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Original article

Costs of pregabalin or gabapentin for painful diabetic peripheral neuropathy

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Abstract

Objective:
To characterize and compare healthcare resource utilization and costs among patients with painful diabetic peripheral neuropathy (pDPN) newly prescribed pregabalin or gabapentin in a real-world clinical setting.

Study design:
Retrospective cohort analysis using the MarketScan Commercial Claims and Encounters and Medicare Supplemental Databases (2007–2009).

Methods:
Patients with new prescriptions for pregabalin or gabapentin (index event) in 2008 and ≥1 healthcare encounter with an ICD-9 code for pDPN (250.6 or 357.2) within 30 days prior to the first prescription were identified and propensity score matched; continuous enrollment 12 months pre- and post-index was required. Pre- to post-index changes in 12-month all-cause and pDPN-attributable resource utilization and costs were compared between pregabalin and gabapentin using a difference-in-difference (DID) approach.

Results:
A total of 910 pregabalin patients (48.6% female; mean age 63.3 ± 12.1 years) were matched with 910 gabapentin patients (48.8% female; mean age 63.3 ± 12.1 years). The DID showed no significant differences between cohorts for pre- to post-index changes in any of the all-cause resource utilization categories. While prescription costs increased significantly more with pregabalin (DID −$563; $p < 0.0001$), the DID of $1603 for total healthcare costs per patient indicated that the pre- to post-index increases of $3081 for pregabalin and $4684 for gabapentin patients were comparable ($p = 0.8474$). Total pDPN-attributable healthcare costs were significantly higher with pregabalin (DID −$385; $p < 0.0001$), resulting from higher prescription costs (DID −$432; $p < 0.0001$). Limitations of this study include the inability to specifically link pDPN with medication prescribing; differences between groups despite propensity score matching; use of proxy measures for adherence parameters; and inability to capture efficacy outcomes.

Conclusions:
Among patients initiating pregabalin or gabapentin, there were no significant differences between the drugs in the pre- to post-index changes in all-cause total healthcare costs, despite the increase in prescription costs for pregabalin.

Introduction

Diabetic neuropathies are among the most common long-term complications of diabetes, occurring with a similar frequency among patients with type 1 (59%) and type 2 (66%) diabetes[1]. Although not all of these neuropathies result in pain, painful diabetic peripheral neuropathy (pDPN) is a variant of distal symmetrical sensorimotor polyneuropathy that generally manifests by neuropathic pain in the extremities. While it has been reported that pDPN may occur in up

to 26% of patients with diabetes[2], best estimates suggest a prevalence of 15%[3]. pDPN results in a substantial patient burden by reducing function, quality-of-life, and productivity[4–8]. Furthermore, pDPN is associated with a significant increase in health resource utilization and costs relative to the general population and to diabetic patients without pDPN[6,8–12]. The economic burden has also been reported to be greater at higher levels of pain severity[6,7,13].

Pharmacologic management has generally relied on several medications used for the treatment of neuropathic pain including tricyclic antidepressants (TCAs), opioids, and gabapentin, despite their lack of approval for the specific indication of pDPN in the US[14–20]. Pregabalin and duloxetine have been approved by the US Food and Drug Administration for the treatment of pDPN, and recently published evidence-based guidelines recommend pregabalin as first-line therapy if clinically appropriate based on Level A evidence, with duloxetine also considered as a treatment option based on Level B evidence[21]. However, prescribing of pregabalin sometimes requires prior authorization or step edits that mandate the use of other, non-approved therapies despite the findings that restricting access to pregabalin did not result in reductions in overall health costs[22,23]. The availability of gabapentin as a low cost generic drug, combined with its recommendation in pDPN-specific guidelines, albeit as a second-tier drug[16,21,24], suggests that managed care organizations concerned with pharmacy budgets may require generic gabapentin as the preferred option. It is thus important to determine if such use does result in lower healthcare costs relative to pregabalin.

A recent retrospective study of patients with pDPN in the LifeLink™ Health Plan Claims Database who initiated treatment with pregabalin or gabapentin reported mean annual direct medical costs of $31,157 and $33,360 for the two drugs, respectively[25]. While these represented significant increases in costs of $4359 for pregabalin and $6334 for gabapentin relative to the year prior to initiating treatment (both $p<0.0001$), the differences between the two drugs for the changes in costs from the pre- to post-treatment initiation periods were not directly compared. Therefore, the purpose of the current study was to characterize and compare the changes in all-cause and pDPN-attributable healthcare resource utilization and associated costs among patients with pDPN newly prescribed pregabalin or gabapentin in a real-world clinical setting.

