management of older individuals with SCI are being increasingly recognized [17] including efficacy and safety issues related to NeP treatment in older individuals [18].

Despite the high costs of SCI and the additional burden conveyed by the presence of NeP, few published studies have characterized the burden of SCI-associated NeP, especially in an older population. A recent cross-sectional observational study of patients with SCI-NeP stratified by self-reported pain severity reported substantial economic and patient burdens that were significantly higher with increasing

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pain severity [19]. While indirect costs were the primary cost driver, overall direct medical costs resulting from high healthcare resource utilization were $8,636, with costs of $11,666 reported among patients having severe pain. However, that study did not evaluate the specific contribution of NeP to the overall costs associated with SCI management. Therefore, the objective of this study is to characterize the healthcare resource utilization (HRU) and costs related to the presence of NeP associated with SCI in a Medicare population.

Methods

Data source

Administrative medical and pharmacy claims derived from the Truven Health Analytics (formerly Thomson Reuters) MarketScan® Medicare Database were used as the data source in this retrospective longitudinal cohort study to evaluate HRU and direct medical costs among SCI patients with NeP. This database includes complete longitudinal records of inpatient services, outpatient services, long-term care, and prescription drug claims covered under a variety of health benefit plans. All database records are de-identified and fully compliant with US patient confidentiality requirements (HIPAA).

Subject selection

Inpatient or outpatient medical claims between January 1, 2006 and June 30, 2011 with ICD-9-CM diagnosis codes of 344.0x (quadriplegia and quadriparesis), 344.1x (paraplegia), 344.6x (cauda equina syndrome), 806.xx (fracture of vertebral column with SCI), or 952.xx (SCI without evidence of spinal bone injury) were used to initially identify of patients with SCI. These patients were required to be ≥ 18 years of age at the date of the SCI claim and to have a minimum of 6 months of continuous medical and pharmacy benefit eligibility prior to the first SCI diagnosis claim and no prior claims for SCI. The SCI-NeP cohort was identified from this population based on either of the following criteria within 12 months following the first SCI claim: a diagnosis of central neuropathic pain (ICD-9-CM code 338.0x), a claim for any NeP-related antiepileptic drug (AED), or a claim for any NeP-related antidepressant drug. The choice of NeP-related AEDs and antidepressants, shown in Table 1, was based on literature review and practitioner recommendations [5,9-11,20,21].

The first medical or pharmacy claim, as outlined above, following the SCI diagnosis was defined as the index date. For inclusion in the analysis, patients were required to have continuous enrollment with both medical and pharmacy benefits for 6 months pre- and 12 months post-index. A patient-level analytic data file was maintained that included medical and pharmacy claims for this period.

Since post-SCI use of these NeP-related medications served as a proxy for identifying patients with SCI-NeP, patients in the this cohort could not have any NeP-related claims during the 6 months prior to the first SCI diagnosis including for NeP-related AEDs or antidepressants. This method for identifying NeP was adopted due to low use of the central NeP diagnostic code in medical claims. Patients were also excluded if claims had diagnostic codes for any of following neurological conditions commonly treated with drugs that may also be used for SCI-NeP: epilepsy (ICD-9-CM codes 345.xx, 780.39); amyotrophic lateral sclerosis (ICD-9-CM code 335.20); multiple sclerosis (ICD-9-CM code 340.xx); diabetic peripheral neuropathy (ICD-9-CM codes 250.6x, 357.2x); or post-herpetic neuralgia (ICD-9-CM code 053.1x). Additionally, medical or pharmacy claims for medications used in multiple sclerosis or amyotrophic lateral sclerosis (intramuscular or subcutaneous interferon beta-1a, interferon beta-1b, glatiramer acetate, fingolimod, or riluzole) at any time during the study period, was also reason for exclusion. Patients may have had a diagnosis for depression and/or non-NeP-related antidepressant claims, and were not excluded for either of those attributes.

Patients in the SCI-NeP cohort were propensity score matched with a control group that consisted of SCI patients without subsequent evidence of NeP (SCI-only cohort). Patients in the SCI-only cohort were subject to the same eligibility criteria as the SCI-NeP cohort except without the NeP diagnosis and use of NeP-related AEDs or antidepressants during the study period. For the SCI-only patients, an index date was assigned using their first SCI diagnosis plus the number of days between a randomly selected SCI-NeP patient's SCI diagnosis and index NeP diagnosis, taking into account the end of the patient's available data.

Propensity score matching was used to insure sufficient similarity between the two groups (SCI-NeP and SCI-only) with respect to observed covariates [22], thereby enhancing the potential to ascribe differences in outcomes between the cohorts to the distinguishing factor, i.e., the onset of neuropathic pain. Thus, the propensity score matching adjusted for the observed covariates in the model using a logistic regression model to predict the probability of developing NeP based on the following pre-index characteristics; age, gender, health plan type, index year, Deyo-Charlson Comorbidity Index (DCI) score [23], number of 3-digit ICD-9-CM codes, number of unique drugs, specific type of SCI diagnosis, presence of specific comorbid conditions, use of specific concomitant medications, and pre-index all-cause healthcare expenditures. One-to-one nearest neighbor matching was used to match from the SCI pool without replacement [24].

Outcome measures

Baseline demographics and clinical characteristics were measured descriptively pre-index. Clinical characteristics, healthcare resource utilization and costs were analyzed descriptively during the 12-month follow-up period (post-index). Utilization and costs were modeled with multivariable analyses adjusting for potential confounders or risk factors.

