

## PRELIMINARY RESEARCH

### Brief Research Reports

## Health Care Expenditure Burden of Persisting Herpes Zoster Pain

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### ABSTRACT

**Objectives.** Pain can persist long after the resolution of herpes zoster, but little is known regarding its health care costs. The objective of this study was to determine the health care expenditures associated with persisting pain following herpes zoster by comparing expenditures for patients with postherpetic neuralgia or subacute herpetic neuralgia with a control group without these conditions.

**Methods.** Health care expenditures attributable to persisting pain in herpes zoster patients were calculated using Thomson-Medstat's MarketScan® databases to examine commercial, Medicare, and Medicaid claims for inpatient and outpatient services and outpatient prescription drugs.

**Results.** Excess annualized costs were \$4,917 for commercially insured patients, \$2,696 for Medicare patients, and \$9,310 for Medicaid patients.

**Conclusions.** The substantial health care costs associated with persisting pain in herpes zoster have important public health implications given evidence that the incidence of herpes zoster is increasing and that the population is aging in the United States. The results provide a basis for evaluating the cost-effectiveness of existing treatments and emerging prevention strategies.

**Key Words.** Herpes Zoster, Postherpetic Neuralgia; Health Care Expenditures; Cost-Effectiveness; Treatment; Prevention

### Introduction

The most common complication of herpes zoster in immunocompetent patients is prolonged pain, which is termed postherpetic neuralgia (PHN). Recent research supports making a distinction between three phases of pain—acute pain occurring within 30 days after rash onset, PHN (pain that persists 120 days or more after rash onset), and subacute herpetic neuralgia (SHN;

pain that persists beyond 30 days but resolves before the diagnosis of PHN is made) [1–3].

Patients with prolonged pain following herpes zoster are often refractory to existing treatments, and their use of health care resources can be substantial. However, few studies have examined these health care expenditures, which is surprising given that PHN may affect as many as one million people in the United States [4]. Information about the costs associated with prolonged pain would be especially relevant in determining the cost-effectiveness of emerging prevention strategies [5,6], in which much larger numbers of individuals are exposed to interventions. The objective of the current study was to determine the health care costs associated with prolonged pain following herpes

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zoster by comparing expenditures for patients with SHN or PHN to a control group without these conditions.

## Methods

The data for this study came from Thomson-Medstat's MarketScan® suite of databases. Three separate databases were used, the Commercial Claims and Encounters (CCAE), Medicare, and Medicaid databases. The commercial database contains the health care experience of several million employees and their dependents (annually), covered under a variety of fee-for-service and capitated health plans, including preferred provider organizations, point-of-service plans, indemnity plans, and health maintenance organizations. The Medicare database contains the health care experience of about one million individuals with Medicare supplemental insurance paid for by employers. Both the Medicare-covered portion of payment (represented as coordination of benefits amount) and the employer-paid portion are included in this database. The Medicaid database contains the pooled health care experience of approximately 10 million Medicaid enrollees from several geographically dispersed states. All these databases link enrollment and medical claims for inpatient, outpatient, and outpatient prescription drug services for each patient.

Patients were included in the PHN/SHN cohort if they had either a health care claim with a primary diagnosis of PHN (ICD-10 053.12, 053.13, 053.19), or a health care claim with primary diagnosis of shingles (ICD-10 053.9x, 053.0x, 053.10, 053.11, 053.2x, 053.7x, 053.8x) and had received at least 30 days of analgesic medication beginning within 30 days after the shingles diagnosis. Medications considered analgesics were those commonly used during the study period, whether appropriately or not, in the treatment of PHN and other neuropathic pain conditions, including gabapentin, 5% lidocaine patch, opioid analgesics, tramadol, tricyclic antidepressants, other anticonvulsants, other antidepressants, and benzodiazepines [7,8].