Methods

Data source

Data for the study were obtained from MarketScan Commercial Claims and Encounters and Medicare Supplemental Databases (Thomson Reuters) for the years 2007–2009. This database includes complete longitudinal records of inpatient services, outpatient services, long-term care, and prescription drug claims covered under a variety of fee-for-service and capitated health plans, including exclusive provider organizations, preferred provider organizations (PPOs), point-of-service (POS) plans, indemnity plans, and health maintenance organizations (HMOs). The data are nationally representative, quality-controlled, and HIPAA (Health Insurance Portability and Accountability Act of 1996) compliant.

Available information in this database includes member age, gender, census region, health insurance eligibility dates, facility claims, provider claims, pharmacy claims, and reimbursed and charged amounts for all claims. All claims for any given patient can be linked using unique encrypted identifiers.

Subject selection

Subjects were plan members ≥18 years of age who had a new prescription (index date) for pregabalin or gabapentin between January 1, 2008 and December 31, 2008 and ≥1 healthcare encounters within 30 days prior to the index date with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code of 250.6 or 357.2; these codes have previously been used to identify patients with pDPN[11,12,25]. The study period consisted of the 12 months before (pre-index) and 12 months after (post-index) the index date; all patients were required to be continuously enrolled during the study period.

Patients were excluded if they had missing data for age or gender, a prescription for pregabalin or gabapentin during the 6-month period prior to the index date; a prescription for both pregabalin and gabapentin on the index date; or claims with an ICD-9-CM diagnosis code for epilepsy (345.XX, 780.39), post-herpetic neuralgia (053.1X), or fibromyalgia (729.1) during the study period, all of which are approved indications for pregabalin.

Patient matching

Since randomization is not possible in retrospective observational studies, propensity score matching was used to gain precision in estimating the measured effects between the pregabalin and gabapentin cohorts[26,27]. Patients were matched 1:1 using logistic regression to estimate the conditional probability (the propensity score) of assignment to the pregabalin vs gabapentin cohort given the observed predictors (covariates). Patients were matched within a 0.01 caliper of their propensity score based on age; gender; 12-month pre-index Deyo-Charlson Comorbidity Score[28]; pre-index count of pain diagnoses; number of

unique pain medications during 90 days pre-index; number of unique hospitalizations during 90 days pre-index; and presence of pre-specified comorbidities (cardiovascular disorder, diabetes-related conditions, mental disorders, sleep disorders, musculoskeletal pain conditions, and neuropathic pain conditions). These comorbidities were determined by two or more outpatient encounters during the entire study period with at least one encounter required during the 12 month pre-index period OR one inpatient healthcare encounter with an associated diagnosis code for the specific comorbidity during the 12-month pre-index period.

A secondary analysis was performed among patients ≥65 years of age. Propensity score matching was used for this population by re-matching from the population of all patients with eligibility using the same selection criteria as the main analysis with the addition of age ≥65 years.

Key outcome measures

Demographic and clinical characteristics of both cohorts were evaluated, including average age, gender distribution, Deyo-Charlson Comorbidity score[28], and prevalence of pre-specified comorbidities.

Adherence and persistence to both drugs were assessed during the post-index period. Adherence was defined as the proportion of days covered (PDC)[29], calculated as number of days with drug during the 12-month follow-up period. Persistence was defined as the duration of time from initiation to a gap in therapy of more than half the previous fill's days supply.

All-cause and pDPN-attributable healthcare utilization and costs were assessed during the pre- and post-index periods. All-cause resource utilization categories included physician office visits; outpatient visits; inpatient visits; emergency department visits; prescriptions filled; lab tests. Diagnostics and procedures that were performed on inpatients and outpatients were included in the respective inpatient and outpatient cost categories. pDPN-attributable healthcare utilization and costs were based on identification of medical claims that included ICD-9-CM codes 357.2 or 250.6x. pDPN-attributable pharmacy claims in the pre- and post-index periods were based on prescriptions for pain-related medications. Additionally, the number of prescription claims was determined in the pre- and post-index periods for both cohorts for the following selected classes of pain-related medications: opioids, non-steroidal anti-inflammatory drugs (NSAIDs), antidepressants, and topical anesthetics.

Analyses

Descriptive statistics were used to describe demographic and clinical characteristics. A difference-in-difference approach (DID; 'difference-in-differences' = [gabapentin cohort post-index period – gabapentin cohort pre-index period] – [pregabalin cohort post-index period – pregabalin cohort pre-index period]) was used to examine incremental differences across comparison groups and to compare pre- to post-index changes between pregabalin and gabapentin. Between-group comparisons were performed using McNemar's (2 categories) or Bowker's (>2 categories) tests for categorical data, paired *t*-test for demographic continuous variables, and Wilcoxon sign rank test for PDC, resource utilization, and cost continuous variables. A Cox proportional hazards model, stratified by matched pairs, was used to compare persistence. A p-value <0.05 was considered statistically significant; all analyses were conducted using SAS version 9.2 (SAS Institute, Inc., Cary, NC).