Clinical characteristics included the type of SCI, three indices indicative of comorbidity burden (DCI, number of unique three-digit ICD-9-CM codes, and number of unique outpatient medications), and prevalence of prespecified comorbidities. Since there is no ICD-9-CM code specific for traumatic SCI, and in the absence of medical records that could be used for its identification, a variable was created ("trauma-related SCI") to proxy traumatic SCI that used a diagnosis code for either vertebral column fracture (806.xx) or for late effects of SCI (907.2x) at any time on or after the initial SCI diagnosis [25].

Categories included in HRU and expenditures were inpatient admissions, emergency department (ED) visits, physician office visits, SCI- and pain-related procedures, physical therapy, and outpatient prescriptions during the post-index period. Evaluation of expenditures

Medication Class	Generic Names
Antiepileptics	Carbamazepine; gabapentin; lamotrigine; oxcarbazepine; phenytoin; pregabalin; topiramate; valproate sodium; valproic acid
Antidepressants	Serotonin-norepineprine reuptake inhibitors (SNRIs): duloxetine, venlafaxine, milnacipran, desvenlafaxine Tricyclics (TCAs): amitriptyline, desipramine, doxepin, imipramine, nortriptyline

Table 1: Antiepileptics and antidepressants used for identifying neuropathic pain in the spinal cord injury population.

used the gross covered payments for medical and pharmacy claims (ie, the amount eligible for payment to the provider before deductibles, copayments, and coordination of benefits). All expenditures were adjusted to 2012 constant dollars using the Medical Care component of the Bureau of Labor Statistics Consumer Price Index [26].

Analysis

Univariate and bivariate descriptive analyses were performed; categorical variables wee compared between cohorts using chi-square or Fisher's exact test, and for quantitative variables the two-sample Student's t-test was used. Data are presented as mean (SD) unless otherwise stated, and for all tests, an alpha of 0.05 was specified a priori as the threshold for statistical significance.

The overall economic impact of HRU and its association with patient demographic and clinical characteristics were evaluated by application of generalized linear models (GLM) to further adjust the propensity score-matched results for effects of potential confounding or risk factors [27]. A GLM using a binomial distribution and its canonical link was applied to binary outcomes such as hospital admissions and ED visits. For count outcomes (e.g. number of hospital admissions or ED visits per patient), models used a Poisson or a negative binomial distribution with the corresponding canonical links and "zero-inflated" distributions for instances where the count data expressed an excessive number of zeroes. All-cause expenditures were modeled using an ordinary least squares (OLS) model fit to the log transformed positive expenditures with retransformation for predicting expenditures; standard errors and confidence intervals were estimated using bootstrapping [28]. All analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC).

Results

Demographic and clinical characteristics

Table 2 presents the incremental attrition, and shows that the final matched SCI-NeP cohorts each consisted of 1,418 patients. Among the index events (Table 3), a central NeP diagnosis was the identifying event for only 5 patients (0.4%). In contrast, initiation of a NeP-related AED accounted for 72.1% of the index events, with gabapentin (50.6%) and pregabalin (18.1%). the primary AEDs. Initiation of SNRIs and TCAs as index events were similar, 15.5% and 14.5%, respectively; duloxetine was the most frequent SNRI and amitriptyline the most frequent TCA.

Slightly more than half of the cohorts were female (55.6% SCI-NeP, 53.2% SCI-only), and the mean age of both cohorts was 77 years, with 3.5% and 2.1% of the SCI-NeP and SCI-only cohorts, respectively < 65 years of age (Table 4). There were no differences in health plans or geographic distribution, but the North Central region had the highest representation, and the majority of the population (85%) lived in an urban area (Table 4).

The most common type of SCI was vertebral column fracture, in about one-third of patients, followed by paraplegia which was significantly higher in the SCI-only cohort (23.9% vs. 20.7%; P = 0.038) (Table 5); the other types of SCI were similar between the cohorts. Just over one-third of patients had diagnosis codes indicative of trauma-related SCI. The three comorbidity indices as well as the prevalence of individual comorbid conditions were all similar between the cohorts (Table 5).

Overall, short-acting opioids were the most commonly used pain-related medication during the pre-index period, with similar use (63%) in the two cohorts (Table 5). With two exceptions, all other pain-related medications were also used to a similar extent between the cohorts. The two exceptions were long-acting opioids, which had significantly higher use in the SCI-NeP cohort (12.9% vs. 10.2%; P = 0.026), and intrathecal medications, which were used to a greater extent among SCI-only patients (4.7% vs. 3.0%; P = 0.015). SCI- and pain-related procedures for spine stabilization and any pain intervention procedure were both significantly higher among SCI-NeP patients (Table 5).

Post-index healthcare resource utilization

Relative to SCI-only, patients in the SCI-NeP cohort had a significantly higher burden of prescription medication use during the 12-month follow-up period for all medication classes ($P < 0.01$) except intrathecal medications, cannabinoids, and non-NeP antiepileptics (Figure 1). As in the pre-index period, short-acting opioids were the most widely prescribed medication, 71.7% in SCI-NeP and 52.0% in SCI-only ($P < 0.0001$).