The date of the PHN or shingles diagnosis was considered the index event. The 6 months preceding the index date was the pre-period, and the 12 months after the index date was the post-period for commercial and Medicare patients. Due to data limitations at the time of analysis, we used a 6-month post-period for Medicaid patients. The index date was between July 1, 2001, and Septem-

ber 30, 2003, for commercial and Medicare patients, and between July 1, 2001, and June 30, 2002, for Medicaid patients.

Patients with any other common painful conditions (arthritis and other arthropathies, cancer, low back and spinal pain, osteoarthritis, or rheumatic conditions) were excluded to ensure that analgesics administered to the patients with persisting pain were not prescribed for comorbid painful conditions. Patients were also excluded if they were insured under a capitated insurance plan, not continuously enrolled from the pre-period through the post-period, or were pregnant during the study period. The control cohort consisted of a 10-fold larger random sample of patients who did not have diagnoses of PHN or shingles but met the exclusion criteria. The index dates for the control patients were randomly assigned from those in the pain cohort and therefore had the same ranges.

The following variables were considered: age, sex, race (available for Medicaid patients only), urban vs rural residence, region of residence, index year, pre-period Psychiatric Diagnostic Group (PDG) [9], pre-period Charlson Comorbidity Index (CCI) score [10], and, for commercial and Medicare patients, whether insured by a traditional indemnity plan or managed care plan (both point-of-service and preferred provider service plans).

Total expenditures were divided into directly PHN/SHN-related, mental health-related, and all other. Health care claims with a primary diagnosis of PHN or shingles, and use of analgesic medications by PHN and shingles patients and by control group patients with other painful conditions was categorized as PHN/SHN-related. Health care claims with a mental health diagnosis (290.xx–319.xx, V61xx–V62xx, V65.42, V71.0–V71.09) or mental health medications (therapeutic class 69, excluding those in the analgesic list) were considered mental health-related. All other health care claims were counted in the “other” category (e.g., inpatient or outpatient care billed for diagnoses other than herpes zoster and PHN). Health care was further categorized by type of service, including inpatient, outpatient, emergency department, and outpatient medications. All expenditure measures are reported in 2004 dollars.

Chi-square tests were used for analyses of dichotomous variables and *t*-tests were used for continuous variables. Propensity score matching was used to equalize measurable differences between PHN/SHN patients and the controls.

**Table 1** Demographic and health status variables and health care expenditures for commercial cohort (12-month period)

	Prior to Propensity Score Matching (Mean or Percentage)			Post Propensity Score Matching (Mean or Percentage)		
	PHN/SHN (N = 1,046)	Control (N = 10,644)	P	PHN/SHN (N = 1,032)	Control (N = 1,032)	P
Demographics and health status						
Age (years)	53.3	39.2	0.001	53.2	53.2	0.907
Female (%)	65.8	52.6	0.001	65.6	67.2	0.890
Charlson Comorbidity Index	0.85	0.32	0.001	0.81	0.74	0.230
Count of Psychiatric Diagnosis Groups	0.27	0.11	0.001	0.25	0.15	0.001
Expenditures						
PHN/SHN-related						
Outpatient ER claims	\$39	N/A	N/A	\$39	N/A	N/A
Outpatient non-ER claims	\$519	N/A	N/A	\$522	N/A	N/A
Inpatient	\$246	N/A	N/A	\$249	N/A	N/A
Prescriptions	\$730	\$91		\$716	\$161	
Total PHN/SHN-related	\$1,534	\$91	0.001	\$1,526	\$161	0.001
Mental health	\$490	\$175	0.001	\$417	\$238	0.001
All other	\$8,310	\$2,923	0.001	\$8,111	\$4,738	0.001
Total	\$10,334	\$3,189	0.001	\$10,054	\$5,137	0.001

ER = emergency room; N/A = not available.