Results

A total of 910 patients initiated on pregabalin were matched with 910 patients initiated on gabapentin. Table 1 shows the incremental attrition associated with each of the inclusion criteria leading to the resultant sample sizes. Table 2 presents the demographic and clinical characteristics of the two cohorts; the mean (standard deviation [SD]) age was similar in each cohort, 63.3 (12.1) years, and the gender distribution was also similar, 51.4% and 51.2% males for pregabalin and gabapentin, respectively. However, while the Southern region had the greatest overall representation, differences were observed between the cohorts for geographic region (Table 2); a higher proportion of patients in the West were prescribed

Table 1. Sample size attrition table.

Attrition criterion	*n*
All patients in MarketScan® database 2007–2009	48,358,810
Patients with pregabalin or gabapentin prescription in 2008	416,676
Patients newly prescribed pregabalin or gabapentin in 2008	270,684
Excluding patients with both pregabalin or gabapentin prescriptions on the index date	270,434
Continuous enrollment during 12 month pre-index through 12 month post-index study period	143,793
Patients ≥18 years of age	142,677
Pregabalin	56,410
Gabapentin	86,267
Patients with pDPN diagnosis ≤1 year prior to or on the index date	5368
Pregabalin	2105
Gabapentin	3263
Patients with pDPN diagnosis ≤30 days prior to or on the index date	2362
Pregabalin	948
Gabapentin	1414
Propensity score matching	
Pregabalin patients	910
Matched gabapentin patients	910

Table 2. Demographic and clinical characteristics of the matched study cohorts.

Characteristic	Pregabalin ($n = 910$)	Gabapentin ($n = 910$)	p-value*
Age, years			
Mean (SD)	63.3 (12.1)	63.3 (12.1)	0.8976
Median	62	62	
Age group, *n* (%)			
18–34 years	10 (1.1)	9 (1.0)	0.8893
35–44 years	49 (5.4)	40 (4.4)	
45–54 years	146 (16.0)	153 (16.8)	
55–64 years	309 (34.0)	325 (35.7)	
≥65 years	396 (43.5)	383 (42.1)	
Gender, *n* (%)			
Male	468 (51.4)	466 (51.2)	0.9235
Female	442 (48.6)	444 (48.8)	
Geographic region, *n* (%)			
Northeast	72 (7.9)	75 (8.2)	<0.0001
North Central	304 (33.4)	262 (28.8)	
South	433 (47.6)	354 (38.9)	
West	101 (11.1)	216 (23.7)	
Unknown	0	3 (0.3)	
Type of benefit plan, *n* (%)			
Comprehensive†	182 (20.0)	171 (18.8)	<0.0001
Exclusive provider organization	12 (1.3)	8 (0.9)	
Health maintenance organization	87 (9.6)	200 (22.0)	
Point of service	83 (9.1)	60 (6.6)	
Preferred provider organization	517 (56.8)	441 (48.5)	
Point of service with capitation	3 (0.3)	4 (0.4)	
Consumer driven health plan	13 (1.4)	8 (0.9)	
Missing/unknown	13 (1.4)	18 (2.0)	
Deyo-Charlson Comorbidity Index, mean (SD)	3.4 (1.8)	3.4 (1.8)	0.6876
Pre-specified comorbidities, *n* (%)			
Sleep disorders	124 (13.6)	118 (13.0)	0.6698
Major depressive disorder	38 (4.2)	34 (3.7)	0.6326
Dysthymic disorder	8 (0.9)	10 (1.1)	0.6374
Depressive disorder	28 (3.1)	29 (3.2)	0.8946
Fatigue	97 (10.7)	108 (11.9)	0.4161
Headache	61 (6.7)	61 (6.7)	1.0000
Chest pain, palpitations	57 (6.3)	41 (4.5)	0.0953
Anxiety, not otherwise specified	18 (2.0)	24 (2.6)	0.3545
Abdominal pain	183 (20.1)	156 (17.1)	0.1122
Myocardial infarction	18 (2.0)	21 (2.3)	0.6219
Old myocardial infarction	13 (1.4)	20 (2.2)	0.2230
Congestive heart failure	86 (9.5)	105 (11.5)	0.1343
Peripheral vascular disease	97 (10.7)	93 (10.2)	0.7590
Cerebrovascular disease	127 (14.0)	106 (11.7)	0.1444
Dementia	2 (0.2)	4 (0.4)	0.4142
Chronic pulmonary disease	160 (17.6)	159 (17.5)	0.9491
Rheumatologic disease	22 (2.4)	25 (2.8)	0.6473
Peptic ulcer disease	13 (1.4)	9 (1.0)	0.3938
Mild liver disease	7 (0.8)	9 (1.0)	0.6171
Moderate-to-severe liver disease	2 (0.2)	7 (0.8)	0.0956
Diabetes	783 (86.0)	776 (85.3)	0.6299
Diabetes with chronic complications	704 (77.4)	689 (75.7)	0.3888
Hemiplegia or paraplegia	7 (0.8)	4 (0.4)	0.3657
Renal disease	79 (8.7)	99 (10.9)	0.1206
Malignancy, including leukemia and lymphoma	73 (8.0)	75 (8.2)	0.8597
Metastatic solid tumor	5 (0.6)	6 (0.7)	0.7389
AIDS	1 (0.1)	1 (0.1)	1.0000