As shown in Table 6, overall HRU was higher among patients with SCI-NeP; significantly greater proportions of patients in the SCI-NeP cohort used each of the HRU categories ($P < 0.05$). Resource intensity, measured as the number of visits per patient with a visit, was significantly higher ($P < 0.05$) in the SCI-NeP cohort for physician visits, physical therapy, CT and MRI radiology procedures, and SCI- and NeP-related outpatient procedures, but not for inpatient admissions or ED visits.

A significantly higher likelihood of inpatient admissions and ED visits was observed for SCI-NeP relative to SCI-only, with estimated odds ratios (OR) of 1.20 (95% confidence interval [CI] 1.02 to 1.41; $P = 0.0242$) and 1.18 (95% CI 1.01 to 1.38; $P = 0.0087$), respectively. Other clinical factors associated with higher inpatient admission included

Attrition Criterion	N	%
Cases		
At least one spinal cord injury (SCI) diagnosis during 1/1/2006 - 06/30/2011	42,450	100.0
Continuous medical and pharmacy benefit enrollment 6 months prior to first SCI diagnosis	27,374	64.5
No SCI diagnosis during the 6 months before the first SCI diagnosis	26,494	62.4
No neuropathic pain (NeP) diagnosis or NeP-related drugs during the 6 months before the first SCI diagnosis	20,408	48.1
NeP diagnosis or NeP-related drug within 12 months following first SCI diagnosis (NeP index event)*	2,417	5.7
Continuous medical and pharmacy benefit enrollment 6 months prior to NeP index event	2,359	5.6
Continuous medical and pharmacy benefit enrollment 12 months following NeP index event	1,760	4.1
No evidence of seizure disorders, multiple sclerosis, amyotrophic lateral sclerosis, diabetic peripheral neuropathy, post-herpetic neuralgia or related medications during pre- or post-index periods	1,418	3.3
Age ≥ 18 years of age at date of SCI index event	1,418	3.3
Patients included in final SCI-NeP cohort after propensity score matching process*	1,418	3.3
*Matched patients had no evidence of NeP diagnosis or NeP-related drugs between July 1, 2005 and June 30, 2012, but otherwise the same selection criteria as the matched SCI-NeP patients		

Table 2: Sample size attrition.

Index event	Number (%) of patients (n = 1,418)
Central neuropathic pain diagnosis	5 (0.4)
Antiepileptic drugs	1,022 (72.1)
Carbamazepine	6 (0.4)
Gabapentin	717 (50.6)
Lamotrigine	7 (0.5)
Oxcarbazepine	3 (0.2)
Phenytoin	12 (0.8)
Pregabalin	257 (18.1)
Topiramate	12 (0.8)
Valproic Acid	8 (06)
Tricyclic antidepressants	171 (12.1)
Amitriptyline	88 (6.2)
Amitriptyline/perphenazine	1 (0.1)
Desipramine	1 (0.1)
Doxepin	22 (1.6)
Imipramine	34 (2.4)
Nortriptyline	25 (1.8)
Serotonin-norepinephrine reuptake inhibitors	220 (15.5)
Desvenlafaxine	9 (0.6)
Duloxetine	153 (10.8)
Venlafaxine	58 (4.1)

Table 3: Index events for defining neuropathic pain diagnosis.

Variable	SCI-NeP (n = 1,418)	SCI-only (n = 1,418)	P
Age, years, mean (SD)	77.5 (7.9)	77.4 (7.8)	0.650
Age group, n (%)			0.076
< 65 y	49 (3.5)	30 (2.1)	
65-74 y	516 (36.4)	506 (35.7)	
≥ 75 y	853 (60.2)	882 (62.2)	
Sex, n (%)			0.200
Male	630 (44.4)	664 (46.8)	
Female	788 (55.6)	754 (53.2)	
Geographic region, n (%)			0.590
Northeast	181 (12.8)	202 (14.2)	
North Central	558 (39.4)	564 (39.8)	
South	396 (27.9)	367 (25.9)	
West	280 (19.7)	280 (19.7)	
Unknown	3 (0.2)	5 (0.4)	
Population density, n (%)			0.680
Urban	1,205 (85.0)	1,213 (85.5)	
Rural	210 (14.8)	200 (14.1)	
Unknown	3 (0.2)	5 (0.4)	
Insurance plan, n (%)			0.150
Comprehensive	715 (50.4)	691 (48.7)	
Exclusive provider organization	1 (0.1)	0	
Health maintenance organization	140 (9.9)	175 (12.3)	
Point-of-service	40 (2.8)	36 (2.5)	
Preferred provider organization	505 (35.6)	490 (34.6)	
Consumer-driven health plan	1 (0.1)	5 (0.4)	
Other	16 (1.1)	21 (1.5)	

Table 4: Demographic characteristics of the study populations at baseline.

an SCI diagnosis of quadriplegia/quadriparesis (OR 1.45, 95% CI 1.11, 1.89; $P = 0.0059$) or paraplegia (OR 1.44, 95% CI 1.07, 1.92; $P = 0.0148$); SCI without spinal bone injury (OR 1.07, 95% CI 1.02, 1.12; $P = 0.0035$); a trauma-related SCI diagnosis (OR 1.82, 95% CI 1.15, 2.87; $P = 0.0101$); and the number of pre-index ICD-9-CM diagnoses (OR 1.04, 95% CI 1.02, 1.05; $P < 0.0001$). Similarly, a significantly increased