The control patients were matched according to the predicted probability of being in the PHN/SHN cohort on the basis of a logistic regression analysis that controlled for patient demographics (age, sex, insurance type, region, urban residency, index year, and race for the Medicaid patients), and overall comorbidities (CCI and PDG) in the pre-period. Patients were matched via a nearest-neighbor, within-caliber, one-to-one approach [11]. Patients who were not matched were eliminated from the sample. A second-stage regression was performed in order to control for differences between the PHN/SHN and control cohorts that remained after propensity matching [12].

In order to ensure that patients who had diagnoses of shingles accompanied by prescription of analgesic medication but no diagnosis of PHN did not unduly affect the results, a sensitivity analysis was conducted by eliminating these patients and re-estimating the model.

## Results

Tables 1–3 present the demographic and expenditure data for both the unmatched and matched commercial, Medicare, and Medicaid cohorts in order to show the impact of the propensity score matching in generating similar groups. The num-

**Table 2** Demographic and health status variables and health care expenditures for Medicare cohort (12-month period)

	Prior to Propensity Score Matching (Mean or Percentage)			Post Propensity Score Matching (Mean or Percentage)		
	PHN/SHN (N = 1,811)	Control (N = 18,215)	P	PHN/SHN (N = 1,811)	Control (N = 1,811)	P
Demographics and health status						
Age (years)	76.8	75.4	0.001	76.8	76.9	0.528
Female (%)	66.6	59.0	0.001	66.6	66.3	0.958
Charlson Comorbidity Index	1.51	1.26	0.001	1.51	1.35	0.006
Count of Psychiatric Diagnosis Groups	0.15	0.10	0.001	0.15	0.09	0.001
Expenditures						
PHN/SHN-related						
Outpatient ER claims	\$25	N/A	N/A	\$25	N/A	N/A
Outpatient non-ER claims	\$359	N/A	N/A	\$359	N/A	N/A
Inpatient	\$256	N/A	N/A	\$256	N/A	N/A
Prescriptions	\$767	\$201		\$767	\$221	
Total PHN/SHN-related	\$1,407	\$201	0.001	\$1,407	\$221	0.001
Mental health	\$257	\$188	0.004	\$257	\$184	0.010
All other	\$8,252	\$6,735	0.001	\$8,252	\$6,815	0.001
Total	\$9,916	\$7,124	0.001	\$9,916	\$7,220	0.001

ER = emergency room; N/A = not available.

**Table 3** Demographic and health status variables and health care expenditures for Medicaid cohort (6-month period)

	Prior to Propensity Score Matching (Mean or Percentage)			Post Propensity Score Matching (Mean or Percentage)		
	PHN/SHN (N = 637)	Control (N = 6440)	P	PHN/SHN (N = 604)	Control (N = 604)	P
Demographics and health status						
Age (years)	51.8	23.7	0.001	51.0	52.1	0.261
Female (%)	62.3	52.7	0.069	61.6	59.3	0.899
Charlson Comorbidity Index	1.29	0.30	0.001	1.23	0.98	0.010
Count of Psychiatric Diagnosis Groups	0.43	0.24	0.001	0.44	0.41	0.592
Expenditures						
PHN/SHN-related						
Outpatient ER claims	\$34	N/A	N/A	\$33	N/A	N/A
Outpatient non-ER claims	\$187	N/A	N/A	\$181	N/A	N/A
Inpatient	\$282	N/A	N/A	\$315	N/A	N/A
Prescriptions	\$493	\$51		\$483	\$148	
Total PHN/SHN-related	\$996	\$51	0.001	\$1,012	\$148	0.001
Mental health	\$679	\$618	0.624	\$666	\$1,042	0.090
All other	\$6,055	\$1,366	0.001	\$7,308	\$3,141	0.001
Total	\$7,730	\$2,035	0.001	\$8,986	\$4,331	0.001

ER = emergency room; N/A = not available.

ber of PHN/SHN patients selected was 1,046 for the commercial cohort (Table 1), 1,811 for the Medicare cohort (Table 2), and 637 for the Medicaid cohort (Table 3). About two-thirds of patients in each group were female. On average, Medicare patients were 25 years older than the other patients and had higher CCI scores.