*McNemar, Bowker, or paired *t*-tests were used to calculate the statistical significance of differences between pregabalin and gabapentin for proportions and for means, respectively.
†A 'comprehensive' plan is defined as one that has no incentive for the patient to use a particular list of providers; coverage is handled by only one policy, with a deductible and coinsurance.

gabapentin prescriptions than pregabalin, and a higher proportion of patients were prescribed pregabalin in the North Central and Southern regions. Similarly, the most frequent type of insurance was preferred provider organizations (PPOs), but significant differences in type of plan were observed between the cohorts (Table 2); gabapentin was prescribed to a greater extent than pregabalin among HMOs (22.0% vs 9.6%).

Table 3. Differences in 12-month all-cause and painful diabetic peripheral neuropathy (pDPN)-attributable healthcare resource utilization per patient.

Resource category	Utilization per patient					
	Pregabalin ($n=910$)		Gabapentin ($n=910$)		DID*	*p*-value
	Pre-index	Post- minus pre-index	Pre-index	Post- minus pre-index		
All-cause, mean (SD) per patient						
Physician office visits	11.5 (7.2)	1.1	12.2 (10.8)	0.9	−0.2	0.4794
Emergency department visits	1.0 (2.1)	0.1	1.0 (2.1)	0.1	0	0.7649
Outpatient visits	27.9 (25.0)	3.5	29.4 (26.9)	4.0	0.5	0.5067
Prescriptions filled	48.4 (31.7)	7.1	48.1 (31.6)	7.8	0.7	0.6590
Inpatient stays	0.5 (1.0)	−0.1	0.5 (1.0)	0.0	0.1	0.7350
Average length of stay, days	1.6 (3.4)	0	1.7 (3.3)	0.1	0.1	0.7564
pDPN-attributable, mean (SD) per patient						
Physician office visits	1.2 (1.6)	0.2	1.1 (1.8)	0.4	0.2	0.0590
Emergency department visits	0.1 (0.3)	0.0	0.1 (0.4)	0.0	0.0	0.7476
Outpatient visits	2.1 (3.2)	0.2	2.0 (2.9)	0.5	0.3	0.1082
Prescriptions filled	6.8 (8.2)	4.4	6.7 (8.1)	4.7	0.3	0.3822
Inpatient stays	0.3 (1.7)	−0.1	0.2 (1.3)	−0.1	0.0	0.9688
Average length of stay, days	0.4 (1.7)	−0.1	0.3 (1.4)	0.0	0.1	0.4211

*Difference-in-differences are calculated as gabapentin pre-to-post-index differences minus pregabalin pre-to-post-index differences.

Table 4. Differences in selected pain-related medications prescribed to patients on pregabalin or gabapentin (percentage of patients with ≥1 prescription, 12 months pre- and post-index).

Variable	Percentage of patients					
	Pregabalin ($n=910$)		Gabapentin ($n=910$)		DID*	*p*-value
	Pre-index	Post- minus pre-index	Pre-index	Post- minus pre-index		
Opioids	60.1	6.1	64.2	1.8	−4.3	0.3490
NSAIDs	35.2	1.8	33.3	−1.3	−3.1	0.0045
Antidepressants	38.0	1.2	37.6	2.6	1.4	0.9849
Topical anesthetics	3.3	1.1	2.2	2.0	0.9	0.8922

*Difference-in-differences is gabapentin pre- to-post-index differences minus pregabalin pre- to-post-index differences.

Both cohorts were characterized by the same mean (SD) Deyo-Charlson Comorbidity Index, 3.4 (1.8), and a range of pre-specified comorbidities that were present in similar proportions of patients (Table 2).

In the post-index period, the PDC was slightly but significantly higher with gabapentin relative to pregabalin (0.47 [0.35] vs 0.42 [0.34]; $p<0.001$). Persistence with therapy was not significantly different: 112.9 (118.0) days for pregabalin and 122.3 (125.0) days for gabapentin ($p=0.51$). Average daily doses were 161.3 (85.3) mg for pregabalin and 768.5 (622.4) mg for gabapentin.