Variable	SCI-NeP (n = 1,418)	SCI-only (n = 1,418)	P
Type of SCI, n (%)*			
Quadriplegia/quadriparesis	176 (12.4)	199 (14.0)	0.200
Paraplegia	293 (20.7)	339 (23.9)	0.038
Cauda equina syndrome	271 (19.1)	295 (20.8)	0.260
Vertebral column fracture	477 (33.6)	504 (35.5)	0.290
SCI without spinal bone injury	249 (17.6)	279 (19.7)	0.150
Trauma-related SCI†	535 (37.7)	524 (37.0)	0.670
Comorbidity indices, mean (SD)			
Deyo-Charlson Comorbidity Index	2.3 (2.2)	2.4 (2.3)	0.250
ICD-9-CM diagnoses‡	17.7 (10.0)	17.7 (9.7)	0.930
Outpatient medications§	11.6 (7.0)	11.8 (7.2)	0.560
Comorbid conditions, n (%)			
Diabetes	299 (21.1)	330 (23.3)	0.16
Neurological pain conditions	500 (35.3)	495 (34.9)	0.84
Musculoskeletal pain conditions	818 (57.7)	805 (56.8)	0.62
Contractures	13 (0.9)	18 (1.3)	0.37
Osteoporosis	183 (12.9)	189 (13.3)	0.74
Arthritis (osteoarthritis and rheumatoid arthritis)	362 (25.5)	362 (25.5)	1.00
Depression	96 (6.8)	84 (5.9)	0.36
Anxiety	81 (5.7)	69 (4.9)	0.31
Insomnia/sleep disorders	115 (8.1)	110 (7.8)	0.73
Substance abuse	39 (2.8)	40 (2.8)	0.91
Migraine or other headache	10 (0.7)	7 (0.5)	0.47
Gastrointestinal conditions‖	419 (29.5)	410 (28.9)	0.71
Cardiovascular conditions			
Deep-vein thrombosis	99 (7.0)	102 (7.2)	0.83
Atherosclerosis	364 (25.7)	386 (27.2)	0.35
Hypotension	77 (5.4)	59 (4.1)	0.11
Hypertension	814 (57.4)	811 (57.2)	0.91
Respiratory conditions¶	249 (17.6)	261 (18.4)	0.56
Renal/Bladder Conditions**	349 (24.6)	351 (24.8)	0.93
Cancer	154 (10.9)	158 (11.1)	0.81
Medications, n (%)			
Opioid analgesics - short acting	897 (63.3)	896 (63.2)	0.97
Opioid analgesics - long acting	183 (12.9)	145 (10.2)	0.026
Intrathecal medications	42 (3.0)	67 (4.7)	0.015
Muscle Relaxants	272 (19.2)	266 (18.8)	0.770
Steroids (systemic)	291 (20.5)	316 (22.3)	0.250
Non-NeP antidepressants	285 (20.1)	282 (19.9)	0.890
Anxiolytics	376 (26.5)	340 (24.0)	0.120
Sedatives/hypnotics	255 (18.0)	234 (16.5)	0.300
Topicals (selected)	101 (7.1)	87 (6.1)	0.290
Cannabinoids	0	2 (0.1)	0.500
Non-NeP antiepileptics	76 (5.4)	58 (4.1)	0.110
NSAIDs	374 (26.4)	360 (25.4)	0.550
SCI- and pain-related procedures, n (%)			
Spinal cord surgery	189 (13.3)	190 (13.4)	0.960
Decompressing the spine	283 (20.0)	245 (17.3)	0.067
Stabilization of the spine	218 (15.4)	178 (12.6)	0.030
Any pain intervention procedure	492 (34.7)	421 (29.7)	0.004

LAOs, long-acting opioids; NeP, neuropathic pain; NSAIDs, nonsteroidal anti-inflammatory drugs; SAOs, short acting opioids.
*Total proportion exceeds 100% since there is some overlap among the SCI types.
†Traumatic-SCI was defined as an ICD-9 diagnosis code of 806.xx or 907.2x at any time on or after the initial SCI diagnosis.
‡Count of unique 3-digit ICD-9-CM codes on medical claims.
§Count of unique outpatient medications.
‖Gastrointestintal conditions include irritable bowel syndrome, abdominal pain, gastroesophageal reflux disease (GERD), ulcers, neurogenic bowel, and constipation.

¶Respiratory conditions include respiratory failure, pulmonary embolism, pneumonia, and chronic obstructive pulmonary disease (COPD)
**Renal/bladder conditions include nephritis, nephrotic syndrome, renal failure, neurogenic bladder, urinary tract infection, and urinary calculi.

Table 5: Clinical characteristics of the study populations at baseline.