The propensity score matching was successful, with 98%, 95%, and 95% of the patients matched and retained for the commercial, Medicare, and Medicaid cohorts, respectively. After matching, PDGs were significantly higher in the PHN/SHN cohort compared with controls in the commercial (Table 1) and Medicare (Table 2) cohorts, and the CCI was significantly higher in the Medicare (Table 2) and Medicaid (Table 3) cohorts. However, the magnitude of these differences was modest and a second-stage regression accounting for the differences (not reported) produced cost estimates nearly identical to the post-matching estimates included in the tables. All other matching variables were similar between the PHN/SHN cohorts and controls.

The annual excess health care expenditures associated with persisting pain in patients with herpes zoster compared with matched controls was \$4,917 for the commercial cohort (Table 1) and \$2,696 for the Medicare cohort (Table 2). The annual costs for the Medicaid cohort, based on doubling the 6-month expenditures (the first 6 months of commercial and Medicare expenditures were approximately half the 12-month expenditures), were estimated to be \$9,310 (Table 3). The excess expenditures were prima-

rily categorized as PHN/SHN-related care (18–44%) and other expenditures (53–90%), with minimal excess costs attributable to mental health services.

The majority of the PHN/SHN patients in the study had a PHN diagnosis (76% of commercial, 82% of Medicare, and 72% of Medicaid patients). When patients without a diagnosis of PHN were excluded, the estimates of health care expenditures remained generally similar, with decreases of 5% for Medicaid, 12% for commercial, and 7% for Medicare patients.

## Discussion

The results indicate that the health care expenditures associated with persisting pain in patients with herpes zoster (i.e., either SHN or PHN) range from almost \$3,000 to over \$9,000 per patient over the first year, depending on whether the patient is covered by Medicare, commercial insurance, or Medicaid. Because the first 6 months of commercial and Medicare expenditures were approximately half the 12-month expenditures for these cohorts, the 6-month Medicaid expenditures were used to derive the annual estimate for the Medicaid cohort. This annual estimate must be interpreted with caution, however, because it is appreciably higher than the other two and assumes that the first 6 months of Medicaid costs accurately reflect the annual expenditures.

This study represents the first assessment of health care costs associated with persisting pain in



patients with herpes zoster in the United States. An early study conducted in the United Kingdom estimated that the lifetime cost of PHN was approximately £770 per patient in 1992 currency [13]. A recent prospective study, also conducted in the United Kingdom, calculated that the average cost of a case of herpes zoster during the first 6 months was \$900 [14], but the costs in the 13.4% of patients with persisting pain were not presented separately. Differences between the U.S. and U.K. health care systems, differences in study methodologies, and the rapid rise in health care costs over the past decade may explain why these estimates of health care expenditures are lower than ours.

A large percentage of the health care costs associated with persisting pain in herpes zoster patients consisted of expenses that were not coded under PHN or shingles diagnoses. It is possible that some of these costs are attributable to PHN or SHN but that their classification in our data did not reflect this. However, it seems likely that persisting pain in patients with herpes zoster (and perhaps other painful conditions) can be associated with substantial indirect increases in health care utilization, for example, by reducing an individual's threshold for seeking evaluation or treatment of other symptoms or illnesses.

Because it is likely that some patients with persisting pain are not diagnosed with PHN, we included patients with a primary diagnosis of shingles who received at least 30 days of analgesic medication beginning within 30 days after the shingles diagnosis. This approach to identifying patients with persisting pain may have led to erroneously attributing some health care costs to persisting pain. However, removal of these patients in the sensitivity analysis did not appreciably affect the results.