As shown in Table 3 for both cohorts, there were small increases in all-cause healthcare resource utilization in the post-index period relative to the pre-index period for nearly all resource categories. The only exceptions were inpatient stays, which decreased slightly with pregabalin and maintained parity with gabapentin, and the average length of stay, which did not change in the pregabalin cohort. None of the differences between cohorts were significant, as indicated by the DID. There were also no significant differences between cohorts in pDPN-attributable healthcare resource utilization (Table 3).

During the post-index period there were generally small increases relative to the pre-index period in the proportion of patients prescribed the various classes of pain-related medications in both cohorts (Table 4). The single exception was for NSAIDs in the gabapentin cohort, which showed a small decrease in the post-index period and resulted in the only significant difference in change from pre- to post-index periods between pregabalin and gabapentin (DID −3.1; $p<0.01$).

The mean pre- to post-index increase in all-cause total healthcare costs was $3081 (from $21,673 pre-index to $24,754 post-index) for pregabalin patients and $4684 (from $23,155 pre-index to $27,839 post-index) for gabapentin patients (Table 5). These increases were driven in the pregabalin cohort by post-index increases in the costs of both outpatient services ($1943) and prescriptions ($1313), and in the gabapentin cohort by the costs of outpatient ($1963) and inpatient services ($1970). The DID

Table 5. Differences in 12-month all-cause and painful diabetic peripheral neuropathy (pDPN)-attributable healthcare costs per patient.

Cost category	Cost per patient, US $					
	Pregabalin ($n=910$)		Gabapentin ($n=910$)		DID*	*p*-value
	Pre-index	Post- minus pre-index	Pre-index	Post- minus pre-index		
All-cause, mean (SD) per patient						
Physician office costs	$972 ($739)	$112	$1,244 ($3,051)	$137	$25	0.8624
Emergency department costs	$476 ($1,427)	0	$645 ($2,924)	$94	$94	0.3955
Outpatient costs	$9,301 ($19,698)	$1943	$11,351 ($34,082)	$1963	$20	0.8248
Prescription costs	$4,838 ($4,821)	$1313	$4,457 ($4,357)	$750	−$563	<0.0001
Inpatient costs	$7,533 ($24,247)	−$174	$7,347 ($20,275)	$1970	$2144	0.3966
Total costs (inpatient + outpatient + prescription)	$21,673 ($38,301)	$3081	$23,155 (43,729)	$4684	$1603	0.8474
pDPN-attributable, mean (SD) per patient						
Physician office costs	$97 ($148)	$14	$97 ($166)	$33	$19	0.0172
Emergency department costs	$21 ($152)	−$9	$115 ($2,388)	−$86	−$77	0.4960
Outpatient costs	$395 ($1,474)	−$63	$498 ($2,331)	−$21	$42	0.0762
Prescription costs	$636 ($2,319)	$697	$473 ($1,037)	$265	−$432	<0.0001
Inpatient costs	$624 ($3,746)	−$93	$769 ($4,723)	−$89	$4	0.6064
Total costs (inpatient + outpatient + prescription)	$1,655 ($4,756)	$540	$1,740 ($5,535)	$155	−$385	<0.0001

*Difference-in-differences is gabapentin pre- to-post-index differences minus pregabalin pre- to-post-index differences.

for prescription cost was significantly higher with pregabalin in the post-index period, by $563. However, when examining total cost, the increase in pregabalin pharmacy cost was offset by higher gabapentin inpatient cost (DID = $2144, $p=0.40$) resulting in a total cost DID of $1603 in favor of pregabalin, although not significant ($p=0.85$).

Both cohorts experienced an increase in pDPN-related total medical costs in the post- vs pre-index periods (Table 5), by $540 and $155 for pregabalin and gabapentin, respectively. The DID showed that these differences in costs were significantly higher with pregabalin, by $385 ($p<0.0001$), resulting from the significant increase of pre- to post-index prescription costs in the pregabalin cohort. The DID in pDPN-attributable physician office visits was significantly higher for gabapentin by $19 ($p<0.05$) but this difference was not enough to offset the higher prescription costs in the pregabalin cohort.

In the secondary analysis, 384 patients aged ≥65 years who were initiated on pregabalin were matched with patients initiated on gabapentin. Demographic characteristics were similar between the cohorts (Table 6), but, as with the all-age cohort, significant differences were observed for region and type of plan, with greater prescribing of pregabalin in the North Central and Southern regions, and generally among all the plans except HMOs.

Adherence parameters were not significantly different between the two elderly cohorts, and values were similar to the main analysis: PDC was 0.45 (0.35) and 0.49 (0.36) for pregabalin and gabapentin, respectively ($p=0.12$), and persistence with therapy was 124.7 (125.7) days for pregabalin and 128.2 (126.8) days for gabapentin ($p=0.33$). Average doses were 145.3 (74.4) mg for pregabalin and 681.5 (695.3) mg for gabapentin, which were slightly lower than for the overall population.