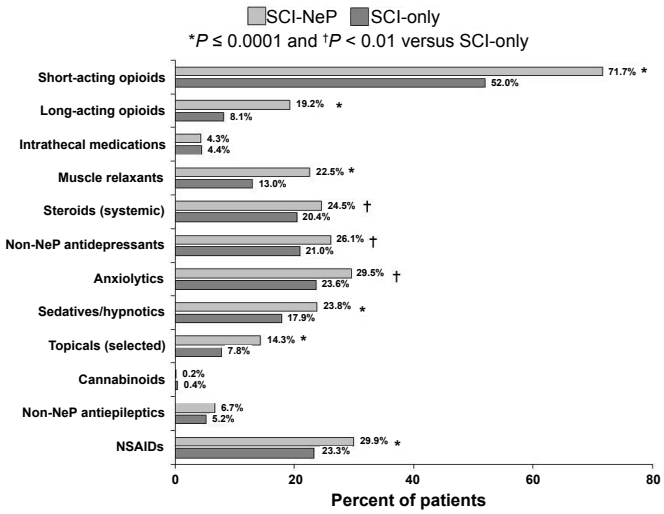

Figure 1: Medication utilization during the 12-month post-index follow-up period.

likelihood of ED visits was associated with quadriplegia/quadriparesis (OR 1.39, 95% CI 1.07, 1.81; $P = 0.0138$) and paraplegia (OR 1.42, 95% CI 1.07, 1.90; $P = 0.0165$); SCI without spinal bone injury (OR 1.05, 95% CI 1.01, 1.10; $P = 0.0273$); a trauma-related SCI diagnosis (OR 1.94, 95% CI 1.22, 3.08; $P = 0.0051$), the number of pre-index ICD-9-CM diagnoses (OR 1.03, 95% CI 1.02, 1.05; $P < 0.0001$); the presence of non-NeP muscle pain (OR 1.24, 95% CI 1.03, 1.50; $P = 0.0205$); and steroid use (OR 1.27, 95% CI 1.03, 1.56; $P = .0223$). Use of non-NeP antidepressants was associated with a reduced risk of ED visits (OR 0.77, 95% CI 0.629, 0.933; $P = 0.0082$). A GLM model showed a difference between SCI-NeP and SCI-only of 0.081 (95% CI 0.009, 0.152; $P = 0.977$) for the number of ED visits. Significant factors increasing ED visits included SCI without spinal bone injury, DCI score, and number of pre-index diagnoses; the only factor associated with decreased ED visits was spinal cord surgery.

Post-index healthcare expenditures

In the propensity score-matched cohorts, total all-cause mean (standard deviation) healthcare expenditures for the 12-month follow-up period (Table 7) were $35,128 ($54,059) for SCI-NeP and $32,323 ($50,802) for SCI-only ($P = 0.16$). The highest component cost in the post-index period was outpatient medical expenditures, which accounted for 51.6% of the total in SCI-NeP and 53.6% in, SCI-only and was not significantly different between the cohorts. While neither expenditures for inpatient admissions nor those for ED visits were different between the cohorts, all other component costs were significantly higher among SCI-NeP patients, including outpatient prescription expenditures, which were $5,807 ($8,780) in the SCI-NeP cohort compared with $4,669 ($7,908) in SCI-only ($P = 0.0004$).

Further adjustment using an OLS model estimated mean expenditures of $35,300 for SCI-NeP and $28,492 for SCI-only, with an incremental difference of $6,808 (95% CI $4,143, $9,764; $P < 0.0001$) for SCI-NeP patients. Factors significantly associated with higher costs included the presence of NeP, type of SCI (quadriplegia/quadriparesis, paraplegia, cauda equine syndrome, and SCI without spinal bone injury), trauma-related SCI, and the presence of neurological pain conditions or depression ($P < 0.001$). Membership in an HMO health plan and a history of spine decompression procedures were associated with lower all-cause expenditures ($P < 0.05$).

Discussion

Although a substantial economic burden among patients with SCI-associated NeP has previously been reported [19], the current study is the first to evaluate the specific contribution of NeP to HRU and expenditures in SCI management in a Medicare population. This study shows that during the 12-month follow-up period after onset of NeP, there was significantly greater HRU across a variety of categories, and higher medical expenditures relative to patients with SCI who did not develop NeP. These results were observed despite clinical characteristics that were generally similar at baseline including comparable comorbidity burdens and medication utilization. The use of matching resulted in SCI-NeP and SCI-only cohorts of sufficiently

Resource category	SCI-NeP (n = 1,418)	SCI-only (n = 1,418)	P
Inpatient utilization			
Patients with any admission, n (%)	571 (40.3)	518 (36.5)	0.041
Admissions per patient, mean (SD)	0.6 (1.0)	0.5 (0.9)	0.074
Admissions per patient admitted, mean (SD)	1.5 (1.0)	1.5 (0.8)	0.77
Length of stay per admission, days, mean (SD)	6.0 (8.2)	7.2 (13.1)	0.067
SCI and NeP-related inpatient procedures, n (%)	92 (6.5)	54 (3.8)	0.0012
Emergency department visits			
Patients with any visit, n (%)	674 (47.5)	619 (43.7)	0.038
Number of visits per patient, mean (SD)	1.1 (2.1)	1.0 (1.9)	0.28
Number of visits per patient with visit, mean (SD)	2.3 (2.5)	2.3 (2.2)	0.87
Physician office visits			
Patients with any visit, n (%)	1,356 (95.6)	1,320 (93.1)	0.0034
Number of visits per patient, mean (SD)	14.0 (10.6)	11.2 (9.3)	< 0.0001
Number of visits per patient with visits, mean (SD)	14.7 (10.4)	12.1 (9.1)	< 0.0001
Physical therapy			
Patients with any visit, n (%)	479 (33.8)	387 (27.3)	0.0002
Number of visits per patient, mean (SD)	11.8 (32.2)	7.6 (23.4)	<.0001
Number of visits per patient with visit, mean (SD)	35.1 (47.4)	28.0 (37.9)	0.017
CT and MRI radiology procedures			
Patients with any visit, n (%)	778 (54.9)	651 (45.9)	< 0.0001
Number of visits per patient, mean (SD)	1.9 (2.8)	1.5 (2.5)	< 0.0001
Number of visits per patient with visit, mean (SD)	3.5 (3.0)	3.3 (2.8)	0.11
SCI- and NeP-related outpatient procedures			
Patients with any visit, n (%)	855 (60.3)	693 (48.9)	< 0.0001
Number of visits per patient, mean (SD)	15.7 (35.2)	9.9 (25.1)	< 0.0001
Number of visits per patient with visit, mean (SD)	26.1 (42.2)	20.3 (32.8)	0.0030
Outpatient prescriptions			
Patients with any prescription, n (%)	1,418 (100.0)	1,342 (94.6)	< 0.0001
Claims per patient, mean (SD)	55.4 (35.8)	43.3 (34.2)	< 0.0001
Claims per patient with prescription, mean (SD)	55.4 (35.8)	45.8 (33.6)	< 0.0001