We estimated only costs paid by commercial insurance, Medicare, and Medicaid. Additional costs, such as out-of-pocket expenses and lost productivity, which are likely considerable, were not examined. Furthermore, the deleterious effects of persisting pain on overall quality of life, including physical, emotional, and social functioning, are also not reflected in these estimates.

The substantial health care costs associated with persisting pain in herpes zoster have important public health implications given evidence that the incidence of herpes zoster is increasing [15] and that the population is aging in the United States. The results provide a basis for evaluating the cost-effectiveness of existing treatments [16,17] and emerging prevention strategies [5,6].

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## References

- 1 Arani RB, Soong SJ, Weiss HL, et al. Phase specific analysis of herpes zoster associated pain data: A new statistical approach. *Stat Med* 2001;20:2429–39.
- 2 Desmond RA, Weiss HL, Arani RB, et al. Clinical application for change-point analysis of herpes zoster pain. *J Pain Symptom Manage* 2002;23:510–6.
- 3 Jung BF, Johnson RW, Griffin DRJ, Dworkin RH. Risk factors for postherpetic neuralgia in patients with herpes zoster. *Neurology* 2004;62:1545–51.
- 4 Bowsher D. The lifetime occurrence of herpes zoster and prevalence of post-herpetic neuralgia: A retrospective survey in an elderly population. *Eur J Pain* 1999;3:335–42.
- 5 Dworkin RH, Schmader KE. Treatment and prevention of postherpetic neuralgia. *Clin Infect Dis* 2003;36:877–82.
- 6 Oxman MN, Levin MJ, Johnson GR, et al. Shingles Prevention Study Group. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med* 2005;352:2271–84.
- 7 Dworkin RH, Backonja M, Rowbotham MC, et al. Advances in neuropathic pain: Diagnosis, mechanisms, and treatment recommendations. *Arch Neurol* 2003;60:1524–34.
- 8 Oster G, Berger A, Dukes E, Edelsberg J, McCarberg B. Use of potentially inappropriate pain-related medications in older adults with painful neuropathic disorders. *Am J Geriatr Pharmacother* 2004;2:163–70.
- 9 Ashcraft ML, Fries BE, Nerenz DR, et al. A psychiatric patient classification system: An alternative to diagnosis-related groups. *Med Care* 1989;27:543–57.
- 10 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chron Dis* 1987;40:373–83.
- 11 Ganguly R, Martin B, Dorfman J, Rizzo J. In search of an unbiased estimate of treatment effect using

- observational data: A comparison of propensity scoring and Heckman two stage sample selection models. *ISPOR Connections* 2004;10:2–5.
- 12 Ozminkowski RJ, Burton W, Goetzel R, Maclean R, Wang S. The impact of rheumatoid arthritis on medical expenditures, absenteeism, and short-term disability benefits. *J Occup Environ Med* 2006;48:135–48.
  - 13 Davies L, Cossins L, Bowsher D, Drummond M. The cost of treatment for post-herpetic neuralgia in the UK. *Pharmacoeconomics* 1994;6:142–8.
  - 14 Scott FT, Johnson RW, Leedham-Green M, et al. The burden of herpes zoster: A prospective population based study. *Vaccine* 2006;24:1308–14.
  - 15 Yih WK, Brooks DR, Lett SM, et al. The incidence of varicella and herpes zoster in Massachusetts as measured by the Behavioral Risk Factor Surveillance System (BRFSS) during a period of increasing varicella vaccine coverage, 1998–2003. *BMC Public Health* 2005;5:68. doi: 10.1186/1471-2458-5-68
  - 16 Dubinsky RM, Kabbani H, El-Chami Z, Boutwell C, Ali H. Practice parameter: Treatment of postherpetic neuralgia: An evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2004;63:959–65.
  - 17 Hempenstall K, Nurmikko TJ, Johnson RW, A'Hern RP, Rice AS. Analgesic therapy in postherpetic neuralgia: A quantitative systematic review. *PLoS Med* 2005;2:e164.