For patients ≥65 years of age, results for all-cause healthcare resource utilization showed increases in both cohorts for all resource categories except inpatient stays, which were the same in the pre- and post-index periods (Table 7). As indicated by the DID, there were no significant differences between cohorts. For pDPN-attributable resource use, the only changes were small increases in the post-index period for office visits and outpatient visits for both pregabalin and gabapentin, and a small increase in length of stay with gabapentin (Table 7); no significant differences were observed between cohorts.

Increases in all-cause direct medical costs were observed in the post-index period for all categories except emergency department costs among patients in the gabapentin cohort (Table 8). However, the only significant difference between the pregabalin and gabapentin cohorts for the pre- to post-index change was for pharmacy costs, which were significantly higher by $685 with pregabalin ($p<0.001$). While total costs were higher with gabapentin in both the pre- and post-index periods, the DID showed that the change in total costs was similar between the two cohorts. pDPN-attributable costs were significantly higher for the pregabalin cohort (DID −$230; $p<0.0001$), resulting from significantly higher prescription costs (DID −$481; $p<0.0001$).

Discussion

With the current emphasis by managed care on containing healthcare costs, information on changes in resource use

Table 6. Demographic and clinical characteristics of the matched study cohorts of patients ≥65 years old.

Characteristic	Pregabalin (*n* = 384)	Gabapentin (*n* = 384)	*p*-value*
Age, years			
Mean (SD)	74.6 (6.2)	74.7 (6.5)	0.8063
Median	74	74	
Gender, *n* (%)			
Male	190 (49.5)	187 (48.7)	0.8096
Female	194 (50.5)	197 (51.3)	
Geographic region, *n* (%)			
Northeast	35 (9.1)	37 (9.6)	0.0013
North Central	164 (42.7)	135 (35.2)	
South	143 (37.2)	122 (31.8)	
West	42 (10.9)	88 (22.9)	
Unknown	0	2 (0.5)	
Type of benefit plan, *n* (%)			
Comprehensive†	146 (38.0)	131 (34.1)	<0.0001
Health maintenance organization	12 (3.1)	59 (15.4)	
Point of service	10 (2.6)	9 (2.3)	
Preferred provider organization	211 (55.0)	179 (46.6)	
Consumer driven health plan	0	2 (0.5)	
Missing/unknown	5 (1.3)	4 (1.0)	
Deyo-Charlson Comorbidity Index, mean (SD)	3.7 (2.0)	3.7 (2.0)	0.7607
Pre-specified comorbidities			
Sleep disorders	53 (13.8)	45 (11.7)	0.3711
Major depressive disorder	11 (2.9)	14 (3.7)	0.5485
Dysthymic disorder	1 (0.3)	2 (0.5)	0.5637
Depressive disorder	10 (2.6)	5 (1.3)	0.1967
Fatigue	35 (9.1)	45 (11.7)	0.2386
Headache	24 (6.3)	12 (3.1)	0.0396
Chest pain, palpitations	26 (6.8)	19 (5.0)	0.2967
Anxiety, not otherwise specified	8 (2.1)	11 (2.9)	0.4913
Abdominal pain	86 (22.4)	69 (18.0)	0.1253
Myocardial infarction	12 (3.1)	14 (3.7)	0.6949
Old myocardial Infarction	11 (2.9)	10 (2.6)	0.8185
Congestive heart failure	52 (13.5)	57 (14.8)	0.5919
Peripheral vascular disease	51 (13.3)	50 (13.0)	0.9165
Cerebrovascular disease	89 (23.2)	63 (16.4)	0.0167
Dementia	1 (0.3)	3 (0.8)	0.3173
Chronic pulmonary disease	79 (20.6)	90 (23.4)	0.3252
Rheumatologic disease	12 (3.1)	11 (2.9)	0.8348
Peptic ulcer disease	8 (2.1)	4 (1.0)	0.2482
Mild liver disease	5 (1.3)	1 (0.3)	0.1025
Moderate to severe liver disease	2 (0.5)	1 (0.3)	0.5637
Diabetes	317 (82.6)	321 (83.6)	0.7029
Diabetes with chronic complications	292 (76.0)	299 (77.9)	0.5480
Hemiplegia or paraplegia	3 (0.8)	0	0.0833
Renal disease	37 (9.6)	53 (13.8)	0.0772
Malignancy, including leukemia and lymphoma	43 (11.2)	44 (11.5)	0.9068
Metastatic solid tumor	5 (1.3)	3 (0.8)	0.4142
AIDS	0	0	1.000

*McNemar, Bowker, or paired *t*-tests were used to calculate the statistical significance of differences between pregabalin and gabapentin for proportions and for means, respectively.
†A 'comprehensive' plan is defined as one that has no incentive for the patient to use a particular list of providers; coverage is handled by only one policy, with a deductible and coinsurance.

and costs after initiating a pharmacologic therapy, and differences in these changes between therapeutic options, is essential for making appropriate formulary and treatment decisions. This analysis complements and supports the results of a previous study, using a different claims database, that reported on changes in resource utilization and costs among patients treated with pregabalin and gabapentin[25].