Table 6: All-cause healthcare resource utilization during the 12-month follow-up period.

Resource type	SCI-NeP (n = 1,418)		SCI-only (n = 1,418)		P
	Mean (SD)	Median	Mean (SD)	Median	
Inpatient admissions	$11,212 ($35,787)	$0	$10,322 ($33,084)	$0	0.50
Emergency department	$465 ($1,371)	$0	$412 ($1,398)	$0	0.32
Physician Office Visits	$1,326 ($1,124)	$1,089	$1,058 ($1,042)	$815	< 0.0001
Other outpatient expenditures*	$16,317 ($31,291)	$8,104	$15,862 ($28,674)	$7,001	0.69
Physical therapy	$792 ($2,548)	$0	$496 ($1,611)	$0	0.0003
CT and MRI radiology procedures	$555 ($1,270)	$68	$453 ($1,305)	$0	0.040
SCI- and NeP-related visits and procedures	$2,149 ($6,320)	$212	$1,410 ($4,930)	$0	0.0006
Total outpatient medical expenditures (not including outpatient prescriptions)	$18,109 ($31,728)	$9,718	$17,332 ($29,176)	$8,338	0.50
Outpatient prescriptions	$5,807 ($8,780)	$3,960	$4,669 ($7,908)	$2,941	0.0004
Total healthcare expenditures	$35,128 ($54,059)	$18,894	$32,323 ($50,802)	$17,220	0.16
*In addition to the categories of Physical Therapy, CT and MRI radiology procedures, and SCI- and NeP-related visits and procedures other outpatient expenditures included all other non-physician-office office visits, laboratory tests, other diagnostic radiology, other procedures (diagnostic or therapeutic), and other covered outpatient services					

Table 7: All-cause healthcare expenditures during the 12-month post-index period.

similar characteristics to enhance the likelihood that any observed differences between cohorts during follow-up may be attributable to the single major difference between the cohorts; the index event of NeP onset.

Patients with SCI-NeP had significantly higher utilization of all HRU resource categories evaluated during the follow-up period, and in particular, SCI-NeP was associated with 20% and 18% higher odds of inpatient admissions and ED visits, respectively relative to SCI-only. Furthermore, all metrics of outpatient prescriptions showed significantly greater use during follow-up among the SCI-NeP patients ($P < 0.0001$), and these patients also experienced greater use of nearly all classes of pain-related medications. While short-acting opioids were the most frequently used medication during follow-up, it should be noted that long-acting opioids were used by more than twice as many patients with SCI-NeP compared with SCI-only (19.2% vs. 8.1%). The increased use of medications by SCI-NeP patients suggests the need for a multimodal approach to treating pain after SCI [29].

For the all-cause expenditure estimates, a GLM model assuming an underlying gamma distribution with a log link function was initially considered but did not provide as good a fit as the OLS model. Although the incremental expenditures of $6,808 among SCI-NeP patients relative to SCI-only that was estimated with the OLS model cannot necessarily be directly attributed to the presence of the NeP, these excess costs were consistent with the higher HRU in this cohort. Nevertheless, the overall results suggest a substantially higher economic burden when SCI is accompanied by NeP. The total direct medical expenditures of $35,300 for SCI-NeP and $28,492 for SCI-only from the OLS model are substantially higher than the adjusted annualized costs of $8,636 previously reported for a population of patients with SCI-NeP [19]. These differences in costs may be accounted for by the older population in the current study, which is likely to use more resources resulting from greater age-related comorbidities, as well as from differences between the studies in the methodologies used for costing the resources.

The identification of clinical variables associated with increased costs suggests that there may be modifiable factors that can help optimize patient management and provides evidence of the need for a multifactorial approach for managing SCI-NeP [29]. Further studies are also warranted to more fully understand the factors that may contribute to NeP onset.

Although traumatic SCI is the most common etiology in a younger population [14], proportions of up to 60% have been reported for non-traumatic SCI [30,31]. Without a specific ICD-9-CM code to distinguish traumatic SCI, a proxy was used for trauma-related SCI to explore the possible associations with utilization and expenditure outcomes. Using this proxy in our Medicare subjects, 37.7% of SCI-NeP and 37.0% of SCI-only patients (p=0.670) were categorized with trauma-related SCI. Trauma-related SCI was a statistically significant factor associated with higher hospitalization and ED visit rates, and higher healthcare expenditures. Further studies are needed to follow up this first attempt with using such a proxy in healthcare claims-based research to validate this definition [25].

Since this study evaluated a Medicare population, patients were older (mean age 77 years) and characterized by different SCI and comorbidity profiles than a general SCI population [13,14,32]. These Medicare patients had a substantial prevalence of conditions generally associated with an older population such as diabetes, osteoarthritis and rheumatoid arthritis, and cardiovascular disorders. Of note, approximately 13% of both cohorts had osteoporosis. While neurogenic osteoporosis is a common sequela of SCI, it is also possible that SCI in at least some of these patients may have been secondary to post-menopausal osteoporosis through the loss of bone density, resulting in an increased risk of falls or spinal fractures that are a common cause of SCI in the elderly [33]. However, there was no difference in the osteoporosis prevalence between the two cohorts.

Because of the older age, Medicare patients represent a special population with regard to management of both SCI and NeP [16-18]. These older individuals, who are generally characterized by multiple comorbidities and polypharmacy, are considered more fragile with regard to pharmacologic therapies, and many drugs are contraindicated because of age-associated metabolic changes, potential drug-drug interactions, or undesirable side effects [34]. Opioids, and in particular SAOs that are often prescribed for use on an "as needed" basis were among the most frequently used pain-related medication in this study despite evidence suggesting that older patients have increased pharmacodynamic sensitivity to opioids [35], potentially amplifying their effects.

Limitations

This study has several limitations, including that the data may be subject to misclassification resulting from diagnostic coding errors. An additional limitation is the low clinical use of ICD-9-CM code 338.0x to identify central neuropathic pain in these patients, which necessitated development of a proxy, ie, prescription of NeP-related AEDs and antidepressants. It is thus possible that prescription of the proxy medications was for causes other than onset of NeP, and that in relation to antidepressants, physicians could potentially have been treating the NeP, depression without NeP, or obtaining a dual benefit for both depression and NeP. It should also be noted that depression could not be used as an exclusion criterion, since this would have introduced an additional source of bias. However, the use of these medications during the pre-index period was an exclusion criterion, as was the exclusion of patients with other conditions approved for their use, thereby increasing the likelihood of correctly identifying patients with NeP. Considering that prior studies showed that 64% of SCI patients reported pain at 6 months and 81% within 1 year, of which 60% was NeP, it is probable that these prescriptions and onset of NeP are likely related [36,37]. Nevertheless, it cannot be confidently determined whether the use of antidepressants was to treat the NeP, depression without NeP, or for obtaining a dual benefit for depression and NeP. Furthermore, excluding patients with depression would have introduced additional bias.

Another limitation is use of a proxy for traumatic-SCI, which resulted in identification of trauma-related SCI in approximately one-third of patients; identification of trauma-related SCI in studies such as these is consistently problematic [25]. The data also did not specify whether the NeP was at-level or below-level, since these may be treated differently in the clinical setting [5,20]. Neither duration nor anatomic location of the SCI was captured, both of which may help distinguish SCI-NeP from SCI-only and impact the clinical course of NeP as well as resource utilization.

It is also important to recognize that slight or modest numerical differences seen in some of the demographics and clinical characteristics, while statistically significant, may have been driven by the large sample size in each group. Nevertheless, statistical modeling provided an additional level of robustness by accounting for the effects of covariates that may have extended beyond their impact on the propensity score. Since causality cannot be determined, no inferences can be made regarding the effects of NeP on resource utilization and expenditures, and the observed relationships should be considered associative. Finally, this analysis focused on a Medicare population, and thus the results are not generalizable to other SCI populations.

Conclusions

This is the first study to comparatively evaluate the economic burden of NeP secondary to SCI in a US Medicare population. In this population, significantly higher HRU and medical expenditures were observed among SCI-NeP patients relative to SCI patients without NeP, with an estimated incremental cost in the year following NeP onset of $6,808 per SCI-NeP patient. While clinical variables contributing to higher expenditures were identified, Medicare patients represent a population that may have special needs regarding appropriate therapeutic choices. Thus, further studies are warranted to more fully account for the contribution of these factors to the differences between SCI patients with and without NeP, and to determine how they may be modifiable to help optimize patient management.