Consistent with that study, when changes in all-cause healthcare resource utilization were observed in the post-index period, these changes were generally small and showed an increase relative to the pre-index period in both cohorts. The resource category characterized by the largest change was prescriptions filled, with increases in the post-index period of 7.1 and 7.8 prescriptions filled per patient for pregabalin and gabapentin, respectively.

Table 7. Differences in 12-month all-cause and painful diabetic peripheral neuropathy (pDPN)-attributable healthcare resource utilization per patient in the matched study cohorts of patients ≥65 years old.

Resource category	Utilization per patient, mean (SD)					
	Pregabalin ($n=384$)		Gabapentin ($n=384$)		DID*	*p*-value
	Pre-index	Post- minus pre-index	Pre-index	Post- minus pre-index		
All-cause, mean (SD) per patient						
Physician office visits	12.2 (7.4)	1.2	13.4 (8.6)	0.8	−0.4	0.7183
Emergency department visits	0.9 (1.5)	0.2	1.0 (2.0)	0.1	−0.1	0.5790
Outpatient visits	28.2 (20.4)	4.1	32.2 (25.0)	3.4	−0.7	0.4614
Prescriptions filled	50.6 (29.3)	5.6	47.8 (26.8)	5.3	−0.3	0.9373
Inpatient stays	0.4 (0.7)	0	0.5 (0.8)	0	0	0.8028
Average length of stay, days	1.8 (3.9)	0.2	1.7 (3.0)	0.4	0.2	0.5200
pDPN-attributable, mean (SD) per patient						
Physician office visits	1.0 (1.6)	0.1	1.2 (2.0)	0.1	0	0.3319
Emergency department visits	0 (0.2)	0	0 (0.2)	0	0	0.6558
Outpatient visits	2.1 (3.6)	0.1	2.3 (3.2)	0.1	0	0.1505
Prescriptions filled	6.0 (7.3)	4.0	5.3 (5.9)	4.1	0.1	0.7512
Inpatient stays	0.1 (0.7)	0	0.2 (1.0)	0	0	0.5352
Average length of stay, days	0.2 (1.6)	0	0.2 (0.9)	0.1	0.1	0.9945

*Difference-in-differences are calculated as gabapentin pre- to-post-index differences minus pregabalin pre- to-post-index differences.

Table 8. Differences in 12-month all-cause and painful diabetic peripheral neuropathy (pDPN)-attributable healthcare costs per patient in the matched study cohorts of patients ≥65 years old.

Cost category	Cost per patient, US $					
	Pregabalin ($n=384$)		Gabapentin ($n=384$)		DID*	*p*-value
	Pre-index	Post- minus pre-index	Pre-index	Post- minus pre-index		
All-cause, mean (SD) per patient						
Physician office visits costs	$978 ($666)	$125	$1,215 ($2,436)	$123	−$2	0.3483
Emergency department costs	$310 ($742)	$17	$593 ($3,783)	−$142	−$159	0.8489
Outpatient costs	$8,150 ($11,458)	$1,595	$11,966 ($32,435)	$1,906	$311	0.9890
Prescription costs	$5,124 ($4,060)	$1,225	$4,595 ($3,427)	$540	−$685	0.0003
Inpatient costs	$5,189 ($16,721)	$1,237	$5,897 ($15,065)	$1,627	$390	0.9866
Total costs (inpatient + outpatient + prescription)	$18,462 ($24,286)	$4,058	$22,459 ($39,290)	$4,073	$15	0.6554
pDPN-attributable, mean (SD) per patient						
Physician office costs	$85 ($135)	−$9	$95 ($177)	$14	$23	0.0511
Emergency department costs	$13 ($115)	−$10	$197 ($3,646)	−$186	−$176	0.7866
Outpatient costs	$399 ($1,684)	−$108	$410 ($1,048)	−$41	$67	0.4294
Prescription costs	$506 ($1,513)	$724	$422 ($940)	$243	−$481	<0.0001
Inpatient costs	$301 ($2,358)	−$160	$521 ($4,305)	$25	$185	0.9862
Total costs (inpatient + outpatient + prescription)	$1,206 ($3,417)	$456	$1,353 ($4,764)	$226	−$230	<0.0001

*Difference-in-differences is gabapentin pre- to-post-index differences minus pregabalin pre- to-post-index differences.

However, our results also demonstrated that, across resource categories, there were no significant differences between pregabalin and gabapentin for changes from the pre-index to the post-index period. Similarly, for pDPN-attributable resources, there were no significant differences between the cohorts.

While the post-index period was characterized by small increases in most pain-related classes of pharmacotherapies in both cohorts, only the reduction in NSAIDs with gabapentin was significant relative to pregabalin. As previously reported, opioids were the most commonly prescribed class of pain-related medications[25].

Initiation of pregabalin resulted in an increase in prescription costs relative to the pre-index period that was significantly greater than the increase observed with gabapentin. This greater increase is likely a result of the higher acquisition costs of pregabalin compared with gabapentin, which is available as a generic formulation. However, these costs were offset by higher, albeit not significant, increases in inpatient costs in the gabapentin cohort. This offset resulted in a DID for the pre- to post-index change in total all-cause direct medical costs of $1603, favoring pregabalin, although this was not significant. While the DID for the changes in total pDPN-attributable

total healthcare costs (−$385; $p<0.0001$) indicated significantly lower costs with gabapentin, this is also likely a result of the higher acquisition costs of pregabalin, as indicated by the significantly higher pDPN-attributable prescription costs (DID −$432; $p<0.0001$) despite no significant differences in the number of pDPN-attributable prescriptions filled (DID 0.3; $p=0.38$).

This DID for all-cause costs was similar in direction but lower in magnitude to the difference in costs between pregabalin and gabapentin that can be estimated from the previous study ($1975)[25]. In fact, the total post-index costs for both pregabalin and gabapentin in the present analysis were substantially lower than those reported in the other study. These lower costs may be accounted for, at least in part, by fewer comorbid conditions and lower comorbidity index among the current study population relative to the previous study. This difference in comorbidities despite an older population indicates that, in contrast to that study, sicker individuals were not channeled to these drugs in the health plans comprising the MarketScan® database. Indeed, the overall results among a specifically older population (≥65 years of age) were similar to those observed in the main analysis; similar changes in all-cause resource utilization between pregabalin and gabapentin, and, for costs, only the greater change in pharmacy costs with pregabalin was significant. Interestingly, among these older individuals, the total direct medical costs per patient were lower than for the general population of the primary analysis. This may be due to the fact that all enrollees present in the database are individuals who are eligible for Medicare, but who also have some level of supplemental coverage from a current or former employer. If a claim is paid for entirely by Medicare with no liability to the patient, then the claim will not be sent to the supplemental insurer and therefore will not flow from the insurer to the MarketScan database. However, there are few situations in which this situation would occur because almost every service covered by Medicare has some form of patient deductible and/or copayment.

These data are consistent with the lack of differences in change in healthcare costs between pregabalin and gabapentin observed in a *post hoc* cost consequence analysis of two prospective cohort studies of patients with pDPN or post-herpetic neuralgia, based on costs derived from the Spanish healthcare system[30]. This concordance suggests that the comparison of differences in costs between pregabalin and gabapentin may be generalizable to a variety of healthcare settings.

Nevertheless, the interpretation of our results is subject to several study limitations including errors in coding and recording that can potentially result in misclassification of the disease state in a proportion of patients. An additional limitation is the inability to link the condition of interest, pDPN, with the prescribing of a particular medication, including those used for pain such as pregabalin and gabapentin, since ICD-9 diagnosis codes are not associated with pharmacy claims and these patients were additionally characterized by comorbid conditions that may also require such medication use. However, this limitation was potentially reduced by requiring the diagnosis of pDPN to take place within 30 days prior to the prescription of interest. Similarly, causal inferences may be complicated by differences between comparison groups due to a non-randomized design. However, propensity score matching was used to minimize any potential bias introduced by such differences between the cohorts. It should also be noted that patient adherence cannot be ascertained in retrospective database studies. Consequently, PDC and persistence can only be considered as proxy measures for adherence. Furthermore, outcomes are not typically collected in claims databases, and thus it is not possible to know what effects, if any, the prescribing of these medications may have had on pain or other outcomes. With regard to costs, the unavailability of data in MarketScan for adjusting costs within capitated plans may also represent a study limitation.

Conclusions

Patients with pDPN initiating pregabalin or gabapentin experienced comparable changes in healthcare resource utilization and total costs. The greater increase in prescription costs seen for pregabalin vs gabapentin, which is generically available, did not translate into an increase in total healthcare costs. These findings support results from similar studies and suggest that factors other than drug acquisition costs should be considered when making formulary decisions or instituting cost reduction policies that may restrict medication access.

Transparency

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Declaration of financial/other relationships
MU, JH, and JM have disclosed that they are employees of Pfizer, Inc. Editorial assistance was provided by E. Jay Bienen, who received funding from Pfizer for his services.

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