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References

1. National Spinal Cord Injury Statistical Center (2013) Spinal Cord Injury. Facts and Figures at a Glance.
2. Westgren N, Levi R (1998) Quality of life and traumatic spinal cord injury. Arch Phys Med Rehabil 79: 1433-1439.
3. Leduc BE, Lepage Y (2002) Health-related quality of life after spinal cord injury. Disabil Rehabil 24: 196-202.
4. Migliorini CE, New PW, Tonge BJ (2011) Quality of life in adults with spinal cord injury living in the community. Spinal Cord 49: 365-370.
5. Baastrup C, Finnerup NB (2008) Pharmacological management of neuropathic pain following spinal cord injury. CNS Drugs 22: 455-475.
6. Siddall P, McClelland JM, Rutkowski S, Cousins M (2003) A longitudinal study of the prevalence and characteristics of pain in the first 5 years following spinal cord injury. Pain 103: 249-257.
7. Jensen MP, Chodroff MJ, Dworkin RH (2007) The impact of neuropathic pain on health-related quality of life. Review and implications. Neurol 68: 1178-1182.
8. Attal N, Mazaltarine G, Perrouin-Verbe B, Albert T (2009) Chronic neuropathic pain management in spinal cord injury patients. What is the efficacy of pharmacological treatments with a general mode of administration? (oral, transdermal, intravenous). Ann Phys Rehabil Med 52: 124-141.
9. Teasell RW, Mehta S, Aubut JA, Foulon B, Wolfe DL, et al. (2010) A systematic review of pharmacologic treatments of pain after spinal cord injury. Arch Phys Med Rehabil 91: 816-831.
10. Dworkin RH, O'connor PW, Backonja M, Farrar JT, Finnerup NB, et al. (2007) Pharmacologic management of neuropathic pain: Evidence-based recommendations. Pain 132: 237-251.
11. Attal N, Cruccu G, Baron R, Haanpää M, Hansson P, et al. (2010) EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol 17: 1113-1123.
12. Lyrica® [pregabalin] capsules prescribing information (2012) Pfizer, Inc., New York, NY.
13. van den Berg ME, Castellote JM, Mahillo-Fernandez I, de Pedro-Cuesta J (2010) Incidence of spinal cord injury worldwide: a systematic review. Neuroepidemiol 34: 184-192.
14. DeVivo MJ (2012) Epidemiology of traumatic spinal cord injury: trends and future implications. Spinal Cord 50: 365-372.
15. Deutsch A, Almagor O, Rowles DM, Pucci D, Chen D (2011) Characteristics and outcomes of aged Medicare beneficiaries with a traumatic spinal cord injury: 2002-2005. Top Spinal Cord Inj Rehabil 16: 17-26.
16. Selvarajah S, Hammond ER, Haider AH, Abularrage CJ, Becker D, et al. (2014) The burden of acute traumatic spinal cord injury among adults in the United States: an update. J Neurotrauma 31: 228-238.
17. Groah SL, Charlifue S, Tate D, Molton IR, Forchheimer M, et al. (2012) Spinal cord injury and aging: challenges and recommendations for future research. Am J Phys Med Rehabil 91: 80-93.
18. Schmader KE, Baron R, Haanpää ML, Mayer J, O'Connor AB, et al. (2010) Treatmentconsiderations for elderly and frail patients with neuropathic pain. Mayo Clin Proc 85: S26-32.
19. Mann R, Bergstrom F, Schaefer C, Bergstrom F, Baik R, et al. (2013) Burden

of spinal cord injury-related neuropathic pain in the United States: retrospective chart review and cross-sectional survey. Spinal Cord 51: 564-570.

20. Siddall PJ (2002) Management of neuropathic pain following spinal cord injury: now and in the future. Spinal Cord 47: 352-359.
21. Finnerup N, Jensen T (2004) Spinal cord injury pain--mechanisms and treatment. Eur J Neurol 11: 73-82.
22. Rosenbaum PR, Rubin DB (1983) The central role of the propensity score in observational studies for causal effects. Biometrika 70: 41-55.
23. Deyo RA, Cherkin DC, Ciol MA (1992) Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 45: 613-619.
24. Austin PC (2011) An Introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 46: 399-424.
25. Hagen EM, Rekand T, Gilhus NE, Gronning M (2009) Diagnostic coding accuracy for traumatic spinal cord injuries. Spinal Cord 47: 367-371.
26. United States Department of Labor Bureau of Labor Statistics.
27. Jones AM, Rice N, Bago d'Uva T, Balia S (2013) Applied Health Economics. (2nd edn), Routledge, New York.
28. Duan N (1983) Smearing Estimate: A Nonparametric Retransformation Method. J Am Stat Assoc 78: 605-610.
29. Multidisciplinary Association of Spinal Cord Injury Professionals (MASCIP) Guidelines for the Management of Neuropathic Pain in Adults following Spinal Cord Injury, 2nd Edition. Multidisciplinary Association of Spinal Cord Injury Professionals (MASCIP).
30. Ones K, Yilmaz E, Beydogan A, Gultekin O, Caglar N (2007) Comparison of functional results in non-traumatic and traumatic spinal cord injury. Disabil Rehabil 29: 1185-1191.
31. Gupta A, Taly AB, Srivastava A, Murali T (2009) Non-traumatic spinal cord lesions: epidemiology, complications, neurological and functional outcome of rehabilitation. Spinal Cord 47: 307-311.
32. DeVivo MJ, Chen Y (2012) Trends in new injuries, prevalent cases, and aging with spinal cord injury. Arch Phys Med Rehabil 92: 332-338.
33. Jabbour P, Fehlings M, Vaccaro AR, Harrop JS (2008) Traumatic spine injuries in the geriatric population. Neurosurg Focus 25: E16.
34. Fick DM, Cooper JW, Wade WE, Waller JL, Maclean JR, et al. (2003) Updating the Beers criteria for potentially inappropriate medication use in older adults. Results of a US consensus panel of experts. Arch Intern Med 163: 2716-2724.
35. Bowie MW, Slattum PW (2007) Pharmacodynamics in older adults: a review. Am J Geriatr Pharmacother 5: 263-303.
36. Siddall PJ, Taylor DA, McClelland JM, Rutkowski S (1999) Pain report and the relationship of pain to physical factors in the first 6 months following spinal cord injury. Pain 81: 187-197.
37. Bryce TN (2010) Pain Management in Persons with Spinal Cord Injury. Demos Medical Publishing, New York.

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